JOINT APPENDIX 69

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

PROTIVA BIOTHERAPEUTICS, INC.,
Patent Owner.

Case IPR2018-00680 (Patent 9,404,127)
Case IPR2018-00739 (Patent 9,364,435)

Record of Oral Hearing
Held: June 6, 2019

Before SHERIDAN K. SNEDDEN, SUSAN L.C. MITCHELL, and RICHARD J. SMITH, *Administrative Patent Judges.*

IPR2018-00680 (Patent 9,404,127)
IPR2018-00739 (Patent 9,364,435)

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The above-entitled matter came on for hearing on Thursday, June 6, 2019, commencing at 1:00 p.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, VA 22314.

P R O C E E D I N G S

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(Proceedings begin at 1:00 p.m.)

JUDGE MITCHELL: Thank you. You may be seated. Sorry.

Good afternoon, everyone. We have a final hearing this afternoon in two cases, IPR 2018-00739 and IPR 2018-00680. I'm Judge Mitchell and seated to my left is Judge Snedden, and with us by video conference is Judge Smith, who should be here. Is Judge Smith on?

JUDGE SNEDDEN: Uh-huh.

JUDGE SMITH: Uh-huh.

JUDGE MITCHELL: Oh, great. Sorry.

JUDGE SMITH: Hello.

JUDGE MITCHELL: Great, thank you.

I would like to get appearances for the parties on the record, and if we could start with the Petitioner.

MR. FLEMING: Good afternoon, Your Honor. I'm Mike Fleming with Irell & Manella, and with me is Morgan Chu, as well as Maclain Wells.

JUDGE MITCHELL: Great.

MR. FLEMING: And we all three will be arguing.

JUDGE MITCHELL: Great. Thank you.

MR. CHU: Good afternoon.

JUDGE MITCHELL: Good afternoon. And for Patent Owner, please.

MR. ROSATO: Good afternoon, Your Honor. Mike Rosato on behalf of Patent Owner. I have with me for the counsel table Sonja Genrard, as well as Franklin Chu. Thank you.

JUDGE MITCHELL: Thank you.

Let me get a quick clarification from both of you-all, because as I understood from your requests for oral hearing, I think Patent Owner requested the two cases be separate, which is fine. It's just we could do the 739 first, adjourn for a short bit, and come back and do the 680, and have one record that gets submitted for both cases, so that you can rely on -- you know, if claim construction issues are similar, you're going to want to have that discussion in both cases. So I want to make sure I understood right or if you really do want separate transcripts.

Petitioner?

MR. FLEMING: Your Honor, we have prepared for having separate hearings.

JUDGE MITCHELL: Okay.

MR. FLEMING: Because I will be arguing the 739 and --

MR. CHU: All right. The way we're going to proceed is Mr. Fleming and I will argue '435.

JUDGE MITCHELL: Okay.

MR. CHU: And Mr. Wells will argue the '127 Patent, referring to the patent numbers, but having a single unified

transcript as constituting the official record --

JUDGE MITCHELL: For both cases.

MR. CHU: For both cases makes sense.

JUDGE MITCHELL: Okay. And -- and Patent Owner?

MR. ROSATO: We have no objection to this suggestion, You Honor. I mean --

JUDGE MITCHELL: Okay. Okay. So we will go forward with the '739. We'll take a short break and then come back on but have one complete record for both cases.

We set forth our procedure for how we're going to handle this oral hearing in our order, but I want to go over a couple of things as a reminder.

Each party will first present argument in the '739 case, and each party will have an hour for that case, and then we will have a second hearing for the '680 case, and that case, there's a 40, 45 minutes per side of total time.

And to assist Judge Smith in following along with your argument and for the clarity of the record, it is very important that you refer to an exhibit. When you refer to an exhibit, that you state the exhibit number and the page number to which you are referring, and when you're referring to a demonstrative, that you state the slide number.

Petitioner has the burden of showing the unpatentability of the challenge claims in both cases, so the Petitioner will go first. The Patent Owner will then have an opportunity to present its response and may reserve a small

amount of time for some rebuttal.

We have reviewed Patent Owner's notice of objections to Petitioner's demonstrative exhibits. We're not going to exclude any of the demonstratives at this time for the hearing. The Patent Owner may certainly address any objectionable demonstrative in your argument time, if you choose.

We also want to furthermore note for the record that demonstratives are evident -- or not evidence and will not be considered as such. They're used for the benefit of those in this room and for the benefit of the transcript that will become part of the public record.

The Panel will distinguish evidence in the record from argument appearing in demonstrative exhibits and all arguments must be supported by evidence; already of record and relied upon in the briefing. The Panel will not consider arguments or evidence appearing only in the demonstrative exhibits.

So with that, let me ask Petitioner if you'd like to reserve time for rebuttal.

MR. FLEMING: Yes, Your Honor. So our understanding, that is when we go first, we'll be addressing both the principal case as well as the motion to amend.

JUDGE MITCHELL: Yes, I'm sorry. Yes, of course.

MR. FLEMING: And --

JUDGE MITCHELL: Well -- yes.

MR. FLEMING: Or --

JUDGE MITCHELL: I'm sorry, yes.

MR. FLEMING: Would it --

JUDGE MITCHELL: That's correct.

MR. FLEMING: Would it be better that we do the principal case and then later, the motion to amend?

JUDGE MITCHELL: I mean, however you've decided to do it, we'll -- we'll take the argument whatever you're comfortable doing. So that's fine, however you do.

MR. FLEMING: Okay. We'll -- we plan to reserve. If we're going to go forward with the principal case and the motion to amend first, we will reserve 30 for rebuttal.

JUDGE MITCHELL: Okay. Whenever you're ready.

MR. FLEMING: Your Honor, may I --

JUDGE MITCHELL: Oh, sure.

MR. FLEMING: Approach the Bench and present hard copies?

JUDGE MITCHELL: Please.

MR. FLEMING: We might need the -- evidently the --

JUDGE MITCHELL: Oh, is it not working?

MR. FLEMING: Well, it was working just a minute ago.

JUDGE MITCHELL: Oh, no.

MR. FLEMING: This is (indiscernible).

JUDGE MITCHELL: Would you like some help?

MR. FLEMING: Yeah, Your Honor. Could we get

technical assistance?

JUDGE MITCHELL: Can we have like a (indiscernible).

FEMALE TECHNICAL STAFF: This equipment that they have it hooked up to, I can't mess with the equipment if they have it hooked up to --

JUDGE MITCHELL: Oh, okay.

FEMALE TECHNICAL STAFF 1: Because surely if somebody -- because it was up and then you shook it. It came up and it (indiscernible).

JUDGE MITCHELL: Whenever you're ready.

MR. FLEMING: Thank you, Your Honor. Appreciate the patience. We should have it up here.

Okay. I'm ready, Your Honor.

JUDGE MITCHELL: Go ahead.

MR. FLEMING: Okay. Good afternoon. May I have Slide 4, please?

The Petition challenges just Claims 1 through 20 of the '435 patent.

And if I can have Slide 6, please? Here is the independent claim before you. It's important to note that what we have is a nucleic acid lipid particle comprising a nucleic acid, a cationic lipid with this particular range and non-cationic lipid with the 13 to 49.5 range and a conjugated lipid from 05 mole to 2 mole range.

The key here, as far as patentability goes, it's the cationic lipid comprising the range of 50 mole percent to 85

mole percent.

I want to point out that the claim is not directed to a particular use or how effective the particle is, and it doesn't require that the particle is to be non-toxic or that it is in vivo or in vitro.

If I have Slide 5, please.

JUDGE SMITH: Counsel, could you speak up or perhaps be moved closer to microphone?

MR. FLEMING: Yes, Your Honor. Can you hear me now?

JUDGE SMITH: Yes. Thank you.

MR. FLEMING: Just to test, can you hear me now?

JUDGE SMITH: Yes.

MR. FLEMING: Okay, great. I'll speak up.

If I can have Slide 5. There's no dispute that the nucleic acid, the cationic lipid, the non-cationic lipid, and the conjugate lipid are all known in the art.

If I can I have Slide 9, please? So turning to claim construction. The term in the preamble is at issue, and that's the nucleic acid lipid particle.

And the board's construction is correct. The nucleic acid lipid particle is a particle that comprises a nucleic acid and lipid, where the nucleic acid may be encapsulated.

Now Slide 11, please. The intrinsic evidence supports this construction in Column 11, Lines 14 through 22. The '435 Patent defines lipid particle has a lipid formulation

that can be used to drive nucleic acid for the nucleic acid making it encapsulated in the lipid.

A person of ordinary skill in the art would derive that the nucleic acid lipid particle comprises a nucleic acid and a lipid. And I want to point to Dr. Janoff's testimony in his reply declaration on Page 13 that affirms this.

May I have Slide 15, please? The '435 Patent in Column 11, Lines 23 through 46 also define a stable nucleic acid lipid particle, SNALP, as a particle made from a lipid, wherein the nucleic acid is fully encapsulated.

So the term nucleic acid lipid particle encompasses SNALP, but does it -- but is not so limited.

JUDGE MITCHELL: What happens to your case, if we agree with Patent Owner and we think that Claim 1 is limited to a SNALP?

MR. FLEMING: Your Honor, as we point out in our petition, that the 554 Publication actually teaches encapsulation of the nucleic acid in the particle. So as you're correctly pointing out, even if they do get this narrower term, which I don't believe is the broadest reasonable, it still won't matter as far as what the prior art teaches.

May I have Slide 19, please? Which really takes me to Ground 3. And Claims 1 through 20 are anticipated by or obvious in view of the 554 Publication.

If I can have Slide 21, please? There is a formula

that was tested, and that is L054 that reads on the claim. The first thing is that it teaches that the nucleic acid lipid particle in Table 4 and in Example 17 encapsulates siNA.

May I have -- can you pull up the Example 17?

MALE TECHNICAL STAFF: I can't get back into that.

MR. FLEMING: Oh, okay. Well, not a problem.

Example 17 is -- explains the preparation of the nanoparticle that encapsulates siNA formulation that's shown in this Table 5 -- 4.

May I have Slide 22, please? So you can see in the Table 4, it teaches a cationic lipid that it's 50 percent -- 50 mole percent, which is within the range.

If I can have Slide 23, please? It also teaches a non-cationic lipid. That's 48 percent. That's within the range.

And if I could have Slide 24, please? It also teaches a conjugated lipid. That's two percent. That's also in the range.

JUDGE MITCHELL: So are these all referring to a starting formulation and not necessarily a particle?

MR. FLEMING: No, Your Honor. This is referring to a particle. And in the art -- and we have testimony for both the experts that that's how they refer to the particle, but, indeed, it was formulated as a particle.

So if we can go to Slide 30, please? We also have overlapping ranges, and we can establish a prima facie case of

obviousness.

So if I can go to Slide 32, please? The 554 Publication teaches, in Paragraph 0313, the nucleic acid particle formulation that in -- formulation that encapsulates siNA and if we have the overlapping ranges.

And if I could have Slide 31. This summarizes and shows side-by-side the overlapping ranges.

If you could go to Slide 61, please? I want to point out that the Patent Owner has not been able to establish unexpected results, and the key here is that looking at Example 3, which they relied on heavily, there's really only three points that are within the range -- within the scope of the claim. And those three points don't show that it's commensurate in scope with the entire range of the claim.

But even if you look closer at what the table is teaching you, if we can go to Slide 62, please? Here, what we have is the Figure 2 that shows all the groups in the comparison. And so Groups 2 through 10 and 12 have cationic lipids less than 50 percent mole. So if you look at Figure 2, it shows the test results of each of these groups. And so what is going on here is you have -- for each group, four mice were administered 1:57 SNALP.

And the upside-down T, if I can show second slide of 62? Can I have the next slide? When you have the upside-down T, it represents experimental error between these experiments. So when you consider the experimental error, Groups 2 through

5 have similar results compared to 14.

So if we can have the next slide, please. So the other aspect of this figure that is important to understand is the vertical axis; lower is better.

Can I have the next slide, please, and the next slide. You don't? Is that all I have?

MALE TECHNICAL STAFF: Yeah, it's all for 62.

MR. FLEMING: So if you look on the Y-axis, the vertical axis, lower is better because what that is showing is that it's showing how effective the formulation is in silencing the target gene, so you want a lower value there to show that it's more effective.

Okay. So if you look at -- if I can go to the next slide? So the prior art is 2:40, and that's the 40 percent cationic lipid and 2 percent conjugate. And that's what you need to compare to determine whether you have unexpected results because that is the closest prior art.

And there, you see, that for Group 7, it's really -- can I have the next slide? See if it does -- so if you look at Group 14, it's worse than the prior art, and if you look at -- if you go to the next slide, please? If you have Group 13, it's no better or worse than the prior art.

If I have next slide, please? And if you look at Group 12 versus Group 11, it's pretty close. So, at best, all you have is one point, but it's certainly not surprising unexpected results. It's very close to what was the prior

art.

May I have the next slide, please? The Patent Owner is relying on surprising results for the placebo. But the problem there is it's not proper to compare to the procedural or placebo. You need to compare to the prior art.

So if we could go to Slide 67? What is not addressed by the Patent Owner is the fact of how broad this claim is. So to be considered -- to be commensurate in scope with this claim, it's not only showing how effective the particle is, but what you also have to show -- well, what about all the payloads? It could be -- because you have a very broad term, nucleic acid, which can be a bunch of different payloads.

So they certainly haven't shown surprising and unexpected results for all the payloads. And, again, there's only a few lipids that were tested and only a few formulations. So there's a problem here. It's just not -- they're showing us -- this is not commensurate in scope for the claim. I'm going to --

JUDGE MITCHELL: Is it your position that -- you know, I'm trying to figure out how much testing would they actually have to show to basically show that they have the full range of their claim? I mean, what is -- what is your suggestion? I mean, they can't possibly formulate every lipid particle that would be within the claim. I mean, we don't hold them to that kind of a standard to say that they already

achieve or at least support the scope of a particular range in a claim.

MR. FLEMING: Yes, Your Honor. What would be required would be enough testing to show that -- to one of ordinary skill in the art that these surprising and unexpected results would result -- you know, that you'd have enough test to show that you would have a same -- unsurprising unexpected results for the entire range, for one. But the other issue though is, again, you also need to show that you have testing across the nucleic acid as well. So here we only have siNA payloads.

So, again, this claim is very, very broad, Your Honor, and so there lies the problem.

If there's not any further questions, I'd like to turn it over to Morgan Chu to argue the motion to amend.

MR. CHU: Good afternoon again, Your Honors.

I want to start with what the Patent Owner argues are two new limitations and then later, I'll go to the modified ranges.

The first alleged limitation is adding to new independent Claim 21, the phrase, serum-stable. And as Your Honors will know, looking at that new proposed Claim 21, serum-stable appears in the preamble.

Now, this is not a lonely patent prosecutor who's overworked writing claims for many different patents. This is a team of lawyers in a hotly contested IPR proceeding where if

they wanted serum-stable to be a limitation, it would have been easy to put it in the body of the claim.

Now, let's suppose for the moment they did that, which they didn't do. If you have your copy of the '435 Patent handy, I want to show that serum-stable does not add a limitation that the claim must be in vivo or involves systemic delivery.

And the second argument that the Patent Owner is making about the term serum-stable is that it requires encapsulation. Those two arguments.

So if you have your patent handy and can go to Column 13, Line 32, or I can pull it up on the screen. We'll do both. Okay. Column 13, Line 32, and then let's highlight that language, third -- Line 32 through 37. Column 13, 32 through 37. And we'll highlight the word -- okay.

You see, serum-stable is defined by the Patent Owner in a particular manner. It is a defined term in the '435 Patent. And if you look at that language, there is nothing in that language that requires in vivo use or systemic delivery whatsoever. Indeed, if you go to the following lines in Column 13, starting at Line 38 through 41, it's the beginning of the definition of another defined term, quote, systemic delivery. And if you look at that language, systemic delivery is intended to be in vivo.

So if the Patent Owner, in proposing amended claims, wanted to have the claims limited to in vivo or systemic use,

instead of using serum-stable, which doesn't include an in vivo limitation, he could use the next definition, systemic delivery. They chose not to do so.

JUDGE SNEDDEN: In the definition for serum-stable, you have a reference to assays that can be used to test whether or not the particle is serum-stable.

MR. CHU: Yes. And we will see actual testimony by Dr. Thompson after I leave the language of the claims where he is saying that the claim includes in vitro, so we will get to that. It can include it. But remember where we are. We're looking at some words added to the preamble, so although there can be an argument that they are -- could be read, as being a limitation, the general law is, no, you start out, it's just the preamble, and unless it's necessary to give life, and meaning, and vitality to the claim, it's just a preamble. It's not a limitation. If the Patent Owner wants it clearly to say it is limited to in vivo, they could have used the definition, systemic delivery.

Second point, on encapsulation. The serum-stable definition we were looking at in Column 13, line -- beginning at Line 32 did not say encapsulate. If the Patent Owner wanted the new proposed Claim 21 to require encapsulation as a limitation, there's a handy word to do that, and that is to add the word encapsulate. But in addition --

JUDGE SNEDDEN: That --

MR. CHU: Yes?

JUDGE SNEDDEN: That would suggest that you can have a serum-stable particle without it being encapsulated.

MR. CHU: Yes, I agree.

JUDGE SNEDDEN: Okay.

MR. CHU: Okay.

JUDGE SNEDDEN: And then --

MR. CHU: But --

JUDGE SNEDDEN: Then the next question will be, how would something pass these assays and also be serum-stable if it was not encapsulated?

MR. CHU: Okay. So let me get to that. But I just --

JUDGE SNEDDEN: Okay.

MR. CHU: I'm told there's some problem if I try to switch to --

JUDGE SNEDDEN: Sure.

MR. CHU: Some pre-prepared slides from the language of the patent. Let me just show you what else the Patent Owner could have done --

JUDGE SNEDDEN: Okay.

MR. CHU: If it wanted to say encapsulate. There's a limitation.

So there's the possibility of using the word encapsulated. There's another possibility. And it includes the possibility of defining the new Claim 21 as a SNALP because if you go to Column 11 starting at Line 23, the term

SNALP is also a defined term, which includes being fully encapsulated.

So quick points, one, serum-stable was just in the preamble. It's no limitation. If we pretend for the moment it was a limitation, which it is not, the choice of the defined -- particular defined terms and not others and not using clear words would not limit the claims to either in vivo or encapsulation.

So let me go to some of the slides. And maybe we'll just go to 78 for a second, and you can see serum-stable there in the preamble.

And then let's go to the next slide. I'm going to do my own work. It's a different definition of full-service lawyer. Someone who's going to advance the slides himself.

So these are the changes that I will be discussing, and I will try to answer Your Honor's questions along the way here. And just to look for a moment at the Whereas clause, there's an argument being made about the Whereas clause possibly adding a limitation other than what the plain language states. And, here, it's pretty clear that this can be done in a Petri dish. So contrary to the lawyer's argument, this is not suggesting anything about in vivo for degradation. And this was Slide 86. Okay.

Let me go to 87, and this is just showing of the three principal references, the 554 Publication, Exhibit 1004, the 196 PCT, which is Exhibit 1002, and the 198 publication,

which is Exhibit 1003 on the Slide 87, that the nuclease degradation resistance was disclosed in the prior art, so the wherein clause is not adding anything new.

Let me go to the new narrow ranges. You see them in blue highlighting in Slide 88. You can tell from the brackets, it shows the original range. So for the cationic lipid, the original range was from 50 to 75 percent of -- the original was from 50 to 85 percent, and the new range is from 50 to 75 percent. And as Mr. Fleming already addressed in the 554 Publication, this is Slide 89, we see the range covered as well as the second range in Slide 90.

And the next Slide 92 shows that the prior art still overlaps for the proposed cationic lipid range from 50 to 75.

And in Slide 93, we show the actual overlap and note that the relative amount of overlap is greater than it was in the original claim, which was from 50 to 85. By narrowing the original claim, there's relatively more overlap as shown in 93.

And then the point about the lack of surprising and unexpected results can be shown in Slide 96. You've seen this before, Figure 2. You see Group 7, and Group 12 is the prior art, 14 is worse than the two pieces of prior art, 13 is worse than Group 12 and about the same as Group 7, so neither worse or no better. And if you compare Group 11 to Group 12, it's hard to tell whether there is any meaningful statistical difference between the two because of the error bars. And, in

fact, Dr. Janoff discusses the fact that in his opinion, looking at the figure, it's hard to read of course. In this tight comparison, he said in effect, it's likely not statistically significant. It's very close.

But let's for the moment, for the purposes of argument, say that the Patent Owner has one data point for this very broad range of 50 to 75 cationic percent.

In answer to Judge Mitchell's question earlier, it cannot be the case for that broad range. A single data point is commensurate with the scope of the range. Indeed, that 50 to 75 percent includes 70 to 75 percent no data point that the Patent Owner points to is in the 70 to 75 percent. And the record is replete with the fact that slightly different combinations can lead to grossly different results.

So even if the Patent Owner has one data point that shows or maybe shows somewhat better results, it is not commensurate with showing surprising and unexpected results for the entire range.

So you've seen the -- we call the PBS, the inert of placebo standard.

And before I go to the next point, I think Judge Snedden, you asked a question, and chemically modified siRNA, for example, can avoid the degradation. I believe that's in the record, and maybe someone's going to find the exact paragraph for that.

If you go to --

JUDGE SNEDDEN: Before we read the spec, is there anything that spec about a chemically modified nucleic acid or a particle?

MR. CHU: We will look that up, and if I don't get to it in the little bit of time, I have here --

JUDGE SNEDDEN: To me, the amended claim essentially refers -- but -- it recites serum-stable, you go to the definition of specification, it -- it gives you a brief definition of that, and what -- in that is that it must survive exposure to nuclease.

MR. CHU: So --

JUDGE SNEDDEN: And you have referenced here DNA's, RNA's acid. And if you read that in the context of the specifications, it seems the only way that they're attempting to achieve that with this invention is through encapsulation; is that correct or --

MR. CHU: Because I've run over the time, let me just on a somewhat different --

First of all, we will answer your question. My colleagues are --

JUDGE SNEDDEN: Okay.

MR. CHU: Looking through the spec and other references now, and when I get up -- stand up to give rebuttal testimony, hopefully, I'll have a cogent answer to that.

Let me just finish by saying there are other slides as well as in our briefs.

Because this is a contingent motion to amend, then Section 112 comes into play. And we put forth in the papers why the written description requirement is not met and the claim -- the amended claim as proposed is not enabled. And if need be, I'll come back and address those in greater detail.

So I have your question in my journal.

JUDGE SNEDDEN: Sure.

MR. CHU: Thank you.

JUDGE MITCHELL: Thank you.

MR. ROSATO: Before I get started, a question on -- a clarification --

JUDGE MITCHELL: Sure.

MR. ROSATO: -- that the order on granting oral hearing, you mentioned the ability that you mentioned here today, Your Honor, to receive a short amount of time?

JUDGE MITCHELL: Yes.

MR. ROSATO: What do you mean by short?

JUDGE SNEDDEN: I think you have a maximum of five minutes of rebuttal time that you can save.

MR. ROSATO: Okay. I'll reserve five. Thank you.

Let start out on Slide 3. So this is actually a point of clarification on the slides that were submitted. I think that this listing of original Claim 1 inadvertently had a typographical error, including the term serum-stable that appears only in the amended claims of course, but that's been corrected here. I hope nobody has a problem with that, but

we're showing the actual claim here.

But just looking at the '435 Patent, and very briefly, these are directed to lipid particles designed for the delivery of nucleic acid (indiscernible) payloads. And the '435 Patent is a very important patent for a number of reasons, but it's -- one of which is it's listed in the FDA's orange book as covering the Patisiran Onpattro commercial product, which was the first in class -- first nucleic acid delivery drug that's been approved by the FDA and is now approved for use in humans in Europe, as well as the United States.

This is of course important because this has been characterized in the literature, and in the industry, as a game-changing development and because Patent Owner's delivery technology has been specifically credited in the literature as a vital component of that success.

There are a number of challenges that have been advanced; each of them fail for a number of reasons. I'm going to attempt to address. It's a little bit out of order on the slides, but I'm hoping following the order that was presented is more convenient for everyone.

So with that in mind, I want to turn to Ground 3, which is at Slide 21 in the demonstrative exhibits.

So while we're getting there, ground -- we know that Grounds 1 and 3 both presented an obviousness theory, and I'll return to the obviousness theory, but I wanted to address

first the anticipation theory that's raised in Ground 3. And that specifically is alleged anticipation over this L054 mixture. And as Your Honor, Judge Mitchell, correctly pointed out, L054 mixture is a lipid mixture for making particles, not a particle itself. There's never been any dispute on that until today.

I was surprised to hear counsel incorrectly characterize the L054 of Table 4 as a particle. That is categorically false. The evidence is uniformly supportive of the falsity of that charge. It's not a particle. It's a starting lipid mixture for making particles. There is never any discussion in the petition materials about any particle. This appears to be a complete oversight and misinterpretation on behalf of Petitioner and the petition materials, but it's not been challenged. In fact, I'm going to bring up Petitioner's demonstrative Exhibit 25.

This issue -- again, this has not been challenged until today, so I was surprised to hear this. Even Dr. Janoff, in his reply declaration, readily admits that the -- the 554 Publication is describing input percentages as opposed to the composition of the final particles.

Their only response to that is, Well, that might all be true, but everybody did that, so that's conventional. So there's -- as far as the factual matter, it's not disputed that that is a lipid mixture, not a particle. In terms of the response that everybody did this and this was conventional,

it's not responsive to the point.

The claims are directed to nucleic acid lipid particles. They're not -- they do not recite a starting mixture for making particles. So pointing to the starting mixture is not sufficient to establish anticipation with this aspect of the claim. And this all matters, of course, because as set forth in the briefing and established with evidence of record, one does not simply assume that the particles that result from a process have the exact same lipid composition as the starting material. And that's particularly important in the context of 554 for a number of reasons, which, again, are laid out in the record and well supported with evidence.

It's particularly important because in 554, there is no disclosure of particle composition. They don't report any, they don't characterize any, and they don't claim to characterize any. It's also important because there were very specific reasons to call into question the -- what the 554 particle composition, whatever those resulting particles look like, there are reasons to call into question the -- exactly how much they would deviate from the starting materials. And there are a number of reasons as explained -- by both the literature explained by Dr. Thompson, agreed upon by Dr. Janoff, that you would expect significant deviations because different components -- different lipid components, given the processes, the limited amount of detail of the processes in 554, you'd expect different incorporation

efficiencies for different lipid components. And that's going to result in particles that throw out of whack the lipid composition compared to what the starting material was.

This is all very well-documented, supported with evidence, not just attorney argument, and doesn't fit in, as far as I can tell, is not opposed anywhere in the record, and for -- in fact, agreed upon as illustrated by Petitioner's own evidence.

Let me turn to that claim construction issue, and I'll go to Slide 4. So as everybody here knows, as part of the Petitioner's responsibility as moving party, they bear the requirement of the statute and the relevant board rules to set forth and establish exactly how claims are to be construed. So we're talking -- we're going to talk about the construction of the term nucleic acid lipid particles. And for that term, there have now been advanced by Petitioner, three different constructions. The first is the construction that was advanced in the petition materials. The second is a construction that is advanced by Dr. Janoff during cross-examination, where he repeatedly testified that he believed that the claim particles were very specifically defined as SNALPS, and we'll go through that testimony. And then third, in the reply, and this was surprising when the reply materials came in, despite having advanced two different constructions, the reply comes out with an entirely conclusory comment that the Board's preliminary construction is appropriate. There's

no analysis as to why that is or why they believe that to be the case. There's no discussion of why that's appropriate in view of the specification or any other piece of evidence. It's entirely conclusory argument as to just a statement that it's appropriate.

I think there is some additional argument or attempted argument to substantiate that here. The lack of explanation is an issue we specifically raised in our sur-reply materials that there was no argument or evidence substantiating this agreement. So to the extent they're trying to add argument here today, that's obviously improper. But there are reasons why it's not appropriate, and we address that in our briefing. I'm happy to address that in further detail here today, but I want to go through each of these constructions in order, and the first one that is very easy to dispense with is the one that was presented in the petition. It's easy to dispense with because that's already been rejected as unduly broad by the Board in the institution decision, and Petitioner seems to have completely abandoned that construction.

Turn to Slide 5. What's curious, however, is that ever since cross-examination, while Dr. Janoff was very specific and very adamant about his position on how the claim terms could -- should be construed, there's been virtually no comment on that position by Petitioner in their briefing or even here today. They've essentially ignored that. And it's

not something that can be ignored. It's -- again, Dr. Janoff was very specific about that. He testified during cross-examination that -- and repeatedly and consistently, that he interpreted the claimed nucleic acid lipid particles as reasonably being defined as SNALPS, and he testified that interpretation was -- supported both by the patent specification, as well as the content and the context of the relevant prior art. And that's shown on some of the testimony on the slide here, on Slide 5.

Let's turn to Slide 6. Not only was Dr. Janoff clear in his position, but he was specific as to the basis of his opinion. As he previously stated, he indicated a support both by the specification as well as the relevant context in the art, and he also pointed to specific content in the specification. Now, he's pointing to the '127 Patent, but the provisions he was pointing to in the '127 Patent, as we point out in our briefing are identically recited in the specification of the '435 Patent.

The answer from Petitioner as to why -- you know, why Dr. Janoff said this and what their response is, I don't know because I haven't heard it at this point.

JUDGE SMITH: Counsel, could you address the issue of this extrinsic evidence from Dr. Janoff and our role -- these -- the extrinsic evidence and the intrinsic evidence that we're looking at is ultimately, it's a question of law that we're going to be deciding, and you know, I want to know

whether it's proper to consider this Janoff testimony or not.

MR. ROSATO: Well, that's a good question.

Of course, it's appropriate to consider it when the moving party's expert and that party who bears the responsibility of setting forth the scope of their challenge, one of those responsibilities being defining how the claims are to be construed, has offered a construction, and we're asking what the basis of the challenge is. So the -- of course that has to be considered on multiple levels.

And you know, I guess, if you were to reject that construction, then I would ask how does that not carry over to the basis of the Petitioner's challenge and ultimate burden of proof to begin with?

JUDGE SMITH: Well, does this extrinsic evidence trump the intrinsic record?

MR. ROSATO: I think there's an assumption there that there's a difference, and I'm not sure that there is.

So if there's some particular difference that's contradicted, I can address that, but I don't -- to be honest, I don't think -- and we'll get to this. We address in our briefing, but I don't think there's any meaningful difference between the construction that Dr. Thompson advanced, which is extremely well-grounded and unassailable in view of the specification and what Dr. Janoff is -- is proposing.

JUDDGE SMITH: Well, I'm just -- I'm a little -- you know, what -- we've already come out with a construction or

proposed construction. And I think it would be helpful to explain why that's wrong if you believe it's wrong, and, you know, relying on -- you know, it'd be more helpful to point to the specification or some of the intrinsic record, if you have that, than just relying on what either expert says.

MR. ROSATO: Well, I mean --

JUDGE SMITH: Like, for me --

MR. ROSATO: I agree, we need to talk about the specification. I would have to say we cannot ignore what the moving party's expert is stating. That cannot be ignored for many reasons.

JUDGE SMITH: Okay.

MR. ROSATO: Okay?

JUDGE SMITH: Thank you.

MR. ROSATO: But turning to -- why don't we turn Slide 7. Okay.

So this -- let me get to maybe some of the -- what you're more interested in, Judge Smith, and that is looking at the Board's preliminary construction versus the construction that was proposed by Dr. Thompson and -- and how that's supported in the specification.

Now, what's shown here on Slide 7 is reflective of Dr. Thompson's construction, rather than the Board's, but what -- the difference -- the key difference is with regard to the encapsulation issue. And with -- what comes out in the Board's construction is an indication that a nucleic acid

lipid particle may permissively include the nucleic acid encapsulated in the particle, so as to protect that nucleic acid from enzymatic degradation. That's where Dr. Thompson took issue as that can -- that construction -- that preliminary construction by the Board as being unduly broad, and not supported by the specification, and overlooking some other pertinent disclosure.

And, in particular, what Dr. Thompson explains is that the construction that was proposed was very focused on disclosure and the specification around a different term, not the term nucleic acid lipid particle, but disclosure about a definition of the more -- the broader term, lipid particle. Okay? So that matters because the claim term is nucleic acid lipid particle, not just lipid particle. And as shown here on Slide 7, there's pertinent disclosure in the specification that requires yet further refinement of the construction that the Board had proposed.

And, in particular, I would point to Column 11, Lines 51 through 54, where the specification states, in no unambiguous terms, that nucleic acids when present in the lipid particles of the present invention are resistant to a -- in aqueous solution to degradation with a nuclease. And you see other areas of the specification. Again, this is addressed in the briefing where stability encapsulation -- I'm sorry -- encapsulation is defined as a -- testable measure based on resistance to enzymatic degradation. That is precisely --

JUDGE SMITH: So how -- counsel, right. Counsel, how does -- so just how does nucleic acid lipid particle, how is that different than a SNALP as defined?

MR. ROSATO: You'd have to ask Dr. Janoff that question. This is the construction that Dr. Thompson proposed. Dr. Janoff was very adamant in his position that, no, it is a SNALP. At the end of the day -- and, again, this is something we addressed in the briefing, as well as Dr. Thompson's testimony that, you know, it's less -- I guess I would answer that as saying, what's explained as, there's not -- it's hard to find any meaningful daylight between what Dr. Janoff is saying about SNALP and the construction that requires encapsulation because encapsulation is -- what's described in the specification as a characteristic that's conferring the stability or instability of the particles.

So to the extent, you know, that's what Dr. Janoff had in mind, well, that makes some sense and is well supported by the specification. But you know, I would say that -- I would pose that question to Petitioner. This is why it's somewhat curious that they've never addressed the position of their expert, and, you know, and that's just a difficult position to put the non-moving party in, when the moving party's expert is proposing a construction, and then I'm the one being asked to defend that position.

We've proposed economic --

JUDGE SMITH: No, I meant -- I'm actually just

asking a simple question. Is it Patent Owner's position that the term nucleic acid lipid particle as used in the claims should be construed in the same manner that we would construe the term SNALP, that those terms are interchangeable or if -- and if not, what is the distinction that Patent Owner views from their patent?

MR. ROSATO: Our position is the term nucleic acid lipid particle must include a nucleic acid encapsulated in the particle so as to protect the nucleic acid from enzymatic degradation, and that's a position that's well-supported and, quite frankly, unassailable in view of the specification.

Now, beyond that, as far as Dr. Janoff's position, if that is the position that is adopted, that's what they're advancing, then our position is we wouldn't oppose it.

As far as the difference that he had in mind, I have no idea. I honestly would like to hear from Petitioner on this point. I don't know.

JUDGE SMITH: Okay. Thank you.

JUDGE SNEDDEN: Now, when we look at claim -- substitute Claim 21, we see the word serum-stable and in reference to a nuclease test, but in the Claim 1 here, there is no -- there's -- you haven't used the word stable or serum-stable. It only -- in the preamble, it states nucleic acid lipid particle, and then there's no indication that the claims cover something that's nuclease resistant.

So how do we get to encapsulation and nuclease

resistance using the words in Claim 1?

MR. ROSATO: So for the original claim, you know, I would direct your attention to the proposed construction where, again, the specification states that nucleic acids, when present in the lipid particles, they are resistant in aqueous solution to degradation with a nuclease. And when you look at the definition of serum-stable, its defining serum stability as resistance to enzymatic degradation. And when you look at description of how to test for encapsulation, it's defined by resistance to nuclease degradation.

This is what I mean by there's -- it's hard to find any meaningful difference between that, and it's also why in our contingent motion, we specifically pointed out that, honestly, there were aspects of putting in that additional terminology, that would seem to be superfluous in view of some aspects of a proper construction.

I would add that there were additional limitations within the body of the claim, the wherein clause that specifically recite a method. The -- basically the standards are -- I know I'm (indiscernible) the claim, but allow me to talk loosely about it, but read -- recite the aspects of nuclease resistance.

JUDGE SNEDDEN: I understand. So are we arguing the motion to amend now or -- because that language is not in Claim 1?

MR. ROSATO: I'm not arguing that. I'm responding to your question.

JUDGE SNEDDEN: Okay, great.

MR. CHU: Yeah.

JUDGE SNEDDEN: So my question though is that I understand this with respect to substitute claim 21, but when I look at Claim 1, the words nucleic acid lipid particle, I understand you, the argument that you're making, there's not much daylight between nucleic acid lipid particle and the SNALP, but that language only appears in the preamble of Claim 1; nowhere else in the claim. So then we have to consider whether or not that's a limitation, even though it appears in the preamble, and then when we get to the body of the claim, there's no -- what is it in the body of the claim that points me to encapsulation or brings me to encapsulation or to an assay that requires a nuclease test?

MR. ROSATO: I would say that the subject there, the language in the claim is what you see here the nucleic acid lipid particles and --

JUDGE SNEDDEN: Which is in the preamble.

MR. ROSATO: Which is in the preamble, and for --

JUDGE SNEDDEN: Then why is that a limitation of this claim?

MR. ROSATO: Because it's hard to say that doesn't breathe life into the claim when it is defined in the specification as the invention. And that is actually where Dr. Janoff's testimony is also quite pertinent, if we're looking at aspects of what it -- how would someone understand

the invention here. His testimony in -- is certainly pertinent in that regard, if he's doing the invention as being these -- as including serum stability, the very aspects that from this construction, I think are very -- it's a very reasonable position to say that this is -- you know, this is included. It's hard to say that what also is reflected in the specification as critical aspects of the invention are not required by the claim or breathe life into the claim.

JUDGE SNEDDEN: Understood. Thank you.

MR. ROSATO: Thank you. Thank you for the question.

If I may, I would like to turn to a discussion of -- let's turn to Slide 8 and the discussion of this theory of obviousness that's advanced for claims -- excuse me -- for Grounds 1 and 3.

So both of those grounds advance an obviousness theory based on these -- identification of these ranges in the prior art. Now, albeit the two grounds are referring to different references, but I'd like to address the theory in general and the theory as presented in the context of both grounds.

But in each of those cases, in each of those instances Grounds 1 and 3, Petitioner's whole case relies on this mere identification of ranges for individual lipid components in the art. And that's essentially the entirety of the argument. Petitioner essentially drops the microphone once they've identified those ranges and concludes that

obviousness must be found. And in doing so, they're pointing to cases like in *In re Peterson*, and now, more recently *DuPont*. It's an important discussion to be had here as to that theory of obviousness.

Before we get, you know, to those cases in that aspect, it is worth pointing out that what is missing from the petition materials, and we've addressed this throughout our briefing, what's missing are these critical aspects of an obviousness inquiry, like analysis as to the subject matter as a whole. There's no analysis as to the individual lipid components, and how those components interact, or how ratios might affect the properties of the particle both physical and functional, and what negative impacts changing aspects of particles might bring about. There's no discussion of any of that, and there is absolutely no discussion as to motivation to combine or reasonable expectation of success.

And this is important, of course, because every obviousness case requires a motivation to combine and every obviousness case requires reasonable expectation of success. And this is stated and supported throughout the case law. We point to the case of *In re Stepan* from the Federal Circuit in our briefing. There are many others, but in *In re Stepan*, they're specifically dealing with the issue of obviousness in view of overlapping ranges and stated expressly that there are no exceptions to the rule; every obviousness case requires motivation, every obviousness case requires

reasonable expectation of success.

And the cases I've read -- overlapping range cases like *Peterson* and *DuPont* are no exception to that. None of those cases obviate the need for a motivation to combine. And instead, as we point out in our briefing, it's not that they obviate a need for motivation. It's that those cases are grounded in a specific motivation or specific rationale, and that is one of routine optimization.

The very important point in this case because in this case routine optimization, it simply doesn't apply.

This is not a case of routine optimization. The evidence is unambiguous and unanimous on this point, and there's no dispute on this. In fact, Petitioner has not even made at any point here, the assertion that formulating lipid particles that these claims would have been a matter of routine optimization. They actually argue just the opposite. What you see throughout their petition materials and the testimony of their expert, as well as the citation to literature that they provide, is the story that the technology is incredibly complex, it's highly unpredictable, and you don't know what's going to happen. And we even heard some of that today when we're talking about the unexpected results.

So there's no dispute that this is not an instance of routine optimization. They agree with that.

Now, that doesn't mean they don't misapply that analysis; I think they do. They misapply that analysis only

to the -- sort of what we refer to as back end of the analysis when they're talking about unexpected results. But when we're talking about, Why are we even getting to unexpected result to begin with? There is no discussion of routine optimization and no assertion, not even the assertion of routine optimization in any of their materials.

And if we look at the evidence, we can understand why. There's simply no evidence to support the notion, that developing the claim subject matter would have been a matter of routine optimization. What we see is description in the evidence that these are multi-component systems. The interactions are unpredictable. They were poorly understood at the time, and there's an expressed recognition in the field that the industry struggled for decades trying to figure out how to provide viable delivery solutions for the -- in this technology.

Again, none of this is in dispute, and that's a very important point to emphasize because, for obvious reasons, but certainly, for the reason that one cannot reach a finding of obviousness under a theory of routine optimization when routine optimization is simply not a viable strategy. And that is precisely this scenario here, and it should be case-dispositive.

I do want to briefly walk through some of this evidence. And I'll turn to Slide 9. Again, as mentioned, this is an area were experts from both sides are in agreement,

that this was not a simple matter of routine optimization. Dr. Thompson was asked this question directly, addressed at both cross-examination and throughout his deposition, but he had stated directly and unequivocally that during the 2008 timeframe, developing nucleic acid lipid particles would not be considered a routine matter of optimizing variables.

Dr. Janoff agreed with this. Again, as I mentioned, he's routinely emphasizing the complexity, unpredictability, and the difficulty in this area. That is not a picture of routine optimization, and this position is echoed throughout the petition materials.

Let's turn briefly to Slide 10. This is addressed in the briefing again. I would direct your attention to the sur-reply, Pages 14 through 17. But the Petitioner is very clearly embracing this notion of complexity and unpredictability. It describes, for example, starting at Page 8 of their petition, the right -- they're pointing to references like the Gao reference and Ahmad reference in describing the field as -- and the subject matter as being influenced by a whole host of different parameters and a whole host of different parameters whose interactions were poorly understood at the time, with a limited guidance in the art.

That is not a picture of routine optimization. And it's -- and this is further supported by various -- throughout the literature and various pieces of evidence that are submitted and discussed in the briefing. But there is

widespread industry recognition and express discussion that this was precisely the opposite of the situation of routine optimization. The industry in the field struggled for decades to try to figure out solutions to this. The technology and the solutions were described as troubling, difficult barriers, highly complex, barriers to the field. When solutions were finally provided like in the nature article, Exhibit 2023 describing the Patisiran product and the development approval, there are multiple points of discussion. Again, this is a nature peer -- one of the most respected peer reviewed articles -- sorry -- journals, but specifically crediting delivery as the key to success of this significant breakthrough.

So as far as obviousness is concerned, again if we're looking in overlapping ranges, if we're looking at an obviousness case based on the theory of routine optimization, that obviousness theory fails because this is simply not a matter of routine optimization, and there's no dispute that it is.

So I want to turn to the unexpected results, so turn to Slide 11. So is -- again, a little surprised by one of the representations of the experimental data. There was a comment that there were only three data points provided. That's not true. We can talk about this in more detail, but most -- this is most readily apparent from Exhibit 2046, which provides a listing of all the various different formulations that were

tested. There are dozens upon dozens of formulations that were tested involved in the scope of the claim.

And they come from two sources: one is the testing that's reported in the '435 Patent itself, the other source is there are various post-filing date publications that have tested formulations within the scope of the claim and showed them to be highly efficacious and have low toxicity, and we'll go through those as well. Both sources as -- obviously as a matter of law are available to support a case of unexpected results and both were presented by Patent Owner and do support that outcome.

So, now, do we need to get here? Well, that's a good question. So to the extent there is ever any sort of presumption of obviousness as was argued in the petition materials, as we already discussed, that presumption would be overcome by answering the question directly as to whether this is a matter of routine optimization to begin with, and the answer is no. That any remaining or any obviousness case -- or any obviousness case that remains would be further overcome by this showing of unexpected results throughout the briefing. And the general reference to the briefing, if it helps, is the Patent Owner response Pages 22 to 27 and 59 to 61 and also the sur-reply Pages 18 and 27.

But let's be clear on what the -- we were talking about unexpected results. We need to understand what the expectations were at the time. And the expectation at the

time was that increasing cationic lipid in a formulation would be expected to decrease the in vivo efficacy and increase the toxicity to the subject. There are a number of reasons for that. Those were discussed throughout the literature and those that -- I have not seen or heard any meaningful rebuttal to any of that. So the expectation is that it's -- again, as you raise the cationic lipid, you expect in vivo efficacy or efficiency to decrease and toxicity to increase. These were recognized as toxic components that caused problems and there some reasons why some had to be included, but there were great downsides that went with that, and those downsides would be expected to manifest as you increase the level of this component.

JUDGE MITCHELL: Will these downsides be considered to increase when you're talking about the particle itself, where you're adding a non-cationic lipid, conjugated lipid? I mean, don't you have to consider the full formulation to really say, Hey, if I increase the cationic lipid, I'm going to have a problem.

MR. ROSATO: That --

JUDGE MITCHELL: I mean, there's an overall charge that you really have to look at in the particle to really see if there's a toxic effect.

MR. ROSATO: Well, let's talk about the charge thing in a moment as that is an important issue.

Let's talk about the threshold question you raised

there, which is, Don't you have to look at the interaction of components? I would say, Yes, you certainly do. Now, where did the petition materials look at the interaction of individual components? The answer is they don't. There's that -- this -- again, because this goes to my earlier comments that the entire case is essentially an identification of ranges and then the end to the inquiry.

That's not sufficient to establish obviousness, and that's one of -- and that's a point that we argue is, you know, we should -- you know, the inquiry, as far as we're concerned, the obviousness inquiry should essentially stop there when we're asking if they met their burden of proof, but, yes, of course, the different components interact, and at the time, that was very poorly understood, and complicated, and unpredictable.

So, yes, they do. Now, how does that -- does that defeat an obviousness assertion? I would say that it does. In terms of looking at the toxicity, at the time, it wasn't really understood. But what was known, and what was unexpected, and what's unchallenged here is that the conventional thinking was you wanted to minimize the component of that ingredient.

There were other components, and we talked about this in the briefing, that could help mask some aspects of that, like charge differences. I think you're referring to the conjugated lipid. So we -- you know, that is an argument

we point out too which is, well, if you are hypothetically going to increase the cationic lipid component, would it logically make sense to decrease the content of this masking or this other component that has some benefit masking that? But that also factors into the inquiry too because what we're looking at are particles that have very high cationic lipid component, very low conjugated lipid component.

We've asked that question, Why would one be motivated to increase the cationic lipid component, yet have a very low conjugated lipid? And that's a question we don't have an answer to. I don't think it does make sense. Dr. Thompson testified that it wouldn't make sense, as to why that's -- you know, how we get to a rationale, we don't have any answer that because there is none.

JUDGE SNEDDEN: Maybe I need to backup a little bit.

So what is your position in terms of -- explain to me the differences between the prior art and Claim 1, and the elements of Claim 1? Are we talking about simply overlapping ranges or are there other differences?

MR. ROSATO: Yes. Before I get to that, can I finish answering --

JUDGE SNEDDEN: Sure.

MR. ROSATO: -- a question, just so I don't lose it.

I want to be clear too. There isn't a -- you know -- that you raised a question about charge, right? Just to be clear, charge on a particle is not the end-all-be-all, the

sole inquiry when it comes to toxicity. The cationic lipids themselves are toxic molecules, and they're toxic for a number of reasons. Both -- some things have to do with charge indirectly. That matters more for aggregation of particles as their -- and a reason why -- one of the reasons why there's difficulty in systemic administration as the charged particles tend to get cleared out before they reach their target site. But as far as toxicity is concerned, that is not dependent solely on charge or really even on charge. The cationic lipid molecules themselves are toxic molecules, as they're immunogenic, they're cytotoxic, they have bioaccumulation problems. The Ahmad and Lin references actually talk about metabolic burden and as the main concerns with toxicity of those molecules.

But just be very clear, you'll see some interchange of toxicity in charge in Petitioner's briefing, and I think they tried to maybe leverage off some languages in the institution decision, but charge is not the issue. There -- it's not interchangeable toxicity. It -- don't fall for that that being switched.

I'm sorry, Your Honor, your question?

JUDGE SNEDDEN: Just look for -- just a highlight of the differences -- what you're describing as a difference between the prior art and Claim 1. And I thought it was just a matter of just overlapping ranges, which means now, we have to establish a criticality within the range, and, therefore,

we moved on expected results. I mean, is that how I understand?

MR. ROSATO: Well, I mean, I don't think so, and that's why I talk about the issue of routine optimization. Right? I mean, there's a tendency to look -- I mean, if you look at the overlapping range, case law -- and this is the point I want to make sure is made because I think it's very important. When we're talking of this overlapping range paradigm, we tend to think of it as, you know, these enumerated or typical options for overcoming that case, and those do include things like establishing criticality by unexpected results, which is what -- why we're talking about expected results here.

But my point in routine optimization is, that's not the only way you overcome an obviousness case in overlapping ranges. Why is that the case? Because every obviousness case requires a motivation for doing something, a rationale, a reasonable expectation of success. The overlapping range cases, if you go through and read the -- I'm sure you do, I'm just saying this figuratively. When you go through and read those cases, you find the explanation of this whole theory, the whole basis of this case law is grounded in the theory of routine optimization. Right? Ranges that are not especially broad invite routine optimization as is the typical mantra, and those cases also go back to the *KSR* case to ground the routine optimization rational back to this sort of inquiry.

So if the fundamental basis for obviousness in an overlapping range case is routine optimization, you cannot reach obviousness on that theory, that theory being routine optimization, if it simply doesn't apply in a given context.

Now, there are various tools for indirectly, as well directly getting to that issue, like unpredictability and so forth, but there are also indirect ways of conducting that inquiry.

Here, we have somewhat of the luxury of going right to the heart of the question and asking whether this is a matter of routine optimization. It's simply not. And there's never been an assertion that it is. Right? That's why I make that point.

So in terms of the differences, well, as you see, what we see in the claim mapping in the petition is really just in pointing to different disclosure where there are general paragraphs or discussions about things that one component at a time, and the art gives some broad ranges, thus, it's talking about the entire universe of various different things.

So the obviousness cases, as I understand it, is that if you go through on an individual ingredient-by-ingredient basis, you see some limited overlap in what's disclosed versus what's claimed. I would say the differences are in part going to Judge Mitchell's question which is, Don't these different components interact in certain ways and don't

some compensate for others, or there are reasons for doing this? The answer is, yes. So, why, you know this gets the ratio issue.

JUDGE SNEDDEN: There's the combination of these ranges that lead to the unexpected results, but there is -- like some criticality in the ranges.

MR. ROSATO: There's criticality in the sense that it's not routine optimization. Yes, I would agree with that.

JUDGE SNEDDEN: Right.

MR. ROSATO: I always found that criticality question -- or description -- anyway, yes, I would say it's supportive. And you see that concept in various aspects of the overlapping range cases as well.

I mean, if you go back to the result effective variable case, the Antoinette (ph) or *Antonie*, that's probably one of the key areas where result effective variable differentiation, you know, still very viable when you're talking about ratios of different components and how those interact and whether there was a recognition in the art of, you know, some predictable outcome from different ratios.

That's an issue here too. But this go -- there are many issues here. This is why, you know, I want to make sure I point out, you know, I'm sure that this is part of a Patent Owner's job as well, but part of the burden.

But part of the job is to point out the deficiencies in the state of the case or respond to what is stated. But

it's one of the challenges here as non-moving party, looking at a petition where there is no explanation as to why this is all being advanced.

I don't know the theory. I've seen case law citations to overlapping range cases, but I've never heard an assertion that this is a matter of routine optimization. I don't know if that's their theory, and I would encourage posing that question to them. I'd love to hear it.

JUDGE MITCHELL: So let me ask you. So how do you respond to -- in the 554 Publication, the L054 formulation, that does show everything, as I understand it or within the ranges, it has everything in the claim within the ranges; is that correct?

MR. ROSATO: It did -- it's not correct.

JUDGE MITCHELL: Okay.

MR. ROSATO: It doesn't. So I think you're referring to the table, Table 4. So, again, those are starting ingredients. We're claiming particles here. Most of those -- actually, I think virtually all, except maybe the one they pointed to, if we're just looking at the numbers for starting ingredients, they point to one that seems to barely touch with the claimed ranges. And that's the one that they're refer -- reciting -- sorry, relying on for the anticipation case.

And for that anticipation case, you know, their argument is you're pointing to a starting mixture, it's barely

touching on the range, and if in the context of this particular application you're expecting various different efficiencies of incorporation into the particle, then this is essentially an unsubstantiated inherency case with the anticipation charge. Right? Making assumptions about what -- there's no disclosure what the particle composition looks like.

So if we're assuming that it meets the claims, that is -- that's why I described it as an unsubstantiated and failed inherency case. There's no -- the probabilities and possibilities tests is not met there. It's pure speculation.

JUDGE MITCHELL: But doesn't that get them closer on obviousness case? That here, there's -- in the art, at least with the starting formulation, they're within the ranges.

MR. ROSATO: I mean, closer than what?

JUDGE MITCHELL: In terms of the rationale to combine. It's already done. Somebody's done it.

MR. ROSATO: Somebody has not done it. There's not a single embodiment that falls within the scope of the claim. So --

JUDGE MITCHEL: Because it's starting? That's your argument? Because it's the starting formulation and not a particle?

MR. ROSATO: They are absolutely not particles.

JUDGE MITCHEL: Okay.

MR. ROSATO: Yes. They are absolutely not

particles, and there's no dispute on that, other than what we've heard here today, which is the first time that we heard that.

So those are absolutely not particles. There is no particle that meets -- that falls within the scope of the claim. All of them are outside.

Now, if we're looking at the numbers in the table, I think you asked, Are they closer? I don't know. I mean, I don't know how to answer that, and they're the closest thing they've pointed to. I guess this is my answer to that.

So I see I'm down to five -- about six-and-a-half minutes. I do want to get through a couple other points. I want to, obviously, that whatever's most important to the Panel is what I'd like to address, but I had a couple other things that I wanted to go through, if I may.

JUDGE MITCHELL: Sure.

MR. ROSATO: Okay. In terms of the -- I'll just say a couple things on the -- couple things further on the unexpected results.

Again, I pointed to the exhibit and then some other briefing material at Exhibit 2046 and the briefing material. But there are dozens and dozens and dozens of formulations that are falling within the scope of the claim. There's no dispute that any of those formulations fall within the scope of the claim. There's no dispute that those formulations are showing potent silencing or potent activity in vivo and low

toxicity. None of that is disputed. And there are, again, dozens and dozens of formulations spanning their range. Even -- what slide is that even? I think it was mentioned here today, but one of Petitioner's demonstratives show the range spanning, I think counsel mentioned, Yeah, but that only -- you know, the coverage only goes up to 70 percent.

So there's that tail end of the range that there's -- where there's not -- we don't have data points. Otherwise, it's spanning the entire range, many different formulations, many different combinations of lipids, different lipid constituents, many different cationic lipids, many different conjugated lipids, many different non-cationic lipids, many different gene targets. Not only siRNA targets, but mRNA targets. And one of those is illustrated on Slide 14.

But again, I mean, if we go through the various pieces of literature, again, there are multiple gene targets, many different gene targets targeted. But one of the arguments that was advanced by the Petitioner was to criticize or question whether these would work for mRNA, which it was a surprising argument, considering that they've published extensively that these formulations work fabulously on mRNA, including the acetic reference shown here on Slide 14. And I think this is Exhibit 2048, if I'm getting that correct.

But here, again, this is Petitioner's own publication but what they did is in trying to deliver mRNA, they literally took the Patisiran formulation off the shelf

and replaced the siRNA with mRNA payloads and then recorded how well it worked, and it does work well.

They've asked our experts about -- so excuse me. They asked Dr. Heyes, Is it completely irrelevant. I don't know why they were asking him this, but they did ask him if Patent Owner had been using their formulations in mRNA. And Dr. Heyes, who works for Arbutus, which is Aldoner Protiva (ph). But Dr. Heyes explained that, Yeah, of course we've been using these for years. So it was surprising to see some of this argument.

As far as unexpected results, there are various -- various embodiments covered far more. If we're talking about relevant case law, this is actually a good point of comparison, maybe answers your question, Your Honor, about how many points -- how many data points are needed. And what we know, or what we can look at as a basis of comparison are the cases where the Federal Circuit has rejected unexpected results or experimental data for not being in commensurate in the scope of the claims. And in each of those instances, like the *Peterson* case, like the *DuPont* case, what we're look at is, literally, like, one or two data points, and that's clearly not the case here. The unexpected results look absolutely nothing like any of those cases where data was -- experiment results were rejected as not being commensurate in scope.

I do want to talk about this toxicity issue as well,

so let's turn to Slide 15. So, again, what has been pointed out in the briefing and supported with evidence is the fact that cationic lipids were known to be toxic and that the conventional thinking at the time was that their content in lipid particle formulations should be minimized. There are various pieces of evidence. And there's actually not a dispute on that point. The response that Petitioner has advanced is something different.

Let's turn to Slide 16. What they've argued is, Well, that might all be true, but there's an exception to that rule. And that exception is this very convenient, but unfortunately, false, narrative that certain types of cationic lipid weren't toxic and that was well known. They argue that ionized cationic lipids, such as DLinDMA, specifically, which they identify as their argument goes, were well-known at the time to be non-toxic.

As far as the evidence is concerned, there is not a shred of evidence to support this argument. In fact, as we point out in our sur-reply briefing, Petitioner has multiple publications that, you know, are within the last couple years, far pre-dating -- sorry, post-dating the '435 Patent, where they're still specifically identifying toxicity concerns with ionizable cationic lipids and specifically identifying DLinDMA, the one specific example that Petitioner has identified. And that can be seen in Exhibit 2051. The quote provided here on Slide 16, as well as 2052, and as -- and

quite frankly, numerous other publications that Petitioner has put out.

So this is simply not a credible argument as far as the toxicity concern and notion that the general thinking at the time was to reduce the content of this component. The conventional thinking was that -- sorry, the decision of Petitioner, I have not heard any opposition to that.

If I can -- if I may, Your Honor, I want to make a few quick points on Ground 2, and then finally, on the encapsulation issue. I didn't mention it, but I think it's apparent that it's an additional basis as to why Ground 3, the anticipation challenge fails. And I would direct -- this is addressed on Slide 22, but also in our sur-reply briefing.

Dr. Janoff was very adamant in his position that encapsulation was a misused term or improperly used in the art at the time. He thinks it means it could be very different things, and he's even published on the topic, criticizing people for using the term encapsulation when they haven't tested for nuclease degradation and criticizing that it is not real encapsulation. That's addressed in our briefing and provided here on the slide. But that's pertinent for the '554 Publication because there is no nuclease degradation test performed in '554 and not even a claim that LO54 encapsulates.

In terms of Ground 2. And I really appreciate the extra time, let's turn to Slide 18. There are a couple of points, and the fundamental distinction here is Lin and Ahmad

are directed to these different types of particles that are referred to and which they call knowing the artist, lipoplexes. Lipoplexes are a fundament different type of particle. They're essentially lipid aggregates that have nucleic acid adherers stuck to them. And they differentiate, obviously, from the type of particles that we are talking about that are encapsulated nucleic acids within the particle.

And Dr. Janoff's publication says, as well as testimony during cross examination, identified those differences and agreed with them. He also testified that -- and this is another reason why his claim construction is pertinent, we asked him if he thought lipoplexes would be within the scope of the invention, the '435, and he indicated that he didn't think it would. So it begs the question, why are you even looking at these references to begin with? And that is not something that's addressed.

Which brings me to Slide 19. Obviously, the Panel's going to be very familiar with case law, whether assertions and speculation about whether somebody could or may have an impact as a basis for obviousness assertion. We know as a matter of law that those types of assertions are insufficient. They've never been sufficient to establish motivation and that's well supported in the case law.

And then, finally, this really will be my final comment, is on Slide 20. We can't discount the fact if we're still considering Lin and Ahmad, we can't discount the fact

that the whole point of those references is how to decrease cationic lipid. It's a point that seems to get lost in some of the Petitioner's argument. This is explained by Dr. Thompson. That's the whole point of those references. This is actually explained by Dr. Janoff in his reply declaration and confirmed in cross-examination. He explained what those references are doing is you're using multivalent cationic lipids in order to have multiple charges on one molecule for the benefit of reducing the amount of the cationic lipid.

Why are they doing that? Well, they tell us exactly why they're doing it. There are multiple benefits, including reducing cost and toxicity concerns. So they're pointing to references that are fundamentally directed to the concept of reducing cationic lipid and pointing to those references for the notion that you demotivated or that you could increase the cationic lipid, and that doesn't make sense.

Thank you.

JUDGE MITCHELL: Thank you. And I'll just add time to Petitioner's time and give you your rebuttal time.

Whenever you're ready.

MR. FLEMING: I'm ready, Your Honor.

JUDGE MITCHELL: Okay.

MR. FLEMING: Your Honor, I would like to address your question about whether or not LO54 is a particle.

First off all, the Patent Owner, as counsel has represented, that there was numerous times that we haven't --

that there's not a dispute. We would like to categorize what he said. Those things are just not true.

As far as the particle, if you look to the reply on Pages 13, we clearly dispute that issue that they raised that it's not a particle.

One very important thing to point out is the '435 Patent. That's how they tell you whether it's a particle is by telling you what is the formulation of the composite. All we're talking about is a composite. We're not talking about a chemical compound. It is a composite. So what -- how do you describe a composite? With the components that make up the composite.

The other important claim is if what he -- the Patent Owner's counsel is arguing is true, then the '435 Patent is not reduced to practice because there's not one aspect of that patent that actually provides you somehow the structure of what the particle looks like. In fact, that's not the way the industry works. Instead, it refers to the components that make up the particle.

The other point I would like to address is the claim construction. And Judge Smith, I want to address your question about whether the intrinsic record is what you should go to first. That is clear case law that the Federal Circuit has instructed the Board that entrance of cations is the first item that you looked through, and if there is and only do you look to the extrinsic evidence, if there's nothing necessary.

Now, I also want to point out that the Patent Owner's counsel is misleading you on what he was saying is the definition of nucleic acid. These terms are defined in the '535 (sic) Patent and nucleic acid -- '435, sorry -- '435 Patent on Column 10, starting on Line 26, defines the terms nucleic acid.

Going over to Column 11. Starting at Line 14, you have a definition of lipid particles. And if you go down to Line 23 of Column 11, you have a definition, a SNALP. What they pointed to for the definition of nucleic acid is part of the definition of the SNALP because the definition goes all the way down to, it looks like, Line 58. And where he was pulling that definition out was simply talking about what the definition of a SNALP is as far as how it is encapsulated to prevent degradation.

JUDGE SNEDDEN: So I take it that your position is that the Claim 1 is not covering a SNALP; it's something different?

MR. FLEMING: That's right, Your Honor, it does not require encapsulation for the definition of nucleic acid lipid particle. And that is clear from the specification of the '435 Patent.

I'd also like to point out in the claim construction, which is really a minor point, and you don't really need to get to it, but they point to Dr. Janoff's cross-examination testimony. And I want to point out that

that's really all taken out of context on what happened there.

The -- Dr. Janoff is answering the question regarding the level of skill of the person of ordinary skill in the art. And the questions aren't in regard to Paragraph 32 of his '127 Patent declaration, and there he is saying that a person of ordinary skill in the art for the field of the '127 Patent but has specific experience with lipid particles.

During that same deposition, when asked what it -- you rely on -- and may I have Slide 17, please? What did you rely on in formulating your definition for nucleic acid lipid particles? Dr. Janoff answered by pointing to the same definition found in '425.

Also, in Dr. Janoff's reply declaration, if you look at Paragraph 13, he agrees with the board's construction of nucleic acid lipid particles. And Patent Owner's counsel chose not to depose Dr. Janoff in questioning on that answer. That testimony in Paragraph 18 in the second deposition, which is -- they could have challenged him then, and they chose not to.

So I'd like to go to routine optimization, if I can. In regard to Patent Owner's Slides 8 through 10, they're arguing in routine opposition is not applicable. I think we need to look to the scope of the claim. And it only, again, requires a composite of nucleic acid and the cationic, non-cationic, and conjugate lipids.

So the question is, when you look to the publication

of the '544 -- maybe we could pull up Slide 33 or did I lose my slides? The '554 teaches that all this is in routine optimization. They specifically point out that all the things that they've set forth in all these ranges could be modified and optimized. And it's all within the skill of the art. And I think that when you --

JUDGE SNEDDEN: I have a question here. I just want to clarify one thing. Are you arguing routine optimization in your petition, and, if so, what variable are we optimizing?

MR. FLEMING: We are -- yes, we did argue routine optimization. You know, what we're talking about is, would you be able to optimize for the overlapping ranges to obtain the range that's being claimed? And, again, all we're talking about is a particle that is a composite. And if we look to Table 4 of the '554 Patent, you can see how they did go about the very thing that they're referring to about, Well, can it easily be able to put -- adjust the cationic lipid?

If you raise the cationic lipid, then you're going to have to lower the other components, and that's exactly what Table 4 does, methodically. So that's well within the skill of the art to create these particles to obtain --

JUDGE SNEDDEN: Where does the art disclose doing that?

MR. FLEMING: What's that?

JUDGE SNEDDEN: Where does the art disclose doing that?

MR. FLEMING: In the '554 Patent. It is --

JUDGE SNEDDEN: Oh, right, okay.

MR. FLEMING: It is talking about that very thing.

JUDGE SNEDDEN: Got it, okay.

MR. FLEMING: And what I was trying to explain to you is that if you look to the specification in Table 4, as well some of the other tables, that's exactly what they did, is it all has to add up to 100 percent mole. So you're going to be able to adjust this to obtain the particle.

JUDGE SNEDDEN: Okay.

MR. FLEMING: I also want to point out, their routine optimization is assuming that it has to be in vivo, and the claim does not require in vivo. We're just talking about a particle of a certain composition. This claim is extremely broad. They wanted to limit the claim to in vivo or -- in that sense, they could have. But all we're talking about is being able to create a composite where you can have the nucleic acid be part of that particle. It doesn't even require it to be inside the particle. It could be attached to the outside of the particle. That's clear from the definition of reciting the specification.

I'd like to also address the unexpected results. And, Your Honors, it's well-settled case law, and I'm sure you're very well aware of it, that the Federal Circuit looks to unexpected results to determine whether or not what we're talking about is a degree of a known property or whether it's

a known property. And where it's a degree of a known property, then they're expecting a much higher surprising result.

If I could point you to the case law, Bristol-Myers Squibb versus Teva Pharmaceuticals, if you look at that set, 752 F.3D 967, it's 2014, and you look at Page 977, again, that's a well-settled case law. And there's nothing here about -- they did not discover a new property. All they're discovering is that -- their alleged discovery is a matter of degree as far as whether it's better than the prior art.

So let's look at the other figure that they've put up and that was on Patent Owner's Slide 11. And the Patent Owner has -- their Figure 3 is an illustration -- and I don't think we'll be able to pull it up. You can't pull yours up? Yeah, Slide 11. While he's pulling it up, Figure 3 is illustrating that they had a demonstrating activity of the 1:57 SNALP, and that's Example 4 and the compared to the data demonstrating the activity of the 2:30 SNALP.

So first problem, 2:30 is not the closest prior art. The closest prior art is 2:40. So we're comparing to oranges here.

The other aspect is that 2:30 is non-cationic lipid is DSPC, and the 1:57 non-cationic lipid is DPPC. So, again, you're not really comparing apples and oranges with that either because you have different composite.

And the other point is this is just one more data

point, but at best, it's one data point.

And then if I could talk about the post-filing data, that's in Exhibits 2017 through 2019, 2021, and then 2047 through 2050. And the problem here is this is -- these are showing -- that's to see how effective the drug is, you know, for the claim formulation, but it's not a comparison to the prior art.

And, again, I don't know if you can pull up Exhibit 2046? This Exhibit 2046 is a summary of all the post-filing data. And, Your Honors, when you look through that, most of the data involves the formulation of 50 mole percent for cationic lipid. There's no test data for the cationic lipids in the higher range, which is problematic because that's what their alleged invention; is the higher the cationic lipids, the better. So we would expect them to be able to show unexpected results in the higher ranges.

Again, I just want to conclude with this, is that if I could have Slide 67 again? Maybe not.

The claim scope is quite broad. And, again, even if they had showing of unexpected results, which I don't believe they do, and, certainly, it's not surprising at the higher level that the Federal Circuit is requiring, but even if you didn't look to that, what's the answer for why they don't have unexpected results for the entire scope of the claim for being able to carry out for all the nucleic acid lipids?

And if you look to Column 10, Lines 26 onward,

there's a huge list of what they define as nucleic acid lipids -- I mean, sorry, nucleic acids. And so that's the payload. So they haven't shown for that type of scope. So they might have a point, maybe if they had limited the claims to siRNA, but they did not. They chose to be very broad.

And, again, so their unexpected result arguments all failed simply because they're covering -- it's not commensurate in scope with all the payloads that they're talking about.

Okay. I want to talk a little bit about toxicity. And just for a minute, I want to point out that the question is, What is the scope of the claim? The scope of the claim does not require an in vivo. The scope of the claim is broader than that. So when you're talking about toxicity, all their arguments have to go for in vivo. So the question is, would this be so toxic that you wouldn't be able to put it in a Petri dish to see if it could deliver it to a cell? That's not -- they have no showing of that as unexpected. In fact, their own -- again, the '554, the LO54, again, is being used and created.

Now, I'm not arguing it's for in vivo, but it's solely good enough to be able to be put into a Petri dish.

So toxicity is kind of a tough term. What -- sure, all of these things have certain amount of toxicity. The real question is, is whether or not it is tolerable for the intended use. And, clearly, for a Petri dish, is certainly

tolerable for its intended use.

They touched briefly on other secondary considerations, kind of trying to bring it into unexpected results, but I want to point out that they were talking about particular drugs that are on the market.

I want to point out though that the Patent Owner has failed to show a nexus to the scope of the claim. And what's interesting about what their information is about is all of that is directed to a particular payload and how effective it is. And there's not anything that shows in the data that those lipid particles is the cat's meow. You know, and certainly, there's not a nexus to this entire scope of the claim.

So if there's not any -- is there a question?

If there's not any other questions, I'd like to turn it over to my colleague, Morgan Chu.

MR. CHU: Let me start first with an answer to Judge Snedden's question.

If you go to the '435 Patent, Column 12, beginning at Line 65, it reads, quote, A number of cationic lipids and related analogs which are also useful in the present invention have been described in, and then there a number of references, including the '554 Patent, continuing with, quote, The disclosures of which are hearing incorporated by reference in their entirety for all purposes.

So, now, let's go to the '554 Patent. And the '554

Patent at Paragraph 0268 goes on with quite some detail, technical detail, for about a column, but I'll just read the last sentence of that paragraph. Quote, As such, chemically modified nucleotides present in the single stranded siRNA molecules of the invention are preferably resistant to nuclease degradation, while at the same time maintaining the capacity to mediate RNAi.

Going to some other issues that were raised, one by opposing counsel. I think it was their Slide 11. And he said, Well, there were a lot of other experiments. And he was making that argument to try and argue unexpected results. But the law is quite clear according to the Federal Circuit *In re Baxter-Travenol Laboratories*, that, quote, Results must be shown to be unexpected compared with the closest prior art. The full citation of the *Baxter-Travenol* case is on Page 9 of the Petitioner's sur-reply to the motion to amend. And it goes on to describe where some other formulations that the Patent Owner wants to hold onto are not being compared to the closest prior art.

There was another question raised by Your Honors, actually, I think it was Judge Snedden again, in reference to criticality. And I think one of the leading cases on that is the Federal Circuit decision in *ClearValue*.

In that case, there was a claimed range. I think it had to do with the amount of alkalinity being 50 parts per million or less, and then there was prior art that overlapped

with that. And the Federal Circuit held that the Patent Owner did not show that there was criticality, and D, there was no allegation of criticality. And that is exactly the situation we have here. No place in the '435 Patent is pointed to by the Patent Owner to show criticality, even with a paid expert, Dr. Thompson. He doesn't say one wit in his declaration or otherwise about criticality.

In terms to the closest prior art, we've already discussed the three data points. And we said, Well, maybe one data point may or may not be slightly better. And I said -- Dr. Jannof said, he thinks it's likely that it's not statistically significant; that one data point cannot be commensurate with the range, the entire range of the narrowed range in Claim 21. And in fact, the other two data points demonstrate that because the other two data points are points that are worse than, or perhaps one of them either worse than or no better than the prior art.

So it cannot be that surprising and unexpected results can be shown or pointed to by the Patent Owner when two of the data points rebut the claim of surprising and unexpected results. And this is the Patent Owner's own data.

Now, I want to go back -- let me start with Slide 98. There was some discussion about various terms. We see it's nucleic acid. It's not one of the other alternative terms. We've already discussed the fact SNALP could have been there. We discussed the fact that the body of the claim could

have said something else. It could have had the word encapsulated.

So let's go to the Section 112 problem that they have, and this depicts in Slide 100. siRNA is 20 to 23 bases. mRNA, there is, in the record, testimony about it being at least several hundred bases, and elsewhere, a thousand or more. Increased size, it's a lot of complexity.

And here's a big picture bases. It's not just a question of size. Let's keep in mind what RNAi interfering or siRNA small interfering RNA is trying to do. It's trying to act like a red light. It's trying to stop or silence gene expression.

What is mRNA trying to do? It's trying to act like a green light. It's trying to enhance gene expression. The functions not only are different, but they're completely opposite. So you've got big differences in complexity by size and otherwise. You've got two completely different functions.

And we see in Slide 104, the payload can impact the performance. Slide 105, that mRNA is typically larger than siRNA and they are expected to affect the physical properties of a particle. Both 104, 105, and now Slide 106, are testimony by the Patent Owner's expert, Dr. Thompson. And 106, he's addressing the question whether one could start with siRNA variables and then use that to optimize for a new mRNA cargo. And he answers by saying, quote, That's speculation. I couldn't -- I can't go there.

So let's go then to enabling. So I think written descriptions requirements are not met, and enablement law on Slide 113 is not just an invitation to go and conduct a bunch of experiments, but Dr. Thompson, again, the Patent Owner's expert in Slide 118, admits that more testing is required.

So too in Slide 119. The Patent Owner's expert is admitting, you don't know what you're going to get inside.

In sum, these items on Slide 120 were the ways in which the Patent Owner tried to argue the validity of the new proposed Claim 21. He pointed to serum-stable as requiring in vivo or systemic use. We've discussed that. It's quite to the contrary. Other definitions could have been used that are in the patent, as well as the words systemic or in vivo, if that's what was intended.

They tried to use the wherein clause and that didn't add anything. It didn't separate it from the prior art. The prior art was showed on an earlier slide in each of the three primary references; discussed nuclease, degradation, resistance.

Then they tried to say, here, we have some different ranges, but the new ranges still overlap with the prior art. There's still anticipation under '554. And if we had to drop in to an obviousness argument with respect to the other references, it's still the case; that the Patent Owner has not shown surprising and unexpected results. If anything, from two out of the three data points, the Patent Owner

demonstrated the exact opposite.

Thank you very much, Your Honors.

MR. ROSATO: We can start while she's taking a minute. And I appreciate the extra time I was allocated. I'll try to not use time, if necessary.

Your Honor, I want to first address this issue of routine optimization again. And the response was that they were arguing or they did argue routine optimization in the petition. I don't see that and I don't think anyone will see that. It's just not there.

There was one comment about optimizing the cationic lipid; not routine optimizing, but a comment about optimizing just the cationic lipid. There's a mention of that in the specification. That's one component. That's not optimizing a formulation. And even with that one component, there's no -- I mean, it's a one-sentence thing. There's no discussions surrounding it, so we don't know whether they believe that is a -- whether optimizing is routine or something else. I have no idea. You won't find the term routine optimization in the petition materials.

And then beyond that, I have to admit, I'm still a bit confused as to the position on this for a number of reasons. Again, we're asking if on the front end of this, if this is -- if the theory is one of routine optimization, we'd like to know that. If the position is that this is also well known as a matter of routine optimization, then I have

difficulty understanding how that's consistent with arguments about undo experimentation that were just discussed when it comes to using other lipid payloads, as well as the arguments as when they get to the experimental results about how unpredictable and difficult it would have been to have any other data points. So, you know, I think they're trying to have it both ways, and it, you know again, you have to start with an identifiable rationale and this emphasizes the importance of that.

Sticking with the rationale theme, I heard some comments about how you can make formulations for use in a Petri dish. Again, this emphasizes the importance of identifying a motivation to combine or a motivation that's underlying this whole theory. If the argument -- and, again, this is a new argument, so it's hard to respond to that, but if the argument that was being advanced in the petition is that a person would be motivated to make these types of formulations solely for the purposes of using it in a Petri dish or in vivo, that just doesn't reflect reality in the art. These are formulations that are made for therapeutic purposes. They are screened in vitro. We would be very happy to have the discussion about whether there'd be motivation to invest in this technology and make developments strictly for the purposes of in vitro Petri dish.

JUDGE SNEDDEN: There's one argument that the Petitioner is advancing, is that your evidence of unexpected

result when compared to a closest prior art is not unexpected. Could you address that?

MR. ROSATO: I do want to address that.

JUDGE SNEDDEN: Okay.

MR. ROSATO: Let's -- and two points on that.

Go to Slide 11, please.

When I first addressed this argument about differences being a matter of degree and not differences in kind, that is not true. And we point out that these are differences in kind, not merely degree, and that's, you know, one of the reasons why we're talking in vivo potency, right? And they were criticized for focusing on vivo, but that is a difference in kind, right, is they surprisingly efficacious result in vivo, combined with low toxicity.

So it's not just one thing, you've got two things that are doing in the complete opposite direction of what would have been expected at the time.

This figure here, which I think is Figure 3, if I'm getting that correctly, from -- not confusing the example versus the figure, but what's shown here and why this is the fairly pertinent, and it goes to a couple points, one of which is this issue, the closest prior art, it's hard to know what that is. I mean, I don't know what they believe to be the closest prior art. They've latched onto this 2:40 formulation as the closest, I guess, for numerical purposes. The comparison was to 2:30 because that was actually one of Patent

Owner's formulations that was believed their -- that was their -- identified as their lead compound.

But the comparison here is quite compelling or the results here is quite compelling because what you see is a -- what's reported as a huge increase in the silencing ability of the -- this is the '157 or the formulation in the scope of the claim. You're seeing a dramatic increase in the potency, and you're seeing that dramatic increase despite a ten-fold lower dose, right?

So it's not just that it was -- you saw difference in degree of in vivo silencing, you saw a huge difference at a ten-fold lower dose, and virtually no toxicity.

So it's the combination of all that. And this is an illustration. The potency and low toxicity is across the entire range of tested formulations. The -- if you're comparing -- if you're looking at toxicity and you're comparing that to 2:30 and seeing much less -- virtually no toxicity compared to lower cationic lipid component when you're expecting higher toxicity, that's a perfectly appropriate comparison.

If their -- with regard to the 2:40, and, again, they're just calling this prior art because they -- you know, it's a convenient argument to be honest, but if there is a comparison of that, it is compared.

They did test 2:40, and this underscores a point where we're talking about unexpected results. And there seems

to be this assumption that you only get -- what they're talking about are superior results, right? The test is unexpected results. Their point of criticism is, Well, it wasn't superior, therefore, it wasn't expected. But we have to ask what was expected and this is why I raised this point earlier. You have to understand what was expected at the time, and the expectation is you're going to see a decrease in potency and an increase in toxicity, and the opposite was observed. Those are unexpected. And they're differences in kind, not degree for the various reasons we talked about.

I want to point briefly, if I can, to Slide 13. This reference was submitted -- sorry, in -- partially in response to this criticism of the closest, all right? So this is Figure 2, I believe, from the Akinc reference, that's Exhibit 2047.

But if we want close comparison, you can't get any closer than this -- the comparison that was recorded here. A whole panel of formulations were tested. Only three of those formulations tested were within the scope of the claim, and the rest -- those three are shown in the red box. The rest not in the red box are outside the scope, but they're only outside the scope of the claim by virtue of the conjugated lipid component. It's only barely outside the scope of the claim.

So here's a whole bunch of formulations outside the scope that are extremely close to those end, and the three

formulations within the scope were superior to what was -- the other formulations tested.

So there are all types of different formulations tested. They're all types of different comparisons that were done. This is one we saw one in the '435 Patent against the 2:30 formulation, which was, again, the lead product at the time. If for performances were drastically better, and then the results of testing of the 240 reported, and the expectation is -- and, again, we're asking what's expected, not what's superior -- or what was unexpected, not what was superior. So there's a difference there. I want to make sure we observed.

And that I'll just --

JUDGE MITCHELL: Yeah, if you could wrap it up.

MR. ROSATO: Yeah, let me just -- final point, which is this nexus issue.

Really, I mean, at times, I feel like we're talking over each other, but I would turn to Slide 27, please, quickly. Again, there is this argument that the drug is -- the success of the drug is due all to the nucleic acid. And I would just point to the nature article on the next slide. That specifically -- this is again, the nature article that goes on and on about the delivery solving the problem and allowing the success of this very commercial product. So it's hard to see how this is singing the praises of the drug rather than the delivery.

Thank you.

JUDGE MITCHELL: Thank you both.

So the case IPR2018-00739 is submitted, and we'll take a ten-minute break, and then reconvene here for the next case, about -- at 25 til if we could reconvene for the second case. Thank you.

(Break was taken.)

JUDGE MITCHELL: You may be seated. So now we are going to have argument in IPR2018-00680.

And, Petitioner, would you like to reserve any time?

MR. WELLS: Yes, Your Honor. I'd like to reserve half of my time, please.

JUDGE MITCHELL: Okay.

MR. WELLS: If we could go to Slide 121, please?

So now I'm going to talk about the '127 Patent. And a lot of the terms and a lot of the substance of what we're going to discuss is going to overlap with what we've already heard regarding the '435 Patent, but it's important to realize that the '127 Patent is a separate patent family from the '435 Patent family. And so the '069 Patent, which is referenced in the briefing, what we're going to talk about here today, is in the same family as the parent of the '435 Patent. It's unrelated to the '127 Patent and this prior art.

JUDGE MITCHELL: Sorry, let me interrupt you --

MR. WELLS: Yes.

JUDGE MITCHELL: To make sure Judge Smith is on.

I'm sorry. I just don't see him on, and I'm wondering --

JUDGE SMITH: Yes, I'm on.

JUDGE MITCHELL: Okay, sorry.

JUDGE SMITH: I'm here.

JUDGE MITCHELL: Thank you. Go ahead. Sorry to interrupt.

MR. WELLS: Okay.

If we can go to Slide 122. So, here, we have the '127 Patent. Again, Protiva and Arbutus are the owners, but again, unrelated.

If you go to Slide 123, please. And this is the independent claim to the '127 Patent, and it's directed to a particle population, and -- but we have the same basic components that we've been discussing with regard to the '435. We have nucleic acid payload, we have the three lipid components throughout the outline that's any cationic lipid in any percentage, any non-cationic lipid in any percentage, and a conjugated lipid in any percentage.

Now, if you go to Slide 124, please. This is the '069 Patent, which is one of the primary references relied upon in the petition for invalidity. It's the parent to the '435 Patent. It has the same substance disclosures regarding -- as the '435 Patent.

Go to the next, Slide 125. And this discloses the same particles. Again, we have a nucleic acid, a cationic lipid, a non-cationic lipid, and a conjugated lipid in certain

percentages in the '069 Patent, but they're the same basic particles.

So go to the next slide. So what did the '127 Patent add? Well, they argued that they added this additional limitation regarding 95 percent of the particles in the given population having a non-lamellar morphology. And so what did they do to get that?

And if we go to the next slide, they looked at the prior art particles that they had previously disclosed in the '069 Patent and in the '435 Patent in that patent family, and they took a picture of them. And then they looked at that picture of the prior TEM image and then said, Okay, well these are dark, and that looks like a dense center, so we're going to associate that with non-lamellar. And then we're going to count them.

And if you can go to the next slide, Slide 128. And so they counted the particles that had this dark center, this non-lamellar morphology, and you can see the particles that were tested were the 2:30 now, the 2:40 now, the 1:57, and the 1:62 now. And you'll recall hearing about those formulations earlier today regarding the '435 Patent.

Now, if you go to Slide 131, this non-lamellar morphology, it's admitted this is a physical characteristic of the particles. That's not in dispute.

And if you can go to the next slide, it's also --

the '127 Patent itself says that by controlling the SNALP formulation and the formation process of the particles, you get this non-lamellar morphology. It's inherent for a given formulation and a given formation process.

If we can go to the next slide, Slide 133. We have their expert. Dr. Thompson admitted that if you have the same formulation and you have the same formation process, you should get the same three-dimensional structure. It's -- you can -- reproducible. It's an inherent property associated with those particles.

If we can go to Slide 134. But the law is clear. Claiming an inherent property of a prior art composition, even if they didn't know it was non-lamellar at the time, it's insufficient as a manner of law to confer patentability.

If we can go to Slide 135. Now, this is their expert, Dr. Thompson, being questioned at deposition about the '435 Patent particles, but you'll recall that's a child of the '069 Patent and has the same specifications. The detail is exactly the same experiments. And he was asked, Would you expect those particles to have this 95 percent non-lamellar structure? And this is their expert saying, Yeah, based upon these experiments, that's their state. That's what I think was happening on the '435 Patent, which, again, is in the same patent family as the '069.

If we can go to Slide 138. So what was tested in the '127 Patent and what formulations? Well, we had certain

lipid components, we had the conjugated lipid, the peg, we have the cationic lipid, DLinDMA or FOSFA (ph) lipid, DSPC and cholesterol; those together make up the non-cationic lipid. And then we have our concentrations and our mole percentages.

If we can go to Slide 139, please. In the '069 Patent, we have the same tested formulations, the same2:30, the same2:40, the1:57, the1:62. This is all laid out in Tables 3 through 6 in the '069 Patent. These were all tested. And the lipid components, exactly the same lipid components. The only variability is that for two of the formulations, the 2:40 and the1:57, DPPC was used instead of DSPC.

But if you can go to the next slide, 140, there, expert admits that that type of small change wouldn't be expected to have any impact on the result in three-dimensional structure.

So we have the same formulations. Now, we have to go to the four formation process and what's disclosed regarding the formation processes.

So if we can go to Slide 141, please. What does the '127 Patent say about the formation processes? Well, it says that you can use any method known in the art to produce these particles and get particles with this non-lamellar morphology. Does that mean that every method known in the art results in these? No. What it means is that a person of skill in the art would know how to use the prior art known methods of

production to achieve this non-lamellar morphology. That's what the '127 Patent says about this. And it goes further. It gives us some examples.

So if we can go to Slide 142, please. It gives two examples. It points to a step-wise dilution method, and it references US Patent publication 2004-0142025, which I believe is Exhibit 1018, and a direct dilution method, and it references there, Patent publication 2007-0042031. And it says -- these are two examples of publications that detail known methods of producing these particles that you can use to get this non-lamellar structure.

If we can go to Slide 143. The '069 Patent references exactly the same publications. Here's two example publications in the '069 Patent that also detail how you can get the particles disclosed in the '069 Patent. And, again, the '025, talking about the step-wise dilution method and the '031 talking about the direct dilution method.

If you go to Slide 144. Now -- actually, go to Slide 145, please. The '127 Patent does discuss formation process parameters, and it provides the formation process parameters used to produce the non-lamellar particles that it says result from the testing in the '127 Patent. And those are produced in Table 1, that's in Column 104, and you can see the DDM there, stands for direct dilution method. And we have six variables, one of them, arguably, the batch size probably has no impact, but several variables.

If you go to Slide 146. But the law is clear. The claims don't have anything about the formation process that has to be used. The claims --

JUDGE SMITH: Counsel, can we go -- just for a second.

MR. WELLS: Yes.

JUDGE SMITH: To your Slide 145, Table 1.

MR. WELLS: Yes.

JUDGE SMITH: Now, under this, the DDM column, is it correct that these were the particular parameters used in the '127 to do some testing or is it your position or to your knowledge -- or your position that to practice the DDM method, you got to use exactly these parameters?

MR. WELLS: Thank you for the question.

So this was -- were the parameters that were used in the testing for the '127 Patent for the direct dilution method. The '127 Patent does not discuss these parameters as having any impact on the non-lamellar morphology, does not state anywhere that these have anything to do with the non-lamellar structure resulting. But Patent Owner pointed to these parameters in the course of the briefing and said, Hey, these parameters are important. That's how we got the non-lamellar structure. And our response there -- well, our first response is obviously, Where does it say that in the '127 Patent? And the answer is, it doesn't. But the law also addresses this fact. The law is very clear.

If we go to Slide 146, the law says, When there's not a limitation in the claims, you can't rely on that limitation to try to defeat inherency. Patent Owner is asking you to read into these claims, limitations that say, Oh, using these DDM method with these specific parameters. And the claim simply don't say that. There's no limitation there, and what we have is the specification of the '127 Patent saying that you can use the opposite. Any method known in the art and a person of skill in the art would know how to make these non-lamellar particles.

If we can go to Slide 147. Now, the '069 Patent is silent -- I'm sorry. If we go to Slide 148. So the '069 Patent is silent on the specific parameters used and the testing for the direct dilution method or the stepwise dilution method, but the '069 Patent references the '031 and the '025publications.

And, again, these parameters are not actually in the claims, but even if they were, the test for anticipation isn't whether it was actually reduced to practice and testing. The question is, do the '031 Patent -- Publication -- I'm sorry -- and the '025 Publication disclose to one of skill in the art using those parameters to produce particles? And the answer there is absolutely. They have to. The '127 Patent references these publications as disclosing exactly that.

And if you go to these publications, they talk about the different parameters that you can use. They talk about

the ranges of the mixing speeds, they talk about the equipment that can be used. It's all in there. And it's actually not disputed that it's in there.

If you can go to Slide 149. Their expert says that the '031 Patent defines the larger set of possibilities and the '127 Patent on Table 1 is simply identifying one of those possibilities, one of the embodiments in the '031 Patent that the '127 Patent acknowledges, result in this inherent three-dimensional structure.

In other words, nothing is missing from the disclosure in the '031 to enable one of skill in the art to produce particles using the formation process that's disclosed therein to result in a non-lamellar structure.

So what do we have now? We have one, the same formulations, basically the same lipid components, the same numbers, the same percentages, and then we also now have the same formulation process to result in those particles. And that's what the '127 Patent says, defines whether or not a specific embodiment has this inherent non-lamellar structure.

Now, Patent Owner also puts forth some evidence of a test that they had one of their employees run. If we can go to Slide 152. This is -- their test is legally irrelevant, first of all. It doesn't matter that an embodiments exists out there in the '031 Publication or the '025 Publication. That might not result in the non-lamellar structure. The law only requires one embodiment that has this inherent property.

Second, if we can go to Slide 154. These tests were designed by counsel for the Patent Owner to fail. They were -- he instructed the employee of the Patent Owner to use manual syringes and did not even attempt to recreate the production methods actually used in the '069 Patent.

If you can go to Slide 155. During this testing, the employee actually held two syringes in his hand and counted one 1,000, two 1,000 to approximate a steady flow rate.

If you can go to Slide 156. And he admits that this is going to add fluctuations to the test results. If you don't have good mixing, you're not going to have a full homogeneous particle population. This testing was -- again, he was instructed to do so. The testing was designed to fail.

If you go to Slide 157. If you looked at the results associated with this testing, these were bad particles. These are badly run tests. The particles had high background that made it difficult to judge the structural features. The particles were far larger than the size called for in the '069 Patent, and large amounts of the particles couldn't be evaluated one way or the other, fully, 22.7 percent for one of the samples. It's hard to address 95 percent non-lamellarity in a particle population when 22 percent of the particles, you can't figure out one way or the other what they are.

In addition, even if the claim non-lamellar

structure was determined not to be an inherent property of the disclosed particles in the '069 Patent, it's obvious. '069 Patent discloses the same formulations. There's no dispute there. The '069 Patent discloses the same formulation processes that were given as examples, specific examples in the '127 Patent regarding how you can make these particles.

The '069 Patent actually identifies having a non-lamellar structure as one of the goals. If you go to Slide 161, please. This is a quote from the '069 Patent, Wherein the therapeutic agent is fully encapsulated within the lipid portion.

What does that mean, within the lipid portion? It doesn't mean simply within a biliary in a liposomal structure. It means it's actually encapsulated in the lipid portion of the particle. Now, that's a three-dimensional structure that results when you had a non-lamellar structure. You either have an inverse hexagonal structure or a cubic structure, according to the '127 Patent.

JUDGE MITHCELL: Can I ask you? Do you have expert testimony that says that the prior art formulations would necessarily result in the non-lamellar particles?

MR. WELLS: We have testimony from both experts that the prior art formulations using the formulation processes disclosed in the '031 Patent will result in the non-lamellar structures. Both experts agree on that. The dispute is whether all of the formulation processes, formation processes

in the '031 Patent must result in the non-lamellar structure. And that's a legal issue that the Federal Circuit has clearly said. It's not required. You need one embodiment. And nobody disputes that that embodiment is disclosed in the '031 Patent. The '127 Patent says it.

JUDGE MITCHELL: Okay.

MR. WELLS: I have no more at this point, Your Honor.

JUDGE MITCHELL: Would you like to reserve five minutes?

MR. ROSATO: Yes, thank you.

JUDGE MITCHELL: Sure.

MR. ROSATO: So we're looking first at Slide 3 here. And this is just the listing of the grounds that were presented in the petition, and I just want to -- worth the clarification that very little remains of the challenge, in the sense that most of the grounds, 2, 3, and 4 have already been deemed insufficient to meet the institution standard, although, of course, the entire petition was instituted, as it should be. The deficiencies of Ground 2 through4, of course, also are incurable, and they have, in fact, not been cured.

So we'll be talking about Ground 1, and Ground 1 really focuses around this limitation of the claim, I'll refer to as the morphology limitation or the at least 95 percent non-lamellar limitation.

Let's turn to Slide 4. And in going through that, I

know that these are very well-known legal principles listed on Slide 4, but they bear repeating in the context of this case. The first is with regard to inherency, the main argument with regard to Ground 1.

It is very well-established that, as we all know, that inherency may not be established by mere probabilities and possibilities. That's not enough for an inherency case, and it's a very high bar. It's not one that is the burden of the Patent Owner to demonstrate.

Patent Owner does not bear the burden of proving no inherency. Proving inherency is the burden of the moving party.

The second principle listed here is the idea that picking and choosing amongst different disclosures and different embodiments is not sufficient to support an anticipation case of any kind, and that includes an inherent anticipation case. This latter principle -- and distinguishing both of them is pretty important here because what seems to be going on in a number of instances is an invitation to pick various different aspects from various different embodiments, and put those together, and then claim that the result would be one of inherent anticipation, but that is not an approach that can substantiate an inherency case. You can't start by going from one place in the specification and looking at it in an embodiment for a formulation, looking at -- picking ingredients or lipid

constituents for that formulation, going somewhere else, looking at different options for formulation methods, picking a method, going within that method, picking various different parameters. That's picking and choosing, and that's what we see going on here quite a bit.

So let's look at the argument that was actually advanced in the petition with regard to inherency. And let's turn to Slide 5.

So the inherency theory is, as one seem to exist, was actually fairly clear. I think it was reiterated here, to the extent that there was reference to the same exact same formulations, lipids, and methods being used. But looking at what was advanced in the petition materials, Petitioner pointed to some very specific lipid formulations in the '069, those listed in Tables 3 through 6, and the petition asserts that the exact same method was used to make those particles as compared to -- identified particles in the '127 Patent, right? So there's specific identification here of particles or embodiments of Tables 3 through 6, and the assertion that everything is the same in terms of composition of those, and everything is the same in terms of the method that was utilized.

There are a number -- oh, and then of course, it draws the conclusion. Because that all was the same, while '069 didn't test morphology or doesn't say anything about morphology, due to the identity between all of these aspects,

the morphology result must -- has no choice but to be exactly the same as well.

So that was the theory that was advanced, and there are a number of problems with that, starting with the fact that the entire case rests on a faulty and unsubstantiated premise, that is, Petitioner fails to establish that everything is in fact exactly the same as they charge. And this is particularly apparent with regard to the formulation method used for the embodiments listed in Tables 3 through 6 of the '069 Patent that are specifically being identified or relied upon.

The '069 Patent provides multiple different formulation methods, and Petitioner never establishes which of those methods was used for the embodiments that are listed in Tables 3 through 6. There is no evidence to support that point, that the exact same formulation method was used. We have no idea what method was used according to the Petitioner, and are different embodiments and a -- simply have not been identified or established which was used.

That alone is sufficient to defeat Petitioner's inherency case. Again, you've got a case that is premised on very specific factual assertions. We've just identified one of them that is completely unsubstantiated and lacks any support in the record. That is an unsubstantiated and faulty premise to the argument. The argument fails at least for that reason.

Let's turn to Slide 6. There's an additional reasons why the inherency theory fails, and that is based on Petitioner's assertion that the formulation method used, and insofar as they go in making assertions, their assertion only goes so far as to assert that the method used was the direct dilution method. They don't say what direct dilution method or anything about the direct dilution method. They just assert that the direct dilution method was used.

We asked Dr. Janoff about this during cross-examination, and he actually recoiled that the notion of using the term, the direct dilution method, explaining that there is no such thing as the direct dilution method. Direct dilution is a class of methodologies. So if he's going to be asked what method we're talking about, you know, it would have to be specified. We were very clear on this. I specifically asked him, if someone walked into his office and said they used the direct dilution method, he indicate he'd have no idea what they're talking about because you would have to specify precisely what direct dilution method you're talking about.

So we're talking about a class of methodologies, and that's really what they're pointing to in the petition, that they say the same method. They haven't substantiated that a direct dilution method was used, but even the assertion of the direct dilution method is referring to a class of methods.

And then just to go along with Dr. Janoff's testimony during cross, they've identified this '031

Publication as being the direct dilution method. If we look at that publication, it's pretty clear that it's not describing one single solitary method. You can see that from Figures 3A and 3B, which are outlined in different apparatuses. And then if you go through the disclosure, what we're seeing are various different parameters being identified and various different options all along the way.

So Dr. Janoff is correct. There is no direct dilution method. We're talking about a class of methods, and the reference we're looking at substantiates that.

By the way, there's not a single citation. I want to be careful with how far we go with '031 because there's not a single citation to anything specific in the petition materials. There's only general reference to the '031 Publication as a broad matter.

JUDGE MITCHELL: If you can hold just a minute. I think we've lost Judge Smith, so I just want to make sure he is reconnected.

MR. ROSATO: Sure. I hope he can't hold that still in real life.

JUDGE MITCHELL: Can you tell if Judge Smith is connected? We lost Judge Smith. Sorry.

Sorry to interrupt you.

MR. ROSATO: No problem.

(Off the record discussion.)

JUDGE SMITH: Hello.

JUDGE MITCHELL: Oh, great. So can you hear and see us?

JUDGE SMITH: I can, yes.

JUDGE MITCHELL: All right. Well, we will resume, Judge Smith.

So when you're ready, Mr. Rosato.

MR. ROSATO: Okay.

JUDGE MITCHELL: Sorry about that.

MR. ROSATO: No problem. Okay.

So I think we were going through the inherency case and trying to take this in a dual burden of proof, one step at a time. And starting with the fact that the issue of the unsubstantiated premise is that everything was the same and focusing first on this method issue.

We pointed out first that the particles that they were -- that they identified, they hadn't established what method or even what class of method they were generated using. Next, looking at their assertion that they were all generated the direct dilution method, we looked at why that isn't good enough, even if accepted as true because we're talking about a class of methods when we say the direct dilution method. But it doesn't specify which direct dilution method and, in particular, which sets of parameters are being contemplated or they think are being used. And there's --

JUDGE SMITH: Counsel, can I stop you there?

So the '127 Patent uses the word, The direct

dilution method, whenever it's referenced. So what is, The direct dilution method?

MR. ROSATO: The direct dilution method is a class of methodologies.

JUDGE SMITH: But why does it say, The? I mean, what's the significance of the word, The?

MR. ROSATO: Well, perhaps, it should say the direct dilution method referring to the class of methodologies. But it's clearly referring to a class of methods as illustrated in the '031 publication, which lists --

JUDGE SMITH: But any of those -- based on your -- the '127 spec, it says any of those then would be acceptable to actually make the particles that you're claiming, the composition that you're claiming.

MR. ROSATO: Well, okay. Let's -- I'm starting with the '069 Patent, not the '127, right? And then it's another issue in -- with the asserted challenge. I mean, we're taking the '127 Patent and trying to use that as a road map to find something. I'm starting with the case that's set forth in the petition materials, and there's specific materials that are identified in the '069 Patent that are allegedly producing inherent -- these particles that are accused of inherently meeting the claimed properties.

So I'm trying to approach the assertion that was made and respond to that. So I -- no, I don't think it'd be appropriate to start -- and the Petitioner does this quite a

bit, but I don't think it's appropriate to then try to backfill the deficiencies in that stated case by reverting back to the '127 Patent and then trying to map things up and see if we can find something here.

Again, this is why -- in part why I started out by saying let's remember that there are two important principles of law that are guiding us here. They're the principles of what constitute a case of inherency and what's required by that. And then there's the principle of law that reminds us all what we know, and that is picking and choosing amongst various different options and different disclosures, embodiments, and so forth is not any type of anticipation case. It's really an assertion of obviousness.

So we're talking about, you know, this assertion again trying to understand what Petitioner means by using the same direct dilution method, and we asked their expert and he said there's no such thing. You have to know more than that, and we looked at the '031 Publication that was cited, and indeed there are a fair amount of details.

Why does this matter? Let's -- can we turn to Slide 7? It matters because knowing what process was used, in particular, some details about that processes, it matters because if you alter aspects of the process of forming particles, what happens is that alters the physical properties of the resulting particles. That is substantiated, supported by testimony from both witnesses. Both witnesses agree that

that's the case.

If you start altering parameters of a formation process, you expect differences in the physical properties of the resulting particles. And that's particularly true, even with using a direct dilution method as -- and Dr. Janoff supported this during cross examination, indicating that if you start changing parameters such as -- he identified three parameters; speed, mixing rate, and temperature, that that is sufficient affect the physical properties of the particles enough or you might not even get the claimed particles.

So we're starting with inherency, and we're asking whether inherency requires more than probabilities and possibilities, which we all know that it does. It's hard to see how this type of evidence and testimony does anything other than demonstrate they failed inherency here.

Okay. Let's turn to Slide 8. So there's no reason -- we have identified several reasons why the inherency theory that's been advanced fails. It also involves a lot of speculation, but there's no reason to speculate as to whether the particles that are being identified would have the same physical properties or not.

We can -- if we're going to do this comparison between the subject matter that's being identified and the respective disclosures, '069 and '127, we can look at that and see that they actually tested and reported physical characterization of those particles to different degrees.

'069 didn't characterize the particle morphology, but it did characterize other physical properties of those particles such as encapsulation, percentage -- sorry, I almost said morphology, I didn't mean that -- size, polydispersity, and various different properties. Similar -- some of those same properties were characterized in '127.

So what's being identified is the exact same particles. We can look at the reported physical characteristics of those, and we see that shown in Tables 5 of '069 next to Table 5 of '127, and what you're seeing by that comparison is a difference in physical properties. So --

JUDGE SMITH: But not necessarily a difference in the morphology.

MR. ROSATO: Morphology is not listed in there, but just to be clear, what we're talking about, no. '069 doesn't characterize morphology. But if we're going to be making assumptions about the physical property of morphology, it's a reasonable assumption that particles having different physical properties, as shown by the data, may not necessarily have the same common morphology, with morphology being also -- another different physical property. So --

JUDGE SMITH: Isn't the -- counsel, isn't the issue not the particles but the disclosure?

MR. ROSATO: I'm not sure what you mean by that, Your Honor. I would say that given the stated case of inherency that's presented in the petition, that there are

specific particles identified, and the assertion is those specific embodiments were made by a very specific process, and, therefore, the logic that's being advanced is you must assume the same outcome. I would say it does matter which particles we're talking about.

Okay. Let's turn to Slide 9. So, I mean again, we're -- non-moving party, we're doing our best to respond to the argument that's made. If they thought there was something other, some other embodiment that they're pointing to, then you know we would be happy to address that. But they're pointing to very specific things; we're addressing those.

Now, if they really wanted to argue is that there would've been some reason why someone would want non-Lamellar particles at a high degree, they could have -- and that somebody would then be motivated to go pick all these different options, pick a particular class of formulations, pick different lipid constituents, pick a method, pick various different parameters, that there'd be sufficient guidance to do that, and there'd be reasonable expectation of success, they could have put that all together in an obviousness challenge, and we would have addressed that. But they didn't do that.

So we can't back into -- present an inherency theory, and then sort of back into what we might really want to address as Petitioner, you know, some sort of shorthanded obviousness theory, and then sort of cut corners and call it

all good.

Inherency theory is on the table, we'll address the inherency theory, and we can move to what was presented in terms of obviousness when we get there.

But continuing along to address the inherency theory. So we're looking at Slide 9 here, and I want to talk about the experimental testing that was performed by Dr. Heyes. There was a comment earlier that the -- that stated that testing was specifically designed by counsel. That's correct, it was designed by counsel.

But what opposing counsel, perhaps, fails to appreciate is that Petitioner's counsel was the one that designed this experiment. They designed it by virtue of what they were providing in terms of their -- what was being asserted as being providing the inherency. And they cited specifically to Column 73, Lines 13 to 39 in their petition, and this was the instance where they had a particular formulation that they were identifying with some content about what type of process was used to prepare it. And Dr. Heyes attempted to reproduce this process by following the formulation guidance, following the syringe press guidance, and then assuming that the accusation of the direct dilution method according to the '031 Publication was true, generating particles using a process according to the '031 Publication. Right?

So all of the detail that can be discerned from what

was presented was followed, and that was precisely what defined the confines of the experiment performed. So if the Petitioner has any complaint as to the type of experiment that was run, they can look to the petition materials as a source of that guidance.

Let's turn to Slide 10. And this is just Dr. Heyes' declaration explaining precisely why he chose what he did.

Turn to slide 11.

JUDGE SMITH: Could you respond to -- I believe before I lost contact, the issue of the Heyes test data not being relevant or not necessary.

MR. ROSATO: I completely agree. It's not --

JUDGE SMITH: Something like that. I forget exactly the way they phrased it, but the fact that they -- their essential point, as I understood it, was the fact that Dr. Heyes failed to come up with a non-lamellar morphology --

MR. ROSATO: I see.

JUDGE SMITH: It doesn't really --

MR. ROSATO: Yeah, I see.

JUDGE SMITH: Factor in --

MR. ROSATO: I understand the question, Your Honor. I would say we're in agreement to the extent that the data is irrelevant because we should never get to the data to begin with. This is a Patent Owner putting forth evidence to disprove a stated inherency case.

So we shouldn't need to get there. There is no

substantiated inherency case to begin with. We can dispense of the inherency case simply by virtue of unsupported unsubstantiated premise on which it's based.

So, in that sense, we in fact never need to get to Dr. Heyes' declaration testimony. I think what they were arguing, and this is a point that we will want to address, is this idea that, well, he may have demonstrated an embodiment or a situation where you follow all the guidance in '069, and it doesn't give you the claim particles. I think the point of criticism was, we should have kept going and kept exploring and varying parameters. That there's got to be something out there somewhere that would meet the claimed limitations. I think that's the suggestion, is that --

JUDGE SMITH: But you would -- yes. But you would agree that if there is a composition that the -- that Claim 1, in this case because Claim 1 is broad, there's a composition in the prior art that Claim 1 reads on, regardless of whether anyone appreciated what the morphology would be, that would be anticipatory; not composition.

MR. ROSATO: Yeah, I guess, I would just -- I don't think Claim 1 is that broad. I mean, it has a very specific limitation.

JUDGE SMITH: I understand. I mean, I -- it can't be as it reads on a composition the prior art -- one composition.

MR. ROSATO: So --

JUDGE SMITH: Inherency isn't -- you don't have to prove that every possible combination or composition has that result.

MR. ROSATO: Sure. I think we can agree on a point of law. I mean, I guess where I struggle with this case is what composition are we talking about?

JUDGE SMITH: Well, my understanding --

MR. ROSATO: Petitioner --

JUDGE SMITH: Again, I -- well, go ahead. Go ahead.

MR. ROSATO: No, I'm sorry, Your Honor. I didn't mean to interrupt you.

JUDGE SMITH: Well, my understanding, part of their argument is what you're stating as the '127 Patent. That's where I wanted to talk about that. A person reading the '127 Patent is going to believe what it says that the -- if you want to practice the invention, you go to the '031 Patent and it tells you exactly the process that you would use because it says, It's described in detail. The direct dilution method is described in detail. And that's what I'm trying to ask you; what -- you know, that's what I'm asking. I mean --

MR. ROSATO: I think I understand the question.

Look, I think the reality is this. What we're really talking about -- and again this is sort of what I wanted to distinguish between the two legal principles up front. What we really seem to want to know is if you go through the '069 disclosure, and you make all the right

choices in terms of the general class of formulations you're using, the right choices in terms of lipid compositions, and then you get to a method, and you make the right choices along the way of the different types of parameters that you're going to be using, if you make all those right choices, will you get the claimed particles?

I set this out upfront as a point of -- a distinction between a point -- two different points of law because what I just described is an obviousness challenge, right? It's picking and choosing amongst a host of different choices and options to try to arrive at -- to --

Now, whether you're trying or you do arrive at the claimed subject matter. So, it's really important to bifurcate the inherency charge from what would be an obviousness charge.

So if we're looking at inherency, we have to find some embodiment -- this is where we all agree, it's a one-embodiment thing. But we have to find that embodiment and a reason to believe without -- about -- above mere probabilities and possibilities, that that meets the limitations. So that hasn't been done.

Separately, there's this inclination -- maybe it's just, you know, the human mind of wanting to go, well, there must be something. But, you know, in an obviousness inquiry, you know, again we're trying to put ourselves in the position of not having the '127 Patent in front of us. Right? We're

trying to avoid this improper hindsight construction, and we're trying to start with the '069 Patent and say, Why would I want particles that are highly non-lamellar? Right? Particles that were believed to be highly unstable and nobody even knew you could get from these types of processes. Certainly, nobody knew how you would get them.

So, if you're starting with '069, and you don't have a reason why you would want this. You wouldn't -- you don't have a reason to believe you could get it even if you did want it, and you don't have any guidance on how you would do it, then that's an unsubstantiated obviousness case as well.

JUDGE SMITH: So are you saying that a person who took the same components, person skilled in the art reading the '031 Patent, with the same components that you -- you know, basically overlap the '127 and the '069. You're saying a person skilled in the art would not be able to make a composition that Claim 1 reads on? I mean, anticipation is directed to a person skilled in the art.

MR. ROSATO: I'm not sure I understand the question.

JUDGE SMITH: Well, I'm not sure I know how to say it differently. I mean, the question is again, the '127 Patent says that the direct dilution method as disclosed in the '031 Patent will get you there for the same -- for Claim 1, again, assuming you have the same components, which the '069 discloses the same components.

And my question is, so a person of ordinary skill in

the art looking at the '069 Patent and says, Okay, I'm going to look at the '031, and I'm going to practice what it tells me to practice on. I'm going to come up with a composition. It doesn't matter whether I know, or whether I'm even looking for the non-lamellar morphology.

MR. ROSATO: Well --

JUDGE SMITH: I'm going to make acomposition, and you're saying -- it sounds like you're saying there's no way you can get there.

MR. ROSATO: I'm not saying -- that's not what I'm saying. I'm saying the standard for inherency is not a -- it asks a specific question. It asks the question in reverse. Would you necessarily, and without variation, get there? Not, Do you have a possibility of getting there, do you have a probability of getting there? It's, Have you necessarily arrived there? That's the question --

JUDGE SMITH: Okay, so --

MR. ROSATO: Right? That's the question we're asking. If we want to --

JUDGE SMITH: Okay, let me -- question -- I guess the question I was trying to ask before. Where in the '127 does it tell you what those parameters are? I mean, you can't have it both ways.

MR. ROSATO: I guess I don't see it as both ways. We're conducting a non-hindsight based analysis, so they're two separate questions. Right? I mean, if we're starting

with -- we're starting with 069. We're looking for a sort of a linear path or an embodiment that gets you to a result that you can substantiate as inherent of the properties we're talking about.

JUDGE SMITH: Let me -- let me break it down.

So I -- and I'm just trying to understand here.

MR. ROSATO: Uh-huh.

JUDGE SMITH: There's been a discussion about this Table 1, and I asked Petitioner's counsel about that, and I don't know if your client's position is that this is the secret sauce that you got to use in those particular parameters and the correct dilution method to get the composition. So that somehow, your claim is limited to those particular parameters.

MR. ROSATO: Yeah. That was -- honestly, that's a straw man argument that was presented in the Petitioner's reply materials, that we're trying to read in some specific table to our claim, and then attack that as not making sense. We didn't make that argument; I mean, we're not arguing that a table be read into our claims.

What we did do, just to differentiate our actual argument versus the one that was attacked, the argument's we've made are consistent with what I'm presenting here. This is the inherency case as we understand it; this is what they're pointing to. This is what they're asserting. Is this premise factually supported? No. Are these particles they're

pointing to, and saying, These inherently possess this property, is there evidence to that? No. We ran testing on some of them to reproduce it, to demonstrate. They don't have the properties.

So the arguments that were presented are directly responsive to what was addressed in the petition materials. I have no idea what they're talking about in terms of tables being read into the claim, because that's not an argument we advanced.

If you're asking me, does the -- a different question of, Does the '127 Patent provide sufficient guidance to make these, and is Table 1 and the corresponding parameters an example of that? I would say it is because it's describing an experiment that has corresponding data that specifically demonstrates that it produced 95 percent non-lamellar particles.

So, yes, it's an experiment that was run and demonstrated to produce the resulting particles. So, yes, that -- of course, I believe that data.

JUDGE SNEDDEN: Can I -- let me just see if I can understand the argument.

MR. ROSATO: Uh-huh.

JUDGE SNEDDEN: So prior -- if we look in the prior art document, you can find a nucleic acid, cationic lipid, and non-cationic lipid, you can find each of the elements in the claim. But what you're saying is there's not one

(indiscernible) presented in that prior art reference, the '069 I believe, that necessarily produces this morphology that's recited in the claim.

Is that the argument, Judge Smith?

MR. ROSATO: I mean --

JUDGE SNEDDEN: Maybe that's too simplified, but --

MR. ROSATO: No, it's not too simplified. Again, like -- sorry. I -- maybe I take too seriously the non-moving party role so look at the very specific things that were identified as being the embodiments, and I'm trying to address whether there's a reason you believe with certainty that they have this. And I don't think that there is. I don't think that, you know, there's a logically cohesive argument in terms of supported premises and so forth, ones that would support the conclusion drawn, in what they've provided.

Now, if you want to ask me --

JUDGE SNEDDEN: That conclusion is, Is there no embodiment in the '069 Patent that necessarily has this non-lamellar morphology.

MR. ROSATO: I'm sorry. I didn't hear the first part, Your Honor.

JUDGE SNEDDEN: That the conclusion is that there's -- no one has identified an embodiment in the '069 Patent that necessarily has this morphology, that displays this -- a composition that displays this morphology.

MR. ROSATO: I think that's true, that they have not

identified an embodiment.

JUDGE SNEDDEN: Right. So without that, how do we -- we're left with picking and choosing amongst the -- everything that has been disclosed. Nucleic acids are disclosed, but which combination will get you to the morphology? That's the question. So --

MR. ROSATO: That's the question.

JUDGE SNEDDEN: Right? So maybe certain combinations will lead to the morphology, certain other ones won't. But that's where we are in terms of probabilities, and there's nothing that necessitates this morphology.

MR. ROSATO: I would agree with that, and I think --

JUDGE SNEDDEN: I'm just trying to rephrase your argument, make sure I understand it.

MR. ROSATO: Yeah, and I think that's what stated in -- if we want to again go back to the '127, and I really -- my nature makes me resist doing that and not -- in addressing a patentability challenge because of the hindsight guard. But if we look at what's described there, and I think there's a slide I'll put this up on the screen, there's some ham-handed description to be honest in how things are written in the specification.

But one of the things that's stated is, the discovery is by controlling these components and controlling the process parameters, we were able to achieve this stuff. And I think that actually does capture some of the essence of

what we're talking about here. That's a matter of make -- you know, making the right choices and controlling the right parameters, and some choices will get you what you want or get you the 95 percent non-lamellarity, and some will not.

In terms of the challenge, we do have this vague assertion that there -- from Petitioner that there must have been some embodiment. I don't know how to respond to that because I don't know what they're -- what embodiment they're talking about, other than the ones that are identified in the petition materials.

JUDGE MITCHELL: But does the '127 tell you which particular formulations are going to get or which particular dilution processes can get you to the claimed invention?

MR. ROSATO: It gives some guidance. I mean, it doesn't lay out a, you know, a matrix to, you know, say, Under these conditions you will get, under these conditions you won't. I mean, it lays out, you know, the categories of methodologies you can work with. And I think what Judge Smith was asking was, Are there experiments that demonstrate how you get this? Yes. You know, and list some parameters that will get you that. But is -- it doesn't have some specific, you know, sort of matrix on how to -- anything like that. But I mean, there's --

JUDGE SMITH: Is there -- as a follow up to that, is there anything in the '127 in terms of the process that you couldn't find or there is not disclosed in the '031?

MR. ROSATO: Yeah, there is some things. I mean, just as an example, they list on Table 1 -- and, again, this is not reading in Table 1 to a claim or anything like that, but because it was up on the screen, and it's fresh in my mind there's a listing of a robotic lipobot press that is something that is not a mixing apparatus that's listed. I know that's true. I think there was some -- maybe some other things that I don't recall at this moment, but -- I mean, that's at least -- you said, Is there anything? And that's one I can think of.

So we were talking about experiment -- Dr. Heyes' experiment and why this was, you know, an attempt to actually follow the direction that was given. There was criticism about using handheld syringe presses. We actually asked Dr. Janoff about this during cross-examination, and he specifically commented on that. But I think we can -- I don't need to run through the results of the experimentation. We all know -- we all know that they demonstrated that it -- the particles didn't meet the morphology. The Petitioner doesn't like the experimentation, but it is evidence of record in the Board and evaluate how much weight to attribute to that.

Let's turn to slide 15. We addressed this in the briefing, and there's a motion to strike on this point too. But there's this issue of whether the '069 Patent can be used for an obviousness challenge. To begin with, and the answer is no, the '069 Patent was issued in November of 2011. That's

after the June, 2010 filing date of the '127 patent. And because '069 is a commonly owned one and to be referenced, it's disqualified under 103(c).

Beyond that, we don't think there's really any obviousness inquiry to be had, beyond that point. If the Board is inclined to review any of the obviousness challenges, it will find -- to be brief, it will find those challenges are conclusory in nature and lacking really any coherent explanation.

And I'll just refer direct -- generally to the obviousness argument that's at page -- and it's in the petition, Page 32 through 33. This is shown on Slide 17. But this is what we're talking about in terms of the types of obviousness challenges that are -- that are met.

There's no -- you know, this is a couple sentences that mention that non-lamellar particles are mentioned elsewhere, and it jumps to the conclusion of obviousness. There are no -- none of the critical aspects of an obviousness inquiry that would be necessary here, and I don't need to enumerate what those are, but they're missing. And I won't waste the amount of time.

JUDGE MITCHELL: Thank you.

MR. CHU: Your Honor, may I be excused because of where I need to get to by the end of the evening for the rest of the hearing?

JUDGE MITCHELL: Sure.

MR. CHU: And you're in good hands with Mr. Wells and Mr. Fleming.

JUDGE MITCHELL: Sure. Thank you.

When you're ready.

MR. WELLS: Thank you, Your Honor.

So I'd like to start with going to the reply brief, at Page 5, and I don't need this pulled up.

There's a discussion of the Federal Circuit's holding in the King matter. And the full citation is 616 F.3d at 1274. And the discussions about what's disclosed in the patent that's being challenged on the anticipation basis. And, here, the Patentee argued that the prior art's disclosure of taking a certain drug with food reduced gastric discomfort. And -- but it was too vague as to the conditions under which the food was actually supplied, and the patent being challenged in that case had discussions of what conditions the food needed to be supplied in order for the drug to be effective and avoid the discomfort. And the claims in that case though, in the patent that was being challenged, were silent on how the food needed to be taken.

And the Federal Circuit said, Look, we're going to look at what you're claiming when we're evaluating anticipation by inherency. And if you're relying on stuff that's not in the claim to differentiate yourself from the prior art, we're not going to listen to it. That's not what the claim covers. And in that case it was an actual

discussion in the specification regarding what the specific parameters you needed to take the food with.

Here, we don't even have that. We have the '127 Patent claims that are completely silent, completely, on the formation process that needs to be used. And there's no discussion in the specification of '127 Patent, no experts pointed to anything where there's a discussion as to how the parameters used in the formulation process influence this claimed non-lamellar morphology. The only thing we have is a reference to the '031 reference as an example of the direct dilution method that can be used, and the stepwise dilution method described in the '025 publication. Both of those exact references are referenced in the '069 Patent that's the prior art.

And then we have the general statement in the '127 Patent that any process known in the art could be used by persons skilled in the art, and they would know how to manipulate the variables to get these particles. So the argument that we should ignore the '127 Patent's disclosures and not engage in hindsight analysis? We're not engaged in hindsight analysis. We're allowed to look at the challenged patent to understand how it treats the claimed inherent property.

JUDGE SNEDDEN: I think the problem identified by Mr. Rosato is that you have, in this claim here, recitation broad classes of components, so a nucleic acid, cationic

lipid, and non-cationic lipid. But the claim narrows when -- in the Wherein clause, which is those components need to come together and produce something with particular morphology, and in the '069 Patent, we have similar starting materials. We have similarly disclosed methods of mixing, but how -- but where's the certainty that every time you do this with these broad classes of components will you get this morphology? Not necessarily. We do not necessarily get that.

MR. WELLS: Sure, and I'm going to take --

JUDGE SNEDDEN: Okay.

MR. WELLS: Your question in two parts as I think I understand it.

JUDGE SNEDDEN: All right.

MR. WELLS: And tell me if I miss any part of it here.

JUDGE SNEDDEN: Okay.

MR. WELLS: So first we have to start with, What are we talking about here?

So we have a property, this non-lamellar structure, and we agree that it's a physical property. And we agree that the '127 Patent says that this physical property is the result of a formulation and a formation process. And for a given formulation and for a given formation process, this should be a reproducible property. It should always arise. It's not speculation. It's not uncertainty. If you have the same formulation and same formation process, all the experts agree

that you should have this physical property. So --

JUDGE SNEDDEN: Can I interrupt?

MR. WELLS: Yes.

JUDGE SNEDDEN: I think I -- I hope I know where you're going. So is there an embodiment in the '127 Patent that you can find in the '069 Patent?

MR. WELLS: Yes. Every embodiment in the '127 Patent is disclosed in the '069 Patent.

JUDGE SNEDDEN: Because I think that's what we're looking for. We're looking for an embodiment that is alleged to have the same properties as what's disclosed as an embodiment in the '127 Patent that's stated to have these properties.

MR. WELLS: So let me start -- the answer is two-fold.

JUDGE SNEDDEN: Okay.

MR. WELLS: The first answer is the broad answer, and then the second answer is looking at the specific, reduced, practiced testing the '069 had, which I -- whereas I think you're going, but we need to start with the broad disclosure.

And your first question was, Was there any embodiment in the '127 Patent that's disclosed as having the non-lamellar structure that's also disclosed in the '069 Patent? And if there's every single one? Why? Because the '069, you don't have to reduce to practice to anticipate

inherency. It's what would be disclosed to a person of skill in the art regarding the formulation and formation process.

And that person doesn't need to know whether it was going to be non-lamellar or not, that's not a requirement. The question is whether a person of skill in the art, based upon the disclosures in the '069 Patent, would have known a formulation and a formation process that's used in the '127 Patent to result in the non-lamellar structures.

So broadly speaking, the exact same disclosures are in the '069 Patent. The '127 Patent says, Oh, you can use nucleic acids, and this is how we define them. It's a verbatim disclosure in the '069 Patent.

If you go through the cationic lipid, the non-cationic lipid, the conjugated lipid, that's all the same too.

And so the actual disclosures to a person of skill in the art are completely encompassed in the disclosures to what an ordinary skill in the art in the '069 had.

Now, your question I believe is going to, Well can you point to a specific embodiment, that was reduced to practice in the '069 Patent, that results in the non-lamellar structure in the '127 Patent? Do I have the second part of your question there correct?

And so the answer there is, yes, as well. So, one, it's not legally required. Reduction to practice is not a requirement for anticipation by inherency. But, even if it were, we already have the formulations that we've been talking

about. We're talking about the same payload, the exact same siRNA payload, being used in the '069 Patent testing as was used in the '127 Patent testing. Nobody disputes that those are the same.

We have the same lipid components. We have the same cationic lipid being used, DLinDMA, which was known to be fusogenic and known to promote a non-lamellar structure. We have the non-cationic lipids, either DSPC or DPPC, and some of the formulations in the '069 Patent do use DPPC instead of DSPC, but their expert admitted that wouldn't be expected to impact the non-lamellar structure. Those are very closely -- very close in structure and -- as a phosphor lipid. We have the same cholesterol, and we have the same conjugated lipid.

So the formulations -- and we have the same concentrations. The2:30, the2:40, the1:57, and the1:62. So the formulations actually tested, we have -- again, complete overlap. The only question is the formation process.

And so in the '127 Patent, we have only one guiding principle for the formation process. Table 4, column 104, for the actual testing that they did. Those parameters. That's the only thing we can divine from the '127 Patent regarding how you get these non-lamellar particles; what the secret sauce is. And there's no discussion whatsoever regarding varying these parameters, what ranges would be acceptable, anything like that. That's just not in there. And that's

also true with regard to the stepwise dilution method.

So then we say, Okay, are those specific parameters disclosed in the '069 Patent? The '069 Patent is silent on the parameters used, but we know that those parameters are encompassed in the '031 disclosures that are referenced in the 127 patent. Again, the experts don't dispute that. They say that these -- the '031 Publication is enabling of the disclosures in the '127 Patent on how to make these particles.

The only difference identified by counsel just now is that, Oh, a Lipobot could be used in the '127 Patent direct dilution method. But there's no discussion in the '127 Patent of using a Lipobot, which is an automated syringe press to get constant flowrate. Is any difference -- different than the stuff that is disclosed in the '069 Patent? And Lipobot's automated syringe presses were known in the art at the time of the invention. That's not an argument that's put forth in the papers that that's any kind of novel piece of equipment.

And so we know that the '031 Patent discloses multiple embodiments, and one of those embodiments has to be the one in the '127 Patent. By definition, the '127 Patent says it, you have to believe the patent. So that is absolutely an embodiment that is one, the formulations overlap or -- are the same. We have no arguments there. The formation process, well, we know from the '031 patent that it's got to be embodiment A, B, or C. And one that's skilled in the art knows from the '031 Patent that A, B, C are enabled

and there's no argument there.

So, yes, an embodiment is disclosed.

JUDGE SNEDDEN: There was one -- that was the formulation processes, they described not one but a class of processes.

MR. WELLS: So --

JUDGE SNEDDEN: That's what --

MR. WELLS: I don't know what a class of processes refers to.

JUDGE SNEDDEN: Or category then.

MR. WELLS: I can tell you that the '031 Patent, the direct dilution method in the context of the '435 Patent and the direct dilution method in the context of the '127 Patent is the direct dilution method as disclosed in the '031 Publication. That's what they're talking about.

And they say, Go to that publication. You're one of skilled in the art, you'll be able to identify the different ways of making these things, embodiments A, B, and C. And as long as one of those embodiments would have been -- clear to one of skill reading that reference, and that embodiment results in a non-lamellar structure, it's end of story as far as the inherency. And it has to have -- include that -- one of those embodiments, including the embodiment specifically listed on Table 4 of the '127 Patent with those specific parameters.

So if we even got to this argument, and again, these

aren't limitations in the claims, but if we got to this argument it has to be in that disclosure. The '127 Patent relies on it for it.

Does that answer your question?

JUDGE SNEDDEN: It does, thank you.

MR. WELLS: Now, just before counsel went off, he put up some testimony from Dr. Janoff. And if we could call up Exhibit 2028, Page 185.

Now, it's the last answer on this page, and they cut it off at line 22. They conveniently left out the rest of the quote, and it's telling. Oh, there's reference to T-2 connectors, so might not necessarily be holding these in your hands. They're apparatuses to push the -- and if you can go to the next page -- the syringe.

So Dr. Janoff didn't say, Oh, stand there with two syringes and press them counting to five, so you get a bad flowrate. That's just a complete mischaracterization of his actual testimony.

If you actually go to the patent, if we can go to Exhibit 1001, and go to Column 104, Line 33 through 43. I'm sorry, yes, go ahead. 104, Lines 33 through 43, if we could blow that up?

And so here, they talked about a syringe press. It's just an automated syringe press as opposed to somebody sitting there pressing a stopper with their hands. And you can imagine how pressing a stopper with their hands -- you

don't get consistent fluid mixing rates, and you get non-homogeneous particles such that some of them are lamellar and some of them are non-lamellar.

So, again, an automated syringe press was not a point of novelty for this patent. No one's alleged that that was new. No one's alleged that having an automated syringe press as opposed to a peristaltic pump or some other mechanism, as described in the '031 Patent, would make any difference.

Now, again, one consistent theme that came up from counsel was it's not the exact same particles that were tested in '069 Patent. That's not the standard. Reduction to practice is not required for anticipation by inherency. It's whether the '069 Patent discloses to one ordinarily skilled in the art particles with the same formation -- formulation and particles used in the same formation processes. That's the standard.

JUDGE SNEDDEN: I understand that the reduction of practice is not required, but what is -- what I need is an identification of some formulation that necessarily has the properties in the claim.

MR. WELLS: Yes, and you need a combination of a formulation and a formation process to get that property. That's what the '127 Patent tells us. We need to believe that if we're going to do any analysis.

And so, as we've already discussed, we have the

formulations. We can look in the '127 Patent and say, Which ones work for the '127 Patent? Right?

We know for the direct dilution method, the 2:30 formulation did, the 2:40 formulation did, the 1:57 formulation did, and the 1:62 formulation -- it might be 2:40 -- did as well. And that was with using a direct dilution method as put forth in Table1, Column 104, right? So we know that. So then we say, Well, what's disclosed in the '069 Patent?

And so I'll skip over the fact that the disclosures broadly encompass all those, and a person skilled in the art would have recognized those disclosures and been able to make particles with those formulations and processes, and move on to the narrower question which is, is there a physical embodiment that we can point to? And so, yes.

We have exactly the same formulations, right? We have the2:30, 2:40, 1:57,1:62. Those numbers are the same. There's some rounding differences, but there's no dispute that those same numeric concentrations are disclosed.

Then we look at the payload. The payloads are exactly the same, exactly the same siRNA. Exactly the same target for silencing. And then we look at the lipid components, and we have exactly the same cationic lipid, exactly the same conjugated lipid, exactly the same non-cationic lipids, except in two instances, DPPC is used instead

of DSPC.

So formulation-wise, we've identified exactly that, right? Are we on the same page, thus far?

JUDGE SNEDDEN: Yeah.

MR. WELLS. Okay. So then we go, Okay, well, what formulation process was used? Was exactly the formulation process used, disclosed in Table 4 of -- on -- Table 1 on Column 104 of Exhibit 1001, the '127 Patent? And we'd say, Oh, well, the '069 Patent doesn't say what specific parameters were used, and it doesn't. Instead, it references the '031 Publication. And we know the '031 Publication discloses all of those parameters on Table1.

Why do we know that? Well, the experts all admit it, and the '127 Patent itself says you can rely on the '031 Publication for how you do the direct dilution method.

So we know it's disclosed in there. And I think your question is, Well, is there anything correlating those specific -- the embodiment -- those specific parameters to what was actually tested in the '069 Patent? And there is evidence that those specific parameters or some other set of parameters that result in non-lamellar particles was used in the '069 Patent.

But I want to stress that's not a requirement for inherency. Inherency doesn't require every embodiment to result in non-lamellar morphology. It's simply saying, Oh, well, some embodiments don't, so then it's -- you know, then

we're talking about picking and choosing and we're talking about --

No, we're not. We're talking about there's multiple embodiments in the '031 Patent. And one of those embodiments by definition, by the -- terms of the '127 Patent itself, has to result in the claimed non-lamellar structure.

Now, if you go through the '031 Patent -- or Publication, I'm sorry. I keep calling it a patent. It's a publication. And you say, Okay, well, where are the disclosures of the ranges of the different parameters and whatnot? They're all disclosed in there. And Example 2 of the '031 Patent sets out a lot of these. But there's a section of the '031 Publication that says, This is how you make the particles, and it spans Paragraph 0039 through 0087, and it gives you all the encompassing ranges. And this is what a person of skill in the art would reference and say, Okay. Using this as the embodiment in Table 1 on Column 104 of the '127 Patent, one of the embodiments that fall within this broader grouping of embodiments. And, yeah, it is. And how do we know that? Well, the experts testify to it. And how do we know that? The '127 Patent says it.

JUDGE SNEDDEN: I understand, thank you.

MR. WELLS: Now, regarding the evidence that a formulation was actually used, which results in non-lamellar particles in the '069 Patent, again, this isn't a requirement for the inherency argument but would relate to an obviousness

argument.

We have the statement that we brought up earlier that one of the goals in the preferred embodiment was to have the nucleic acid in the lipid portion. And in the lipid portion refers to inside, encased within the lipid superstructure that you find in these non-lamellar structures.

In addition, could we go to Slide 161? So this is the reference to being encapsulated within the lipid portion of the particle. In addition, we have the '069 Patent incorporates by reference -- reference the 613 reference, which is Exhibit 1017, and this is incorporated at Column 11, Line 64 of Exhibit 1002 in its entirety. And the '613 Patent talks about the benefits of having a non-lamellar structure, and that it can increase your fusogenicity, and in fact, discloses embodiments where all of the particles -- it's a homogenous particle population of non-lamellar particles, and those are at Columns 7, Lines 22 through 26, and 763 through 84 of the 613 patent.

We also have expert testimony. Their expert specifically testified that if a particle is showing poor encapsulation, it's probably lamellar. And if it has high encapsulation, you would expect it to have a non-lamellar morphology. And he did this at Exhibit1023, Page 126, Lines 4 through 11. And so we have plenty of evidence that the '069 particles that were actually formulated were indeed non-lamellar. But, again, not a requirement for anticipation by

inherency.

Very briefly, regarding the obviousness challenges; the obviousness challenges still do exist. The '069 Patent has a publication date on its face. The Board is entitled to rely on the publication date for determining whether it is 102(a)(2) art. It says it was published. The Patent Owner says, Oh, there could be differences, different claims. It's a continuation application, the claims had to be supported by the original specification. So the scope of the disclosures is the same.

In addition, the 817 reference, which is the basis for Grounds 2 and 4, now this reference has very similar disclosures to the '069 Patent. They claim the same -- priority to the same provisional application. In the original PCT -- oh, I'm sorry -- in the original petition, we identified where in the provisional application the corresponding disclosures could be found for '817 patent because it has the same disclosures as the '069 Patent. So that made it seem to make sense. I understand that the Board didn't like that approach and didn't want to have to go looking through the '817 patent for the specific correlation. That correlation was divided in the reply brief. So that is before the Board.

The 817 reference, there's no dispute that that can qualify as an obviousness reference for the purposes of the analysis under 102(a)(2), so that the -- obviates any problem with

regard to that issue.

And it looks like I'm over, so with that, I will thank you, unless you have any other questions.

JUDGE MITCHELL: Okay. Thank you.

MR. ROSATO: A few brief comments.

So on Slide 7, I'm not going to bring up the demonstratives again here, but I'll note it for the record. On Slide 7, we point to content of record that talks about this notion that the parameters, the specific parameters of a formulation process are important because they affect the physical properties of the resulting particles. So if you change process parameters, that changes the physical properties of the resulting particles. And that there are a wide range of parameters that can be varied in a process used to formulate particles.

We also pointed to Dr. Janoff's deposition testimony or during cross-examination, where he identified three specific parameters that would affect the output or the outcome such that, as he described, you might not get the claimed particles.

I point that out again because I think I understood counsel to state several times that the '069 Patent is silent on the parameters used in their formulation processes. So putting two and two together there, it sounds like we're talking about probabilities and possibilities.

Second, there's a -- Judge Smith had posed a

question to me, and I identified the Lipobot syringe press as one of the things I could think of that wasn't found in the '069 Patent. The response that I heard was that is in the prior art there's no documentation or any evidence to -- in this record to support that, but it's in the prior art.

I don't know how to respond to those types of arguments. I haven't seen any prior art to substantiate that. We can't make assertions that -- or hearing about what is or is not known at the time, and we can't dismiss those types of things by merely returning argument.

And, finally, there was an argument or an assertion that Dr. Thompson admitted that particles with a high encapsulation percentage would be understood to be non-lamellar particles. That actually was a position taken by Dr. Janoff in his declaration. Dr. Thompson addressed that in his declaration, Exhibit 2009, Paragraphs 67 and 68, and explained why that actually makes no sense.

With that, I will thank the Panel for the time and the extra time in particular. Thank you.

JUDGE MITCHELL: Thank you, all. The arguments were very helpful and thank you for your patience with our snafu with the equipment.

And so with that, IPR 2018-00680 is submitted. Thank you so much and we are adjourned.

(Proceedings concluded at 5:19 p.m.)

IPR2018-00680 (Patent 9,404,127)
IPR2018-00739 (Patent 9,364,435)

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JOINT APPENDIX 70

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Moderna Therapeutics, Inc.

Petitioner

v.

Protiva Biotherapeutics, Inc.

Patent Owner

U.S. Patent No. 9,364,435

Issued: June 14, 2016

Named Inventor: Edward Yaworski, Kieu Lam, Lorne Palmer, Ian MacLachlan

Title: Lipid Formulations for Nucleic Acid Delivery

DECLARATION OF ANDREW S. JANOFF, PH.D. IN SUPPORT OF MODERNA THERAPEUTICS, INC.'S PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,364,435

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Alexandria, VA 22313-1450

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I, Dr. Andrew S. Janoff, PhD, declare as follows:

I. INTRODUCTION

1. My name is Andrew S. Janoff. I am a consultant in biotechnology and drug delivery, primarily focusing on lipid and liposome technology.

2. I have been engaged by Moderna Therapeutics, Inc. ("Moderna") as an expert in connection with matters raised in the Petition for *Inter Partes* Review ("Petition") of U.S. Patent No. 9,364,435 (the "'435 patent") owned by Protiva Biotherapeutics, Inc. ("Patent Owner").

3. This declaration is based on the information currently available to me. To the extent that additional information becomes available, I reserve the right to continue my investigation and study, which may include a review of documents and information that may be produced, as well as testimony from depositions that have not yet been taken.

II. SUMMARY OF OPINIONS

4. The '435 patent is entitled "Lipid Formulations for Nucleic Acid Delivery." Ex. 1001. The '435 patent is directed to a composition of nucleic acid-lipid particles (*e.g.*, particles that can be used to deliver therapeutic nucleic acid payloads to a patient) comprising three lipid components (*i.e.*, cationic lipid, non-cationic lipid and conjugated lipid), each of which fall within a claimed proportion with regard to the total lipid in the particles. *See, e.g.*, *id.*, cl. 1. The Petition challenges claims 1-20 of the '435 patent.

5. Petitioner's Ground 1 challenges claims 1-20 of the '435 patent as obvious under 35 U.S.C. § 103 in view of Patent Owner's prior disclosures in PCT/CA2004/001051, Publication No. WO2005007196 A2 ("'196 PCT"), Ex. 1002, or U.S. Publication No. US2006/0134189 ("'189 publication"), Ex. 1003. Based on studying the petition and the exhibits cited in the petition as well as other documents, it is my opinion that claims 1-20 of the '435 patent are obvious in view of the '196 PCT or '189 publication.

6. Petitioner's Ground 2 challenges claims 1-20 of the '435 patent as obvious in view of the Patent Owner's prior disclosures in light of Lin (Ex. 1005) and/or Ahmad (Ex. 1006) under 35 U.S.C. § 103. Based on studying the petition and the exhibits cited in the Petition as well as other documents, it is my opinion that claims 1-20 of the '435 patent are obvious in view of the Patent Owner's prior disclosures in light of Lin and/or Ahmad.

7. Petitioner's Ground 3 challenges claims 1-20 of the '435 patent as anticipated by the disclosures in U.S. Publication No. US2006/0240554 ("'554 publication"), Ex. 1004, under pre-AIA 35 U.S.C. § 102(b) or, in the alternative, as obvious under 35 U.S.C. § 103 in view of the '554 publication. Based on studying the petition and the exhibits cited in the petition as well as other documents, it is my opinion that claims 1-20 of the '435 patent are anticipated by the '554 publication. In the alternative, it is my opinion that claims 1-20 of the '435 patent are obvious in view of the '554 publication.

III. QUALIFICATION AND EXPERIENCE

8. I am formally trained as a membrane biophysicist. I obtained my Ph.D. degree in Biophysics from Michigan State University in 1980. Before that, I received my MS in Biophysics from Michigan State University in 1977, and my BS in Biology from The American University in 1971. I received postdoctoral training in Pharmacology at the Harvard Medical School and in Anesthesia at the Massachusetts General Hospital.

9. I have played leadership roles in the discipline of pharmaceutical liposomology from its inception in 1981.

10. After my post-doctoral work, I was recruited from Harvard by the industrialist, Jack Whitehead, and became the first senior founding scientist at the Liposome Company, Inc. I eventually became the Vice President of Research and Development at the Liposome Company. I led the team at the Liposome Company that discovered, formulated, and developed ABELCET, a novel lipid structure that is approved worldwide for systemic fungal infections. I first published the physical chemical characterization of this structure, along with an explanation of why it would yield a less toxic alternative to the traditional micelle formulation in the *Proceedings of the National Academy of Sciences*.

11. I led the team at the Liposome Company that developed Staclot LA, a diagnostic reagent comprised of Hexagonal (II) lipid that is a standard

practice for diagnosing lupus anticoagulant. The work leading to this product was also published in the *Proceedings of the National Academy of Sciences*.

12. In addition I lead teams at the Liposome Company that formulated and characterized Myocet (Liposomal Doxorubicn Injection). This product is currently approved in Canada and the European Union and is used to treat metastatic breast cancer.

13. From 2001-2002, I was Chairman, and from 2002-2005, I was Chairman and CEO, of Celator Technologies, Inc. I was involved in the creation of Celator's intellectual property platform and built the company from a Canadian start up into an international pharmaceutical corporation with research, manufacturing, clinical development, regulatory, commercial, and legal functions. From 2005-2008, I was Chairman and CEO of its successor, Celator Pharmaceuticals, Inc., a company using controlled-release liposomes to deliver combinations of chemotherapeutic agents to tumors. Celator's drug Vxyeos was recently approved by the FDA for the treatment of leukemia.

14. From 2009-2011, I was CEO of TranslationUP, which was a consortium of authorities from academic research, drug development, policy, finance, public relations, and law seeking to create a new model to more effectively advance government funded late-stage discovery concepts into clinical development.

15. In my career, I have overseen the filing of eight INDs, two NDAs and one MAA in the areas of oncology, antiinfectives, and acute respiratory distress syndrome, all involving liposome or lipid-delivery systems.

16. I have worked and published in the area of pulmonary surfactants involving treatment modalities in which lamellar lipid for instilling into neonate lungs was constructed to rearrange into the Hexagonal II architecture at body temperature. An article that I published on this topic in *Science* was reviewed and highlighted in *Lancet*, a leading British Medical Journal.

17. I have lectured and have conducted Grand Rounds in the areas of liposomes, lipid physical chemistry and drug delivery at many prestigious medical centers in the United States and Canada, and have been invited to speak on these topics at major industry, financial, scientific and medical symposia worldwide.

18. I have also served on various government advisory committees. For example, I taught at the NATO Advanced Study Institute in Cape Sunion, Greece, participated in FDA symposia regarding the quality and performance of controlled release parenterals, served on the Committee of Science and the Arts at the Franklin Institute in Philadelphia, and was a founding member on the Scientific Advisory Board at Rider University. I have also advised the Centre for Drug Research and Development in Vancouver, Canada on liposomal delivery systems.

19. I have served as an Adjunct Professor in the Department of Pathology, Anatomy and Cell Biology at Thomas Jefferson University Medical School. I have also been a visiting Research Scholar at Princeton University and have held appointments in the Departments of Physics, Molecular Biology, and Chemical Engineering.

20. I am the Editor-in-Chief Emeritus of the *Journal of Liposome Research*. I served on the editorial board of this Journal from 1994-1997, and was the Editor-in-Chief from 1997-2008.

21. I am an editor of *Liposomes: Rational Design* (Marcel Dekker, New York, 1999), a volume of expert reviews in the field of liposomology.

22. I hold over 75 U.S. patents in lipid nanotechnology and drug delivery, and I have authored more than 90 scientific articles and reviews principally related to nanotechnology, lipid supramolecular structure, liposomes, and drug delivery including fusogenic liposomes and triggerable lipid assemblies.

23. My *curriculum vitae* is attached as Exhibit 1018.

24. I am being compensated by Moderna for my time spent in developing this declaration at a rate of $750 per hour, and for any time spent testifying in connection with this declaration at a rate of $750 per hour. My compensation is not contingent upon the substance of my opinion, the content

of this declaration or any testimony I may provide, or the outcome of the *inter partes* review or any other proceeding.

25. I have no financial interest in Moderna.

26. My opinion expressed in this declaration are based on the Petition and exhibits cited in the Petition, and other documents and materials identified in this declaration, including the '435 patent (Ex. 1001) and its prosecution history (Ex. 1016), the prior art references and materials discussed in this declaration, and any other references specifically identified in this declaration.

27. I am aware of information generally available to, and relied upon by, persons of ordinary skill in the art at the relevant times, including technical dictionaries and technical reference materials (including, for example, textbooks, manuals, technical papers, articles, and relevant technical standards).

28. I reserve the right to supplement my opinions to address any information obtained, or positions taken, based on any new information that comes to light throughout this proceeding.

IV. LEVEL OF ORDINARY SKILL IN THE ART

29. It is my understanding that the '435 patent should be interpreted based on how it would be read by a person of ordinary skill in the art at the time of the effective filing date of the application. It is my understanding that factors such as the education level of those working in the field, the

sophistication of the technology, the type of problems encountered in the art, the prior art solutions to those problems, and the speed at which innovations are made may help establish the level of skill in the art.

30. I am familiar with the technology at issue and the state of the art at the earliest priority date of the '435 patent.

31. It is my opinion, based upon a review of the '435 patent, its file history, and my knowledge of the field of the art, a person of ordinary skill in the art ("POSITA") for the field of the '435 patent would have specific experience with lipid particle formation and use in the context of delivering therapeutic payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience. This level of skill is representative of the inventors on the '435 patent and authors/inventors of prior art cited herein. *See* Exs. 1001-1006.

32. I have considered the issues discussed in the remainder of this declaration from the perspective of a person of ordinary skill in the art. Although I used this perspective, I do not believe that any of my opinions would change if a slightly higher or lower level of skill were adopted.

V. LEGAL PRINCIPLES

A. Claim Construction

33. I am not a patent attorney and my opinions are limited to what I believe a person of ordinary skill in the art would have understood, based on the patent documents. I use the principles below, however, as a guide in formulating my opinions.

34. My understanding is that a primary step in determining validity of patent claims is to properly construe the claims to determine claim scope and meaning.

35. In an *inter partes* review proceeding, as I understand from Moderna counsel, claims are to be given their broadest reasonable interpretation ("BRI") in light of the patent's specification. 37 C.F.R. § 42.100(b). In other forums, such as in federal courts, different standards of proof and claim interpretation are operative, which are not applied by the patent office for *inter partes* review. Accordingly, I reserve the right to argue for a different interpretation or construction of the challenged claims in other proceedings, as appropriate.

36. It is my understanding that in determining whether a patent claim is anticipated or obvious in view of the prior art, the patent office must construe the claim by giving the claim its broadest reasonable construction with the specification. For the purposes of this review, I have construed each claim term in accordance with its plain and ordinary meaning under the required broadest reasonable construction.

B. Prior Art

37. I understand that a patent or other publication must first qualify as prior art before it can be used to invalidate a patent claim. I understand that a U.S. or foreign patent qualifies as prior art to an asserted patent if the date of issuance of the patent is prior to the invention of the asserted patent. I further understand that a printed publication, such as an article published in a magazine or trade publication, qualifies as prior art to an asserted patent if the date of publication is prior to the invention of the asserted patent.

38. I understand that a U.S. or foreign patent also qualifies as prior art to an asserted patent if the date of issuance of the patent is more than one year before the filing date of the asserted patent. I further understand that a printed publication, such as an article published in a magazine or trade publication, constitutes prior art to an asserted patent if the publication occurs more than one year before the filing date of the asserted patent.

39. I understand that a U.S. patent qualifies as prior art to the asserted patent if the application for that patent was filed in the United Stated before the invention of the asserted patent.

40. I understand that documents and materials that qualify as prior art can be used to invalidate a patent claim via anticipation or obviousness.

C. Anticipation

41. I understand that, once the claims of a patent have been properly construed, the second step in determining anticipation of a patent claim requires a comparison of the properly construed claim language to the prior art on a limitation-by-limitation basis.

42. I understand that a prior art reference "anticipates" an asserted claim, and thus renders the claim invalid, if all elements of the claim are disclosed in that prior art reference, either explicitly or inherently (*i.e.*, necessarily present).

43. I understand that anticipation in an *inter partes* review must be shown by a preponderance of the evidence.

D. Obviousness

44. I understand that even if a patent is not anticipated, it is still invalid if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the pertinent art.

45. I understand that a person of ordinary skill in the art at the time the invention was made provides a reference point from which the prior art and claimed invention should be viewed. This reference point prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

46. I also understand that an obviousness determination includes the consideration of various factors such as (1) the scope and content of the prior art, (2) the differences between the prior art and the asserted claims, (3) the level of ordinary skill in the pertinent art, and (4) the existence of secondary considerations such as commercial success, long-felt but unresolved needs, failure of others, etc.

47. I understand that an obviousness evaluation can be based on a combination of multiple prior art references. I understand that the prior art references themselves may provide a suggestion, motivation, or reason to combine, but other times the nexus linking two or more prior art references is simple common sense. I further understand that obviousness analysis recognizes that market demand, rather than scientific literature, often drives innovation, and that a motivation to combine references may be supplied by the direction of the marketplace.

48. I understand that if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

49. I also understand that practical and common sense considerations should guide a proper obviousness analysis, because familiar items may have obvious uses beyond their primary purposes. I further understand that a person

of ordinary skill in the art looking to overcome a problem will often be able to fit together the teachings of multiple publications. I understand that obviousness analysis therefore takes into account the inferences and creative steps that a person of ordinary skill in the art would employ under the circumstances.

50. I understand that a particular combination may be proven obvious merely by showing that it was obvious to try the combination. For example, when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. The result is likely the product not of innovation but of ordinary skill in the art and common sense.

51. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill in the art can implement a predictable variation, the patent claim is likely obvious.

52. It is further my understanding that a proper obviousness analysis focuses on what was known or obvious to a person of ordinary skill in the art, not just the patentee. Accordingly, I understand that any need or problem

addressed by the patent that was known in the field of endeavor at the time of invention can provide a reason for combining the elements in the manner claimed.

53. I understand that a claim can be obvious in light of a single reference, without the need to combine references, if the elements of the claim that are not found explicitly or inherently in the reference can be supplied by the common sense of one of skill in the art.

54. I understand that the disclosure of overlapping ranges in the prior art establishes a *prima facie* case of obviousness under 35 U.S.C § 103, but that a petitioner still has the burden of demonstrating invalidity by the preponderance of the evidence.

55. I understand that secondary indicia of non-obviousness may include (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success of processes covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) taking of licenses under the patent by others; (6) deliberate copying of the invention; (7) failure of others to find a solution to the long felt need; and (8) skepticism by experts.

56. I also understand that there must be a relationship between any such secondary considerations and the invention. I further understand that

contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

57. I understand that unexpected results can support a non-obviousness determination but must show unexpected results for the entire claimed range. This can be done by demonstrating that an embodiment has an unexpected result and providing an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner.

58. In sum, my understanding is that prior art teachings are properly combined where a person of ordinary skill in the art having the understanding and knowledge reflected in the prior art and motivated by the general problem facing the inventor, would have been led to make the combination of elements recited in the claims. Under this analysis, the prior art references themselves, or any need or problem known in the field of endeavor at the time of the invention, can provide a reason for combining the elements of multiple prior art references in the claimed manner.

59. I understand that obviousness in an *inter partes* review must be shown by a preponderance of the evidence.

VI. BACKGROUND

A. Lipid carrier particles for nucleic acid payloads

60. Gene therapy—addressing disease at the level of the genetic cause, typically with nucleic acids—is an area of intensive medical research. Therapeutic nucleic acids can be used for both gene delivery (*e.g.*, mRNA) and gene silencing (*e.g.*, small interfering RNA ("siRNA")). *See* Ex. 1008 (Gao), E92; Ex. 1005 (Lin), 3307. Long before the '435 patent, it was known that systems comprised of combinations of different types of lipids with nucleic acids could result in lipid-nucleic acid particles, an accepted delivery strategy for nucleic acid therapeutics. *See* Ex. 1008 (Gao), E95.

61. The '435 patent refers to such nucleic acid-lipid carrier particles as "stable nucleic acid-lipid particles" or "SNALPs." Ex. 1001, 5:62-6:2. The '435 patent discloses three lipid components: a "cationic lipid," a "non-cationic lipid," and a "conjugated lipid." *Id.*, cl. 1 (components). These lipid components were known to be basic building blocks of nucleic acid-lipid particles long before the '435 patent. *See* Ex. 1006 (Ahmad), 740, 746 ("[cationic lipids] for transfection typically consist of a mixture of cationic and neutral (helper) lipid" and "strategies for optimization … could involve introducing PEG-lipids … to block … unspecific interactions"); Ex. 1008 (Gao), E95 (cationic lipid carrier particles "are often formulated with a noncharged phospholipid or cholesterol as a helper lipid … PEG-lipid

conjugates have been incorporated … to minimize interaction with blood components ….").

62. Cationic lipids have been used in the construction of nucleic acid-lipid particles because they interact with the negative charges on nucleic acid payloads facilitating the formation of such particles. *See* Ex. 1008 (Gao), E95. Effective delivery of the nucleic acid (called the "transfection efficiency") is thought to require fusion between the particle [lipoplex] and a cell membrane. *See* Ex. 1009 (Bennett), 48; Ex. 1008 (Gao), E95. Since cationic lipids can also interact with negative charges on cell membranes, this has been believed to promote, in some cases, the fusion event necessary for the effective delivery of the nucleic acid. *See* Ex. 1006 (Ahmad), 745 ("[A]n overall positive [cationic lipid]-DNA charge is required to promote initial electrostatic interactions with cell membranes.").

63. Moreover, it was known that non-cationic "helper" lipids, *e.g.*, certain phospholipids and/or cholesterols, could be combined with the cationic lipid to influence the ability of the particles to transfect cells. *See* Ex. 1008 (Gao), E95 (cationic lipids "are often formulated with a noncharged phospholipid or cholesterol as a helper lipid to form liposomes"); Ex. 1009 (Bennett), 47 (helper lipids used).

64. A "conjugated lipid" (*e.g.*, a PEG-lipid) can be added to increase *in vivo* circulation time by providing a neutral, hydrophilic coating to the

particle's exterior. *See* Ex. 1008 (Gao), E97 ("PEG-lipid conjugates have been incorporated into the lipoplexes to minimize the nonspecific interaction of lipoplexes with blood components."); Ex. 1010 (Heyes), 277 ("PEG-lipids both stabilize the particle during the formulation process and shield the cationic bi-layer, preventing rapid systemic clearance.").

65. "The structure of lipoplexes [was known to be] influenced by multiple factors, including the charge ratio, the concentration of individual lipids and DNA, the structure of the cationic lipid and the helper lipid, [and] the physical aggregation state of the lipids ([*e.g.*,] multilamellar or unilamellar liposomes, or micelles) …." Ex. 1008 (Gao), E95. Transfection efficacy is complex because "[a] large number of parameters [are] involved." Ex. 1006 (Ahmad), 740. Different transfection mechanisms "may be facilitated by alterations in liposome formulation…." Ex. 1009 (Bennet), 48.

66. The claims of the '435 patent are not limited to a specific combination of lipids and encompass broad ranges of lipids that have dramatically varying structures likely resulting in drastically different activities. Effective proportions of lipid components for one set of lipid species may not be effective for an alternative lipid species.

67. For example, it was well-established at the time of the '435 patent that "[t]he chemical structure of the cationic lipid ha[d] a major impact on the transfection efficiency." Ex. 1008 (Gao), E95. Indeed references incorporated

into the ’435 patent acknowledge that “alternative cationic lipids” to the one tested would have “different [transfection] efficiencies.” *See* Ex. 1011 (’613 patent), 1:26-28 (“[A]lternative cationic lipids … work in essentially the same manner but with different efficiencies.”).

68. Cationic lipid variables impacting transfection efficiency included “the chemical structure of the cationic lipid [and] … the charge ratio between the cationic lipid and the DNA ….” Ex. 1008 (Gao), E95. These variables could impact the proportion of cationic lipid that is most effective for a given lipid component combination.

69. Hundreds of cationic lipids, both univalent and multivalent, were known at the time of the ’435 patent, some with differing charges. *Id.*, E95 (“[H]undreds of new cationic lipids have been developed … [that] differ by the number of charges in their hydrophilic head group and by the detailed structure of their hydrophobic moiety.”). Thus the charge density on the surface of a nucleic acid-lipid particle, at a fixed cationic lipid proportion, can be modulated by introducing cationic lipids of different valancies (*i.e.*, using cationic lipids with different charges). This would have been expected to impact the ability of the particle to promote fusion events with target cell membranes. *See* Ex. 1006 (Ahmad), 740. Both Ahmad and Lin identified charge density as an important determinate of transfection efficacy in the systems studied. *Id.*, 744; Ex. 1005 (Lin), 3312.

70. It was also well-known at the time of the '435 patent that certain lipid component combinations favor having a 50% or greater proportion of cationic lipid. First, early researchers often chose a 50% proportion of cationic lipid as a default in evaluating particle transfection efficiency. *See, e.g.*, Ex. 1009 (Bennett), 49 (50% cationic lipid); Ex. 1012 (U.S. Patent 7,939,505) ("'505 patent"), 44:61-65 (cationic lipid of "about 0.5% to about 70% (mol %) of the total amount of lipid"), 96:40-67 (Example 32 and Table 12) (formulations with 50% cationic lipid), 99:34-101:45 (Examples 34-35 and Tables 15-18) (same). Second, Researchers determined that, in some cases, increasing the cationic lipid proportion above 50% increased transfection efficiency. Ex. 1006 (Ahmad), 744; Ex. 1005 (Lin), 3312.

71. At the time of the '435 patent the number of species of non-cationic lipids that could be employed was large, and differences among such lipids had been reported to impact the structure and perhaps the function of the resulting nucleic acid-lipid particles. Ex. 1008 (Gao), E95 (transfection efficiency varies with "the structure and proportion of the helper lipid in the complexes"). For instance, in the blood, the non-cationic lipid cholesterol seemed to stabilize certain formulations, "while formulations containing DOPE [another non-cationic lipid] tend[ed] to fall apart more easily." *Id.*, E96. In addition, variations in the proportions of non-cationic lipids in certain

formulations have been reported to impact their ability to deliver nucleic acid payloads. Ex. 1009 (Bennett), 51.

72. The selection of conjugated lipid was also known to potentially impact the particle's chemistry and efficacy. Ex. 1002 ('196 PCT), [0094] ("By controlling the composition and concentration of the bilayer stabilizing component, one can control … the rate at which the liposome becomes fusogenic.").

73. A POSITA at the time of the '435 patent would have known that varying specific lipid species as well as the lipid proportions could change the performance of the nucleic acid-lipid particle. The range of lipids falling under the scope of the claims of the '435 patent is immense and a POSITA would have had no way of knowing if lipid combination at any given proportion would have resulted in formulations of superior therapeutic index to other formulations. *See* Ex. 1006 (Ahmad), 740 ("[I]n comparative studies, typically only one or two data points per lipid are evaluated, allowing the ideal lipid composition (the ratio of neutral to cationic lipid) or cationic lipid/DNA ratio to be overlooked.").

B. The '435 patent disclosure

74. The '435 patent is premised on an alleged "surprising discovery" that prior art lipid components in certain proportions perform better than expected *in vitro* and *in vivo*. Ex. 1001, 5:55-62 (lipids "comprising from

about 50 mol% to about 85 mol% of a cationic lipid, from about 13 mol% to about 49.5 mol% of a non-cationic lipid, and from about 0.5 mol% to about 2 mol% of a lipid conjugate provide advantages ….”). According to the ’435 patent, using the claimed lipid proportions result in “increased activity of the encapsulated nucleic acid … and improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index ….” *Id.*, 5:62-6:2.

75. The ’435 patent acknowledges that the following was known to a POSITA before its priority date:

- Nucleic acid-lipid particles comprising a nucleic acid, cationic lipid, non-cationic lipid, and a conjugated lipid that inhibits aggregation of particles. *See id.*, 11:34-36 (“SNALP and SPLP typically contain a cationic lipid, a non-cationic lipid, and a lipid conjugate (*e.g.*, a PEG-lipid conjugate).”).
- Preparation of such nucleic acid-lipid particles. *See id.*, 11:54-58 (“Nucleic acid-lipid particles and their method of preparation are disclosed in, e.g., U.S. Patent Publication Nos. 20040142025 and 20070042031, the disclosures of which are herein incorporated by reference in their entirety for all purposes.”).
- In addition, the prior art cited in the ’435 patent discloses nucleic

> acid-lipid particles with the listed component lipids having overlapping ranges: a cationic lipid range of "about 2% to about 70%," a non-cationic lipid range of "about 5% to about 90%," a cholesterol range of "about 20% to about 55%," and a PEG-lipid conjugate range of "about 0.5% to about 20%." *See, e.g.*, Ex. 1013 ('031 publication), [0033].

Thus, nucleic acid-lipid particles with (1) the claimed nucleic acid payload and (2) the same lipid components in overlapping ranges were admittedly known in the art. The sole basis for alleged novelty of the '435 patent claims is that a nucleic acid-lipid particle comprising component lipids in the claimed proportions achieves unexpected efficacy making the claims patentably distinct from the prior art.

76. During the prosecution of the application leading to the parent of the '435 patent, the examiner cited Patent Owner's earlier, unrelated US2006/0008910 publication ("'910 publication") (Ex. 1014) as prior art disclosing nucleic acid-lipid particles with the claimed components and overlapping ranges of those components. *See, e.g.*, Ex. 1015 ('069 patent file history excerpts), 7/30/2010 Rejection at 3–5. The Patent Owner put forth the following chart illustrating the overlapping ranges from the '069 patent:

Lipid Component	Claim 1 as Amended	US 2006/0008910*
Cationic Lipid	50-65 mol %	"2-60, 5-50, 10-45, 20-40, 30 mol%"
Phospholipid	4-10 mol %	"5-90 mol%"
Cholesterol	30-40 mol %	"20-55 mol %"
Conjugated Lipid	0.5-2 mol %	"1-20 mol %"

Id., 8/11/2011 Amendment at 7–9. In the '435 patent, the identified lipid components are the same, but the phospholipid and/or cholesterol are referred to as a single "non-cationic lipid" component. *See* Ex. 1001, claim 1. The ranges for the '435 patent vary slightly from those found in the '069 patent, but similarly overlap with the disclosures in the cited '910 publication. *Id.*

77. In response to the rejection, the Patent Owner argued that the specific claimed ranges in the '069 patent lead to "***new and unexpected results***" and cited to test results regarding the "1:57 SNALP" in the specification. Ex. 1015, 1/31/2011 Amendment at 11. Patent Owner argued that "[a]pplicants have found that SNALP formulations having increased amounts of cationic lipid, *e.g.*, one or more cationic lipids comprising from about 50 mol% to about 65 mol% of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent …." *Id.* Patent Owner relied on Examples 3-4 from the specification arguing that these examples demonstrated that the 1:57 SNALP formulation was "more efficacious as compared to a nucleic acid-lipid

particle previously described ('2:30 SNALP') … [and] more effective at silencing the expression of a target gene as compared to nucleic acid-lipid particles previously described ('2:40 SNALP')." *Id.*

78. Patent Owner further argued that the "claimed narrower ranges are not disclosed with 'sufficient specificity' [in the '910 publication] to constitute an anticipation …." *Id.*, 8/11/2011 Amendment at 7–9. Thereafter, the examiner allowed the claims.

79. The claims of the '435 patent are substantially similar to the claims in the '069 patent and were allowed subject only to a non-statutory double patenting rejection vis-à-vis the '069 patent claims. Ex. 1016 ('435 patent file history) (1/27/16 terminal disclaimer). Based upon the intrinsic record, it is clear that the examiner allowed the claims of the '435 patent based upon the Patent Owner's prior arguments regarding unexpected results resulting from increasing the cationic lipid percentage to above 50%.

80. The '435 patent includes *in vitro* (Example 2) and *in vivo* (Examples 3-4) testing of various nucleic acid-lipid formulations and comparison of those formulations to the admitted prior art (*i.e.*, the 2:30 and 2:40 formulations). Ex. 1001, 69:6-74:4.

81. Example 2 is the *in vitro* test in the '435 patent. *Id.*, 69:6-70:52. It involved a siRNA payload targeting the Eg5 gene with various lipid components in various proportions. *Id.*, Table 2. Of the tested lipid

formulations, only Sample 9 (a 1:57 SNALP) and Sample 10 fall within the lipid ranges in claim 1 of the '435 patent. *Id.*, claim 1. Other than the proportions in Samples 9 and 10, the '435 patent did not test any combinations of lipid components covered by the claims for comparison to the admitted prior art.

82. Samples 1 and 16 in Table 2 reflect the 2:40 SNALP that is admitted prior art. *Id.*, Table 2. Sample 12 is similar to the 2:40 formulation, but with slight variations in the lipid proportions. As can be seen from Figures (1)(a)-1(b), Sample 10 (a claimed formulation) appears to have performed worse than each of Sample 16 (admitted prior art 2:40 SNALP), Sample 12 (a 2:40 type SNALP with 40.4% cationic lipid), and Sample 9 (1:57 SNALP), (2) Sample 9 (1:57 SNALP) appears to be no more effective at gene silencing than Sample 12 (a 2:40 type SNALP with 40.4% cationic lipid), which it overlaps at every data point, and (3) Sample 9 (1:57 SNALP) appears to outperform Sample 16 (2:40 SNALP) only at extremely low total siRNA amounts. The takeaway is that there is no clear advantage of using the claimed formulations, nor is there data that the entire claimed range of nucleic acid-lipid particles is superior to particles with less than 50% cationic lipid.

83. Example 3 involved testing the silencing activity of an siRNA payload targeting the Apo B gene with various lipid components in various proportions. *Id.*, 70:54-72:59; Table 4. Of the tested lipid combinations, only

Sample 11 (1:57 SNALP) and Samples 13-14 fall within the lipid ranges claimed in the '435 patent. Samples 2, 4-5 and 7 reflect the 2:40 SNALP proportions (Samples 4-5 employ different species of lipids from Sample 2 and 7).

84. As can be seen from Figure 2, the 1:57 SNALP (Group 11) is likely not statistically significantly more efficacious than Group 12, which is comprised of only 40.4% cationic lipid (*see* Table 4). On the other hand, Group 12 appears to be more efficacious than Groups 2 and 7 (both examples of the admitted prior art 2:40 SNALP formulation) even though it varies only slightly from this formulation, comprising of 1 mol% rather than 2 mol% PEG-2000-C-DMA. Group 14 (also in the claimed range) appears to have performed worse than Group 7, and perhaps Group 2 as well.

85. Example 4 compares the silencing activity of the 1:57 SNALP formulation with the 2:30 SNALP formulation. Both SNALPs were formulated with a siRNA payload targeting the Apo B gene. *Id.*, 72:60-74:4; Table 5. Of note, the phospholipid used in formulating the 2:30 SNALP (DSPC) was a different phospholipid than was used in formulating the 1:57 SNALP (DPPC). *Id.*, 73:18-49. A POSITA would have been aware that varying the phospholipid species could impact transfection efficacy separate and apart from varying the lipid component proportions. In addition, the dosing and lipid to drug ratios were different regarding the two formulations. *Id.*, 73:50-67. The results of

testing are shown in Figure 3. At most, this testing established that the 1:57 SNALP comprised of the specific species of lipid components and nucleic acid to lipid ratio disclosed, dosed as disclosed, outperformed the 2:30 SNALP comprised of the lipid species disclosed and dosed as disclosed.

86. Several other examples in the '435 patent illustrate that transfection efficiency may be influenced by varying just the species of lipid components used. For instance, comparing Groups 2 & 6 to Group 4 in Example 5, in which DLinDMA was replaced with DODMA without changing the ratios of the components used (*see id.*, Table 6), it can be seen that Group 4 apparently exhibited inferior results. Example 5 also shows by comparing Groups 2 & 6 (PEG(2000)-c-DMA to Group 5 (PEG(5000)-c-DMA), that variation of the conjugated lipid apparently impacts efficacy. In this Example, Group 5 appears inferior.

C. Claim construction

87. Claim 1 of the '435 patent contains the limitation "Nucleic acid-lipid particle." Under the BRI standard, a POSITA would understand the term "nucleic acid-lipid particle" to mean "a composition of lipids and a nucleic acid for delivering a nucleic acid to a target site of interest." *See id.*, 11:14-17.

88. Claim 1 of the '435 patent contains the limitation "Cationic Lipid." Under the BRI standard, a POSITA would understand the term "cationic lipid" to mean "any of a number of lipid species that carry a net

positive charge at a selected pH, such as physiological pH (e.g., pH of about 7.0)." *See id.*, 12:59-61.

D. Prior art

89. The '435 patent family is but one of many patent families with substantially overlapping disclosures. Because these unrelated patent families, with differing inventors, do not claim priority to one another, the earlier disclosures are prior art to the '435 patent. Ex. 1002 ('196 PCT cited herein); Ex. 1003 ('189 publication); Ex. 1014 ('910 publication relied on by examiner during prosecution of the parent '069 patent).

90. Patent Owner filed the provisional applications leading to the unrelated '196 PCT in 2003—five years before the priority date of the '435 patent. Ex. 1002. The '196 PCT inventors are Ian MacLachlan, Ellen Ambegia, and James Heyes, a different inventive entity from the '435 patent inventive entity. *Id.* The '196 PCT was published on Jan. 27, 2005. *Id.* Also, the '196 PCT and the '435 patent do not claim priority to one another. *See* Exs. 1001, 1002. The '196 PCT is therefore prior art to the '435 patent under 35 U.S.C. § 102(b) (pre-AIA).

91. The '196 PCT is titled "Lipid Encapsulated Interfering RNA" and discloses "a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." Ex. 1002, [0002]. The disclosed SNALPs comprise "a cationic lipid, a non-

cationic lipid, a conjugated lipid that inhibits aggregation of particles and a siRNA." *Id.*, [0011]. The non-cationic lipids may include a phospholipid, cholesterol, and a PEG-conjugated lipid. *Id.*, [0089].

92. The '196 PCT discloses not only the same lipid components as claimed in the '435 patent, but also overlapping ranges of those components. According to the '196 PCT, "[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle … [i]n other preferred embodiments, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle." *Id.*, [0088]. Enough cationic lipid is added to "produce a charge ratio [cationic lipid to nucleic acid] … of about 2:1 to about 6:1." *Id.*, [0126].

93. "The non-cationic lipid typically comprises from about 5% to about 90% of the total lipid present … [and] [t]he nucleic acid-lipid particles … may further comprise cholesterol … from about 20% to about 45% of the total lipid present …." *Id.*, [0091]. "[T]he SNALP further comprises a bilayer stabilizing component (BSC). …. [T]he BSC is a conjugated lipid that inhibits aggregation of the SNALPs … present from about 0.5% to about 25% of the total lipid …." *Id.*, [0092-0093].

94. The '196 PCT specifically discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.*, [0088]. In addition, the '196 PCT

incorporates by reference U.S. Patent No. 5,264,618 (the "'618 patent"). *Id.*, [0087], [0146]. The '618 patent in turn discloses a nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol, as well as various other formulations over 50% cationic lipid. Ex. 1017, 34:54-35:23.

95. Patent Owner filed the provisional applications leading to the '189 publication in 2004-2005—three years before the priority date of the '435 patent. Ex. 1003. The '189 publication inventors are Ian MacLachlan, Lloyd Jeffs, Adam Judge, Amy Lee, Lorne Palmer, and Vandana Sood, a different inventive entity from the '435 patent inventive entity. *Id.* The '189 publication was published on Jun. 22, 2006. *Id.* Also, the '189 publication and the '435 patent do not claim priority to one another. *See* Exs. 1001, 1003. The '189 publication is therefore prior art to the '435 patent under 35 U.S.C. § 102(b) (pre-AIA).

96. The '189 publication discloses SNALPs comprising overlapping ranges of the four lipid components similar to those discussed above for the '196 PCT. Ex. 1003, [0009-0012], [0014], [0148-0181]. In addition, the '189 publication discloses testing relating to the 2:40 formulation that the Patent Owner identified as a prior art formulation. *Id.*, [0350-0391].

97. The '554 publication was published as US 2006/0240554 A1 on October 26, 2006. Ex. 1004, cover page. The '554 publication is therefore prior art to the '435 patent under 35 U.S.C. § 102(b).

98. The '554 publication is titled "Lipid Nanoparticle Based Compositions and Methods for the Delivery of Biologically Active Molecules." Ex. 1004. The '554 publication discloses "novel cationic lipids, transfection agents, microparticles, nanoparticles, and short interfering nucleic acid (siNA) molecules." *Id.*, Abstract. The cationic LNPs disclosed are comprised of, for example, "(a) a cationic lipid …; (b) a neutral lipid; (c) a polyethyleneglycol-diacylglycerol (PEG-DAG) conjugate …; and (d) a short interfering nucleic acid (siNA) molecule …." *Id.*, [0103]. Of note, these are the same components and payload described in the '435 patent.

99. The '554 publication discloses various ranges for the lipid components that overlap or encompass the ranges disclosed in the '435 patent, including the cationic lipid (*e.g.*, about 2% to about 60%), the neutral, non-cationic lipid (about 5% to about 90%), and the PEG conjugate (about 1% to about 20%). The '554 publication also includes various specific formulations, including formulation L054, which contains 50% cationic lipid (DMOBA), 48% non-catioinc lipid (Chol/DSPC), and 2% conjugate lipid (PEG-n-DMG). *Id.*, Table 4. This formulation was tested, for example, with siRNA for reducing HBsAg levels. *See id.* Fig. 16. The disclosed nucleic acid-lipid particles meet all of the limitations in claim 1 of the '435 patent.

100. Lin et al. ("Lin") is a publication titled "Three-Dimensional Imaging of Lipid Gene-Carriers: Membrane Charge Density Controls

Universal Transfection Behavior in Lamellar Cationic Liposome-DNA Complexes." Ex. 1005. It was published in *Biophysical Journal* in May 2003, in Volume 84, at pages 3307–16. *See id.* Lin is therefore prior art to the '435 patent under 35 U.S.C. § 102(b).

101. Lin studied the impact of cationic lipid mole fraction on the transfection efficiency of lipid particles with a DNA payload in *ex vivo* experiments. Ex. 1005, 3307. Using the cationic lipids DOTAP, DMRIE and DOSPA and the helper lipid DOPC, Lin determined that transfection efficiency increased as the cationic lipid mole fraction increased. *Id.*, 3309. In Figure 4(a), Lin shows the transfection efficiency as a function of the mole fraction of neutral lipid (DOPC). *Id.*, Fig. 4. The mole percentage of cationic lipid (*e.g.*, DOTAP, DOSPA, DMRIE) is derived by deducting the mole fraction of neutral lipid from 1 and multiplying by 100.

102. As can be seen from the figure, for each formulation the transfection efficiency increased with the mole percentage of cationic lipid incorporated. Starting at about 35 mole percent, transfection efficiency increased monotonically with increasing mole percentage for DOTAP formulations. For DMRIE formulations, over the same range, there was a steep increase in transfection efficiency from about 45-55 mole percent. For formulations comprised of the multivalent lipid DOSPA, transfection efficiency seemed to be biphasic—it increased monotonically up to about 35

mole percent and then seemed to saturate. A POSITA would understand the testing of Lin to suggest that the mole percentage of cationic lipid in nucleic acid-lipid particles can impact transfection efficiency, and that for certain cationic lipids transfection efficiency might continue to improve at mole percentages above 50 percent. A POSITA would further understand that precisely how the mole percent of cationic lipid might impact transfection efficiency depends on both the cationic lipid species and neutral lipid species chosen.

103. Ahmad et al. ("Ahmad") is a publication titled "New multivalent cationic lipids reveal bell curve for transfection efficiency versus membrane charge density: lipid–DNA complexes for gene delivery." Ex. 1006. It was published in *The Journal of Gene Medicine* on January 31, 2005, in Volume 7, at pages 739–48. *See id.* Ahmad is therefore prior art to the '435 patent under 35 U.S.C. § 102(b).

104. Ahmad studied the impact of membrane charge density on the transfection efficiency of cationic liposome-DNA complexes comprised of cationic and neutral helper lipids. Ex. 1006, 739. Ahmad also contemplated adding cholesterol and PEG-lipids to these lipid complexes. *Id.*, 744 ("[C]holesterol, which leads to lamellar complexes, is increasingly used as a neutral lipid for *in vivo* applications."), 746 ("strategies for optimization … could involve introducing … PEG–lipids … to block the unspecific

electrostatic interactions ….”). Thus all three lipid components from the ’435 patent were disclosed.

105. Ahmad found that a variety of cationic lipids increased the transfection efficiency in the DOPC formulations he studied as shown on Figure 3(a). At equivalent mole fractions, cationic lipids with multiple charges were observed to provide higher transfection efficiencies than a monovalent cationic lipid. *Id.*, 740 (“Numerous lipids with varied chemical and physical properties have been synthesized to improve the transfection efficiencies …. These include multivalent lipids, which have been described as superior to their monovalent counterparts.”). More specifically, Ahmad determined that for the multivalent cationic lipids he studied, a maximum transfection efficiency occurred at around 50 mole percent. Yet for the monovalent lipid DOTAP, transfection efficiency increased monotonically from a cationic lipid percentage of about 35 mole percent to a cationic percentage of about 90 mole percent. *Id.*, 744. Ahmad reported that the optimal transfection efficiency for MLV 5 (a multivalent cationic lipid) was at 55 mole percent when incorporated into DOPC formulations, whereas the maximal TE for DOTAP, incorporated into DOPC formulations was at 90 mole percent. *Id.*, 743. A POSITA would understand the testing of Ahmad to suggest that the mole percentage of cationic lipid in nucleic acid-lipid particles can impact transfection efficiency, and that for certain cationic lipids transfection efficiency might continue to improve at

mole percentages above 50 percent.

VII. THE CHALLENGED CLAIMS ARE INVALID

A. Ground 1: Claims 1-20 are obvious in view of the Patent Owner's Prior Disclosures

106. It is my opinion that claims 1-20 of the '435 patent are obvious under 35 U.S.C. § 103 in view of the Patent Owner's prior disclosures, *e.g.*, the '196 PCT. While the '196 PCT does not disclose the exact same range of lipid components from claim 1 of the '435 patent explicitly, it discloses encompassing and overlapping ranges that establish a *prima facie* case of obviousness and the testing in the '435 patent does not support alleged unexpected results for the claimed ranges.

107. The '189 publication is substantively similar to the '196 PCT and discloses SNALPs comprising overlapping ranges of the lipid components similar to those discussed below for the '196 PCT. Ex. 1003, [0009-0012], [0014], [0148-0181]. In addition, the '189 publication discloses testing relating to the admitted prior art 2:40 formulation. Ex. 1003 [0350-0391].

Claim element 1[a]: A nucleic acid-lipid particle comprising:

108. The '196 PCT teaches "compositions and methods for silencing gene expression by delivering nucleic acid-lipid particles comprising a siRNA molecule to a cell." Ex. 1002, (Abstract). From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim element 1[b]: A nucleic acid

109. The '196 PCT patent teaches "the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." *Id.*, [0002]. siRNA is a nucleic acid. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim element 1[c]: a cationic lipid comprising from 50 mol% to 85 mol% of the total lipid present in the particle

110. The '196 PCT teaches "[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle … [i]n other preferred embodiments, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle." *Id.*, [0088]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.* In addition, the '196 PCT incorporates by reference the '618 patent, which discloses nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol, as well as various other formulations containing over 50% cationic lipid. Ex. 1017, 34:54-35:23. Given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious. In addition, determining the optimal proportion of cationic lipid for a given lipid combination would be a simple matter of varying the proportion using prior art methodologies.

111. The testing in the '435 patent does not support alleged unexpected results for the claimed ranges. In the '435 patent, the only asserted unexpected results occurred vis-à-vis the 2:30 and 2:40 formulations (testing for the 2:40 formulation was disclosed in the '189 publication). The prior art, however, is not so limited. For example, the Patent Owner ignores Group 12 in Figure 2 of the '435 patent that has a cationic lipid percentage of 40.4% and is clearly in the prior art given the admitted 2:40 formulation. Numerous other prior art formulations contain cationic lipid percentages over 50%. *See, e.g.*, Exs. 1005-1006. Patent Owner thus failed to address the entire scope of the prior art in asserting unexpected results.

112. In addition, given the disclosures in the '435 patent, a POSITA would not expect all alternative data points falling within the recited numeric range to perform like the 1:57 SNALP. The *in vivo* testing in Example 3 shows that even minor variations in lipid percentages together perhaps with variations in drug/lipid ratios appeared to impact efficacy. Sample 2 and Sample 12 from Table 4 contain the exact same lipid species in the respective ratios 2/40/10/48 and 1/40.4/10.1/48.5. The drug/lipid ratios were 12.4 and 23.6 respectively. Ex. 1001, Table 4. According to Figure 2, these slight variations in lipid proportions and changes in drug/lipid ratio led to apparently different transfection efficiencies. *Id.*, Fig. 2. A POSITA would expect that similar minor variations in lipid proportions and drug/lipid ratios within the claimed

range might lead to similar variations in transfection efficiency. Yet, the range of lipids falling under the scope of the claims of the '435 patent is immense and a POSITA would have had no way of knowing if any subset of lipids at any given proportion would have resulted in a formulation or formulations of superior therapeutic index. *See* Ex. 1006 (Ahmad), 740 ("[I]n comparative studies, typically only one or two data points per lipid are evaluated, allowing the ideal lipid composition (the ratio of neutral to cationic lipid) or cationic lipid/DNA ratio to be overlooked."). In addition, the 1:57 SNALP (Group 11) is likely not statistically significantly more efficacious than Group 12, which is comprised of only 40.4% cationic lipid (*see* Table 4). Group 14 (also in the claimed range) also appears to have performed worse than Group 7 (the 2:40 prior art formulation), and perhaps Group 2 as well.

113. The '435 patent defines "cationic lipid" as "any of a number of lipid species that carry a net positive charge at a selected pH, such as physiological pH (e.g., pH of about 7.0)." Ex. 1001, 12:59-61. The '435 patent includes almost three dozen examples of cationic lipids. *Id.*, 47:44-50:3. At the time of the '435 patent, hundreds of additional lipids that are cationic at physiological pH were known in the art. Ex. 1008 (Gao), E95 ("[H]undreds of new cationic lipids have been developed …."). In addition, because claim 1 of the '435 patent does not contain any limitation to a specific pH, the additional lipids that are cationic at a certain pH would also meet the definition of the

term.

114. The testing in the '435 patent compares only one cationic lipid, DLinDMA, to the admitted prior art formulations to illustrate alleged unexpected results. Ex. 1001, Tables 2, 4, 5. Example 5 in the '435 patent shows variation of the cationic lipid apparently impacts efficacy. *Id.*, Table 6 (Samples 2 & 6 (DLin-DMA) vs. Sample 4 (DODMA)). A POSITA would understand these results to suggest that a preferred proportion for one cationic lipid (*e.g.*, DLinDMA) does not necessarily apply to all other cationic lipids (*e.g.*, DODMA).

115. It was well-known in the art that "[t]he chemical structure of the cationic lipid [had] a major impact on the transfection efficiency." Ex. 1008 (Gao), E95. Indeed the '613 patent incorporated by reference in the '435 patent acknowledges that "alternative cationic lipids" to the one tested would have "different [transfection] efficiencies." *See* Ex. 1011, 1:26-28 ("… alternative cationic lipids that work in essentially the same manner but with different efficiencies."). A POSITA would have no reason to believe that the alleged unexpected advantages of a 50-85% proportion of DLinDMA would be applicable to all cationic lipids.

Claim element 1[d]: a non-cationic lipid comprising from 13 mol% to 49.5 mol% of the total lipid present in the particle

116. The '196 PCT teaches that "[t]he non-cationic lipid typically

comprises … preferably from about 20% to about 85% of the total lipid present in said particle." Ex. 1002, [0091]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.*, [0088]. In addition, the '196 PCT incorporates by reference the '618 patent, which discloses a nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol. Ex. 1017, 34:54-35:23. Given the breadth of the claimed range, these disclosures are sufficiently specific to disclose the claimed range. In addition, given the explicit disclosure of an encompassing range, this limitation is *prima facie* obvious.

Claim element 1[e]: a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol% to 2 mol% of the total lipid present in the particle

117. The '196 PCT teaches that "[t]he SNALP further comprises a bilayer stabilizing component (BSC). …. [T]he BSC is a conjugated lipid that inhibits aggregation of the SNALPs … present from about 0.5% to about 25% of the total lipid …." Ex. 1002, [0092-0093]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.*, [0088]. "By controlling the composition and concentration of the bilayer stabilizing component, one can control … the rate at which the liposome becomes fusogenic" impacting the transfection efficiency. *Id.*, [0094]. Given the breadth of the claimed range for

the conjugated lipid, these disclosures are sufficiently specific to disclose the claimed range.

118. In addition, this limitation would have been obvious in view of the '196 PCT in light of the knowledge of a POSITA. A POSITA would have been aware that conjugated lipids stabilize carrier particles by inhibiting fusogenicity. It would have been obvious for a POSITA to try to increase fusogenicity, and hence potentially transfection efficiency, by choosing a proportion of conjugated lipid in the 0.5%-2% range. Moreover, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious.

Claim 2: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid comprises an interfering RNA, mRNA, an anti-sense oligonucleotide, a ribozyme, a plasmid, an immunostimulatory oligonucleotide, or mixtures thereof

119. The '196 PCT patent teaches "the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." Ex. 1002, [0002]. siRNA is an interfering RNA, one of the alternatives put forth in the claim. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 3: the nucleic acid-lipid particle of claim 2, wherein the interfering RNA comprises a small interfering RNA (siRNA), an asymmetrical interfering RNA (aiRNA), a microRNA (miRNA), or mixtures thereof

120. The '196 PCT patent teaches "the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." *Id.*, [0002]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 4: the nucleic acid-lipid particle of claim 1, wherein the cationic lipid comprises from 50 mol% to 65 mol% of the total lipid present in the particle

121. *See* Claim 1(c). Given the breadth of the claimed range, the disclosures above are sufficiently specific to disclose the claimed range. Not only does the disclosed broader range substantially overlap with the claimed range, a preferred embodiment in the reference recites a narrower range that also partially overlaps. In addition, given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious.

Claim 5: the nucleic acid-lipid particle of claim 1, wherein the non-cationic lipid comprises a mixture of a phospholipid and cholesterol or a derivative thereof

122. The '196 PCT teaches that the non-cationic lipids may include a phospholipid and cholesterol. *Id.*, [0089]. "The non-cationic lipid typically comprises … preferably from about 20% to about 85% of the total lipid present

in said particle … If present … preferably the cholesterol comprises from about 20% to about 45% of the total lipid." *Id.*, [0091]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 6: the nucleic acid-lipid particle of claim 5, wherein the phospholipid comprises dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), or a mixture thereof

123. The '196 PCT patent teaches that "[e]xamples of noncationic lipids useful in the present invention include: phospholipid-related materials, such as … DSPC … DPPC …." *Id.*, [0089]. The '196 PCT patent also teaches using more than one phospholipid (*i.e.*, a mixture). *Id.*, [0128]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 7: the nucleic acid-lipid particle of claim 5, wherein the phospholipid comprises from 3 mol% to 15 mol% of the total lipid present in the particle

124. The '196 PCT teaches that "[t]he non-cationic lipid typically comprises … preferably from about 20% to about 85% of the total lipid present in said particle." Ex. 1002, [0091]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.*, [0088]. In addition, the '196 PCT incorporates by reference the '618 patent, which discloses nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol. Ex. 1017,

34:54-35:23. Not only does the disclosed range encompass the claimed range, when combined with a cationic lipid proportion of 60%, the available range for cholesterol is 20-40% and the range for the other non-cationic lipid (*e.g.*, a phospholipid) is decreased to 0%-20%. Given the breadth of the claimed range for the phospholipid, these disclosures are sufficiently specific to disclose the claimed range. In addition, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious.

Claim 8: the nucleic acid-lipid particle of claim 5, wherein the cholesterol or derivative thereof comprises from 30 mol% to 40 mol% of the total lipid present in the particle

125. The '196 PCT teaches that "If present … preferably the cholesterol comprises from about 20% to about 45% of the total lipid …." Ex. 1002, [0091]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.*, [0088]. In addition, the '196 PCT incorporates by reference the '618 patent, which discloses nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol. Ex. 1017, 34:54-35:23. Given the breadth of the claimed range for cholesterol, these disclosures are sufficiently specific to disclose the claimed range. In addition, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious.

Claim 9: the nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particles comprises a polyethyleneglycol (PEG)-lipid conjugate

126. The '196 PCT patent teaches that "[b]ilayer stabilizing components include, but are not limited to, conjugated lipids that inhibit aggregation of the SNALPs, polyamide oligomers (*e.g.*, ATTA-lipid derivatives), peptides, proteins, detergents, lipid-derivatives, PEG-lipid derivatives …." Ex. 1002, [0052], *see also* [0013]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 10: the nucleic acid-lipid particle of claim 9, wherein the PEG-lipid conjugate comprises a PEG-diacylglycerol (PEG-DAG) conjugate, a PEG-dialkyloxypropyl (PEG-DAA) conjugate, or a mixture thereof

127. The '196 PCT patent teaches that "[t]he PEG-lipid conjugate may be one or more of a PEG-dialkyloxypropyl (DAA), a PEG-diacylglycerol (DAG), … and combinations thereof." *Id.*, [0013]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 11: the nucleic acid-lipid particle of claim 10, wherein the PEG-DAA conjugate comprises a PEG-dimyristyloxypropyl (PEG-DMA) conjugate, a PEG-distearyloxypropyl (PEG-DSA) conjugate, or a mixture thereof

128. The '196 PCT patent teaches "three exemplary PEG-dialkyloxypropyl derivatives suitable for use in the present invention, *i.e.*, …

PEG-C-DMA … PEG-A-DMA … and … PEG-S-DMA." *Id.*, [0031]. The '196 PCT patent teaches "[o]ther PEG DAAs suitable for use in the present invention can be synthesized using similar protocols. For instance, PEG-A-DSA and PEG-C-DSA can be synthesized …." *Id.*, [0242]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 12: the nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particles comprises from 1 mol% to 2 mol% of the total lipid present in the particle

129. *See* Claim 1(e). For the reasons stated above, the '196 PCT discloses this range with sufficient specificity to disclose this limitation. In the alternative, this range is *prima facie* obvious given the overlapping range in the '196 PCT.

Claim 13: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid is fully encapsulated in the nucleic acid-lipid particle

130. The '196 PCT patent teaches "[i]n some embodiments, the siRNA molecule is fully encapsulated within the lipid bilayer of the nucleic acid-lipid particle such that the nucleic acid in the nucleic acid-lipid particle is resistant in aqueous solution to degradation by a nuclease." *Id.*, [0011]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 14: a pharmaceutical composition comprising a nucleic acid-lipid particle of claim 1 and a pharmaceutically acceptable carrier

131. The '196 PCT patent teaches "[t]he invention also provides for pharmaceutically acceptable compositions comprising a nucleic acid-lipid particle." *Id.*, [0019]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 15: a method for introducing a nucleic acid into a cell, the method comprising: contacting the cell with a nucleic acid-lipid particle of claim 1

132. *See* Claim 1. The '196 PCT patent teaches "the present invention provides for a method of introducing a siRNA molecule into a cell by contacting a cell with a nucleic acid-lipid particle …." *Id.*, [0017]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 16: a method for the in vivo delivery of a nucleic acid, the method comprising: administering to a mammalian subject a nucleic acid-lipid particle of claim 1

133. *See* Claim 1. The '196 PCT patent teaches "the present invention provides a method of treating a disease or disorder in a mammalian subject. A therapeutically effective amount of a nucleic acid-lipid particle comprising a cationic lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles, and siRNA is administered to the mammalian subject …." *Id.*,

[0021]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 17: a method for treating a disease or disorder in a mammalian subject in need thereof, the method comprising: administering to the mammalian subject a therapeutically effective amount of a nucleic acid-lipid particle of claim 1

134. *See* Claim 1. The '196 PCT patent teaches "the present invention provides a method of treating a disease or disorder in a mammalian subject. A therapeutically effective amount of a nucleic acid-lipid particle comprising a cationic lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles, and siRNA is administered to the mammalian subject …." *Id.*, [0021]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 18: the method of claim 17, wherein the disease or disorder is a viral infection

135. The '196 PCT patent teaches "[i]n some embodiments, the disease is a viral disease such as, for example, hepatitis (*e.g.*, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Hepatitis G, or a combination thereof)." *Id.*, [0021]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 19: the method of claim 17, wherein the disease or disorder is a liver disease or disorder

136. The '196 PCT patent teaches "[i]n some embodiment, the disease

or disorder is a liver disease or disorder, such as, for example, dyslipidemia." *Id.*, [0021]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 20: the method of claim 17, wherein the disease or disorder is cancer

137. The '196 PCT patent teaches "the present invention provides a method of treating a disease or disorder in a mammalian subject. A therapeutically effective amount of a nucleic acid-lipid particle comprising a cationic lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles, and siRNA is administered to the mammalian subject (*e.g.*, a rodent such as a mouse, a primate such as a human or a monkey) with the disease or disorder. In some embodiments, the disease or disorder is associated with expression and/or overexpression of a gene and expression or overexpression of the gene is silenced by the siRNA." *Id.*, [0021]. A POSITA would be aware that genetic changes that lead to cancer development are associated with aberrant gene expression including overexpression of genes. Thus, the disclosure in the '196 PCT of the use of siRNA to address gene overexpression discloses or renders obvious the use of siRNA in the context of cancer treatment.

B. Ground 2: Claims 1-20 are obvious in view of the '196 PCT in light of Lin and/or Ahmad

138. It is my opinion that Claims 1-20 of the '435 patent are obvious

under 35 U.S.C. § 103 in view of the Patent Owner's prior disclosures, *e.g.*, in the '196 PCT and '189 publication, in light of Lin and/or Ahmad. To the extent that those disclosures alone are determined not to disclose a proportion of cationic lipid in the 50%-85% range (Claim 1) and/or the 50%-65% range (Claim 4), a POSITA would have understood from Lin and/or Ahmad that such proportions of cationic lipid may increase transfection efficacy and would have been motivated to combine those disclosures with the system disclosed in the '196 PCT and '189 publication.

Claim element 1[c]: a cationic lipid comprising from 50 mol% to 85 mol% of the total lipid present in the particle

139. To the extent that the disclosures in the'196 PCT are determined not to disclose the claimed range for cationic lipids, this limitation would have been obvious in view of the '196 PCT in light of Lin and/or Ahmad. Exs. 1005-1006. A POSITA would understand the testing of Lin to suggest that the cationic lipid mol% of nucleic acid-lipid particles can impact transfection efficiency and that for certain lipid components a mol% greater than 50% may increase the transfection efficiency of the carrier particles. Ex. 1005 (Lin), Fig. 3(a). A POSITA would understand the testing of Ahmad to support the proposition that for certain formulations, cationic lipids can increase transfection efficiency when they are incorporated above 50 mol%. Ex. 1006 (Ahmad), 739–40; Fig. 3(a). In these formulations, transfection efficiency was

reported to decrease above a certain mol% cationic lipid (*e.g.*, around 70%). *Id.* It would have been obvious for a POSITA to combine the disclosed ranges in the '196 PCT with the teaching of Lin and/or Ahmad to increase the cationic lipid to the 50%-85% range in order to potentially increase the transfection efficiency.

Claim 4: the nucleic acid-lipid particle of claim 1, wherein the cationic lipid comprises from 50 mol% to 65 mol% of the total lipid present in the particle

140. *See* Claim 1(c). For the reasons stated above, this range is obvious in view of the '196 PCT when combined with Lin and/or Ahmad.

Motivation to combine the Patent Owner's prior disclosures with Lin and/or Ahmad

141. A POSITA would have been motivated to combine the teachings of the Patent Owner's prior disclosures with Lin and/or Ahmad. First, the Lin and Ahmad systems tested helper lipids and cationic lipids to create carrier particles for nucleic acids, *i.e.*, "nucleic acid-lipid particles," the same general carrier particles described in the Patent Owner's prior disclosures. Second, the Patent Owner's disclosures specifically state that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *See, e.g.*, Ex. 1002, [0088]. A POSITA would have been aware that the lipid proportions used could impact transfection efficiency. A POSITA would have looked to the prior art, including Lin and Ahmad, in order to

determine the appropriate proportions of, *e.g.*, cationic lipid. Third, given the success of generating nucleic acid-lipid particles with a cationic lipid proportion greater than 50% as described in the Patent Owner's prior disclosures, a POSITA would have appreciated a reasonable expectation of doing so. Given that Ahmad builds on the work described in Lin, a POSITA would have been motivated to combine the references.

142. In short, a POSITA would have found it obvious to use the insights of Lin regarding increasing the cationic mole fraction of nucleic acid-lipid particles to increase transfection efficiency and the disclosures of the Patent Owner's prior disclosures regarding nucleic acid-lipid particles with a cationic lipid proportion greater than 50%.

C. Ground 3: Claims 1-20 are anticipated by or obvious in view of the '554 publication

143. It is my opinion that Claims 1-20 of the '435 patent are anticipated under 35 U.S.C. § 102(b) or obvious under 35 U.S.C. § 103 in view of the '554 publication. While the '554 publication does not disclose exactly the same ranges of lipid components from claim 1 of the '435 patent explicitly, it discloses encompassing and overlapping ranges and specific examples falling within the claimed ranges with sufficient specificity to anticipate. Moreover, the disclosed ranges establish a *prima facie* case of obviousness and the testing in the '435 patent does not support alleged unexpected results for the claimed

ranges.

Claim element 1[a]: A nucleic acid-lipid particle comprising:

144. The '554 publication teaches "novel cationic lipids … and formulations thereof with biologically active molecules." Ex. 1004, [0019]. As one example, "the invention features a composition comprising a biologically active molecule (e.g., a polynucleotide such as a siNA, … [or] other nucleic acid molecule …), a cationic lipid, a neutral lipid, and a polyethyleneglycol conjugate, such as a PEG-diacylglycerol, PEG-diacylglycamide, PEP-cholesterol, or PEG-DMB conjugate." *Id.*, [0082]. One example of such particles with siRNA for reducing HBsAg levels using the L054 formulation are described in Figure 16. *Id.*, [0395] ("FIG. 16 shows a non-limiting example of in vitro efficacy of siNA nanoparticles in reducing HBsAg levels in HepG2 cells … treated with formulated active siNA L053 and L054 nanoparticles ….). From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim element 1[b]: A nucleic acid

145. The '554 publication teaches "compositions … with biologically active molecules" including "nucleic acids." *Id.*, [0018]-[0019]. As one example, "the invention features a composition comprising a biologically active molecule (e.g., a polynucleotide such as a siNA, antisense, aptamer,

decoy, ribozyme, 2-5A, triplex forming oligonucleotide, [or] other nucleic acid molecule …)." *Id.*, [0082]. One example is siRNA for reducing HBsAg levels as described in Figure 16. *Id.*, [0395]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim element 1[c]: a cationic lipid comprising from 50 mol% to 85 mol% of the total lipid present in the particle

146. The '554 publication teaches "[c]ationic lipids that are useful in the present invention can be any of a number of lipid species which carry a net positive charge at a selected pH, such as physiological pH." *Id.*, [0454]. "[T]he cationic lipid component … comprises from about 2% to about 60% … or from about 40% to about 50% of the total lipid …." *Id.*, [0116]. For example, the L054 formulation tested in Figure 16 contains 50% cationic lipid (DMOBA). *Id.*, Table 4.

147. The '554 publication also teaches particles "can transition from a stable lamellar structure adopted in circulation (i.e., in plasma or serum) at physiologic pH (about pH 7.4) to a less stable and more efficient delivery composition having an inverted hexagonal structure at pH 5.5-6.5, which is the pH found in the early endosome." *Id.*, [0137]. The cationic lipid is the active component in such the pH-dependent nucleic acid-lipid particles: "[s]uitable cationic lipid include those cationic lipids which carry a net positive charge at a selected pH …." *Id.*, [0083]. A POSITA would understand that increasing the

mol% of a cationic lipid with pH sensitivity in these particles might increase transfection efficiency since this event is fusion related and thought to occur as a result of the described phase shift.

148. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. For example, not only does the disclosed range overlap with the claimed range, a specific example falls within the claimed range. In addition, a POSITA would be compelled to choose cationic lipid proportions at the top end of the recited range to increase the efficiency of the described phase shift.

149. In addition, given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious. As discussed above and the testing in the '435 patent does not support alleged unexpected results for the claimed ranges.

Claim element 1[d]: a non-cationic lipid comprising from 13 mol% to 49.5 mol% of the total lipid present in the particle

150. The '554 publication teaches "[t]he noncationic lipids used in the present invention can be any of a variety of neutral uncharged, zwitterionic or anionic lipids capable of producing a stable complex." *Id.*, [0455]. Neutral lipids are defined as "any lipophilic compound having non-cationic change (e.g., anionic or neutral charge)." *Id.*, [0315]. "[T]he neutral lipid component … comprise[s] … from about 20% to about 85% of the total lipid present in the

formulation." *Id.*, [0313]. For example, the L054 formulation tested in Figure 16 contains 48% non-cationic lipid (cholesterol and DSPC). *Id.*, Table 4. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. *Id.* In addition, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious.

Claim element 1[e]: a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol% to 2 mol% of the total lipid present in the particle

151. The '554 publication teaches "[i]n addition to cationic and neutral lipids, the formulated molecular compositions of the present invention comprise a polyethyleneglycol (PEG) conjugate." *Id.*, [0457]. "[T]he PEG conjugate … comprises from about 1% to about 20% … of the total lipid present …." *Id.*, [0118]. The '554 publication further teaches "[i]t is often desirable to include other components that act in a manner similar to the DAG-PEG conjugates and that serve to prevent particle aggregation …." *Id.*, [0504]. For example, the L054 formulation tested in Figure 16 contains 2% conjugate lipid (PEG-n-DMG). *Id.*, Table 4. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range.

152. In addition, this limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. A POSITA would have been aware that conjugated lipids stabilize carrier particles by inhibiting fusogenicity. It would have been obvious for a POSITA to try to increase the

fusogenicity, and hence potentially the transfection efficiency, by choosing a proportion of conjugated lipid in the 0.5%-2% range. Moreover, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious.

Claim 2: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid comprises an interfering RNA, mRNA, an anti-sense oligonucleotide, a ribozyme, a plasmid, an immunostimulatory oligonucleotide, or mixtures thereof

153. The ’554 publication teaches “formulations for the delivery of chemically-modified synthetic short interfering nucleic acid (siNA) molecules that modulate target gene expression or activity in cells, tissues, such as in a subject or organism, by RNA interference (RNAi).” *Id.*, [0020]. One example is siRNA for reducing HBsAg levels as described in Figure 16. *Id.*, [0395]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 3: the nucleic acid-lipid particle of claim 2, wherein the interfering RNA comprises a small interfering RNA (siRNA), an asymmetrical interfering RNA (aiRNA), a microRNA (miRNA), or mixtures thereof

154. The ’554 publication teaches “formulations for the delivery of chemically modified synthetic short interfering nucleic acid (siNA) molecules that modulate target gene expression or activity in cells, tissues, such as in a subject or organism, by RNA interference (RNAi).” *Id.*, [0020]. The ’554

publication further teaches "the invention features novel … formulations that effectively transfect or deliver small nucleic acid molecules, such as short interfering nucleic acid (siNA) … [and] micro-RNA (miRNA) … to relevant cells and/or tissues …." *Id.*, [0019]. One example is siRNA for reducing HBsAg levels as described in Figure 16. *Id.*, [0395]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 4: the nucleic acid-lipid particle of claim 1, wherein the cationic lipid comprises from 50 mol% to 65 mol% of the total lipid present in the particle

155. *See* Claim 1(c). Given the breadth of the claimed range, the disclosures above are sufficiently specific to anticipate the claimed range. In addition, given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious.

Claim 5: the nucleic acid-lipid particle of claim 1, wherein the non-cationic lipid comprises a mixture of a phospholipid and cholesterol or a derivative thereof

156. The '544 publication teaches "[t]he noncationic lipids used in the present invention can be any of a variety of neutral uncharged, zwitterionic or anionic lipids capable of producing a stable complex." *Id.*, [0455]. "Examples of noncationic lipids useful in the present invention include phospholipid-related materials …." *Id.* "[S]uitable neutral lipids include … cholesterol, as well as other neutral lipids described herein below, and/or a mixture thereof." *Id.*, [0085]. For example, the L054 formulation tested in Figure 16 contains

48% non-cationic lipid (cholesterol and DSPC). *Id.*, Table 4. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 6: the nucleic acid-lipid particle of claim 5, wherein the phospholipid comprises dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), or a mixture thereof

157. The '554 publication teaches "suitable neutral lipids include … DSPC … DPPC … and/or a mixture thereof." Ex. 1004, [0085]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 7: the nucleic acid-lipid particle of claim 5, wherein the phospholipid comprises from 3 mol% to 15 mol% of the total lipid present in the particle

158. The '554 publication teaches "[t]he noncationic lipids used in the present invention can be any of a variety of neutral uncharged, zwitterionic or anionic lipids capable of producing a stable complex." *Id.*, [0455]. "[T]he neutral lipid component … comprises … from about 20% to about 85% of the total lipid present in the formulation … the cholesterol component … comprises … from about 20% to about 45% of the total lipid present …." *Id.*, [0117-0119]. When cholesterol is present, the range for a phospholipid is thus 0-40%. Not only does the disclosed range encompass the claimed range, when combined with a cationic lipid proportion in the 60% range and cholesterol in

the 20-40% range, the range for the phospholipid is decreased to 0%-20%. *Id.* Given the breadth of the claimed range for the phospholipid, these disclosures are sufficiently specific to anticipate the claimed range. *Id.*

159. Moreover, given the explicit disclosure of a non-cationic lipid range "from about 20% to about 85%," including cholesterol "from about 20% to about 45%," an overlapping range of 0%-40% is disclosed. This limitation is *prima facie* obvious.

Claim 8: the nucleic acid-lipid particle of claim 5, wherein the cholesterol or derivative thereof comprises from 30 mol% to 40 mol% of the total lipid present in the particle

160. The '554 publication teaches "the cholesterol component … comprises … from about 20% to about 45% of the total lipid present." *Id.*, 29:60-30:4. In addition, the '554 publication also includes various specific formulations which include cholesterol at a 30% proportion. *Id.*, Table 4 (*e.g.*, L106). Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Moreover, given the explicit disclosure of an encompassing range, this limitation is *prima facie* obvious.

Claim 9: the nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particles comprises a polyethyleneglycol (PEG)-lipid conjugate

161. The '554 publication teaches "[i]n addition to cationic and neutral

lipids, the formulated molecular compositions of the present invention comprise a polyethyleneglycol (PEG) conjugate." *Id.*, [0457]. For example, the L054 formulation tested in Figure 16 contains 2% conjugate lipid (PEG-n-DMG). *Id.*, Table 4. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 10: the nucleic acid-lipid particle of claim 9, wherein the PEG-lipid conjugate comprises a PEG-diacylglycerol (PEG-DAG) conjugate, a PEG-dialkyloxypropyl (PEG-DAA) conjugate, or a mixture thereof

162. The '554 publication teaches "[s]uitable polyethyleneglycol-diacylglycerol or polyethyleneglycol-diacylglycamide (PEG-DAG) conjugates …." *Id.*, [0086]. Because one of the listed species of PEG-lipid conjugates is disclosed, this element is anticipated.

Claim 11: the nucleic acid-lipid particle of claim 10, wherein the PEG-DAA conjugate comprises a PEG-dimyristyloxypropyl (PEG-DMA) conjugate, a PEG-distearyloxypropyl (PEG-DSA) conjugate, or a mixture thereof

163. This limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. A POSITA would have been aware that PEG-dialkyloxypropyl (PEG-DAA) conjugates could be used in lieu of PEG-diacylglycerol (PEG-DAG) conjugates and that PEG-dialkyloxypropyl (PEG-DAA) conjugates can comprises a PEG-dimyristyloxypropyl (PEG-DMA) conjugate, a PEG-distearyloxypropyl (PEG-

DSA) conjugate, or a mixture thereof. Indeed, the Patent Owner's prior disclosures from years before the '435 patent priority date address using PEG-DAA conjugates (*e.g.*, PEG-DMA or PEG-DSA) in lieu of PEG-DAG conjugates. *See, e.g.*, Ex. 1014 ('910 publication), [0016].

Claim 12: the nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particles comprises from 1 mol% to 2 mol% of the total lipid present in the particle

164. *See* Claim 1(e). For the reasons stated above, the '554 publication discloses this range with sufficient specificity to anticipate. In the alternative, this range is *prima facie* obvious given the overlapping range in the '554 publication.

Claim 13: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid is fully encapsulated in the nucleic acid-lipid particle

165. The '554 publication teaches "[t]he encapsulation of anionic compounds using cationic lipids is essentially quantitative due to electrostatic interaction." Ex. 1004, [0011]. A POSITA would understand that full encapsulation requires only an excess of cationic lipid with regard to the nucleic acid for electrostatic interaction. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 14: a pharmaceutical composition comprising a nucleic acid-lipid particle of claim 1 and a pharmaceutically acceptable carrier

166. The '554 publication teaches "[t]he pharmaceutical carrier is generally added following formulated siNA composition formation. Thus, after the formulated siNA composition is formed, the formulated siNA composition can be diluted into pharmaceutically acceptable carriers such as normal saline." *Id.*, [0502]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 15: a method for introducing a nucleic acid into a cell, the method comprising: contacting the cell with a nucleic acid-lipid particle of claim 1

167. *See* Claim 1. The '554 publication teaches "[t]he invention relates to … methods for delivering nucleic acids … to cells by facilitating transport across cellular membranes …." Ex. 1004, [0003]. A POSITA would understand this to include contacting the cell with the carrier particle. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 16: a method for the in vivo delivery of a nucleic acid, the method comprising: administering to a mammalian subject a nucleic acid-lipid particle of claim 1

168. *See* Claim 1. The '554 publication teaches "'[s]ubject' also refers to an organism to which the nucleic acid molecules of the invention can be

administered. A subject can be a mammal or mammalian cells, including a human or human cells." Ex. 1004, [0369]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 17: a method for treating a disease or disorder in a mammalian subject in need thereof, the method comprising: administering to the mammalian subject a therapeutically effective amount of a nucleic acid-lipid particle of claim 1

169. *See* Claims 1 & 16. The '554 publication teaches "the invention features a method for treating or preventing a disease, disorder, trait or condition related to gene expression in a subject or organism comprising contacting the subject or organism with a formulated molecular composition of the invention under conditions suitable to modulate the expression of the target gene in the subject or organism." Ex. 1004, [0274]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 18: the method of claim 17, wherein the disease or disorder is a viral infection

170. The '554 publication teaches "[i]n one embodiment, the degree of reduced immunostimulatory response is selected for optimized RNAi activity. For example, retaining a certain degree of immunostimulation can be preferred to treat viral infection …." *Id.*, [0310]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 19: the method of claim 17, wherein the disease or disorder is a liver disease or disorder

171. The ’554 publication teaches “the invention features compositions and methods that independently or in combination modulate the expression of target genes encoding proteins, such as proteins associated with the maintenance and/or development of a disease, trait, or condition, such as a liver disease, trait, or condition.” *Id.*, [0021]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 20: the method of claim 17, wherein the disease or disorder is cancer

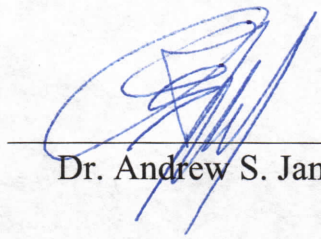
172. The ’554 publication teaches “the invention features a method for treating or preventing cancer in a subject or organism comprising contacting the subject or organism with a formulated molecular composition of the invention ….” *Id.*, [0275]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

VIII. CONCLUSION

173. In sum, it is my opinion that Grounds 1-3 advanced in the Petition demonstrate that the challenged claims of the ’435 patent are disclosed or rendered obvious by the cited prior art.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code.

Executed on March 5, 2018 in Princeton, NJ.



Dr. Andrew S. Janoff, Ph.D.

JOINT APPENDIX 71

Liposome Drug Products

Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2018
Pharmaceutical Quality/CMC

Liposome Drug Products

Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2018
Pharmaceutical Quality/CMC

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Liposome Drug Products Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance discusses what types of information you, the applicant, should submit in your new drug application (NDA) or abbreviated new drug application (ANDA) for a liposome drug product reviewed by the Center for Drug Evaluation and Research (CDER). The discussion addresses the following topics for liposome drug products: (A) chemistry, manufacturing, and controls (CMC); (B) human pharmacokinetics and bioavailability or, in the case of an ANDA, bioequivalence; and (C) labeling in NDAs and ANDAs. It finalizes the revised draft guidance for industry *Liposome Drug Products, Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation* that published in October 2015.[2] The recommendations in this guidance focus on the unique technical aspects of liposome drug products. This guidance does not provide recommendations on clinical efficacy and safety studies; nonclinical pharmacology/toxicology studies; or drug-lipid complexes.[3]

Although this guidance does not provide recommendations specific to liposome drug products to be marketed under biologics license applications (BLAs), many scientific principles described in this guidance may also apply to these products.

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[1] This guidance has been prepared by the Liposome Working Group in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] Drug-lipid complexes are chemically and physically defined nonvesicular associations of drugs with certain lipids. Drug-lipid complexes are formed by mixing a drug with lipids in such a way that liposomes are not created. The CMC, pharmacokinetics, and bioavailability recommendations for drug-lipid complexes and liposomes can be similar. When the submission is for an NDA, contact the specific drug product's review division with questions. When the submission is for an ANDA, submit a Controlled Correspondence via email to GenericDrugs@fda.hhs.gov. For the definition of a *controlled correspondence* as well as the process to submit a *controlled correspondence*, see the final guidance for industry *Controlled Correspondence Related to Generic Drug Development (September 2015)* and the proposed revisions in the draft guidance issued in November 2017.

In addition, you should consider recommendations in this guidance during drug development that may lead to the submission of an investigational new drug application (IND) for a liposome drug product. In connection with ANDA submissions, you should consider recommendations in any product-specific guidances, including bioequivalence and information necessary to demonstrate pharmaceutical equivalence to the reference listed drug (RLD).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Liposomes are vesicles composed of a bilayer (uni-lamellar) and/or a concentric series of multiple bilayers (multi-lamellar) separated by aqueous compartments formed by amphipathic molecules such as phospholipids that enclose a central aqueous compartment. In a liposome drug product, the drug substance is generally contained in liposomes.[4] Typically, water soluble drugs are contained in the aqueous compartment(s) and hydrophobic drugs are contained in the lipid bilayer(s) of the liposomes. Release of drugs from liposome formulations, among other characteristics such as liposomal clearance and circulation half-life, can be modified by the presence of polyethylene glycol and/or cholesterol or other potential additives in the liposome.

A liposome drug formulation is different from (1) an emulsion, which is a dispersed system of oil in water, or water in oil phases containing one or more surfactants, (2) a microemulsion, which is a thermodynamically stable two phase system containing oil or lipid, water and surfactants, and (3) a drug-lipid complex.

III. DISCUSSION

A. Chemistry, Manufacturing, and Controls

1. Description and Composition

You should include the following information in your application:

a. The drug product components listed by their established names, as follows:

i. Drug substance
ii. Lipids
iii. Nonlipid components of the liposome

[4] The word *contained* includes both *encapsulated* and *intercalated* drug substance. Encapsulated refers to drug substance within an aqueous space and intercalated refers to incorporation of the drug substance within a bilayer.

iv. Nonliposome inactive ingredients (e.g., buffer components)

b. An expression of the amount of each lipid component used in the formulation based on the final form of the product:

- For liquid – mg/ml and mg/vial
- For dry powder for reconstitution – mg/ml after reconstitution and mg/vial
- For semisolid – w/w (g/g)

An expression of the molar ratio of each individual lipid to the drug substance is also recommended for each individual lipid in the finished formulation.

c. An expression of the amount of drug substance in the formulation.

We recommend expressing the composition of the drug product as milligram of drug substance per milliliter of drug product and also milligram of drug substance per vial for liquid drug products. For dry powders, only the total amount of the drug should be listed.

d. Ranges in the composition and/or attributes of components.

Because the pharmacological and toxicological properties and the quality of a liposome product can vary significantly with changes in the formulation, including the lipid composition, the ranges should be specified based on the following:

i. Product development studies
ii. How the ranges were selected
iii. If and how the source of key excipients affects finished product quality

These ranges should be linked to the factors that were analyzed during drug product development and supported by data.

2. Physicochemical Properties

Liposome structure and integrity are important physicochemical properties and they reflect the ability of the liposome drug formulation to contain the drug substance and to retain the drug substance within the appropriate liposome structure. The following properties are generally useful to characterize a liposome drug formulation. Variability in the following properties may lead to changes in the quality of the liposome drug product, including leakage of the drug from the liposomes. Properties that apply to your liposome drug product may vary from those listed below.

a. Morphology of the liposomes including, if applicable, lamellarity determination.

b. Surface characteristics of the liposomes, as applicable, e.g., pegylation.

c. Net charge, typically measured as zeta potential of the liposomes.

d. Drug product viscosity.

e. Parameters of the contained drug.

For example, drug encapsulation efficiency (the amount of drug contained inside liposomes compared with total amount of drug) and liposome drug loading (the amount of drug contained relative to the amount of the lipid used, which is the drug-to-lipid ratio).[5] This information should be supported by development data, including test results on batches of liposome drug used in pivotal clinical trials or bioequivalence studies.

f. Particle size (i.e., mean and distribution profile), preferably defined on the basis of volume or mass if particle density is known.

g. Liposome phase transition temperature.

h. In vitro release of the drug substance from the liposome drug product under the stated/described experimental conditions with supportive data and information regarding the choice of those conditions.

i. Leakage rate of drug from the liposomes throughout shelf life.

j. Liposome integrity changes (e.g., drug release, drug encapsulation efficiency, liposome drug loading, size) in response to changes in factors such as salt concentration, pH, temperature, or addition of other excipients, as applicable.

k. Liposome structure supported by spectroscopic or other analytical method(s).

[5] Xu, X, Khan, M, and Burgess, D, 2012, A Quality by Design (QbD) Case Study on Liposomes Containing Hydrophilic API: II. Screening of Critical Variables, and Establishment of Design Space at Laboratory Scale, International Journal of Pharmaceutics, 423: 543-553; and Liposomes as Carriers for Controlled Drug Delivery, Long Acting Injections and Implants, chapter 11, pages 195 to 220, ISBN 978-1-4614-0553-5, Publisher: Springer.

3. Critical Quality Attributes

Critical quality attributes (CQAs) particular to liposome drug products include some of the physicochemical properties described above including vesicle/particle size and size distribution, and morphology. For general information on drug product development, see the International Council for Harmonisation (ICH) guidance for industry, *Q8(R2) Pharmaceutical Development*.

4. Description of Manufacturing Process and Process Controls

We recommend including a detailed process flow diagram and a description of unit operations with ranges for the process parameters and process controls. These ranges should be supported by pharmaceutical development studies. The process and mechanism of liposomal drug loading, as well as the removal of free (un-incorporated) drug from the liposome formulation via purification should be described in detail. The manufacturing process should be validated to demonstrate manufacturing process consistency and reproducibility before commercial distribution.[6]

Liposome drug products are sensitive to changes in the manufacturing conditions, including changes in scale (size of the batches). Appropriate process controls should be established during product development. Prior knowledge can be leveraged and risk assessment techniques can be used to identify manufacturing process parameters that potentially affect finished product quality.

Some examples of manufacturing process parameters that may affect liposome drug performance are shear force, pressure, pH, temperature, batch-size-related hold times, lyophilization parameters, etc. You should provide adequate justification for the selection of the operating ranges for different batch sizes.

The physical and chemical complexity of liposome drug products present unique challenges to the sterilizing filtration process. For example, components of liposomes could interact with the filter matrix and clog it. Therefore, validated product-specific purification and sterilization methods should demonstrate the ability of the microbial sterilizing filters to function correctly, without compromising the integrity and structure of liposomes.

5. Control of Lipid Components

The quality of lipid components, including modified lipids (e.g., polyethylene glycol (PEG) modified lipids), can affect the quality and performance of the liposome drug product. In case of a novel lipid component, i.e., any lipid component not listed in the Inactive Ingredient Database (IID),[7] or a component that exceeds the amount listed in the IID for the intended route of administration, the level of detail provided in the submission should be comparable to that for a

[6] See guidance for industry *Process Validation: General Principles and Practices*.
[7] See http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

drug substance.[8] This information should be provided in the application or in a Type IV Drug Master File (DMF).[9]

In addition, you should provide the following information specific to lipid components:

a. Description and Characterization of Lipid Components

If the lipid is synthetic (e.g., a lipid manufactured by chemical synthesis from specified starting materials) or semi-synthetic (e.g., a lipid manufactured by modification of naturally occurring precursors such as dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), or dimyristoylphosphatidylcholine (DMPC)), you should provide proof of structure, including fatty acid composition and positional specificity. You should specify the lipid composition (e.g., percentage of each lipid and fatty acid, positional specificity of acyl side chains, and degree of fatty acid unsaturation).

In the case of naturally-sourced lipid mixtures, (e.g., egg lecithin), you should provide the lipid composition as a range of percentages for each stated lipid present in the mixture and its fatty acid composition.

b. Manufacture of Lipid Components

The information provided on the manufacture of lipid components depends on whether the lipid is synthetic, semi-synthetic, or naturally sourced.

For synthetic and semi-synthetic lipids, we recommend you provide the following information:

i. A complete description of the synthetic process and purification procedures, as applicable
ii. Specifications for starting materials,[10] raw materials, solvents, and reagents
iii. Controls for critical steps and intermediates, including the manufacturing controls that ensure positional specificity of acyl side chains, if applicable

For naturally-sourced lipid mixtures, and any naturally-sourced materials that start the synthetic segment of a semi-synthetic process, you should provide the following information:

i. Biological source (e.g., eggs)
ii. Country of origin for animal-sourced material
iii. Supplier
iv. A description of extraction and purification procedures, as applicable[11]

[8] For further information, see ICH *Q11 Development and Manufacture of Drug Substances* (ICH Q11).
[9] See guidance for industry *Drug Master Files: Guidelines.*
[10] See ICH Q11 for recommendations about the selection of starting materials.
[11] Ibid.

Procedures to ensure the avoidance, removal, and/or inactivation of animal proteins and viruses and any other infectious agents should be described, where applicable.

You should address the avoidance and/or removal of pyrogenic material and bacterial endotoxins by establishing appropriate controls during the manufacturing process, and include this information in the application.

c. Specifications for Lipid Components

You should provide the following specification information for each lipid component used to manufacture the drug product.

i. The identity test capable of distinguishing the intended lipid component from lipids with similar structures.
ii. The assay based on a stability-indicating analytical procedure.
iii. The validated analytical procedures accompanied by the validation data.
iv. Impurity testing:
    1. Trans-fatty acid
    2. Free-fatty acid
    3. Peroxides (associated with unsaturated fatty acids)
    4. Lysophospholipids
    5. Solvents and catalysts used in the synthesis or purification processes
v. Other testing:
    1. Counterion content and limits on divalent cations, when appropriate
    2. The degree of unsaturation of the fatty acid side chains (for lipid mixtures)

Information about impurities, including synthetic by-products, where applicable, should be provided. Impurities may warrant identification and qualification, depending on the following:

i. The amount of the impurity in the final liposome drug product
ii. Known toxicities of the impurity
iii. Structural alerts[12]

For synthetic lipids and semi-synthetic lipids, compare the lipid under test with the reference standard or material using an analytical procedure that is capable of distinguishing the desired lipids from their impurities (e.g., HPLC, TLC).

[12] Ashby, J, Paton, D, March 1993, The Influence of Chemical-Structure on the Extent and Sites of Carcinogenesis for 522 Rodent Carcinogens and 55 Different Human Carcinogen Exposures, Mutation Research, Volume 286, Issue 1, Pages 3-74; and guidance to industry *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*. When final, this guidance will represent the FDA's current thinking on this topic.

Information about the preparation, qualification, and storage conditions for each reference standard or material used in testing lipid components should be provided.

d. Stability of Lipid Components

For each lipid used to manufacture the liposome, you should provide results from stability studies and stress testing (e.g., after exposure to high (e.g., 50 ºC) and low (e.g., -20 ºC) temperatures, light, pH, and oxygen) that were used to determine the degradation profile, to develop an appropriate stability-indicating analytical procedure, and to establish appropriate storage conditions and retest period(s). Reference to a DMF is acceptable when the stability studies referenced in the DMF used the same lipids (source, grade, supplier) as proposed to be used in the drug product. Stability studies and validation of analytical procedures should be conducted according to ICH guidelines.[13]

You should retest the lipid component after its storage beyond the lipid manufacturer's stated "retest period" or when the lipid component is exposed to temperatures other than its labeled storage temperature to ensure conformance to its specification prior to use in a drug product. For example, if unusual conditions occur during shipping or transit leading to exposure of the lipid component to elevated temperatures for a significant time period, you should retest the lipid component to ensure conformity with specification.

6. Drug Product Specification

You should provide a drug product specification that accounts for specific attributes for your liposome products. The following are examples of characteristics or attributes specific to the liposome formulation that should be included in the specification:

a. Physicochemical parameters of the liposome determined to be the CQAs of the product (e.g., mean particle size and size distribution of liposomes, osmolality, zeta-potential and physical stability)

b. Liposome contained and free drug substance

c. Total drug substance content, as labeled

d. Degradation products related to the lipids (e.g., lysolipids) or drug substance

e. Lipid content (to demonstrate consistency with the intended formulation)

f. Residual solvent(s), if any organic solvent(s) are used in the manufacture of the liposome product

[13] See guidances for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*; *Q2(R1) Validation of Analytical Procedures: Text and Methodolology*.

The residual solvents acceptance criteria should be based on the performance of the liposome drug product as well as safety concerns.

g. In vitro release of drug substance from the liposome drug products

A validated analytical procedure for in vitro release should be established, preferably using an appropriate physiological medium (e.g., simulated physiological medium or human plasma) with suitable agitation. When a liposome drug product is extremely stable under physiological conditions, an in vitro quality control (QC) release test can be performed under nonphysiological conditions to accelerate the release of drug substance from the liposomes. For all drug products, information about any relationship or correlation between the in vitro quality control release test and the in vivo pharmacokinetic profile should be provided to justify the use of such a QC test, as established through analytical method development studies. In some cases, a test using cell culture or animal models may be appropriate.

h. For injectable liposome drug products, sterility and the absence of pyrogens or bacterial endotoxins

7. Stability

Stability studies should address the microbiological, physical, and chemical stability of the liposome drug product, including the integrity of the liposomes in the drug product.[14]

The physical stability of liposome drug products can be affected by a number of factors (e.g., the liposome integrity,[15] the size distribution of the lipid vesicles, unsaturation of the fatty acid groups). Some liposomes are susceptible to fusion (i.e., irreversible coalition of smaller liposomes to form larger liposomes), aggregation (i.e., reversible conglomeration or pooling of two or more liposomes without fusion), and leakage of the contained drug substance during storage. Fusion, aggregation, or leakage can be affected by the lipid components in the liposome or by the contained drug substance. Stability testing should include tests to assess liposome size distribution and integrity.

You should evaluate the chemical stability of the lipid components in the liposome as well as the chemical stability of the contained drug substance. Lipids with unsaturated fatty acids are subject to oxidative degradation, while both saturated and unsaturated lipids are subject to hydrolysis to form lysolipids and free fatty acids. It may be appropriate to conduct stress testing of unloaded liposomes to assess possible degradation or other reaction processes unique to the liposomes.

When designing stress and accelerated stability testing studies, you should recognize that liposome drug products behave differently near or above the phase transition temperature(s).

[14] See ICH *Q1A(R2) Stability Testing of New Drug Substances and Products.*
[15] See section III.A.2.

If the liposome drug product is marketed as an approved kit containing unloaded liposomes and drug substance in separate containers, your stability program should include testing of the unloaded liposomes and the drug substance in their commercial container-closure systems.

If the liposome product is labeled for use after reconstitution with a co-packaged or other specified diluent, or is labeled for use after mixing it with other approved drug products (e.g., large volume injectable solutions), supporting stability data on the product under the in-use conditions of its storage and use should be submitted in the application. This should include physical, chemical, and microbiological studies to support the in-use period. A specified in-use or storage interval, after which an admixed and/or unused liposome product must be discarded, should be determined through an in-use stability study. A statement regarding the appropriate in-use period(s) for the reconstituted/admixed drug product should be included in the labeling, together with instructions for reconstitution or mixing.

8. Postapproval Changes in Manufacturing

Liposome drug products are complex and sensitive formulations and response to CMC changes is less predictable than with more conventional formulations. Therefore, changes to the formulation, container closure, site of manufacture, or manufacturing process (including substantive equipment and scale changes) will usually require a prior approval supplement. In vivo studies may be needed to assess changes that can affect the performance of the drug product. You can contact the appropriate review division[16] associated with your application if you have questions regarding the type of information to generate or the appropriate reporting mechanism for a postapproval change.[17]

B. Human Pharmacokinetics: Bioavailability and Bioequivalence

For ANDA submissions for liposome drug products, please refer to applicable product-specific FDA guidance documents[18] that outline recommendations regarding human pharmacokinetic and other bioequivalence studies for generic liposome drug products. These guidance documents also discuss additional characterization studies and information (e.g., drug product composition and active ingredient loading) necessary to demonstrate pharmaceutical equivalence to the RLD. When no product-specific guidance exists for a generic product, this guidance applies. If you are contemplating submitting an ANDA, you should consider contacting OGD[19] to request a pre-ANDA meeting.

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[16] When the submission is for an NDA, contact the specific drug product's review division with questions. When the submission is for an ANDA, submit a Controlled Correspondence via email to GenericDrugs@fda.hhs.gov. For the definition of a *controlled correspondence* as well as the process to submit a *controlled correspondence*, see the final guidance for industry *Controlled Correspondence Related to Generic Drug Development (September 2015)* and the proposed revisions in the draft guidance issued in November 2017.

[17] See 21 CFR 314.70 and FDA guidances related to submission of postapproval changes to the chemistry, manufacturing, and controls section of drug applications.

[18] See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[19] See draft guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.

Because of the complex interaction between drug release from the liposome drug product and the tissue and/or cellular uptake of the drug substance and/or the liposome, a simple measurement of total drug substance concentration in plasma[20] may not be reflective of bioavailability of the drug at the intended target organ (i.e., site of action).[21] Therefore, for NDA submissions, you should consult the appropriate CDER review division[22] for advice concerning the determination of bioavailability of liposome drug products.

1. Clinical Pharmacology Studies

a. Pharmacokinetic and Mass Balance Studies for Liposome Drug Products

Information from pharmacokinetic studies is useful for establishing dosing regimens and developing dose-concentration-response relationships. The study design should be based on the anticipated dosing regimen in the intended patient population. We recommend using a population pharmacokinetics approach, where appropriate.[23]

The pharmacokinetic measures or parameters should include area under the plasma concentration versus time curve (AUC), peak plasma concentration, time to peak plasma concentration, elimination half-life, volume of distribution, total clearance, renal clearance, and accumulation for both free and total drug, as appropriate. For mass balance studies, you should collect and assay blood (i.e., plasma or serum, as appropriate), urine, and fecal samples for the radiolabeled moiety. For these studies, you should monitor and quantify both parent drug and any metabolites present, as appropriate.

You should determine major metabolites associated with the therapeutic and toxic effects of the drug substance. We also recommend conducting the following in vivo studies:

i. Multiple-dose study evaluating the drug pharmacokinetics after administration of the liposome drug product.
ii. Dose-proportionality study over the expected therapeutic dose range of the liposome drug product.
iii. Exposure-response studies if available.

Depending on the target patient population and the proposed therapeutic indication for the drug, you should consider conducting drug interactions studies in specific populations.

You should consult the appropriate CDER review division[24] regarding the conduct and design of these studies if you have questions.

[20] See 21 CFR 320.24(b)(1)(i).
[21] See 21 CFR 320.21.
[22] See footnote 16.
[23] See guidance for industry *Population Pharmacokinetics.*
[24] See footnote 16.

b. Comparison Clinical Pharmacology Studies with Nonliposome Drug Product

The drug disposition and pathways of elimination (including distribution, metabolism and excretion) as well as several important pharmacokinetic measures (Cmax, AUC) and parameters (e.g., clearance, volume of distribution, half-life) of a liposome formulation are likely to be different than those of a nonliposome formulation given by the same route of administration. For example, a liposome drug formulation may exhibit extended-release characteristics in comparison to a non-liposome formulation with the same active pharmaceutical ingredient.

If nonliposome formulations have been approved, we recommend comparing the proposed liposome to the corresponding approved nonliposome formulation to elucidate differences in absorption, distribution, metabolism, and excretion (ADME). Conducting a mass balance study of a drug substance labeled with a radioactive isotope (e.g., ^{14}C, ^{3}H) in a liposome formulation and in a nonliposome formulation can be helpful in comparing drug distribution in organs of interest.

You should conduct comparative studies to define and assess differences in ADME of the active ingredient between liposome and nonliposome drug products when the following apply:

i. Two products have the same active ingredient.
ii. Two products are given by the same route of administration.
iii. The nonliposome drug product is approved and available for comparison.

In a single dose pharmacokinetic study, you should compare the liposome and nonliposome drug products using either a crossover or parallel study design that employs an appropriate number of subjects considering the study drug, disease for which it is used, use in specific populations, and other factors that apply. Depending on the drug substance under investigation, different doses of liposome and nonliposome drug products may be appropriate.

2. Biopharmaceutics

a. Drug Release Characteristics

You should demonstrate that the release characteristics of the liposome product meet the label claim, and describe any release differences between the liposome product and nonliposome product with the same active ingredient.

b. In Vitro/In Vivo Correlation (IVIVC)

Although it is challenging to establish IVIVC for liposome products, we encourage you to attempt it for your liposome product. Some in vitro/in vivo relationships (IVIVRs) may be established even if a complete IVIVC is not feasible.

c. Bioanalytical Methods

You should use validated bioanalytical methods when evaluating the pharmacokinetics and bioavailability of the liposome-contained and free drug substance (drug released from the liposome).[25]

d. Liposome-Protein Interaction

Depending on the types of lipids used in formulating liposomes, interactions between liposome surface and blood proteins may affect the drug release and pharmacological properties of a liposome drug product in vivo. Such interactions can have safety implications because of "dose dumping." Submission of information from prior studies of protein-liposome interactions may suffice for a new liposome drug product if the following apply:

i. Lipid composition of the formulation ingredients is the same as in the previously studied liposome drug product.
ii. Physicochemical characteristics of the two liposome drug products are similar.

C. Labeling

Specific recommendations regarding labeling content for liposome drug products are provided below. Additional guidance on current labeling requirements is available on the CDER guidance Web site. In particular, the guidance on *Safety Considerations for Container Labels and Carton Labeling Designs to Minimize Medication Errors* provides general labeling recommendations.

1. Nonproprietary Names of Drug Products Approved under the Federal Food, Drug, and Cosmetic Act

The nonproprietary name of a drug product approved under the Federal Food, Drug, and Cosmetic Act is its established name, which, in most instances, will be the United States Pharmacopeia (USP) drug product monograph title for that product. If there is no USP monograph for the liposome drug product, refer to 21 CFR 299.4, USP General Chapter <1121> *Nomenclature*,[26] and the USP Nomenclature Guidelines.[27] The liposome drug product nonproprietary name should include terminology to express that the product is a liposome or a pegylated liposome.

Examples:

[DRUG] Liposome Type X [DOSAGE FORM]
[DRUG] Pegylated Liposome Type X [DOSAGE FORM]

[25] See draft guidance for industry *Bioanalytical Method Validation*.
[26] United States Pharmacopeia-National Formulary (USP 40-NF 35, supplement 2 <1121> NOMENCLATURE.
[27] Refer to USP Nomenclature Guidelines on the USP website at http://www.usp.org/health-quality-safety/compendial-nomenclature.

The first liposome product approved for a particular drug and dosage form will be type A, but the type should not be given (i.e., "Type A" should not be included in the labeling). For subsequent drug products of the same drug and dosage form, you should list the type and replace "X" sequentially with B, C, D, . . . Z.[28]

2. Description Section

You should include a cautionary note emphasizing that liposome drug products may behave differently from nonliposome drug products or other liposome products even though the active ingredient is the same. The applicant should specifically describe such differences. Note: this is not necessary for liposome drug products determined by FDA to be therapeutically equivalent.

3. Dosage and Administration

You should include a statement recommending against substituting the liposome drug product for the nonliposome product or another liposome drug product that contains the same active ingredient unless FDA has determined that the products are therapeutically equivalent.

Where appropriate, reconstitution instructions[29] and a statement regarding the appropriate in-use period should be provided. This information should be provided for both unloaded liposomes that are reconstituted with a drug substance-containing solution at the time of use and for products in which the drug substance is loaded into the liposomes during manufacturing. For liposome drug products that are labeled for use after mixing with other approved drug products (e.g., large volume injectable solutions), admixing instructions and a statement regarding the appropriate in-use period of the admixed product should be included. As warranted, include storage conditions for the reconstituted drug, robustness of the liposome drug product under varied reconstitution conditions (e.g., degree of shaking), and use of in-line filters.

[28] Note that with respect to ANDA submissions, the product name is the same as the nonproprietary or established name of the RLD.
[29] See 21 CFR 201.57(c)(3)(i)(J)(iv).

IV. REFERENCES

Guidance for Industry[30]

Bioanalytical Method Validation

Changes to an Approved NDA or ANDA

Controlled Correspondence Related to Generic Drug Development

Drug Master Files Guidelines

Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA

Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Population Pharmacokinetics

Process Validation: General Principles and Practices

ICH, Q*1A(R2) Stability Testing of New Drug Substances and Products*

ICH, *Q2(R1) Validation of Analytical Procedures: Text and Methodology*

ICH, *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

ICH, *Q8(R2) Pharmaceutical Development*

ICH, *Q11 Development and Manufacture of Drug Substances*

[30] The guidances listed in the References are available on the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

JOINT APPENDIX 72

No. 2020-1184, -1186

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

MODERNATX, INC., FKA MODERNA THERAPEUTICS, INC.,
Appellant,

v.

PROTIVA BIOTHERAPEUTICS, INC.,
Cross-Appellant,

ANDREI IANCU, DIRECTOR, U.S. PATENT AND TRADEMARK OFFICE,
Intervenor

Appeal from the United States Patent and Trademark Office,
Patent Trial and Appeal Board in No. IPR2018-00739

NONCONFIDENTIAL OPENING BRIEF OF CROSS-APPELLANT PROTIVA BIOTHERAPEUTICS, INC.

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July 27, 2020

CERTIFICATE OF INTEREST

Counsel for Cross-Appellant Protiva Biotherapeutics, Inc. certifies the following:

1. Represented Entities. Provide the full names of all entities represented by undersigned counsel in this case. Fed. Cir. R. 47.4(a)(1): Protiva Biotherapeutics, Inc.

2. Real Party in Interest. Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. Fed. Cir. R. 47.4(a)(2): Genevant Sciences, Ltd., Genevant Sciences Holdings, Ltd., Genevant Sciences Corporation, Genevant Sciences, Inc., and Genevant Sciences, GmbH.

3. Parent Corporations and Stockholders. Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. Fed. Cir. R. 47.4(a)(3): Protiva Biotherapeutics, Inc. existed as a wholly-owned subsidiary of Arbutus Biopharma Corporation. Protiva Biotherapeutics, Inc. was amalgamated into Arbutus Biopharma Corporation in January 2018. No publicly held company owns more than 10% of Arbutus Biopharma Corporation's stock.

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are

expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47(a)(4): Edward R. Reines and Derek C. Walter of Weil, Gotshal & Manges LLP.

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). *See also* Fed. Cir. R. 47.5(b): The following case may be directly affected by this Court's decision in the pending appeal: *Moderna Therapeutics, Inc. v. Protiva Biotherapeutics, Inc.*, Case No. IPR2018-00680 (PTAB).

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b)(organizational victims in criminal cases) and 26.1(c)(bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6): None/Not applicable.

July 27, 2020

/s/ Michael T. Rosato
Michael T. Rosato
Attorney for Cross-Appellant
Protiva Biotherapeutics, Inc.

TABLE OF CONTENTS

Confidential Material Statement Pursuant to Federal Circuit Rule 25.1 (e)(B)

The redacted material at page 8 relates to a provision of the sublicense between Acuitas and Moderna.

TABLE OF AUTHORITIES

CASES

STATUTES

RULES

STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, counsel for Cross-Appellants states:

(a) There have been no prior appeals in this case.

(b) There are no cases involving the patent at issue pending.

(c) This Court has vacated and remanded the appeal of IPR2018-00680, involving US Patent No. 9,404,127, Case No. 2020-1183, in light of *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019).

INTRODUCTION

The nucleic-acid lipid particles of the challenged claims have achieved tremendous recognition and success in the gene therapy field and have solved a long-felt need for compositions that could safely and effectively deliver nucleic acids to target cells of patients.

Moderna only appeals the Board's obviousness conclusions as to a few dependent claims, which the appeal brief only addresses in passing. Given the innovation protected by the '435 patent, Moderna's petition was an ill-conceived challenge, relying on short-cuts rather than actual analysis of the prior art and the claims. In its obviousness challenges, Moderna relied upon prior art that taught extremely broad ranges but failed to address a reason to arrive at the claimed invention, much less a reasonable expectation of success. To the extent Moderna relied on the caselaw of "overlapping ranges," a presumption of obviousness based on overlapping ranges is grounded in routine optimization. Yet both parties and their experts agree that routine optimization is inapplicable here.

Recognizing the deficiencies of its petition materials, Moderna attempts to reconstitute it arguments on appeal. Specifically, Moderna strains to oversimplify the technology of the claimed particles, speaking simply of "four lipid components" that total 100 mol%. In doing so, it endeavors to reconstitute the art, relying on the perspective of all the cited references, as can be seen from the new

chart it presents on appeal, but never presented to the Board below. Blue Brief ("BB") at 19-20. Moderna should not be allowed to do so.

Moreover, extensive evidence of secondary considerations, much of which Moderna failed to address before the Board, supports the patentability of the claims. The Board's conclusion that Moderna failed to show the obviousness of the claims is supported by substantial evidence and should be affirmed.

Regarding the cross-appeal, Moderna's anticipation challenge is based on the erroneous assumption that composition of the particle is the same as the composition of the lipid mixture used in formulating the particles. The Board's finding that certain of the challenged claims are anticipated should be reversed as it is not supported by substantial evidence and is legally erroneous.

Finally, the Board's final written decision improperly denied Protiva's motion to amend based on an anticipation analysis that was never presented by Moderna, and, to the extent it need be addressed, the Board's denial should be reversed or, at a minimum, vacated and remanded.

STATEMENT OF JURISDICTION

I. Appeal

Moderna's appeal should be dismissed because Moderna lacks Article III standing, already admitting as much before this Court in its briefing seeking remand in view of *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir.

2029) ("*Arthrex*"). Jurisdiction is a threshold issue and need be decided before the merits of Moderna's appeal can be addressed.

In its appeal brief, Moderna argues it has suffered an injury in fact because 1) it is a current licensee of the patent at issue here, U.S. Patent No. 9,364,435 ("the '435 patent") as to four viral targets, with resulting monetary obligations, and prospective licensee more generally as to the '435 patent as well as other related patents; and 2) concerns over collateral estoppel resulting from the instant proceeding in a second IPR filed against a related patent, U.S. Patent No. 8,058,069 ("the '069 patent") (hereinafter, "the '069 IPR").[1] BB at 7. As discussed below, neither of these activities in itself rises to the level of providing an injury-in-fact, and thus Moderna fails to demonstrate that it has Article III standing.

A. Moderna's Admission of Lack Of District Court Standing Further Supports Lack Of Standing Before This Court

For Moderna to have Article III standing, there must be a case or controversy that is "justiciable under Article III." *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 126-27 (2007). There is no such case or controversy here and

[1] Moderna filed an IPR against the '069 patent on January 9, 2019. The '435 patent is a continuation of the '069 patent and the two patents share a specification.

Moderna has admitted as much. Specifically, Moderna admitted that it does not have Article III standing in its request for remand under *Arthrex.*

On March 6, 2020, Moderna filed a motion with this court requesting remand under *Arthrex*. In its reply brief filed March 20, 2020, Moderna attempted to distinguish *Ciena Corp. v. Oyster Optics, LLC*, Appeal No. 19-2117, Order (Fed. Cir. Jan. 28, 2020) (non-precedential) (holding that petitioners forfeit any Appointments clause challenge by bringing an IPR) on the basis that "there was no available district court action." ECF No. 40 at 3. Specifically, Moderna explained:

> Nor could there have been any such action. Any alleged use of the claimed technology by Moderna would be subject to the safe harbor provision of 35 U.S.C. § 271(e)(1) and thus an injury-in-fact supporting jurisdiction in a district court action would be lacking.

Id. at n.3. Moderna does not explain why it has standing in this Court but not in a district court. Moreover, Moderna issued a press release as recent as July 24, 2020 proclaiming it has developed its own proprietary LNP, its products are not covered by Arbutus'[2] patents, and does not have "any significant intellectual property impediments for any products we intend to commercialize."[3] As Moderna has

[2] Protiva Biotherapeutics, Inc. existed as a wholly owned subsidiary of Arbutus Biopharma Corporation. Protiva Biotherapeutics, Inc. was amalgamated into Arbutus Biopharma Corporation in January 2018.

[3] https://investors.modernatx.com/news-releases/news-release-details/statement-moderna-patent-trial-and-appeal-board-ptab-ruling/

admitted that it lacks Article III standing, Moderna's appeal should be dismissed for lack of jurisdiction.

B. Moderna's License or Potential License Do Not Support Article III Standing

Moderna cites *Phigenix, Inc. v. Immunogen, Inc.*, 845 F.3d 1168 (Fed. Cir. 2017) and *Samsung Elecs. Co. v. Infobridge Pte. Ltd.*, 929 F.3d 1363, 1368 (Fed. Cir. 2019) to support its argument that standing may be established by being an actual or prospective licensee of a patent. BB at 7. Moderna's argument fails for at least several reasons. First, a license in itself is not sufficient to establish Article III standing. Moderna assumes what it must prove. Second, even assuming Moderna's assertions as true fails to identify an injury-in-fact traceable to the sublicenses. Any "obligations" identified are nothing but rank speculation, which even Moderna characterizes as an if and when proposition.

Moderna cites to *Samsung,* but that case is inapposite to the facts presented here. Samsung and Infobridge both owned patents that were licensed as a pool. *Samsung*, 929 F.3 at 1368. Any patent that is declared invalid is removed from the pool and the other patents receive a higher level of the fixed royalty. *Id.* Thus, removing a patent from the pool in those circumstances would shift the relative amount of the royalty between Infobridge and other patent holders, including Samsung. This Court explained that "[w]hile *other licensing and royalty structures might compel a different result* where other standard-essential patents

are involved, the unique pool licenses here satisfies us that Samsung has standing in this appeal." *Id.* (emphasis added).

Moderna does not allege that, like Samsung, it is losing licensing revenue on one of its own patents. Samsung accomplished that by demonstrating that if Infobridge's patent were to be invalidated, its licensing income would be increased. Moderna, however, has failed to establish any actual or imminent injury in fact based on the '435 patent: rather, as discussed below, it merely speculates as to benefit it may receive if the claims of the '435 patent were determined to be unpatentable. Unfortunately for Moderna, as the precedent of the United States Supreme Court, as well as of this Court, makes clear, such speculative injury is not sufficient to establish Article III standing.

Moderna also argues that speculative obligations arising under the sublicenses also establish an injury-in-fact. Arbutus had entered into a cross-license agreement regarding the LNP technology with Acuitas, which Acuitas then illegitimately sublicensed to Moderna. BB at 7-8; Appx5750. Arbutus accordingly brought suit against Acuitas and was granted an injunction. Moderna was allowed to keep its four non-exclusive viral vaccine sublicenses as part of a settlement agreement. Appx5750. These sublicenses define certain milestone payment obligations for certain clinical activities should they actually occur. BB at 8; Appx6395-6396 (¶4). Moderna asserts that those milestone obligations can be

traced back to the validity of the '435 patent. BB at 8. If the '435 patent were found to be invalid, Moderna asserts that: its "financial obligations to Acuitas for practicing the '435 patent would extinguish;" it would be able to more easily attract "prospective partners;" and the amounts the parties are considering for further rights to the '435 patent would decrease. BB at 8-9.

But Moderna fails to identify any recent milestone payment or any such payment reasonably forthcoming. Moderna paid a milestone payment to Acuitas on or before February 2016, before Arbutus settled its suit with Acuitas. Exhibit 1, ¶10. Moderna does not allege that it has paid any additional milestone payments, much less any royalty payments, under the sublicenses.

Nor does Moderna assert, let alone establish, that any future milestone payments are forthcoming. Regarding the milestone payment due in relation to a potential future Phase II clinical trial, Moderna asserts only that such payment would be due if and when Phase II trials are initiated. Appx6396-6397 (¶5). "If and when" is a far cry from "actual" or "imminent" harm: rather, such a statement effectively demonstrates the speculative nature of Moderna's putative injury-in-fact. Moreover, as noted above, Moderna issued a press release as recent as July 24, 2020 proclaiming it has developed its own proprietary LNP and that its products are not covered by Arbutus' patents.

Modera also nowhere alleges that its milestone and other obligations are only due to the '435 patent, but in fact notes that the licensed LNP technology includes the '435 patent, and that other patents cover that technology. BB at 7-8, Appx6394-6395, Appx6397 (¶¶3-4). That other Arbutus patents may cover the LNP technology makes it speculative at best, and realistically unlikely, that its financial obligations would be extinguished if the claims of the '435 patent were unpatentable. *See*, *e.g.*, *Moment Pharm. v. Bristol-Myers Squibb Co.* 915 F.3d 764, 769 (Fed. Cr. 2019) (rejecting as too speculative the argument that petitioner may receive a royalty payment from a third party if that third party should produce a product covered by the claims). Moreover, Moderna [redacted] Provision of Sublicense [redacted] any theoretical economic concerns. *E.g.*, Appx6143 (§11.3(b)).

Moderna asserts further that it has manufactured its own standing because it has been in negotiations with Protiva regarding providing Moderna additional rights to the '435 patent, among other patents. Moderna alleges the "potential monetary amounts that Moderna is considering associated with such rights are directly impacted by the Board's validity determinations." BB at 8-9; Appx6398 (¶9). Moderna appears to be referencing potentially settling the IPRs it chose to file. Moderna, of course, cannot manufacture Article III standing by filing IPRs and then "considering" settling them.

Beyond that, Moderna's allegation is mere speculation, as it can point to no actual or imminent injury, but only to "potential monetary amounts" that Moderna is subjectively considering. Moreover, the fact that other patents cover the technology makes any potential injury even more speculative. As this Court has held, a "claim is not ripe for adjudication if it rests upon contingent future events that may not occur as anticipated, or indeed may not occur at all." *Altaire Pharm. v. Paragon BioTeck*, 889 F.3d 1274, 1283 (Fed. Cir. 2018) (in finding standing, noting that the injury was "inevitable"); *see also AVX Corp. v. Presidio Components, Inc.*, 923 F.3d 1357, 1366 (Fed. Cir. 2019).

C. Moderna's Filing of a Second IPR Against a Related Patent Does Not Manufacture an Injury-In-Fact

Moderna asserts that it has been harmed by the Board's Final Written Decision here because it might impact a subsequently filed IPR against the related '069 patent. BB at 9. According to Moderna, it "faces a threatened injury from the collateral estoppel effect…that is actual and real, and not merely conjectural." *Id.* (citing *Altaire Pharm.*, 889 F.3d at 1283 and *Electrical Fittings Corp. v. Thomas & Betts Co.*, 307 U.S. 241, 242 (1939)). Moderna's assertion was factually untrue and is rebutted by its own Exhibit 9.

Moderna points to Protiva's preliminary response, in which Protiva plainly argues that Moderna is improperly filing serial challenges against Protiva's patents and plainly requests the Board to exercise discretion to deny institution in the '069

IPR. BB at 9; Appx5759-5767. Protiva never argues estoppel or issue preclusion, but instead invokes a Board precedent against serial petitions as a harassment tool and poor use of Board resources, citing *General Plastic Industrial Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, 9-10 (addressing discretionary denial of serial petitions). Appx5759. The Board opted not to exercise its discretion and Protiva did not preserve its discretionary-denial argument in its response.

If the '069 IPR is relevant here, it is because it further illustrates that the very obviousness theory Moderna urges before this Court has never been substantiated before the Board and has been repeatedly disavowed by Moderna's own expert. Moderna incredibly asserts that, in view of the cited prior art, making a particle claimed in the '435 patent would have been "mere optimization to a person of skill in the art." BB at 21. Yet, Moderna's own expert testified that *the same* person of skill would view the lipid component ranges in *the same* prior art references as "immense," requiring "undue experimentation, not simple optimization." Appx5818, Appx5836. Thus, while the '069 IPR further illustrates that the Board was correct in this case in finding no "routine optimization" exists, the '069 IPR fails to manufacture Article III standing for Moderna where none otherwise exists.

For the reasons discussed above, Moderna has not met is burden of demonstrating that it has standing under Article III to appeal the Board's final

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written decision here, and Protiva respectfully requests this court to dismiss Moderna's appeal.

II. Cross-Appeal

This Court has jurisdiction over the issue presented on cross-appeal under 28 U.S.C. § 1295(a)(4)(A) (providing for appeal from a Board decision with respect to *inter partes* review under Title 35) and 35 U.S.C. § 141(c) (providing that any party to the underlying proceeding "who is dissatisfied with" the Board's final written decision may appeal only to this Court). The cross-appeal is timely under 37 C.F.R. § 90.3(a)(1) and Fed. R. App. P. 4(a)(3) because the notice of appeal was filed on November 13, 2019, which is within 14 days after Appellant's notice filed November 13, 2019.

STATEMENT OF THE ISSUES

1. Whether Moderna has Article III standing to appeal the Board's final written decision.
2. Was the Board correct in determining that Moderna never developed a meaningful obviousness case against dependent claims 7, 8, 10, 11, 13, and 16-20.
3. Is the Board's findings of no substantiated obviousness case with respect to dependent claims 7, 8, 10, 11, 13, and 16-20 supported by record evidence.

4. Can obviousness be found on a theory (routine optimization) Moderna never fully developed and its expert ultimately disavowed.
5. As to Protiva's cross-appeal, is the Board's finding of anticipation as to claims 1-6, 9, 12, and 14-15 over the '554 publication lacking substantial evidence and legally erroneous.
6. Did the Board err in denying Protiva's contingent motion to amend.

STATEMENT OF THE CASE

Moderna's appeal and Protiva's cross-appeal arise from an IPR proceeding brought by Moderna challenging claims from the '435 patent.

The '435 patent discloses and claims nucleic acid-lipid particles, wherein the nucleic acid is encapsulated in the particle. Such particles may be used to deliver a nucleic acid to a target, for example, in gene therapy methods. At the time of invention, the industry recognized that developing such particles was far from routine, and the claimed nucleic-acid lipid particles have achieved tremendous recognition in the field of gene therapy. *See* Appx285-286. In fact, patisiran, tradename "Onpattro,"—for which the '435 patent is listed in the Orange Book and serves as a protecting patent—was designated by the FDA as a "first-in-class" drug and has received regulatory approval not only in the U.S., but also in Europe. Appx5078-5080; Appx5081-5082; Appx5085-5087; *see also* Appx284; Appx4959-4960 (¶¶191-193).

Once that first lipid particle-based drug was approved for use in humans, the development was hailed in the field with express discussion of the difficulties in overcoming the technical hurdles associated with effective delivery. Appx5076-5077 ("[Delivery] proved to be a substantially harder problem than we anticipated..."), ("All of those tear-your-hair out days were worth it to get to today") *see also* Appx4959 (¶190). The literature explicitly credits the nucleic acid-particle delivery technology for the success of patisiran. Appx5076-5077; Appx5526-5535. The nucleic acid-lipid particles of the '435 patent thus solved a long-felt need for compositions that could safely and effectively deliver nucleic acids to patient target cells.

Moderna advanced both anticipation and obviousness theories against the challenged claims before the Board. Moderna's obviousness analysis rested on the disclosure of overlapping ranges in the prior art. As Protiva noted in response, Moderna failed to address a reason to combine or a reasonable expectation of success. Protiva also noted that an obviousness theory based on overlapping ranges is predicated on routine optimization and that both parties and both experts agreed that routine optimization was not applicable. Further, Protiva presented extensive evidence of unexpected results, as well as evidence of other secondary considerations such as commercial success and long felt need. Moderna failed to address much of that evidence.

In its final written decision, the Board determined that claims 1-6, 9, 12, and 14-15 had been shown to be anticipated, but concluded that Moderna had failed to demonstrate the obviousness of claims 7-8, 10-11, 13, and 16-20. The Board also denied Protiva's motion to amend.

I. Technological Background

A. There was a need to systemically deliver genetic material, i.e., nucleic acids, to patients

An objective of genetic therapy is the development of drugs—nucleic acids—to treat systemic diseases such as cancer, inflammation, viral infection, and cardiovascular disease. Delivery of nucleic acids, however, has been particularly challenging because they are large, negatively charged molecules that cannot simply be given to a patient systemically (*e.g.*, intravenously, orally) and allowed to passively enter cells. Appx4883-4884 (¶25). Therapeutic nucleic acids require an effective delivery vehicle, which has proven to present considerable technical obstacles. *See, e.g.*, Appx5021 ("The major hurdle right now is delivery, delivery, delivery"), (stating in 2003, "Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved."); Appx5035 ("Merck's Alan Sachs on RNAi's Big Challenge: Delivery, Delivery, Delivery); *see also* Appx4883-4884; Appx284-285, Appx291-292.

B. The field struggled for decades to identify an effective nucleic acid delivery system

The therapeutic potential of genetic therapy has been appreciated for over 25 years, but effectively delivering nucleic acid acids to target cells without eliciting vehicle-related toxicity prevented realization of this potential. *See, e.g.*, Appx4990, Appx4992; Appx5021. That the field struggled for 20+ years to find such a delivery vehicle speaks to the difficulty of the task. For example, an MIT immunologist noted that "physical delivery of the [siRNA] to diseased cells is extremely challenging." Appx4990; *see also* Appx5001 ("The intrinsic complexity of any such gene delivery vehicle can be expected to present continued challenges...."). Phillip Sharp, who shared the Nobel Prize in Physiology or Medicine for his work on RNA splicing, stated that "[t]he major hurdle right now [for RNAi therapeutics] is delivery, delivery, delivery." Appx5021; *see also* Appx5041 ("What's interesting about what we do is that the drug isn't the problem. It's the delivery of it."); Appx5024; Appx4992; Appx5035. By 2008, the industry-wide failure to identify a solution to the delivery problem resulted in waning confidence. Appx5024, Appx5032.

C. Toxicity Concerns Would Have Led An Ordinary Artisan Away From the Claimed Particles

The evidence developed before the Board established that the high cationic lipid levels required by the claims would have been disfavored in view of well-

established toxicity concerns. Appx4181. The toxicity of cationic lipids occurs at the cellular and organ levels, as these lipids are often not readily biodegradable and accumulate to cytotoxic concentrations in the liver and spleen. Cationic lipids also have immunostimulatory capacity and are associated with immunogenic and inflammatory responses. It was also appreciated that cationic lipid interacts with serum proteins, which can lead to aggregation and rapid clearance from the body. Appx4185. Consequently, the prior art expressly taught minimization of the cationic lipid component. *E.g.*, Appx4104. As one industry executive stated, "I wouldn't want anyone injecting cationic lipids into my bloodstream." Appx4992; *see also* Appx4104; Appx4181-4182, Appx4185; Appx4885-4887 (¶¶28-35); Appx292.

D. Both Parties Agree Routine Optimization is Simply Inapplicable

As is now acknowledged by both parties and their experts and corroborated throughout the literature, formulating nucleic acid lipid particles was complex, highly unpredictable, and not a matter of simple, routine optimization. Appx4626 ("Q. In the 2008 timeframe, was developing nucleic acid-lipid particles considered a routine matter of optimizing variables? A. No."); Appx4895 (¶58) ("The effects of making changes to the proportion of other components in the lipid particle would be unpredictable..."), Appx4896 (¶60) ("Making safe and effective nucleic acid-lipid particle formulations was not simply a matter of 'varying the proportion'

of cationic lipid in prior art formulations …"); *see also* Appx4895 (¶¶57-59), Appx4933-4934 (¶136); Appx4254, Appx4255, Appx4264, Appx4266, Appx4401, Appx4403; Appx4627; Appx511-514. Petitioner and its expert, Dr. Janoff, repeatedly emphasized the complexity of the field of art at the time. *See* Appx430-431; Appx73-74; Appx4127-4128 (¶¶65-68), Appx4130 (¶73); Appx5231-5232; Appx4659 (¶25); *see also* Appx512-513.

During his deposition in the '069 IPR,[4] Dr. Janoff went even further, repeatedly describing the very same prior art disclosure of lipid ranges (from the same artisan perspective) as so 'immense' that they would require "undue experimentation, not simple optimization." ("There is no way—there is no way a person of ordinary skill in the art would know what specific proportions might give results that are desired."), ("If the range is immense, there would be undue experimentation I believe to find a combination or a range that behaved in a desirable light."), ("By immense, I mean that in order to come up, in order for a person of ordinary skill in the art to find utility because of the immenseness of the range, this would require undue experimentation, not simple optimization"). Appx5836.

[4] Moderna attached Protiva's patent owner response in the '069 IPR as Exhibit 10 to its non-confidential opposition to Protiva's motion to dismiss for lack of standing.

The prior art cited by Moderna during the '435 IPR further corroborates the expert testimony that forming functioning lipid particles at the time was far from routine, but instead was a function of multiple parameters whose interactions were poorly understood, with limited guidance existing. *See, e.g.*, Appx4009 ("...the lack of mechanistic understanding of gene delivery by CL-DNA complexes is due to the large number of parameters involved."), ("[I]n comparative studies, typically only one or two data points per lipid are evaluated, allowing the ideal lipid composition (the ratio of neutral to cationic lipid) or cationic lipid/DNA ratio to be overlooked."); *see also* Appx4650 (¶25); Appx4184. Ahmad, relied upon by Moderna in a challenge not being appealed here, emphasizes the lack of mechanistic understanding of lipid-based delivery systems at the time "due to the large number of parameters involved" and observes the lack of empirical investigation ("few investigations to date include a complete examination of lipid performance as a function of lipid-bilayer composition and lipid/DNA charge ratio (ρchg)." *Id.* (references omitted); *see also* Appx4650 (¶25); Appx4184.

Record evidence also incontrovertibly establishes industry recognition that developing lipid particle formulations for drug delivery was not a simple or routine matter of optimizing variables. Appx5021 ("The major hurdle right now is delivery, delivery, delivery."); Appx5035, Appx5041 ("What's interesting about what we do is that the drug isn't the problem. It's the delivery of it."); Appx5024;

Appx4992; Appx5076-5077 ("[Delivery] proved to be a substantially harder problem than we anticipated..."), ("All of those tear-your-hair-out days were worth it to get to today"); Appx4990; Appx5001; *see also* Appx513-514. Thus, not only did Moderna never develop a routine optimization theory, it effectively disavowed the notion.

II. Protiva's Invention

The '435 patent is directed to the surprising discovery that nucleic acid-lipid particles with high levels of cationic lipids and low levels of conjugated lipids exhibit favorable *in vivo* transfection efficiencies, as well as "improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described." Appx842 (5:66-6:1, 6:2-14); Appx845 (11:31-42); *see also* Appx4883-4885 (¶¶25-28). The '435 patent claims nucleic acid-lipid particles with high levels of cationic lipid (50-85 mol%) and low levels of conjugated lipid (0.5-2 mol%), with specific amount of non-cationic lipid (13-49.5 mol%).

The understanding of the ordinary artisan at the time of invention, as demonstrated by all of the references cited by Moderna, was that formulations with a high level of cationic lipid were toxic and poorly tolerated *in vivo*, and would have little to no *in vivo* transfection efficiency. *E.g.*, Appx888 (¶6); Appx4096; Appx2269 (30:34-4); Appx4884-4887 (¶¶26-34). Additionally, where conjugated

lipids were utilized, the art instructed much higher levels as compared to those claimed. Appx4181; Appx4885-4886 (¶¶30-32).

Yet, contrary to these teachings, the claimed formulations uniformly withstood rigorous *in vivo* tests that established stability following systemic, *in vivo*, administration, suitability for mammals with no considerable toxicity, and transfection efficiencies superior to conventional formulations. *E.g.*, Appx842 (5:55-6:14); *see also* Appx4898-Appx4907 (¶¶66-81); Appx1664-1665, Appx1694-1695.

III. Procedural History

Moderna is appealing only the Board's conclusion of obviousness over the US2006/0134189 ("the '189 publication") and US2006/0240554 ("the '554 publication") with respect to claims 7, 8, 10, 11, 13, and 16-20. BB at 10. Moderna has thus waived any argument as to the Board's conclusions as to the remaining claims and grounds.

On cross-appeal, Protiva is appealing the Board's finding that claims 1-6, 9, 12, 14, and 15 are anticipated by the L054 lipid mixture of the '554 publication. Protiva is also appealing the Board's denial of its motion to amend based on grounds introduced by the Board for the first time in the final written decision.

A. Moderna's IPR

1. Moderna's Petition

Moderna offered three obviousness challenges in its petition: 1) Claims 1-20 as obvious over WO2005/007196 ("the '196 PCT") and the '189 publication; 2) Claims 1 and 4 over the '196 PCT and the '189 publication in light of the disclosures of Lin and/or Ahmad; and 3) Certain claims, *e.g.*, claims 7, 8, and 11, over the '554 publication. Moderna only appeals the Board's obviousness findings as to the '189 and '554 publications, and has thus waived any argument as to the Board's findings regarding the '196 PCT, as well as the '196 PCT and '189 publication in light of Lin and Ahmad.

Moderna's obviousness challenge argued for a *prima facie* case of obviousness on a per-limitation basis for what it contended were overlapping ranges of individual claim elements in the '196 PCT and the '189 publication. *E.g.*, Appx99, Appx104, Appx105, Appx119, Appx120; *see generally* Appx98-105, Appx117-121; *see also* Appx297-298. Moderna never addressed the claims as a whole as required by statute. Moderna's challenge focused primarily on independent claim 1, with only cursory comment and little analysis on the dependent claims being challenged. Moderna asserted that the testing disclosed in the '435 patent was insufficient to rebut the *prima facie* case, but provided

discussion (with faulty analysis) of only a subset of the testing disclosed. Appx97, Appx99.

Other than conclusory assertions that the individual limitations of the challenged claims were rendered *prima facie* obviousness over the ranges disclosed by the '196 PCT and the '554 publication, Moderna provided little else to substantiate its challenge. Discussion of specific reason to arrive at the claimed invention with a reasonable expectation of success was lacking entirely. *E.g.* Appx97-113, Appx116-1129; *In re Stepan*, 869 F.3d 1342, 1346 n.1 (Fed. Cir. 2017).

Besides being poorly developed and, at times, indiscernible, Moderna's challenge was also internally contradictory. Specifically, Moderna repeatedly cited to *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003), which explains a framework of obviousness under the theory of "routine optimization." 315 F.3d at 1330-31. Yet, Moderna's petition and the prior art cited repeatedly emphasized the complexity in the field and the corresponding unpredictability of formulating the claimed particles. *See, e.g.*, Appx73-74; Appx4127-4128 (¶¶65-68), Appx4130 (¶73).

As to anticipation, Moderna also asserted in its petition that certain claims were anticipated by the '554 publication. As noted above, Moderna lumped this assertion together with its obviousness challenge, making it difficult (in some instances, impossible) to discern on a claim-by-claim basis which theory applied to

which claims. Appx116. With so little discussion of the dependent claims, it was entirely unclear for certain claims what theory of unpatentability it was challenging the dependent claims—anticipation or obviousness. *Id.*; *see, e.g.*, Appx125-126, Appx127-129 (claims 9, 14-20). For some of the claims, Moderna referenced the L054 formulation in its challenge. Appx117-120; Appx1408. Pointing to Table IV in the '554 publication (listing starting ingredients for making lipid particles), Moderna concluded that, the L054 formulation included 50% cationic lipid, 48% cationic lipid, and 2% conjugate lipid. Appx117-118, Appx120.

The Board, in its institution decision, relied on the declaration of Moderna's expert, Dr. Janoff, which stated:

> The '554 publication also includes various specific formulations, including formulation L054, which contains 50% cationic lipid (DMOBA), 48% non-cationic lipid (Chol/DSPC), and 2% conjugate lipid (PEG-n-DMG). Ex. 1004, Table 4. This formulation was tested, for example, with siRNA for reducing HBsAg levels. *See id.*, Fig. 16. The disclosed nucleic acid-lipid particles meet all of the limitations in claim 1 of the '435 patent.

Appx249 (quoting Appx4120 (¶143)).

2. Protiva's Response

Despite the thinly developed (and, at times, completely unclear) challenges advanced, Protiva robustly responded to Moderna's challenges to the best it understood them. *See generally* Appx281-345; Appx4874-4960. As Protiva

pointed out, Moderna did little more than broadly assert individual limitations of some (though not all) challenged claims were *prima facie* obvious in view of specific prior art disclosure. Moderna never addressed the claims as a whole and never provided any meaningful discussion of reasons to combine prior art disclosure with a reasonable expectation of successfully arriving at the claimed subject matter. Appx298, Appx330. Its arguments that the known toxicity of cationic lipids would have not taught away from the claimed particles is contradicted by its own publications. Moderna also never addressed that making the claimed particles was not a simple matter of routine experimentation as confirmed by its own expert and throughout the scientific literature, failed to meaningfully address extensive experimental data showing unexpected and surprising results, or any of Protiva's evidence of additional secondary considerations, such as long felt need and commercial success. *See generally* Appx496-534.

In its obviousness challenge, Moderna rested entirely on its putative "*prima facie*," per-limitation case as though that alone met its ultimate burden of proof—which, of course, it did not. Record evidence underscored that Moderna's failure to address the claims as a whole is a substantial failing given the interdependency of the lipid components. *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006); Appx297, Appx301, Appx329. That is, properties such as toxicity and efficacy are

not a property of any single component, but are a property of the particle as a whole. Appx4895 (¶59); Appx302.

Protiva also cited *Stepan* for the proposition that every obviousness analysis requires a motivation to make the combination and a reasonable expectation that such a combination would be successful. Appx303-305; 869 F.3d at 1346 n.1. As noted in Protiva's response, Moderna failed to address a motivation to make the claimed combination, much less a reasonable expectation of success. Appx303-304; *see also* Appx301-303, Appx329-331. Even though Moderna failed to address the fundamental obviousness considerations of reason to combine and reasonable expectation of success, Protiva provided extensive evidence that the prior art did not provide such. For example, as to a reason to combine, Protiva explained that one could not just vary one lipid component, but would have to decide how it would then vary another, or all, of the remaining components, and that such changes would be unpredictable. Appx301-303; Appx4895 (¶¶57-58); Appx4932-4934 (¶¶133-37). If it had been that easy, the field would not have struggled for 20 years to arrive at an effective safe and effective delivery vehicle. Appx302, Appx4895 (¶59).

Protiva explained further that particles with high levels of cationic lipid and low levels of conjugated lipid would have been expected to be toxic and result in unstable particles that aggregate and are ineffective, teaching away from the

claimed particles. Appx304; Appx4897 (¶¶63-65). Moreover, the prevailing wisdom at the time was that, if the amount of cationic lipid were to be increased, one would also have to increase the amount of conjugated lipid. Appx302-303; Appx5340, Appx5356, Appx943 (¶216), Appx946 (¶228), Appx947 (¶232); Appx4185; Appx4104; Appx4896-4898 (¶¶61-68), Appx4933 (¶135).

Moderna, in reply, attempted to mislead the Board by offering a false narrative that certain cationic lipids (non-ionizable lipids) were recognized as non-toxic. Appx421-423. There was no evidence to support this assertion, and Moderna ignored that it had extensively published about toxicity concerns due to ionizable cationic lipids, the same lipids it asserted were somehow non-toxic. Appx525; Appx416, Appx421-423; Appx525; Appx3735; Appx3820-3821; Appx525-526. Thus, the known toxicity of cationic lipids, which Moderna's own publications acknowledge, taught away from the claimed particles, and further undermined any motivation (none ever provided by Moderna) to arrive at the claimed invention with reasonable expectation of success.

In reply, Moderna reiterated that it was relying on overlapping ranges to establish obviousness in its reply. Appx425 (citing *E.I. duPont de Nemours & Co. v. Synvina C.V.* 904 F.3d 996, 1006-8 (Fed. Cir. 2018)). But as Protiva noted, an obviousness theory grounded on overlapping ranges is predicated on the specific rationale of "routine optimization." Appx509. And certain challenged dependent

claims recited components with no corresponding overlapping range provided in the cited art. *E.g.*, Appx885 (claim 7). Moderna, however, never asserted routine optimization and was reasonably viewed as disavowing the theory with argument and prior art citation regarding the complexity and unpredictability in the field. Appx512-513; Appx73-74, Appx76-77, Appx87, Appx101.

Furthermore, any *prima facie* case that existed was rebutted with extensive experimental data demonstrating surprising in vivo efficacy and tolerability in dozens and dozens of different tested lipid particle compositions within the challenged claims. The extensive scope of the experimental testing conducted in the specification included many different formulations with many different combinations of different lipid components, gene targets, nucleic acid payloads and methods of production. *See* Appx5420-5423 (summary of exemplary formulations tested and within the scope of the '435 patent claims); *see also* Appx515-517. Such testing is more than sufficient to rebut any *prima facie* case of obviousness.

In particular, the prior art instructs that high-level cationic lipid compositions were expected to have poor efficacy and increased cytotoxicity and immunogenicity relative to low-level cationic lipid formulations. *See* Appx4096; Appx4104; Appx4181; Appx2269 (30:34-41). Contrary to these expectations, the claimed formulations are well-tolerated and efficacious at far lower dosages than

prior art compositions. Appx4898 (¶68); *e.g.* Appx876 (74:1-4) (Figure 3). These results are "an unexpected difference in kind that supports nonobviousness." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015). Thus, to the extent any *prima facie* case of obviousness was ever established, it was overcome by the extensive experimental data in the '435 patent and post-filing publications showing unexpected results. Appx304-311, Appx336-344.

Moderna ignored much of the experimental data presented in the '435 patent, offered no meaningful critique to the data that it did address, and failed to address that the claimed nucleic acid-lipid particle compositions are substantially non-toxic and non-immunogenic. *See also* Appx4899; Appx5420-5423; Appx516. Moderna also failed to acknowledge that the present case is nothing like previous instances where testing was rejected as not commensurate. *See, e.g.*, *Peterson*, 315 F.3d at 1331 (two data points were tested,); *duPont*, 904 F.3d at 996 (only a single data point was tested); *In re Greenfield*, 571 F.2d 1185, 1189 (Fed. Cir. 1978) (similar).

Protiva also presented evidence of other secondary considerations, such as long-felt need and commercial success. Appx336-344; Appx531-532. Rather than provide any meaningful analysis of the extensive objective indicia, Moderna in reply responds with citations to inapposite case law and raw speculation by its expert witness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016)

("[A] patent challenger cannot successfully rebut the presumption with argument alone—it must present evidence."); Appx531-532.

In response to the anticipation challenge instituted by the Board, Protiva pointed out that the lipid amounts listed in Table IV for the L054 formulation were for the lipid mixture used in formulating the particles and not for the composition of the particle itself. Appx322-323; *see also* Appx4921-4923 (¶¶109-110). Protiva also cited extensive evidence demonstrating that the input formulation and the output formulation are not identical and that the finished particle must be tested to determine its final composition. Appx323-324; *see also* Appx879 (79:50-80:9); Appx5242, Appx5243-5244, Appx5244-5245; Appx4921-4925 (¶¶109-115); Appx4995; Appx5007, Appx5012. The evidence cited by Protiva clearly demonstrated that Moderna's anticipation challenge was based on the erroneous assumption that the composition of a particle is the same as the lipid mixture used to produce the particle.

did not dispute its own oversight or the shortcomings of the cited art. Rather, it urged the Board to ignore them, arguing that reporting input concentrations was conventional. Appx428-429. As Protiva noted in its surreply, Moderna's dubious assertion missed the point—it had conceded no express anticipation and failed to substantiate inherent anticipation. Appx504-506.

Beyond that, Moderna attempted to inappropriately shift the burden from where it belongs—Moderna to prove anticipation—to Protiva to prove no inherency.

3. Protiva's Motion to Amend

Protiva's contingent motion to amend proposed substitute claims 21-40. The proposed amendments would narrow the claimed ranges of cationic lipid non-cationic lipids. Appx357. The proposed amendments would also explicitly add "serum stable," as well as the language "wherein the particle is formulated such that the nucleic acid is not substantially degraded after exposure of the particle to a nuclease at 37°C for 20 minutes," to the independent claim. *Id.*

Moderna, in opposition, did not set forth any explicit challenge over the prior art to the substitute claims as amended, referring vaguely to the prior art without identifying anything specific or explaining how it applies to the substitute claims. Appx483-484; *see also* Appx455-457. To the extent that a challenge could be discerned, Protiva explicitly noted that Moderna did not appear to be advancing an anticipation theory. Appx483.

B. The Board's Final Written Decision

The Board declined to reach Moderna's obviousness challenges of independent claim 1 after concluding that claim 1 had been shown to be anticipated. Appx25-26. The Board did, however, reach the obviousness of certain dependent claims that were not shown to be anticipated. Appx35-37.

Moderna does not challenge the Board's decision to not reach the obviousness of the claims that it found were anticipated, and thus that issue is not before this Court.

With regard to the remaining challenges, the Board agreed with Protiva as to the convoluted and confusing nature of Moderna's case—describing it as "not a model of clarity." Appx26. Nevertheless, the Board gave Moderna the benefit of the doubt in working through what challenges it could discern.

The Board determined that Moderna had set forth an obviousness challenge over the '554 publication only as to claims 7, 8, and 11. Appx29-30. The Board rejected Moderna's argument that the '554 publication rendered claim 7 obvious based on its finding that Moderna failed to demonstrate that it expressly disclosed a phospholipid range that overlapped that recited by that claim as Moderna had charged. Appx35-36; *see also* Appx123-124. The Board further rejected the notion that such a range could be achieved by "mere optimization or routine experimentation," as neither that rationale or any other was advanced and substantiated by Moderna. Appx35-36. As for claim 8, the Board concluded again that the claimed cholesterol range could not be achieved by "mere optimization or routine experimentation." Appx36. As for claim 11, which depends from claim 10, the Board found that Moderna did not set forth an obviousness challenge as to

claim 10, and had failed to demonstrate the claim was anticipated, and had thus also failed to establish that claim 11 was obvious. *Id.*

As to the obviousness of dependent claims 7, 8, 10, 11, 13, and 16-20 over the '196 PCT, the Board agreed with Protiva that Moderna's challenges to these dependent claims suffered from numerous shortcomings. Moderna "does not address the relationship between the different ranges for the components of the particles or any reason why one of skill in the art would combine these teachings with those that allegedly taught the limitations from which the claim at issue depends." Appx37. The Board noted further that Moderna failed to address a reasonable expectation of success, or why the claims as a whole would have been obvious over the '196 PCT. *Id.*

As to Protiva's cross-appeal, in concluding that the '554 publication anticipated claims 1-6, 9, 12, 14, and 15 of the '435 patent, the Board improperly rejected Protiva's argument that Table IV reported the lipid mixture that was used to make the particle and not the lipid composition of the particle itself. Appx21. Although the Board acknowledged the factual accuracy of that distinction, it based its inherent anticipation on 1) the irrelevant and incorrect assertion the '435 publication also used the same convention; and 2) Protiva's alleged failure to prove no inherency. Appx21-22.

The Board, however, concluded that Moderna had failed to show that claims 7, 8, 10, 11, 13, and 16-20 were anticipated by the '554 publication. Appx26. Neither party challenges these findings on appeal.

In denying Protiva's contingent motion to amend, the Board cited Judge O'Malley's concurrence in *Aqua Products v. Matal*, 872 F.3d 1290, 1306 (Fed. Cir. 2017), for the proposition that the "Board itself may justify any finding of unpatentability by reference to evidence of record in the proceeding." Appx47. The Board concluded that the contingent proposed claims were inherently anticipated by the L054 formulation of the '554 publication for the same reasons it found the certain original claims inherently anticipated. Appx50. Not only was the inherent anticipation conclusion flawed for the reasons explained vis-à-vis the original claims, such a conclusion was improper as Moderna never asserted that the proposed substitute claims were anticipated by the 554 publication's L054 formulation in its opposition to Protiva's contingent motion to amend.

SUMMARY OF ARGUMENT

Moderna's appeal addresses the Board's conclusion that Moderna failed to demonstrate the obviousness of claims 7-8, 10-11, 13, and 16-20. Before the Board and again before this court, however, Moderna only addresses those claims in passing, arguing broadly for a *per se* rule of obviousness under *Peterson* and *duPont*.

The Board's finding of anticipation based on the '554 publication, which is one basis for Protiva's cross-appeal, is rife with legal and evidentiary errors. Protiva provided unrebutted evidence that the concentration of lipids of the formulation the Board relied upon was for the lipid mixture used in making the particles, and not the lipid composition of the particles themselves. Protiva also provided unrebutted evidence that the concentration of the lipids in the mixture used to make the particles is not the same as the concentration of the lipids in the particle. The Board, however, improperly dismissed that evidence, instead relying on Moderna's argument that listing the composition of the starting lipid mixture was "conventional" in the art. In so doing, the Board improperly relied on an unsubstantiated inherency analysis, and improperly shifted the burden to Protiva to "definitively" prove no inherency.

Finally, Protiva cross-appeals the Board's denial of its motion to amend. To the extent the court reaches this issue, the denial should be reversed given the unsubstantiated inherent anticipation conclusion and improper shifting of the burden to Protiva to prove no inherency. Moreover, the Board denied the motion on a ground that Moderna did not present in the context of the motion to amend but was raised for the first time in the Board's final written decision.

STANDARD OF REVIEW

This Court reviews decisions of the Board under the standards set forth in the Administrative Procedure Act ("APA"). 5 U.S.C. § 706. Under the APA, factual findings of the Board are reviewed for substantial evidence. *Id*.; *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1078 (Fed. Cir. 2015); *Randall Mfg. v. Rea,* 733 F.3d 1355, 1362 (Fed. Cir. 2013). This includes factual findings as to the scope of prior art and whether a claim is anticipated or rendered obvious by the prior art. "Substantial evidence" is a deferential standard of review and requires "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1324 (Fed. Cir. 2017) (quoting *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938)). A review under the "substantial evidence" standard involves examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision. *See Universal Camera Corp. v. NLRB*, 340 U.S. 474, 487-88 (1951).

Anticipation is a question of fact and is reviewed for substantial evidence. A claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference. *Nidec*, 851 F.3d at 1273; *Crown Ops. Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375 (Fed. Cir. 2002). Although anticipation may be found even when a prior art reference fails to disclose a claim

element expressly, disclosure of a claim element cannot be assumed. *Nidec*, 851 F.3d at 1274 (reversing anticipation finding); *In re Chudik*, 851 F.3d 1365, 1371-72 (Fed. Cir. 2017) (same). In an *inter partes* proceeding, the burden of showing inherency is on the challenger. *Crown Ops.*, 289 F.3d at 1377-78 & n.4.

In order to establish that a patent claim is obvious under 35 U.S.C. § 103, one must first determine (1) the scope of the prior art, (2) differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the art—"Against this background, the obviousness or nonobviousness of the subject matter is determined," with additional "secondary considerations" given to certain indicia of nonobviousness. *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 404 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1950)). Those challenging a claim must provide some articulated reasoning that includes identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* Petitioners must also "explain *how* specific references could be combined." *ActiveVideo Networks v. Verizon Communications*, 694 F.3d 1312, 1327 (Fed. Cir. 2012).

In addition to providing a rationale for combining references, it is also Petitioner's "burden to demonstrate…that the skilled artisan would have had a reasonable expectation of success in [combining the references]." *Intelligent Bio-Sys. v. Illumina Cambridge*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016); *see also*

Arctic Cat Inc. v. Bombardier Recreational Prod. Inc., 876 F.3d 1350, 1360-61 (Fed. Cir. 2017) ("[W]here a party argues a skilled artisan would have been motivated to combine references, it must show the artisan would have had a reasonable expectation of success from doing so."). Unpredictability of the field is a key issue with respect to ascertaining a reasonable expectation of success. *Honeywell*, 865 F.3d at 1356 ("Unpredictability of results equates more with nonobviousness rather than obviousness, whereas that which is predictable is more likely to be obvious."). As this Court has explained, every obviousness challenge requires motivation to combine with an expectation of success. *Stepan*, 868 F.3d at 1346 n.1.

ARGUMENT

I. Scope of Review

Moderna asserts that it is appealing the Board's determination that dependent claims 7, 8, 10, 11, 13, and 16-20 are not obvious over the '189 publication and the '554 publication. BB at 10. However, Moderna's appeal is much narrower in view of the record below and corresponding issues of waiver. Additionally, Moderna's opening brief contains improper new arguments that are raised for the first time on appeal. As explained below, the proper scope of Moderna's appeal is limited to whether the Board properly found claims 7, 8, and 11 nonobvious over the '554 publication.

(a) Issues That Moderna Has Necessarily Waived

With respect to the Board's decision on Moderna's challenge based on the '196 PCT and '189 publication, Moderna does not present argument in its opening appeal brief as to: (1) findings made by the Board that are relevant to the alleged obviousness of claims 1-6, 9, 12, 14, and 15; and (2) findings made by the Board based on the '196 PCT. Accordingly, these issues are outside the scope of this appeal.

These waived challenges are particularly pertinent because Moderna never addresses the specific limitations of claims 7, 8, 10, 11, 13, and 16-20 in its opening brief (nor did it do so below). *See* Appx313-315; Appx532-533; Appx37.

Moreover, Moderna fails to inform this Court that, before the Board, it relied on the '196 PCT as representative of its obviousness challenge—the '189 publication was barely an afterthought which was mentioned briefly in the introductory remarks:

> The '189 publication is substantively similar to the '196 PCT and also discloses SNALPs comprising overlapping ranges of the lipid components similar to those discussed below for the '196 PCT…. In addition, the '189 publication discloses testing relating to the admitted prior art 2:40 formulation.

Appx97-98. The actual discussion of the challenge in Moderna's petition only refers to the '196 PCT. Moderna notes that the '189 publication includes testing of the 2:40 formulation (BB at 15, n.3), but fails to inform this Court that it did not rely on the testing in the '189 publication to argue its differential relevance to its challenge of the '189 publication as opposed to the '196 PCT, and that it in fact relied on the '196 PCT exclusively in the statement of the challenge. *See, e.g.*, Appx97-113. Moderna did not map disclosure in the '189 publication onto the limitations of claims 7, 8, 10, 11, 13, and 16-20— or, for that matter, any other claim of the '435 patent, only mapping disclosure of the '196 PCT onto the limitations of the challenged claims. *See* Appx97-113.

Because Moderna does not challenge findings based on '196 PCT, the Board's decision as to claims 7, 8, 10, 11, 13, and 16-20 should be affirmed

irrespective of any arguments Moderna now presents vis-à-vis the '189 publication.

Moreover, Moderna does not present argument in its opening appeal brief as to the Board's determination that claims 7, 8, 10, 13, and 16–20 are not anticipated by the '554 publication. For reasons discussed in more detail below, the scope of appeal as to the '554 publication is thus limited to obviousness of claims 7, 8, and 11.

(b) Argument Raised for the First Time on Appeal

"[A]bsent exceptional circumstances, a party cannot raise on appeal legal issues not raised and considered in the trial forum." *Hylete LLC v. Hybrid Ath., LLC*, 931 F.3d 1170, 1174 (Fed. Cir. 2019) (quoting *Finch v. Hughes Aircraft Co*., 926 F.2d 1574, 1576 (Fed. Cir. 1991)). None of the exceptional circumstances delineated by this Court (*see id*.) apply here.

Moderna argues for the first time on appeal that the Board should have found claims 10, 13, and 16-20 of the '435 patent unpatentable as obvious over the '554 publication. Moderna did not make such a challenge below—its obviousness challenge to dependent claims over the '554 publication before the Board was limited to only claims 7, 8 and 11. The Board directly addressed this in its decision, which Moderna does not contest. Appx29-30 (citing Appx123-129).

Accordingly, the scope of review as to the '554 publication is limited to the Board's determination that claims 7, 8, and 11 are not obvious.

Moderna also presents a new theory of obviousness based on an allegedly recognized "four lipid component system." *E.g.*, BB at 16-17 (citing Appx97-98) ("[T]he Petition asserted that the disclosure of overlapping ranges for each of the four lipid components in a four-lipid carrier system established a prima facie case of obviousness."). Moderna refers to "four lipid component" systems or "four lipid carrier" systems over sixty times in its opening brief, yet such systems were never mentioned in its petition.

Besides being untimely and beyond the scope of the Board's decision or record below, the tenuous four lipid component system argument is unfounded and undermined by record evidence. Cationic lipid, phospholipid, cholesterol, and conjugated lipid are the allegedly established components of these four lipid systems, *e.g.*, BB at 19, but the record evidence demonstrates these components are omitted entirely or, at best, optional in prior art systems. For example, Lin and Ahmad (references asserted in Ground 2 of the petition) disclose two-component lipid particles, lacking both cholesterol and conjugated lipid. Appx4089 (describing particles comprising cationic and phospholipid); Appx4099-4100 (same). Furthermore, the '554, '196, and '189 publications describe phospholipid, cholesterol, and conjugated lipid as strictly optional components. Appx1321

(¶¶12), Appx1334 (¶120), Appx1332-1334 (¶¶97-11), Appx1331 (¶92); Appx1248 (¶¶150, 152), Appx1240 (¶79). There was no "established" four-lipid component system.

Because Moderna's arguments as to four lipid component systems are both meritless and raised for the first time on appeal, these arguments should be dismissed.

II. The Board's Conclusion that Moderna Failed to Demonstrate the Obviousness of Claims 7-8, 10-11, 13, and 16-20 Should Be Affirmed

Moderna contends that the Board's conclusion that claims 7-8, 10-11, 13, and 16-20 were not shown to be obvious is in error. BB at 10. Moderna, however, fails to expressly address the limitations required by these dependent claims, instead focusing almost exclusively on its generic argument that the Board failed to properly apply the presumption of obviousness under the framework of the *Peterson/duPont* line of cases.

Moderna faults the Board for not sufficiently explaining its reasoning as to its obviousness determinations. The reasons for the Board's conclusions, however, are clear. Moderna's petition offered very little analysis of the appealed claims, failing to address numerous critical aspects of an obviousness inquiry, including the claimed subject matter as a whole, a reason to combine, a reasonable expectation of success, and whether the ordinary artisan would have found in the

cited art overlapping lipid ranges recited in the dependent claims, let alone arrived at the claimed ranges given the broad ranges disclosed by the prior art.

A. The Board's Conclusion That Claims 7-8, and 11 Were Not Obvious Over the '554 Publication Was Adequately Explained and Is Supported by Substantial Evidence

1. Claim 7

Claim 7 adds the limitation that the particle comprises from 3 to 15 mol% phospholipid. According to the Board, despite claiming such a range was expressly disclosed in the cited art Moderna failed to point to a phospholipid range that overlapped with the claimed range. Appx35.

Moderna's petition offered very little analysis of this claim and claimed an explicit disclosure of a phospholipid range. According to Moderna, the '554 publication disclosed that when combined with a cationic lipid portion "in the 60% range and cholesterol in the 20-40% range, the range of phospholipid is decreased to 0%-20%." Appx124. This argument fails as a threshold matter. As the Board correctly found, it is undisputed that the '554 publication fails to explicitly disclose a phospholipid range. *E.g.*, Appx35.

Moderna now argues on appeal that that it is sufficient if the ordinary artisan could manufacture a range from the prior art disclosure from a series of assumptions—and that such a manufactured range (as opposed to one expressly disclosed) creates a presumption of obviousness. BB at 33. Moderna, however,

cites no authority that the presumption of obviousness under *Peterson* and *duPont* would allow one to conjure a range by selective, hindsight-driven picking and choosing, and especially not when dealing with the broad ranges of the prior art and the interdependency of the components involved. *Peterson*, 315 F.3d at 1330 n.1; *duPont*, F.3d at 1011 n.15 (in distinguishing *Genetics*, noting that the "case [in *duPont*] presents 'not especially broad' ranges of temperature and pressure."); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (noting that the burden of production shifts to patentee "where there is a range disclosed in the prior art, and the claimed invention falls within that range"); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006) ("where a claimed range overlaps with a range disclosed in the prior art, there is a presumption of obviousness."). Moderna also fails to provide any justification for extending the reasoning of *Peterson* and *duPont* to provide a presumption of obviousness when the range is not explicitly disclosed but is arrived at by making a series of assumptions. That is especially important here, where Moderna made a series of unexplained and unreasonable assumptions to manufacture a phospholipid range. *E.g.*, Appx124 (assuming, without explanation, a cationic lipid range of about 60%).

On appeal, Moderna now assumes a 50-60% cationic lipid range, arriving at a 0-28% phospholipid range, whereas, the petition offered 60% cationic lipid range

and cholesterol in the 20-40% range, and a phospholipid lipid range of 0%-20%." *Compare* Appx124 *with*, BB at 32. Moderna's new calculation on appeal is not only untimely and improper, but it also further illustrates the fallacies and inaccurate assumptions innate in Moderna's manufactured phospholipid range.

The Board also correctly concluded that Moderna never addressed, let alone established, that arriving at the claimed phospholipid range would have required only mere optimization or routine experimentation. Appx35-36. As is discussed extensively above in the Statement of the Case, both parties agree that formulating nucleic acid lipid particles was complex and highly unpredictable, and not a matter of simple, routine optimization.

The Board thus properly concluded that Moderna failed to point to an overlapping phospholipid range. Appx35. Accordingly, the Board's conclusion that the '554 publication does not render the claim 7 obvious is adequately explained and is supported both by the caselaw and substantial evidence.

2. Claim 8

Claim 8 adds the limitation that the range of cholesterol or derivative-thereof present in the particle is from 30 to 40 mol%. In its petition, Moderna asserts that the '554 publication provides a generic disclosure of 20 to 45% cholesterol, and also points to the L106 lipid mixture of Table IV of the '554 publication as having 30% cholesterol. Appx124-125. Based on this limited analysis, the Board

properly found that Moderna had not demonstrated how that range would be achieved by mere optimization or routine experimentation.

On appeal, Moderna does not argue that it had made a showing of routine optimization; rather, it argues that such a showing is not necessary under *Peterson* and *duPont*. BB at 35. Moderna is incorrect, as those cases are predicated on routine optimization. *E.g., Peterson*, 315 F.3d at 1330 n.1 ("[Overlapping] ranges ***that are not especially broad*** invite ***routine experimentation*** to discover optimum values, rather than require nonobvious invention") (emphasis added); *duPont,* 904 F.3d at 1006 ("The legal principle at issue in this case is old....it is not inventive to discover the optimum or workable ranges by ***routine experimentation***."). Its failure to address routine optimization is thus fatal to its obviousness challenge.

Accordingly, the Board's conclusion that the '554 publication does not render the claims obvious is adequately explained and is supported both by the caselaw and substantial evidence.

3. Claim 11

As to claim 11, which depends from claim 10, the Board noted that Moderna had failed to establish that claim 10 was anticipated by the '554 publication and had failed to challenge that claim as obvious. Appx36. Moderna does not contest the Board's finding as to claim 10, and had thus waived any challenge to the

Board's finding as to that claim. Accordingly, Moderna has also failed to establish that the Board erred as to claim 11.

B. The Board's Conclusion That Claims 7-8, 10-11, 13, and 16-20 Were Not Obvious Over the '189 Publication Was Adequately Explained, Is Now Waived, and Is Supported by Substantial Evidence

1. Claims 7 and 8

Claim 7 adds the limitation that the "phospholipid comprises from 3 mol% to 15 mol%" of the total lipid, and claim 8 adds the limitation that the cholesterol or derivative thereof comprises 3 mol% to 15 mol% of the total lipid. The petition, in addressing these claims, never mentions the '189 publication, but solely relies on the '196 PCT. *See* Appx107-109. In addition, in its analysis of these claims, the petition relies on an example from another patent that was incorporated by reference into the '196 PCT that has 56% cationic lipid, 14% phospholipid, and 30% cholesterol. That example, however, fails to meet the lipid components of claim 1, as it contains no conjugated lipid, and Moderna fails to explain how one would use that disclosure to arrive at the specific ranges required by claims 7 and 8.

On appeal, Moderna argues that its petition "provided detailed analysis how Protiva's own prior art '189 publication discloses…the exact same four-lipid carrier system addressed in the '435 patent claims," as well as *in vivo* testing, which the Board dismissed with no substantive analysis. BB at 39. Moderna

complains that the Board failed to address the overlapping ranges for each component or the prior art 2:40 formulation. But as already noted, far from providing any "detailed analysis," Moderna did not even reference the '189 publication in its analysis of claims 7 and 8. *See* Appx107-109.

The Board correctly found that Moderna failed to address a reason to combine or a reasonable expectation of success. Appx37. Moderna does not challenge that finding but appears to be asserting that the presence of overlapping ranges is sufficient, and thus it did not need to address those factors. But no matter what the obviousness theory "there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful." *Stepan*, 868 F.3d at 1346 n.1. This is particularly pertinent where Moderna has disavowed the very "routine optimization" rationale underlying the *Peterson/duPont* cases it cites on appeal.

And as discussed above, a presumption of obviousness based on overlapping ranges under *Peterson* and *duPont* is predicated on routine optimization, and the Board specifically found that Moderna failed to address routine optimization. Appx37. Notably, Moderna does not state that finding is in error, nor does it attempt to show where it made such a showing below.

The Board also found that Moderna failed to address the claim as a whole, nor does Moderna challenge that finding on appeal. Appx37. Rather, Moderna

argues is did not need to do so. That is incorrect. Indeed, as the statute itself states: "if the differences between the subject matter sought to be patented and the prior art are such that the ***subject matter as a whole*** would have been obvious." 35 U.S.C. §103(a) (2012) (emphasis added).

Accordingly, given the numerous and substantial deficiencies of Moderna's obviousness challenge of claims 7 and 8, the Board performed the correct analysis, provided specific finding that Moderna failed to address a reason to combine, reasonable expectation of success, and routine optimization. The Board thus provided more than sufficient explanation.

2. Claims 10, 11, and 13

Claim 10 specifies certain PEG-lipid conjugates, and claim 11, which depends from claim 10, and further specifies the PEG-lipid conjugates. Claim 13 adds the limitation that the "nucleic acid is fully encapsulated in the nucleic acid-lipid particle."

In addressing these claims, Moderna never bothered to mention the '189 publication in its petition materials. Appx109-111. In addition, Moderna's petition engages only in claim mapping, pointing out where the additionally claimed limitation may be found in the '196 PCT, without addressing the claim as a whole. *Id.* Finally, Moderna's argument on appeal that the Board failed to address overlapping ranges, the *in vivo* testing, or the 2:40 formulation of the '189

publication does not apply to these claims. BB at 39-40. Moderna, on appeal, has thus failed to demonstrate Board error.

3. Claims 16-20

The remaining appealed claims are method claims. Claim 16 is drawn to a method of in vivo delivery of the particle of claim 1. Claim 17 is drawn to a method of treating a disease or disorder using the particle of claim 1, and claims 18-20 further specify the diseases.

Yet again, Moderna fails to mention to this court that it never bothered to provide any argument or analysis of the '189 publication vis-à-vis claims 16-20 in its petition challenge. Appx111-113. As with claims 10, 11, and 13, Moderna engages only in claim mapping, pointing out where the additionally claimed limitation may be found in the '196 PCT, without addressing the claim as a whole. *Id.* And yet again, Moderna's argument that the Board failed to address overlapping ranges, the *in vivo* testing, or the 2:40 formulation of the '189 publication does not apply to these claims. BB at 39-40. Moderna, on appeal, has again failed to demonstrate Board error.

C. Moderna Invoked an Obviousness Theory That It Never Developed and Conceded Was Inapplicable Before the Board

Moderna uses the bulk of its brief to generically argue that the Board failed to follow the framework of *Peterson* and *duPont* that a *prima facie* obviousness is established when the prior art discloses ranges that overlap with the claimed

ranges. *E.g.*, BB at 2. If this Court is inclined to entertain Moderna's new, broader theory of obviousness made on appeal (which it should not), engaging in a reweighing of the evidence developed below in view of that new theory, Moderna's appeal still fails.

Moreover, even to the extent that overlapping ranges creates a presumption of obviousness, that presumption is predicated on determining optimum or workable ranges by ***routine experimentation***. But both parties and their experts agree that routine optimization does not apply to the appealed claims. As discussed above in the Statement of the Case, the petition embraced the unpredictability of formulating the claimed particles, arguing, for example, that "minor variations in lipid percentages…may appreciably impact efficacy;" in essence, disavowing the same obviousness theory it was advocating. *E.g.*, Appx87.

Finally, the Board did appreciate and apply the framework of *Peterson* and *duPont*. That theory was heavily litigated and addressed before the Board. Protiva presented extensive evidence before the Board demonstrating that the only evidence of obviousness proffered by Moderna was identification of immensely broad ranges (which its expert described as requiring "undue experimentation, not simple optimization") and conclusory assertions that ranges rendered individual elements of the challenged claims "prima facie" obvious. But, as demonstrated

during trial, the ranges disclosed by the prior art were very broad, and the petition presented no evidence that one would have arrived at the claimed ranges in view of the broad disclosed ranges of the prior art. Protiva also presented extensive evidence that there would have been no reasonable expectation of success of arriving at the claimed ranges, which evidence was also unrebutted. The unrebutted evidence of record also established that it would not have been a simple matter of routine optimization to arrive at the claimed ranges. As such, to the extent any routine optimization challenge was presented to the Board, it was dead on arrival given the testimony of the experts from both parties and extensive, uncontroverted evidence establishing that arriving at the claimed subject matter in view of the immense lipid ranges in the art would have required undue experimentation, not simple optimization.

Thus, the Board's conclusion that Moderna did not meet its burden of demonstrating the obviousness of the claims was sufficiently explained and supported by substantial evidence.

1. Moderna Is Improperly Advocating for a *Per Se* Rule of Obviousness

Moderna's appeal brief makes clear it is advocating for a *per se* rule of obviousness based upon a showing of some encompassing or overlapping ranges, regardless of the breadth of the disclosed ranges, the predictability of the art, or whether it would be a simple matter of routine experimentation to arrive at the

claimed range. *See* BB at 10 ("did the Board err in requiring more than a showing of overlapping ranges to establish a *prima facie* case of obviousness under *Peterson* and *duPont*"), 17-18 (asserting that the Board erred by "misapplying *Peterson* and *duPont* in holding that more than a showing of overlapping ranges is required to establish a *prima facie* case of obviousness…."), 18, 21, 24 ("Under *Peterson* and *duPont*, a showing of such overlapping is all that is required to establish a *prima facie* case of obviousness, *i.e.*, such a showing subsumes the need for a separate showing of motivation and a likelihood of success for a *prima facie* case."), 35 ("[T]he Board improperly held that Moderna had to make additional showings, including 'optimization or routine experimentation'…and 'reasonable expectation of success'…to support its *prima facie* obviousness case").

Even putting aside that Moderna's challenges before the Board suffered from numerous critical deficiencies, including failure to identify disclosure of actual overlapping ranges in the cited art for many of the claims it challenged, the unpatentability standard it advocates is clearly not the law. First, the Supreme Court has admonished against *per se* rules in patent law. *Bilski v. Kappos*, 561 U.S. 593, 603 (2010) ("A categorical rule denying patent protection for 'inventions in areas not contemplated by Congress. . .would frustrate the purposes of the patent law.'"), *citing Diamond v. Chakrabarty*, 447 U.S. 303, 315 (1980). This Court has also been loath to endorse *per se* rules in patent law. *In re Ochiai*,

71 F.3d 1565, 1569 (Fed. Cir. 1995), *cited in TorPharm, Inc. v. Ranbaxy Pharm., Inc.*, 336 F.3d 1322, 1329 n.6 (Fed. Cir. 2003) ("We note again that *per se* rules do not govern the nonobviousness inquiry.").

Moreover, the *Peterson* line of cases does not support a *per se* rule of obviousness. *Peterson* concluded that disclosing "a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness," confirming that the relationship between the breadth of the disclosed range and the claimed range at least must be considered. *Peterson*, 315 F.3d at 1330; *see also duPont*, 904 F.3d at (noting "disclosure of very broad ranges may not invite routine optimization); *Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015) (acknowledging that a disclosed range may be so broad that the burden of producing evidence of evidence such as teaching away, unexpected results, or other secondary indicia does not shift to the patentee). As discussed below, these cases are grounded on a theory of routine optimization.

Moderna's invitation to this Court to adopt a *per se* rule of obviousness based on the mere presence of overlapping ranges should thus be flatly rejected.

2. *Peterson* and *duPont* Cases Are Predicated on Routine Optimization

This Court has explained that overlapping ranges, without evidence to the contrary, may invoke a rebuttable presumption of obviousness under the specific rationale of "routine optimization." *See, e.g.*, *Peterson*, 315 F.3d at 1330 n.1

("[Overlapping] ranges ***that are not especially broad*** invite ***routine experimentation*** to discover optimum values, rather than require nonobvious invention") (emphasis added); *duPont,* 904 F.3d at 1006 ("The legal principle at issue in this case is old....it is not inventive to discover the optimum or workable ranges by ***routine experimentation***."); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) ("Simply put, the typical desire of scientists to find ***an optimum value within a narrow disclosed range*** does not apply to the facts in this case."); *In re Applied Materials, Inc.*, 692 F.3d 1289, 1298 (Fed. Cir. 2012) (explaining that in the context of overlapping ranges evidence that variables interact in an unpredictable or unexpected way support nonobvious); *Stepan*, 868 F.3d at 1346, 1346 n.1 (rejecting obviousness in view of overlapping ranges because "[m]issing from the Board's analysis is an explanation as to *why* it would have been routine optimization to arrive at the claimed invention"). These cases make clear that to the extent a *prima facie* case of obviousness may have been established, it is overcome with a showing that routine optimization does not apply.

a. It is Undisputed That Making Nucleic-Acid Lipid Particles was Not a Simple Matter of Routine Optimization

Moderna did not explain in its case before the Board how the claimed ranges would be obtained by "optimization" and "routine experimentation." Making non-

toxic and effective nucleic acid-lipid particle formulations was not simply a matter of "varying the proportion" of cationic lipid in prior art formulations. *E.g.*, Appx99. As discussed above in the Statement of the Case, it is undisputed that making nucleic-acid lipid particles was not a matter of routine optimization. *E.g.* Appx511-514. Moderna thus invoked a theory of obviousness based on overlapping ranges that, as discussed above in the Statement of the Case, it disavowed in its petition. Moderna should not be allowed to now argue on appeal that obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable expectation of success." BB at 36 (quoting *Pfizer, Inc. v. Apotex*, *Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007)).

3. Moderna Never Provided a Reason for Selecting the Claimed Ranges from the Prior art Ranges, Much Less a Reasonable Expectation of Success

Regardless of whether the *Peterson* presumption (that overlapping ranges, without evidence to the contrary, may invoke a rebuttable presumption of obviousness under the specific rationale of routine optimization) applies here (it does not), Moderna still must provide articulated reasoning with some rational underpinning to support a conclusion of obviousness. *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 418 (2007); *see also Stepan*, 868 F.3d at 1346n.1 (explaining no matter what the obviousness theory "there must be a motivation to make the

combination and a reasonable expectation that such a combination would be successful."). As discussed above in the Statement of the Case and as the Board found, Moderna failed to address a reason to combine or a reasonable expectation of success.

Moderna attempts to assert on appeal that the Board ignored other formulations that have lipid concentrations that fall within the claimed ranges. BB at 4 (referencing the L054 formulation of the '554 publication), 22 (asserting that the "four-lipid carrier systems in both the '554 and '189 publications make clear the interplay between the individual lipid components in the particles"), 29 (referencing the 2:40 formulation of the '189 publication); 31 (referencing Table IV of the '554 publication). One of the problems for Moderna with that argument is that it is being made for the first time on appeal. Moderna did not provide any reason in its petition materials as to why the ordinary artisan would start with any of these specific disclosed formulations to arrive at the claimed formulations, much less addressing a reasonable expectation of success of doing so.

Moderna also attempts to oversimplify the analysis in its appeal brief by arguing that amount of the four lipid components in the particles of the dependent claims total 100 mol% and that the overlapping ranges are disclosed in the same paragraph. BB at 29, 37. The petition fails to address how the lipid components interact with one another and how the ordinary artisan would have accounted for

that interaction in attempting to optimize the components separately given the broad ranges of the prior art. Appx4892 (¶49), Appx4895 (¶¶58-59).

a. Claim as a Whole/Interaction of Components

Moderna's petition separately parsed the claimed amounts of cationic lipids, conjugated lipids, and non-cationic lipids from the references, in a vacuum, without regard to one another and their interdependency. *E.g.*, Appx98-105, Appx117-121; *see also* Appx297-298.

Moderna asserts on appeal that the Board ignored that the references provide working examples that provide context for the interplay of the lipid ranges. BB at 31. As discussed above in the Statement of the Case, however, Moderna never explained any such interplay in its petition. Moreover, as for the '189 publication, although Moderna noted in a single sentence in its petition that the publication discloses testing of the 2:40 (conjugated lipid:cationic lipid) formulation (Appx98), it failed to explain how that would lead one to the claimed particle, especially as the other formulation tested in the '189 publication is a 2:30 formulation. *E.g.*, Appx1260-1266 (Examples 2-12). And as to the '554 publication, Table IV (Appx1408) discloses a variety of lipid formulations, and Moderna's petition again failed to explain how any results obtained for those formulations would have led the ordinary artisan to the claimed ranges. In fact, the petition recognized the

unpredictability of such interplay by noting that "minor variations in lipid percentages…may appreciably impact efficacy." Appx87.

4. The Broad Ranges Disclosed by the References Do Not Invite Routine Experimentation

Obviousness under *Peterson* and *duPont* also does not apply when the disclosed range is so broad so as to encompass a large amount of distinct compositions. *duPont*, 904 F.3d at 1006 ("we have reasoned that disclosure of very broad ranges may not invite routine optimization."); *Genetics*, 655 F.3d at 1306 (explaining it is "the typical desire of scientists to find an optimum value within a ***narrow disclosed*** range," not ranges that are unduly broad) (emphasis added).

Dr. Janoff, Moderna's expert, however, repeatedly testified during his cross-examination in the '069 IPR that narrower lipid ranges than what is found in the art would be considered "immense" at the time and require "undue experimentation." Appx5836 ("There is no way—there is no way a person of ordinary skill in the art would know what specific proportions might give results that are desired."), ("If the range is immense, there would be undue experimentation I believe to find a combination or a range that behaved in a desirable light."), ("Immense is big. And by immense maybe I can help a little bit more. By immense, I mean that in order to come up, in order for a person of ordinary skill in the art to find utility because of the immenseness of the range, this would require undue experimentation, not simple optimization").

Specifically, the '189 publication teaches that "[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid" present in said particle (Appx1237 (¶152)), and the '554 publication teaches that the cationic lipid component can comprise from about 2% to about 60% of the total lipid (Appx1363 (¶313)). These ranges are dramatically broader than the claimed range of 50 mol% to 65 mol% recited in the challenged claims. *E.g.*, Appx300-301, Appx328.

For the conjugated lipid, the range for the more expansive "bilayer stabilizing component" genus that is disclosed by the '189 publication is "from about 0.5% to about 20% of the total lipid present in the particle" (Appx1237 (¶152)), and the broadest range disclosed by the '554 publication is "from about 1% to about 20%" (Appx1363 (¶313)). Again, those ranges are much broader than the claimed range of 0.5 mol% to 2 mol% of the total lipid. And the range of noncationic lipid disclosed by '189 and '554 publications is 5 to 90%, which is almost so broad as to not constitute a range. Appx1237 (¶152); Appx1362-1363 (¶312). Moderna provided no explanation in its petition as to why the ordinary artisan would have chosen the more limited claimed ranges given the breadth of the ranges taught by the '554 and '189 publications. *E.g.*, Appx509-511.

5. Moderna Never Substantively Addressed Protiva's Extensive Evidence of Secondary Considerations

As discussed above in the statement of the case, Protiva presented extensive evidence of unexpected and surprising results, as well as secondary considerations,

including long-felt need, failure of others, skepticism, and commercial success. Notably, as part of commercial success, the '435 patent is listed as protecting Patisiran, a first-in-class drug. Appx5078-5080; Appx5083; Appx5085-5087.

In its appeal brief, Moderna asks for a remand for the Board to consider its obviousness case as well as Protiva's evidence of secondary consideration. BB at 38. To the extent any *prima facie* case may have been established (it was not), the evidence of unexpected results is more than sufficient to demonstrate the criticality of the claimed ranges when compared to the broad ranges taught by the prior art. Moderna also failed to meaningfully address Protiva's evidence of secondary considerations before the Board, and it should not be given a chance to do so in the face of that failure. Accordingly, Moderna's failure to address Protiva's extensive evidence of secondary considerations provides an alternate reason to affirm the Board's conclusion that Moderna failed to establish the obviousness of the challenged claims.

PROTIVA'S CROSS-APPEAL

I. The Board's Finding That Claims 1-6, 9, 12, and 14-15 Are Inherently Anticipated is Legally Erroneous and Lacks Substantial Evidence

Neither Moderna nor the Board ever resolved the critical distinction between 1) starting ingredients for making lipid particles; and 2) the different lipid composition of particles resulting from the fabrication process. The claims of the '435 patent are directed to "nucleic acid-lipid particles" of defined composition.

Moderna in its challenge, and the Board in its decision, cites only the L054 formulation of Table IV in the '554 publication as allegedly anticipating claims 1-6, 9, 14, and 15 of the '435 patent. Appx118, Appx20.

But the L054 formulation of Table IV is a lipid mixture for making particles—not itself a particle. *See, e.g.*, Appx884 (claim 1 directed to a "nucleic acid-lipid particle"). The '554 publication does not disclose lipid compositions of resulting particles, nor does it disclose sufficient detail to reasonably assume the resulting particles fall within the scope of claim 1. Testimony from both experts, as well as corroborating literature (including FDA guidelines), describe an expected deviation between the L054 starting lipid ingredients and the resulting particles. Appx5007, Appx5012; Appx4921-4925 (¶¶109-116); Appx5242, Appx5243-5244, Appx5244-5255; Appx4995; Appx4924-4925 (¶¶113-115); Appx4442, Appx4447-4449, Appx4449; Appx324; Appx504-505. While it was never Protiva's burden as the non-moving party to prove no inherency, Protiva's expert provided reasoned explanation with corroborating evidence why the '554 publication's particle fabrication process would be expected to skew L054 particle lipid composition (particularly the conjugated lipid) outside the scope of the challenged claims. *E.g.*, Appx4924-4925 (¶¶113-15); Appx4446, Appx4449; Appx5244-5245; *see also* Appx506. Neither Moderna nor the Board dispute any of this.

Nevertheless, the Board found claims 1-6, 9, 12, 14, and 15 anticipated by the L054 formulation. Appx17-18. The basis of the Board's decision was not based on affirmative evidence that L054 resulting particles met the claim limitations (there is no such evidence), but on the irrelevant (and incomplete) observation that the challenged '435 patent also identifies mole percent of a formulations starting composition. Appx21-22. Beyond that, the Board merely criticized Protiva's expert for not "definitively" proving no inherency. Appx22-25. In so doing, the Board erred as a matter of law and improperly shifted the burden to Protiva, and the decision in this regard lacks the support of substantial evidence. The Board's finding that claims 1-6, 9, 12, 14, and 15 are anticipated by the L054 formulation of the '554 publication should thus be reversed.

A. It is Undisputed That L054 is Not a Lipid Particle Composition as Claimed

Moderna argued that the L054 formulation as described in Table IV of the '554 publication anticipated claim 1. Appx117-121. But as Protiva pointed out, the claims are to a nucleic acid-lipid particle not a composition for making a particle. Appx504-506. This was a critical oversight because Table IV lists compositions for making particles not the particles themselves. Appx1408.

Protiva established that the '554 publication does not disclose L054 particle composition, and that composition of a lipid formulation is not the necessarily the same as that of the lipid particle. *E.g.*, Appx5242, Appx5243-5244, Appx5244-

5245; Appx879 (79:50-80:9); Appx4995; Appx5007; Appx4921-4925 (¶¶109-116); Appx323-324; Appx504-505. Protiva further established that the method used for formulating particles often affects the composition of finished product, and most certainly would have done so in the case of L054. Appx1339 (¶165), Appx1381 (¶463); Appx4921-4924 (¶¶109-114). Protiva's expert, Dr. Thompson, explained how the detergent-based formulation method of the '554 publication, in particular, results in less efficient incorporation of cholesterol in the finished particles relative to the conjugated lipid. *E.g.*, Appx4924 (¶113), Appx4924-4925 (¶115). Lowering the cholesterol level in finished particles, in turn, alters the levels of the remaining components. Appx4449 ("If we have lower cholesterol, that conjugate lipid concentration is going up, not down."), Appx4446 (explaining that the cationic lipid would be expected outside the claimed range); Appx5244-5245 (Dr. Janoff describing failure to recover cholesterol in a particle altering the amount of the remaining components).

Consequently, alteration in the amounts of the remaining components and, in particular, conjugated lipid, results in particles that are outside the scope of claim 1. L054 has the starting composition including 2% conjugated lipid (PEG-n-DMG), which is right at the edge of the 0.5 mol% to 2 mol% range claimed in the '435 patent. *Compare* Appx1408 (Table 4) *with,* Appx884 ('435 patent, claim 1). As such, an increase in the conjugated lipid component in the finished product due

to differential efficiency of lipid component incorporation would knock the finished particle product outside the claimed range. Neither Moderna nor the Board dispute any of this.

That L054 is not a lipid particle is not disputed by the parties or the Board. It is also undisputed that the '554 publication does not report lipid composition of finished particles, it is entirely silent on this aspect. In fact, Moderna freely admitted that Table IV lists the composition of input materials not that of lipid particles. Appx4651 (¶27). The Board also acknowledges that Table IV lists the composition of input materials. Appx21. Accordingly, it is undisputed that the disclosure of L054 in Table IV is not an express disclosure of lipid particles within the scope of claim 1. Additionally, there is unrebutted record evidence that the '554 publication fabrication process (what scant detail is provided) would be expected to at least skew the cholesterol component downward and the conjugated lipid component upward relative to the starting ingredient composition.

B. The Board's Finding of Inherent Anticipation Lacks Substantial Evidence

Lacking express disclosure, a conclusion of anticipation requires evidence that the L054 formulation necessarily produces lipid particles within the scope of claim 1. *HTC Corp. v. Cellular Communs. Equip., LLC*, 877 F.3d 1361, 1368 (Fed. Cir. 2017) ("To anticipate a claim, a single prior art reference must disclose every limitation of the claimed invention either expressly or inherently."); *id.*

(citing *Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)) ("A party seeking to establish inherent anticipation must show that a person of ordinary skill in the art would recognize that missing descriptive matter in a prior art reference is nevertheless necessarily present.").

Moderna never submitted, and the Board's decision does not cite, evidence that a skilled artisan would recognize that the '554 publication, and, in particular, the disclosed L054 formulation, necessarily produces lipid particles within the scope of claim 1. All arguments in favor of anticipation were based on conjecture. This alone is sufficient reason to reverse the Board's decision.

Despite lacking such evidence, the Board found anticipation based on factual findings that are either irrelevant or wrong or both. For example, the Board found that "the '435 patent describes nucleic acid-lipid particles in terms of mole percent of the formulation's composition, not the particle, just as in the '554 Publication." Appx21.

First, the Board's finding is irrelevant to the scope and content of the '554 publication. There is no dispute that fabrication methods of the '435 patent are different from those of the '554 publication. Further, and as discussed above, there is no dispute regarding the expected results of fabricating particles according to the '554 publication. Even accepting the dubious assertion that using lipid percentages in the formulations for a nucleic acid-lipid particle "was accepted practice in the

field," Appx21 (citing Appx4651 (¶27)), it has no bearing on whether lipid particles fabricated from the L054 formulation are necessarily within the scope of the claims. Likewise, it is also not important, much less dispositive of the issue that Dr. Thompson, during his two-day deposition, could not recall in a moment a description of cationic lipid analysis after particle formulation in the '435 patent. Appx21, Appx4385.

Second, the Board's assessment of the facts is simply wrong. As Protiva pointed out to the Board, unlike the '554 publication, the '435 patent provides extensive characterization of finished particles including the lipid-to-drug ratio, particle size, polydispersity, and percentage encapsulation. Appx874, (Table 2); *see also*, Appx875-877 (Tables 4, 6 and 7); Appx505-506. Further, the '435 patent explains that its fabrication methods result in only minor variation between the input and the lipid composition of finished particles. *See, e.g.*, Appx873-874, (68:36-69:4) (describing "[l]ipid encapsulation of siRNA" and lipid composition variation). The '554 publication, on the other hand, does not disclose any characterization of finished particles, including those made from L054.

It is also not sufficient (and legally erroneous—see below) to simply knock down Protiva's evidence as "not definitively" proving no inherency. Beyond improperly allocating burden, the Board's comments fail to provide substantial evidence. *In re NuVasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016) ("[I]t is not

adequate to summarize and reject arguments without explaining why the PTAB accepts the prevailing argument."). The Board also side-stepped the conjugated lipid component entirely. For example, Protiva pointed out that the L054 particle composition is not disclosed and explained why the methods of the '554 publication would skew conjugated lipid amounts outside the scope of the claims. *E.g.*, Appx4924-4925 (¶¶113, 115). The Board responded that "any loss of the other lipid components, such as cholesterol, should result in a higher mole percentage of *cationic lipid*, which would be within claim 1's range." Appx22 (citing Appx4385) (emphasis added). Besides dodging Protiva's conjugated lipid argument, the Board's made an inaccurate and incomplete assessment of Dr. Thompson's testimony. For instance, the Board cites to Appx4385, but Dr. Thompson was not discussing the '554 publication at that time. He did address later in his deposition when he was asked about cationic lipid content in L054 particles, which the Board overlooks. Appx4447, Appx4446 ("...very likely that these particles are outside the range."). Dr. Thompson's testimony simply provides no support for the Board's finding.

The Board improperly faulted Dr. Thompson for "not definitively testify[ing] that the nucleic acid-lipid particle that is formed from the L054 formulation would fall outside of the claimed range." Appx23; *see also* Appx24 (faulting Dr. Thompson for not definitively testifying that the conjugated lipid

would be outside the scope of the claims). This is not Protiva's burden to prove. Dr. Thompson was not tasked with definitively proving no inherency, and his testimony should have been credited as dispositive of the issue in Protiva's favor. Appx23 (quoting Appx4447). Specifically, Dr. Thompson testified that whether any L054 particle is within the scope of the claims is "not an answerable question with any precision." *See HTC Corp*, 877 F.3d at 1368 (requiring that the missing disclosure is "necessarily present"). Dr. Thompson further testified "I don't know any more than the authors [of the '554 publication report] what's in their composition"—that is, the '554 publication is silent on the issue. Appx4446.

Despite repeatedly faulting Dr. Thompson for failing to testify definitively that L054 particles are outside the scope of the claims, the Board also gave no weight to his testimony that does address this issue. Appx24 ("[W]e find Dr. Thompson's opinion that no particles formed using the L054 formulation would be within the mole percentage ranges for lipids as required by claim one is speculative, and thus, not accorded weight."). Moreover, the summary dismissal Dr. Thompson's testimony as "speculative" is improper given the reasoned explanation given—contrasted with lack of disclosure in the '554 reference, the exacting standard for inherency, and the complete absence of evidence to the contrary.

The Board's comments regarding the broader range of distribution of particles amount to speculation regarding lipid particles that might be produced from L054. Appx24. Further, the Board's dismissal of Dr. Thompson's testimony that the '554 publication discloses the "wrong technique and unreliable in producing particles" as a "practical concern" does not change that the composition of such particles is an unanswerable question. Appx4447.

Finally, the Board relies on *Titanium Metals* to assert that anticipation "does not require that all of the formed particles from the L054 formulation, or even the majority of them, be within the claimed ranges as required by claim 1." Appx25 (citing *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985)). While it is true that a "claim is 'anticipated' if one of [the claimed compositions] is in the prior art," there still must be evidence that one composition of the '554 publication is within the scope of the claims. That evidence is lacking here and thus *Titanium Metals* is inapposite.

C. Finding Inherent Anticipation Based on Probabilities or Possibilities is Legally Erroneous

Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *MEHL/Biophile Int'l. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). Thus, the relevant inquiry under an inherent anticipation theory is whether there is evidence

that the L054 lipid mixture described in the '554 publication necessarily produces the claimed particles. Moderna did not submit, and the Board's decision does not cite, evidence that particles fabricated from the L054 lipid mixture are necessarily within the scope of the claims.

As described above, possibilities and probabilities alone underlie the Board's conclusion of inherent anticipation. Appx21-25. Accordingly, the Board's decision is legally erroneous.

D. The Board Improperly Shifted the Burden to Protiva to Prove No Inherency

"[Moderna] bears an evidentiary burden to establish that the limitation was necessarily present." *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1377 (Fed. Cir. 2002). But "[Moderna] offers only an assumption and its own contentions." *Id.*, 1378; *see also id.*, n.4 ("this Court finds puzzling [challenger's] reluctance regarding this approach to generate extrinsic proof that the [prior art] patent inherently meets the [claim] limitation").

Despite bearing the burden, Moderna presented no affirmative evidence that lipid particles produced according to the '554 publication necessarily meet the limitations of claim 1. This should be the end of the inquiry. *In re Magnum Tools Int'l*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (citing *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)) ("In an inter partes review, the burden of persuasion is on the petitioner to prove unpatentability by a

preponderance of the evidence, 35 U.S.C. § 316(e), and that burden never shifts to the patentee.") (internal quotes omitted).

In the absence of evidence, the Board improperly placed the burden on Protiva to "definitively" prove that the L054 lipid mixture did not produce the claimed particles. Appx23 ("Dr. Thompson does not definitively testify that the nucleic acid-lipid particle that is formed from the L054 formulation would fall outside of the claimed range"); Appx24 (Dr. Thompson would not confirm that none of the particles produced by the L054 formulation process would have less than 2 mole percent of conjugated lipid"). In so doing, the Board improperly shifted the burden to Protiva to prove that particles that might be produced by L054 would necessarily fall outside the claims. That is, the Board found anticipation on an unsubstantiated inherency theory that it required the non-moving party to disprove. The Board's decision is legally erroneous in that it represents an improper burden shift.

II. Board Improperly Denied Motion to Amend

This Court need not reach the amended claims should it affirm the Board's non-obviousness findings challenged by Moderna and reverse the Board's anticipation findings per Protiva's cross-appeal. Under such circumstances, the contingency in Protiva's contingent motion to amend will never have been

triggered. To the extent the issue is reached, the Board's denial of the motion to amend was improper.

In response to the preliminary claim construction adopted by the Board in its institution decision, Protiva offered a contingent motion to amend making explicit the claim construction it proffered in its preliminary response of requiring serum stability, and hence, encapsulation[5] of the nucleic acid.

The Board found inherent anticipation of the amended claims over the L054 formulation in the '554 publication for the same rationale if determined original claim 1 was anticipated. *See* Section Protiva's Cross-Appeal, Section I.B, above. The Board's findings are erroneous for at least the same reasons explained above.

Additionally, Moderna did not bring a prior art challenge in its opposition paper. *E.g.*, Appx483-484 (noting that the opposition did not articulate a prior art challenge, requiring Protiva to speculate as to its theory of the unpatentability of the amended claims). Despite Moderna's failure to mount a prior art unpatentability case in its opposition, the Board assumed that petition grounds were asserted in opposition. Appx47 (citing Appx455-467); 37 C.F.R. §42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document.").

[5] Protiva preserves this issue of claim construction if remanded to the Board.

Perhaps tacitly acknowledging that the opposition did not present a prior art unpatentability ground, the Board cites *Bosch Auto. Serv. Sols., LLC v. Matal*, 878 F.3d 1027, 1040 (Fed. Cir. 2017), *as amended on reh'g in part* (Mar. 15, 2018) for the proposition that the "Board itself also may justify any finding of unpatentability by reference to evidence of record in the proceeding." Appx46-47. However, the fact that the '554 publication was of record does not remedy that the first time Protiva was put on notice of a challenge to the proposed substitute claims based on anticipation over the L054 formulation was the Board's final written decision. Because Protiva did not have an opportunity to address that challenge before the issuance of the final written decision, to the extent this Court remands this case to the Board to address the obviousness of the claims, it should be further instructed to allow Protiva the opportunity to respond to the anticipation challenge of the amended claims set forth by the Board in its final written decision. *See Nike, Inc. v. Adidas AG*, 955 F.3d 45, 51 (Fed. Cir. 2020) (noting that if the Board *sua sponte* raises a patentability issue as to substitute claims, it should provide notice and an opportunity to respond to the parties); *see also Hunting Titan, Inc. v. Dynaenergetics Europe GMBH*, IPR2018-00600, Paper 67 at 4 (PTAB, July 6, 2020) (precedential) (noting that the Board should only raise own ground of unpatentability as to a motion to amend "in certain rare circumstances.").

CONCLUSION

Accordingly, Protiva respectfully requests that the Board's decision as to the non-obviousness of claims 7, 8, 10, 11, 13, and 16-20 be affirmed. Protiva also requests that the Board's decision as to the anticipation of claims 1-6, 9, 12, 14, and 15 be reversed.

July 27, 2020

/s/ Michael T. Rosato
Michael T. Rosato
Attorney for Cross-Appellant
Protiva Biotherapeutics, Inc.

ADDENDUM

EXHIBIT 1

NO. S169829
VANCOUVER REGISTRY

IN THE SUPREME COURT OF BRITISH COLUMBIA

BETWEEN

ACUITAS THERAPEUTICS INC.

PLAINTIFF

AND

ARBUTUS BIOPHARMA CORPORATION

DEFENDANT

RESPONSE TO COUNTERCLAIM

Filed by: **The Plaintiff, Acuitas Therapeutics Inc. (the "responding party")**

PART 1: RESPONSE TO COUNTERCLAIM FACTS

DIVISION 1 – RESPONSE TO FACTS

1. The facts alleged in none of the paragraphs of Part 1 of the Counterclaim are admitted.

2. The facts alleged in paragraphs 1 and 2 of Part 1 of the Counterclaim are denied.

3. The facts alleged in none of the paragraphs of Part 1 of the Counterclaim are outside the knowledge of the responding party.

DIVISION 2 – RESPONDING PARTY'S VERSION OF FACTS

1. The responding party denies each and every allegation contained in the Counterclaim except as admitted herein.

2. The responding party repeats and relies on the facts set out in the Notice of Civil Claim.

3. In response to paragraph 10 of the Response to Civil Claim (relied on in the Counterclaim), gene therapy is not as described by the Defendant; rather, it is the delivery of mRNA or DNA into cells to express a protein. In the case of therapeutic applications of gene therapy, the expressed protein would provide a pharmacological benefit.

4. In response to paragraph 11 of the Response to Civil Claim (relied on in the Counterclaim), the meaning of "target" is not as described by the Defendant; rather, the meaning is defined in the Cross License Agreement. Further, gene therapy targets may comprise entire coding regions of the gene or the entire gene.

5. In response to paragraph 24 of the Response to Civil Claim (relied on in the Counterclaim), on or about May 27, 2015, Acuitas provided Arbutus (then Tekmira Pharmaceuticals Corp.) a copy of the sublicense granted to Moderna (the "Moderna Sublicense"), in accordance with the terms of the Cross License Agreement.

6. The Moderna Sublicense specifically refers to the terms of a Development and Option Agreement entered into by Acuitas and Moderna.

7. The terms of the Moderna Sublicense provide that the sublicense is for a licensed target, in this case Influenza A, as opposed to a specific formulated product.

8. Further, the Moderna Sublicense expressly grants Moderna a sublicense to technology in-licensed to Acuitas, pursuant to the terms of the applicable in-license.

9. As such, as of May 2015, Arbutus was aware of Acuitas' work with Moderna under the Moderna Sublicense and the specific terms of the sublicense.

10. Arbutus has also benefitted from Acuitas' work with Moderna. In February 2016, Acuitas notified Arbutus that Acuitas had achieved a milestone under the Cross License Agreement in connection with its work with Moderna and paid Arbutus a milestone payment, as required by the Cross License Agreement. Arbutus has never returned this payment.

11. Until June 2016, at no time did Arbutus express concerns with respect to Acuitas' work with Moderna or the Moderna Sublicense.

12. In response to paragraph 25 of the Response to Civil Claim (relied on in the Counterclaim), at all times, Acuitas has abided by the terms of the Cross License Agreement. Specifically,

    (a) Acuitas was never assisted by, nor did it collaborate with, Moderna using Arbutus' technology without a license; no rights are provided to Moderna to use Arbutus technology in the Development and Option Agreement unless and until a sublicense is entered into;

(b) Acuitas did not grant a sublicense to Moderna before it had developed a Sublicensable Product;

(c) The Cross License Agreement does not restrict sublicensing to a "specific formulated product", as alleged; rather, it permits Acuitas to grant Moderna a target license:

(i) Sublicensable Product is defined in the Cross License Agreement as

> …a Supplemental Field Product that has been developed by Acuitas and for which Acuitas has shown (i) in the case of an Antisense product, a pharmacological effect of that product against the Target or (ii) in the case of a Gene Therapy product a pharmacological effect resulting from expression of the protein, in both cases in *in vivo* studies in a small animal species;

(ii) Target is defined in the Cross License Agreement as

> …any of (a) a nucleic acid that encodes or is required for expression of a polypeptide (including without limitation messenger RNA and miRNA), together with all variants of such polypeptide; (b) the set of nucleic acids that encode a defined non-peptide entity, including a microorganism, virus, bacterium or a single cell parasite; provided that the entire genome of a microorganism, virus, bacterium, or single cell parasite shall be regarded as a single Target; or (c) naturally occurring interfering RNA or miRNA or a precursor thereof;

(iii) Section 3.1 of the Cross License Agreement provides:

> For the purposes of section 3.1, a Supplemental Field Product shall be considered the same Supplemental Field Product provided that the intended Targets remain the same and, for greater certainty, any change of the lipid nanoparticle formulation or any other drug delivery particle, vehicle and/or mechanism or change in the Antisense or DNA plasmids or mRNA (the "Acuitas Payloads") or any chemical modification to the Acuitas Payloads, any change in dosages strength, an change in the sequence of the Acuitas Payloads for the intended Target, or any addition of or change in any other active pharmaceutical ingredients delivered with the Acuitas payloads, does NOT constitute a new Supplemental Field Product if the intended Target remains the same;

(d) The Moderna Sublicense is for a vaccine; a vaccine is a Gene Therapy product as defined in the Cross License Agreement; and

(e) The Moderna Sublicense otherwise complied with the definition of Supplemental Field Product.

13. In response to paragraph 27 of the Response to Civil Claim (relied on in the Counterclaim), the Cross License Agreement does not prohibit Acuitas from developing products jointly with third parties. Further, the licensing options granted to Moderna pursuant to the Development and Option Agreement were merely options, not sublicenses; no rights were granted to Moderna thereunder unless and until a sublicense was granted by Acuitas in accordance

with the Cross License Agreement. Accordingly, Acuitas was not required to test products over which those options were granted in a small animal species, or meet any other of the requirements of the Cross License Agreement.

14. In response to paragraph 28 of the Response to Civil Claim (relied on in the Counterclaim), Acuitas gave notice to Arbutus of a second sublicense entered into with Moderna, in accordance with the Cross License Agreement. Acuitas denies that it breached the Cross License Agreement in respect of the second sublicense and repeats and relies on the facts pleaded in paragraph 12 herein with respect to that sublicense.

15. In response to paragraph 29 of the Response to Civil Claim, Acuitas has not provided Arbutus' technology to other third parties in breach of its obligations under the Cross License Agreement or otherwise.

DIVISION 3 – ADDITIONAL FACTS

16. N/A

PART 2: RESPONSE TO RELIEF SOUGHT

17. The responding party consents to the granting of the relief sought in none of the paragraphs of Part 2 of the Counterclaim.

18. The responding party opposes the granting of relief sought in paragraph 3 of Part 2 of the Counterclaim.

19. The responding party takes no position on the granting of the relief sought in none of the paragraphs of Part 2 of the Counterclaim.

PART 3: LEGAL BASIS

20. The whole of the Counterclaim should be dismissed as there are no breaches of contract, no wrongful gains, and no damages suffered by the Defendant.

21. Acuitas has not breached its obligations under the Cross License Agreement, as alleged, or at all, and, in specific response to paragraph 4 of the Counterclaim:

(a) the Cross License Agreement does not restrict sublicensing to a "specific formulated product", as opposed to a target;

(b) the sublicenses granted by Acuitas are for products that are Supplemental Field Products, specifically, Gene Therapy products, as these terms are defined in the Cross License Agreement;

(c) Acuitas is free to grant sublicensing options to third parties; the Cross License Agreement does not require Acuitas to demonstrate a pharmacological effect in a small animal study prior to granting a sublicensing *option*;

(d) at no time did Acuitas grant *sublicenses* for Supplemental Field Products prior to demonstrating their pharmacological effects in a small animal study;

(e) the sublicenses granted were for products that were developed by Acuitas;

(f) Acuitas did not provide or sell Arbutus' technology to third parties independent of a Supplemental Field Product; and

(g) Acuitas did not encourage or permit any third party to use Arbutus' technology without a license or a sublicense.

22. In the alternative, if the Defendant suffered any damages, which is denied, then the damages claimed are remote, not available at law, and the Defendant failed to mitigate the damages.

23. Further, and in the alternative, if Acuitas breached the Cross License Agreement, which is denied, then Acuitas is entitled to equitable relief and Arbutus is estopped from relying on its rights under the Cross License Agreement on the basis that its conduct, including its awareness of the terms of the Moderna Sublicense and its acceptance of milestone and other payments from Acuitas, encouraged Acuitas to believe that Arbutus did not intend to rely on its strict rights, which caused Acuitas to act to its prejudice.

Address for service of the responding party:

Address for service:	McCarthy Tétrault LLP Barristers & Solicitors Suite 2400, 745 Thurlow Street Vancouver BC V6E 0C5 **Attention: Miranda Lam**
Fax number for service (if any):	604-622-5764
Email address for service (if any):	mlam@mccarthy.ca

DATED: December 9, 2016

For Miranda Lam
Counsel for the Plaintiff

Rule 7-1 (1) of the Supreme Court Civil Rules states:

1. Unless all parties of record consent or the court otherwise orders, each party of record to an action must, within 35 days after the end of the pleading period,

   (a) prepare a list of documents in Form 22 that lists

      (i) all documents that are or have been in the party 's possession or control and that could, if available, be used by any party at trial to prove or disprove a material fact, and

      (ii) all other documents to which the party intends to refer at trial, and

   (b) serve the list on all parties of record.

CERTIFICATE OF COMPLIANCE

I certify that this brief complies with the type-volume limitation of Fed. Cir. R. 28.1(b)(2)(A). The brief contains 16,352 words, excluding the parts of the brief exempted by Fed. R. App. P. 32 (f) and Fed. Cir. R. 32(b)(2). This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in 14 point Times New Roman font.

July 27, 2020

/s/ Michael T. Rosato
Michael T. Rosato
Attorney for Cross-Appellant
Protiva Biotherapeutics, Inc.

CERTIFICATE OF SERVICE

I certify that counsel for the parties have been served with a true and correct copy of the foregoing document via this Court's CM/ECF system on July 27, 2020.

/s/ Michael T. Rosato
Michael T. Rosato
Attorney for Cross-Appellant
Protiva Biotherapeutics, Inc.

FORM 31. Certificate of Confidential Material

Form 31
July 2020

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

CERTIFICATE OF CONFIDENTIAL MATERIAL

Case Number: 20-1184, -1186

Short Case Caption: ModernaTX, Inc. v. Protiva Biotherapeutics, Inc.

Instructions: When computing a confidential word count, Fed. Cir. R. 25.1(d)(1)(C) applies the following exclusions:

- Only count each unique word or number once (repeated uses of the same word do not count more than once).
- For a responsive filing, do not count words marked confidential for the first time in the preceding filing.

The limitations of Fed. Cir. R. 25.1(d)(1) do not apply to appendices; attachments; exhibits; and addenda. *See* Fed. Cir. R. 25.1(d)(1)(D).

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☑ This number does not exceed the maximum of 15 words permitted by Fed. Cir. R. 25.1(d)(1)(A).

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☐ This number exceeds the maximum permitted by Federal Circuit Rule 25.1(d)(1), and the filing is accompanied by a motion to waive the confidentiality requirements.

Date: 07/27/2020

Signature: /s/ Michael T. Rosato

Name: Michael T. Rosato

JOINT APPENDIX 73

No. 2020-1184, -1186

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

MODERNATX, INC., FKA MODERNA THERAPEUTICS, INC.,
Appellant,

v.

PROTIVA BIOTHERAPEUTICS, INC.,
Cross-Appellant,

ANDREI IANCU, UNDERSECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,
Intervenor

Appeal from the United States Patent and Trademark Office,
Patent Trial and Appeal Board in No. IPR2018-00739

REPLY BRIEF OF CROSS-APPELLANT PROTIVA BIOTHERAPEUTICS, INC.

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Counsel for Cross-Appellant Protiva Biotherapeutics, Inc.

November 9, 2020

CERTIFICATE OF INTEREST

Counsel for Cross-Appellant Protiva Biotherapeutics, Inc. certifies the following:

1. Represented Entities. Provide the full names of all entities represented by undersigned counsel in this case. Fed. Cir. R. 47.4(a)(1): Protiva Biotherapeutics, Inc.

2. Real Party in Interest. Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. Fed. Cir. R. 47.4(a)(2): Genevant Sciences, Ltd., Genevant Sciences Holdings Limited, Genevant Sciences Corporation, Genevant Sciences, Inc., and Genevant Sciences GmbH.

3. Parent Corporations and Stockholders. Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. Fed. Cir. R. 47.4(a)(3): Protiva Biotherapeutics, Inc. existed as a wholly-owned subsidiary of Arbutus Biopharma Corporation. Protiva Biotherapeutics, Inc. was amalgamated into Arbutus Biopharma Corporation in January 2018. No publicly held company owns more than 10% of Arbutus Biopharma Corporation's stock.

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are

expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47(a)(4): Edward R. Reines and Derek C. Walter of Weil, Gotshal & Manges LLP.

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). *See also* Fed. Cir. R. 47.5(b): The following case may be directly affected by this Court's decision in the pending appeal: *Moderna Therapeutics, Inc. v. Protiva Biotherapeutics, Inc.*, Case No. IPR2018-00680 (PTAB); and *ModernaTX, Inc. v. Arbutus Biopharma Corporation*, Case No. 20-2329 (CAFC).

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b)(organizational victims in criminal cases) and 26.1(c)(bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6): None/Not applicable.

November 9, 2020

/s/ Michael T. Rosato
Michael T. Rosato
Attorney for Cross-Appellant
Protiva Biotherapeutics, Inc.

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INTRODUCTION

The Board erred in its final written decision in finding that claims 1-6, 9, 12, and 14-15 of U.S. Patent No. 9,364,435 ("the '435 patent') are anticipated by the L054 formulation disclosed in Table IV of U.S. Publication No. 2006/0240554 ("the '554 publication"). Independent claim 1 is drawn to a nucleic acid-lipid particle of specified lipid concentrations. It was undisputed before the Board that the relied upon L054 formulation is a list of starting ingredients used in making particles and not the lipid concentrations of the particles that ultimately result from the downstream fabrication process. It was also undisputed before the Board and corroborated with record evidence that 1) the '554 publication is silent regarding particle composition; and 2) the ordinary artisan knew that finished particle compositions could, depending on fabrication method, deviate significantly from the starting ingredient composition.

Moreover, although proving no inherency was never Protiva's burden, Protiva provided argument and evidence as to why merely assuming anticipation is improper. For example, Protiva's expert explained, and Moderna's expert never disputed, that the '554 fabrication process would preferentially extract out cholesterol compared to conjugated lipid, thereby skewing the resulting particle composition to be relatively higher in conjugated lipid compared the starting ingredient composition. This is particularly significant here since the conjugated

lipid of the L054 starting formulation is at the upper edge (2 mol %) of the claimed range, such that any upward skewing of the conjugated lipid component in the resulting particles knocks the particles outside the scope of the challenged claims. Moderna, like the Board's decision, sidesteps this evidence entirely.

Despite the silence of the cited reference on the critical issue of particle composition and the lack of alternate evidence to fill the void, the Board nevertheless found the claims anticipated by the '554 publication. In so doing, the Board improperly shifted the burden to Protiva to "definitively" prove no inherency, erred as a matter of law, and reached a conclusion lacking the support of substantial evidence.

In its reply before this Court, Moderna backpedals, attempting to re-write the record in a manner that remedies the Board's erroneous analysis. Moderna attempts to dispense with the Board's legal error by now arguing that, because the term "inherency" is not recited in the decision, the entire legal framework of inherent anticipation was not before the Board. If this is true, it merely simplifies the basis for reversal.[1] A claim is anticipated if the subject matter is disclosed in the prior art either expressly or inherently. There is no finding by the Board that the '554 publication expressly discloses the lipid composition of finished L054

[1] This is particularly true if Moderna concedes that inherent anticipation is unsubstantiated.

particles, and there could not be because no such disclosure exists. Thus, if Moderna only raised an express anticipation theory in its petition, that theory unquestionably fails because, as acknowledged by all, Moderna's petition pointed only to a list of starting ingredients for L054 and not any particle with a lipid composition that satisfies the limitations of the challenged claim. Beyond that, Moderna does not meaningfully rebut the Board's legal error and improper burden shifting as it pertains to the inherent anticipation theory that is plainly evident in the Board's decision.

Moderna attempts to rewrite supporting evidence as well. Before the Board, Protiva correctly pointed out Moderna's petition case misapprehended the content of the '554 publication by pointing to a list of starting ingredients rather than finished particles (on which the reference is silent). Moderna did not dispute this fact, only arguing that such starting ingredient information is conventionally included. Even if Moderna's argument is accepted as true, the resulting particle composition remains unaddressed. Perhaps realizing too late the insufficiency of this assertion, Moderna now argues something different—i.e., that starting ingredient information is "an indicator" of final particle composition. Not only was this argument never advanced before the Board, and therefore waived, it lacks supporting evidence. Record evidence, including expert testimony and multiple corroborating literature reference, states precisely the opposite.

This Court should also decline to remand the case for consideration of Moderna's alternate obviousness theory. Moderna never developed any meaningful obviousness theory before the Board, as the Board's decision correctly observed, and routine optimization, on which obviousness based on overlapping ranges is predicated, was effectively conceded as inapplicable. Moderna would not be able to remedy its misplaced and deficient obviousness case on remand, making such a remand futile. The new arguments and theories Moderna raise on appeal were not before the Board and have therefore been waived.

Finally, the Board legally erred in denying Protiva's contingent motion to amend. Besides being procedurally infirm, the Board's anticipation finding as to the proposed substitute claims suffers presents the same shortcomings as the Board's anticipation finding as to the original claims.

Accordingly, Protiva respectfully requests this Court to reverse the Board's finding that claims 1-6, 9, 12, 14, and 15 are anticipated by the '554 publication. Moreover, given the legal and factual deficiencies in Moderna's obviousness case, Moderna's request for a futile remand on obviousness should be denied.

ARGUMENT

I. Moderna's Retreat from Inherent Anticipation Underscores Board Error

The claims of the '435 patent are drawn to nucleic acid-lipid *particles* having a specified lipid composition. The Board found that claims 1-6, 9, 12, 14, and 15

are anticipated by the L054 formulation disclosed in Table IV of the '554 publication. Appx0017-0018. Protiva pointed out, however, that the L054 formulation is a listing of starting ingredients used in making particles, and that the reference is silent as to the lipid compositions of the final particles themselves. Appx0322-0326; Appx0504-0508. Neither Moderna nor the Board has ever rebutted these facts. Appx0020-0021; Appx0428-0430. Before the Board, Moderna freely acknowledged that the '554 publication only discloses the input percentages. Appx0428 ("The '554 publication uses input percentages in describing its formulations as opposed to lipid percentages in the final particles, but that was accepted practice in the field."); Appx4651 (¶27) (same).

There are two ways a claim may be anticipated, either expressly or inherently. *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001). Moderna now argues that inherent anticipation was not before the Board. Moderna's Corrected Reply Brief and Response to Cross-Appeal ("Reply") at 40. To the extent this argument is accepted, the issues before this court are simplified. Moderna, like the Board's decision, never identifies any express disclosure in the '554 publication regarding lipid particle composition because there is no such disclosure.

Moreover, Moderna's waiver arguments are misplaced. *E.g.*, Reply at 40. Before the Board, Protiva specifically argued, and Moderna never disputed, that

the '554 publication is silent as to lipid composition of finished L054 particles. Appx0322-0326, Appx0504-0508. Protiva also presented argument and evidence, including expert testimony corroborated with scientific literature, establishing that skilled artisans did not simply assume that finished particles presented the same lipid composition as the starting ingredient formulation. Appx0323-0326 (citing Appx5242-5244 (Moderna's expert, Dr. Janoff, testifying that the input and output formulation are not identical, for example, because cholesterol may not be recovered in the lipid particle); Appx4993-5001, *e.g.*, Appx4995 (noting that a finished lipid particle must be tested to determine its final composition); Appx5001-5019 (FDA guidelines recommending labeling with the recommending labeling with the "amount of each lipid component used in the formulation based on the *final form* of the product" and "[a]n expression of the molar ratio of each individual lipid to the drug substance is also recommended for each individual lipid in the *finished formulation*)). In sur-reply, Protiva further elaborated on those deficiencies and the lack of argument or evidence (and seeming acknowledgement) from Moderna in reply. Appx0504-0508; Appx4921-4925 (¶¶110-115) (Protiva's expert, Dr. Thompson, testifying that one would not expect the starting formulation to be the same as the resulting particle). In other words, Protiva comprehensively addressed why the cited L054 formulation failed to anticipate the challenged claims, expressly or otherwise. There is no requirement that Protiva foresee and

preemptively address errors that arise in the Board's final decision in order to challenge them on appeal.

There is no viable or substantiated anticipation theory, express or inherent, because Moderna never developed one and the record evidence simply does not support such a finding.

II. Neither Moderna's New Arguments Nor the Evidentiary Record Support Anticipation

Before the Board, Moderna acknowledged that the '554 publication only disclosed the input ingredients for making particles but is silent regarding lipid composition of the finished particles. Appx0428 ("The '554 publication uses input percentages in describing its formulations as opposed to lipid percentages in the final particles, but that was accepted practice in the field."); Appx4651 (¶27) (same).

In reply, Moderna attempts to remedy this evidentiary deficiency by recasting its arguments as something substantively different than what was presented to the Board. *Carbino v. West*, 168 F.3d 32, 34 (Fed. Cir. 1999) (A late or improper presentation of an argument—even on a question of law—need not, and ordinarily should not, be considered). Moderna now argues not just that starting ingredients were conventionally provided, but also that a starting formulation is "*indicative* of the lipid percentages in formulated particles." Reply at 42. The Board never found, and the evidence does not support, this new

assertion that a starting formulation is indicative of lipid composition of the resulting finished particles.

As Protiva pointed out, the basis of the Board's anticipation finding was not based on affirmative evidence that L054 resulting particles met the claim limitations (no such evidence exists), but on the irrelevant (and incomplete) observation that the '435 patent also identifies formulation starting composition. Protiva's Opening Brief of Cross-Appellant ("RB") at 61-63, 66-68; Appx0021 ("the '435 patent describes nucleic acid-lipid particles in terms of mole percent of the formulation's composition, not the particle, just as in the '554 publication.").

Furthermore, the evidence regarding starting ingredient composition compared to the finished particle is one sided. Protiva's expert, Dr. Thompson, explained with citation to corroborating scientific literature, that skilled artisans did not simply assume that finished particles presented the same lipid composition as the starting ingredient formulation. Appx0504-0508; Appx4921-4925 (¶¶110-115), Appx4993-5001; Appx5002-5019. Moderna never challenged this before the Board and there is no record evidence to the contrary.

Moderna also advances the new argument that the '554 publication uses the term "formulated molecular compositions" and cites to disparate pieces of disclosure to suggest that the starting ingredient composition listed in Table IV would identically present in some finished lipid particle product. Reply at 43-44.

This argument was not advanced by the Board and no expert witness provided this interpretation Moderna's attorneys now suggest. Before the Board, both experts acknowledged that the ''554 publication provides only lipid starting ingredient composition, but is silent with regard to the lipid composition of finished particles. RB at 61-65; Appx0020-0021, Appx0428-0429.

In reply, Moderna mischaracterizes Protiva's argument as "an enablement challenge" and attacks this strawman. Reply at 45. Rather than arguing enablement, Protiva responded to the anticipation challenge by pointing out the cited reference was silent regarding the lipid composition of finished particles (a point still unrebutted), thereby dispensing of express anticipation. Appx0322-0326; Appx0504-0508. With regard to inherent anticipation, Protiva argued with supporting evidence, including expert testimony and citation to corroborating literature, that the '554 publication does not provide "sufficient detail to reasonably assume the resulting particles fall within the scope of claim 1." RB at 62; Appx5007; Appx5012; Appx4921-4925 (¶¶109-116); Appx5242; Appx5243-5244; Appx5244-5255; Appx4995; Appx4924-4925 (¶¶113-115); Appx4442; Appx4447-4449; Appx4449; Appx0324; Appx0504-0505. It was Moderna's burden to demonstrate that the '554 publication and, specifically, the L054 formulation expressly or necessarily results in finished particles that meets all of the limitations of the nucleic acid-lipid particle of the challenged claims. Moderna failed to do so,

whereas Protiva provided evidence demonstrating that anticipation could not merely be assumed.

Moderna, in its reply, attempts to argue that the claims do not require a method of making. Reply at 44-45. Moderna misses the point. Regardless of the method used to formulate the starting ingredients into the particles, the final particles must necessarily have the claimed lipid composition. *Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) ("A party seeking to establish inherent anticipation must show that a person of ordinary skill in the art would recognize that missing descriptive matter in a prior art reference is nevertheless necessarily present.").

It was undisputed before the Board that fabrication methods of the '435 patent are different from those of the '554 publication, and there was also no dispute that the method used for formulating particles often affects the composition of finished product and most certainly would have done so in the case of L054. RB at 64. Reasons and evidence as to why a disparity between starting ingredients and finished particles would be of particular concern in the context of the '554 publication were provided and went unrebutted. RB at 63-65; Appx0323-0324; Appx0504-0508. As Table IV of the '554 publication provides only the lipid composition of the L054 starting formulation and includes 2% conjugated lipid (PEG-n-DMG), which is right at the edge of the 0.5 mol % to 2 mol % range

claimed in the '435 patent, the method of making the particles as disclosed in the '554 publication is relevant. RB at 64-65. The undisputed evidence of record also demonstrates that those methods would more likely than not result in particles with lipid ratios well outside of the claimed ranges. Appx0505-0506. Neither Moderna nor the Board cites to any evidence that the L054 formulation of the '554 publication *necessarily* produces nucleic acid-lipid particles having the claimed lipid percentages. *Cont'l Can*, 948 F.2d at 1268.

Moderna's argument that the claims do not recite a method of making the particles is attempted misdirection and side-steps both Moderna's burden as moving party and the pertinent issue of whether the cited '554 publication expressly or inherently meets the requirements of the challenged claims. *E.g.*, Reply at 45. Moderna cannot escape the fact that the prior art simply does not address particle composition at all, let alone disclose a nucleic acid-lipid particle as required by claim 1.

Despite disclaiming inherent anticipation as the operative legal theory before the Board, Moderna returns to arguing inherency in asserting one would have expected a bell-shape curve for the lipid percentages of the formed particles. Reply at 45-46. Moderna speculates as to the shape of a curve, but points to no evidence establishing lipid particles actually produced according to the '554 publication would necessarily fall within the scope of the challenged claims. There

is no such evidence in the record and Moderna identifies none. In contrast, Dr. Thompson testified that whether any lipid particles would actually meet the challenged claims is "not an answerable question with any precision." Appx0023 (citing Appx4447). Moderna's argument, and the Board's decision, falls far short of the exacting standard necessary to substantiate a charge of inherent anticipation.

Furthermore, Moderna is wrong in characterizing identified aspects of the Board's decision as credibility determinations (Reply at 47-48), rather than the readily apparent improper burden shifting and legal error Protiva identified (RB at 67-70). Even a cursory review of the Board's findings reveals that it improperly placed the burden on Protiva to prove no inherency, rather than where the burden properly belongs, on Moderna to demonstrate inherency. *In re Magnum Tools Int'l*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (citing *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)) ("In an inter partes review, the burden of persuasion is on the petitioner to prove unpatentability by a preponderance of the evidence, 35 U.S.C. § 316(e), and that burden never shifts to the patentee.") (internal quotes omitted), *Crown Ops. Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1377-78 (Fed. Cir. 2002) (noting that in an *inter partes* proceeding, the burden of showing inherency is on the challenger).

Specifically, in discussing Dr. Thompson's testimony, the Board stated "Dr. Thompson does not *definitively* testify that the nucleic acid-lipid particle would fall

outside of the claim range." Appx0023 (emphasis added). The Board also noted that "Dr. Thompson's opinion that *no particles formed using the L054 formulation* would be within the mole percentage ranges for lipids as require by claim one *is speculative*, and thus, not accorded weight." Appx0024 (emphasis added). As is clear from the Board's decision, the Board required Protiva, as the non-moving party, to definitively demonstrate a lack of inherency. This is an improper shifting of burden and constitutes legal error. Even in doing so, however, the Board acknowledged Dr. Thompson's testimony that "the final formulation of the particles may be different from that of the [starting] formulation." Appx0023

Protiva respectfully requests that the Board's finding that claims 1-6, 9, 12, and 14-15 are anticipated by the L054 starting formulation disclosed by the '554 publication be reversed. Moderna's Reply fails to demonstrate that reversal is not warranted.

III. Moderna's Defective Obviousness Challenge Cannot be Remedied By Remand

If this Court agrees that the Board's finding of anticipation is erroneous, this Court should decline to remand the proceeding to the Board for a decision on Moderna's obviousness case. Moderna's obviousness theory developed before the Board as to claims 1-6, 9, 12, 14, and 15 fails for the same reasons elaborated in Protiva's opening brief as to claims 7-8, 10-11, 13, and 16-20. RB at 50-61. Specifically, Moderna's petition offered very little analysis with respect to alleged

obviousness of any challenged claim, failed to address numerous critical aspects of an obviousness inquiry, including the claimed subject matter as a whole, a reason to combine, a reasonable expectation of success, and whether the ordinary artisan would have found in the cited art overlapping lipid ranges recited in the dependent claims, let alone arrived at the claimed ranges given the broad ranges disclosed by the prior art. As the Board correctly determined in rejecting obviousness when the issue was reached, Moderna's obviousness challenge suffered from a comprehensive failure of proof. *E.g.*, Appx0035-0037. Any remand to address this deficient theory would be futile.

Specifically, it is Moderna's burden to demonstrate the obviousness of the claims. *Magnum Tools*, 829 F.3d at 1375. In meeting that burden, a petitioner cannot merely rely on conclusory statements, but must articulate specific reasoning, supported by the evidence of record, to support the legal conclusion of obviousness. *Id.* at 1380. In addition, this Court "must avoid 'hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.'" *Arendi SARL v. Apple Inc.*, 832 F.3d 1355, 1361 (Fed. Cir. 2016). Moreover, "[i]t is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.'" *Intelligent Bio-Systems v. Illumina Cambridge*, 821 F.3d 1359, 1369 (Fed. Cir. 2016).

In its reply, Moderna relies heavily on the L054 formulation of the '554 publication, as well as the 2:40 formulation of the '189 publication, as a basis from which an optimized cationic lipid proportion could be determined. *E.g.*, Reply at 33. However, Moderna did not make that argument in its petition. In addition, Moderna has still never provided a reason as to why the ordinary artisan would have picked those formulations as a starting point over the other formulations disclosed by the references. *E.g.*, *Takeda Chem. Ind., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) (noting the failure to establish why the ordinary artisan would have chosen a certain compound as a lead compound, such as improved properties, and thus a target for modification). The only reason Moderna appears to have chosen those particular formulations as a starting point is their proximity to the claimed ranges, which is classic improper hindsight.

In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003) and *E.I. duPont de Nemours & Co. v. Synvina C.V.* 904 F.3d 996, 1006-8 (Fed. Cir. 2018) are also not applicable in an overlapping range case when the range disclosed by the prior art is so broad as to encompass a large amount of distinct compositions, as arriving at the claimed range goes beyond routine optimization. *E.g.*, Appx0300-0301 (discussing that the petition's reliance on broad ranges is misplaced), Appx0328 (noting that considerable differences exist between the prior art ranges and the claimed ranges); Appx0509-0510 (citing *Peterson* for proposition that ranges that

are not overly broad invite routine optimization). The ranges disclosed in the '189 and '554 publications are dramatically broader than the claimed ranges. *E.g.* Appx1248-1249 (¶152) ('189 publication disclosing a "bilayer stabilizing component range" of "from about 0.5% to about 20% of the total lipid present in the particle," which is much broader than the claimed range of 0.5 mol% to 2 mol%); Appx1363 (¶313) ('554 publication disclosing a "bilayer stabilizing component range" of "from about 1% to about 20%"). Other than arguing the presence of encompassing and overlapping ranges, Moderna never provided any reason to pick the portion of the ranges taught by the prior art to arrive at the ranges required by claim 1. Again, the only apparent reason is improper hindsight.

IV. The Board Erred in Denying Protiva's Motion to Amend

This Court need not reach the amended claims should it affirm the Board's non-obviousness findings challenged by Moderna and reverse the Board's anticipation findings per Protiva's cross-appeal. Under such circumstances, the contingency in Protiva's contingent motion to amend will not be triggered. To the extent it is necessary to reach the issue, the Board's denial of the motion to amend was improper.

Moderna argues that the Board did not rely on inherent anticipation to reject Protiva's contingent motion to amend. Reply at 50. That is, Moderna argues that Protiva never brought up inherent anticipation and that substantial evidence

supports that it was accepted practice in the field to use input formulations as representing the lipid concentrations in the resulting particles. *Id.* These arguments fail for the same reasons that Moderna's arguments as to inherent anticipation of the original claims above fail.

Moderna asserts also that Protiva was on notice regarding anticipation of the amended claims over the L054 formulation because the L054 formulation, as well as the related disclosures, have been front and center throughout the proceeding. Reply at 50. In that regard, Moderna points out that Ground 3 of its petition raised anticipation and that it stated in its opposition that the proposed substitute claims did not remedy the invalidity issues in the petition. *Id.* at 50-51. According to Moderna, there is no rule requiring it to rehash the arguments made in its petition in its opposition to the motion to amend. *Id.* at 51-52. Moderna asserts also that the Board was required to address the patentability of the proposed substitute claims based on the entirety of the record. *Id.* at 52. Moderna asserts further that Example 9 of the '554 publication, which the Board relied upon, was addressed in Ground 3 of the petition, as well as in its reply. Reply at 52.

The Board has specifically rejected the above arguments in its precedential decision, *Hunting Titan, Inc. v. Dynaenergetics Europe GMBH*, IPR2018-00600, Paper 67 (PTAB, July 6, 2020) (precedential). Petitioner argued in that case that a ground of unpatentability that was raised in the petition provides sufficient notice

as to the ground for a proposed substitute claim. *Id.* at 14. The Board firmly disagreed, noting that the proposed substitute claims include new limitations that were not in the original claims and which would not have been addressed in the petition. *Id.* at 15. According to the Board, such an approach "fails to balance the burdens on the parties properly," as it leaves it to patent owner to guess which original challenges may be asserted against the proposed substitute claims, while absolving petitioner of any responsibility of identifying the challenges it believes are meritorious against the proposed substitute claims. *Id.* The Board concluded that "due process requires that a patent owner receive notice of how the prior art allegedly discloses the newly-added limitations of each proposed substitute claim, as well as a theory of unpatentability asserted against those claims." *Id.* While holding that the Board may raise a ground of unpatentability that petitioner failed to advance or failed to insufficiently develop, the Board also held that the Board should only do so under rare circumstances. *Id.* at 13.

Protiva should not have had to guess which of the challenges Moderna asserted in its petition Moderna considered to be applicable against the amended claims. Moreover, Moderna's opposition to the motion to amend never raised anticipation as to the proposed substitute claims. *See generally*, Appx0448-0467. Rather, all Moderna asserted was that the narrowed claim concentrations remained obvious. Appx0455. The simple statement in its introduction that the "set of

substitute claims . . . do not remedy the invalidity issues raised" is not sufficient to put Protiva on notice that Moderna was asserting that the L054 formulation anticipated the amended claims. Appx0448, 37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document.").

Moderna argues that *Nike, Inc. v. Adidas AG*, 955 F.3d 45, 51 (Fed. Cir. 2020) does not support Protiva's argument that it should have been given an opportunity to respond. Reply at 53. Specifically, Moderna argues that the ground relied upon by the Board in *Nike* in finding against the proposed substitute claims was entirely new, whereas, as discussed above, the L054 formulation has been squarely at issue throughout this proceeding. *Id.*

In *Nike*, this Court held that the Board may sua sponte raise a ground of unpatentability based on prior art of record, but that it must provide notice as well as an opportunity to respond. *Nike*, 955 F.3d at 51. And the fact that the ground on which the motion to amend was denied in *Nike* not made in the petition is not sufficient to distinguish the case. The Board's reasoning in *Hunting Titan* is equally applicable here. That is, the grounds as set forth in the petition do not address the limitations added to the proposed substitute claims.

Thus, as established above, it was legal error for the Board in this proceeding to deny the proposed substitute claims based on anticipation by the

L054 formulation of the '554 publication, and to the extent the Board's denial of the motion to amend is reached, it should be reversed. To the extent that this Court denies Protiva's cross-appeal, or remands this proceeding to address the obviousness of claims 1-6, 9, 12, and 14-15, it should also vacate and remand the Board's denial of Protiva's motion to amend.

CONCLUSION

The Board's finding that claims 1-6, 9, 12, and 14-15 are anticipated by the '554 publication is legally erroneous and not supported by substantial evidence, and Protiva respectfully requests that it be reversed. Moreover, given that Moderna never developed a meaningful obviousness case before the Board, which could not be remedied on remand, this Court should decline Moderna's request to remand the proceeding to the Board.

Finally, to the extent it need be reached, Protiva requests that this Board reverse the Board's denial of its contingent motion to amend, or, at a minimum vacate it and remand it to the Board.

November 9, 2020

/s/ Michael T. Rosato
Michael T. Rosato
Attorney for Cross-Appellant
Protiva Biotherapeutics, Inc.

CERTIFICATE OF COMPLIANCE

I certify that this brief complies with the type-volume limitation of Fed. Cir. R. 28.1(b)(3)(A). The brief contains 4,522 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b)(2). This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in 14-point Times New Roman font.

November 9, 2020

/s/ Michael T. Rosato
Michael T. Rosato
Attorney for Cross-Appellant
Protiva Biotherapeutics, Inc.

CERTIFICATE OF SERVICE

I certify that counsel for the parties have been served with a true and correct copy of the foregoing document via this Court's CM/ECF system on November 9, 2020.

/s/ Michael T. Rosato
Michael T. Rosato
Attorney for Cross-Appellant
Protiva Biotherapeutics, Inc.

JOINT APPENDIX 74

United States Court of Appeals

for the Federal Circuit

MODERNATX, INC., FKA MODERNA THERAPEUTICS, INC., Appellant	Case No. 2020-1184, 2020-1186
v.	
ARBUTUS BIOPHARMA CORPORATION, FKA PROTIVA BIOTHERAPEUTICS, INC., Cross-Appellant	
ANDREW HIRSHFELD, PERFORMING THE FUNCTIONS AND DUTIES OF THE UNDERSECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE, Intervenor	

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2018-00739.

October 7, 2021

MARSHAL: All rise. The United States Court of Appeals for the Federal Circuit is now open and in session. God save the United States and this Honorable Court.

JUDGE 1: Please be seated, and good morning, ladies and gentlemen. We have five cases on the calendar this morning, two from the PTAB, two from the Veterans Court, and one from the District Court. One of the veteran's cases is being submitted on the [PH] breach and not argued. The first case is 2020-1184, Moderna versus Arbutus. Ms. Wigmore? I don't want to tell you how to argue your case, but I assume you'll begin with standing, which you are doing in front of us right now.

AMY WIGMORE: Good morning, your honor, and may it please the court, my name is Amy Wigmore, and together with my colleague Katherine Kieckhafer, I represent the appellant and cross-appellee ModernaTX, Inc. This case involves an inter partes review proceeding addressing Arbutus's 435 patent on lipid formulations for nucleic acid deliveries. Now, there are a number of legal errors that infected that proceeding, but given the court's statement, I will begin with the issue of standing. Moderna had, and continues to have, standing to pursue this appeal. At the outset, when this appeal was filed in November of 2019, there was a series of sublicenses that Moderna had from Acuitas, which has sublicensed these patents, including the 435, from Arbutus's predecessor. Those sublicensees applied to four different targets, and at the time the appeal was filed, there was active development going on with respect to one of those targets, RSV. Now, this court has

recognized that standing can be established in a number of ways. One of those ways, of course, is the concrete activity leading to a possible infringement suit. That was not the basis for standing at the time this appeal was filed. The basis was contractual rights that are affected by a determination of patent validity, and the [PH 00:02:35] J-Tect by this court recognizes that basis for standing. As of November 19, 2019, Moderna had the sublicenses in place, and it had already paid milestone payment under the licenses.

JUDGE 2: How much time had – my recollection is that it had been about five years since a milestone payment had been made, right?

AMY WIGMORE: It had been several years since the original milestone payments had been made, but...

JUDGE 2: Any milestone payments, the last milestone payment that was made prior to the filing of the complaint was when?

AMY WIGMORE: I don't have that specific date, but it is correct that it was not within a year of the appeal being filed. That said, there was an active development program with a third party for this RSV target, and the license was very much still in place, all four sublicenses were still in place, these programs had not been abandoned.

JUDGE 1: Well, if you’re licensed, what’s the threat of infringement?

AMY WIGMORE: There does not need to be a threat of infringement under this court’s precedent in the J-Tect case. There needs to be contractual rights that are implicated by patent validity, and the issue here was there were potential future milestone and other royalty

payment obligations in connection with those programs, the four viable targets that had been sublicensed. In addition, Moderna had the right to sublicense these programs to third parties, and the impact of having to pay these royalty obligations was something that would impact their ability to sublicense them [INDISCERNIBLE].

[OVERLAY]

JUDGE 2: Part of the problem is towards the weak evidence that you submitted with respect to the likelihood of these payments being affected? So you've got testimony that says if and when there is a phase II clinical trial, but no testimony that says we're anticipating it within some period of time, or working toward that, and in this case there are multiple patents and there's nothing that says that this particular patent is what was driving the milestone payment, and so how do you fill that gap?

AMY WIGMORE: Your honor, this is a case that is very much distinguishable from the Apple versus Qualcomm case, which was cited by Arbutus in their briefing. In that case, Apple had attempted

[00:05:00]

to argue standing based on the possibility of some future royalty payment. They had a license, but they had settled two infringement cases with a global settlement. They also submitted what the court referred to as an incredibly sparce declaration, and the only issue there was whether within six or eight years after this license agreement, settling all the infringement litigation expired, could there be potentially some financial obligation. This case is much

different. There is a detailed set of declarations that were submitted by Shaun Ryan, Vice President and General Counsel of Moderna.

JUDGE 2: Can I interrupt you for a minute? I think the problem here is immediacy. How do you show the immediacy specifically? Just forget about the other cases for a minute.

AMY WIGMORE: With respect to standing in IPR proceedings, it is true that the injury in fact requirement remains, but because there is a statutory right to appeal, under 35 U.S.C. 141(c), the requirements for immediacy or traceability and redressability are more relaxed in this context, due to the statutory ability to appeal, and in this case, there was an ongoing development program at the time the appeal was filed with another party. To the extent that development program led to a phase II trial, there would be further obligations [PH 00:06:22] owed. That is concrete, and that is the type of activity the court has recognized. It can be current or even future activity that can implicate standing.

JUDGE 2: Well, I understand that there was probably some concerns about the confidentiality and not giving too much information, but my concern is still with the too little information. You said there's a detailed affidavit, but it's pretty vague.

AMY WIGMORE: The affidavit describes the existence of this development program. The development program, if successful, would have led to further royalty payments. That was the situation in November of 2019, when this appeal was filed. Now, the situation has evolved, and it's this court's obligation not just to look at standing at the time

the appeal was filed, but whether there is an ongoing live case or controversy, and it is true that facts have evolved [INDISCERNIBLE 00:07:09].

[OVERLAY]

JUDGE 2: But you still have to have standing as of the time the case is filed.

AMY WIGMORE: Absolutely.

JUDGE 2: So to what extent do you believe there's authority for the proposition that subsequent events can reflect on the nature of standing when it's filed?

AMY WIGMORE: The initial existence of this sublicense is sufficient. It was a concrete program. There was a concrete development effort being undergone, at least with respect to RSV, and that was something that was actually actively being worked on that is a concrete plan that the company had at the time, and that development program was subject to royalty payments. In addition, there is this ability to sublicense, which was burdened, as set forth in the Ryan declaration, by these royalty payments. Now your honor,...

JUDGE 2: Can I interrupt you for a minute? So do I understand you to be saying that the initial basis for standing would be based on those plans and the license, the plans to develop something, maybe that kind of fell by the wayside at some point, but that at least provided the initial basis for standing, and that at some point it evolved, I guess. As your client created the vaccine, it evolved to a different basis for standing?

AMY WIGMORE: I wouldn't say a different basis for standing. I would say that that evolution keeps this controversy alive. Standing is assessed at the time the appeal is filed, and that time, there was this active program under the sublicense that had a royalty burden. Over time, as set forth in our supplemental declaration, that particular RSV program was not pursued, the sublicense is still in place, there is potential future development, but that particular program, which was very concrete at the time the appeal was filed, did change. Now, that said, at the same time, the COVID vaccine was developed and ultimately delivered to the market and commercialized, and...

JUDGE 2: Above all, after the date, that activity is after the date on which the appeal was filed.

AMY WIGMORE: That is correct. In the Momenta case, this court recognized that it need not only look at standing at the time the appeal was filed, which here we're relying on the license and the active development program for standing as of November 2019, but we still need to evaluate whether there's a live controversy moving forward as the appeal is still pending, and there we do have this COVID vaccine...

JUDGE 1: But you're concerned about royalty obligations, financial burdens under a license that you don't need, you could have terminated a license, couldn't you?

AMY WIGMORE: There are two different situations here. With respect to the four targets of the sublicense, it's not disputed that those targets, as they were being developed at the time, were

practicing the patents at issue, so there would have been a royalty burden had those patents not been invalidated, and that's what Mr. Ryan's declaration makes clear. As for the COVID vaccine, certainly it's the case that Moderna does not concede any infringement, and the case law makes clear that for standing based on potential litigation, you need not concede infringement, nor need there be a specific threat of an infringement case. There needs to be concrete plans and activity that could lead to a possible infringement action.

JUDGE 2: But it can't be so remote, I mean you can't say that we had a license to do a bicycle, and then we later did a car, and so therefore we're concerned about an infringement car, so that is part of your problem. They are not arguing that the RSV program that you said was live somehow morphed into where we are now. You're arguing that they are completely separate, and that the patents don't cover what's going on now, so that's part of the problem. I understand what you're saying, but I think you're taking it too far.

AMY WIGMORE: Now, in the Momenta case, this court recognized that the basis for standing and case controversy are not necessarily coextensive. The court recognized that situation evolve, even after appeals are filed. There's no question at the time this appeal was filed, there was an active licensing program that had royalty implications. Since that time, it's been a couple of years, there has been some change to that program, that license is still in place, but there's no more development of that one particular RSV vaccine under that license, but there has been this change in circumstances where the

COVID vaccine – COVID didn't even exist at the time this appeal was filed, as far as anyone knew – and that time, we were not relying on the risk of infringement, but now it's a concrete...

JUDGE 2: But you really only discussed those activities in connection with the other appeal, right? There is nothing in this first appeal where I see that discussion of the development of the COVID vaccine as something you were relying upon.

AMY WIGMORE: We did supplement the record, your honor. It's docket number, I believe it's 118, where we put in the line – in the declaration that was filed in the 069 appeal – we put it into this appeal, not only to advise the court of this ongoing live controversy, but also to advise the court that the development program we had been discussing in the original declaration at the time of the appeal being filed, that that program had changed.

JUDGE 1: Do you want to spend a few minutes on the merits?

AMY WIGMORE: Absolutely.

JUDGE 1: And we will make sure you get some rebuttal time.

AMY WIGMORE: Okay, thank you, so in terms of the merits, there is a fundamental legal flaw of the IPR decision, and that is the court failed to apply the proper framework and shift the burden of production to Arbutus. There are overlapping ranges in the prior art that the board failed to recognize. In addition, the board failed to adequately explain its decision. It had a little over two pages of a 51-page opinion addressing the issue of obviousness. It did not properly analyze the legal framework or apply it, nor did it adequately explain

its decision. Now, in terms of the ranges that were disclosed in the prior art, these patents, this 435 patent, addresses a composition containing four categories of lipids – conjugated lipids, cationic lipids, and two noncationic lipids, cholesterol and phospholipid. Ranges of the three...

JUDGE 2: Just to make sure I'm being clear here, are you addressing primarily the claims other than claim 7 and claim 8?

AMY WIGMORE: We're addressing all of the claims because the error was fundamental. When the court turned from anticipation, which it found for some of the claims, to obviousness, with respect to all the claims it was analyzing for obviousness that had not been anticipated, it failed to apply this burden-shifting framework, and these ranges...

JUDGE 2: And there are some claims, if I remember correctly, there are some claims that don't have the phospholipid in them, right?

AMY WIGMORE: They have cholesterol, and the court made the same error with respect to cholesterol. In fact, even greater error because it said in its opinion that the cholesterol range was not disclosed, when even Arbutus concedes that the prior art discloses a 20% to 45% range of cholesterol...

JUDGE 2: So is it your view that what we should do, if we reach the merits, is not reverse, but to vacate and remand, so that the burden shifting can apply, and the board consider it under that standard?

AMY WIGMORE: That's correct, that it was a fundamental error not to shift the burden, and to impose upon Moderna the obligation to prove motivation to optimize. Motivation to optimize is presumed when there is an overlapping range, and based on the description we provided in our brief, there was a clear overlap.

[00:15:00]

That overlapping range need not be stated verbatim in the prior art here. It was with respect to three of the four lipids at issue. Those ranges were explicitly described, and there can be no question, they overlap with what's in the claims.

JUDGE 2: And so in the case law, I'm going to say, they can be either overlapping or encompass, that is the prior ranges can either overlap with the claim range or encompass the claim range, either way.

AMY WIGMORE: That is correct.

JUDGE 2: The presumption applies, okay.

AMY WIGMORE: All you need is a slight overlap, the In re Peterson case makes that clear, as do other cases. This case is squarely on point with the Dupont case that this court decided, it was also an IPR, where a nonobviousness finding was reversed. Here, there are multiple variables, but the Dupont case recognized that those can form the basis of an overlapping range presumption. The fundamental error here...

JUDGE 2: Was there anything in the record, I mean putting aside whether they should have formally shifted the burden, is there anything in the record that would indicate that the narrower range or the

specific range was somehow surprising or somehow different from what the prior art showed?

AMY WIGMORE: The basis for their patent, they allege, is this amount of cationic lipid, above 50%, but the prior art, including the 554 publication and the 189 publication, both expressly disclosed a cationic lipid range of up to 60%, so that's the fundamental issue here. 60% cationic lipid is in the prior art, and so it cannot be the basis for distinguishing this patent from the prior art.

JUDGE 1: So let’s hear from the other side, and then we’ll give you three minutes rebuttal. Mr. Berl.

DAVID BERL: Good morning, your honors, David Berl for Arbutus. I’ll start where my opponent started, with regard to the issue of standing, and what’s missing here are multiple things. First, any notion of immediacy is entirely absent from the evidence that Moderna has presented to this court. It is speculative, and today we’ve heard for the first time that they admit that this RSV vaccine program, which was the basis for their standing as of notice of appeal, November 2019, has been abandoned, so they have now shifted...

JUDGE 2: But we need to look at November 2029.

DAVID BERL: Indeed.

JUDGE 2: So why is the fact that it was at least ongoing at that point, and there was an intention to move forward with it at that point, why isn’t that enough?

DAVID BERL: Here’s what’s missing, and the key cases here are the Samsung case, in which multiple patents were licensed and standing

was found, and the Apple versus Qualcomm case, where multiple patents were licensed, and standing was not found, and the difference is crucial here. In Samsung, this court found that the invalidation of the patent at issue in that case would have changed the royalty obligation. Because of the way the patent pool worked, if you eliminate one patent, more money would be paid on other patents, so Samsung would have profited. That was missing in Apple versus Qualcomm, where this court found that Apple presented no evidence that the invalidation of the particular patents it was challenging would change its royalty obligations. That evidence is missing here too. If you look at Mr. Ryan's declaration, he addresses this, at A57:45-46, and he acknowledges that Moderna here has licensed numerous patents, not just the 435 and 069, numerous patents. Those patents are found at Exhibit D to his declaration, at A58:28-69, it's actually in the other index, because they supplemented it, and what you see there are 40 pages of patents. These are two of them, only one at issue in this appeal.

JUDGE 2: Okay, but patent portfolio licensing is pretty normal, so assuming that patent portfolio licensing is normal, can't a clinical trial or ultimately a product read on a number of patents in portfolio?

DAVID BERL: It could, but the crucial question under the Apple-Qualcomm case is whether the requested relief – here the invalidation of the 435 patent – would affect the payment obligation for Moderna, and there is no evidence from Mr. Ryan that it would. There is no evidence on the Samsung case that says if the 435 patent is invalidated

and we had continued this RSV program, we would have owed Arbutus less money.

JUDGE 2: Well, we've said you don't have to admit infringement in order to establish standing.

DAVID BERL: That's not a question of admitting infringement, it's a question of whether the requested relief would affect their payments under the license, so whether they infringe or not. Let's assume for a moment that they would, best case scenario for their standing case, there is no evidence that if you take out the 435 patent, that they owe one red cent less if they would have progressed their RSV program, because they have to pay on all of the patents,

[00:20:00]

so the elimination of one or two of them doesn't change their royalty obligation. They have to show evidence. under the Apple-Qualcomm case, that it does.

JUDGE 2: Your point, I think the point of your argument is that that makes it less concrete, less likely to occur, combined with the fact that also there had been a lot of times in saying the milestone payments had been made anyway, so it was a little bit less concrete that they would even – that this product would come to fruition and they would have to pay any milestone payments.

DAVID BERL: Absolutely, and even if they did have to pay milestones, which again is not concrete and speculative, there is no evidence that the requested relief would have redressed in any way their obligations. They would have paid exactly the same amount under

the evidence that they have advanced, and the Apple-Qualcomm case says this defeats injury in fact under the MedImmune analysis, and so you can't have a situation where you have a bunch of licenses, 40 pages of licenses, 40 pages of patents, without any evidence, and they have an absence of proof here. You can read the Ryan declaration front-to-back, you won't see any evidence that invalidation of the 435 patent, or for that matter, the 069 patent in the next case, affects their payment obligations, and the Apple-Qualcomm case [INDISCERNIBLE 00:21:12],

[OVERLAY]

JUDGE 2: Are you saying that they need – while you have those multiple patents – that they essentially would need to establish that infringement would occur based on the ongoing program, or are you saying they need to establish that not only would infringement likely occur, but that it wouldn't occur with respect to the other patents?

DAVID BERL: That would be one way of solving the Apple versus Qualcomm problem, if they had advanced that sort of evidence that said, "We don't infringe the other 40 pages of patents, so therefore invalidation of the 435 would mean we don't have to pay any royalties if we progress this RSV vaccine." That sort of evidence would have been sufficient under Apple-Qualcomm. They don't say that. What Moderna says in reply, they cite the Shen Yang case, for the proposition that eliminating the 435 would eliminate a major obstacle for them, consistent with their payment obligations, but that was addressed also in the Apple versus Qualcomm case. Footnote 4 of that case said that Apple doesn't present any evidence as to why invalidation of this one

patent would remove a major obstacle. For example, they could have said, "If the 435 patent is invalidated, that would mean all of these other patents also would be invalid, so we wouldn't have to pay" or "we don't infringe the other patents, so that's really the major obstacle," but they have no evidence of any of that, and so just like Apple-Qualcomm, which I would submit is on all [PH] fours with this case, with respect to the pool of patents and the absence of evidence that the payment obligations would be affected by the requested relief, I would say, respectfully, resolves the standing issue here.

JUDGE 2: Isn't a bit of a catch-22, though? I mean you have to basically say that you're liable in order to have standing?

DAVID BERL: No, you could have said exactly what your honor suggested, they could have said, "We challenge the 435 patent, we don't infringe the other 39 pages of patents, so therefore invalidation of the 435 patent would remove any payment obligations even if we did infringe." We agree, they don't have to admit infringement, but they do have to show some imminent threat here of having to pay their royalty for their activities. They admit that they had no threat when they filed this notice of appeal with respect to COVID. They admit that at some point after their last payment obligation, which was back in 2016, was made, that they abandoned their RSV program that's relevant to this patent. We have no evidence of when that happened versus when their COVID vaccine came into being and recreated in their mind that imminent threat. There is no timeline that indicates that at all times, they had an imminent threat of suit and that they had standing. They have no

evidence of that. They're just saying, well, at some point, the RSV program went away, and at some point, the COVID vaccine program came up, so we probably had standing somewhere in that, and it's good enough for government work.

[OVERLAY]

JUDGE 2: What do you make of the argument, and this goes to the question of the supplemental authority, that post-filing activities are relevant? I thought post-filing activities are relevant not because they help to establish standing, but because even with standing, there might not be any case for controversy.

DAVID BERL: Absolutely, I agree with your honor's interpretation. It is a fundamental tenant of standing, and frankly, jurisdiction in Article III case law, that at all points, at every point, including the filing of the notice of appeal, and all points thereafter, standing must be present. Any gap, one minute...

JUDGE 1: Counsel, do you want to address the merits?

DAVID BERL: Happy to address the merits, your honor. This is a case in which the board made numerous factual findings that are explicitly relevant under this court's range case law, that resolved this case conclusively. For example, the board found that the various components

[00:25:00]

disclosed in the prior art interrelate with each other in an unpredictable way. That is explicitly relevant under this court's applied materials case, under this court's case law, for example, in

the Horizon case, where the court said it's important to distinguish in these cases between systems, like the one in Dupont, like the one in Applied Materials.

JUDGE 2: Why isn't that something that would be considered after the presumptions applied? It seems to me that once you have a prior art reference that discloses the mole percentages for the ingredients in the claim, that at that point, the presumption applies, and there should be some shifting. That seems to be the problem here.

DAVID BERL: Let me address that in two ways. First, the Horizon case does not stand for that proposition. In that case, where the various components interacted unpredictably with each other, as the board found here in an unchallenged factual finding, no presumption was applied by the district court, none, and this court affirmed that finding, and Moderna's only response to that is that Horizon isn't a range case, and somehow the active ingredient was not disclosed in the prior art as arranged, that's not true. If you look at the district court case at star 5, it makes clear that the [PH] Kazai reference disclosed an overlapping range of diclofenac sodium, the active ingredient.

JUDGE 2: Even if that's true, there's plenty of other cases that take a different approach.

DAVID BERL: Well, none of them suggest that in a situation where the various components of the prior art interact unpredictably with each other, a presumption is invoked, and I would suggest the applied materials case suggests exactly the opposite.

JUDGE 2: Are you saying we should say that even though there is a clear overlap in the ranges, that just because there appears to be interaction between the ingredients, that we ignore those overlaps?

DAVID BERL: First of all, I don't think there is a clear disclosure of an overlap, there is no disclosure...

JUDGE 2: Well, how can 20% to 45% not overlap at least somewhat, or 30% to 40%.

DAVID BERL: It does, of course, but there is no disclosure of a phospholipid range anywhere in the prior art.

JUDGE 2: But that’s not in all the claims.

DAVID BERL: No, that's in claim 7.

JUDGE 2: Okay, so set claim 7 aside.

DAVID BERL: If we set claim 7 aside, what I would observe, your honor, is that the range case law, whether it’s Dupont or Applied Materials or any of the others, does not exist separate and apart from this court’s obviousness jurisprudence and the KSR obviousness jurisprudence. They’re trying to get at the same thing, and they can’t be applied in a way that is abjectly defying KSR and all of the principles of obviousness. To take one example, in the Dupont case as well as the Peterson case that they cite, the court observed that the issue here is do we have routine experimentation which leads to obviousness, because you experiment routinely within the ranges, or do we have nonobvious invention. That's the crucial distinction here, and the court said the exact same thing in the Genetics Institute case. It’s getting at the same thing as KSR and all of the obviousness cases.

It's not some separate doctrine that can exist hermetically sealed from everything else in Section 103, and here the board found repeatedly, in an unchallenged factual finding, that it would not be routine experimentation, that it would be difficult experimentation. Their own expert agrees that it would be experimentation. So which side of the ledger are we on, routine experimentation, as in Dupont, as in Peterson, or not routine experimentation, as in Genetics Institute and Horizon? The board answered that question, repeatedly.

JUDGE 1: Do you want to deal with claim 1?

DAVID BERL: Sure. I think claim 1 is exactly the same principle. The board found that those ranges would not have been achieved by routine experimentation, therefore precluding any finding of obviousness. There is no finding in any of the range cases, whether it's Stepan, Dupont, Peterson, or any of the others, that where you have nonroutine...

JUDGE 1: These cases aside, the L054 formulation is right within the claim range of claim 1.

DAVID BERL: I'm sorry, I might have misunderstood your honor's question. Your honor is asking about anticipation of claim 1, rather than the obviousness issue, and I apologize, your honor, I didn't understand your question. I'd happily move to anticipation. The problem with Moderna's anticipation argument and the board's finding is that it has the right numbers, but it's about the wrong thing. The L054 formulation provides the numbers for the inputs into the formulation, not the outputs, and Moderna admits that at A46:51, they say that those

are the inputs, and their expert admits at 52:42 through 52:44 that the inputs and outputs are not the same, they change, and our expert provides a careful explanation of why that is, as a result of the detergent process used in the 554. Our expert explains, at A49:24-25, that it removes some of the cholesterol lipid,

[00:30:00]

and so the amount of conjugated lipid increases, it goes up, he explained, there and in his deposition.

JUDGE 2: A lot of this is interesting, but the problem is it's not in the claims.

DAVID BERL: Well, it is in the claims. The claims were construed, and everyone agrees that they addressed the final formulation percentages. Moderna agrees with that, and we agree with that too. This claim is directed to a particle, a final particle, not the inputs of what you put in before you manufacture the particle, so that is in the claim, and the prior art is addressing something different. The prior art is addressing what you put in, not what you get out, and Moderna knows that it has a problem here. They don't try to defend the proposition that there's no difference between inputs and outputs. They respectfully try to manufacture a finding from the board that doesn't exist, that somehow the inputs are indicative of the outputs, that's their response, and they cite to A20 and A21 of the board's opinion. That finding is not there.

JUDGE 2: But didn't Moderna rely on the entirety of the 554 publication, and not just on the L054 formulation?

DAVID BERL: Well, the board found their argument with respect to the rest of the 554 unpersuasive, and I don't think that's being refuted here on appeal, that the ranges are not enough to anticipate the claims, so the board relied only on that particular example, the L054 example as being anticipatory.

JUDGE 2: Isn't that an overly narrow view of the prior art?

DAVID BERL: Well, the board addressed the rest of the 554, it addressed the ranges, it explained that the ranges were not the sort of ranges that can anticipate the claim, and Moderna doesn't argue otherwise. It doesn't quibble with the board's rejection of their anticipation argument on that basis. It simply tries to defend the anticipation argument on the basis of the L054 formulation, but again, that addressed the wrong thing. Everyone agrees that the L054 is about the inputs, not the outputs, and there is a difference. The conjugated lipid goes up, and contrary to what Moderna said, our expert did not say otherwise. His testimony is at A44:47-50. He never said, he never said that there would be particles that have less than 2% conjugated lipid. They tried to suggest that he did, but if you read the testimony, he didn't say that. On the contrary, he said the amount of conjugated lipid will go up, and it's 2% already in the L054 example.

[OVERLAY]

JUDGE 1: Thank you. You have consumed your time, but we'll give you two minutes for rebuttal on a cross appeal if there is something to rebuff.

DAVID BERL: I appreciate that, thank you very much, your honor.

JUDGE: We're giving you three minutes, Ms. Wigmore.

AMY WIGMORE: Thank you, your honor. In terms of anticipation, there was a factual finding by the board that should be reviewed, under substantial evidence standard, that L054 species, there's no dispute that it contains all the components that can be found in the claimed ranges. The only dispute is about whether you can take the formulation molar concentration to mean what's in the claim, and that's exactly what Arbutus did in both the 554 publication and in the 435 patent. They described the formulation and the molar concentrations, and they claim them. There is absolutely no evidence in the 435 patent, the patent here at issue, of what the amount would be in the composition. It's different.

JUDGE 2: Do you support the board's finding that when you make the particle, at least some will fall within the claim ranges, even if some are outside, and so therefore there is anticipation?

AMY WIGMORE: That's certainly a supportable finding, and I think what the board found is there is no evidence to the contrary. There is no evidence that anything would be outside the range, other than pure speculation in this case by their expert, Dr. Thompson. That was a credibility finding. He alleged, but did not support, that the numbers would be different in the final composition, and importantly, the disclosure of the 435 patent, all it has is the formulation concentration. It contains no information about any different, if they would be different, concentrations in the final composition, so it's exactly the same disclosure in both the 554 publication and in the

patent at issue here, and this is a factual finding that is entitled to deference. In terms of standing, I just want to point out paragraph 8 of Mr. Ryan's declaration, that can be found in the appendix at page 6397 and 6398. In that paragraph, unlike in the Apple case, he expressly says that there would be financial implications with respect to the 435 patent, if this patent were invalidated.

JUDGE 2: What's the cite?

AMY WIGMORE: It's 6397 and 6398,

[00:35:01]

that's paragraph 8 of the Ryan declaration, so there's a lot more evidence in this record than in the Apple case, and from a practical standpoint, it cannot be the case that if you have a portfolio, you can never appeal an IPR, because you have to challenge the patents sequentially. That's going on here. We have a separate appeal we're about to argue on the 069. We can't take them all together in the same appeal. The key is to remove an obstacle, and that's what this appeal is designed to do.

JUDGE 2: Is there any evidence that the 435 relates in any way to the vaccine efforts?

AMY WIGMORE: There are broad statements by Arbutus that are in the record in the appendix, that they think they cover the whole landscape of lipid nanoparticles.

JUDGE 2: Those broad statements being in the press articles?

AMY WIGMORE: Yes, in the press articles, these are quotes from Arbutus's CEO, and they certainly have not...

JUDGE 2: But not in a deposition testimony or anything, it's just generally saying, "I've got a lot of [INDISCERNIBLE]."

[OVERLAY]

AMY WIGMORE: That's correct, no deposition testimony, this was not an issue [INDISCERNIBLE].

[OVERLAY]

JUDGE 2: And is there a reference in that specifically to the 435?

AMY WIGMORE: Not with respect to the vaccine specifically, they have not made a specific threat, nor need they under the case law. There needs to be a risk of possible infringement based on Moderna's activities, and there clearly is because the vaccine is being widely distributed. There has been no covenant not to sue, that's set forth in the Ryan declaration, and there have been broader discussions between Moderna and Arbutus about a broader license.

JUDGE 2: And this will all come up in the next case, right?

AMY WIGMORE: This will come up again, yes, thank you.

JUDGE 1: Thank you, counsel. Mr. Berl, you do have a little time on the cross appeal.

DAVID BERL: Thank you, your honor. My opponent referred to a factual finding by the board that did not find persuasive our expert's testimony that all of the particles would fall outside the ranges. Respectfully, the board got it wrong, that has it backwards. We don't have to come forward with evidence of non-anticipation and of non-inherency in order to prevail. The burden falls on Moderna and remains

with Moderna the whole time. The board cited not a shred of evidence in the record that the amounts would be the same, and on the contrary, their expert admitted that they wouldn't be. At A52:42 through 52:44, he says it can change during manufacture, so even if the board rejected our expert's testimony as non-persuasive, for whatever reason, that would leave an absence of proof.

JUDGE 2: What about the patent itself, why doesn't the patent itself provide some proof of what the board is asserting, based on the fact that the specification – written description, that is – refers to the formulation percentages, and the claims refer to the particle percentages, why would someone think they'd be different based on the fact that the particle percentages aren't disclosed in the written description?

DAVID BERL: So our expert addresses that question in explaining that the 554 manufacturing process is a particular process that uses detergent that would change substantially the lipid percentages.

JUDGE 2: I understand what you're saying, but what do we do with the board finding that not credible and not thinking that it makes sense technically, based on the reading of the specification? What do we do with that?

DAVID BERL: Well, based on the reading of our specification, and the board did rule on our specification in suggesting that that's what we did too. The problem with that evidence is that our process is different. There was no finding that in our process, you would have substantial changes. We had a very different process in our

specification than the 554 manufacturing process in its specification, so the evidence, and this is the only evidence. It's not as if there's evidence that Moderna brought forward that said it doesn't change, it's all the same. Moderna agrees that the percentages change when you use the 554 process, so there can be no credibility of determination that sort of rejects all that evidence. That's the only evidence there was. Their expert didn't dispute it. Our specification, which of course is not prior art and is an entirely different matter, doesn't have the same manufacturing process. It has an entirely different manufacturing process, no detergent. It doesn't lose all that phospholipid, thereby increasing – or sorry – cholesterol, thereby increasing the other components, and most importantly here for present purposes, the conjugated lipid.

JUDGE 1: Thank you, counsel, thank you.

DAVID BERL: Thank you very much.

JUDGE 1: The case has been submitted.

I, Anders Nelson, hereby certify that the foregoing is, to the best of my knowledge and belief, a true and accurate transcription in English.

Anders Nelson
Anders Nelson (Dec 18, 2023 13:35 EST)

Anders Nelson

Project Manager

TransPerfect Legal Solutions

December 18, 2023

JOINT APPENDIX 75

United States Court of Appeals for the Federal Circuit

MODERNATX, INC., FKA MODERNA THERAPEUTICS, INC.,
Appellant

v.

ARBUTUS BIOPHARMA CORPORATION, FKA PROTIVA BIOTHERAPEUTICS, INC.,
Cross-Appellant

ANDREW HIRSHFELD, PERFORMING THE FUNCTIONS AND DUTIES OF THE UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,
Intervenor

2020-1184, 2020-1186

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2018-00739.

Decided: December 1, 2021

AMY K. WIGMORE, Wilmer Cutler Pickering Hale and Dorr LLP, Washington, DC, argued for appellant. Also

represented by MARK CHRISTOPHER FLEMING, EMILY R. WHELAN, Boston, MA.

DAVID I. BERL, Williams & Connolly LLP, Washington, DC, argued for cross-appellant. Also represented by THOMAS S. FLETCHER, JESSICA PALMER RYEN; SONJA ROCHELLE GERRARD, STEVEN WILLIAM PARMELEE, MICHAEL T. ROSATO, Wilson Sonsini Goodrich & Rosati, Seattle, WA; LORA MARIE GREEN, RICHARD TORCZON, Washington, DC.

ROBERT MCBRIDE, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, for intervenor. Also represented by THOMAS W. KRAUSE, FARHEENA YASMEEN RASHEED.

Before LOURIE, O'MALLEY, and STOLL, *Circuit Judges*.

LOURIE, *Circuit Judge*.

ModernaTx, Inc. ("Moderna") appeals from the decision of the U.S. Patent and Trademark Office Patent Trial and Appeal Board ("Board") holding that claims 7–8, 10–11, 13, and 16–20 of U.S. Patent 9,364,435 are not unpatentable as obvious. *See Moderna Therapeutics, Inc. v. Protiva Biotherapeutics, Inc.*, IPR2018-00739, 2019 Pat. App. LEXIS 13612 (Sept. 11, 2019) ("*Board Decision*"). Arbutus Biopharma Corporation ("Arbutus")[1] cross-appeals from the Board's decision holding that claims 1–6, 9, 12, and 14–15

[1] At the time that this appeal was filed in November 2019, the cross-appellant was named Protiva Biotherapeutics, Inc. ("Protiva"). Subsequently, in June 2021, Protiva moved the court to revise the official caption to replace Protiva with Arbutus. In this opinion, unless otherwise indicated, we use "Protiva" and "Arbutus" interchangeably based on the relevant context to refer to the cross-appellant in this appeal.

are unpatentable as anticipated. *Id.* For the reasons provided below, we dismiss Moderna's appeal for lack of standing. Regarding Arbutus's cross appeal, we affirm.

BACKGROUND

I. The '435 Patent

Arbutus owns the '435 patent directed to "stable nucleic acid-lipid particles (SNALP) comprising a nucleic acid (such as one or more interfering RNA), methods of making the SNALP, and methods of delivering and/or administering the SNALP." '435 patent at Abstract. The patent, which issued on June 14, 2016, claims priority from a provisional application filed on April 15, 2008.

As described in the '435 patent, RNA interference ("RNAi") is a biological process in which recognition of double-stranded RNA "leads to posttranscriptional suppression of gene expression." *Id.* at col. 1 ll. 39–42. That biological process is mediated by small interfering RNA ("siRNA"), "which induces specific degradation of mRNA through complementary base pairing." *Id.* at col. 1 ll. 42–45. The '435 patent recognized that RNAi provided "a potential new approach to downregulate or silence the transcription and translation of a gene of interest." *Id.* at col. 1 ll. 52–54.

A "safe and effective nucleic acid delivery system is required for RNAi to be therapeutically useful." *Id.* at col. 1 ll. 63–64. The delivery system "should be small" and "should remain intact in the circulation for an extended period of time in order to achieve delivery to affected tissues." *Id.* at col. 2 ll. 38–42. This requires a "highly stable, serum-resistant nucleic acid-containing particle that does not interact with cells and other components of the vascular compartment." *Id.* at col. 2 ll. 42–45. The particle should also "readily interact with target cells at a disease site in order to facilitate intracellular delivery of a desired nucleic acid." *Id.* at col. 2 ll. 45–47. The '435 patent thus recognized that

there remained "a strong need in the art for novel and more efficient methods and compositions for introducing nucleic acids such as siRNA into cells." *Id.* at col. 2 l. 66–col. 3 l. 1.

The '435 patent describes the invention as "novel, serum-stable lipid particles comprising one or more active agents or therapeutic agents, methods of making the lipid particles, and methods of delivering and/or administering the lipid particles (e.g., for the treatment of a disease or disorder)." *Id.* at col. 3 ll. 9–13. The lipid particles are comprised of one or more cationic lipids, one or more non-cationic lipids, and one or more conjugated lipids. *See id.* at col. 3 ll. 22–31. As described in the patent, "[t]he present invention is based, in part, upon the surprising discovery that lipid particles comprising from about 50 mol % to about 85 mol % of a cationic lipid, from about 13 mol % to about 49.5 mol % of a non-cationic lipid, and from about 0.5 mol % to about 2 mol % of a lipid conjugate provide advantages when used for the in vitro or in vivo delivery of an active agent, such as a therapeutic nucleic acid (e.g., an interfering RNA)." *Id.* at col. 5 ll. 55–62. The '435 patent further states that the stable nucleic acid-lipid particles "advantageously impart increased activity of the encapsulated nucleic acid (e.g., an interfering RNA such as siRNA) and improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index" as compared to prior art nucleic acid-lipid particle compositions. *Id.* at col. 5 l. 62–col. 6 l. 2. And the particles are "stable in circulation, e.g., resistant to degradation by nucleases in serum, and are substantially non-toxic" to humans. *Id.* at col. 6 ll. 2–5

The '435 patent contains 20 claims. Claim 1, the only independent claim, recites:

1. A nucleic acid-lipid particle comprising:

    (a) a nucleic acid;

(b) a cationic lipid comprising from 50 mol % to 85 mol % of the total lipid present in the particle;

(c) a non-cationic lipid comprising from 13 mol % to 49.5 mol % of the total lipid present in the particle; and

(d) a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol % to 2 mol % of the total lipid present in the particle.

Id. at col. 89 ll. 55–63. Many of the dependent claims contain additional limitations directed to one of the various components in the nucleic acid-lipid particle of claim 1. For example, claims 2 and 3 are directed to the nucleic acid component, claim 4 is directed to the cationic lipid component, claims 5–8 are directed to the non-cationic lipid component, and claims 9–12 are directed to the conjugated lipid component. *Id.* at col. 89 l. 64–col. 91 l. 21. The remaining dependent claims pertain to the encapsulation of the nucleic acid within the particle, *id.* at col. 91 ll. 22–24 (claim 13), pharmaceutical compositions comprising the particle, *id.* at col. 92 ll. 1–3 (claim 14), and methods for introducing a nucleic acid into a cell, in vivo delivery of a nucleic acid, and treatment using the particle, *id.* at col. 92 ll. 4–22 (claims 15–20).

II. *Inter Partes* Review of the '435 Patent

Moderna petitioned for *inter partes* review of the '435 patent. In its petition, Moderna asserted three grounds challenging all claims of the '435 patent. In the first ground, Moderna alleged that all claims of the '435 patent would have been obvious under 35 U.S.C. § 103 over a combination of International Pat. Publ. WO 2005/007196 ("the '196 PCT") and U.S. Pat. Publ. 2006/0134189 ("the '189 publication"). In the second ground, Moderna alleged that all claims of the '435 patent would have been obvious over

a combination of the '196 PCT, the '189 publication, Lin,[2] and Ahmad.[3] In the third ground, Moderna alleged that all claims of the '435 patent were anticipated by U.S. Pat. Publ. 2006/0240554 ("the '554 publication") under 35 U.S.C. § 102, and alternatively that the claims would have been obvious over the '554 publication.

Moderna's obviousness arguments with respect to all grounds centered on alleged overlapping ranges of components. For example, claim 1 of the '435 patent recites a composition range for the cationic lipid that is "from 50 mol % to 85 mol % of the total lipid present in the particle." *See* '435 patent at col. 89 ll. 57–58. In comparison, the '196 PCT and the '189 publication each disclose a range of between 2 mol % and 60 mol % for the cationic lipid. *See* '196 PCT ¶ 88; '189 publication ¶ 152. According to Moderna, the range for each lipid component in the claims—i.e., the cationic lipid, the non-cationic lipid, and the conjugated lipid—overlaps with the range for that lipid component taught by the prior art.

Moderna's anticipation argument was based on one formulation—the "L054 formulation"—disclosed in the '554 publication. Moderna argued that the L054 formulation contained all of the claimed components in amounts within the claimed ranges of the '435 patent. Specifically, Moderna contended that the L054 formulation contained 50 mol % cationic lipid (which is within the 50–85 mol % range of claim 1), 48 mol % non-cationic lipid (which is

[2] Alison J. Lin, et al., Three-Dimensional Imaging of Lipid Gene-Carriers: Membrane Charge Density Controls Universal Transfection Behavior in Lamellar Cationic Liposome-DNA Complexes, 84 Biophysical J. 3307–16 (2003).

[3] Ayesha Ahmad, et al., New Multivalent Cationic Lipids Reveal Bell Curve for Transfection Efficiency Versus Membrane Charge Density: Lipid-DNA Complexes for Gene Delivery, 7 J. Gene Med. 739–48 (2005).

within the 13–49.5 mol % range of claim 1), and 2 mol % conjugated lipid (which is within the 0.5–2 mol % range of claim 1).

The Board found that Moderna proved by a preponderance of the evidence that claims 1–6, 9, 12, and 14–15 were anticipated by the L054 formulation in the '554 publication. However, the Board found that Moderna failed to prove that the remaining claims were anticipated, or that those claims would have been obvious over the prior art.

Moderna appealed from the Board's decision that it had failed to show that claims 7–8, 10–11, 13, and 16–20 were not anticipated and/or would not have been obvious. Protiva cross-appealed from the Board's decision that claims 1–6, 9, 12, and 14–15 were anticipated. Subject to the parties' dispute about Moderna's standing to pursue its appeal, which we discuss further below, we have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4).

DISCUSSION

I. Moderna's Appeal

Before we consider Moderna's arguments on the merits of the Board's decision upholding claims of the '435 patent, we must first determine whether Moderna has standing to pursue its appeal. After all, "no principle is more fundamental to the judiciary's proper role in our system of government than the constitutional limitation of federal-court jurisdiction to actual cases or controversies." *DaimlerChrysler Corp. v. Cuno*, 547 U.S. 332, 341–42 (2006) (quoting *Raines v. Byrd*, 521 U.S. 811, 818 (1997)).

Since the America Invents Act took effect nearly a decade ago, we have had a number of occasions to consider the question of standing in appeals from Board decisions in

IPR proceedings.[4] Our precedent generally makes clear that, as in all appeals before this court, an appellant seeking review of a Board decision in an IPR must have "(1) suffered an injury in fact, (2) that is fairly traceable to the challenged conduct of the [appellee], (3) that is likely to be redressed by a favorable judicial decision." *Phigenix*, 845 F.3d at 1171–72 (Fed. Cir. 2017) (quoting *Spokeo, Inc. v. Robbins*, 136 S. Ct. 1540, 1547 (2016)).

Under the IPR statute, there is no standing requirement for petitioners to request institution of IPR by the Board. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2143–44 (2016) ("Parties that initiate [IPRs] need not have a concrete stake in the outcome; indeed, they may lack constitutional standing."). And we recognize that where a statute grants judicial review, as the IPR statute does, *see* 35 U.S.C. § 319, the criteria of immediacy and redressability may be "relaxed." *See Momenta*, 915 F.3d at 768. But we have always maintained that a party's participation in the underlying IPR before the Board is insufficient by itself to confer standing on that party to appeal the Board's decision to this Article III court. *See Phigenix*, 845 F.3d at 1175; *see also Momenta*, 915 F.3d at 768 ("Although the statutory grant of judicial review may 'relax' the Article III criteria, judicial review of agency action remains subject to the constitutional foundation of injury-in-fact, lest the court occupy only an advisory role."); *JTEKT*, 898 F.3d at 1219 ("[T]he statute cannot be read to dispense with the

[4] *See, e.g.*, *Apple Inc. v. Qualcomm Inc.*, 992 F.3d 1378 (Fed. Cir. 2021); *Samsung Elecs. Co. v. Infobridge Pte. Ltd.*, 929 F.3d 1363 (Fed. Cir. 2019); *Momenta Pharms., Inc. v. Bristol-Myers Squibb Co.*, 915 F.3d 764 (Fed. Cir. 2019); *JTEKT Corp. v. GKN Auto. Ltd.*, 898 F.3d 1217 (Fed. Cir. 2018); *Phigenix, Inc. v. Immunogen, Inc.*, 845 F.3d 1168 (Fed. Cir. 2017); *Consumer Watchdog v. Wis. Alumni Research Found.*, 753 F.3d 1258 (Fed. Cir. 2014).

Article III injury-in-fact requirement for appeal to this court."). Accordingly, even when an appellant is "sharply opposed to the Board's decision and the existence of [a] patent, that is not enough to make th[e] dispute justiciable." *Consumer Watchdog*, 753 F.3d at 1263.

As the party seeking judicial review, Moderna "has the burden of establishing that it possesses the requisite injury." *See JTEKT*, 898 F.3d at 1220. Moreover, Moderna must show that standing existed at the time it filed its appeal and has continued to exist at all times throughout the appeal. *See Steffel v. Thompson*, 415 U.S. 452, 459 n.10 (1974) ("[A]n actual controversy must be extant at all stages of review, not merely at the time the complaint is filed."); *Momenta*, 915 F.3d at 770 ("[I]t is established that jurisdiction must exist throughout the judicial review, and an intervening abandonment of the controversy produces loss of jurisdiction.").

Shortly after Moderna filed this appeal in November 2019, Protiva moved to dismiss for lack of standing. Protiva argued that Moderna had never established that it suffered an injury in fact. *See Protiva Opening Standing Br.*[5] at 1. Protiva emphasized that it had never initiated a patent infringement action or directly accused Moderna of infringing its patents, and thus Moderna could only show standing to appeal the Board's decision if it were "currently using claimed features" of the '435 patent "or nonspeculatively planning to do so." *Id.* at 4 (citing *Fischer & Paykel Healthcare Ltd. v. ResMed Ltd.*, No. 2018-2262 (Fed. Cir. Nov. 27, 2019) (Order, non-precedential)). Indeed, Protiva argued, Moderna had consistently taken the position that it was not using Protiva's patented technology and did not intend to do so. *Id.* at 5.

[5] Dkt. 22.

In opposing Protiva's motion to dismiss, Moderna expressly stated in January 2020 that it did "not base its Article III standing on the threat of an impending infringement suit or Protiva's accusations of infringement." *Moderna Resp. Standing Br.*[6] at 3. Rather, Moderna argued, its standing was based on its status as a "current licensee to the '435 patent for four viral targets . . . with actual monetary obligations . . . that are impacted by the Board's validity determinations." *Id.* at 3–4. Moderna relied on our case law for the proposition that "[t]he risk of a future infringement suit is not the only way an IPR petitioner can show injury-in-fact." *Id.* at 4 (citing *Gen. Elec. Co. v. United Techs. Corp.*, 928 F.3d 1349, 1357 (Fed. Cir. 2019)). Moderna repeatedly cited our decision in *Samsung Electronics Co. v. Infobridge Pte. Ltd.*, to support its position that financial impacts to an appellant based on licensing obligations can be an independent means by which to establish an injury-in-fact supporting standing. *See Moderna Resp. Standing Br.* at 4, 8–9 (citing *Samsung*, 929 F.3d at 1368).

In support of its responsive brief in opposition to Protiva's motion to dismiss, Moderna submitted a declaration from Shaun Ryan, who was its Senior Vice President and Deputy General Counsel.[7] In his declaration, Mr. Ryan described information relating to Moderna's status as a

[6] The non-confidential version of Moderna's responsive brief is Dkt. 28. Moderna filed the confidential version of its brief as Dkt. 30.

[7] For confidentiality purposes, Moderna filed Mr. Ryan's declaration under seal with the confidential version of its responsive brief in Dkt. 30. In this opinion, to the extent we reference information from that confidential declaration, we reference only material that Moderna has subsequently made public through its briefing and oral argument in this appeal.

sublicensee of the '435 patent. Specifically, Mr. Ryan attested that Protiva had licensed the '435 patent among other patents to a company called Acuitas Biotherapeutics ("Acuitas"), and that Acuitas had, in turn, granted a series of sublicenses to Moderna to practice the patented technology for four viral targets, one of which was Respiratory Syncytial Virus ("RSV"). Mr. Ryan further stated that, under its rights from the Acuitas sublicenses, Moderna was engaged in an active development program for the RSV viral target. According to Mr. Ryan, Moderna had already made one milestone payment to Acuitas, and potentially could have additional milestone and royalty obligations in the future. Thus, Moderna argued, the royalty and milestone obligations owed to Acuitas for the use of the '435 patent caused harm to Moderna by increasing the financial burdens on Moderna's RSV development program.

We denied Protiva's motion, but we specifically noted that our denial was without prejudice to allow Protiva to raise its standing argument in its merits brief. *See* Dkt. 35. Shortly thereafter, Moderna filed its opening brief on the merits, relying in its jurisdictional statement mainly on the same arguments and evidence it had presented in opposing Protiva's motion to dismiss. *Moderna Opening Br.* at 6–9. Protiva then filed its responsive brief, including its response to Moderna's assertions of standing. *Protiva Resp. Br.* at 5–9. Protiva argued that the mere existence of a license is not sufficient to support Article III standing, and that Moderna's alleged "obligations" were "nothing but rank speculation, which even Moderna characterizes as an if and when proposition." *Id.* at 5. Protiva noted that the last milestone payment Moderna had made to Acuitas was on or before February 2016, and emphasized that Moderna "fail[ed] to identify any recent milestone payment or any such payment reasonably forthcoming." *Id.* at 7.

In March 2021, approximately nine months after Moderna had filed its opening brief on the merits, Moderna filed a motion to supplement the record to provide

additional evidence of standing. In that motion, Moderna argued that "new facts supporting Moderna's ongoing standing to appeal have arisen, and the existing facts have continued to develop." *Moderna Mot. to Suppl.*[8] at 3.

The "existing facts" to which Moderna referred were those that Mr. Ryan had described in his original declaration more than a year earlier. With its motion to supplement, Moderna submitted a supplemental declaration from Mr. Ryan,[9] in which he stated that Moderna had, at some point during the previous year, terminated the RSV development program that had been active at the time that the appeal was filed. He also admitted that none of the four viral targets that were covered under the Acuitas sublicenses were being pursued to further phases, though he noted that they had not been fully abandoned. Importantly, Mr. Ryan did not provide an approximate date on which that RSV development program had been terminated, nor did he describe any concrete plans to further pursue development programs for any of the four viral targets.

The "new facts" to which Moderna referred related to Moderna's ongoing development of a vaccine for COVID-19. Mr. Ryan's supplemental declaration described Moderna's

[8] The non-confidential version of Moderna's motion is Dkt. 111. Moderna filed the confidential version of its brief as Dkt. 112.

[9] Like his original declaration, Mr. Ryan's supplemental declaration also purports to contain confidential information. Again, we reference only material from the supplemental declaration that Moderna has made public. Moreover, attached to Mr. Ryan's supplemental declaration in this appeal was a supplemental declaration that he submitted on the same day in Appeal No. 20-2329. For purposes of this opinion, we treat these two supplemental declarations as one.

work that led to its concrete plans as of September 2020 to release a COVID-19 vaccine, its emergency use authorization as of December 2020, and its subsequent commercial shipments of the vaccine. Mr. Ryan also described a series of public statements made by Arbutus in 2017 regarding the alleged extensive scope of its patents. According to Mr. Ryan, those aggressive public statements by Arbutus, in combination with Arbutus's refusal to grant Moderna a covenant not to sue and Arbutus's consistent insistence that Moderna requires a license to Arbutus's patents, created a significant risk that Arbutus would sue for patent infringement.

During oral argument, counsel for Moderna explained its position that "Moderna had and continues to have standing to pursue this appeal." Oral Arg. at 1:32, https://oralarguments.cafc.uscourts.gov/default.aspx?fl=20-1184_10072021.mp3. Moderna's counsel began by arguing that the basis for Moderna's standing "at the outset when this appeal was filed in November of 2019," *id.* at 1:38, was "contractual rights that are affected by a determination of patent validity," *id.* at 2:27. Counsel repeatedly emphasized the "active" status of Moderna's RSV development program at that time, which had resulted in one milestone payment and potentially could have resulted in future milestone and royalty obligations. But Moderna's counsel then argued that "the situation has evolved," *id.* at 6:53, and the "evolution keeps this controversy alive," *id.* at 8:24. Specifically, counsel conceded that "over time, . . . that particular RSV program was not pursued," *id.* at 8:36, but "at the same time, the COVID vaccine was developed and ultimately [] delivered to the market and commercialized," *id.* at 8:53.

Arbutus's counsel responded by challenging each aspect of Moderna's standing timeline, as well as the timeline as a whole. Counsel began by arguing, regarding Moderna's position on standing at the time the appeal was filed, that "any notion of immediacy is entirely absent"

from the evidence that Moderna presented on its "speculative" licensing obligations. *Id.* at 16:50. Arbutus's counsel also insisted that it was crucial that the '435 patent was only one of many patents licensed under the Acuitas sublicenses, and that Moderna had not shown how its payment obligations would change if the '435 patent were to be invalidated. Next, Arbutus's counsel turned to Moderna's concession that the RSV development program had at some point been abandoned, focusing on the lack of evidence regarding "when that happened versus when their COVID vaccine came into being and recreated" standing. *Id.* at 23:33.

We agree with Arbutus that Moderna lacked standing at the time the appeal was filed. Even if the '435 patent was the only patent that Moderna had licensed under the Acuitas sublicenses, Moderna's evidence of financial burdens from the validity of that patent is too speculative. Notwithstanding Moderna's counsel's repeated characterization of the RSV development program as "active" at the time this appeal was filed, Moderna concedes that the last milestone payment it made under the Acuitas sublicenses was approximately five years earlier, and Mr. Ryan's declaration states only that Moderna would have to make an additional milestone payment "if and when" a future milestone is reached. On this evidence, Moderna falls short of its burden to demonstrate that at the time it filed this appeal, it had suffered or was suffering a "concrete" injury from the existence of the '435 patent. *See Phigenix*, 845 F.3d at 1171 ("To constitute a 'concrete' injury, the harm must 'actually exist' or appear 'imminent'—a 'conjectural or hypothetical' injury will not suffice." (internal citations omitted)).

Even more problematic for Moderna, the '435 patent is not the only patent licensed under the Acuitas sublicenses, but rather it is one of many licensed patents. On this point, the parties appear to agree that the two crucial cases are *Samsung* and *Apple*. In *Samsung*, we held that the

appellant had standing because, even though multiple patents were licensed, the appellant had provided evidence demonstrating that the express terms of the contract structured the patent pool in such a way that invalidation of the patent at issue in the underlying IPR would have changed the amount of royalties. *Samsung*, 929 F.3d at 1368. In contrast, in *Apple* we held that the appellant lacked standing because multiple patents had been licensed, and the appellant failed to present evidence that invalidation of the particular patents it was challenging would affect its contractual rights by changing its royalty obligations. *Apple*, 992 F.3d at 1383.

The facts here resemble those in *Apple*, not those in *Samsung*. Moderna has provided no evidence as to how, if at all, its obligations under the Acuitas sublicenses would change if it is successful in its attempts to have the '435 patent declared invalid while the remaining licensed patents continue to exist. Thus, Moderna has failed to meet its burden of demonstrating that it suffers an injury from the existence of the '435 patent, or that any such injury would be redressed by invalidation of that patent. *See id.* at 1383–84. Accordingly, we agree with Arbutus that Moderna lacked standing at the time this appeal was filed.

We also agree with Arbutus that, even if Moderna had standing at the time it filed this appeal, Moderna has failed to demonstrate that it continuously had standing throughout the pendency of the appeal. Under our precedent, an "intervening abandonment of the controversy produces loss of jurisdiction." *Momenta*, 915 F.3d at 770. Moderna's evidence fails to show an approximate date when the RSV development program was terminated. Thus, on the record before us, it is impossible to determine whether, by the time the RSV development program was terminated, Moderna was already sufficiently underway with its development of a COVID-19 vaccine to "create[] a substantial risk of future infringement or likely cause the patentee to assert a claim of infringement." *E.I. DuPont de Nemours*

& Co. v. Synvina C.V., 904 F.3d 996, 1004–05 (Fed. Cir. 2018).

As the appellant, Moderna bears the burden on the issue of standing, *JTEKT*, 898 F.3d at 1220, including the burden to demonstrate that there has been no gap in its standing while this appeal has been pending, *Momenta*, 915 F.3d at 770. In view of Moderna's concession that the basis for its standing shifted during the pendency of this appeal—*i.e.*, from the financial burdens of the Acuitas sublicenses to a potential infringement suit for the COVID-19 vaccine—Moderna had to come forth with evidence to demonstrate the necessary continuity of jurisdiction. Moderna failed to do so.

For the reasons explained above, we find that Moderna has failed to meet its burden on its standing to pursue this appeal. Therefore, Moderna's appeal must be dismissed.

II. Arbutus's Cross-Appeal

With respect to the cross appeal, there is no dispute that Arbutus, as the patent owner, has standing to appeal the Board's decision that claims 1–6, 9, 12, and 14–15 are unpatentable. Thus, we proceed to the merits.

Arbutus argues that the Board erred by failing to recognize a critical distinction between starting ingredients versus a final product. Arbutus contends that the claims of the '435 patent are directed to completed lipid particles of defined composition. In contrast, Arbutus argues, the L054 formulation disclosed in the '554 publication is a lipid mixture of starting ingredients for making lipid particles, not a completed lipid particle itself. According to Arbutus, expert testimony and corroborating literature demonstrated that a person of ordinary skill in the art would have expected the composition of components in a final lipid particle to deviate from the composition of components in the mixture of starting ingredients. Arbutus further argues that its expert provided evidence that the '554 publication's

fabrication process would skew the L054 formulation's final lipid particle such that the final composition would fall outside the range of the '435 patent claims.

Moderna responds that substantial evidence supports the Board's factual findings regarding the disclosures of the '554 publication. Moderna notes that the Board specifically considered Arbutus's argument that the L054 formulation failed to teach the composition of the final lipid particle, but the Board rejected that argument. Moderna argues that after weighing the evidence, the Board found that it was standard practice in the field to describe lipid particles by the composition of components in the input formulation. The Board further relied on the disclosures of the prior art and the '435 patent itself, as well as the testimony of expert witnesses.

We review the Board's legal determinations de novo, *In re Elsner*, 381 F.3d 1125, 1127 (Fed. Cir. 2004), but we review the Board's factual findings underlying those determinations for substantial evidence, *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). A finding is supported by substantial evidence if a reasonable mind might accept the evidence as adequate to support the finding. *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938).

"Anticipation is a question of fact that we review for substantial evidence." *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1341 (Fed. Cir. 2016) (citing *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)). A prior art reference anticipates a claim if it discloses "each and every element of the claimed invention . . . arranged or combined in the same way as in the claim." *Id.* (quoting *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009)).

We agree with Moderna that substantial evidence supports the Board's decision. Arbutus's arguments pertain to whether a person of ordinary skill in the art would have reasonably understood from the disclosure in a prior art

reference that every element of the claims is disclosed, which is the "dispositive question regarding anticipation." *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010). In evaluating that question, the Board first considered the substantial evidence that Moderna presented that a person of ordinary skill would understand that the mol % of each component in the L054 formulation would result in lipid particles within the claimed ranges of the '435 patent, which also describes lipid particles in terms of mol % of the formulation. *Board Decision*, 2019 Pat. App. LEXIS 13612, at *23. Thus, the Board turned to Arbutus's evidence and found that it, at best, suggested that there would be some variation in the final compositions of the lipid particles fabricated from the L054 formulation. *See id.* at *23–24. But the Board rejected as speculative Arbutus's expert's opinion that all of the particles formed from L054 formulation would fall outside the claimed ranges. *Id.* at *24–27. And the Board noted that anticipation "does not require that all of the formed particles from the L054 formulation . . . be within the claimed ranges . . . . Anticipation merely requires that a composition within the claimed ranges be disclosed." *Id.* at *28 (citing *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985)).

The Board's legal conclusions regarding the requirements of anticipation were correct. "When a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within the range." *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015) (citing *Titanium Metals*, 778 F.2d at 782). Furthermore, an anticipating reference need not show that every disclosed compound anticipates; rather it is sufficient that it contains a disclosure of "at least one compound which anticipates." *See In re Sasse*, 629 F.2d 675, 682 (Fed. Cir. 1980). Thus, to anticipate the claims of the '435 patent, the question for the Board was whether the

'554 publication discloses at least one composition that falls within the claimed ranges.

The Board weighed the evidence and found, as a factual matter, that the '554 publication disclosed at least one composition that anticipates the claims. In challenging that factual determination in this appeal, Arbutus relies on the same evidence and argument that failed to convince the Board that the L054 formulation does not anticipate the completed lipid particles of the '435 patent claims. But Arbutus fails to persuade us that Moderna's evidence was insufficient to allow the Board to find that the L054 formulation does anticipate. Substantial evidence supports the Board's decision.

CONCLUSION

We have considered the parties' remaining arguments but we find them unpersuasive. Accordingly, we dismiss Moderna's appeal for lack of standing. We affirm the Board's final written decision that claims 1–6, 9, 12, and 14–15 are unpatentable as anticipated.

DISMISSED-IN-PART, AFFIRMED-IN-PART

COSTS

No costs.

JOINT APPENDIX 76

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3 September 2018

Dear Sirs

Re: EP No 2 279 254
Protiva Biotherapeutics Inc.
PB Reference GSI-O001EP

The following is the Proprietor's response to the notices of opposition filed against the above noted patent.

With this response we file:

Auxiliary Requests 1 to 4 (AR1 to AR4), in both clean and marked-up form;
D28: Uyechi-O'Brien & Szoka *Pharmaceutical Gene Delivery Systems* 2003: 79-108;
D29: Song *et al. Biochimica et Biophysica Acta* 2002; 1558: 1-13;
D30: Ambegia *et al. Biochimica et Biophysica Acta* 2005; 1669: 155-163.

The Proprietor's requests are set out in Section A of this response. In particular, oral proceedings are requested under Article 116 EPC in the event that the OD cannot grant the Proprietor's main request (i.e. maintenance as granted) on the basis of the written proceedings.

Yours faithfully

/ BROUGHTON, Jon Philip /

Patent Boutique LLP
Association of Professional Representatives No. 651

RESPONSE TO OPPOSITIONS BY MERCK, SHARP & DOHME CORP. AND MODERNA TX, INC.

EP 2 279 254 B1
"NOVEL LIPID FORMULATIONS FOR NUCLEIC ACID DELIVERY

A. Introduction and Requests

1. EP 2 279 254 B1 (the **Patent**) of Protiva Biotherapeutics Inc. (**Proprietor**) has been opposed by Merck, Sharp & Dohme Corp (**O1**) and ModernaTX, Inc. (**O2**). The Patent was granted on application number EP 09 731866.1 (PCT application number PCT/CA2009/000496) having a filing date of 15 April 2009. The Patent claims the priority of US 61/045,228 and therefore has a priority date of 15 April 2008.

2. Although priority has been challenged by O1 on the basis of lack of entitlement of Protiva Biotherapeutics Inc. (**Applicant**) to claim priority from this document, no prior art attacks rely upon the consequential alleged loss of priority. The Proprietor maintains that the Applicant was entitled to claim priority at the filing date of the PCT application since it was the successor in title of the inventors and applicants of US 61/045,228, by virtue of Canadian law and employment contracts. The Proprietor reserves the right to substantiate its position at a later date, should O1's objection to priority become relevant in the future.

3. D1 to D8 were cited in O1's opposition statement. The documents that were cited as D1 to D23 in O2's opposition statement have been renumbered. A revised consolidated list of cited documents is provided in Annex 1.

4. The Proprietor requests that the opposition be rejected and the patent be maintained on the basis of the claims of the main request (**MR**; the claims as granted). If the Opposition Division (**OD**) does not consider the MR to be allowable, the Proprietor requests that the Patent be maintained on the basis of one of auxiliary request 1 (**AR1**) to auxiliary request 4 (**AR4**). The Proprietor reserves the right to present further auxiliary requests based upon combinations of AR1-AR4 should it be necessary. Oral proceedings are requested under Article 116 EPC in the event that the OD cannot grant the Proprietor's MR on the basis of the written proceedings.

5. The Proprietor reserves the right to provide further comments on any of the issues raised in the oppositions at a later date if necessary.

B. The Invention

6. The Patent relates to an important technological advance in the emerging field of gene delivery systems. In particular, it discloses novel nucleic acid-lipid particle formulations that can be used, for instance, to treat cancer, liver disease, and viral infections.

7. The nucleic acid-lipid particles of the invention are serum-stable lipid particles, formed from a cationic lipid, a non-cationic lipid, and a conjugated lipid that prevents aggregation of the particle. These nucleic acid-lipid particles have important technical advantages over the use of cationic liposome complexes (also known as lipoplexes). As the Patent explains at [0005]:

> **[0005]** Cationic liposome complexes are large, poorly defined systems that are not suited for systemic applications and can elicit considerable toxic side effects (Harrison et al., Biotechniques, 19:816 (1995); Li et al., The Gene, 4:891 (1997); Tam et al, Gene Ther., 7:1867 (2000)). As large, positively charged aggregates, lipoplexes are rapidly cleared when administered *in vivo*, with highest expression levels observed in first-pass organs, particularly the lungs (Huang et al., Nature Biotechnology, 15:620 (1997); Templeton et al., Nature Biotechnology, 15:647 (1997); Hofland et al., Pharmaceutical Research, 14:742 (1997)).

8. Unlike cationic liposome complexes and other nucleic acid delivery systems in the prior art, the nucleic acid-particles of the invention are small, serum-stable and substantially non-toxic, making them suitable for systemic applications.

9. Prior to the Patent, the trend in the field was to use delivery systems with low levels of cationic lipid. This prevailing mind-set was due to the fact that cationic liposome complexes were understood to be toxic due to the cationic lipid, the nucleic acid and/or the physical attributes of the liposome complex (see for example, page 99 of **D28**). This mind-set is also acknowledged in paragraph [0005] of the Patent, which states that "*[c]ationic liposome complexes are large, poorly defined systems that are not suited for systemic applications and can elicit considerable toxic side effects*". Furthermore, high levels of cationic lipid were known to result in *in vivo* aggregation, immunogenicity, and rapid clearance of these complexes from the circulation (see also paragraph [0005] of the Patent).

10. Another trend in the field was the incorporation of higher than the claimed levels of conjugated lipids to stabilise the particles so that the therapeutic nucleic acid payloads could reach the target cells. It was widely understood that failure to use such high levels of conjugated lipids would cause the particles to degrade or undergo dissolution before reaching their targets.

11. The invention of the Patent solved these problems by requiring a combination of:

    (a) cationic lipid at 50 mol % to 65 mol %;

    (b) non-cationic lipid at up to 49.5 mol %;

    (c) cholesterol or cholesterol derivative at 30 mol % to 40 mol %; and

    (d) conjugated lipid at 0.5 mol % to 2 mol %.

12. This specific combination was found to be surprisingly effective for the systemic administration of the claimed nucleic acid-lipid particles *in vivo*, and does not elicit the feared toxic effects associated with formulations having a high level of cationic lipid.

C. The Claims Do Not Add Matter (Art 123(2) EPC and Art 100(c) EPC)

13. Both Opponents have objected to claim 1 of the Patent as adding matter contrary to Art 123(2) EPC. O1 has additionally objected to claims 8 and 10, whereas O2 has not objected to those claims.

Claim 1 does not add matter

14. The Opponents objections against claim 1 can be summarised as follows:

Objection	Opponent
The combination of features in claim 1 parts (b) and (c) can only be derived by selecting from two or three lists including: Selection of the cationic lipid mol % range Selection of whether or not to incorporate cholesterol (or derivatives thereof) and phospholipids The mol % range of cholesterol	O1 and O2
Claim 1(c) adds matter because the mol % range of cholesterol derivatives is disclosed only in combination with a mol % range of phospholipids (not specified in claim 1).	O1
A lower limit of 13% for non-cationic lipids has been omitted from claim 1(c)	O2
There is no basis in the Application as Filed for a range of "*a very small amount ε to 19.5%"* for the phospholipid – the only concrete definition of a range of phospholipids that is originally disclosed in combination with a range of 30-40 % cholesterol is 4-10% phospholipid.	O2

15. The Opponents' objections are unfounded as shown in the following passages which explain the basis for claim 1 of the Patent.

16. Claim 13 of the Application as Filed provides the following (when incorporated into the language of claim 1 of the Application as Filed upon which it is dependent):

- A nucleic acid lipid particle comprising:
  - a) a nucleic acid;
  - b) a cationic lipid comprising from about 50 mol % to about 85 mol % of the total lipid present in the particle;
  - c) a non-cationic lipid comprising from about 13 mol % to about 49.5 mol % of the total lipid present in the particle <u>and comprising a mixture of a phospholipid and cholesterol or a derivative thereof</u>;
  - d) a conjugated lipid that inhibits aggregation of particles comprising from about 0.5 mol % to about 2 mol % of the total lipid present in the particle.

(underlined subject matter is derived from claim 13 of the Application as Filed).

17. Claim 1 of the Patent differs from the above in the following respects only:

- a mol % range has been specified for the cholesterol or derivative thereof;
- a lower limit of 13 mol % in part (c) is not explicitly recited; and
- claim 1 of the Patent recites a narrower range for the mol % range of cationic lipid.

The mol % range for cholesterol or derivatives thereof is derivable from the description of the Application as Filed

18. In order to determine whether these differences result in the addition of matter it is necessary to determine what the skilled person would have understood from the Application as Filed in respect of these features.

19. It is reasonable to assume that the skilled person would turn to the description to determine a suitable range for the mol % of the cholesterol or cholesterol derivative component of the above noted compositions. Section B of the description, starting at page 67 of the Application as Filed, is entitled: "*B. Non-Cationic Lipids*" and provides the skilled person with additional detail as to suitable non-cationic lipids and amounts thereof. At paragraph [0253] the specification teaches that in lipid particles containing a mixture of phospholipids and cholesterol, the cholesterol may comprise from about 30 mol % to about 40 mol % of the total lipid present in the particle. Certain sub-ranges are also provided in this paragraph, however the range of 30 to 40 mol % is the broadest disclosure in this paragraph.

20. It is further clear that the same range is also suitable for cholesterol derivatives. Paragraph [0130] of the Application as Filed teaches, in its first sentence, that in preferred embodiments the cholesterol or a derivative thereof is present in a range of from about 30 mol % to about 40 mol % of the total lipid present in the particle.

21. Opponent 1 has criticised this disclosure since it is provided in the context of embodiments in which an amount of phospholipid is also disclosed. However, there is no technical justification to support the notion that the skilled person, reading paragraphs [0253] and [0130], would conclude that the recited range for cholesterol or derivatives thereof is **only** applicable in embodiments having the recited phospholipid range.

22. In fact, it is clear from, for example, claim 13 as originally filed, and paragraph [0119] that, as a generality, cholesterol may be substituted in the particles of the invention by cholesterol derivatives. The skilled person would understand that cholesterol derivatives are intended to play the same role as cholesterol itself, and are therefore functionally equivalent to cholesterol in the particles. There is no teaching in the specification that would lead the skilled person to separate the teachings relating to cholesterol from those relating to cholesterol derivatives, and no reason for the skilled person to conclude that the mol % range for cholesterol derivatives is inextricably linked to the mol % range for phospholipids recited in the first sentence of paragraph [0130].

23. Indeed, the specification makes it quite clear that the mol % range for cholesterol derivatives is not (technically) tied to the range of 4 to 10 mol % of phospholipids. From paragraph [0129] it is apparent that a range of 30 to 40 mol % cholesterol derivative is suitable for use even in a phospholipid-free particle (i.e. where the mol % of phospholipid is zero). Moreover, in the second part of paragraph [0130] the skilled person is taught that the phospholipid may be present at *inter alia* 3 mol % to 15 mol % and (in the same particle) the cholesterol or derivatives thereof may be present at, *inter alia* 30 mol % to 40 mol %[1]. The clear teaching is that a range of 30 to 40 mol % for cholesterol derivatives is technically suited for use with a much wider range of phospholipid mol % amounts than that recited in the first sentence of paragraph [0130].

24. In summary, the skilled person is taught, overall, in paragraph [0253] that in embodiments in which the non-cationic lipid comprises a phospholipid and cholesterol, the cholesterol may be present at 30 to 40 mol % regardless of the amount of phospholipid present. The specification further teaches, *inter alia* at paragraph [0119], that, as a generality, cholesterol may be replaced by cholesterol derivatives. Paragraph [0130] confirms that the mol % range of 30 to 40 is suitable for both cholesterol and cholesterol derivatives. Although disclosed in the context of embodiments having a particular range of phospholipid mol % amounts, it is clear to the skilled reader that the suitability of the mol % range for cholesterol derivatives is no more dependent on the range of phospholipid mol % amounts than is that for cholesterol itself.

25. Accordingly, taking into account the overall teaching of the specification, it is clear that the mol % range recited in claim 1(c) of the Patent does not add matter, whether applied to cholesterol or to cholesterol derivatives.

The lower mol % limit of non-cationic lipids in claim 1 as filed is redundant and its omission does not therefore add matter

26. Claim 1 of the Patent requires that the non-cationic lipid component of the particles comprises cholesterol or a cholesterol derivative at between 30 and 40 mol % of the total lipid of the particle. Since the cholesterol or derivatives thereof are non-cationic lipids, claim 1 of the Patent is limited to embodiments having at least 30 mol % of non-cationic lipids[2]. The lower limit of 13 mol % recited in claim 1 of the Application as Filed is therefore exceeded in all embodiments of the granted claims and its mention in claim 1 of the Patent is therefore wholly redundant.

27. There can be no addition of matter by the omission of a feature that is made redundant in a claim by the inclusion of other features (see, e.g. decision T 917/94 of the Technical Board of Appeal, Catchword 1 and point 1.1 of the Reasons for the Decision).

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[1] It is immaterial that in paragraphs [0129] and [0130] multiple different ranges are provided for phospholipid mol % ranges and for cholesterol/cholesterol derivatives mol %. Whether or not these paragraphs provide basis for any particular combination of ranges or sub-ranges is not relevant to the overall technical conclusion that the skilled person would draw, which is that a range of 30 – 40 mol % of cholesterol derivative is broadly applicable to particles having a wide range of phospholipid mol % amounts.

[2] In fact the claim requires more than 30 mol % of non-cationic lipids because in addition to the cholesterol or derivative thereof, it must further comprise phospholipids.

Accordingly, there can be no addition of matter by omitting reference to 13 mol % non-cationic lipids.

The mol % amount recited for claim 1(b) does not add matter

28. It is often the case that a patent application as filed discloses suitable ranges for the amount of a component in a composition by reference to a broadest range, and by reference to preferred sub-ranges within that broad range. Whilst in some circumstances it might be correct to argue that a reference in a claim to one such sub-range might be considered a selection from a list, the same is not correct for the broadest disclosed range. The normal practice of the EPO (ranging from examining divisions through opposition divisions to technical boards of appeal) is to recognise that the broadest disclosed range is a generic teaching, applicable to all embodiments of the disclosed invention. That is, of course, a completely logical position to take, since the broadest disclosed range sets the boundaries within which the skilled person is instructed to work. No act of selection is required on behalf of the skilled person to arrive at that broadest range – rather, it is a starting point for all embodiments intended to fall within the scope of the invention.

29. The Application as Filed disclosed at paragraph [0113] that within the lipid particles of the invention, the cationic lipid component may comprise from about 50 mol % to about 90 mol % of the total lipid present in the particle. This disclosure therefore established the upper and lower boundaries within which the cationic lipids should be kept, offering no choice to the skilled person to work outside of those boundaries.

30. During prosecution of the Application as Filed, the claims were limited, as discussed above, to specify that the cholesterol or derivative thereof comprises, at a minimum, 30 mol % of the total lipid present in the particle. Together with the conjugated lipid of part (d) of claim 1, the cholesterol (or derivative thereof), and phospholipids comprise at a minimum, just over 30.5 mol % of the total lipids present in the particle (30 mol % cholesterol or derivative thereof; 0.5 mol % conjugated lipid; and an unspecified amount of phospholipid).

31. The skilled person is therefore fully able to determine, without any additional knowledge, that the maximum amount of cationic lipid in the particle cannot (as a matter of logic) exceed just under 69.5 mol %. Clearly the broadest disclosed range of 50 mol % to 90 mol % would be understood by the skilled person as not applying in circumstances where the upper boundary of the range is unworkable (both in logic and in practice).

32. For the sake of clarity and enablement, the claim must, of course, exclude unworkable combinations of mol % amounts and it is therefore necessary to define the range of mol % of cationic lipid in such a way that the upper limit is compatible with the lower limits of all other recited lipid components. The claim was therefore amended during prosecution to refer to the range now found in claim 1 of the Patent (50 mol % to 65 mol %).

33. This range is compatible with the recited amounts of other lipid components in the claim, and is disclosed at line 29 on page 24 of the Application as Filed (in paragraph [0113]).

34. In amending to this range, no selection has been made from a list of ranges. Rather, as would be apparent to the skilled person, the claim has been amended to define the broadest disclosed range that is compatible with the other recited components in the claim. The range recited in claim 1 maintains the same lower boundary (50 mol %) as in claim 1 as filed, and merely restricts the upper boundary to that of the broadest disclosed range that works in the claims (65 mol %). No selection from a list is necessary to arrive at this upper boundary.

35. O2 argues that other ranges disclosed in paragraph [0114] are also compatible with the recited amounts of other components within the claim. Of course, since as discussed above, the claim is limited to the broadest disclosed range that is compatible with the minimum amounts of other components recited in the claim. That there are other ranges falling within the broadest disclosed range is not surprising, nor does it impact upon the Patentee's position as discussed above. O2's arguments are simply irrelevant.

36. In summary, the limitation of the range of mol % amount for the cationic lipid component of claim 1 of the Patent is not arrived at by the selection from a list of ranges. Overall, therefore claim 1 finds basis in the Application as Filed by the simple combination of claim 13 as originally filed with the clear disclosure of a suitable amount of cholesterol or derivative thereof from paragraphs [0130] and [0235], and a necessary adjustment to the upper boundary of the range for cationic lipid amounts in the particle, disclosed at paragraph [0113]. Claim 1 does not, therefore, add matter in the sense of Art 123(2) EPC.

Claim 8 does not add matter

37. O1 has objected to claim 8 as adding matter on the grounds that the mol % amount ranges for cholesterol or derivatives thereof of claim 8 (a) are allegedly not disclosed "*for the same reasons as discussed in connection with granted claim 1*".

38. Claim 8, part (a) of the Patent recites that the cholesterol or derivative thereof comprises from 30 mol % to 35 mol % of the total lipid present in the particle. This range is disclosed in paragraph [0253] of the Application as Filed, and for the same reasons as discussed above in connection with claim 1 of the Patent this disclosure would be understood by the skilled person to apply equally to cholesterol and to derivatives thereof. There is no addition of matter in claim 8 part (a).

39. O1 has further objected to claim 8 part (b) because it alleges that the range of 32 mol % to 36 mol % for cholesterol (or derivatives thereof) is not disclosed in combination with the range of 3 mol % to 15 mol % for phospholipids. However, paragraph [0130] expressly teaches (from page 27 line 29 onwards) that the non-cationic lipids may comprise a mixture of phospholipids from about 3 mol % to about 15 mol %, together

with cholesterol (or derivatives thereof) within certain ranges. Whilst the disclosure teaches that it might be desirable to narrow down the range of mol % amounts for phospholipids, it is explicitly taught to the skilled person that each range for cholesterol or derivatives thereof may be combined with each range of phospholipids disclosed in the paragraph.

40. Claim 8 part (b) merely reflects one of these recited combinations – the broadest range for phospholipids, combined with a narrower range for cholesterol or derivatives thereof. No selection from lists is required to arrive at this combination.

41. In view of the above, claim 8 of the Patent does not add matter.

Claim 10 does not add matter

42. O1 has also objected to claim 10 under Art 123(2) on the grounds that in claims 38 and 33 of the Application as Filed, the recited phospholipids or cholesterol (or derivatives thereof) were not explicitly specified as being non-cationic (a requirement of claim 10 of the Patent).

43. Claim 38 of the Application as Filed disclosed precisely the same embodiment as in claim 10 of the Patent. It would be immediately apparent to the skilled person that the mixture of phospholipids and cholesterol (or a derivative thereof), recited in part (c) of claim 33 (upon which claim 38 is dependent), are intended as a different component from the cationic lipids of part (b) of claim 33. Part (b) of claim 33 recites a cationic lipid and provides a range, implying that there are no further cationic lipids contributed by either parts (c) or (d) of the claim.

44. Moreover, this understanding is fully supported throughout the specification which repeatedly teaches that non-cationic lipids suitable for the particles of the invention are phospholipids and cholesterol (or derivatives thereof). There is no new teaching whatsoever in claim 10 of the Patent in this regard, and claim 10 therefore does not add matter.

D. Exclusion From Patentability (Art 53 EPC)

45. O2 (but not O1) has presented an argument that claim 12[3] should be excluded from patentability under Art 53(c) EPC (pages 11 and 12 of O2's opposition statement).

46. O2 has misinterpreted the case law of the Enlarged Board of Appeal in decision G1/07, and has ignored an entire section of the Enlarge Board of Appeal's opinion in that case. O2's conclusions are wrong.

47. In approving the earlier decision G1/04, decision G1/07 states, at section 3.2.3.1 (second paragraph) of the Reasons for the Decision:

> "*In the above cited passage of its opinion G 1/04 the Enlarged Board clearly and explicitly approved that jurisprudence, as regards method steps for treatment by surgery or therapy. Whether an obiter dictum or not, the cited passage is drafted in such clear terms as to leave no doubt that the Enlarged Board thereby endorsed the principle developed in the jurisprudence of the boards of appeal that a method claim falls under the prohibition of Article 52(4) EPC 1973 if it includes at least one feature defining a physical activity or action that constitutes a method step for treatment of a human or animal body by surgery or therapy.*" (emphasis added).

48. Decision G1/04 made it clear that to be excluded a method claim should "*include*" at least one feature defining a physical activity or action that constitutes a method step for treatment of a human or animal body by surgery or therapy. Claim 12 of the Patent does not, of course, include any such method step.

49. At section 3.2.5 of the Reasons for the Decision, the Enlarged Board of Appeal in G1/07 went on to state:

> "*Concluding from the above, the Enlarged Board sees no good reason not to uphold the principle confirmed in opinion G 1/04, point 6.2.1 of the Reasons, and underlying the whole body of hitherto practice and jurisprudence that a method claim falls under the prohibition of patenting methods for treatment by therapy or surgery now under Article 53(c) EPC if it comprises or encompasses at least one feature defining a physical activity or action that constitutes a method step for treatment of a human or animal body by surgery or therapy.*" (emphasis added).

50. It is clear that the Enlarged Board in G1/07, whilst using slightly different language to the Enlarged Board in G1/04 ("*comprises or encompasses*" instead of "*includes*"), did not intend to depart from the meaning of the decision in G1/04. Rather, it intended to "*uphold the principle confirmed in opinion G 1/04*". The use of the term "*encompasses*"

[3] O2 refers to claim 11 but this appears to be an erroneous reference. The arguments appear to relate actually to claim 12.

does not expand the range of method claims that should be found unallowable under G1/07 beyond those found unallowable under the principle as originally set out in G1/04.

51. This is made clear from section 4 of the Reasons for the Decision in G1/07, addressing Question 2 of the referred questions. Question 2 was:

> "*If the answer to question 1 is in the affirmative, could the exclusion from patent protection be avoided by amending the wording of the claim so as to omit the step at issue, or disclaim it, or let the claim encompass it without being limited to it?*"

52. Section 4.1 addresses the question of claims left to encompass a surgical step. The paragraph spanning pages 65 and 66 of the decision explains that "*"encompassing" in the terminology of the present decision*" means "*a claim of a higher level of abstraction embracing…subject-matter excluded from patent protection without explicitly claiming it*". The Enlarged Board was concerned in this section with broad claims which included method steps having inadequate specificity to be determined to be surgical steps within the accepted meaning, but which, nonetheless encompassed surgical steps.

53. This section is quite distinct from section 4.3 of the Reasons for the Decision, in which the Enlarged Board addressed "*Omission of the step*". In this section, the Enlarged Board confirmed, subject to the requirements of Art 84 (which of course is not a relevant consideration post-grant), and Articles 123(2), 83 and 56, that claims in which the method step in question is omitted, are allowable (see section 4.3.3 of the Reasons for the Decision).

54. O2 has not argued that claim 11 adds matter, or lacks sufficiency or inventive step for the reason that it omits a critical method step, and according to the reasoning of the Enlarged Board of Appeal, the claims are therefore allowable under Art 53(c) EPC.

55. O2 has noted that the description of the Patent, at paragraph [0132] indicates that, following delivery of an interfering RNA in vitro, cells may be reinjected into the patient. From that, O2 concludes that claim 11 clearly "*encompasses*" therapeutic methods performed upon the human or animal body. However, this conclusion ignores the context of the Enlarge Board's use of the term "*encompass*", and further leads to an absurd conclusion. If O2 was correct in its logic, then very many valid patents would be objectionable under Art 53(c) EPC. For example, a patent disclosing and claiming a new synthesis method for a pharmaceutical compound might be objectionable under Art 53(c) if the patent disclosed that, once synthesised, the compound could be used to treat individuals for a particular disease.

56. Such a conclusion is clearly contrary to the normal practice of the EPO, and also to the position taken by the Enlarged Board of Appeal in G1/07. In Section 5 of the Reasons for the Decision the Enlarged Board made this very clear, stating:

> "*Since in that case the imaging method is a complete teaching per se the fact that it can be used in a potentially particularly advantageous way in the course of a surgical intervention does not preclude the imaging method from being claimed per se. Furthermore, even if used in the course of a surgical intervention that does not alter the character of the imaging method of not being a surgical step in itself.*
>
> *Article 53(c) EPC prohibits the patenting of surgical methods and not the patenting of any methods which can be used in the context of carrying out a surgical method. Otherwise, many methods which are used during surgical interventions even if not requiring themselves a surgical step to be carried out on the body, e.g. all methods for operating devices used in context with surgical activities would be unpatentable.*"
>
> and
>
> "*Hence, the fact that one of the possible and described uses of the imaging method is the use by a surgeon during a surgical intervention allowing the surgeon to decide on the course of action to be taken in the intervention by taking note of the immediately produced image data, does not render that imaging method excluded from patentability.*"

57. Although explained in the context of surgical methods, the Enlarged Board's conclusions are equally applicable to therapeutic methods.

58. Thus, where a claimed method is a complete teaching *per se* (as is the case with the method of claim 12, see below), the fact that the method can be used in a particularly advantageous way in the course of a therapeutic intervention (e.g. as described at paragraph [0132] of the Patent) does not preclude the method from being claimed *per se*.

59. As noted by the Enlarged Board, Art 53(c) EPC does not prohibit the patenting of any methods which can be used in the context of carrying out a surgical method. The same is of course true for methods which can be used in the context of carrying out a therapeutic method. Otherwise, as noted by the Board, many methods which are used during therapy, even if not requiring themselves a therapeutic step to be carried out would be unpatentable.

60. Just as in G1/07, the fact that one of the possible and described uses of the method of claim 12 is the use during a therapeutic treatment by reintroduction of transfected cells, does not render that method excluded from patentability.

61. Subsequent decisions of the Technical Board of Appeal have followed the above reasoning in determining whether or not a claim which does not recite a therapeutic or surgical step, nonetheless "*encompasses*" such a step, contrary to Art 53(c) EPC.

62. For example, in T699/12 the Technical Board of Appeal pointed out that the Enlarged Board of Appeal in G1/07 "*avoided to state that a surgical step that is not mentioned in a claim could nevertheless be read into the claim*" (see paragraph 3.1.7 of the Reasons for the Decision). Applying the law to the case in question, the Board stated:

> "*In the present case, the claimed method implies an irradiation of the patient, because otherwise a quantification of the dose delivery in the radiotherapy treatment of the patient (i.e. "the verification of the treatment") would not be possible. However, according to Art. 84 EPC 1973, the claims define the matter for which protection is sought. Moreover, according to Art. 69 EPC 1973, they determine the extent of protection conferred by a European patent. Hence, when carefully considering the wording of the claims, there is no basis for identifying a step like an "intermediate treatment of irradiating the patient for therapeutic purposes" that is de facto not claimed.*" (paragraph 3.1.8 of the Reasons for the Decision, emphasis added).

63. Thus, even where part of the claimed method would not be possible without a therapeutic or surgical step (in that case, the irradiation of a patient), the Technical Board of Appeal saw no justification for identifying a therapeutic or surgical step that is de facto not claimed.

64. In decision T429/12 the Technical Board of Appeal gave further consideration to when a surgical step that is not recited in a claim is, nonetheless, "*encompassed*" according to the language of G1/07.

65. In the case of the patent in question in that case, the claims neither explicitly defined nor excluded a particular surgical step. The Board stated:

> "*Under these circumstances it is appropriate to assess, inter alia with the help of the description, whether or not this step belongs to the claimed activity, namely the production of an aligning plate with an aperture for drilling a hole in the bone of a jaw.*" (section 3.4, second paragraph, Reasons for the Decision, emphasis added).

66. The Board therefore found it convenient to determine whether the unallowable step "*belongs to*" the claimed activity. In the invention in question in that case, the Board decided that the unallowable step did indeed belong to the claimed invention because it was *"…not only required for the claimed method…but represents the gist of the invention…*" (section 3.4, third paragraph, Reasons for the Decision).

67. Having regard to the specification of the Patent, the same cannot be said, however, of the method of claim 12. The Patent teaches, for example, at paragraph [0022] that the invention provides a method for introducing a nucleic acid into a cell, comprising contacting the cell *in vitro* with a nucleic acid-lipid particle of the invention. This

teaching provides no hint that returning cells to a host, or any other therapeutic intervention is required for the invention, nor is indeed the gist of the invention. Further, at Section VII (starting at page 39 of the Patent), *in vivo* and *in vitro* methods are dealt with separately and are distinguished (see paragraph [0289] which refers to "*in vitro* or *in vivo*" methods (emphasis added)). This section is separated into two separate sub-sections dealing separately with *in vivo* administration (paragraphs [0295] to [0307]) and *in vitro* methods (paragraphs [0308] to [0311]). In the latter section, no reference whatsoever is made to reintroducing cells to a patient. It cannot be concluded that any therapeutic method belongs to the invention of claim 12, in the sense that it is required for, or represents the gist of that invention.

68. In view of all of the above, the OD should not decide that claim 12 "*encompasses*" steps that are unallowable under Art 53(c) EPC, and claim 12 should therefore be found allowable.

E. Novelty (Article 54 EPC)

69. Both Opponents raise novelty attacks against the Patent.

70. O1 asserts that claim 1, claims 2-8 and claims 11-15 lack novelty over US 2008/0020058 (D1). O2 asserts that claim 1, claims 2-9 and claims 11-15 lack novelty over US 2006/0240554 (D25). D1 and D25 are related US patent applications that are derived from the same provisional application, and are therefore identical in large parts.

Claim 1, claims 2-8 and claims 11 – 15 are novel over D1

Claim 1

71. D1 does not disclose the product of claim 1. Claim 1 specifies a nucleic acid-lipid particle comprising four distinct components:

(a) a nucleic acid;
(b) a cationic lipid comprising 50 mol % to 65 mol % of the total lipid present in the particle;
(c) a non-cationic lipid comprising up to 49.5 mol % of the total lipid present in the particle and comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle; and
(d) a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol % to 2 mol % of the total lipid present in the particle.

72. O1 relies upon the specific formulation of L109 in Table IV of D1 as anticipating claim 1:

TABLE IV-continued

Lipid Nanoparticle (LNP) Formulations

Formulation #	Composition	Molar Ratio
L109	DMOBA/DSPC/Cholesterol/2KPEG-Chol, N/P ratio of 2	50/20/28/2

N/P ratio = Nitrogen:Phosphorous ratio between cationic lipid and nucleic acid

Excerpt from Table IV on pages 101 to 102 of D1.

73. However, formulation L109 does not disclose the components specified by claim 1. In particular, it does not satisfy the requirement of feature (c) of claim 1 that the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle. Table IV of D1 states that formulation L109 comprises 28 mol % cholesterol, which falls outside of the range specified by claim 1.

74. In light of this deficiency in the disclosure of D1, O1 asserts that a portion of 2KPEG-Chol in formulation L109 should be treated as "*cholesterol or derivative thereof*" in

order to satisfy the requirement of feature (c) of claim 1, whilst the remaining portion be treated as a conjugated lipid in order to satisfy the requirement of feature (d) of claim 1.

75. There is no objective or technical basis for interpreting the 2KPEG-Chol component of formulation L109 in this way.

76. The disclosure of the Patent is directed to lipid particles that typically comprise three distinct lipid components: (i) a cationic lipid; (ii) a non-cationic lipid; and (iii) a conjugated lipid that inhibits aggregation of particles. The Patent teaches that PEG conjugated to cholesterol is a preferred embodiment of the conjugated lipid component (see paragraph [0242]).

77. PEG conjugated to cholesterol and cholesterol derivatives are also clearly taught as distinct components of the formulations disclosed in D1. For example, paragraph [0125] of D1 states as follows:

> **[0125]** In one embodiment, the invention features a composition comprising a biologically active molecule (e.g., a polynucleotide such as a siNA, miRNA, RNAi inhibitor, antisense, aptamer, decoy, ribozyme, 2-5A, triplex forming oligonucleotide, or other nucleic acid molecule), a cationic lipid having any of Formulae CLI-CLXXXII, a neutral lipid, and a PEG-DAG (i.e., polyethyleneglycol-diacylglycerol or polyethyleneglycol-diacylglycamide), PEG-cholesterol, or PEG-DMB conjugate. In another embodiment, the composition further comprises cholesterol or a cholesterol derivative.

78. The teaching in paragraph [0125] of D1 that the composition "***further comprises***" cholesterol or a cholesterol derivative in addition to PEG-cholesterol clearly demonstrates that O1's interpretation of 2KPEG-Chol as being both a conjugated lipid and a cholesterol derivative is contrary, not only to the correct interpretation of claim 1 of the Patent, but also to the teaching of D1.

79. Therefore, the skilled person would not understand D1 to disclose a nucleic acid-lipid particle wherein cholesterol or a derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle.

80. If *ad arguendo*, contrary to the clear teaching in D1 and the Patent regarding the classification of PEG conjugated to cholesterol as being distinct from a cholesterol derivative, the opposite conclusion were to be reached, there is no objective or technical basis for O1's approach of treating the 2KPEG-Chol in formulation L109 as being in part a conjugated lipid and in part a cholesterol derivative.

81. There is even less basis for O1's entirely arbitrary classification of 0.5 mol % of the 2KPEG-Chol as a conjugated lipid and 1.5 mol % as a cholesterol derivative. Such a

classification is not taught by D1 and only arises as a result of O1's knowledge of claim 1 of the Patent. O1's interpretation of formulation L109 cannot therefore be said to be clearly and unambiguously derivable from the teaching of D1. The skilled person would simply not understand the disclosure of D1 in this way.

82. However, even if *ad arguendo* the 2KPEG-Chol of formulation L109 could be treated in the manner put forward by O1, the result would be that formulation L109 comprises 29.5 mol % cholesterol derivative, which falls outside of the claimed range of 30 mol % to 40 mol %.

83. O1 states that whilst granted claim 1 requires 30 mol % to 40 mol % of cholesterol or a derivative thereof, the lower limit of 30 mol % fails to distinguish the claimed particle from formulation L109 because granted claim 1 does not require "30.0" mol % of cholesterol or a derivative thereof, but merely "30" mol % (without any decimal places). O1 therefore asserts that for the purpose of comparison to claim 1, any values should be rounded up to the next integer.

84. However, it is clear that the level of precision of the values in claim 1 is to the nearest half-integer, not to the nearest whole integer. This can be seen in both features (c) and (d) where the lower ends of the ranges are given as 49.5 mol % and 0.5 mol % respectively. Furthermore, it should be noted that the figure of 49.5 mol % in feature (c) of claim 1 is the total amount of non-cationic lipid that may be present in the claimed particles, which includes the 30 mol % to 40 mol % of cholesterol or derivative thereof that is also referred to in feature (c). The fact that the total amount of lipid is expressed to the nearest half-integer means that the mol % of the individual components must also be considered to the same degree of precision.

85. In support of its position, O1 cites the following decisions of the boards of appeal T 871/08, T 2203/14, T 1186/05, T 770/00, T 1735/09, T 234/09 and T 83/13, which relate to rounding up figures derived from the prior art to claimed ranges.

86. However, in each of the case the boards have simply applied the well-established approach set out in T 871/08:

> "*When comparing a value from the state of the art […] with those claimed […], the state of the art value has to be given the same accuracy as the one claimed*".

87. Whilst in the cases cited by O1 the application of this approach led to rounding up of the value from the state of the art, in the present case the same approach leads to a different result because the value obtained *ad arguendo* from D1 (29.5 mol %) is given to the same accuracy as the claimed ranges (i.e. to the nearest half-integer). Accordingly, this value falls outside of the claimed range of 30 mol % to 40 mol %.

88. Furthermore, in T 74/98 it was held by board of appeal that:

> "*In the Board's view, to interpret the single number of "5" so as to include all values that, upon application of rounding up rules, would have that number as the outcome, would expand the scope of the claim beyond the indicated limits, thus casting doubt upon the meaning of ranges in general. This is not in conformity with the standard practice of the Boards of Appeal.*"

89. It should also be noted that, whilst O1 wishes to round up the value of 29.5 mol % for the purpose of calculating the mol % of cholesterol or cholesterol derivative in feature (c) of claim 1, O1 takes an entirely different approach when calculating the mol % of total non-cationic lipid in feature (c) of claim 1, where O1 chooses not to round up as doing so would take the value of total non-cationic lipid to 50%, i.e. beyond the claimed limit of up to 49.5 mol %.

90. Accordingly, there is no clear and unambiguous disclosure of a product with the features claimed in claim 1 in D1. O1's arguments are based on an artificial reading of the document, which is motivated by hindsight and does not accord with what the skilled person would understand D1 to teach. O1 also applies an arbitrary and inconsistent approach to the figures in D1, which is at odds with the clear teaching of both the Patent and the prior art. Claim 1 is therefore novel over D1.

Claims 2 to 8 and 11 to 15

91. Claims 2 to 8 and 11 to 15 are dependent on claim 1. The subject matter of these claims is therefore novel having regard to D1 for the reasons explained in relation to claim 1 above. We refer below to additional reasons in respect of the novelty of claims 2, 3 and 6 over D1.

Claim 2

92. D1 does not disclose the product of claim 2, which is dependent on claim 1 and additionally requires that the nucleic acid in the claimed particle comprises a small interfering RNA (siRNA). O1 seeks to rely on the disclosure in D1 of formulation L109 in Table IV in combination with the disclosure of short interfering nucleic acid (siNA) in paragraph [0123] of D1 and the disclosure of short interfering RNA (siRNA) as a subclass of siNA in paragraph [0017] of D1. This requires a selection from **three** lists to be made in order to arrive at the specific combination of features in claim 2:

(a) First, it is necessary to choose formulation L109 from the list of formulations provided by D1. Table IV, in which formulation L109 is provided, itself contains **59** different nucleic acid-lipid particle formulations.

(b) Second, it is necessary to select siNA from the list of **10** types of nucleic acids listed in paragraph [0123]: (i) siNA; (ii) miRNA; (iii) RNAi inhibitor; (iv) antisense; (v) aptamer; (vi) decoy; (vii) ribozyme; (viii) 2-5A; (ix) triplex forming oligonucleotide; and (x) other nucleic acid molecule.

(c) Third, it is necessary to select siRNA as the specific subclass of siNA.

93. There is no clear and unambiguous disclosure of this combination in D1, neither in the description, nor in the examples, nor in the claims. The subject matter of claim 2 is therefore novel over D1.

Claim 3

94. D1 does not disclose the product of claim 3, which is dependent on claim 2 and additionally requires in alternative (b) that the siRNA comprises at least one modified nucleotide.

95. O1 relies on the disclosure in paragraph [0363] of D1 that "*siNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically-modified nucleotides*". This represents a selection from a **fourth** list, since paragraph [0363] teaches that the siNA molecules may include one or more of at least **11** types of feature, only one of which is the inclusion of chemically-modified nucleotides.

96. There is no clear and unambiguous disclosure in D1 of the combination of features claimed in claim 3. The subject matter of claim 3 is therefore novel over D1.

Claim 6

97. D1 does not disclose the product of claim 6, which is dependent on claim 1 and additionally requires in alternative (a) that the nucleic acid-lipid particle is not substantially degraded after incubation of the particle in serum at 37°C for 30 minutes.

98. There is no disclosure in D1 of this feature in relation to formulation L109 or generally. O1 alleges that this feature is an implicit feature of formulation L109. However, O1 provides no evidence that formulation L109, which falls outside of the scope of granted claim 1, for the reasons explained above, would not be substantially degraded after incubation of the particle in serum at 37°C for 30 minutes.

99. Furthermore, the Boards of Appeal have held that an alleged disclosure can only be considered "*implicit*" if it is immediately apparent to the skilled person that nothing other than the alleged implicit feature forms part of the subject-matter disclosed (see T 95/97 and T 51/10). In other words, a prior art disclosure is novelty-destroying only if the subject-matter claimed can be inferred directly and unequivocally from that disclosure (see T 677/91, T 465/92 and T 511/92).

Claim 1, claims 2-9 and claims 11-15 are novel over D25

Claim 1

100. D25 does not disclose the product of claim 1.

101. O2 relies on the disclosure in D25 of various ranges of lipid components that are said to overlap with or encompass the ranges that are claimed in claim 1. In particular O2 relies on a combination of the generic ranges disclosed in [0116]-[0120] when considered in the light of what is said to represent the disclosure of the remainder of

D25 as a whole. In this regard, O2 relies on 2 formulations (L054 and L073) that are described in D25, but clearly do not represent the entirety of the remainder of the teaching of D25.

102. In relation to the cationic lipid component O2 relies upon the following:

(a) the disclosure in [0116] of D25 of the range of "about 2% to about 60%" and the subrange of "about 40% to about 50%"; and

(b) the disclosure in [0120] of D25 of the range of "about 30 to about 50%" and the subrange of "about 40% to about 50%" for the cationic lipid.

103. The claimed range for the cationic lipid component is 50 mol % to 65 mol % of the total lipid present in the particle. In comparison to the ranges disclosed in D25, the claimed range is both narrow and far removed from the endpoints of the ranges upon which O2 relies. Whilst O2 relies on the ranges and subranges of D25 sharing the endpoint of 50% with the range in claim 1 of the Patent, 50% is at the upper endpoint of the ranges disclosed in D25, but is the lower endpoint of the claimed range. As explained above, prior to the Patent, the trend in the field was to use delivery systems with low levels of cationic lipid since minimising the amount of cationic lipid was considered to be desirable to reduce the potential toxic effects of cationic lipids. There is nothing in D25 that would dispel this concern and cause the skilled person to alight on the range of cationic lipid required by claim 1.

104. In relation to the non-cationic lipid component, O2 relies on the disclosure in [0120] of D25 of the range of about 30 to 50% of the total lipid present in the formulation. At paragraph 79 of its opposition statement, O2 engages in a convoluted mathematical exercise seeking to establish that the range for the total neutral/non-cationic lipid according to claim 1 differs only minutely from the lower limit of the corresponding range in [0120] of D25. However, this exercise is founded on an incorrect legal approach to novelty, as O2 chooses to examine each range individually and fails to consider whether the combination of ranges claimed in the Patent has been disclosed by the prior art. It is the combination of the claimed components in the amounts taught by the Patent which confers the technical advantage of the claimed nucleic acid-lipid particles, and it is this combination of claimed ranges which should be considered for novelty.

105. For example, in order to calculate the range for total neutral/non-cationic lipid required by the claim, O2 uses the upper limit of the claimed range for cationic lipid, i.e. 65 mol %. This amount of cationic lipid is outside of the range for cationic lipid disclosed by [0120] of D25. Therefore, the range of total neutral/non-cationic lipid which O2 calculates for claim 1 requires the use of an amount of cationic lipid which is higher than the range disclosed in [0120] of D25.

106. This is just one example of the erroneous approach which O2 repeatedly takes when comparing the claimed ranges to those disclosed by D25. As explained above, O2 fails to consider the claimed features in combination, but instead erroneously treats the range for each component in isolation.

107. In relation to the conjugated lipid component, O2 relies on the disclosure in paragraph [0120] of D25 of the range of 0 to 10% of the total lipid present in the formulation. The claimed range (0.5 to 2%) is significantly narrower than that disclosed in paragraph [0120]. Furthermore, the embodiment of paragraph [0120] fails to satisfy the claimed cholesterol component. Again, O2 seeks to treat the ranges for each component in isolation rather than considering the claimed combination in its entirety.

108. In relation to the cholesterol component of the non-cationic lipid, O2 relies on the disclosure in paragraph [0119] of D25 of the range of about 10% to about 60%, and the subrange of about 20% to about 45% of the total lipid present in the formulation. However, paragraph [0119] relates to a different embodiment to that disclosed in paragraph [0120]. In contrast to the claimed nucleic acid-lipid particles, the embodiment of paragraph [0120] has no requirement for a cholesterol component. Therefore O2 is seeking to combine features from multiple embodiments in order to arrive at the claimed invention. O2's approach is contrary to the established case law of the Boards of Appeal which state that it is "*not permissible to combine separate items belonging to different embodiments […] unless of course such combination had been specifically suggested*" (see T 305/87). There is no specific suggestion in the Patent to combine the teaching of paragraph [0119] with the teaching of paragraph [0120]. Furthermore the claimed range (30 to 40 mol %) is significantly narrower than either of the ranges disclosed in paragraph [0119].

109. Even if *ad arguendo* D25 disclosed each of the individual ranges of claim 1 (which is denied), O2 has failed to show that the specific combination of components in claim 1 has been clearly and unambiguously disclosed by D25. O2's novelty attack based on the disclosure of paragraphs [0116] to [0120] of D25 must therefore fail.

110. In addition to the disclosure of paragraphs [0116] to [0120], O2 relies on the disclosure of formulations L054 and L073 in D25. O2 accepts that each of these formulations differs from the features of claim 1 of the Patent as they have a cholesterol content of 28 mol %, which is outside of the claimed range of 30 mol % to 40 mol %. O2 states that the skilled person would "*seriously contemplate applying the technical teaching of paragraphs [0116], [0120] and [0119] within the combined ranges of overlap with granted claim 1*" (paragraph 87 of O2's opposition statement) and that the skilled person "*would without question seriously contemplate applying the generic teaching of paragraphs [0116], [0120] and [0119], in combination*". However, O2 has provided no explanation as to why the skilled person would do so. L054 and L073 are two of the 33 specific formulations disclosed in Table IV of D25. There is no suggestion to the skilled person anywhere in D25 that these formulations should be modified. There is therefore no reason to believe that the skilled person would make any modification to formulations L054 or L073.

111. At paragraph 96 of its opposition statement, O2 states "*L054 and L073 of [D25] provide pointers towards the combination of 3 of the 4 generic range features in question specifically within each area of overlap*". However, no such pointers exist and it is the established case law of the Boards of Appeal in respect of Article 123(2) that:

> "*The content of the application as filed must not be considered to be a reservoir from which individual features pertaining to separate sections can be combined in order to create a particular combination. In the absence of any pointer to that particular combination, this combined selection of features does not, for the person skilled in the art, emerge clearly and unambiguously from the content of the application as filed.*" (see T 686/99).

112. The same rule must apply for considerations under Article 54. Whilst O2 claims that "*pointers*" which link L054 and L073 with paragraphs [0116] to [0120] exist, it is telling that it has conspicuously failed to identify them in its opposition statement.

113. O2's novelty attack based on L054 and L073 seeks to blur the distinction between the assessment which should be performed under Article 54 with that which should be performed under Article 56. The Technical Board of Appeal in T 666/89 specifically warns against this.

114. Furthermore, the similarities which O2 seeks to draw between the disclosure of the prior art in T 666/89 and the disclosure of D25 do not stand up to scrutiny. In T 666/89, the skilled person did not need to make any decisions when combining the two components which were taught generically by the prior art. However, if the skilled person were to combine formulations L054 and L073 with the ranges of cholesterol taught in paragraph [0119] of D25, it would be necessary for the skilled person to make at least the following four choices, which are not taught by D25, in order to make a formulation falling within the scope of claim 1:

(a) First, the skilled person would need to decide whether to change the amount of cholesterol in formulations L054 and L073. Paragraph [0119] teaches that the cholesterol component may comprise from about 10 mol % to 60 mol % or from about 20 mol % to about 45 mol %. L054 and L073 both contain 28 mol % cholesterol, which falls within the ranges taught by paragraph [0119]. Therefore, the skilled person would have the choice of not changing the amount of cholesterol and still being within the ranges disclosed in paragraph [0119] of D25. However, in order to create a formulation falling within the scope of claim 1, the skilled person would have to choose to change the amount of cholesterol in L054 and L073.

(b) Second, if the skilled person were to choose to change the amount of cholesterol, the skilled person would have the choice to increase or decrease the amount of cholesterol in order to fall within the ranges disclosed in paragraph [0119] of D25. However, in order to create a formulation falling within the scope of claim 1, the skilled person would have to choose to increase the amount of cholesterol in L054 and L073.

(c) Third, if the skilled person were to choose to increase the amount of cholesterol, the skilled person would have to choose to increase it to between 30 mol %

and 40 mol % in order to fall within the claims. However, paragraph [0119] of D25 teaches that the amount of cholesterol may be increased to about 45 mol % or to about 60 mol %.

(d) Fourth, even if the skilled person were to choose to increase the level of cholesterol to an amount falling within the claimed range of the Patent (i.e. 30 mol % to 40 mol %), it would be necessary for the skilled person to make a choice about which of the other components in these formulations to reduce. This is because, unlike in the case of the prior art in T 666/89, the individual components in formulations L054 and L073 add up to 100 mol %. Furthermore, if the skilled person were to reduce the cationic lipid component of L054 or L073 by 2 mol % (i.e. due to an increase the amount of cholesterol to 30 mol %, which is the minimum amount required to fall within the claimed range of the Patent), the resulting formulations would contain only 48 mol % cationic lipid and therefore fall outside of the claims of the Patent.

115. Therefore, even if *ad arguendo* the skilled person were to combine formulations L054 and L073 with paragraph [0119] of D25, it cannot be said that a formulation falling within the scope of the claims of the Patent would be an inevitable outcome. Furthermore, T 793/93 states that:

> "*In deciding what is or is not the inevitable outcome of an express literal disclosure in a particular prior art document, a standard of proof much stricter than the balance of probability, to wit "beyond all reasonable doubt" needs to be applied. It follows that if any reasonable doubt exists as to what might or might not be the result of carrying out the literal disclosure and instructions of a prior art document, in other words if there remains a "grey area" then the case on anticipation based on such a document must fail.*"

116. Accordingly, there is no clear and unambiguous disclosure of a product with the features claimed in claim 1 in D25. O2's arguments are based on an artificial reading of the document, which is motivated by hindsight, requires the skilled person to make multiple choices not taught by D25, and does not accord with what the skilled person would understand D25 to teach.

Claims 2 to 9 and 11 to 15

117. Claims 2 to 9 and 11 to 15 are dependent on claim 1. The subject matter of these claims is therefore novel having regard to D1 for the reasons explained in relation to claim 1 above. We refer below to additional reasons in respect of the novelty of claims 2, 3 and 6 over D25.

Claim 2

118. D25 does not disclose the product of claim 2, which is dependent on claim 1 and additionally requires that the nucleic acid in the claimed particle comprises a small interfering RNA (siRNA). O2 relies on the disclosure in paragraphs [0101]-[0123] and

[0319] of D25. To arrive at siRNA requires a selection from at least **two** lists to be made:

(a) First, it is necessary to select siNA from the list of **8** types of nucleic acids listed in paragraphs [0100] and [0121]: (i) siNA; (ii) antisense; (iii) aptamer; (iv) decoy; (v) ribozyme; (vi) 2-5A; (vii) triplex forming oligonucleotide; or (viii) other nucleic acid molecule.

(b) Second, it is necessary to select siRNA as the specific subclass of siNA. Paragraph [0319] lists the following **6** options: (i) siRNA; (ii) dsRNA; (iii) miRNA; (iv) shRNA; (v) short interfering oligonucleotide; and (vi) chemically modified siRNA.

119. There is no clear and unambiguous disclosure of this combination in D25. The subject matter of claim 2 is therefore novel over D1.

Claim 3

120. D25 does not disclose the product of claim 3, which is dependent on claim 2 and additionally requires in alternative (b) that the siRNA comprises at least one modified nucleotide.

121. In relation to alternative (b) O2 relies on the disclosure in paragraph [0319] of D25, which contains the same disclosure as paragraph [0363] of D1. The arguments at paragraph 95 above are therefore repeated.

122. There is no clear and unambiguous disclosure in D25 of the combination of features claimed in claim 3. The subject matter of claim 3 is therefore novel over D25.

Claim 6

123. D25 does not disclose the product of claim 6, which is dependent on claim 1 and additionally requires in alternative (a) that the nucleic acid-lipid particle is not substantially degraded after incubation of the particle in serum at 37°C for 30 minutes.

124. In relation to alternative (a), O2 relies upon the disclosure of paragraph [0592] of D25. However, there is no disclosure in [0592] that a formulation of claim 1 would not be substantially degraded after incubation of the particle in serum at 37°C for 30 minutes. The subject matter of claim 6 is therefore novel over D25.

F. Inventive step (Article 56 EPC)

The closest prior art

125. O1 alleges that D1 is the closest piece of prior art, whilst O2 alleges that D25 is the closest piece of prior art. As mentioned above, D1 and D25 are related US patent applications that are derived from the same provisional application, and are therefore identical in large parts. We address inventive step below on the basis that either of D1 or D25 is the closest piece of prior art, as it is essentially irrelevant which of these documents is the closest piece of prior art. However, the Proprietor reserves the right to refer to alternative documents as the closest prior art at a later stage of these opposition proceedings, if appropriate.

Problem and solution

126. The technical problem to be solved in light of the Patent and D1/D25 is the provision of improved formulations for nucleic acid-lipid particles for the systemic delivery of nucleic acids into cells *in vivo*.

127. O1 and O2 allege that the formulations of the Patent demonstrate no improvement over the formulations of the prior art. In particular, O2 refers to the data in Examples 2 and 3, which it alleges show that the claimed embodiments perform worse than prior art formulations or show no advantage over the prior art. However, whilst it is not accepted that these data show what O2 claims, these data are not by themselves relevant to the improvement conferred by the formulations of the invention, namely the fact that the formulations of the invention have reduced toxicity, making them suitable for systemic use *in vivo*.

128. As paragraph [0029] of the Patent explains:

> "*In particular, as illustrated by the Examples herein, described herein are stable nucleic acid-lipid particles (SNALP) that advantageously impart increased activity of the encapsulated nucleic acid (e.g., an interfering RNA such as siRNA) and improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described*." (emphasis added)

129. The low toxicity of the claimed formulations, which was shown *inter alia* by the data in Figure 13 of the Patent, was an unexpected and surprising finding due to the high cationic lipid content of the claimed formulations and demonstrated for the first time that nucleic acid-lipid particles with lipid components in the claimed ranges were suitable for systemic use *in vivo*.

The solution is not obvious from D1/D25

130. It would not have been obvious from D1/D25 to arrive at the nucleic acid-lipid particles of the invention. Neither D1 nor D25 teaches any of the claimed ranges of components nor does either document provide any formulation falling within those ranges.

131. O1 has asserted that the claimed invention would have represented an obvious modification to embodiments in the prior art. In particular, O1 has asserted that it would have been obvious to increase the cholesterol content in 4 specific formulations listed in Table IV of D1: formulations L054, L073, L097 and L109. The specific lipid composition of these formulations is summarised as follows:

TABLE IV

Lipid Nanoparticle (LNP) Formulations

Formulation #	Composition	Molar Ratio
L054	DMOBA/DSPC/Chol/2KPEG-DMG	50/20/28/2
L073	pCLinDMA or CLin DMA/DMOBA/DSPC/ Chol/2KPEG-DMG	25/25/20/ 28/2
L097	DMLBA/DSPC/Cholesterol/2KPEG-DMG	50/20/28
L109	DMOBA/DSPC/Cholesterol/2KPEG-Chol, N/P ratio of 2	50/20/28/2

N/P ratio = Nitrogen:Phosphorous ratio between cationic lipid and nucleic acid

(excerpt from Table IV on pages 101 to 102 of D1)

132. Likewise, O2 relies on the disclosure of formulations L054 and L073 in D25, which are the same as formulations L054 and L073 in D1.

133. Each of these formulations differs from the features of claim 1 of the Patent in the same way; namely each formulation has a cholesterol content of 28 mol %, which is outside of the claimed range of 30 mol % to 40 mol %.

134. There is nothing in the teaching of D1 or D25 which suggests that the cholesterol content of these formulations should be increased, and neither O1 nor O2 provides any rationale for such a change to be made. O1 describes the change in the amount of cholesterol needed to bring the formulations in Table IV to which it refers within the claimed range as "*miniscule*". However, this change in fact represents a more than 7% increase in the amount of cholesterol in the formulation.

135. Furthermore, O1 has provided no explanation as to why the skilled person ***would*** have been motivated to modify the lipid nanoparticles in D1 to arrive at the invention. Such a modification would have required the skilled person to make a number of choices, including:

(a) The choice of formulation L054, L073, L097 or L109 as a starting point. There are 59 formulations listed in Table IV of D1. O1 has provided no explanation as to why the skilled person would select these 4 formulations as a starting point for a systemic therapy. Each of these formulations has a high level of cationic lipid, which, in the absence of data indicating otherwise, would lead the skilled person to conclude that they would be unsuitable for systemic use. Importantly, none of these formulations was evaluated for toxicity and only one

of them was evaluated for serum stability, properties identified by the Patent as being critical for embodiments formulated for systemic use *in vivo*. Furthermore, whilst another exemplary formulation in D1 was tested *in vivo*, none of the formulations relied upon by O1 were. The skilled person would therefore have had no motivation for choosing any of these formulations from the list in Table IV as a starting point for the development of a nucleic acid-lipid particle for systemic use. Rather the teaching of D1 would direct the skilled person away from these formulations.

(b) The choice to modify the cholesterol component of these formulations. The skilled person could choose to modify any of the 4 (or 5, in the case of formulation L073) components of these formulations. O1 has provided no explanation as to why the skilled person would select the cholesterol component to modify. Indeed, insofar as the skilled person were to choose these formulations as a starting point, he or she would be motivated to decrease the cationic lipid component in order to reduce the toxicity of these formulations and increase their suitability for systemic use.

(c) The choice to increase, not decrease, the cholesterol content of these components. O1 has provided no explanation as to why, even if the skilled person had been motivated to modify the cholesterol content of these formulations, he or she would have been motivated to ***increase*** the cholesterol content, rather than decrease it.

(d) The choice to decrease the content of the other neutral lipid rather than the other components in the formulation. O1 states that the skilled person would have chosen to decrease the content of the other neutral lipid rather than the other components of the formulation because he or she "*would have proceeded carefully*" and tried to maintain the molar ratios between neutral lipid, cationic lipid and conjugated lipid (see paragraph 6.1.5 on page 30 of O1's opposition statement). There is nothing in D1, however, that teaches the importance of maintaining these ratios as opposed to maintaining the ratio of cholesterol to the other components in the formulation. Indeed, the claims of D1 are addressed to a specific ratio of cholesterol to the other components in the claimed formulation. The approach which O1 alleges that the skilled person would have taken is one which only would have occurred to him or her after having read the Patent. However, even if the skilled person had been cautious about increasing the overall content of the neutral lipids, the skilled person would have been equally cautious about modifying the individual neutral lipid components. There is nothing in D1 which suggests that one type of neutral lipid may be substituted for another. Finally, and for the reasons already explained, the skilled person would have been concerned about the toxic effects of the high levels of cationic lipid in these formulations. Therefore, the skilled person would have been more likely to reduce the amount of cationic lipid rather than the amount of neutral lipid.

136. O1 has failed to provide reasons why the skilled person ***would*** make any one of these choices, let alone choosing to make ***all*** of them. The claimed invention would thus not have been obvious from consideration of D1 alone or from consideration of D25 alone.

The solution is not obvious from D1 combined with D2

137. O1 cites D2 in an attempt to establish that it would have been obvious to increase the cholesterol content of formulations L054, L073, L097 and L109 in D1 from 28 mol % to 30 mol %. In particular, O1 relies on the "*2:30:20+10%DODAC*" formulation disclosed on page 73, lines 22 to 25 of D2, which comprises 20 mol % non-cationic lipid (DSPC), 38 mol % cholesterol, 2 mol % conjugated lipid (PEG-C-DMA) and 40 mol % cationic lipid (30 mol % DLinDMA and 10% DODAC). However, O1 provides no explanation for the reason why the skilled person would choose only the cholesterol component from the formulation in D2 as the basis for modifying the formulations disclosed in D1, and D2 provides no data showing any advantage in increasing the cholesterol content for the formulations of D1. Furthermore, the skilled person would recognise that it is the particular combination of lipids in each formulation which gives rise to its technical characteristics, and it would therefore make no technical sense to the skilled person to cobble together the disparate teaching of D1 and D2 in manner in which O1 seeks to do.

138. D2 also teaches that the "*2:30:20+10%DODAC*" formulation would not have been suitable for systemic use due to the high concentration of cationic lipid and would therefore only have been suitable for local or regional delivery, because D2 explains that "*for systemic delivery, the cationic lipid may comprise from about 5 mol % to about 15 mol % of the total lipid present in said particle and for local or regional delivery, the cationic lipid may comprise from about 30 mol % to about 50 mol %, or about 40 mol % of the total lipid present in the particle*" (page 40, lines 29-32 of D2). Therefore, the skilled person reading D2 would have appreciated that in order make a nucleic acid-lipid particle suitable for systemic use, it would have been necessary to reduce the concentration of cationic lipid to about 5 mol % to 15 mol % of the total lipid present. The resulting nucleic acid-lipid particle would have fallen outside the scope of the claims of the Patent.

The solution is not obvious from D1 combined with D3 or D4

139. O1 also alleges that the claims of the Patent are obvious in light of D1 in combination with D3 or D4. However, D3 and D4 relate to an entirely distinct technical field, namely cationic liposome complexes, not nucleic acid-lipid particles, which are the subject of the Patent. The skilled person would have recognised that it would make no technical sense to apply the teaching of D3 or D4 (which relate to cationic liposome complexes) with the teaching of D1 (which relates to entirely different nucleic acid delivery system, namely nucleic acid-lipid particles).

140. In addition, the data presented in D3 and D4 relate to *ex vivo* cell transfection experiments, and it is stated in D3 and D4 that these data cannot be used to predict efficacy of the complexes *in vivo*:

> "*A final important observation is that the work we have described here should apply to transfection optimization in ex vivo cell transfection, where cells are removed and returned to patients after transfection. In particular, the results of this article should aid clinical efforts to develop efficient CL-vector cancer vaccines in ex vivo applications. However, the current work is not expected to be predictive of transfection behavior in blood for systemic in vivo applications in the presence of serum. Further studies should reveal other types of well-defined structure-function correlations for transfection in vivo in the presence of serum.*" (Page 3315, right hand column of D3).
>
> "*The presented transfection optimization strategy is directly relevant for gene therapy using ex vivo methods, where cells are removed, transfected, and returned to patients after selection. Further work on model systems relating to in vivo gene therapy is in progress.*" (Page 747, left hand column of D4).

141. The skilled person would therefore not consider the disclosure in D3 or D4 to be applicable to the behaviour of either cationic liposome complexes or nucleic acid-lipid particles *in vivo*.

142. Furthermore, D4 teaches away from the use of high levels of cationic lipid (such as in formulations L054, L073, L097 or L109 in D1) for *in vivo* administration:

> "*Minimising the amount of cationic lipid is desirable to reduce cost as well as potential toxic effects of the cationic lipid.*" (Page 745, right hand column of D4).
>
> "*This ability to use fewer cationic molecules for high [transfection efficiency] is important for cost reduction and possibly in vivo toxicity of cationic components*". (Page 747, left hand column of D4).

143. Therefore, insofar as the skilled person were to consider combining the teaching of D1 with the teaching of D4, the skilled person would be motivated to design complexes that have a significantly reduced cationic lipid component in order to improve their suitability for systemic use. The resulting complexes would have fallen outside the scope of the claims of the Patent.

The solution is not obvious from D25 combined with D23

144. O2 also cites D23 in an attempt to establish that it would have been obvious to increase the cholesterol content of the formulations in D25 from 28 mol % to 30-40 mol %. However, like D3 and D4, D23 relates to cationic liposome complexes, not nucleic acid-lipid particles and it would therefore make no technical sense for the skilled person to combine the teaching of D23 with that of D25, which relates to nucleic acid-lipid particles.

145. Furthermore, the cationic liposome complexes disclosed in D23 are evaluated only for transfection efficiency in cell culture. See, for example, page 50 of D23:

> "*To investigate the possibility that added cholesterol could enhance liposomal transfection ability, liposomes containing mixtures of the cationic lipid DORI and a neutral lipid component, DOPE and/or cholesterol, were formulated and screened for their ability to transfect pCMVL DNA into human airway epithelial cells and NIH 3T3 murine fibroblasts.*"

146. Importantly, none of the cationic liposome complexes in D23 was evaluated for serum stability or toxicity. The skilled person would therefore have no way of knowing whether any of these complexes would be suitable for systemic use *in vivo*. This is a further reason why the skilled person would therefore have no motivation to combine any aspect of the teaching in D23 with the formulations disclosed in D25.

147. Additionally, and in any event, O2's conclusions in relation to D23 are wrong, notwithstanding the above. Referring to D23, O2 states:

> "*Cholesterol content of 30% (just as in granted claim 1) is found to be optimal, but a content of 40% also performs well (see the 2nd bars from the left in Figures 1 and 2).*"

However, Figures 1 and 2 of D23, clearly show that the composition containing a ratio of DOPE:DORI:Chol of 30:50:20 provided the strongest performance, whilst (in particular in Figure 1), the 20:50:30 formulation is amongst the worst performers. If the skilled person would understand anything from D23, it would be that better results are obtained by lowering cholesterol to 20 mol%, rather than raising the cholesterol content of the formulations disclosed in D25.

The solution is not obvious from D26 combined with D4 or D5

148. As the Opposition Division is aware, the primary consideration when identifying the closest prior art is that it should be taken from the same technical field and relate to the same underlying purpose or effect as the invention. As explained above, the claims of the Patent are directed to nucleic acid-lipid particles, which the Patent explains are serum stable particles suitable for systemic use. D26 relates to cationic liposome complexes, which the Patent explains in paragraph [0005] are "*large, poorly defined systems that are not suited for systemic applications and can elicit considerable toxic side effects*". For example, column 14 of D26 states that "*the CLs [cationic lipids] are combined with other lipids in formulations for the preparation of lipid vesicles or liposomes for use in intracellular delivery systems*". Therefore, D26 cannot be considered to be the closest prior art and would not be used by the skilled person as the starting point for the development of a nucleic acid-lipid particle for systemic use.

149. Furthermore, the skilled person would have had no motivation to combine D26 with either D4 or D5 in the manner alleged by O2.

150. O2 refers to the fact that D4 teaches that optimum *in vitro* transfection efficiency was achieved when cationic liposome complexes were used with a cationic lipid content of about 50 mol %. However, as we explain above (paragraph 142), D4 also teaches that it is necessary to minimise the amount of cationic lipid in order to reduce toxic effects.

151. The same concern is also taught by D5, which identifies severe toxicity effects associated with high levels of cationic lipids and concludes that the cationic liposome complexes were unsuitable for use in humans:

> "*Detailed toxicological studies […] revealed that the cationic lipid contributes significantly to the toxicity observed. Similar toxic effects are also noticeable in systemic gene delivery via the tail vein with other types of cationic lipids. Symptoms include acute pulmonary hypotension, induction of inflammatory cytokines, tissue infiltration of neutrophils in lungs, decrease in white cell counts, and in some cases tissue injury in liver and spleen. In humans, various degrees of adverse inflammatory reactions, including flulike symptoms with fever and airway inflammation, were noted among subjects who received aerosolized GL67 liposomes alone or lipoplexes. These early clinical data suggest that these lipoplex formulations are inadequate for use in humans.*" (emphasis added)

152. The skilled person would therefore have considered the use of such a high level of cationic lipid, in nucleic acid-lipid particles for systemic use, to be highly undesirable. Therefore, both D4 and D5 teach away from the claimed invention by instructing the skilled person to avoid the use of high levels of cationic lipid due to concerns over toxicity.

153. O2 cites the left hand column of page E97 of D5 in an attempt to establish that it would have been obvious to add a PEG-lipid conjugate to the 56/14/30 formulation of Example 18 of D26. D5 provides no information about the amount of PEG-lipid conjugate that should be added. Had the skilled person wanted to add a PEG-lipid conjugate in light of the teaching of D5, he or she would have referred to the papers cited by D5 in the section which addresses the addition of PEG-lipid conjugate. The relevant papers (references 93 and 94 in D5; cited as **D29** and **D30** respectively) state that the PEG-lipid conjugate comprised 5 mol % and 10 mol % of the disclosed formulations. If *ad arguendo* the skilled person had followed this teaching and added either 5 mol % or 10 mol % PEG-lipid conjugate to the 56/14/30 formulation of D26, the resulting formulation would have fallen outside of the claimed range of 0.5 mol % to 2 mol % for conjugated lipid.

154. Furthermore, in order to add a PEG-lipid conjugate to the 56/14/30 formulation of D26, it would be necessary to reduce one of the other components. O2 suggests that the most obvious solution would have been to reduce the amount of cationic lipid and/or phospholipid. D5 identifies severe toxicity effects associated with the use of cationic lipids and states that "*[d]etailed toxicological studies […] revealed that the cationic lipid*

contributes significantly to the toxicity observed". Therefore, if *ad arguendo*, the skilled person had, following the teaching of D5 and D30, sought to add 10 mol % PEG-lipid conjugate to the 56/14/30 formulation of D26, the most likely path that would have been taken by the skilled person would have been to reduce the cationic lipid component of the 56/14/30 formulation by 10 mol %, resulting in a formulation containing 46 mol % cationic lipid, which would also have fallen outside of the claimed range.

The solution is not obvious from D16

155. O2 relies on the disclosure in D16 of various ranges that are disclosed for the components of nucleic acid-lipid particles, which O2 alleges, when combined, overlap with the ranges claimed by the Patent. In particular, O2 relies on a combination of the disclosure in paragraph [0088] of D16 that the cationic lipid may be present, e.g., in amounts of 2-60% or 40-50%, with the disclosure in paragraph [0091] that the non-cationic lipid may preferably be present in a range of 20-85% and may optionally contain cholesterol at about 20-45%, and the disclosure in [0093] that the formulation may preferably contain a conjugated lipid in amounts, e.g., of 0.5-25% or 1-20% of the total lipid.

156. However, O2 ignores the fact that D16 specifically teaches in [0088] against the use of high levels of cationic lipid, particularly in the context of nucleic acid-lipid particles for systemic use:

> "*The cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle, preferably from about 5 % to about 45% of the total lipid present in said particle. […] For example, for systemic delivery, the cationic lipid may comprise from about 5% to about 15% of the total lipid present in said particle and for local or regional delivery, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle.*"

157. Furthermore, D16 discloses the use of a single formulation of nucleic acid-lipid particle *in vivo*, which comprises non-cationic lipid (DSPC) at 20 mol %, cholesterol at 55 mol %, cationic lipid (DODMA) at 15 mol % and conjugated lipid (PEG-Lipid) at 10 mol %. The skilled person would recognise that the amount of cationic lipid used in the formulation was at the upper end of the acceptable range taught by D16 for systemic use.

158. The skilled person faced with the problem of creating improved nucleic acid-lipid particles for systemic use would have had no reason to have increased the amount of cationic lipid above 15 mol % as used in the formulation taught by D16 and, in fact, would have been strongly motivated against doing so by the teaching in [0088] of D16.

The solution is not obvious from D16 combined with D3 or D4

159. As explained above D3 and D4 relate to an entirely distinct technical field and the skilled person would have had no reason to combine the teaching of these documents with the teaching of D16. Furthermore, both D3 and D4 teach that the cationic liposome complexes which they disclose may not be suitable for systemic use *in vivo*,

and D4 reinforces the teaching in D16 that a high cationic lipid content is undesirable. Therefore, the claims of the Patent would not have been obvious from D16 in combination with D3 or D4.

G. Sufficiency (Art 83 EPC)

160. Only O1 has made an argument under Art 100(b) (Art 83) EPC.

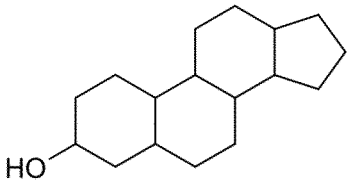
161. The argument put forward by O1 is, however, unconvincing and should not be found prejudicial to the validity of the claims of the Patent. In fact, O1's objection is nothing more than inadmissible comments on the clarity of the claims, and lacks any evidence of serious doubts, substantiated by verifiable facts, that the invention could be worked by the skilled person. The objection that has been put forward requires an unrealistic interpretation of claim 1 that would not be reached by the skilled person, and misapplies the principle that an invention must be enabled across its scope.

162. O1 points out that "*[f]or the assessment of patentability, the terms in a claim have to be given their broadest technically sensible meaning…"* (section 7.1 second paragraph of O1's opposition statement). Yet in its subsequent argument, O1 ignores this correct approach, by forgetting that the broadest meaning given to the terms in a claim must be "*technically sensible*".

163. Thus, O1 argues that essentially any conceivable chemical substance, conjugated to cholesterol, should be considered to fall within the meaning of the term "*cholesterol or a derivative thereof*", even if the skilled person would not know how to synthesise those substances. This is plainly a far-fetched interpretation that has no regard to what is technically sensible, or what would occur to the skilled person as being encompassed by the claims.

164. The unrealistic nature of O1's argument becomes apparent from just a moment's consideration. It is very often the case that patent claims cover embodiments which could not be put into effect at the filing date because the relevant technology is not, at that time available. This is not a barrier to patentability – it is well known and accepted that patents often, validly, cover follow-on inventions, which (by their nature as inventions) were not available without undue burden at the filing date of the earlier claims. The scenario envisaged by O1 in its objection is merely such a situation. If there are useful cholesterol conjugates that fall within the scope of the claims which were not known (in the sense of not being enabled for their production) at the filing date of the Patent, then those conjugates might well be follow-on inventions. But there is no reason why the Patent claims should not cover the use of future inventions, in the normal way.

165. Further, the false objection put forward by O1 could equally be applied to almost any generically defined chemical component of a product invention. Consider, for example, if claim 1 had referred more generically to "*a sterol*" instead of to "*cholesterol or a derivative thereof*". According to O1's logic, the term "*a sterol*" would be interpreted to mean any conceivable chemical substance which includes the following structure:



166. Since there are inevitably chemical substances including this sterol structure which the skilled person cannot prepare on the basis of his or her common general knowledge, then, according to O1's logic, the generic term "*a sterol*" in a patent claim would also lack sufficient disclosure under Art 83 EPC. Such a conclusion, which is an inevitable extrapolation of O1's position, is clearly wrong, and out of step with the EPO's normal application of Art 83 EPC.

167. Since it would be wrong to object to a more generic term ("*a sterol*") on this basis, it would also be wrong to object to the narrower term "*cholesterol or a derivative thereof*", for the same reasons.

168. A more sensible approach to the interpretation of claim 1 is that the skilled person understands the type of cholesterol derivatives intended for use in the claimed nucleic acid-lipid particles. Indeed, example derivatives are provided in paragraphs [0104], [0233] and [0410] of the Patent, and the skilled person is perfectly capable of identifying other derivatives by the application of his or her common general knowledge. By taking a realistic view of what the skilled person is trying to achieve when working within the scope of the claim, it is possible to attribute a meaning to the terms of the claim that is in line with the "…*broadest technically sensible meaning…*" of the case law, referred to by O1. Any doubts that remain about the boundaries of that interpretation are merely matters of clarity under Art 84 EPC, and cannot be raised, post-grant, in opposition proceedings.

169. It should also be noted that, even if O1's approach was legitimate (which is denied), O1 has failed to substantiate its opposition in any way. O1 has not mentioned a single derivative that cannot be produced (let alone explained why such a species would be a technically sensible interpretation of the term), and has therefore produced no serious doubts, substantiated by verifiable facts as required by the case law of the Technical Boards of Appeal (see e.g. T 19/90).

170. Lastly, it is pointed out that the Boards of Appeal themselves seem unconcerned about the impact, under Art 83, of including derivatives within a claim. By way of example only, in decisions T 833/03[4] and T 388/15[5] (and several others), the claims under investigation by the Boards included un-specified derivatives of certain components.

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[4] Claim 1 of EP 0 674 506 B1 related to polymeric microspheres formed from, *inter alia* "…*polymers of ethylenevinyl acetate and other acyl substituted cellulose acetates and derivatives thereof…*" (emphasis added, Section I of the Summary of Facts and Submissions). The claim was found sufficient under Art 84 (paragraph 2.2 of the Reasons for the Decision).

[5] Claim 1 of the Main Request before the Board in EP 1 482 815 B1 related to a paper wrapper for a smoking article comprising, *inter alia* "…*a cellulose derivative, starch, a starch derivative…*" (emphasis added, Section IV of the Summary of Facts and Submissions). The claim was found sufficient under Art 84 (paragraph 18.8 of the Reasons for the Decision).

In both cases, the claims were extensively examined by the Boards for their compliance with Art 83 EPC, and in both cases the claims were upheld as being enabled. Whilst in neither case was the impact of the term "*derivatives*" specifically considered, the Boards of Appeal making the decision were fully at liberty to determine that the term resulted in a lack of sufficiency of their own motion (Art 114 EPC), but did not do so. These cases further illustrate that, in heavily contested patent matters before the Boards of Appeal, other opponents have not considered the term "*derivative*" to be harmful for the sufficiency of patent claims.

171. O1's objection is therefore wrong and should be ignored.

Signed this 3rd day of September 2018

/ BROUGHTON, Jon Philip /

Patent Boutique LLP

Association of Professional Representatives No. 651

ANNEX 1

D-number for Patentee Response	Document title	D-number for O1's Notice of Opposition	D-number for O2 's Notice of Opposition
D1	US 2008/0020058	D1	
D2	WO 2006/053430 A1	D2	D4
D3	Lin et al. Biophys J, 2003; 84(5): 3307-16	D3	D21
D4	Ahmad et al. J Gene Med, 2005; 7(6): 739-48	D4	D22
D5	Gao et al. AAPS J, 2007; 9(1): E92-104	D5	D12
D6	Filing receipt for the priority application US 61/045,228 of the opposed patent	D6	
D7	Excerpt from the USPTO register on US 61/045,228	D7	
D8	PCT request for the application WO 2009/127060 underlying the opposed patent	D8	
D9	US 2007/0042031 A1		D1
D10	US 2005/0064595 A1		D2
D11	US 2006/008910 A1		D3
D12	WO 2007/056861 A1		D5
D13	WO 2005/035764 A1		D6
D14	WO 2005/120152 A2		D7
D15	WO 2006/002538 A1		D8
D16	WO 2005/007196 A2		D9
D17	EP 1 648 519 B1		D10
D18	EP 2 567 693 B1		D11
D19	Li & Szoka Pharmaceutical Research, 2007; 2383: 438-499		D13
D20	MacLachlan Antisense Drug Technology 2nd Edition 2007		D14
D21	Declaration of Dr Andrew S Janoff dated 5 March 2018		D15
D22	US 9,364,435		D16
D23	Bennet et al. Bioscience Reports 1995; 15: 47-53		D17
D24	Heyes et al. Journal of Controlled Release 2005; 107: 276-78		D18
D25	US 2006/0240554 A1		D19
D26	US 5,264,618 A		D20
D27	US2008317839A1		D23
D28	Uyechi-O'Brien & Szoka Pharmaceutical Gene Delivery Systems 2003: 79-108		
D29	Song et al. Biochimica et Biophysica Acta 2002; 1558: 1-13		
D30	Ambegia et al. Biochimica et Biophysica Acta 2005; 1669: 155-163		

JOINT APPENDIX 77

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IN ITS

ENTIRETY

JOINT APPENDIX 78

Moderna Announces $40 Million In Financing To Advance Development Of New Biotherapeutic Modality: Messenger RNA Therapeutics™

Company announces appointment of Executive Leadership Team and Scientific Advisory Board

NEWS PROVIDED BY
Moderna Therapeutics →
06 Dec, 2012, 12:01 ET

CAMBRIDGE, Mass., Dec. 6, 2012 /PRNewswire/ -- Moderna Therapeutics announced today that it has closed more than $40 million in financing to date, led by Flagship Ventures and private investors, which will be used to advance multiple programs toward clinical stage development. Moderna is pioneering messenger RNA Therapeutics™, a novel biotherapeutic modality with the unprecedented capability of stimulating the body's natural ability to produce therapeutic proteins. If successful in human clinical trials, this advance will usher in the first entirely new way of making therapeutic proteins since the development of recombinant technology more than 30 years ago, with dramatic implications for both patients and industry.

Moderna was founded within Flagship VentureLabs™, an innovation foundry dedicated to institutional entrepreneuring. Over the past 18 months, Moderna has conducted proof-of-concept studies in preclinical models, including non-human primates, and has demonstrated the ability to induce *in vivo* production of dozens of intracellular and

secreted therapeutic proteins through intramuscular, subcutaneous or intravenous administration across multiple preclinical models. The company anticipates publishing and presenting the results of these studies in 2013.

Moderna has appointed an accomplished executive leadership team and scientific advisory board, and implemented a comprehensive intellectual property strategy surrounding messenger RNA Therapeutics, filing over 80 patent applications reciting more than 4,000 claims covering novel chemical modifications, RNA engineering, formulation, composition of matter, route of administration and dosing. The company has established preclinical programs in four key therapeutic areas: oncology supportive care, inherited genetic disorders, hemophilia and diabetes.

"Our messenger RNA Therapeutics platform has the potential to revolutionize the treatment of a wide variety of illnesses by opening up a completely new biotherapeutic modality, and by offering a technologically and financially superior path for the discovery, creation and endogenous production of therapeutic proteins," said Stephane Bancel, president and founding CEO of Moderna. "In the last 18 months, we have charged ahead in this space, vigorously pursuing a robust IP portfolio. We have hired an experienced employee base and cultivated leadership and advisory teams who are offering deep insights as we advance key programs into clinical development. We are working with great urgency and great care to translate this groundbreaking science into new treatments for patients."

Moderna's Leadership Team

Before joining Moderna, Bancel served for five years as the CEO of bioMerieux, a world leader in diagnostics, where he led the company through 10 successful acquisitions in the U.S., Europe and Asia/Pacific; nearly doubled the company's sales growth rate to above nine percent per year; and doubled the company's market capitalization despite the 2008 global financial crisis. Prior to his time at bioMerieux, Stephane was Managing Director of Eli Lilly in Belgium and Executive Director of Global Manufacturing Strategy and Supply Chain at Eli Lilly in Indianapolis, Indiana. He started at Lilly in its UK manufacturing plant outside London. Before joining Lilly he also served as Asia-Pacific Sales and Marketing Director for bioMerieux while based in Tokyo. He holds a Master of Engineering from Ecole

Central Paris, a Master of Science in Chemical Engineering from the University of Minnesota and an MBA from Harvard Business School, and is named as an inventor on more than 45 patent filings in the field of messenger RNA (mRNA) technology.

Bancel has assembled a seasoned executive team composed of biotech and pharmaceutical professionals who have played key roles in successfully developing and commercializing biotech products. Susan Whoriskey, Ph.D., senior vice president of technology strategy, served on the founding executive teams of Momenta Pharmaceuticals and Cubist Pharmaceuticals. Chief scientific officer Tony de Fougerolles, Ph.D., brings more than 15 years of research and development experience to this role, having served previously as chief scientific officer at Tolerx, and on the management team at Alnylam Pharmaceuticals as vice president of research for immunology, metabolic and viral disease. Louis O'Dea, MB, BCh, BAO, chief medical officer and head of regulatory affairs, previously led clinical and regulatory activities at Radius Health and was worldwide head of clinical development for reproductive health and metabolism at Serono.

Moderna's leadership is supported by an engaged and experienced board of directors, chaired by Noubar Afeyan, Ph.D., co-founder of Moderna, and also co-founder, managing partner and CEO of Flagship Ventures, a leading early-stage venture capital firm. Dr. Afeyan is joined on the board by: Robert Carpenter, President, Boston Medical Investors, Inc.; Peter Barton Hutt, Senior Counsel, Covington & Burling; Robert Langer, Sc.D., David H. Koch Institute Professor at MIT; John Mendlein, Ph.D., Executive Chairman and CEO of aTyr Pharma; Derrick Rossi, Ph.D., assistant professor in the Stem Cell Regenerative Biology Department at Harvard Medical School and Harvard University; and Timothy Springer, Ph.D., Latham Family Professor at Harvard Medical School and Professor of Medicine at Children's Hospital Boston. Board members Robert Langer and Derrick Rossi are academic co-founders of Moderna, along with scientific advisory board member Kenneth Chien from Harvard University.

"Moderna's promise rivals that of the earliest biotechnology companies over 30 years ago -- adding an entirely new drug category to the pharmaceutical arsenal in the fight against important diseases," said Noubar Afeyan, co-founder and chairman of Moderna. "The

executive team, board of directors and scientific advisors all combine the expertise and passion needed to create an unparalleled company that fits the extraordinary scope of this opportunity," he added.

Moderna has assembled a scientific advisory board of world-renowned experts led by Jack Szostak, Ph.D.,2009 winner of the Nobel Prize in medicine, Howard Hughes Medical Institute investigator, professor of genetics at Harvard Medical School and Alex Rich Distinguished Investigator, Department of Molecular Biology at the Center for Computational and Integrative Biology at Massachusetts General Hospital. The scientific advisory board also includes Douglas Cole, MD, General Partner, Flagship Ventures; Kenneth Chien, MD, Ph.D., professor in the Department of Cell and Molecular Biology and Department of Medicine at the Karolinska Institute, and visiting professor in the Department of Stem Cell and Regenerative Biology, Harvard University.; David Liu, Ph.D., Professor of Chemistry and Chemical Biology at Harvard University, a Howard Hughes Medical Institute Investigator and a Senior Associate Member of the Broad Institute of Harvard and MIT; Douglas Melton, Ph.D., Thomas Dudley Cabot Professor in the Natural Sciences at Harvard University and an Investigator of the Howard Hughes Medical Institute; Elizabeth Nabel, MD, President of the Brigham and Women's Hospital (BWH) and Professor of Medicine, Harvard Medical School; and Ulrich H. von Andrian, M.D., Mallinckrodt Professor of Immunopathology at Harvard Medical School. Board members Robert Langer, Derrick Rossi and Timothy Springer also sit on the scientific advisory board.

About Moderna

Moderna is pioneering messenger RNA Therapeutics™, an entirely new treatment modality that enables the body to produce therapeutic proteins *in vivo*. Moderna is using this approach to develop first-ever treatments for a wide range of diseases that cannot be addressed today using existing technologies, and to drastically reduce the time and expense associated with creating therapeutic proteins using recombinant technologies. The company has demonstrated proof-of-concept using messenger RNA Therapeutics for a variety of indications and is moving multiple programs into the clinic. Visit www.modernatx.com to learn more.

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Phone: 202-729-4089

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SOURCE Moderna Therapeutics

JOINT APPENDIX 79

Paper No. ___
Filed: April 17, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

PROTIVA BIOTHERAPEUTICS, INC.,
Patent Owner.

Case IPR2018-00739
Patent No. 9,364,435

PATENT OWNER'S SUR-REPLY

TABLE OF CONTENTS

I. INTRODUCTION

This sur-reply is filed in response to Petitioner's Reply filed March 22, 2019. *See* EX2056.

The Reply illustrates precisely why attorney argument should be accorded no weight, and why such argument cannot take the place of evidence in the record. Much of the Reply relies on attacking arguments Patent Owner never made, mischaracterizing the deposition testimony of Patent Owner's expert, and flatly ignoring detrimental testimony from Petitioner's own expert. Beyond that, the Reply attempts to weave false narratives about non-toxic cationic lipids and inoperable formulations that not only lack a shred of supporting evidence, but are contradicted by Petitioner's own publications.

In the end, Petitioner's unpatentability challenges lack supporting evidence, and the Reply fails to show otherwise. Petitioner's sole remaining anticipation challenge fails in that neither the L054, nor any other composition in the '554 publication, represents ***particles*** (as opposed to starting ingredients) having a lipid composition required by the challenged claims—nor does the L054 composition or any other composition disclosed in the '554 patent encapsulate nucleic acid in the particle so as to protect the nucleic acid from enzymatic degradation.

Regarding Petitioner's obviousness assertions, Patent Owner previously pointed out those challenges fail for being premised on the false notion that

overlapping lipid ranges in the prior art alone necessarily render the '435 patent claims obvious. The Reply perpetuates this erroneous argument, now citing to *E.I. duPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996 (Fed. Cir. 2018). But *duPont*, like all other overlapping range cases, is based the specific rationale of "routine optimization"—rather than obviating the need for the critical aspects of an obviousness inquiry (*e.g.*, motivation, reasonable expectation of success). *Id.* at 1006. Petitioner has never established that formulating nucleic acid-lipid particles as claimed would have been a matter of routine optimization (or any other obviousness rationale). Here, the evidence is overwhelming — achieving the nucleic acid-lipid particles of the '435 patent was *not* a matter of routine optimization.

To the extent any *prima facie* case of obviousness was established by identification of overlapping lipid ranges in the art, that case is rebutted by the extensive experimental data in the '435 patent and numerous post-filing publications, including Petitioner's own publications. As explained previously, and as corroborated throughout the literature at the time (and unrebutted by Petitioner), high-level cationic lipid formulations (*e.g.*, 50-85% cationic lipid) were expected to have poor *in vivo* activity and elicit increased toxicity and immunogenicity relative to lower-level cationic lipid formulations. EX1005, 3315; EX1006, 745; EX1008, E96; EX2007, 30:34-41.

Patent Owner, however, found that the claimed formulations surprisingly impart increased activity of the encapsulated nucleic acid and improved tolerability of the formulations *in vivo*, resulting in a significant increase in the therapeutic index. EX1015, 38-39, 68-69. Moreover, the claimed formulations are stable in circulation and are substantially non-toxic when administered to mammals. These surprising results are different in kind, not merely degree. The Reply fails to demonstrate otherwise.

As such, when all the evidence of record is weighed and considered, Petitioner has failed to meet its burden of demonstrating unpatentability by a preponderance of the evidence, and the challenges in the Petition should be rejected and the claims of the '435 patent found *not unpatentable*.

II. CLAIM CONSTRUCTION

Petitioner now abandons the construction of the term "nucleic acid-lipid particle" that was proffered in the Petition and rejected in the Institution Decision (*e.g.*, Pet. 24; Decision 10-11). The Reply (3) instead provides a single conclusory sentence stating that the Board's preliminary construction of this term "is appropriate."[1] EX1021, ¶13. Petitioner offers no argument or analysis as to <u>why</u>

[1] This represents the third different construction for this term advanced by Petitioner.

this construction is appropriate (*e.g.*, reasonable in view of the specification), and provides no meaningful response to the evidence presented in the Response *(e.g.*, 11-13).

As explained in the Response (11-12), the "preliminary construction" puts misplaced reliance on limited discussion of a different term ("lipid particle"), does not account for pertinent disclosure elsewhere in the specification, and is unreasonably broad.

As explained by Dr. Thompson, a "nucleic acid-lipid particle" (as opposed to a "lipid particle") ***does*** include a nucleic acid encapsulated in the particle so as to protect the nucleic acid from enzymatic degradation. Response, 11-12; EX2009, ¶¶38-40, 44-45. Such an interpretation is supported throughout the specification of the '435 patent. *E.g.*, EX1001, 11:51-54 ("nucleic acids, ***when present in the lipid particles*** of the present invention, are resistant in aqueous solution to degradation with a nuclease") (emphasis added); *see also id*., Examples and Tables (*e.g.*, Tables 2, 4, 6, 7) all reporting high encapsulation; 11:20-22 (equating encapsulation with resistance to nuclease degradation); *cf*. 68:56-58 ("For vehicle controls, ***empty particles*** with identical lipid composition were formed in the

absence of siRNA."). Petitioner does not dispute this interpretation in its Reply or elsewhere—nor can it.[2]

The Reply (4-5) is largely spent attacking a strawman, incorrectly stating that Patent Owner proposed importing various "SNALP" and "*in vivo*" limitations into the claims. But it was ***Petitioner's expert*** who repeatedly testified during cross-examination that the patent ***defines*** the claimed nucleic acid-lipid particles as SNALPs. *E.g.*, EX2028, 118:19-119:4 ("...we're defining them in this invention as SNALPs and what they comprise of.... So that would seem to me to be a definition."), 120:5-6 ("It's a definition in the context of this patent."), 121:14-25 ("So it's pretty clear that we're talking about lipid particles of the invention, and it's pretty clear we're talking about SNALPs...").

The Reply (4) attempts to whitewash Dr. Janoff's testimony in this regard with a heavily edited quotation from the transcript—that is, edited to remove counsel's improper coaching objection and Dr. Janoff's unequivocal affirmance of

[2] Dr. Janoff embraced this interpretation during cross-examination. EX2028, 195:20-22 ("...what [the '435 patent] says is when nucleic acids are present in the lipid particles, they're resistant to a degradation."); *see also id.*, 194:3-195:22, 198:4-22, 199:10-18.

defining the claimed particles as SNALPs (highlighted below). The more complete quotation is shown here:

Q. So from your perspective, the '127 patent is defining a lipid particle as a SNALP?
MR. WELLS: Objection, misstates testimony.
A. No, I didn't say that. I said that the definition of a lipid particle in the context of this invention is defined -- looks like, in my opinion, in column 5, starting on line 15, and in the context of this invention it's being called an SNALP, which is specific to this particular invention, as I've said before.
So if we're looking for a definition of a particle, there it is in the '127 patent. May

EX2028, 119:5-17; *see also id.*, 119:23-121:25 (confirming at least 3 more times his position that the specification defines lipid particles as SNALPs); Response, 12; EX2028, 16:13-25.

As stated in the Response (12-13), a reasonable reading of the ’435 patent supports Dr. Janoff’s position in that there is no meaningful distinction between descriptions of a “lipid particle” containing a nucleic acid (nucleic acid-lipid

particle) and particle characteristics that confer serum stability.[3] Nothing in the Reply demonstrates otherwise.

III. IT IS NOW UNDISPUTED THAT L054 DOES NOT ANTICIPATE THE CHALLENGED CLAIMS

The L054 formulation fails to anticipate the challenged claims for several reasons.[4] The Reply attempts to sidestep these points, but does not directly address, let alone rebut, them.

First, the Petition cites the L054 formulation of Table 4, but that is a lipid mixture for making particles—not itself a particle (*See, e.g.*, claim 1 directed to a "nucleic acid-lipid particle"). Dr. Thompson explained the erroneous nature of

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[3] During prosecution of the parent application leading to U.S. Patent No. 8,058,069 ('069 patent), Patent Owner described the claimed "nucleic acid-lipid particle" as "SNALP formulations advantageously impart ***increased activity*** of the encapsulated nucleic acid (*e.g.*, an interfering RNA such as siRNA) and ***improved tolerability*** of the formulations *in vivo*." EX1015, 38 (emphasis original). *See Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015).

[4] Petitioner appears to have abandoned its anticipation arguments that disclosure of the prior art ranges are sufficiently specific to anticipate. *E.g.*, Pet. 38 (1(d)), 39 (1(e)), 43 (Claim 7); EX1007, ¶¶116-117, 124.

simply assuming resulting complexes have the same composition as the starting lipid mixture. *E.g.*, EX2009, ¶110 (citing EX2012; EX2013).

The Reply (13) makes the conclusory assertion that listing only starting formulations, and not the particle composition, was "accepted practice in the field." This dubious assertion misses the point.[5] The claims are directed to a "nucleic acid-lipid ***particle***." The '554 publication does not disclose lipid compositions of resulting particles, nor does it disclose sufficient detail to reasonably assume the resulting particles fall within the scope of claim 1. *E.g.*, Response, 40-43. Petitioner disputes none of this, and the anticipation challenge fails for this reason alone.

The Reply (14) mischaracterizes Patent Owner's argument as an unfounded assumption of one-directional variation. As a threshold matter, it is not Patent

[5] The Reply (13-14) attempts to pivot to a discussion of the '435 patent, which is a different document (with different disclosure) irrelevant to the deficient content of the '554 publication. In contrast to the '554 publication, the '435 patent discloses detailed descriptions of particle production methods and extensive characterization of finished particles. *E.g.*, EX1001, 57:60-60:59, Tables 2, 4, 6, 7, 76:26-48; 68:58-69:5 (describing typical variation in lipid composition); EX1019, 168:7-172:14.

Owner's burden to prove the composition of the L054 particle when that composition is not provided in the reference. Petitioner fails to establish the '554 publication's particles would have a lipid composition within the scope of claim 1. *See* 35 U.S.C. § 316(e). Beyond that, the '554 publication provides only cryptic description of its production methods, and what scant detail is provided more reasonably predicts different incorporation efficiencies for different lipid components, thereby resulting in particles with lipid ratios well outside the claimed ranges. *E.g.*, EX2009, ¶113 ("The predictable result of using cholesterol-based detergents is less cholesterol in the finished particles than in the starting materials."), ¶115; EX1020, 226:7-11 ("If we have lower cholesterol, that conjugate lipid concentration is going up, not down."); EX2028, 157:12-158:16 (Dr. Janoff describing failure to recover cholesterol in a particle altering the amount of the remaining components); EX1020, 223:14-21 (explaining that the cationic lipid would be expected outside the claimed range).[6] The Reply offers no meaningful rebuttal.

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[6] The Reply (14) mischaracterizes Dr. Thompson's testimony as somehow supporting Petitioner's argument, where he actually expressly rejected it. *See* EX1020, 224:6-21, 223:14-21 ("...very likely that these particles are outside the

(continued...)

Second, there is no evidence that L054-derived lipid particles encapsulate nucleic acid as required by the '435 patent (*i.e.*, encapsulated in the particle so as to protect the nucleic acid from enzymatic degradation). *See* Section II; *see also* EX2028, 199:10-18, 198:4-17, 194:3-21. The '554 publication makes no assertion that L054 encapsulates nucleic acid in the particle as specifically required by the '435 patent, or in any capacity at all, let alone verify such encapsulation with any evidence.

The Reply (14-15) again attempts to sidestep the encapsulation issue and avoid detrimental testimony of its own expert. Instead, the Reply offers only the cryptic assertion that the '554 publication "discusses encapsulation." None of the citations to the '554 publication discuss L054 encapsulation. *See* Reply, 14-15 (citing EX1004, ¶11 (background discussing different particles), ¶136 (not addressing L054), ¶317 (not addressing L054, encapsulation only as a possibility), ¶400 (no mention of encapsulation)).

And Petitioner offers no explanation as to how "encapsulation" would be understood in the context of the '554 publication. This is critically pertinent in

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(...continued from previous page)
range [for cationic lipid]."), 226:13-23 ("I'm not taking the bait on that one. The point is clear.").

view of Dr. Janoff's repeated testimony (and publications) that encapsulation means very different things in different contexts. *Compare* EX2028, 137:16-138:16 ("[Encapsulation] has many different meanings..."), 147:18-22 ("[Encapsulation is] a fungible term. It means different things to different people in different contexts."), 146:22-147:1, *and* EX2007, 4:11-19, *with* EX2028, 199:10-18, 198:4-22, 194:3-21, *and* 195:12-22. There is no evidence or argument that L054 (or any other particle produced using the compositions disclosed by the '554 publication) encapsulates nucleic acid in the particle so as to protect the nucleic acid from enzymatic degradation.[7]

Accordingly, Petitioner fails to establish that L054 (or any other composition in the '554 publication) 1) includes ***particles*** having a lipid composition required by the challenged claims; or 2) encapsulates nucleic acid so as to protect the nucleic acid from enzymatic degradation.

[7] Petitioner fails to inform the Board that the '554 publication takes a fundamentally different approach and relies on nuclease-resistant RNA constructs. EX1004, ¶¶522, 523, 578. The reliance on such modified RNA indicates particle construction that fails to prevent nuclease exposure.

IV. THERE IS NO RATIONALE/MOTIVATION SUPPORTING OBVIOUSNESS

Patent Owner previously pointed out that the obviousness challenges of at least Grounds 1 and 3 in the Petition fail to identify any particular motivation or rationale to combine components specifically in the proportions required by the claims (or any discussion of reasonable expectation of success). POPR, 27-28, 44; Response, 18-20, 46-47. Rather, those challenges rest on the false notion that overlapping lipid ranges in the prior art alone necessarily render the '435 patent claims obvious. The Reply (10-11) perpetuates this erroneous argument, now citing to *duPont*.

Petitioner, however, fails to acknowledge that none of *duPont*, *Peterson*, or any other overlapping range case stands for the proposition that an overlapping range in the prior art obviates the requirements for motivation to combine and reasonable expectation of success in an obviousness challenge. Instead, the Federal Circuit has explained that overlapping ranges, without evidence to the contrary, may invoke a rebuttable presumption of obviousness under the specific rationale of "routine optimization." *See, e.g.*, *In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017) (explaining no matter what the obviousness theory "there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful."); *In re Peterson*, 315 F.3d 1325, 1330 n.1 (Fed. Cir. 2003) ("[Overlapping] ranges that are not especially broad invite ***routine***

experimentation to discover optimum values, rather than require nonobvious invention"); *duPont,* 904 F.3d at 1006 ("The legal principle at issue in this case is old....it is not inventive to discover the optimum or workable ranges by ***routine experimentation***."); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) ("Simply put, the typical desire of scientists to find an optimum value within a narrow disclosed range does not apply to the facts in this case."). [8]

This distinction is important because "routine optimization" simply does not apply here. In fact, Petitioner has never established that formulating nucleic acid-lipid particles as claimed would have been a matter of routine optimization (or any

[8] At institution, the Board suggested the Petition may be based on a theory of routine optimization. Decision, 23. That is not so clear. Petitioner carefully avoids assertions of routine experimentation and, as discussed below, actually embraces the complexity of the technology when pivoting to experimental data supporting the criticality of the claimed lipid ranges. But this exposes an internal contradiction in Petitioner's case and Petitioner cannot have it both ways. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1298 (Fed. Cir. 2012) (Explaining that in the context of overlapping ranges evidence that variables interact in an unpredictable or unexpected way support nonobvious.).

other obviousness rationale).[9] The obviousness challenges fail for at least that reason alone. *See, e.g.*, *Stepan*, 868 F.3d at 1346, 1346 n.1 (rejecting obviousness in view of overlapping ranges because "[m]issing from the Board's analysis is an explanation as to *why* it would have been routine optimization to arrive at the claimed invention.").

Even if Petitioner's obviousness challenges are deemed to include a *sub silentio* rationale of routine optimization, such a theory has been addressed directly, lacks any supporting evidence, and has been thoroughly rebutted. As explained in detail below, the evidence is overwhelming — achieving the nucleic acid-lipid particles of the '435 patent was *not* a matter of routine optimization.

A. Formulating Nucleic Acid-Lipid Particles Was Not a Matter of Routine Optimization

At the time of invention, formulating nucleic acid-lipid particles was not a matter of routine optimization. Dr. Thompson addressed this issue directly. EX1020, 403: 22-25 ("Q. In the 2008 timeframe, was developing nucleic acid-lipid particles considered a routine matter of optimizing variables? A. No."); EX2009,

[9] Dr. Janoff's declaration includes only a single conclusory sentence regarding determining an "optimal proportion" of cationic lipid, one component of the formulation. EX1007, ¶110; *see also* 37 C.F.R. § 42.65(a).

¶58 ("The effects of making changes to the proportion of other components in the lipid particle would be unpredictable..."), ¶60 ("Making safe and effective nucleic acid-lipid particle formulations was not simply a matter of 'varying the proportion' of cationic lipid in prior art formulations …"); *see also id*., ¶¶57-59, 136; EX1019, 32:3, 31:22-23 ("Change solvent, change additives, change lots of different variables"), 32:9, 41:4-6 ("plenty of places to go wrong"), 43:9-10, 178:17-18, 180:6; EX1020, 404:11-18 ("As I stated multiple times in my deposition, these are multicomponent systems and varying one component at a time was not a viable strategy.").

Petitioner and its expert actually embrace the complexity of formulating nucleic acid-lipid particles, repeatedly arguing unpredictability in adjusting lipid proportions. Reply, 15-16; Pet. 8-9 ("The structure of lipoplexes is influenced by multiple factors.... Transfection efficacy is complex because '[a] large number of parameters are involved."); EX1007 ¶¶65-68 (same), ¶73 ("[A] POSITA would have had no way of knowing if lipid combination at any given proportion would have resulted in formulations of superior therapeutic index to other formulations."). During deposition, Dr. Janoff repeatedly emphasized the complexity of the field of art at the time. EX2028, 144:18-145:1 ("We're in deep waters, and what you think are simple questions belie — and I don't mean to be pejorative — belie an ignorance of the field that you're questioning me in"), 57:19

("it's a very technical area"), 58:22-59:1 ("we're in deep water here talking about very technical issues), 61:9-11 ("You're asking me a very, very, very technical question..."), 63:5-11 ("we're in technical deep waters"), 68:12 ("we're in deep technical territory here"); *see also* EX1021, ¶25 (discussing "the complicated nature of what affects transfection efficiencies"). A highly technical and unpredictable state of the art is the very antithesis of routine optimization.

Prior art cited in the Petition corroborates the expert testimony that forming functioning lipid particles at the time was far from routine, but instead was a function of multiple parameters whose interactions were poorly understood, with limited guidance existing. *See, e.g.*, EX1006, 740 ("...the lack of mechanistic understanding of gene delivery by CL-DNA complexes is due to the large number of parameters involved."), ("[I]n comparative studies, typically only one or two data points per lipid are evaluated, allowing the ideal lipid composition (the ratio of neutral to cationic lipid) or cationic lipid/DNA ratio to be overlooked."); *see also* EX1021, ¶25; EX1008, E99 ("[It is] essential for us to identify the critical parameters limiting gene delivery in the current systems.").

The evidence also illustrates recognition in the industry that developing lipid particle formulations for drug delivery was not a simple or routine matter of optimizing variables. EX2011, 38 ("[P]hysical delivery of the drugs to diseased cells is extremely challenging."); EX2012, 7248 ("The intrinsic complexity of any

such gene delivery vehicle can be expected to present continued challenges ..."); EX2014, 11 ("The major hurdle right now is delivery, delivery, delivery."); EX2016, 7 ("What's interesting about what we do is that the drug isn't the problem. It's the delivery of it."); EX2015, 2; EX2011, 42; EX2016, 1; EX2023, 291-292 ("[Delivery] proved to be a substantially harder problem than we anticipated..."), ("All of those tear-your-hair-out days were worth it to get to today").

Accordingly, "routine optimization" is not a viable rationale for arriving at the claimed subject matter.

B. Petitioner's New Picking and Choosing Argument Should be Rejected

The Reply (8-10) now argues that low PEG-lipid amounts were "known in the art" and that "the amount of conjugated lipid (*e.g.*, PEG) ***could*** be minimized." Reply, 9 (emphasis added). Such assertions have never been sufficient to support obviousness. *PersonalWeb Techs., LLC v. Apple, Inc.*, 848 F.3d 987 (Fed. Cir. 2017) ("reasoning...that [references] *could* be combined...is not enough: it does not imply a motivation") (emphasis in original).

Similarly, the Reply (9, 11) newly argues high cationic/low PEG was "known" and then leaps to the conclusion that one would pick and choose from various different formulations (from the '189 patent and '554 publication) to arrive at the claim. As a threshold matter, this untimely new combination/theory was not

presented in the petition. Even if considered, the argument is factually incorrect and entirely conclusory. None of the cited formulations are within the claimed ranges—the "2:40" composition is well outside the claim, and the newly cited '554 publication formulations (like L054) are merely a listing of starting ingredients (*see* discussion above) and are outside the claimed ranges. Furthermore, the Reply (11) cites to Dr. Janoff (EX1021, ¶22), which merely cites back to his previous erroneous and conclusory testimony. *Cf.* EX2009, ¶¶61-62; EX1020, 404:5-18; Section IV.A. While it is not Patent Owner's burden to prove no motivation, one would more logically expect increased conjugated lipid (*i.e.*, at or above the more typical 5-10%) to accompany a hypothetically increased cationic lipid. Response, 14, 20; EX2009, ¶¶61-62. The Reply does not rebut this point.

V. UNEXPECTED RESULTS FURTHER REBUT ANY *PRIMA FACIE* OBVIOUSNESS

As explained above, to the extent any *prima facie* case of obviousness in view of overlapping ranges was ever established in the first place, it is rebutted by uncontroverted evidence that developing nucleic acid-lipid particles as claimed was *not* a matter of routine optimization of lipid variables. The Federal Circuit has explained in *Peterson* and elsewhere, one may also overcome a *prima facie* case of obviousness "by showing that the claimed range achieves unexpected results." 315 F.3d 1325, 1330-1331. Any such *prima facie* case here is even further overcome

by the extensive experimental data in the '435 patent and post-filing publications showing unexpected results.

The Reply (15-16) argues that the test data is not commensurate with the scope of the claims because only a "small portion" of formulations were tested. But neither Petitioner nor Dr. Janoff specify what "portion" of formulations were believed to have been tested. Nor does the Reply provide any analysis as to why this portion is too "small" to overcome the *prima facie* obviousness challenge of the Petition. In addition, the Reply (16-19) only addresses a subset of the test data disclosed in the '435 patent, largely ignoring the post-filing data provided and discussed in the Response (59-61). *See* EX2046; EX2055, 44:19-45:9 (Dr. Janoff referring to only the data in the '435 patent), 70:18-73:4, 75:25-77:7 (admitting he did not consider Petitioner's own publications reporting testing of claimed formulations).

Lacking any meaningful analysis, the Reply fails to acknowledge that the present case is nothing like previous instances where testing was rejected as not commensurate. *See, e.g.*, *Peterson*, 315 F.3d at 1331 (unexpected results not commensurate where only two data points were tested, and only one data point produced unexpected results); *duPont*, 904 F.3d at 996 (only a single data point was tested); *In re Greenfield*, 571 F.2d 1185, 1189 (Fed. Cir. 1978) (testing only one species in a large genus).

Here, the '435 patent presents testing on ***dozens*** of different formulations falling within the scope of claim 1. Publications following the '435 patent (including Petitioner's own publications) tested dozens more formulations within the scope of claim 1, finding those formulations efficacious and well-tolerated. *Genetics Inst.*, 655 F.3d at 1307 ("[W]e have held that evidence of unexpected results may be used to rebut a case of *prima facie* obviousness even if that evidence was obtained after the patent's filing or issue date….").

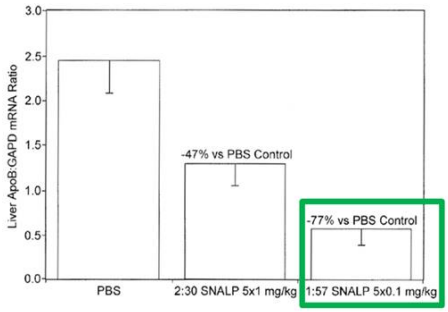
As addressed in more detail below, the extensive scope of the experimental testing conducted—and essentially ignored in the Reply—included many different formulations, with many different combinations of different lipid components, gene targets, nucleic acid payloads and methods of production. *See* EX2046 (summary of exemplary formulations tested and within the scope of the '435 patent claims). Such testing is more than sufficient to rebut any *prima facie* case of obviousness.

A. The '435 Patent Reports Extensive Testing of Numerous Formulations Within the Claimed Range

The '435 patent specification provides experimental data for numerous formulations within the scope of claim 1 supporting the unexpected degree of tolerability and efficacy of the claimed compositions. The Reply and Dr. Janoff's opinions appear to be based on a misconception of the testing actually presented in the '435 patent. EX2055, 39:16-40:5, 66:8-67:3.

For instance, Example 3 in the '435 patent specification report that each of the tested formulations falling within the scope of claim 1 (Groups 11, 13, 14) demonstrated potent silencing activity *in vivo*. The 1:57 formulations were substantially more effective at silencing the expression of a target gene as compared to all other nucleic acid-lipid particle formulations tested. *E.g.*, EX1001, 72:20-23, Table 4.

Example 4 demonstrates that 1:57 formulations were ***10 times more efficacious*** as compared to a nucleic acid-lipid particle formulation previously described ("2:30 SNALP") in mediating target gene silencing *in vivo* ***at a 10-fold lower dose***. *E.g.*, *id.*, 73:64-67, Figure 3 (annotated shown - left); *see also* EX1016, 39.



Example 5 describes testing of ***seven additional formulations*** within the scope of claim 1. EX1001, 74:1-53, Table 6 (Groups 2-8), Figure 4. Those formulations included combinations of different conjugated lipids (PEG_{2000} and PEG_{5000}), cationic lipids (DLinDMA and DODMA), phospholipids (DPPC and DPPE), and cholesterol/derivative (cholesterol and cholestanol). As disclosed in Example 5 and illustrated in Fig. 4, each of those formulations demonstrated potent silencing activity *in vivo*.

Example 6 describes testing of ***fourteen additional formulations*** within the scope of claim 1. EX1001, 74:60-75:49, Table 2 (Groups 2-15), Figure 5. Each of the tested formulations demonstrated potent silencing activity *in vivo*.

Examples 7 and 8 describe testing of tolerability and efficacy using "1:57" SNALPs prepared by various different manufacturing processes. *Id.*, 75:41-80:45. The tested SNALPs were well-tolerated and efficacious in mediating target gene silencing *in vivo*.

The examples presented in the '435 patent further demonstrate that nucleic acid-lipid particles were efficacious in silencing multiple different gene targets *in vivo*. Examples 3-8 demonstrate potent silencing of ApoB expression *in vivo*. Examples 9-11 further demonstrate *in vivo* silencing of polo-like kinase 1 (PLK-1) expression using different SNALP formulations within the scope of claim 1. *Id.*, 80:46-86:19.

The Reply (16-17) limits consideration to only Examples 3-4 and repeats the legally and factually misplaced argument that not all claimed formulations were superior to all other tested formulations. The potent silencing activity and low toxicity across an entire range of dozens of different formulations was categorically unexpected, and Petitioner fails to demonstrate otherwise.

B. Post-Filing Publications Provide Testing Data for a Broad Range of Lipids and Cargo Molecules (including both siRNA and mRNA)

Various post-filing publications (including those by Petitioner) have reported testing of numerous formulations within the scope of claim 1. This includes testing of different nucleic acid payloads (*e.g*, siRNA and mRNA) many different cationic lipids, numerous gene targets, various *in vivo* animal models, and humans. Such publications are ignored in the Reply.

U.S. Patent No. 8,236,943 (EX2017) discloses testing of several formulations within the scope of claim 1. For instance, the '943 patent evaluated several 1:57 formulations comprising 1.4% PEG2000-cDMA, 57.1% cationic lipid, 7.1% DPPC, and 34.3% cholesterol. EX2017, 150:25-47, Table 1 (describing the siRNA cargo). Examples 11 and 13 disclose such formulations comprising five different cationic lipids (*i.e.*, DLin-K-C2 DMA, DLenDMA, γ-DLenDMA, γ-DLen-C2K-DMA, and DLen-C2K-DMA), which were tested for their capacity to silence the ApoB gene in animals following intravenous injection. EX2017, 151:29-37, 150:59-151:55, 153:25-55, Figures 4, 7. Each of these formulations demonstrated potent gene silencing activity *in vivo*.

U.S. Publication No. 2013/0116307 (EX2018) discloses testing of additional formulations within the scope of claim 1, including formulations comprising 1.4% PEG2000-cDMA, 57.1% cationic lipid, 7.1% DPPC, and 34.3% cholesterol.

EX2018, ¶421, Table 1 (describing the siRNA cargo). Such formulations included seven different cationic lipids (*i.e.*, DLin-MC3-DMA, LenMC3, CP-LenMC3, CP-γ-DLen-C2K-DMA, CP-DLen-C2K-DMA, γ-Len-MC3, CP-γ-Len-MC3) that were tested for their capacity to silence gene expression in mice following intravenous injection. EX2018, Examples 17, 18, ¶¶430, 432-439, Figures 4, 5. As illustrated in Figures 4 and 5, each of these nine formulations were efficacious in silencing target gene activity *in vivo*.

Semple (EX2021) discloses testing of formulations within the scope of claim 1 in multiple different *in vivo* animal models. For instance, Semple tested formulations comprising 1.4% PEG2000-cDMA, 57.1% DLin-KC2-DMA, 7.1% DPPC, and 34.3% cholesterol. EX2021, 177 ("Preparation of KC2-SNALP"), (describing the TTR siRNA cargo). The formulation was tested for its capacity to silence the TTR gene in mice, rats, and non-human primates following a single intravenous injection. EX2021, 175, 178 ("In vivo nonhuman primate experiments"), Figure 3. As reported, the 1:57 formulation "was well-tolerated in both rodent and nonhuman primates and exhibited *in vivo* activity at siRNA doses as low as 0.01 mg/kg in rodents, as well as silencing of a therapeutically significant gene (TTR) in nonhuman primates." EX2021, 175, Table 2; EX2022, Supplementary Table 4. The formulations were both efficacious and well-tolerated.

EX2021, 175 ("…well tolerated at the dose levels tested, with no treatment-related changes in animal appearance or behavior.").

Bettencourt (EX2019) discloses testing of the commercial product, Onpattro™ (*i.e.*, patisiran). Patisiran includes 50% DLin-MC3-DMA, 1.5% PEG-cDMG, 10% DSPC, 38.5% cholesterol. EX2019, ¶46, Table 1; *see also id.*, ¶43 (describing the TTR siRNA cargo). Testing demonstrated that patisiran is both efficacious and well-tolerated in human subjects. EX2019, ¶¶103, 121, 132.

The Reply (17) makes vague arguments about comparisons to the closest formulations (though never identifies what it believes is closest or why). Despite claiming to have worked for Alnylam, Dr. Janoff's opinions did not account for publications such as Akinc (EX2047)—which discloses testing of even more formulations within the scope of claim 1. EX2055, 68:11-69:17; EX1018, 2. As illustrated in Fig. 12 below (annotated), Groups 23-25 were superior in silencing gene expression of Factor VII ("FVII") *in vivo* relative to formulations having conjugated lipid levels above the claimed range. EX2047, Figure 12, 112, 120, Table 3 (describing the FVII siRNA cargo), Example 16.

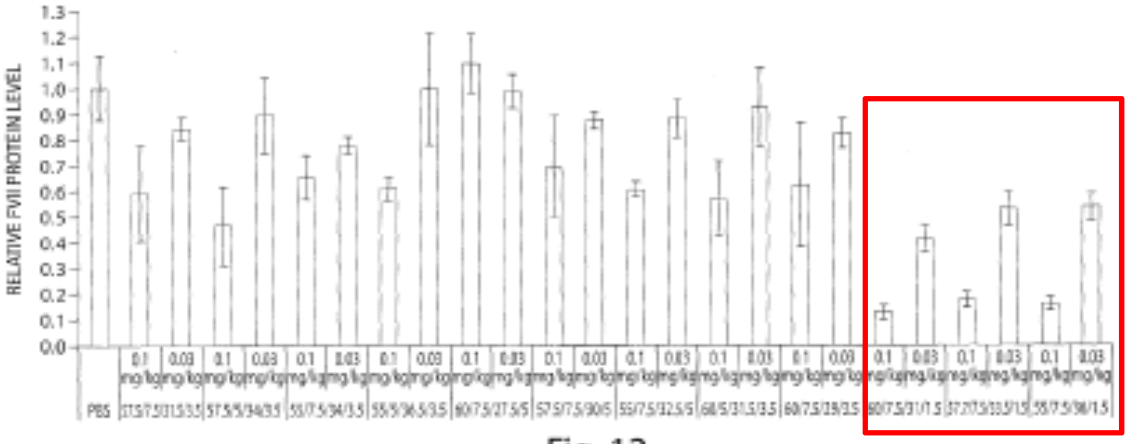


Fig. 12

Remarkably, the Reply and Dr. Janoff ignore that Petitioner has published extensively that the claimed formulations are efficacious and well-tolerated for various nucleic acid payloads, including mRNA. *See* EX2055, 70:18-73:4, 75:25-77:7 (confirming his opinions ignored Petitioner's publications); Sedic (EX2048); EX2049; EX2050. For example, Sedic tested mRNA therapeutic payloads in the LNPs using the same "off-the-shelf" formulation as patisiran (*i.e.*, 50% DLin-MC3-DMA, 1.5% PEG-cDMG, 10% DSPC, 38.5% cholesterol). EX2048, 2 ("850-nucleotide messenger RNA"), 3; EX2019, ¶46. Consistent with the various other reports in the literature, Petitioner reported that the LNPs were efficacious and well-tolerated. EX2048, Abstract ("Overall, these combined studies indicate that LNP-formulated modified mRNA can be administered by intravenous infusion in 2 toxicologically relevant test species and generate supratherapeutic levels of protein (hEPO) in vivo.").

The Reply (18-19) sole response to the numerous post-filing publications (including its own publications) is to cherry pick a single formulation, from one experiment in one reference and falsely assert inoperability. EX1020, 411:14-412:25. In sum, the extensive testing reported in the '435 patent and other publications is more than sufficient to rebut any *prima facie* case of obviousness. The Reply fails to demonstrate otherwise.

C. Petitioner Remaining Arguments are Unavailing

The Reply (15) argues that "payload, identity of lipid components, or production techniques can all impact the particle properties and efficacy." This may be, but does not rebut the data demonstrating that a wide variety of nucleic acid-lipid particle formulations within the scope of claim 1 — reflecting different payloads, lipids, and concentrations — were tested and found to be unexpectedly efficacious and well-tolerated.

VI. PETITIONER'S FALSE NARRATIVE OF NON-TOXIC CATIONIC LIPIDS SHOULD BE REJECTED

Cationic lipids were known to be toxic at the time of invention, and the conventional thinking at that time was that their content in lipid particle formulations should be minimized. This is well-established in the current record, and there is no evidence, other than uncorroborated testimony of Dr. Janoff, indicating otherwise. These unrebutted facts are relevant because they 1) further undermine any motivation/expectation of success at the time (an aspect wholly

lacking from the Petition materials); and 2) if anything, would have more reasonably led away from the claimed compositions.

The Reply (1, 6-8) offers, through attorney argument, a false narrative that ionizable cationic lipids used (*e.g.*, DLinDMA) were known as being non-toxic. This argument is remarkable considering that Petitioner has published extensively about toxicity concerns due specifically to ionizable cationic lipids, including DLinDMA. For instance, one of Petitioner's recent publications states the following:

> Ionizable cationic lipids, such as, but not limited to, DLinDMA, Dlin-KC2-DMA, and Dlin-MC3-DMA, have been shown to accumulate in plasma and tissues over time and may be a potential source of toxicity.

EX2051, 21:10-12; EX2052, 57:29-58:9 ("[T]he lipid compounds disclosed herein have a lower immunogenicity as compared to a reference amino lipid (*e.g.*, MC3, KC2, or DLinDMA)."). Petitioner own publications explicitly attribute toxicity of ionizable cationic lipids (including DLinDMA) not to charge at physiologic pH —

which by its own admission is neutral— but to accumulation and immunogenicity.[10] [11]

The Reply (6) falsely asserts that toxicity is "largely a function of such particles having a net positive charge." Reply, 6. This lacks supporting evidence and is factually incorrect. As noted above, Petitioner's own publications attribute toxicity to bioaccumulation and immunogenicity—not net charge. Ahmad expressly advocates for multivalent cationic lipids so as to maintain charge with a *lower amount* of molecules, identifying bioaccumulation and metabolic burden as toxicity mechanisms. EX1006, 7.

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[10] These publications by Petitioner were not previously disclosed to Patent Owner (*see* §42.51(b)(1)(iii)), nor were they considered by Dr. Janoff in rendering his opinions set forth in EX1021. EX2055, 70:18-73:4, 75:25-77:7.

[11] Moreover, the record is replete with evidence that cationic lipids are toxic, without qualification between certain types of cationic lipid. *E.g.*, EX1006, 7 ("Minimizing the amount of cationic lipid is desirable....fewer, more highly charged molecules should mean a smaller metabolic effort..."); EX1008, 5 ("the cationic lipid contributes significantly to the toxicity observed."); EX2011, 42 ("I wouldn't want anyone injecting cationic lipids into my bloodstream.").

Petitioner's (Reply 6, citing Paper 15) reliance on the institution decision is misplaced because Agency commentary is not evidence (and incorrect in this instance). *Brand v. Miller*, 487 F.3d 862, 869 (Fed. Cir. 2007). The Reply (13) later even acknowledges the link between toxicity and cationic lipid amount. *See also* EX1021, ¶26; EX2055, 39:4-9 ("Q. …And according to Ahmad, [multivalent cationic lipids are] beneficial because it allows one to obtain the charge, but do it with less cationic lipid; is that correct? A. According to Ahmad, yes."), 31:7-39:9; EX1020, 409:2-19 ("...the bottom line message of Lin and Ahmad is how to reduce cationic lipid concentration in a formulation..."); EX1019, 65:24-66:5 ("…the even bigger concern is about the essentially long-term toxicity that might arise from bioaccumulation..."). While lower particle charge might mitigate particle aggregation, the evidence (including Petitioner's own publications) identifies various mechanisms of toxicity independent of particle net charge.

The Reply (7) also erroneously points to testing of a 40% DLinDMA formulation as evidence that "high cationic lipid concentrations" were known in the art and non-toxic. First, the 40% DLinDMA composition is well below the claimed range of 50% to 85% cationic lipid. Second, Petitioner conflates observations about a particle formulation with the different concept of toxicity of the cationic lipid component specifically. The '189 publication does not attribute

the low toxicity of the composition to DLinDMA or the charge of particles at physiologic pH.

The Reply (7-8) mischaracterizes the deposition testimony of Dr. Thompson, but none of his testimony (or any other evidence) supports the notion that ionizable cationic lipids were recognized as non-toxic. For example, the Reply (7) truncates the citation to EX1019, 64:15-65:14, and falsely claims that Dr. Thompson admitted to non-toxicity. Dr. Thompson explained just the opposite—why "[c]ationic lipids in general were widely known as toxic" and "you wanted to minimize your cationic lipid content." EX1019, 63:18-25. Dr. Thompson then went on to identify concerns over, *inter alia*, biodegradation, immunogenicity, cytotoxicity, and long term bioaccumulation. Dr. Thompson directly rejected the false notion that toxicity is merely a function of surface charge. *E.g.*, EX1020, 411:10-12 ("Cationic lipids are toxic. Some are — have greater toxicity than others, but they're all toxic."), 244:8-9 ("It doesn't matter whether [the cationic lipid is] protonatable or not. It's still toxic."), 244:25-245:6, 246:17-250:21.

VII. LIN/AHMAD DO NOT SUPPLY THE MISSING MOTIVATION FOR GROUND 2

As a threshold matter, it is now undisputed that "lipoplexes" as in Lin and Ahmad are a fundamentally different type of particle compared to a "nucleic acid-lipid particle," excluded from the scope of the challenged claims, and are expressly differentiated both in the challenged patent and the cited art. *E.g.*, Response, 34-35;

EX2009, ¶¶95-98 ("Lipoplexes are ***not*** nucleic acid-lipid particles."); EX2028, 122:1-24 (Dr. Janoff identifying lipoplexes as outside the scope of the challenged claims); EX2007, 2:26-40, 2:54-65 (identifying lipoplexes as structurally and functionally distinct); EX1001, 2:19-29, 3:9-21 (differentiating nucleic acid-lipid particles from lipoplexes); EX1002, ¶6 (same). The Reply (12) acknowledges Lin and Ahmad tested only lipoplex formulations, but still does not explain why one would have looked to this fundamentally different technology to modify a SNALP of the cited '196 publication (or '189 publication) or that they would have reasonably expected success in doing so. *See* EX1021, ¶25 (acknowledging Lin and Ahmad as lipoplexes).

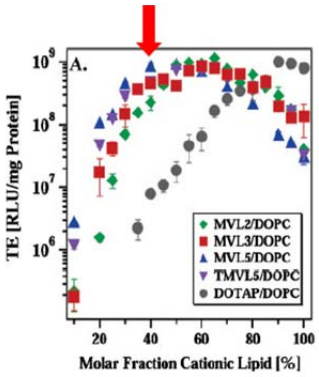
Moreover, as previously pointed out, Petitioner's argument that increasing cationic lipid "could" increase transfection efficiency is insufficient to establish obviousness. Response, 36-37; *compare* Pet. 49 ("***may*** increase..."), 50 ("...***potentially*** increase..."), ("...***could*** impact..."), *and* EX1007, ¶¶138-141 (parroting the same language), *with InTouch*, 751 F.3d at 1351-52 (obviousness analysis failed for stating "that one of ordinary skill in the art *could* combine these references, not that they *would* have been motivated to do so.") (original emphasis); *PersonalWeb*, 848 F.3d at 993-4 (same); *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (same). The Reply (12) identifies "the complicated nature of what affects transfection efficiencies" and repeats the

assertion that "...above 50% ***can*** have a positive effect...," which only underscores this deficiency.

While it is not Patent Owner's burden to prove no motivation or reasonable expectation of success, that is the only reasonable conclusion in view of the evidence. Dr. Thompson explained that neither Lin nor Ahmad would reasonably be viewed as advocating cationic lipid above 50 mol% in a formulation. EX2009, ¶¶100, 101. Rather, the central point of those references was to ***reduce*** cationic lipid (and the corresponding metabolic burden/toxicity) through use of multivalent lipids (MVLs)—that is, lipids that have more positive charge per individual molecule. EX1020, 409:2-19 ("...the bottom line message of Lin and Ahmad is how to reduce cationic lipid concentration in a formulation..."), 251:3-22, 252:11-19. Dr. Janoff acknowledges that Ahmad advocates the use of MVL as a means for reducing the amount of cationic lipid. EX2055, 39:4-9, 31:7-39:9. The Reply (13) acknowledges this key aspect of the cited references, but fails to appreciate that prior art references advocating reduction in cationic lipid actually undermines the obviousness assertion.

Moreover, while Lin/Ahmad tested different lipoplex formulations to compare saturation dynamics relative to control, neither reference instructs the use of any particular cationic lipid concentration in a formulation. In fact, as Dr. Thompson pointed out, Ahmad's experiment shows reaching saturation around 40

mol%, after which point the rate of enhanced metabolic burden far exceeds any further minimal TE gain. EX1006, Fig. 4A (annotated – shown), 1 ("...at intermediate σ_M, TE exhibits saturated behavior..."), 7 ("This means that much more cationic lipid is required to achieve optimal TE at large lipid/DNA charge ratios."), ("Minimizing the amount of cationic lipid is desirable to reduce cost as well as potential toxic effects of the cationic lipid.").



VIII. OBJECTIVE INDICIA CONFIRM PATENTABILITY OF CLAIMS

Rather than provide any meaningful analysis of the extensive objective indicia, the Reply (20-22) responds with citations to inapposite case law and raw speculation by its expert witness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016) ("[A] patent challenger cannot successfully rebut the presumption with argument alone—it must present evidence.").

For instance, the Reply (21) states pointing to evidence of long felt need is "erroneous." But Dr. Janoff confirmed he conducted no meaningful evaluation, he simply didn't know the facts. EX2055, 82:20-84:7 ("Q. Why did you think it could be attributable [to other technology]? A. Because I don't know. Q. You don't know? A. It could be. I said it could be. I didn't say it was. I said it could be."). Similarly, for the evidence that Roche adopted Patent Owner's SNALP technology

for non-human primate studies, Petitioner offers only unfounded speculation. EX2055, 85:9-86:4 ("No, I don't have any knowledge one way or the other. And that's the point of — that's the point of my opinion."). Speculation is neither evidence nor meaningful rebuttal. *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) (finding no substantial evidence where Board's conclusion of no nexus rested solely on conjecture).

Regarding the commercial product Patisiran, the Reply (22) argues the success and industry recognition should be discounted as being due "to the siRNA payload, not the delivery vehicle." But the very evidence cited states precisely the opposite. *See, e.g.*, EX2023 (repeatedly linking the success of Patisiran to the delivery vehicle); EX2055, 77:8-81:5, 86:5-87:2, 80:19-22; *see also Rambus*, 731 F.3d at 1257 (licensing activity is evidence of commercial success). Petitioner's conjecture is not a meaningful response to the objective indicia provided.

IX. DEPENDENT CLAIMS

The Reply (22-23) offers no meaningful response to the identified deficiencies in the petition vis-a-vis the dependent claims. Response, 29-33, 48-52. Dr. Janoff offers only a single generic and conclusory sentence. EX1021, ¶35. The argument in the Reply (23) for an omnibus combination of all references is improperly new, undeveloped, and not responsive. For example, Petitioner's attack on the experimental data is even more tenuous for claim 4. Despite relying on

overlapping ranges, Petitioner never identified overlapping phospholipid ranges for claim 7. The lack of motivation and expectation of success is even more pronounced for the *in vivo* methods of claims 16-20.

X. CONCLUSION

Accordingly, the challenges in the Petition should be rejected and the claims of the '435 patent found ***not unpatentable***.

Respectfully submitted,

Date: April 17, 2019

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

CERTIFICATE OF COMPLIANCE

Pursuant to § 42.24(d), the undersigned certifies that this paper contains no more than 7,100 words (see EX2056 authorizing an additional 1,500 words) , not including the portions of the paper exempted by § 42.24(b). According to the word-processing system used to prepare this paper, the paper contains 6,935 words.

Respectfully,

Dated: April 17, 2019

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

LIST OF EXHIBITS

EXHIBIT NO.	DESCRIPTION
2001	Declaration of Edward R. Reines in Support of Patent Owner's Motion for *Pro Hac Vice* Admission
2002	*In re Reines*, No. 14-MA004 (14-4) (Fed. Cir. Nov. 5, 2014)
2003	Personal Statement of Edward R. Reines
2004	Tam P. et al., *Stabilized Plasmid-Lipid Particles for Systemic Gene Therapy* 7 GENE THERAPY 1867-1874 (2000)
2005	Huang L. et al., *Liposomal Gene Delivery: A Complex Package* 15 NATURE BIOTECHNOLOGY 620-621 (1997)
2006	Pak C.C., Erukulla R.K., Ahl, P.L., Janoff, A.S. and Meers, P., *Elastase-Activated Liposomal Delivery to Nucleated Cells*. 1419 BIOCHIM. BIOPHY. ACTA 111-126 (1999)
2007	U.S. Patent No. 7,491,409
2008	Transcript of October 2, 2018 Conference Call
2009	Declaration of David H. Thompson, Ph.D.
2010	*Curriculum Vitae* of David H. Thompson, Ph.D.
2011	Charles W. Schmidt, *Therapeutic Interference: Small RNA Molecules Act as Blockers of Disease Metabolism* AM. CHEM. SOC'Y 37 (2003)

2012	C. Russell Middaugh & Joshua D. Ramsey, *Analysis of Cationic-Lipid-Plasmid-DNA Complexes*, ANALYTICAL CHEMISTRY 7240 (2007)
2013	*Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation, Guidance for Industry*, FOOD AND DRUG ADMINISTRATION (2018)
2014	Erika Check, *RNA to the Rescue?* 425 NATURE 10 (2003)
2015	Dirk Hausseker, *The Business of RNAi Therapeutics in 2012*, 2 AM. SOC'Y OF GENE & CELL THERAPY (2012)
2016	Luke Timmerman, *Merck's Alan Sachs, on RNAi's Big Challenge: Delivery, Delivery, Delivery*, XCONOMY (Jan. 21, 2010), https://xconomy.com/national/2010/01/21/mercks-alan-sachs-on-rnais-big-challenge-delivery-delivery-delivery/
2017	U.S. Patent No. 8,236,943
2018	U.S. Publication No. 2013/0116307
2019	U.S. Publication No 2017/0307608
2020	Combined Declaration for Patent Application and Power of Attorney in U.S. Patent Application No. 90/914,615.
2021	Sean C. Semple, et al., *Rational Design of Cationic Lipids for siRNA Delivery*, 28 NATURE BIOTECH. 172 (2010)
2022	Supplementary Figures to Sean C. Semple, et al., *Rational Design of Cationic Lipids for siRNA Delivery*, 28 NATURE BIOTECH. 172 (2010)
2023	Heidi Ledford, *Gene-Silencing Drug Approved: US Government Okays First RNA-Interference Drug — After a 20-Year Wait* 560 NATURE 291 (2018)

2024	*FDA Approves First-of-its Kind Targeted RNA-based Therapy to Treat a Rare Disease*, FOOD AND DRUG ADMIN. (2018), https://www.fda.gov/newsevents/newsroom /pressannouncements/ucm616518.htm
2025	*New Medicine for Hereditary Rare Disease,* EUROPEAN MED. AGENCY (2018), https://www.ema.europa.eu/en/news/new-medicine-hereditary-rare-disease
2026	*Arbutus' LNP Licensee Alnylam Announces FDA Approval of ONPATTRO™ (patisiran), for the Treatment of ATTR Amyloidosis*, ARBUTUS BIOPHARMA (2018), https://investor. arbutusbio.com/news-releases/news-release-details/arbutus-lnp-licensee-alnylam-announces-fda-approval-onpattrotm
2027	Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, *Patent and Exclusivity for: N210922*, FOOD AND DRUG ADMIN. *available at* https://www.accessdata. fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001& Appl_No=210922&Appl_type=N (last visited Dec. 19, 2018)
2028	Deposition Transcript of Andrew S. Janoff, December 4, 2018
2029	U.S. Patent No. 9,404,127
2030	Intentionally Left Blank
2031	Intentionally Left Blank
2032	Ian MacLachlan & Pieter Cullis, *Diffusible-PEG-Lipid Stabilized Pasmid Lipid Particles*, 53 ADVANCES IN GENETICS 157 (2005)
2033	Sean C. Semple et al., *Immunogenicity and Rapid Blood Clearance of Liposomes Containing Polyethylene Glycol-Lipid Conjugates and Nucleic Acid*, 312 THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 1020 (2005)

2034	Doxil Label – FDA (Revised May, 2007), https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050718s029lbl.pdf
2035-2039	Intentionally Left Blank
2040	Declaration of David H. Thompson, Ph.D. in Support of Patent Owner's Contingent Motion to Amend
2041	U.S. Provisional Patent Application Number 61/045,228
2042	U.S. Patent Application Number 12/424,367
2043	U.S. Patent Application Number 13/253,917
2044	U.S. Patent Application Number 13/928,309
2045	U.S. Patent Application Number 14/462,441
2046	Listing of Example Formulations Falling Within the Scope of the '435 Patent Claims
2047	International Publication No. WO 2010/088537
2048	Maja Sedic et al., *Safety Evaluation of Lipid Nanoparticle-Formulated Modified mRNA in the Sprague-Dawley Rat and Cynomolgus Monkey*, VETERINARY PATHOLOGY (2017)
2049	International Publication No. WO 2013/090648
2050	Kapil Bahl et al., *Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses*, MOLECULAR THERAPY (2017)
2051	International Publication No. WO 2017/223135
2052	International Publication No. WO 2018/232357
2053	Intentionally Left Blank
2054	Intentionally Left Blank
2055	Deposition Transcript of Andrew S. Janoff, April 15, 2019

2056	April 2, 2019 Email from Trials

CERTIFICATE OF SERVICE

This is to certify that I caused to be served a true and correct copies of the foregoing Patent Owner's Sur-Reply and Exhibits 2046-2056, on this 17th day of April, 2019, on the Petitioner at the correspondence address of the Petitioner as follows:

Michael Fleming
C. Maclain Wells
IRELL & MANELLA LLP
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Respectfully submitted,

Date: April 17, 2019

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

JOINT APPENDIX 80

Summary of Molar Ratio Patents

Patent No. (**Abbreviation**)	Patent App. Filing Date	Patent Issue Date	IPR Proceeding **(Abbreviation)**	IPR Appeal **(Abbreviation)**
8,058,069 **'069 Patent**	Apr. 15, 2009	Nov. 15, 2011	IPR2019-00554 **'069 IPR**	*ModernaTX, Inc. v. Arbutus Biopharma Corp.*, Case No. 2020-2329 (Fed. Cir.) **'069 Appeal**
8,492,359 **'359 Patent**	Oct. 5, 2011	Jul. 23, 2013	None	None
8,822,668 **'668 Patent**	Jun. 26, 2013	Sept. 2, 2014	None	None
9,364,435 **'435 Patent**	Aug. 18, 2014	Jun. 14, 2016	IPR2018-00739 **'435 IPR**	*ModernaTX, Inc. v. Arbutus Biopharma Corp.*, Case Nos. 2020-1184, 2020-1186 (Fed. Cir.) **'435 Appeal**
11,141,378 **'378 Patent**	Apr. 12, 2021	Oct. 12, 2021	None	None

JOINT APPENDIX 81

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JOINT APPENDIX 82

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

Moderna Therapeutics, Inc.

Petitioner

v.

Protiva Biotherapeutics, Inc.

Patent Owner

_____

Case No. IPR2019-00554
U.S. Patent No. 8,058,069

_____

PETITIONER'S REPLY TO PROTIVA'S RESPONSE

Mail Stop: PATENT BOARD
Patent Trial and Appeal Board
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

LIST OF EXHIBITS RELIED UPON IN THE REPLY

Exhibit No.	References
1020	Declaration of Thomas J. Anchordoquy, Ph.D. iso Petitioner's Reply to Protiva's Response ("Anchodoquy")
1021	Curriculum Vitae of Thomas J. Anchordoquy
1022	Final Written Decision in IPR2018-00739, Paper 51, Entered September 11, 2019
1023	Onpattro Labeling, Application No. 210922Orig1s000
1024	Ian MacLachlin, Liposomal Formulations for Nucleic Acid Delivery (2007)
1025	Deposition of David H. Thompson, Ph.D. taken January 15, 2020
1026	Akinc *et. al.*, Onpattro story and clinical translation of nanomedicines containing nucleic acid-based drugs, Nature Nanotechnology, Vol. 14, Dec. 2019, pp. 1084-1087
1027	Zimmerman *et. al.*, RNAi-mediated gene silencing in non-human primates, 2006 Nature Publishing Group
1028	U.S. Patent No. 7,799,565 issued to MacLachlan, Sept. 21, 2010

I. INTRODUCTION

The Board ordered an IPR over the'069 patent with respect to grounds 1-3 for claims 1-22. In response, Patent Owner Protiva relies upon the mistaken premises that (1) the prior art references do not teach overlapping ranges for the phospholipid component (Response, 12-18) and (2) the disclosed ranges are too broad to support routine optimization (*id.*, 19-30). Both are demonstrably false. First, Protiva's expert admits that the cited references disclose an overlapping phospholipid range and actual prior art testing demonstrating phospholipid concentrations overlapping with the claimed range. Second, Protiva's own prior test data confirms the regular practice in the field of optimizing lipid concentrations and provides a starting point for such routine optimization.

Protiva relies heavily on its expert's belief that all the "cationic lipids should be minimized" because of toxicity concerns. Response, 29. This oversimplification evinces Protiva's expert's inexperience with lipid carrier particles. It was well known years before the '069 patent that ionizable cationic lipids can be used in high amounts to create particles that are substantially non-toxic. *See, e.g.*, EX1004, [0151].

Faced with prior disclosures of particle formulations with overlapping ranges for all claimed lipid components rendering the claims *prima facie* obvious, Protiva seeks to cloud the matter as much as possible. For example, Protiva points to the

therapeutic Patisiran (tradename—Onpattro) as alleged support for secondary considerations of non-obviousness, but fails to inform the Board that the actual commercial product ***does not use the claimed lipid ranges***. Protiva cannot rebut Petitioner's obviousness showing by ignoring express disclosures in the prior art, denying comparable teachings, importing limitations into the claims, mischaracterizing test data, and making demonstrably false assertions.

II. PROTIVA'S EXPERT HAS MINIMAL EXPERIENCE WITH CATIONIC LIPIDS

Protiva's expert, Dr. Thompson, researches carrier molecules using polymers, not lipids. EX2005, 21:9-25 ("…we make stabilized nucleic acid particles, but they're not lipid particles. We make them out of polymers."). His experience with SNALPs is limited to using them as benchmarks in research. *Id.*, 46:3-10, 49:11-17. He admits that he has not worked with ionizable cationic lipids, like DLinDMA, used in the '069 patent. *Id.*, 74:20-75:13. In its Final Determination in the related '435 patent IPR, the Board repeatedly discounted Dr. Thompson's opinions: "…we find Dr. Thompson's opinion…is speculative and thus, not accorded weight." EX1022, 24. Here, Dr. Thompson's opinions are again unsupported and counter to the prevailing wisdom in the field.

As an example, Dr. Thompson identifies Onpattro as a commercial embodiment of the '069 patent. EX2031, ¶¶117-118, 134-136. He relies on a 2014 patent for the alleged lipid formulation (EX2012) instead of the 2018 FDA approved

label for the product (EX1023). The FDA label, however, shows that a different formulation is actually used that does not practice the claims. Anchordoquy,[1] ¶¶139-142.

III. CLAIM CONSTRUCTION

The Board's prior construction of "nucleic acid-lipid particle" as "a particle that comprises a nucleic acid and lipids, in which the nucleic acid may be encapsulated in the lipid portion of the particle" from the '435 patent IPR is appropriate and Petitioner agrees therewith. EX1008, ¶88; Anchordoquy, ¶¶27-29. Dr. Anchordoquy agrees with Dr. Janoff that a POSITA would adopt this construction using the appropriate standard in light of the intrinsic record. *Id.,* citing EX1001, 11:4-12.

To avoid prior art, Protiva seeks to import limitations arguing that the claims "necessarily including a nucleic acid ***encapsulated in the lipid portion*** of the particle,[2] thereby protecting it from enzymatic degradation." Response, 9. The Board soundly rejected this argument previously. EX1022, 11-13 ("Dr. Thompson attempts to shoehorn the statement that nucleic acids…."). Moreover, it conflicts with the '069 patent's disclosure of "…delivery of ***associated or encapsulated*** therapeutic agents…." EX1001, 6:20-23. Encapsulation is just one means of preventing

[1] Petitioner's prior expert, Dr. Janoff, passed away in December 2019 and Dr. Anchordoquy has thus been engaged.
[2] All emphasis added unless otherwise noted.

degradation. Anchordoquy, ¶¶29-35. Other options include chemical modification of the payload to resist degradation. EX1001, 44:33-35 (chemical modification); *see also* EX1005, ¶20 ("…use of chemically-modified siNA … [has] increased resistance to nuclease degradation….").

Protiva also attempts to narrow the term to exclude lipoplexes addressed in Lin (EX1006) and Ahmad (EX1007). Response, 5; EX2031, ¶111. But a POSITA would understand that lipoplex and liposomal structures existed at the time of the '069 patent that can meet the claim limitations. Anchordoquy, ¶¶36-41, 87-91. Indeed, the '189 publication, also directed at SNALPs, specifically identifies liposomes and lipoplexes as "…alternative lipid-based carrier systems suitable for use with the present [SNALP] invention…." EX1004, [0149].

IV. THE INSTITUTED GROUNDS

Protiva relies on arguments directed at the claimed range for the phospholipid and cholesterol components. Response, 14, 17. Protiva fails, however, to demonstrate "that there is something special or critical about the claimed range" for these components. *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1341 (Fed. Cir. 2020). For example, there is no evidence that 11mol% phospholipid or 41mol% cholesterol, as opposed to points in the claimed ranges, would have any impact on the particle efficacy. Anchordoquy, ¶43.

A. AN OVERLAPPING PHOSPHOLIPID RANGE IS DISCLOSED

Even if the phospholipid range is considered, the Board's initial determination that EXS1003-1005 disclose overlapping ranges for each lipid component is correct. Initial Determination ("ID"), 16-18, 22-24, 34-37; Anchordoquy, ¶¶44-50. Protiva does not dispute that each reference discloses a non-cationic/neutral lipid range of 5-90mol% (*see* EX1003, [0091], EX1004, [0152]; EX1005, [0313]) or that a phospholipid is one of the disclosed species of non-cationic/neutral lipids (EX1003, [0089]; EX1004, [0159]; EX1005, [0455]). During prosecution, the patentee admitted that the same disclosures in Protiva's prior '910 publication (EX1015, ¶85) provides a phospholipid range of 5-90mol% confirming that a POSITA would be put on notice of an overlapping phospholipid range. EX1016, 5-6.

Protiva argues that there is no "*express* disclosure of a phospholipid range" (Response, 6; EX2031, ¶39)[3]—that is irrelevant. The applicable legal standard is what a "POSITA reading [the reference] would understand." *See IXI IP, LLC v. Samsung Elecs. Co., Ltd.*, 903 F.3d 1257, 1264-1265 (Fed. Cir. 2018) (rejecting arguments based upon lack of an "express disclosure"). At deposition, Protiva's expert agreed that a POSITA would understand from the above disclosures that a

[3] The Board in the '435 patent IPR similarly focused on the lack of a "*specific* range for the amount of phospholipid." EX1022, 31.

phospholipid range is disclosed. EX1025, 167:10-22 ("…this is a range that is of composition 5mol% and 90mol% of any number of different phospholipids that are recited here.").

B. THE SAME FOUR LIPID-COMPONENT CARRIER PARTICLES ARE DISCLOSED

Carrier particles comprising the exact same four lipid components in the '069 patent claims (*i.e.,* cationic lipid, phospholipid, cholesterol, and conjugated lipid) are expressly disclosed in the working examples of each prior art reference. EX1004, [0369]; EX1003, [0223]; EX1005, Table IV (L051, L053, L054, L069, L077, L080, L082, L083, L109), Anchordoquy, ¶¶51-55. Protiva's expert admits that such working examples would help inform a POSITA. EX1025, 110:1-8. Yet, Protiva completely ignores these working examples in arguing that the Petition only addresses "the individual lipid components" as opposed to the particles as a whole. Response, 27; EX2031, ¶73.

For example, the '189 publication discloses effective transfection using the closest prior art—a carrier particle with the formulation 40/10/48/2 (cationic lipid/phospholipid/cholesterol/conjugated lipid) ("2:40 formulation") that uses the same basic species for each lipid component[4] to carry the same nucleic acid

[4] DPPC is used instead of DSPC in the '069 patent testing, but Protiva's expert acknowledges that the two phospholipids would behave similarly. EX2031, ¶102; EX2005, 158:20-159:4 ("I don't think it's going to have that much of an impact.").

payload as tested in the '069 patent. Compare, *e.g.*, EX1004 (Examples 13-17) with EX1001 (Examples 2-3); Anchordoquy, ¶¶51-55. This reference thus expressly spells out the lipid components combined as in the '069 patent claims. EX1025, 115:7-21 (Protiva's expert admitting same four-lipid component particle described).[5]

C. ROUTINE OPTIMIZATION OF LIPID-CARRIER PARTICLES

As the Board noted, "it has long been recognized that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." ID, 24 citing *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (internal quotations omitted). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012). The Board's determination that "in view of the high level of ordinary skill in the art…optimization of the ranges of components to achieve the claimed composition would be the 'normal desire of scientists or artisans to improve upon what is already generally known'" (ID, 25) is correct. Given the defined efficacious prior art systems discussed above (*e.g.*, the 2:40 formulation in

[5] Protiva also argues that "the prior art is not limited to a formulation requiring a phospholipid." Response, 26; EX2031, ¶41. There is no such legal requirement.

EX1004), a POSITA would have used the general conditions of such systems as a starting point and been motivated to optimize the lipid formulations therein. EX1008, ¶108; Anchordoquy, ¶¶56-69.

The intrinsic record establishes that such optimization is routine once the general conditions of the system have been defined. *Id.* The '069 patent states that "[i]t will be readily apparent to one of skill in the art that depending on the intended use of the particles, the proportions of the components can be varied…." EX1001, 49:62-65. Similarly, during prosecution, the examiner concluded that "MacLachlan ['910 publication]…teaches that the proportions of the components can be varied by those of skill in the art. Thus, by routine experimentation towards optimization, one of skill in the art could arrive at the instantly claimed proportions." EX1016, 6 (emphasis added). As Protiva's expert admitted: "[y]ou're trying to vary different proportions to see where the best *in vivo* performance, the best tolerance of ranges are identified." EX1025, 83:19-84:17, 84:3-11 (optimizing phospholipid), 85:3-21 (optimizing cationic lipid).

The prior art similarly establishes that "[i]t will be readily apparent to one of skill in the art that the proportions of the components of the nucleic acid-lipid particles may be varied." EX1004, [0152]; EX1003, [0088] ("…the proportions of the components are varied…."). This is further confirmed by the inventors' publications at the time. EX1024, 251 ("…SNALP formation by ethanol dilution is

optimized by balancing ionic strength, cationic lipid, and PEG lipid content.").

The testing in the '069 patent illustrates just this type of optimization. EX1001, Example 2 (Table 2) below:

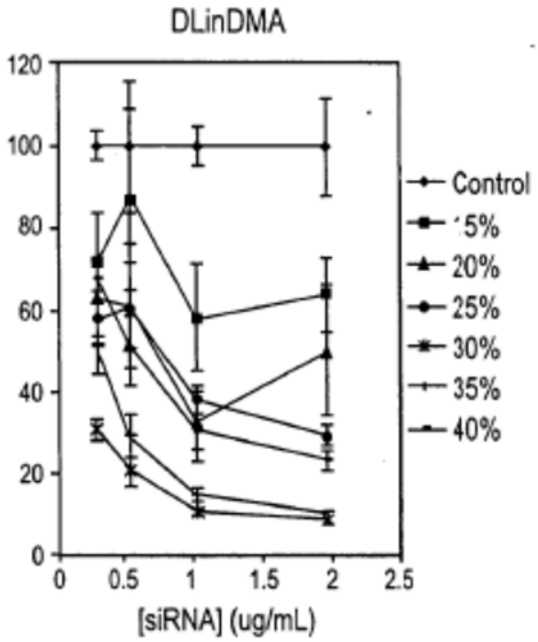
TABLE 2

Characteristics of the SNALP formulations used in this study.

Sample No.	Formulation Composition, Mole % PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol	Lipid/Drug Ratio	Finished Product Characterization		
			Size (nm)	Polydispersity	% Encapsulation
1	2 | 40 | 10 | 48	12.4	57	0.07	90
2	1.8 | 36.4 | 18.2 | 43.6	14.0	72	0.12	89
3	1.4 | 27.0 | 6.8 | 64.9	16.5	70	0.12	92
4	1.3 | 25.3 | 12.7 | 60.8	18.1	76	0.07	93
5	3.9 | 39.2 | 9.8 | 47.1	13.5	53	0.27	86
6	3.6 | 35.7 | 17.9 | 42.9	15.1	58	0.18	87
7	2.7 | 26.7 | 6.7 | 64.0	17.6	56	0.17	92
8	2.5 | 25.0 | 12.5 | 60.0	19.2	61	0.13	92
9	1.4 | 57.1 | 7.1 | 34.3	17.8	84	0.10	88
10	1.3 | 53.3 | 13.3 | 32.0	19.5	83	0.10	89
11	1.1 | 42.6 | 5.3 | 51.1	22.0	80	0.10	93
12	1.0 | 40.4 | 10.1 | 48.5	23.6	78	0.11	88
13	2.8 | 56.3 | 7.0 | 33.8	19.0	62	0.14	80
14	2.6 | 52.6 | 13.2 | 31.6	20.6	66	0.14	82
15	2.1 | 42.1 | 5.3 | 50.5	23.1	71	0.16	91
16	2 | 40 | 10 | 48	24.7	67	0.14	92

As can be seen, the payload and lipid species are defined and the lipid proportions and lipid:drug ratio are varied to optimize the formulation. Anchordoquy, ¶¶61-62.

As another example, Protiva's '910 publication discloses experiments with a SNALP with a siRNA payload with a cationic lipid concentration ranging from 5-40mol%. EX1015, [0335]. As can be seen from Figure 23, increasing concentrations of DLinDMA were tested to determine optimal knockdown levels. Anchordoquy, ¶63.



As another example, EX2014, 15-20 (Tables 1 and 2) illustrates in detail testing of formulations for a wide variety of lipid percentages for each lipid component (*e.g.*, a cationic lipid range of 20-80mol%) to optimize formulations. *See also id.*, 116-120 (discussing optimization based on results); Anchordoquy, ¶64.

Protiva argues that the field involves complex technology and significant unpredictability in particle formulation. Response, 12, 19-24; EX2031, ¶¶59-61. This misses the point. The prior art defines an effective four-lipid carrier particle system for the same payload and with substantively the same lipid species as used in the '069 patent, just with slight differences in lipid concentrations. EX1004 (Examples 13-17); Anchordoquy, ¶¶66-68. A POSITA would not start from scratch, but use the general conditions of this proven systems as a starting point.

Applied Materials, 692 F.3d at 1295.[6]

(1) **OPTIMIZATION OF THE CATIONIC LIPID**

Protiva's focus on the cationic lipid concentration alone evincing a fundamental misunderstanding of lipid carrier particles—what matters is the ***amount*** of cationic lipid, not merely the concentration. Positively charged cationic lipids are added to carrier particles offset the negatively charged nucleic acid phosphate groups (the resulting ratio is called the "N/P ratio"). EX1008, ¶62; EX1025, 111:2-24, 199:1-8, 112:11-16 ("one of the ways that you would increase the charge neutralization [is] to increase the proportion of cationic lipid."); Anchordoquy, ¶¶70-72. The amount of cationic lipid depends not only on the cationic lipid concentration, but also on the lipid:drug ratio.[7] *Id.* For example, if you double the cationic lipid concentration from 25 to 50mol%, but at the same time halve the lipid:drug ratio, there is no net impact on the ***amount*** cationic lipid.

For the 2:40 formulation in EX1004, the N/P ratio was approximately 6. *See* EX1004, [0350]-[0391]; Anchordoquy, ¶73. This N/P ratio is optimized for the siRNA payload and the ionizable cationic lipid used, DLin-DMA. *Id.* The pKa of

[6] Protiva's argument that the Board's determinations regarding obviousness in the '435 patent IPR obviate this issue are misplaced. Response, 4. While the Board found that Petitioner in that IPR had not carried its burden to demonstrate obviousness (*see* EX1022, 36-37), that decision is under appeal and involves different claims, facts and arguments than are at issue here.

[7] N/P ratios are not listed in the '069 patent, but a POSITA can calculate the ratio by using the lipid:drug ratio and the lipid component molar ratios. Anchordoquy, ¶72.

DLinDMA is 6.7. EX1011, 281. At that pKa, one-sixth of the cationic molecules possess a positive charge at physiological pH (*i.e.*, 7.4). Anchordoquy, ¶¶86-87. An N/P ratio of 6 thus fully neutralizes the negative charge on the nucleic acids in serum. *See* EX1004, [0062] (goal to neutralize 90% of the negative charges); EX1027, 3 (2006 publication from inventors using N/P ratio of 6 with DLinDMA).

Consistent with this testing in the '189 publication, in Example 3 of the '069 patent, the 1:57 formulation (Group 11) on which Protiva relies has exactly the same relative ***amount*** of cationic lipid (N/P of 6) as the prior art 2:40 type formulation (Group 12)—and also as the 2:40 formulations used in the '189 publication. Anchordoquy, ¶¶73-76. A POSITA would expect in such similar systems that cationic lipid amounts at similar N/P ratios would behave similarly. *Id.* Having a consistent optimized N/P ratio provides further motivation to increase the cationic lipid concentration while decreasing the lipid:drug ratio accordingly and a basis for expecting the resulting particles to be effective at the higher cationic lipid concentration.[8] *Id.*

Even if one focuses on only the cationic lipid concentration, the prior still demonstrates that a range of 50-65mol% would have been obvious. It is undisputed that each prior art reference discloses a cationic lipid range of 2-60mol%,

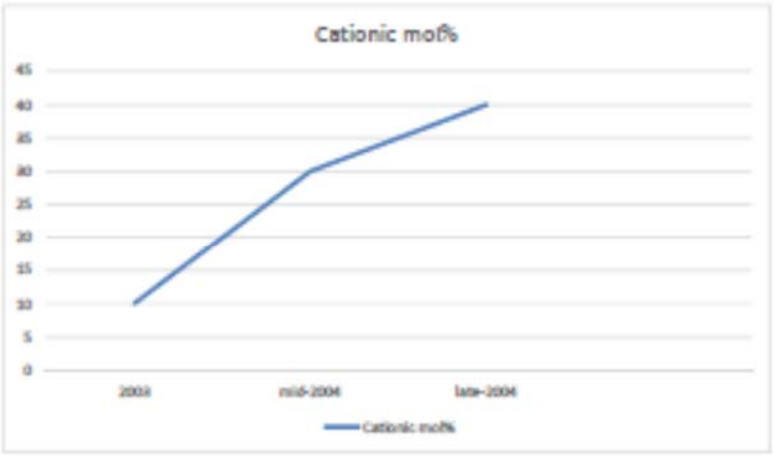
[8] One potential benefit of increasing the cationic lipid concentration while decreasing the lipid:drug ratio (with a constant N/P ratio) is a net decrease in the amount of helper lipids. Anchordoquy, ¶77.

substantially overlapping with the claimed range. *See* EX1003 [0088]; EX1004, [0152]; EX1005 [0313]. Additionally, each reference discloses a narrower range of 40-50mol% that also overlaps. *Id*. A POSITA would have understood from these disclosures potential cationic lipid concentration ranges (including the 50-60mol% portion) for safe, effective lipid-carrier particles. Anchordoquy, ¶¶52-54.

Moreover, a POSITA would have known that an excess of positive charge promotes endosomal release of the payload once a target is reached. EX1008, ¶62; EX1024, 230 ("Cationic lipids also function by providing the liposome with a net positive charge, which in turn enables binding of the NA complex to anionic cell surface molecules."). Protiva's expert himself admits to evaluating ranges of cationic lipid concentrations in titration-like experiments that "were quite high" prior to the '069 patent. EX1025, 41:2-16; *see also* 87:18-88:6 (using 50-65mol% cationic lipid was obvious for *in vitro* use).

The Protiva's prior art disclosures also illustrate a trend toward using higher cationic lipid concentrations. The '196 PCT (2003) discloses testing SNALPs with siRNA in a four-lipid system with lipid percentages of **15**/20/55/10 (**cationic lipid**/phospholipid/ cholesterol/conjugated lipid). EX1003, [0232]. Protiva's U.S. Patent No. 7,799,565 (mid-2004) discloses testing SNALPs with siRNA in a four-lipid component system with lipid percentages of **30**/20/48/2. EX1028, 52:54-53:17. Protiva's '189 publication (late 2004) discloses testing SNALPs with

siRNA in a four-lipid component system with lipid percentages of **40**/10/48/2. EX1004, [0351]-[0385]. Over time, there is thus a consistent increase in cationic lipid concentrations used:



Anchordoquy, ¶¶78-80; *see also* EX1025, 136:20-137:21 (Protiva expert admitting POSITA would consider trend toward higher concentrations), 142:14-143:3 (50mol% cationic lipid was "one of many possible avenues to explore…."). This understanding is confirmed by Protiva's '910 publication which, as discussed above, discloses testing varying the cationic lipid concentration from 5-40mol% and illustrating better performance at higher concentrations. EX1015, [0335], Fig. 23.[9] These disclosures would further motivate a POSITA, using the 2:40 formulation as a starting point, to create particles with a cationic lipid in the

[9] Protiva incorrectly asserts "the 2:30 SNALP formulation contains the greatest amount of cationic lipid of all the SNALP formulations prepared and tested" in the '910 publication. Response, 35.

claimed range with a reasonable expectation of success. Anchordoquy, ¶¶81-82.

Protiva's argument that all cationic lipids are toxic also misses the point. Response, 7; EX2031, ¶¶80-88. First, Protiva again improperly equates the cationic lipid ***concentration*** with the ***amount*** of cationic lipid. Anchordoquy, ¶¶83-84. Second, a POSITA would have been aware that toxicity in lipid particles is largely a function of having a net positive charge in serum (*i.e.*, at physiological pH). *Id.*; EX1025, 62:22-63:14 (Protiva's expert admitting to need to shield charge of cationic lipid). To address potential toxicity issues, years before the '069 patent priority date, ionizable cationic lipids had been developed whose charge was low at physiological pH, but became strongly cationic in the acidified environment of the endosome. Anchordoquy, ¶¶85-88; EX1004 [0223] (using ionizable lipid DLinDMA); EX1011, 280 (same), Fig. 1 (substantially neutral charge at pH 7.4); EX1009, 6 ("Cationic lipids that are charged only at mildly acidic but not at neutral pH … may also be a potential solution to the toxicity issues …."); EX1005, [0462] (same); EX1025, 239-240 (same); EX2021, 173 (neutral particles at physiological pH preferred). This understanding still holds true today: "…such positively charged systems induce pronounced toxicity in vivo due to immune activation…[t]o circumvent this problem, we developed ionizable cationic lipids…." EX1026, 1085.

Consistent with this reasoning, the examples in both the '069 patent and the

prior art demonstrate the use of high cationic lipid concentrations to achieve an optimal N/P ratio of 6 in substantially non-toxic particles. EX1004 [0351-0391] (*in vivo* testing using DLinDMA), [0076, 0151] (particles "substantially non-toxic"); EX1025, 123:16-124:10 (Protiva's expert admitting '189 data indicates no toxicity); 133:20-134:4 (formulation effective and safe); EX1001, Example 3, Table 4 (Groups 11-12).

Protiva's expert admits that cationic lipids are designed to be non-toxic. EX2005, 64:15-65:14 ("Because they're toxic. They are--they tend to be, unless designed properly….") (emphasis added); EX2006, 260:11-18. He also admits that the class of cationic lipids which includes DLinDMA used in the '189 publication was known not to have significant toxicity concerns: "[t]he data that…I've reviewed for this class of cationic lipids has--in vivo has not suggested that there are significant toxicity concerns." *Id.*, 266:18-267:20; *see also id.*, 267:22-268:15 ("known that [DLinDMA] had a low toxicity profile….").

Protiva points to accumulation in the plasma and immunogenicity as alternative sources of toxicity. Response, 29-30; EX2031, ¶86. Protiva has confirmed, however, the lack of such toxicity issues for the 2:40 formulation: "[t]here was no evidence for complement activation, delayed coagulation, pro-inflammatory cytokine production…or changes in hematology parameters…toxicities that have been observed previously with treatments using

related approaches."[10] EX1027, 3; Anchordoquy, ¶¶94-95.

Lin and Ahmad (EXS1006-1007) provide further support that a POSITA would have been motivated to employ greater amounts of cationic lipid. Anchordoquy, ¶¶89-91. The testing therein establishes that for certain cationic lipids, increasing the N/P ratio by elevating the cationic lipid concentrations above 50mol% enhanced transfection efficiency. EX1008, ¶¶102-106.

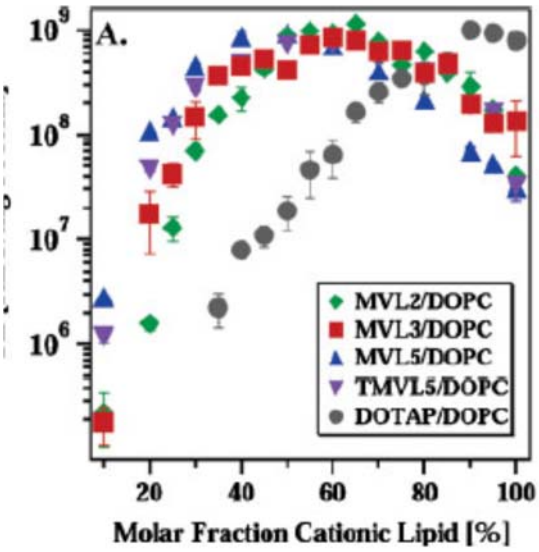
Protiva's arguments that Lin and Ahmad are irrelevant are misplaced. First, as discussed above, the claims of the '069 patent are not limited to non-lipoplex particles. Second, in this field, it was common to look at prior research regarding various types of lipid carrier particles. Anchordoquy, ¶¶36-41. Both of the Protiva's prior art disclosures cite to prior work done on liposomes and lipoplexes. EX1003, [0132], [0175]; EX1004, [0203], [0156] (incorporating '618 patent directed to lipoplexes).

Protiva's argument that Ahmad teaches away from increasing the cationic lipid concentration (Response, 59) is also misplaced. Ahmad specifically noted that *in vitro*, the tested cationic lipid amounts showed "no toxic effects on the cells as judged by cell morphology and the amount of total cellular protein." EX1006, 745-

[10] Protiva also points to Moderna publications stating that toxicity issues with modern cationic lipids can be further minimized. Response, 29-30. That cationic lipids may be further improved does not negate their use at tolerable levels at the time of the '069 patent.

46. In addition, Ahmad utilized multivalent cationic lipids to achieve very high charge densities in order to test their hypothesis, and it was known by a POSITA that such extreme charge densities with multivalent cationic lipids were typically not suitable for *in vivo* use due to their toxicity. Anchordoquy, ¶92.

Protiva also mischaracterizes Ahmad as reaching "saturation" at 50mol% cationic lipid. Response, 58. Ahmad shows no such thing. As can be seen, the monovalent cationic lipids do not level off until about 80mol% (EX1007, Fig. 3):



Anchordoquy, ¶93.

(2) **OPTIMIZATION OF THE CONJUGATED LIPID**

A second lipid typically optimized is the conjugated lipid, *e.g.*, PEG. *See* EX1001, 68:35-48; Anchordoquy, ¶¶96-98. A POSITA would have been motivated to add PEG to carrier particles to provide a neutral, hydrophilic coating to the particle's exterior and thus prevent aggregation. EX1008, ¶64; EX1025, 58:1-13. In

the art, there is a known "PEG dilemma"—including enough PEG to stabilize the particle, but not so much that the particle is unable to engage the target *in vivo*. EX2005, 145:9-23 ("…another factor which is referred to in the literature as the PEG dilemma."). In other words, it was known that the amount of conjugated lipid should be minimized to allow the nucleic acid payload to interact with the target. EX1024, 241. Consistent with this understanding, the '189 publication discloses a low concentration for the conjugated lipid that overlaps with the claimed range. EX1004, [0152] (2mol%).

The formulations tested in the cited prior art similarly have low amounts of PEG coupled with high cationic lipid concentrations. EX1004 [0351-0391] (2:40 formulation in the '189 patent showing *in vivo* efficacy with 2mol% PEG); EX1005, Table IV (L077, L069, L080, L082, L083, L060, L061, and L051 showed efficacy *in vivo* with 2-3mol% PEG). While these specific formulations vary slightly from the claimed ranges, they establish that a POSITA would have been motivated to use PEG in low amounts coupled with high levels of cationic lipid with a reasonable likelihood of success. Anchordoquy, ¶¶99-101.

Protiva's expert points to unrelated systems using 5-10% PEG (EX2031, ¶48), but that is irrelevant. That other systems using higher PEG percentages may have existed does not negate that a POSITA would have been well aware of the examples above, in which lower levels of PEG were used. Anchordoquy, ¶102.

(3) **OPTIMIZATION OF THE CHOLESTEROL**

A POSITA would be motivated to include cholesterol to provide increased rigidity to the particle. EX1008, ¶71; EX1025, 55:5-18; EX1010, 6; Anchordoquy, ¶¶103-105. A POSITA would have been aware that a minimum amount of cholesterol was thought to be required to saturate the lipid mixtures and to provide stability (*e.g.*, in the 20-25mol% range). *Id.* A POSITA would also have been aware of the risk of cholesterol precipitating out of solution if too much was used. *Id.*; EX1025, 92:4-19. Upper limits of 40-55% were thus commonly implemented.

Each reference discloses that cholesterol, when present, is in a certain range consistent with these understandings. EX1003, [0091] (20-45mol%); EX1004, [0152] (20-55mol%); EX1005, [0311] (20-45mol%). In addition, each prior art reference discloses the four lipid component particles that are effective *in vivo* which contain cholesterol in the disclosed ranges. *See, e.g.,* EX1004, [0289], [0369] (48% cholesterol); EX1003, [0223] (20mol% cholesterol); EX1005, Table IV (L051, L053, L054, L069, L077, L080, L082, L083, L109) (10-48mol% cholesterol). The claimed range of 30-40mol% cholesterol is squarely within the generally acceptable ranges in the field. Anchordoquy, ¶106. Given the prior art disclosures, it would have been obvious to a POSITA to include cholesterol in carrier particle formulations in the claimed range with a likelihood of success. *Id.*

(4) **OPTIMIZATION OF THE PHOSPHOLIPID**

A POSITA at the time of the '069 patent would have been motivated to include a phospholipid as a bilayer stabilizing component. Anchordoquy, ¶¶107-109; EX1025, 28:8-22 (known to add to "stabilize complex"). As discussed in the '554 publication, it was desirable to design delivery systems to maintain the bilayer structure for stability in the blood, but to transition to the fusogenic structure inside the target cell. EX1005, [0137]; EX1024, 239-240. This balance required the use of components that served to promote the bilayer structure, and a POSITA would have understood that most phospholipids (including DSPC, DPPC) would serve this purpose. Anchordoquy, ¶109. As with the conjugated lipid, a POSITA would have been aware that having some amount of phospholipid can provide structural stability to the resulting particles, but having too much will inhibit release of the payload upon contact with the endosome. *Id.*

As discussed above, each reference discloses a range of 5-90mol% for the phospholipid. While these ranges are broad at first blush, each reference also specifically discloses using phospholipids with cholesterol. EX1003, [0158] ("The method is especially useful for vesicles made from phospholipids (which can contain cholesterol)…."); EX1004, [0238] (same); EX1005, [0499] (same). As Protiva acknowledges, "the concentrations of different lipid components are highly interdependent." Response, 28. When cholesterol is added to the mix, the range of

the phospholipid must be decreased accordingly. Anchordoquy, ¶¶53-54; EX1025, 110:1-8.

Protiva argues that the disclosed non-cationic range is too broad for optimization. Response, 3. Protiva completely ignores the working examples in the '189 publication in which the four lipid component particles tested included 10mol% phospholipid (within the claimed range). *See, e.g.*, EX1004, [0369]. Moreover, a POSITA would have been motivated to test phospholipid concentrations at the lower end of the disclosed ranges to avoid inhibiting release of the payload upon contact with the endosome. Anchordoquy, ¶109. Given the demonstrated efficacy of the 2:40 formulation tested in the '189 publication, a reasonable likelihood of success also existed. *Id.*

D. DEPENDENT CLAIMS

Many of the dependent claims recite slightly narrower ranges for the lipid components (claims 8/15/20/21), as with claim 1, these narrower ranges are *prima facie* obvious and the state of the art supports routine optimization. Anchordoquy, ¶¶110, 113, 118-119.

Claim 14, recites specific lipid concentrations, but includes the term "about"—which implicates a range. While Protiva argues that "this claim is drawn to a 1:57 particle" (Response, 61), during prosecution, the examiner stated in this context that "'comprising about' could embrace an amount ±10, 20, 30mol% of a

lipid component." EX1016, 5/12/11 Rejection, 2. This would result in ranges far wider than those addressed above for the independent claims and, regardless, the same obviousness reasoning applies. Anchordoquy, ¶¶111-112.

Claims 16 and 17 address degradation resistance and encapsulation, which is disclosed in the prior art. EX1008, ¶¶136-137, 175-176; Anchordoquy, ¶¶114-116. Fully encapsulated is defined as being "not significantly degraded" in serum. EX1001, 22:63-23:6. Protiva's own prior publication regarding the 2:40 formulation confirm no substantial degradation: "[n]ucleic acid encapsulation efficiencies were 92-97%". EX1027, 2-3.

Claim 18 specifies a lipid:nucleic acid mass ratio of from about 5 to about 15. The prior art discloses "the nucleic acid to lipid ratios (mass/mass ratios) in a formed nucleic acid-lipid particle will range from…about 0.01 to about 0.08." EX1004, [0198]; EX1003, [0127] (same); EX1005, [0167], [0468] (same). A nucleic acid:lipid ratio of 0.08 is equivalent to a lipid:nucleic acid ratio of 12.5 squarely within the range and optimization of the mass ratios would be obvious given the impact on the N/P ratio. Anchordoquy, ¶117.

Claim 22 specifies a "pharmaceutical composition comprising a nucleic acid-lipid particle of claim 1 and a pharmaceutically acceptable carrier." Protiva does not dispute that the payloads in the prior art were typically siRNA and "pharmaceutically acceptable carriers" like saline were common. EX1008, ¶183; EX1005, [502];

EX1004, 242 (same); EX1003, [0175]. Anchordoquy, ¶120.

V. SECONDARY CONSIDERATIONS CANNOT OVERCOME PETITIONER'S OBVIOUSNESS SHOWING

Protiva's alleged secondary considerations of non-obviousness, including unexpected results, long felt need, failures of others, and commercial success, lack the required nexus and do not support Protiva's arguments. "[S]econdary considerations of nonobviousness...simply cannot overcome a strong prima facie case of obviousness" as is found here. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). Moreover, "[f]or objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *Id.* (quotation omitted). "If commercial success is due to an element in the prior art, no nexus exists." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) Such evidence must also be reasonably commensurate in scope with the claims. *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990).

A. THE TEST DATA IS NOT COMMENSURATE WITH CLAIM SCOPE

Protiva relies on test data that covers only a small portion of the potential numeric ranges in the claims, and an even smaller portion of the potential lipid components and payloads. EX1008, ¶¶81-87. All experts agree that changes to the payload, identity of lipid components, or production techniques can impact efficacy. EX2001, 182:12-20 (Protiva's expert admitting physical properties of particles are

dependent on lipid compositions and ratios); EX2006, 231:23-232:10 ("…does the composition affect transition-pardon me, transfection performance. And the answer is yes."), 259:20-260:18 (production technique impacts efficacy), 393:21-394:24 ("…it's a different molecule [cationic lipid]. So you would expect that it may have different behavior."); EX2005, 29:7-15 (payload "one of a host of factors that can impact--performance."), 36:8-37:4 (same), 59:22-60:7 (phospholipid identity impacts efficacy), 156:18-157:4 ("…the conjugate lipid can impact the particle performance. That's what the data show.").

The '069 patent test data compares only a single data point, the 1:57 formulation, to the closest prior art 2:40 formulation. *See* EX1001, Fig. 2. Protiva's own expert admits "an ordinary artisan would not understand a single formulation as defining a range for the lipid component." EX1025, 173:4-174:1; EX2005, 188:8-20 (range changes impact efficacy: "I'm much less confident that–of what the outcome would be [changing lipid component by 5%]."); Anchordoquy, ¶121. Moreover, the claims cover all lipid species for the identified genus—given the limited subset of payloads, lipid components, and production techniques tested, there is no reason to believe the 1:57 test data would apply to all other claimed particle formulations.

B. TEST DATA DOES NOT SHOW UNEXPECTED RESULTS

Protiva also mischaracterizes the testing in the '069 patent. Regarding Figure

1, the prior art 2:40-type SNALP (Sample 12) possess the same efficacy as the 1:57 SNALP. EX1001, Fig. 1B. Protiva's assertion that the data illustrate increased potency (Response, 33-34) is not supported. Anchordoquy, ¶122.

Protiva's arguments regarding Example 3 of the '069 patent are equally unsupported. Response, 4-5. As discussed above, Groups 11-12 in Figure 2 are the only two samples tested at a N/P ratio of 6. That such samples outperform the other samples formulated at a N/P ratio of 3 would have been expected when using an ionizable cationic lipid. Anchordoquy, ¶¶123-124. Protiva argues that Sample 12 may have performed marginally better than Sample 11. Response, 43; EX2031, ¶100; EX1025, 102:20-8. (Groups 11 and 12 "very close"). But, at the very least, the data indicates that the samples behave similarly—not surprisingly.

Protiva improperly relies on testing in Example 4 regarding the prior art 2:30 formulation. Response, 35. The 2:30 formulation is not the closest cited prior art. Protiva's expert argues that he expects the 2:30 and 2:40 formulations to behave comparably (EX1025, 183:23-191:10), but he bases his opinions on data from two separate tests involving different dosing regimes, different lipid species and different durations. EX1004, [0326]-[0333], [0360]-[0367]. Given this variability, drawing such parallels is not scientifically appropriate. Anchordoquy, ¶¶126-128. Even if you could make such a comparison, the different dosing regimes used between samples in Example 4 alone, without dose response data, makes Protiva's conclusions

improper. *Id*.

Unable to show unexpected results, Protiva points to other experiments in the '069 patent (Response, 35-37) and data post-dating the '069 patent (Response, 37-42; EX2008) to argue that the bar for unexpected results should be any apparent efficacy. Response, 32 (expect "little, if any, efficacy"); EX2004, ¶¶66-67. This is not the law. When evaluating unexpected results, "the results must be shown to be unexpected compared with the closest prior art." *In re Baxter-Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991). In addition, (1) this argument is premised upon the same erroneous assertion above that a POSITA would have assumed high levels of cationic lipids to be too toxic to show any efficacy and (2) even if considered, the data is still not commensurate with the scope of the claims. Anchordoquy, ¶¶129-134. Protiva also fails to inform the Board that this testing showed that several formulations falling within the scope of the claims did not perform any better than the PBS standard. EX2006, 401:6-21 (Protiva's expert admitting other cationic lipids using 1:57 formulation "have similar knockdown levels as--as PBS."), 393:21-394:24; EX2010, Fig. 2; EX2011, Fig. 3; EX2011, Fig. 3.

C. OTHER SECONDARY CONSIDERATIONS LACK THE REQUIRED NEXUS OR ARE ATTRIBUTABLE TO THE PRIOR ART

Protiva cites to articles from 2003 for long felt need. Response, 45-46; EX2016, EX2018. Protiva also cites to a 2012 article detailing lipid nanoparticles investments in the early 2000s that discusses "a seminal paper on systemic small

interfering RNA (siRNA) delivery" that changed the industry. EX2019, n.5. This 2006 paper, authored by the named inventors on the '069 patent, details experiments done with the prior art 2:40 formulation. EX1027, 3.

Protiva also erroneously points to a "$2.5-3.5 billion in investment" (Response, 45), but that investment related to the therapeutic siRNA, not just lipid-carrier particles. Anchordoquy, ¶¶135-137. Protiva also points to its "500 person-years and $200M" investments in "SNALP technology." Response, 46. But, a significant portion of the investment could be attributable to the work leading to the Protiva's prior art SNALP disclosures (e.g., EX1003-1004, EX1011). As another example, Protiva points to Roche switching to "[Protiva's] SNALP liposome." EX2019, 10. But there is no indication that Roche used the SNALPs of the '069 patent as opposed to prior art systems.

Regarding failure of others and skepticism, Protiva repeats its mistaken mantra that toxicity favored teaching away. Response, 47; Anchordoquy, ¶138. Protiva ignores that prior art cationic lipids were developed that were substantially non-toxic, *e.g.*, DLinDMA, and that these ionizable cationic lipid were used extensively *in vivo* in high amounts. EX1004, [0351]-[0391].

For commercial success, Protiva points to the commercial release of Onpattro. Response, 49-50; Anchordoquy, ¶¶139-141. The commercial product does not use the claimed lipid ranges. *Id.*; EX1023. Moreover, the developers of Onpattro identify

the development of the second-generation cationic lipid DLin-MC3-DMA as the relevant breakthrough: "[a] first breakthrough was reached with the development of the ionizable lipid DLinKC2DMA." EX1026, 1085.

Given the lack of sufficient nexus to the claimed ranges and scope of the prior art, a POSITA would consider Protiva's evidence of non-obviousness to be insufficient to overcome the strong obviousness showing. Anchordoquy, ¶142.

Dated: March 2, 2020

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24(d), I certify that the present paper contains 5,586 as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, table of exhibits, mandatory notices, certificate of service, or this certificate of word count.

Dated: March 2, 2020

/Michael R. Fleming/
Michael R. Fleming

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. section 42.6, that on March 2, 2020, a complete copy of the **PETITIONER'S REPLY TO PROTIVA'S RESPONSE** and **EXHIBITS 1020-1028** are being served via electronic mail upon the following:

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JOINT APPENDIX 83

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Moderna Therapeutics, Inc.

Petitioner

v.

Arbutus Biopharma Corporation

Patent Owner

U.S. Patent No. 8,058,069

Issued: November 15, 2011

Named Inventors: Edward Yaworski, Kieu Lam, Lloyd Jeffs, Lorne Palmer, Ian MacLachlan

Title: Lipid Formulations for Nucleic Acid Delivery

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,058,069

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LIST OF EVIDENCE AND EXHIBITS RELIED UPON IN THE PETITION

Exhibit No.	Reference
1001	U.S. Patent No. 8,058,069 ("'069 patent")
1002	U.S. Patent No. 9,364,435 ("'435 patent")
1003	International Publication No. WO 2005/007196 ("'196 PCT")
1004	U.S. Publication No. US2006/0134189 ("'189 publication")
1005	U.S. Publication No. US2006/0240554 ("'554 publication")
1006	Lin, Alison J. et al., *Three-Dimensional Imaging of Lipid Gene-Carriers: Membrane Charge Density Controls Universal Transfection Behavior in Lamellar Cationic Liposome-DNA Complexes*, 84 BIOPHYSICAL JOURNAL, 3307–16 (2003) ("Lin")
1007	Ahmad, Ayesha et al., *New multivalent cationic lipids reveal bell curve for transfection efficiency versus membrane charge density: lipid-DNA complexes for gene delivery*, 7 J GENE MED 739–48 (2005) ("Ahmad")
1008	Declaration of Dr. Andrew S. Janoff
1009	Gao, Xiang et al., *Nonviral Gene Delivery: What We Know and What Is Next*, 9 AAPS JOURNAL Article 9, pp. E92-E104 (2007) ("Gao")
1010	Bennett, Michael J. et al., *Cholesterol Enhances Cationic Liposome-Mediated DNA Transfection of Human Respiratory Epithelial Cells*, 15 Bioscience Reports, pp. 47-53 (1995) ("Bennett")
1011	Heyes, James et al., *Cationic lipid saturation influences intracellular delivery of encapsulated nucleic acids*, 107 JOURNAL OF CONTROLLED RELEASE 276–87 (2005) ("Heyes")
1012	U.S. Patent No. 5,753,613 ("'613 patent")
1013	U.S. Patent No. 7,939,505 ("'505 patent")
1014	U.S. Publication No. US2007/0042031 ("'031 publication")
1015	U.S. Publication No. US2006/0008910 ("'910 publication")
1016	Excerpts from '069 Patent File History
1017	U.S. Patent No. 5,264,618 ("'618 patent")
1018	Curriculum Vitae of Dr. Andrew S. Janoff
1019	Kauffman, Kevin J. et al., *Optimization of Lipid Nanoparticle Formulations for mRNA Delivery in Vivo with Fractional Factorial and Definitive Screening Designs*, NANO LETTERS (2015) ("Kaufman")

In accordance with 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42.100 *et seq*., Moderna Therapeutics, Inc. ("Petitioner") respectfully requests that the Board institute *inter partes* review and cancel claims 1–22 of U.S. Patent 8,058,069 ("'069 patent") (Ex. 1001).

I. INTRODUCTION

The Board has already instituted *inter partes* review of the direct descendant of the '069 patent, U.S. Patent No. 9,364,435 ("'435 patent") (Ex. 1002), in IPR2018-00739. The claims of both patents are directed to a composition of nucleic acid-lipid particles (*e.g.*, particles that can be used to deliver therapeutic nucleic acid payloads to a patient) comprising four lipid components (*i.e.*, cationic lipid, phospholipid, cholesterol and conjugated lipid), each of which fall within a claimed proportion with regard to the total lipid in the particles. *See, e.g.*, Ex. 1001, cl. 1; Ex. 1002, cl. 1. The single independent claim in each of the two patents differ in the claimed proportion of cationic lipid (50%-65% for the '069 patent; 50%-85% for the'435 patent) and a corresponding change to the amount of non-cationic lipid.[1] *Id.* As with the '435 patent, the overlapping and encompassing ranges for the lipid components are disclosed in the prior art anticipating or rending obvious the claims of the '069 patent.

[1] The '069 patent also delineates two types of non-cationic lipids.

The'069 and '435 patents belong to one iteration of unrelated patent families prosecuted by Arbutus Biopharma Corporation, some of which date back to the early 2000s, that disclose substantially the same nucleic acid-lipid particles with only trivial differences in claim scope. By obtaining overlapping claims in these unrelated patent families, Patent Owner has improperly extended its patent protection. Patent Owner is using these patent families, including the '069 patent, to improperly block the public and industry participants from using basic combinations of nucleic acid-lipid particle components explicitly described long before the '069 patent's priority date.

For example, Patent Owner's own disclosures in PCT Application No. PCT/CA2004/001051, Publication No. WO2005/007196 A2 ("'196 PCT") (Ex. 1003) and U.S. Patent Publication No. US2006/0134189 ("'189 publication") (Ex. 1004), and other prior art, including US Patent Publication No. 2006/0240554 A1 ("'554 publication") (Ex. 1005), show that the claimed composition of lipid components was available well before the priority date of the '069 patent. These references disclose overlapping and encompassing ranges for each of the four lipid components with sufficient specificity to anticipate.

Moreover, the disclosure of overlapping ranges for the four lipid components demonstrates a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("[E]ven a slight overlap in range establishes a *prima facie*

case of obviousness."); *E.I. Dupont De Nnemours & Co. v. Synvina C.V.*, No. 2017-1977, slip op. at 18-20 (Fed. Cir. Sept. 17, 2018) (same). These disclosures, the knowledge of a POSITA and the '069 patent's own testing data also establish obviousness by the preponderance of the evidence. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364 (Fed. Cir. 2016) (petitioner's burden of showing invalidity by preponderance of the evidence). A POSITA would appreciate that generating lipid complexes with lipid components in the ranges claimed in the '069 patent would have been a simple matter of using prior art production methods to combine appropriate proportions of prior art lipid components. *Peterson*, at 1330 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."). Thus, in the alternative, the references render the challenged claims obvious.

During prosecution, Patent Owner overcame other cited prior art disclosing overlapping ranges based upon alleged unexpected test results disclosed in the '069 patent attributable to a cationic lipid proportion greater than 50%. This testing, however, was restricted to a single set of lipid components and proportions falling within the claimed ranges (*e.g.*, the cationic lipid was fixed at 57.1 mole percent ("mol%")). But it is well-settled that a patentee must show "unexpected results" for the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1035 (C.C.P.A. 1980).

In addition, the prior art references Lin (Ex. 1006) and Ahmad (Ex. 1007) teach that there was a recognized potential benefit in certain systems to using a cationic lipid proportion greater than 50%. A POSITA would have been motivated to combine these disclosures with the '196 PCT or '189 publication as described herein, further rendering the claims obvious. In addition, the skilled artisan would have had a reasonable expectation of success in doing so.

II. MANDATORY NOTICES

A. NOTICE OF REAL PARTY-IN-INTEREST (37 C.F.R. § 42.8(b)(1))

The real party-in-interest is Moderna Therapeutics, Inc.

B. NOTICE OF RELATED MATTERS (37 C.F.R. § 42.8(b)(2))

Petitioner identifies the following related matters: *Moderna Therapeutics, Inc. v. Protiva Biotherapeutics, Inc.*, IPR2018-00739 ('435 patent) and *Moderna Therapeutics, Inc. v. Protiva Biotherapeutics, Inc.*, IPR2018-00680 (U.S. Patent No. 9,404,127).

C. DESIGNATION OF LEAD AND BACK-UP COUNSEL (37 C.F.R. § 42.8(b)(3))

Lead Counsel: Michael Fleming (Reg. No. 67,933). Email: mfleming@irell.com.

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D. SERVICE INFORMATION (37 C.F.R. § 42.8(b)(4))

Please address all correspondence to ModernaIPR@irell.com.

E. PAYMENT OF FEES (37 C.F.R. § 42.103)

The Office is authorized to charge required fees to Deposit Account No. 09-0946.

F. CERTIFICATION OF GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Petitioner certifies that the '069 patent is eligible for *inter partes* review and that Petitioner is neither barred nor estopped from requesting a review of the challenged claims on the grounds identified herein.

III. CHALLENGE AND RELIEF REQUESTED

Petitioner respectfully requests *inter partes* review and cancellation of all claims of the '069 patent based on the grounds in Section IX.

A. GROUND 1: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF PATENT OWNER'S PRIOR DISCLOSURES IN EITHER THE '196 PCT OR THE '189 PUBLICATION

B. GROUND 2: CLAIMS 1-22 ARE OBVIOUS IN VIEW OF THE '196 PCT OR THE '189 PUBLICATION IN VIEW OF LIN AND AHMAD

C. GROUND 3: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '554 PUBLICATION

IV. PRIORITY DATE

The '069 patent claims priority to provisional application No. 61/045,228, filed on April 15, 2008. Ex. 1001, cover page. For purposes of this paper only,

Petitioner assumes (without conceding) that the '069 patent is entitled to this date.

V. PERSONS HAVING ORDINARY SKILL IN THE ART

A POSITA would have specific experience with lipid particle formation and use in the context of delivering therapeutic nucleic acid payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience. *See* Ex. 1008, Declaration of Dr. Andrew S. Janoff ("Janoff"), ¶¶29-32. This level of skill is representative of the authors/inventors of prior art cited herein. *Id.*

VI. BACKGROUND

A. LIPID CARRIER PARTICLES FOR NUCLEIC ACID PAYLOADS

Gene therapy—addressing disease at the level of the genetic cause, typically with nucleic acids—is an area of intensive medical research. Therapeutic nucleic acids can be used for both nucleic acid delivery and gene silencing (*e.g.*, small interfering RNA ("siRNA")). Janoff, ¶60; *see also* Ex. 1009 (Gao), E92; Ex. 1006, 3307.

Long before the '069 patent, it was known that systems comprised of combinations of different types of lipids with nucleic acids could result in lipid-nucleic acid particles, an accepted delivery strategy for nucleic acid therapeutics. Janoff, ¶60; *see also* Ex. 1009, E95. The '069 patent specification describes nucleic acid-lipid carrier particles that the patentees refer to as "stable nucleic acid-lipid

particles" or "SNALPs." Ex. 1001, 5:51-58.

B. THE '069 PATENT CLAIMS ARE DIRECTED TO KNOWN LIPID COMPONENTS

The '069 patent discloses four lipid components: a cationic lipid, two non-cationic lipids (a phospholipid and cholesterol), and a conjugated lipid (*e.g.*, a polyethylene glycol ("PEG") lipid). Ex. 1001, claim 1. These lipid components were known to be basic building blocks of nucleic acid-lipid particles long before the '069 patent. Janoff, ¶61; *see also* Ex. 1007, 740, 746 ("[cationic lipids] for transfection typically consist of a mixture of cationic and neutral (helper) lipid" and "strategies for optimization … could involve introducing PEG-lipids … to block … unspecific interactions"); Ex. 1009, E95, 97 (cationic lipid carrier particles "are often formulated with a noncharged phospholipid or cholesterol as a helper lipid … PEG-lipid conjugates have been incorporated … to minimize interaction with blood components ....").

Cationic lipids interact with the negative charge on nucleic acid payload facilitating formation of complexes. Janoff, ¶62; *see also* Ex. 1009, E95. Effective delivery of the nucleic acid (called the "transfection efficiency") is thought to require fusion between the lipid complex and a cell membrane.[2] Janoff, ¶62; *see also* Ex.

[2] In the art, "[t]he term 'fusogenic' refers to the ability of a lipid particle … to fuse with the membranes of a cell" thereby delivering its payload. Ex. 1001, 13:12-15.

1010 (Bennett), 48; Ex. 1009, E95; Ex. 1007, 746. Under appropriate conditions, depending on the specific mixture of lipids in the carrier particle, the positive charge on cationic lipids can interact with negative charges on cell membranes. Janoff, ¶62. This is believed to promote, in some cases, the fusion event necessary for the effective delivery of the nucleic acid. *Id.*; *see also* Ex. 1007, 745-746 ("[A]n overall positive [cationic lipid]-DNA charge is required to promote initial electrostatic interactions with cell membranes.").

Non-cationic "helper" lipids, *e.g.*, certain phospholipids and/or cholesterols, can be combined with the cationic lipid to influence the ability of the particles to transfect cells. Janoff, ¶63; *see also* Ex. 1009, E95 (cationic lipids "are often formulated with a noncharged phospholipid or cholesterol as a helper lipid …").

In addition, a conjugated lipid can increase *in vivo* circulation time by providing a neutral, hydrophilic coating to the particle's exterior. Janoff, ¶64; *see also* Ex. 1011 (Heyes), 277 ("PEG-lipids both stabilize the particle during the formulation process and shield the cationic bi-layer, preventing rapid systemic clearance."). The amount of conjugated lipid is often minimized to prevent unnecessary decreases in fusogenicity of the resulting LNPs. Ex. 1003, [0094] ("By controlling the … concentration of the bilayer stabilizing component, one can control … the rate at which the liposome becomes fusogenic."); Ex. 1005, Table IV (molar ratios of conjugated lipid 2-3%).

C. THE OPTIMAL LIPID COMPONENT PROPORTIONS IN A NUCLEIC ACID-LIPID PARTICLE VARY

"The structure of lipoplexes is influenced by multiple factors, including the charge ratio, the concentration of individual lipids and DNA, the structure of the cationic lipid and the helper lipid, [and] the physical aggregation state of the lipids ([*e.g.*,] multilamellar or unilamellar liposomes, or micelles) …." Ex. 1009, E95. Transfection efficacy is complex because "[a] large number of parameters [are] involved." Ex. 1007, 740. It was well-known that different transfection mechanisms "may be facilitated by alterations in liposome formulation …." Ex. 1010, 48. The claims of the '069 patent are not limited to a combination of specific lipids, formation protocols, or the type of nucleic-acid payload, and encompass broad ranges of lipids that have dramatically varying structures likely resulting in drastically different activities. Janoff, ¶66. Effective proportions of lipid components for one set of lipid species and payload may not be effective for alternative lipid species and payloads. *Id.*

It was well-established at the time of the '069 patent that "[t]he chemical structure of the cationic lipid ha[d] a major impact on the transfection efficiency." Ex. 1009, E95; Janoff, ¶67. References incorporated into the '069 patent acknowledge that "alternative cationic lipids" to the ones tested would have "different [transfection] efficiencies." *See* Ex. 1012 (U.S. Patent No. 5,753,613 ("'613 patent")), 1:26-28 ("… alternative cationic lipids [] work in essentially the

same manner but with different efficiencies."). Cationic lipid variables impacting transfection efficiency include "the chemical structure of the cationic lipid [and] … the charge ratio between the cationic lipid and the DNA …." Ex. 1009, E95. One example is whether the cationic lipid includes tertiary or quaternary amines—ionizable cationic lipids with tertiary amines have a pKa less than 7 resulting in a net neutral particle charge at physiological pH. Ex. 1011, 284. A POSITA would have known that these variables could impact the proportion of cationic lipid that is most effective for a given lipid component combination. Janoff, ¶68.

For example, hundreds of cationic lipids, both univalent and multivalent, were known at the time of the '069 patent, some with differing charges. Ex. 1009, E95 ("[H]undreds of new cationic lipids have been developed … [that] differ by the number of charges in their hydrophilic head group and by the detailed structure of their hydrophobic moiety."); Ex. 1011, 286. The charge density on the surface of a nucleic acid-lipid particle, at a fixed cationic lipid proportion, can be modulated by introducing cationic lipids with different charges. Janoff, ¶69; Ex. 1011, Abstract. This would have been expected to impact the ability of some particles to promote fusion events with target cell membranes. *Id.*; *see also* Ex. 1007, 740. Both Ahmad and Lin identified charge density as an important determinate of transfection efficacy in some of the systems. Ex. 1007, 744; Ex. 1006, 3312; Janoff, ¶69.

It was also well-known at the time of the '069 patent that certain lipid

component combinations favor having a 50% or greater proportion of cationic lipid. Janoff, ¶70. Researchers often chose a 50% proportion of cationic lipid as a default in evaluating particle transfection efficiency. *See, e.g.*, Ex. 1010, 49 (50% cationic lipid); Ex. 1013 (U.S. Patent 7,939,505), 44:61-65 (cationic lipid of "about 0.5% to about 70% (mol%) of the total amount of lipid"), 96:40-67 (Example 32 and Table 12) (formulations with 50% cationic lipid), 99:34-101:45 (Examples 34-35 and Tables 15-18) (same). Researchers also determined that, in some cases, increasing the cationic lipid proportion above 50% increased transfection efficiency. Ex. 1007, 744; Ex. 1006, 3312.

As with cationic lipids, at the time of the '069 patent the number of species of non-cationic lipids that could be employed was large, and differences among such lipids had been reported to impact the structure of the resulting nucleic acid-lipid particles. Janoff, ¶71; Ex. 1009, E95 (transfection efficiency varies with "the structure and proportion of the helper lipid in the complexes"). Variations in the proportions of non-cationic lipids in certain formulations were reported to impact their ability to deliver nucleic acid payloads. Ex. 1010, 51; Ex. 1007, 744. Similarly, the selection of conjugated lipid was also known to potentially impact the particle's chemistry and efficacy. Janoff, ¶71; Ex. 1003, [0094].

In addition, the claims of the '069 patent encompass various types of "nucleic acids." A POSITA at the time of the '069 patent would have known that the species

of nucleic acid payload would impact the optimal LNP formulation. Janoff, ¶72. For example, there are well-understood chemical and structural differences between mRNA and siRNA in terms of length, stability, and charge density of the nucleic acid. A POSITA would not have expected a formulation optimized for siRNA to perform similarly for mRNA. *Id.*; Ex. 1019 (Kaufman).

In short, a POSITA at the time of the '069 patent would have known that varying the nucleic-acid payload, the specific lipid species or the lipid proportions could change the performance of the nucleic acid-lipid particle. Janoff, ¶74. The range of lipids falling under the scope of the claims of the '069 patent is immense and a POSITA would have had no way of knowing if lipid combinations at any given proportion would have resulted in formulations of superior therapeutic index to other formulations. *Id.*; *see also* Ex. 1007, 740 ("… typically only one or two data points per lipid are evaluated, allowing the ideal lipid composition (the ratio of neutral to cationic lipid) or cationic lipid/DNA ratio to be overlooked.").

D. THE '069 PATENT WAS GRANTED ON ALLEGED UNEXPECTED RESULTS FOR A SINGLE FORMULATION OF LIPID COMPONENTS

The '069 patent is premised on an alleged "surprising discovery" that prior art lipid components in certain proportions perform better than expected *in vitro* and *in vivo*. *Id.*, 5:44-51 (lipids "comprising from about 50 mol% to about 85 mol% of a cationic lipid, from about 13 mol% to about 49.5 mol% of a non-cationic lipid, and from about 0.5 mol% to about 2 mol% of a lipid conjugate provide advantages ….").

According to the '069 patent, using the claimed lipid proportions result in "increased activity of the encapsulated nucleic acid … and improved tolerability of the formulations *in vivo*, resulting in a significant increase in the therapeutic index …." *Id.*, 5:51-58; Janoff, ¶75.

The '069 patent acknowledges that the following was known to a POSITA before to its priority date (*see* Janoff, ¶76):

- Nucleic acid-lipid particles comprising a nucleic acid, cationic lipid, non-cationic lipid, and a conjugated lipid that inhibits aggregation of particles. *See* Ex. 1001, 11:24-26 ("SNALP and SPLP typically contain a cationic lipid, a non-cationic lipid, and a lipid conjugate (e.g., a PEG-lipid conjugate).").
- Preparation of such nucleic acid-lipid particles. *See id.*, 11:44-48 ("Nucleic acid-lipid particles and their method of preparation are disclosed in, e.g., U.S. Patent Publication Nos. US2004/0142025 and US2007/0042031, the disclosures of which are herein incorporated by reference in their entirety for all purposes.").
- In addition, the prior art cited in the '069 patent discloses nucleic acid-lipid particles with the listed component lipids having overlapping ranges: a cationic lipid range of "about 2% to about 70%," a non-cationic lipid range of "about 5% to about 90%," a cholesterol range of "about 20% to about

55%," and a PEG-lipid conjugate range of "about 0.5% to about 20%." *See, e.g.*, Ex. 1014 (U.S. Publication No. US2007/0042031 ("'031 publication")), [0033].

Thus, nucleic acid-lipid particles with (1) the claimed nucleic acid payload and (2) the same lipid components in overlapping ranges were admittedly known in the art. Janoff, ¶76. The sole basis for alleged novelty of the '069 patent claims is that a nucleic acid-lipid particle comprising component lipids in the claimed proportions achieves unexpected efficacy. *Id.*

1. '069 PATENT: THE PROSECUTION HISTORY CONFIRMS PATENT OWNER'S RELIANCE ON UNEXPECTED RESULTS

During the prosecution of the '069 patent, the examiner cited Patent Owner's earlier, unrelated '910 publication (Ex. 1015) as prior art disclosing nucleic acid-lipid particles with the claimed components and overlapping ranges of those components. *See, e.g.*, Ex. 1016 ('069 file history excerpts), 7/30/2010 Rejection, 3–5. Patent Owner put forth the following chart illustrating the overlapping ranges:

Lipid Component	Claim 1 as Amended	US 2006/0008910*
Cationic Lipid	50-65 mol %	"2-60, 5-50, 10-45, 20-40, 30 mol%"
Phospholipid	4-10 mol %	"5-90 mol%"
Cholesterol	30-40 mol %	"20-55 mol %"
Conjugated Lipid	0.5-2 mol %	"1-20 mol %"

Id., 8/11/2011 Amendment, 7–9.

In response to the rejection, Patent Owner argued that the specific claimed

ranges in the '069 patent lead to "***new and unexpected results***" and cited to test results regarding the "1:57 SNALP" in the specification. *Id.*, 1/31/2011 Amendment, 11. Patent Owner argued that "[a]pplicants have found that SNALP formulations having increased amounts of cationic lipid, *e.g.*, one or more cationic lipids comprising from about 50 mol% to about 65 mol% of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent …." *Id.* Patent Owner relied on Examples 3-4 from the specification arguing that these examples demonstrated that the 1:57 SNALP formulation was "more efficacious as compared to a nucleic acid-lipid particle previously described ('2:30 SNALP') … [and] more effective at silencing the expression of a target gene as compared to nucleic acid-lipid particles previously described ('2:40 SNALP')." *Id.*

2. '069 PATENT: PATENTEE TESTED ONLY ONE FORMULATION COVERED BY THE CLAIMS

The '069 patent includes *in vitro* (Example 2) and *in vivo* (Examples 3-4) testing of various nucleic acid-lipid formulations and comparison of those formulations to the admitted prior art (*i.e.*, the 2:30 and 2:40 formulations). Ex. 1001, 68:50-73:67. As discussed above, Patent Owner argued during prosecution that these tests establish unexpected advantages. In these examples, however, only the 1:57 SNALP contains lipid proportions within the ranges claimed in the '069

patent.[3] *Id.*; Janoff, ¶81.

a) EXAMPLE 2 SHOWS THAT *IN VITRO* THE 1:57 SNALP WAS NO MORE EFFECTIVE THAN SEVERAL PRIOR ART FORMULATIONS

Example 2 is the *in vitro* test in the 069 patent. Ex. 1001, 68:50-70:50. Example 2 involved a siRNA payload targeting the Eg5 gene with various lipid components in various proportions. *Id.*, Table 2 (annotated below):

TABLE 2

Characteristics of the SNALP formulations used in this study.

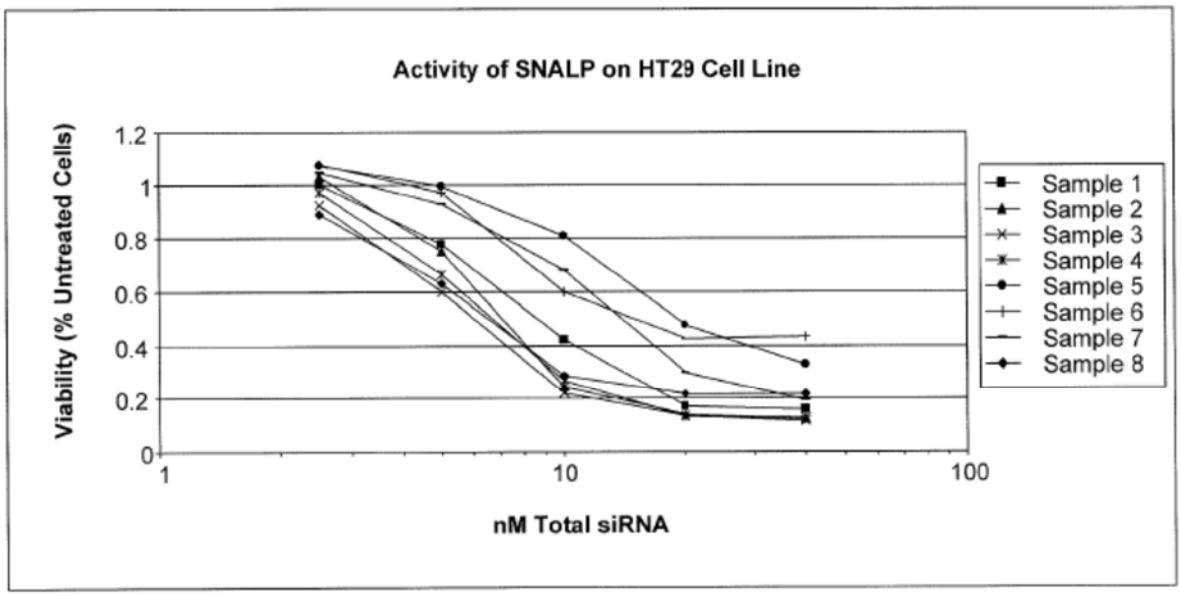
Sample No.	Formulation Composition, Mole % PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol	Lipid/Drug Ratio	Finished Product Characterization		
			Size (nm)	Polydispersity	% Encapsulation
1	2 | 40 | 10 | 48	12.4	57	0.07	90
2	1.8 | 36.4 | 18.2 | 43.6	14.0	72	0.12	89
3	1.4 | 27.0 | 6.8 | 64.9	16.5	70	0.12	92
4	1.3 | 25.3 | 12.7 | 60.8	18.1	76	0.07	93
5	3.9 | 39.2 | 9.8 | 47.1	13.5	53	0.27	86
6	3.6 | 35.7 | 17.9 | 42.9	15.1	58	0.18	87
7	2.7 | 26.7 | 6.7 | 64.0	17.6	56	0.17	92
8	2.5 | 25.0 | 12.5 | 60.0	19.2	61	0.13	92
9	1.4 | 57.1 | 7.1 | 34.3	17.8	84	0.10	88
10	1.3 | 53.3 | 13.3 | 32.0	19.5	83	0.10	89
11	1.1 | 42.6 | 5.3 | 51.1	22.0	80	0.10	93
12	1.0 | 40.4 | 10.1 | 48.5	23.6	78	0.11	88
13	2.8 | 56.3 | 7.0 | 33.8	19.0	62	0.14	80
14	2.6 | 52.6 | 13.2 | 31.6	20.6	66	0.14	82
15	2.1 | 42.1 | 5.3 | 50.5	23.1	71	0.16	91
16	2 | 40 | 10 | 48	24.7	67	0.14	92

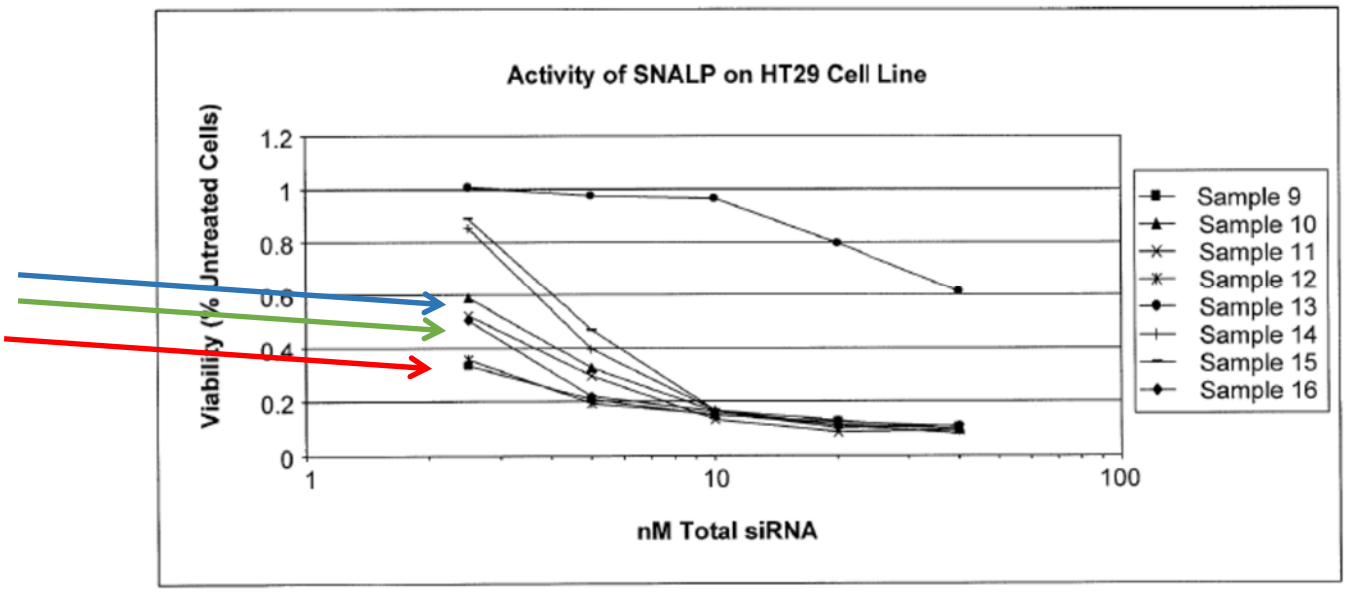
Of the tested lipid formulations, only Sample 9 (the 1:57 SNALP) falls within the

[3] The 1:57 SNALP is "1.4% PEG-cDMA [conjugated lipid]; 57.1% DLinDMA [cationic lipid]; 7.1% DPPC [phospholipid]; and 34.3% cholesterol [neutral lipid]." Ex. 1001, 68:23-25.

lipid ranges in claim 1 of the '069 patent. *Id.*, cl. 1; Janoff, ¶82. Other than the 1:57 SNALP, the '069 patent did not test any combinations of lipid components covered by the claims for comparison to the admitted prior art. *Id.*

Samples 1 and 16 in Table 2 reflect the 2:40 SNALP that is admitted prior art. Ex. 1001, Table 2, Janoff, ¶83. Sample 12 is similar to the 2:40 SNALP, but with slight variations in the lipid proportions. *Id.* The results of the testing from Example 2 are shown in Figures 1(a)-(b) (reproduced below):





As can be seen from the figures, (1) Sample 9 (1:57 SNALP indicated by red arrow) appears to be no more effective at gene silencing than Sample 12 (a 2:40-type SNALP with 40.4% cationic lipid also indicated by red arrow), which it overlaps at every data point; (2) Sample 9 (1:57 SNALP) appears to outperform Sample 16 (2:40 SNALP indicated by green arrow) only at extremely low total siRNA amounts; and (3) Samples 9 (1:57 SNALP) and 12 (2:40-type SNALP) outperform sample 10 (indicated by blue arrow) which is also comprised of greater than 50% cationic lipid (*i.e.*, 53.3%). Janoff, ¶83.

Therefore, there is no clear advantage in Example 2 of using the 1:57 SNALP, nor is there data that the entire claimed range of nucleic acid-lipid particles is superior to particles with less than 50% cationic lipid. *Id.*

b) EXAMPLES 3-4 SHOW THAT THE 1:57 SNALP WAS NO MORE EFFECTIVE THAN THE FORMULATIONS WITH LESS THAN 50% CATIONIC LIPID

Examples 3-4 of the '069 patent compare the 1:57 SNALP to various formulations with lipid components outside of the claimed ranges *in vivo*. Ex. 1001, 70:51-73:67. Example 3 involved testing the silencing activity of a siRNA payload targeting the Apo B gene with various lipid components in various proportions. *Id.*, 70:51-72:55; Table 4 (below):

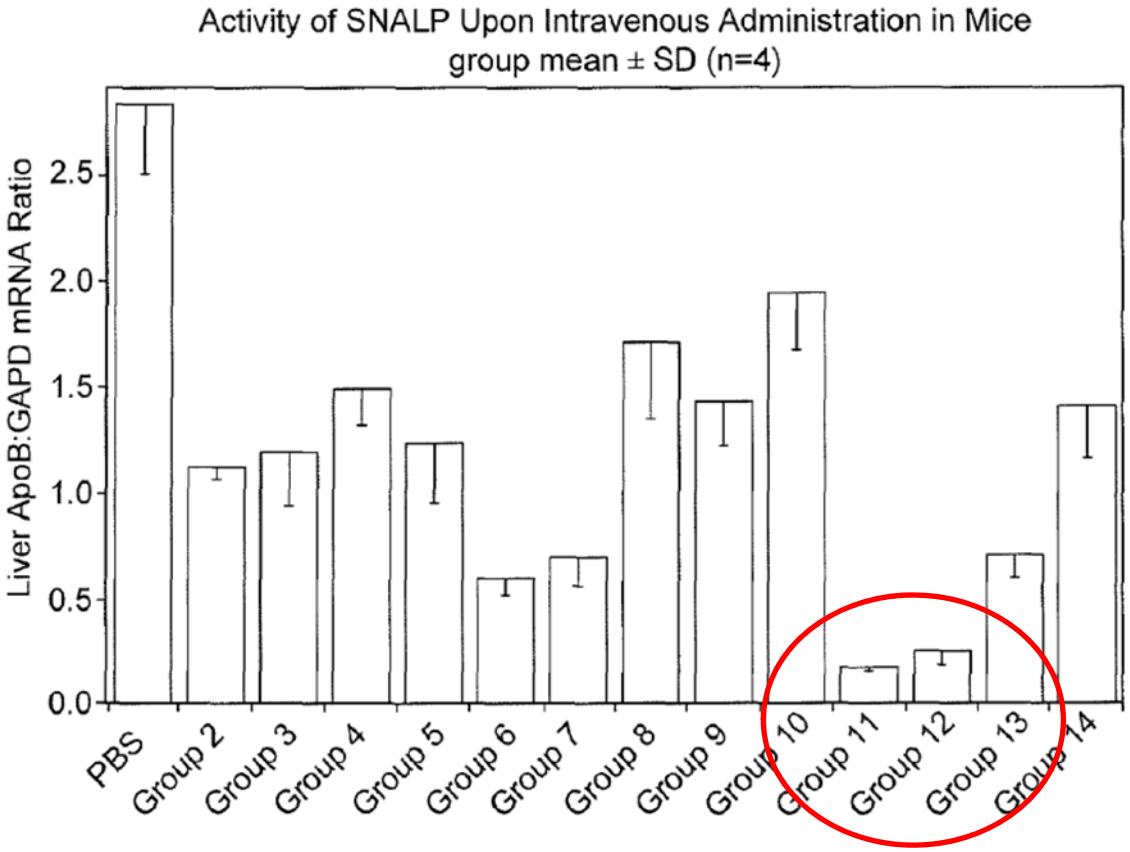
TABLE 4

Characteristics of the SNALP formulations used in this study.

	Formulation Composition	Lipid/Drug	Finished Product Characterization		
Group	Lipid Name & Mole %	Ratio	Size (nm)	Polydispersity	% Encapsulation
2	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 2 | 40 | 10 | 48	12.4	59	0.15	93
3	PEG(2000)-C-DMA | DLinDMA | Cholesterol 2.2 | 44.4 | 53.3	10.7	55	0.17	91
4	PEG(2000)-C-DMA | DLinDMA | DOPC | Cholesterol 2 | 40 | 10 | 48	12.5	59	0.16	92
5	PEG(2000)-C-DMA | DLinDMA | DMPC | Cholesterol 2 | 40 | 10 | 48	12.2	56	0.11	92
6	PEG(2000)-C-DMA | DLinDMA | DPPE | Cholesterol 1.8 | 36.4 | 18.2 | 43.6	13.8	66	0.16	93
7	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholestanol 2 | 40 | 10 | 48	12.4	56	0.12	92
8	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.4 | 27.0 | 6.8 | 64.9	16.5	60	0.10	93
9	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.3 | 25.3 | 12.7 | 60.8	18.1	74	0.13	92
10	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 2.5 | 25.0 | 12.5 | 60.0	19.2	60	0.13	93
11	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.4 | 57.1 | 7.4 | 34.3	17.8	79	0.09	94
12	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.0 | 40.4 | 10.1 | 48.5	23.6	72	0.11	93
13	PEG(2000)-C-DMA | DLinDMA | DPPC 2 | 70 | 28	8.7	73	0.09	87
14	PEG(2000)-C-DMA | DLinDMA | DPPC 1.6 | 54.7 | 43.8	11.3	65	0.11	87

Again, of the tested lipid combinations, only Sample 11 (1:57 SNALP) falls within the lipid ranges claimed in the '069 patent. *Id.*; Janoff, ¶84. Samples 2, 4-5 and 7 reflect the 2:40 SNALP proportions (Samples 4-5 employ different species of certain lipid components than Samples 2 and 7). Janoff, ¶84. The results of testing

are shown in Figure 2 (annotated below):



As can be seen from Figure 2, the 1:57 SNALP (Group 11) is likely not statistically significantly more efficacious than Group 12 (which is comprised of only 40.4% cationic lipid (*see* Table 4 above)). Janoff, ¶85. On the other hand, Group 12 appears to be more efficacious than Groups 2 and 7 (both examples of the admitted prior art 2:40 SNALP formation) even though it varies only slightly from this formulation in that it is comprised of 1 mol% rather than 2 mol% PEG-2000-C-DMA. *Id.*

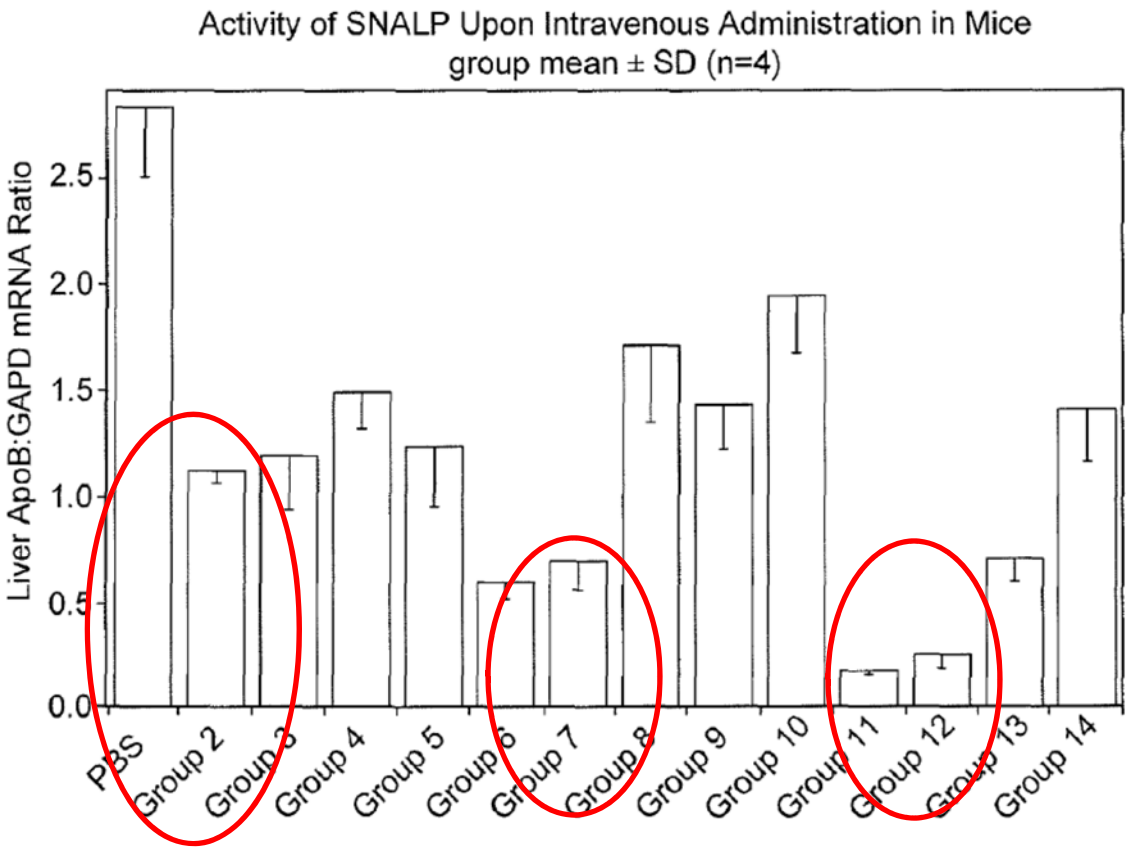
Example 4 compares the silencing activity of the 1:57 SNALP formulation with the 2:30 SNALP formulation. Both SNALPs were formulated with a siRNA

payload targeting the Apo B gene. Ex. 1001, 72:60-74:4; Table 5. At most, this testing established that the 1:57 SNALP comprised of the specific species of lipid components and nucleic acid to lipid ratio disclosed, dosed as disclosed, outperformed the 2:30 SNALP comprised of the lipid species disclosed and dosed as disclosed. Janoff, ¶86.

In conclusion, the identified testing fails to demonstrate that all formulations that fall within the '069 patent claims perform better than prior art formulations. Janoff, ¶87.

3. THE '069 PATENT: THE TESTING SHOWS THAT EVEN SLIGHT VARIATIONS OF THE LIPID COMPONENT PROPORTIONS AND/OR THE SPECIES OF LIPID COMPONENT IMPACT EFFICACY

The *in vivo* testing in Example 3 shows that minor variations in lipid percentages may appreciably impact efficacy. Janoff, ¶84. Specifically, Samples 2, 7 and 12 from Table 4 contain the same lipid components. Ex. 1001, Table 4. Samples 2 and 7 are comprised of exactly the same ratios (*i.e.*, 2/40/10/48). *Id.* Sample 12 is comprised of the ratio 1/40.4/10.1/48.5. *Id.* According to Figure 2, Sample 12 is comparable to the alleged advantages of using Sample 11, the 1:57 SNALP, but apparently superior to Samples 2 and 7 (the admitted prior art 2:40 formulations).



Several other examples in the '069 patent illustrate that transfection efficiency may be influenced by varying just the species of lipid components used. Janoff, ¶87. For instance, comparing Groups 2 & 6 to Group 4 in Example 5, in which DLinDMA was replaced with DODMA without changing the ratios of the components used (*see* Ex. 1001, Table 6), Group 4 apparently exhibited inferior results. Example 5 also shows by comparing Groups 2 and 6 (PEG(2000)-c-DMA) to Group 5 (PEG(5000)-c-DMA), that variation of the conjugated lipid apparently impacts efficacy. Janoff, ¶87.

VII. CLAIM CONSTRUCTION

A. CLAIM 1: "NUCLEIC ACID-LIPID PARTICLE"

In the '435 patent IPR, the Board determined that under the broadest reasonable interpretation standard, the term "nucleic acid-lipid particle" in independent claim 1 was the only claim term needing construction and means "a particle that comprises a nucleic acid and lipids, in which the nucleic acid may be encapsulated in the lipid portion of the particle." IPR2018-00739, Paper 15, at 10-11. Given that this construction is based upon express disclosures in the specification, it is also applicable under the current claim construction standard under *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). Janoff, ¶88. For purposes of this paper only, Petitioner assumes (without conceding) that this is the only necessary construction.

VIII. PRIOR ART

A. PATENT OWNER'S PRIOR DISCLOSURES ARE PRIOR ART UNDER 35 U.S.C. § 102(b)

The '069 patent family is but one of many patent families with substantially overlapping disclosures. Because these unrelated patent families, with differing inventors, do not claim priority to one another, the earlier disclosures are prior art to the '069 patent. Janoff, ¶89; Ex. 1003; Ex. 1004.

One example of such a prior, unrelated disclosure is the '196 PCT. Ex. 1003. Patent Owner filed the provisional applications leading to it in 2003. *Id*. The

inventors are Ian MacLachlan, Ellen Ambegia, and James Heyes, a different inventive entity from the '069 patent inventive entity. *Id.* The '196 PCT was published on Jan. 27, 2005. *Id.* The '196 PCT and the '069 patent do not claim priority to one another. *See* Exs. 1001, 1002. The '196 PCT is therefore prior art to the '069 patent under 35 U.S.C. § 102(b) (pre-AIA). Janoff, ¶91.

The '196 PCT discloses SNALPs comprise "a cationic lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles and a siRNA." Ex. 1003, [0011]. The non-cationic lipids may include a phospholipid and cholesterol. *Id.*, [0089]; Janoff, ¶92. The '196 PCT thus discloses the same lipid components as claimed in the '069 patent.

The '196 PCT also discloses overlapping ranges of these components. According to the '196 PCT, "[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle … [i]n other preferred embodiments, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle." Ex. 1003, [0088]. "The non-cationic lipid typically comprises from about 5% to about 90% of the total lipid present … [and] [t]he nucleic acid-lipid particles … may further comprise cholesterol … from about 20% to about 45% of the total lipid present …." *Id.*, [0091]. "[T]he SNALP further comprises a bilayer stabilizing component (BSC) …. the BSC is a conjugated lipid that inhibits aggregation of the SNALPs … present from about 0.5% to about 25%

of the total lipid ….” *Id.*, [0092-0093]; Janoff, ¶93. The ’196 PCT discloses that “[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied ….” Ex. 1003, [0088]; Janoff, ¶94. The ’196 PCT recognized that compositions with an overall neutral charge are preferred. Ex. 1003, [0015]; Janoff, ¶92.

In addition, the ’196 PCT incorporates by reference U.S. Patent No. 5,264,618 (the “’618 patent”). Ex. 1017, [0087], [0146]. The ’618 patent in turn discloses a nucleic acid-lipid complex with 56% cationic lipid, 14% phospholipid and 30% cholesterol, as well as various other formulations with over 50% cationic lipid. Ex. 1017, 34:54-35:23.

Another example of Patent Owner’s prior, unrelated disclosure is the ’189 publication. Ex. 1004. Patent Owner filed the provisional applications leading to it in 2004-2005. *Id*. The inventors are Ian MacLachlan, Lloyd Jeffs, Adam Judge, Amy Lee, Lorne Palmer, and Vandana Sood, a different inventive entity from the ’069 patent. *Id.* The ’189 publication was published on June 22, 2006. *Id.* Also, the ’189 publication and the ’069 patent do not claim priority to one another. *See* Exs. 1001, 1004. The ’189 publication is therefore prior art to the ’069 patent under 35 U.S.C. § 102(b) (pre-AIA). Janoff, ¶95.

The ’189 publication discloses SNALPs comprising overlapping ranges of the four lipid components similar to those discussed above for the ’196 PCT. Ex. 1004,

[0009-0012], [0014], [0148-0181]; Janoff, ¶96. In addition, the '189 publication discloses testing relating to the 2:40 formulation that Patent Owner identified as a prior art formulation. Janoff, ¶96; Ex. 1004 [0350-0391]. This formulation includes 40% cationic lipid and 2% conjugated lipid, 10% phospholipid and 48% cholesterol. *Id.*, [0351]. According to the '189 publication, this formulation demonstrated efficacy *in vitro* and *in vivo*. *Id.*, [0016]. These additional disclosures confirm that formulations with high cationic lipid percentages (*e.g.*, 40%) and low conjugated lipid percentages (*e.g.*, 2%) were known.

B. THE '554 PUBLICATION IS PRIOR ART UNDER 35 U.S.C. § 102(b)

The '554 publication was published as US 2006/0240554 A1 on October 26, 2006. Ex. 1005, cover page. The '554 publication is therefore prior art to the '069 patent under 35 U.S.C. § 102(b) (pre-AIA). Janoff, ¶97.

The '554 publication discloses "novel cationic lipids, transfection agents, microparticles, nanoparticles, and short interfering nucleic acid (siNA) molecules." Ex. 1005, Abstract. The cationic LNPs disclosed are comprised of, for example, "(a) a cationic lipid … (b) a neutral lipid; (c) a polyethyleneglycol conjugate … and (d) a short interfering nucleic acid (siNA) molecule …." *Id.*, 28:36-48. These are the same components and payload described in the '069 patent. Janoff, ¶98.

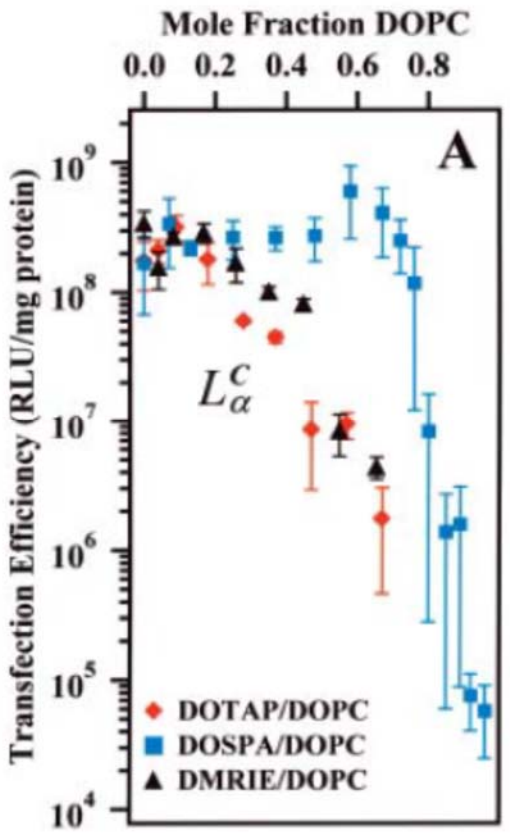
The '554 publication discloses various ranges for the lipid components that overlap or encompass the ranges disclosed in the '069 patent, including the cationic

lipid (about 2% to about 60%), the neutral, non-cationic lipid (about 5% to about 90%), cholesterol (about 20% to about 45%) and the PEG conjugate (about 1% to about 20%). The '554 publication also includes various specific formulations including 50% or greater cationic lipid. Ex. 1005, Table 4 (*e.g.*, L054 DMOBA/Chol/DSPC/PEG-n-DMG (50/20/28/2).

C. LIN IS PRIOR ART UNDER 35 U.S.C. § 102(b)

Lin et al. ("Lin") is a publication titled "Three-Dimensional Imaging of Lipid Gene-Carriers: Membrane Charge Density Controls Universal Transfection Behavior in Lamellar Cationic Liposome-DNA Complexes." Ex. 1006. It was published in *Biophysical Journal* in May 2003. *See id.* Lin is therefore prior art to the '069 patent under 35 U.S.C. § 102(b) (pre-AIA). Janoff, ¶100.

Lin studied the impact of cationic lipid mole fraction on the transfection efficiency of lipid particles with a DNA payload in *in vitro* experiments. Ex. 1006, 3307. Using the cationic lipids DOTAP, DMRIE and DOSPA and the helper lipid DOPC, Lin determined that transfection efficiency increased as the cationic lipid



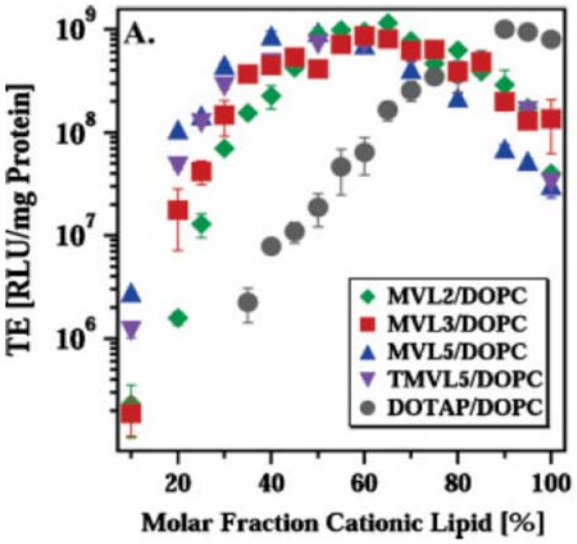
mole fraction increased. *Id.*, 3309. In Figure 4(a), Lin shows the transfection efficiency as a function of the mole fraction of neutral lipid (DOPC). *Id.*, Fig. 4. The mol% of cationic lipid (*e.g.*, DOTAP, DOSPA, DMRIE) is derived by deducting the mole fraction of neutral lipid from 1 and multiplying by 100 (the highest mol% would be on the left of the x axis and decrease as you proceed right on the x axis). As can be seen from the figure, for each formulation the transfection efficiency increased with the mol% of cationic lipid incorporated. Janoff, ¶102. Starting at about 35 mol%, transfection efficiency increased monotonically with increasing mol% for DOTAP formulations. For DMRIE formulations, over the same range, there appeared to be a steep increase in transfection efficiency from about 45-55 mol%. For formulations comprised of the multivalent lipid DOSPA, transfection efficiency seemed to be biphasic—it increased monotonically up to about 35 mol% and then seemed to saturate. *Id.*

A POSITA would understand the testing of Lin to suggest that the mol% of cationic lipid in nucleic acid-lipid particles can impact transfection efficiency, and

that for certain cationic lipids (*e.g.*, DOTAP) transfection efficiency might continue to improve at a mol% above 50 percent. *Id.*, ¶103. A POSITA would further understand that precisely how the mol% of cationic lipid might impact transfection efficiency depends on both the cationic lipid species and neutral lipid species chosen. *Id.*

D. AHMAD IS PRIOR ART UNDER 35 U.S.C. § 102(b)

Ahmad et al. ("Ahmad") is a publication titled "New multivalent cationic lipids reveal bell curve for transfection efficiency versus membrane charge density: lipid–DNA complexes for gene delivery." Ex. 1007. It was published in *The Journal of Gene Medicine* on January 31, 2005. *See id.* Ahmad is therefore prior art to the '069 patent under 35 U.S.C. § 102(b) (pre-AIA). Janoff, ¶104.



Ahmad studied the impact of membrane charge density on the transfection efficiency of cationic liposome-DNA complexes comprised of cationic and neutral helper lipids. Ex. 1007, 739. Ahmad also contemplated adding cholesterol and PEG-lipids to these lipid complexes. *Id.*, 744 ("[C]holesterol, which leads to lamellar complexes, is increasingly used as a neutral lipid for *in vivo* applications."),

746 ("strategies for optimization … could involve introducing PEG –lipids … to block ... unspecific interactions …."). Thus all four lipid components from the '069 patent were disclosed. Janoff, ¶105.

Ahmad found that a variety of cationic lipids increased the transfection efficiency in the DOPC formulations he studied as shown on Figure 3(a). In Ahmad, cationic lipids with multiple charges were observed to provide higher transfection efficiencies. Ex. 1007, 740 ("Numerous lipids with varied chemical and physical properties have been synthesized to improve the transfection efficiencies … These include multivalent lipids, which have been described as superior to their monovalent counterparts."). More specifically, Ahmad determined that for the multivalent cationic lipids studied, a maximum transfection efficiency occurred at around 50 mol%. Yet for the monovalent lipid DOTAP, transfection efficiency increased monotonically from a cationic lipid percentage of about 35 mol% to a cationic percentage of about 90 mol%. *Id.*, 744. Ahmad reported that the optimal transfection efficiency for MLV 5 (a multivalent cationic lipid) was at 55 mol% when incorporated into DOPC formulations, whereas the maximal TE for DOTAP, incorporated into DOPC formulations was at 90 mol%. *Id.*, 743; Janoff, ¶106.

A POSITA would understand the testing of Ahmad to suggest that the mol% of cationic lipid in nucleic acid-lipid particles can impact transfection efficiency, and that for certain cationic lipids transfection efficiency might continue to improve at a

mol% above 50 percent. Janoff, ¶106.

Ahmad includes a statement that "[m]inimizing the amount of cationic lipid is desirable to reduce cost as well as potential toxic effects of the cationic lipid." Ex. 1007, 745. But, Ahmad also noted that "with the amounts of cationic lipid employed in our *in vitro* experiments, we find no toxic effects on the cells as judged by cell morphology and the amount of total cellular protein." *Id.*, 746. Given that the disclosures in the '069 patent are not limited to *in vivo* applications, a POSITA would understand the insights of Ahmad could apply to the particles disclosed in the '069 patent. Moreover, a POSITA would be aware that a cationic lipid resulting in particles that are neutral at physiological pH could be used to limit toxicity. Janoff, ¶107; Ex. 1011, 284.

IX. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE '069 PATENT IS UNPATENTABLE

A. GROUND 1: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF EITHER THE '196 PCT OR THE '189 PUBLICATION

Claims 1-22 of the '069 patent are anticipated under 35 U.S.C. § 102(b) (pre-AIA) or obvious under 35 U.S.C. § 103 in view of either the '196 PCT or the '189 publication. These references are presented together because the '189 publication is substantively similar to the '196 PCT, the primary difference being that it also discloses testing relating to the admitted prior art 2:40 formulation. Ex. 1004 [0350]-[0391]; Janoff, ¶108.

The '196 PCT and '189 publication disclose encompassing and overlapping

ranges with sufficient specificity to anticipate the range of lipid components recited in claim 1 of the '069 patent. Janoff, ¶108. Additionally, the disclosed ranges establish *prima facie* obviousness, which creates a presumption of obviousness. *E.I. Dupont*, No. 2017-1977, slip op. at *18-20. Moreover, the testing in the '069 patent does not support alleged unexpected results for the claimed ranges. *Id.*

1. CLAIM 1

a) CLAIM 1(A): A NUCLEIC ACID-LIPID PARTICLE COMPRISING:

Patent Owner's prior disclosures teach "compositions and methods for silencing gene expression by delivering nucleic acid-lipid particles comprising a siRNA molecule to a cell." Ex. 1003, (Abstract); Ex. 1004, (Abstract); Janoff, ¶110.

b) CLAIM 1(B): A NUCLEIC ACID

Patent Owner's prior disclosures teach "the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." Ex. 1003, [0002]; Ex. 1004, [0182]. siRNA is a nucleic acid. Janoff, ¶111.

c) CLAIM 1(C): A CATIONIC LIPID COMPRISING FROM 50 MOL% TO 65 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

Patent Owner's prior disclosures teach "[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle … [i]n other preferred embodiments, the cationic lipid comprises from about 40% to

about 50% of the total lipid present in said particle." Ex. 1003, [0088]; Ex. 1004, [0152]. Patent Owner's prior disclosures disclose that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." Ex. 1003, [0088]; Ex. 1004, [0152]. In addition, Patent Owner's prior disclosures incorporate by reference ('196 PCT) or directly reference ('189 publication at [0155, 0157]) the '618 patent, which discloses nucleic acid-lipid complex with 56% cationic lipid, 14% phospholipid and 30% cholesterol, as well as various other formulations containing over 50% cationic lipid. Ex. 1016, 34:54-35:23. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Janoff, ¶112. Not only does the disclosed range substantially overlap with the claimed range, a preferred embodiment in the reference recites a narrower preferred range that also partially overlaps. *Id.*

Given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious. *E.I. Dupont*, No. 2017-1977, slip op. at *18-20; Janoff, ¶112. Moreover, determining the optimal proportion of cationic lipid for a given lipid combination would be a simple matter of varying the proportion using prior art methodologies. *See Peterson*, 315 F.3d at 1330 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.").

A POSITA would have had a reasonable expectation that nucleic-acid lipid particles could be successfully formulated with cationic lipid the 50 mol% to 65 mol% range, especially given the disclosure in the '618 patent of various formulations containing over 50% cationic lipid. Ex. 1016, 34:54-35:23.

The testing in the '069 patent cannot overcome the presumption of obviousness as it is insufficient to show alleged "unexpected results" with regard to the prior art for the entire claimed range. *In re Clemens*, 622 F.2d at 1035. Here, the claim limitation includes two ranges: (1) a numeric range for the cationic lipid proportion, and (2) a range of species of "cationic lipids" as that claim term is defined in the '069 patent. It is well-known that "[t]he structure of lipoplexes is influenced by multiple factors, including the charge ratio, the concentration of individual lipids and DNA, the structure of the cationic lipid and the helper lipid, [and] the physical aggregation state of the lipids …." Ex. 1009, E95; *see also* Ex. 1007, 740 (for "CL-DNA complexes … [a] large number of parameters involved"); Ex. 1010, 48 ("transfection pathway may be facilitated by alterations in liposome formulation"). The testing in question, however, dealt with only a single formulation of lipid species and proportions falling within the claim scope.

During prosecution Patent Owner only asserts unexpected results occurred vis-à-vis the 2:30 and 2:40 formulations. Janoff, ¶113. The prior art, however, is not so limited. *See Ex parte Lunsford*, No. Appeal 2008-4023, at *11 (P.T.A.B. Nov.

26, 2008) (no criticality of a claimed variable characteristic for unexpected results where the comparison results were "not based on a comparison between the claimed invention and the closest prior art"). For example, Patent Owner ignores Group 12 in Figure 2 of the '069 patent that has a cationic lipid percentage of 40.4% and is clearly in the prior art given the admitted 2:40 formulation. *Id.* In addition, as discussed above in Sections VI-VII, numerous other prior art formulations contain cationic lipid percentages over 50%. *See, e.g.*, Exs. 1006-1007. Patent Owner thus failed to address the entire scope of the prior art in asserting unexpected results. Janoff, ¶113.

Regarding the numeric range, during prosecution, the patentee argued that testing in Examples 2-4 regarding the 1:57 SNALP rebutted the *prima facie* case *vis a vis* the '910 publication. Ex. 1016, 1/31/2011 Amendment, 8–10. But a single data point alone is insufficient to demonstrate unexpected results over a claimed range. *Peterson*, 315 F.3d at 1331 (finding data at 0-2% rhenium insufficient to show unexpected results for claimed range of 1-3% rhenium); *In re Patel*, 566 Fed. App'x. 1005, 1012 (Fed. Cir. 2014) (unexpected improvement at two points (0.913 and 0.915 g/cm3) only one of which falling in the range (0.915-0.950 g/cm3) was insufficient to "establish unexpected results through factual evidence for the entire claimed range"). This testing cannot rebut the showing of obviousness.

Given the disclosures in the '069 patent, a POSITA would not expect all

alternative data points falling within the recited numeric range to perform similarly. *See In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) ("If an applicant demonstrates that an embodiment has an unexpected result and provides an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with [the] scope of the claims."). As discussed above, the *in vivo* testing in Example 3 shows that even minor variations in lipid percentages appeared to impact efficacy. Janoff, ¶114. Specifically, Samples 2 and 12 from Table 4 contain the exact same lipid species in the respective ratios 2/40/10/48 and 1/40.4/10.1/48.5. Ex. 1001, Table 4. According to Figure 2, these slight variations in lipid proportions lead to apparently different transfection efficiencies. *Id.*, Fig. 2; Janoff, ¶114. A POSITA would expect that similar minor variations in lipid proportions within the claimed range might lead to similar variations in transfection efficiency. Janoff, ¶114. *See also Ex parte Lunsford*, No. Appeal 2008-4023, at *11 (P.T.A.B. Nov. 26, 2008) ("cause-and-effect relationship" between claimed limitation and results missing because "multiple unfixed variables" could have caused the unexpected results).

Regarding the range of cationic lipids falling within the claim limitation, the '069 patent defines "cationic lipid" as "any of a number of lipid species that carry a net positive charge at a selected pH, such as physiological pH (e.g., pH of about 7.0)." Ex. 1001, 12:51-53. The '069 patent includes almost three dozen examples

of cationic lipids. *Id.*, 47:34-49:55. At the time of the '069 patent, hundreds of lipids that are cationic at physiological pH were known in the art. Janoff, ¶115. In addition, because claim 1 of the '069 patent does not contain any limitation to a specific pH, the additional lipids that are cationic at a certain pH would also meet the claim limitation.

The testing in the '069 patent compares only one cationic lipid, DLinDMA, to the admitted 2:40 and 2:30 prior art formulations to illustrate alleged unexpected results. Ex. 1001, Tables 2, 4, 5; Ex. 1015, 1/31/2011 Amendment, 8-10; Janoff, ¶116. There is no support, however, for "the conclusion that other embodiments falling within the claim will behave in the same manner" as DLinDMA. *See Kao*, 639 F.3d at 1068. To the contrary, Example 5 in the '069 patent shows variation of the cationic lipid impacts efficacy. Ex. 1001, Table 6 (Samples 2 & 6 (DLin-DMA) vs. Sample 4 (DODMA)). A POSITA would understand these results to suggest that a preferred proportion for one cationic lipid (*e.g.*, DLinDMA) does not necessarily apply to all other cationic lipids (*e.g.*, DODMA). Janoff, ¶116.

In addition, it was well-known in the art that "[t]he chemical structure of the cationic lipid [had] a major impact on the transfection efficiency." Ex. 1009, E95; Janoff, ¶117. Indeed, the '613 patent incorporated by the '069 patent acknowledges that "alternative cationic lipids" to the one tested would have "different [transfection] efficiencies." *See* Ex. 1012, 1:26-28 ("[A]lternative

cationic lipids that work in essentially the same manner but with different efficiencies."); Janoff, ¶117. A POSITA would have no reason to believe that the alleged unexpected advantages of a 50-65% proportion of DLinDMA would be applicable to all cationic lipids. *Id.*

d) CLAIM 1(D): A NON-CATIONIC LIPID COMPRISING A MIXTURE OF A PHOSPHOLIPID AND CHOLESTEROL OR A DERIVATIVE THEREOF, WHEREIN THE PHOSPHOLIPID COMPRISES FROM 4 MOL% TO 10 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE AND THE CHOLESTEROL OR DERIVATIVE THEREOF COMPRISES FROM 30 MOL% TO 40 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

Patent Owner's prior disclosures teach that the non-cationic lipids may include a phospholipid and cholesterol. Ex. 1003, [0089]; Ex. 1004, [0159]. "The non-cationic lipid typically comprises … preferably from about 20% to about 85% of the total lipid present in said particle … If present … preferably the cholesterol comprises from about 20% to about 45% of the total lipid." Ex. 1003, [0091]; Ex. 1004, [0152] (overlapping range). Patent Owner's prior disclosures disclose that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." Ex. 1003, [0088]; Ex. 1004, [0152]. In addition, Patent Owner's prior disclosures incorporate by reference ('196 PCT) or directly reference ('189 publication) the '618 patent, which discloses a nucleic acid-lipid complex with 56% cationic lipid, 14% phospholipid and 30% cholesterol. Ex. 1017, 34:54-35:23.

Not only do the disclosed ranges encompass the claimed ranges, when combined with a cationic lipid proportion at the high end of the disclosed range (*i.e.*, 60%), the available range for cholesterol is decreased to 20-40%. Janoff, ¶119. The range for the other non-cationic lipid (*e.g.*, a phospholipid) is also decreased to the portion not filled with cholesterol (or PEG conjugate as described below in Claim 1(e)), namely 0%-19.5%. *Id.* The following table compares the claimed and disclosed lipid component percentages under this scenario:

	Cationic Lipid	Cholesterol	Phospholipid	PEG
'069 claims	50-65%	30-40%	4-10%	0.5-2%
Prior disclosures	60%	20-40%	0-19.5%	0.5-25%

Given the breadth of the claimed ranges for the phospholipid and cholesterol, these disclosures are sufficiently specific to anticipate the claimed ranges. *Id.*

Given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, the testing in the '069 patent does not support alleged unexpected results for the claimed ranges. Janoff, ¶119.

e) CLAIM 1(E): A CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISING FROM 0.5 MOL% TO 2 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

Patent Owner's prior disclosures teach that "[t]he SNALP further comprises a bilayer stabilizing component (BSC). …. [T]he BSC is a conjugated lipid that

inhibits aggregation of the SNALPs … present from about 0.5% to about 25% of the total lipid ….” Ex. 1003, [0092-0093]; Ex. 1004, [0152] (overlapping range). Patent Owner’s prior disclosures disclose that “[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied ….” Ex. 1003, [0088]; Ex. 1004, [0152]. “By controlling the composition and concentration of the bilayer stabilizing component, one can control … the rate at which the liposome becomes fusogenic,” impacting the transfection efficiency. Ex. 1003, [0094]; Ex. 1004, [0095]. Given the breadth of the claimed range for the conjugated lipid, these disclosures are sufficiently specific to anticipate the claimed range. Janoff, ¶120.

This limitation would have been obvious in view of Patent Owner’s prior disclosures in light of the knowledge of a POSITA. A POSITA would have been aware that conjugated lipids stabilize carrier particles by inhibiting fusogenicity. *Id.*, ¶121. It would have been obvious for a POSITA to try to increase fusogenicity, and hence potentially transfection efficiency, by choosing a proportion of conjugated lipid in the 0.5%-2% range. *Id.*

Given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, the testing in the ’069 patent does not support alleged unexpected results for the claimed ranges. Janoff, ¶121.

2. CLAIM 2: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID COMPRISES A SMALL INTERFEREING RNA (SIRNA)

Patent Owner's prior disclosures teach "the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." Ex. 1003, [0002]; Ex. 1004, [148] (siRNA); Janoff, ¶122.

3. CLAIM 3: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN THE SIRNA COMPRISES FROM ABOUT 15 TO ABOUT 60 NUCLEOTIDES

Patent Owner's prior disclosures teach "[t]he siRNA molecule may comprise about 15 to about 60 nucleotides." Ex. 1003, [0011]; Ex. 1004, [0021]; Janoff, ¶123.

4. CLAIM 4: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN THE SIRNA COMPRISES AT LEAST ONE MODIFIED NUCLEOTIDE

Patent Owner's prior disclosures teach "a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated." Ex. 1003, [0062]; Ex. 1004, [0099]. Patent Owner's prior disclosures further teach that the term "nucleic acid" "encompasses nucleic acids containing … modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring …." Ex. 1003, [0076]; Ex. 1004, [0272] (modified siRNA); Janoff, ¶124.

5. CLAIM 5: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN THE SIRNA COMPRISES AT LEAST ONE 2'-O-METHYL (2'OME) NUCLEOTIDE

Patent Owner's prior disclosures teach that the term "nucleic acid" "encompasses nucleic acids containing … modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring …. Examples of such analogs include, without limitation … 2-O-methyl ribonucleotides …." Ex. 1003, [0076]; Ex. 1004, [0129]. A 2-O-methyl ribonucleotide is a 2'-O-methyl nucleotide. Janoff, ¶125.

6. CLAIM 6: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN SAID SIRNA IS ABOUT 19 TO ABOUT 25 BASE PAIRS IN LENGTH

Patent Owner's prior disclosures teach "siRNA … of about … 19-25 (duplex) nucleotides in length." Ex. 1003, [0065]; Ex. 1004, [0057]; Janoff, ¶126.

7. CLAIM 7: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN SAID SIRNA COMPRISES 3' OVERHANGS

Patent Owner's prior disclosures teach that "siRNA duplexes may comprise 3' overhangs of about 1 to about 4 nucleotides, preferably of about 2 to about 3 nucleotides and 5' phosphate termini." Ex. 1003, [0065]; Ex. 1004, [0057]; Janoff, ¶127.

8. CLAIM 8: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CATIONIC LIPID COMPRISES FROM 52 MOL% TO 62 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(c). For the reasons stated above, Patent Owner's prior disclosures

disclose this range with sufficient specificity to anticipate. Janoff, ¶128. Overlapping ranges of this narrower range also renders this limitation *prima facie* obvious. *Id.*

9. CLAIM 9: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE PHOSPHOLIPID COMPRISES DIPALMITOYLPHOSPHATIDYLCHOLINE (DPPC), DISTEAROYLPHOSPHATIDYLCHOLINE (DSPC), OR A MIXTURE THEREOF

Patent Owner's prior disclosures teach that "[e]xamples of noncationic lipids useful in the present invention include: phospholipid-related materials, such as … DSPC … DPPC …." Ex. 1003, [0089]; Ex. 1004, [0159]. Patent Owner's prior disclosures also teach using more than one phospholipid. Ex. 1003, [0128]; Ex. 1004, [0159]; Janoff, ¶129.

10. CLAIM 10: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISES A POLYETHYLENEGLYCOL (PEG)-LIPID CONJUGATE

Patent Owner's prior disclosures teach that "[b]ilayer stabilizing components include, but are not limited to, conjugated lipids that inhibit aggregation of the SNALPs, polyamide oligomers (*e.g.*, ATTA-lipid derivatives), peptides, proteins, detergents, lipid-derivatives, PEG-lipid derivatives …." Ex. 1003, [0052], *see also* [0013]; Ex. 1004, [0088]; Janoff, ¶130.

11. CLAIM 11: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 10, WHEREIN THE PEG-LIPID CONJUGATE COMPRISES A PEG-DIACYLGLYCEROL (PEG-DAG) CONJUGATE, A PEG-DIALKYLOXYPROPYL (PEG-DAA) CONJUGATE, OR A MIXTURE THEREOF

Patent Owner's prior disclosures teach that "[t]he PEG-lipid conjugate may be one or more of a PEG-dialkyloxypropyl (DAA), a PEG-diacylglycerol (DAG) … and combinations thereof." Ex. 1003, [0013]; Ex. 1004, [0088]; Janoff, ¶131.

12. CLAIM 12: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 11, WHEREIN THE PEG-DAA CONJUGATE COMPRISES A PEG-DIMYRISTYLOXYPROPYL (PEG-DMA) CONJUGATE, A PEG-DISTEARYLOXYPROPYL (PEG-DSA) CONJUGATE, OR A MIXTURE THEREOF

Patent Owner's prior disclosures teach "three exemplary PEG-dialkyloxypropyl derivatives suitable for use in the present invention … PEG-C-DMA … PEG-A-DMA … and … PEG-S-DMA." Ex. 1003, [0031]; Ex. 1004, [0292] (PEG-DMA). Patent Owner's prior disclosures teach "[o]ther PEG DAAs suitable for use in the present invention can be synthesized using similar protocols. For instance, PEG-A-DSA and PEG-C-DSA can be synthesized …." Ex. 1003, [0242]; Janoff, ¶132.

13. CLAIM 13: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 12, WHEREIN THE PEG HAS AN AVERAGE MOLECULAR WEIGHT OF ABOUT 2,000 DALTONS

Patent Owner's prior disclosures teach "[i]n a preferred embodiment, the PEG has an average molecular weight of from about 1000 to about 5000 daltons, more preferably, from about 1,000 to about 3,000 daltons and, even more preferably, of

about 2,000 daltons." Ex. 1003, [0097]; Ex. 1004, [0083]; Janoff, ¶133.

14. CLAIM 14: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 10, WHEREIN THE NUCLEIC ACID-LIPID PARTICLE COMPRISES ABOUT 57.1 MOL% CATIONIC LIPID, ABOUT 7.1 MOL% PHOSPHOLIPID, ABOUT 34.3 MOL% CHOLESTEROL OR A DERIVATIVE THEREOF, AND ABOUT 1.4 MOL% PEG-LIPID CONJUGATE

It is unclear from the '069 patent specification what "comprises … about…" encompasses in the identified claim. The specification is silent on the meaning of the term "about" in this context. Janoff, ¶134. During prosecution, the examiner stated in this context that "'comprising about' could embrace an amount ±10, 20, 30 mol% of a lipid component." Ex. 1016, 5/12/11 Rejection, 2. Using this construction, the claim is invalid for the reasons presented above for Claim 1. Janoff, ¶134.

15. CLAIM 15: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLE COMPRISES FROM 1 MOL% TO 2 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(e). For the reasons stated above, the Patent Owner's prior disclosures disclose this range with sufficient specificity to anticipate. Janoff, ¶135. In the alternative, this range is obvious given the overlapping range in Patent Owner's prior disclosures. *Id.*

16. CLAIM 16: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID IN THE NUCLEIC ACID-LIPID PARTICLE IS NOT SUBSTANTIALLY DEGRADED AFTER INCUBATION OF THE PARTICLE IN SERUM AT 37°C FOR 30 MINUTES

Patent Owner's prior disclosures teach "[i]n some embodiments … the nucleic acid in the nucleic acid-lipid particle is resistant in aqueous solution to degradation by a nuclease." Ex. 1003, [0011]; Ex. 1004, [0076]. Patent Owner's prior disclosures teach "'[s]erum-stable' in relation to nucleic acid-lipid particles means that the particle is not significantly degraded after exposure to a serum or nuclease assay that would significantly degrade free DNA." Ex. 1003, [0082]; Ex. 1004, [0105]. Patent Owner's prior disclosures teach "[s]amples are incubated at 37°C for 30 min …." Ex. 1003, [0204]; Ex. 1004, [0291-0292] (incubated). Given these disclosures, a POSITA would have understood the limitation to be disclosed. Janoff, ¶136.

In the alternative, this limitation would have been obvious in view of Patent Owner's prior disclosures in light of the knowledge of a POSITA. A POSITA would have been aware that the disclosed sample incubation parameters could have been used to establish serum stability as disclosed in Patent Owner's prior disclosures. *Id.*, ¶137. It would have been obvious to incubate samples at 37°C for 30 min to establish serum stability. *Id.*

17. CLAIM 17: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS FULLY ENCAPSULATED IN THE NUCLEIC ACID-LIPID PARTICLE

Patent Owner's prior disclosures teach "[i]n some embodiments, the siRNA molecule is fully encapsulated within the lipid bilayer of the nucleic acid-lipid particle such that the nucleic acid in the nucleic acid-lipid particle is resistant in aqueous solution to degradation by a nuclease." Ex. 1003, [0011]; Ex. 1004, [0151]; Janoff, ¶138.

18. CLAIM 18: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID-LIPID PARTICLE HAS A LIPID:NUCLEIC ACID MASS RATIO OF FROM ABOUT 5 TO ABOUT 15

Patent Owner's prior disclosures teach "the nucleic acid to lipid ratios (mass/mass ratios) in a formed SNALP will range from about 0.01 to about 0.08 … and, more preferably, about 0.04 …." Ex. 1003, [0127]; Ex. 1004, [0198]. This corresponds to a lipid:nucleic acid mass ratio of 12.5 to 100. Janoff, ¶139. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. *Id.*

This limitation would have been obvious in view of Patent Owner's prior disclosures in light of the knowledge of a POSITA. *Id.*, ¶140. A POSITA would have been aware that the total mass of the lipid frequently needs to exceed the mass of the nucleic acid to ensure that the negative charge on the nucleic acid is overcome by the positive cationic lipid charge. Moreover, given the explicit disclosure of an

overlapping range, this limitation is obvious. Janoff, ¶140.

19. CLAIM 19: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID-LIPID PARTICLE HAS A MEDIAN DIAMETER OF FROM ABOUT 40 NM TO ABOUT 150 NM

Patent Owner's prior disclosures teach "[t]he SNALPs made by the methods of this invention are typically about 50 to about 150 nm in diameter." Ex. 1003, [0120], [0139]; Ex. 1004, [0201]. Given the breadth of the claimed range, this disclosure is sufficiently specific to anticipate the claimed range. Janoff, ¶141.

Given the explicit disclosure of an overlapping range, this limitation is obvious and, as discussed above, the testing in the '069 patent does not support alleged unexpected results for the claimed ranges. Janoff, ¶141.

20. CLAIM 20: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE PHOSPHOLIPID COMPRISES FROM 5 MOL% TO 9 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(d). For the reasons stated above, Patent Owner's prior disclosures disclose this range with sufficient specificity to anticipate. Janoff, ¶142. In the alternative, this range is *prima facie* obvious given the overlapping range in Patent Owner's prior disclosures. *Id.*

21. CLAIM 21: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CHOLESTEROL OR DERIVATIVE THEREOF COMPRISES FROM 32 MOL% TO 36 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(d). For the reasons stated above, Patent Owner's prior disclosures disclose this range with sufficient specificity to anticipate. Janoff, ¶143.

In the alternative, this range is *prima facie* obvious given the overlapping range in Patent Owner's prior disclosures. *Id.*

22. CLAIM 22: A PHARMACEUTICAL COMPOSITION COMPRISING A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1 AND A PHARMACEUTICALLY ACCEPTABLE CARRIER

Patent Owner's prior disclosures teach "[t]he invention also provides for pharmaceutically acceptable compositions comprising a nucleic acid-lipid particle." Ex. 1003, [0019]; Ex. 1004, [0018]; Janoff, ¶144.

B. GROUND 2: CLAIMS 1-22 ARE OBVIOUS IN VIEW OF PATENT OWNER'S PRIOR DISCLOSURES IN LIGHT OF LIN AND AHMAD

Claims 1-22 of the '069 patent are obvious under 35 U.S.C. § 103 in view of Patent Owner's prior disclosures in light of Lin and Ahmad. Claims 1-22 are disclosed by Patent Owner's prior disclosures as discussed in Ground 1 above. To the extent that those disclosures alone are determined not to disclose a proportion of cationic lipid in the 50%-65% range, a POSITA would have understood from Lin and Ahmad that such proportions of cationic lipid may increase transfection efficacy and would have been motivated to combine those disclosures with the system disclosed in the '196 PCT and '189 publication with a reasonable expectation of success. Janoff, ¶145.

1. CLAIM 1(C): A CATIONIC LIPID COMPRISING FROM 50 MOL% TO 65 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

To the extent that Patent Owner's prior disclosures are determined not to disclose the claimed range for cationic lipids, this limitation would have been

obvious in view of Lin and Ahmad.

As discussed above, a POSITA would understand the testing of Lin to suggest that the cationic lipid mol% of nucleic acid-lipid particles can impact transfection efficiency and that for certain cationic lipid components a mol% greater than 50% may increase the transfection efficiency of the carrier particles. Ex. 1006, Fig. 4(a); Janoff, ¶146. While Lin acknowledges the complicated nature of maximizing transfection efficiencies, a particular cationic lipid tested in Lin (DOTAP) is specifically identified as a potential cationic lipid that can be used in the system claimed in the '069 patent. Ex. 1001, 18:5. Similarly the helper lipid in Lin, DOPC, is disclosed for use in the '069 patent. *Id.*, 57:60. A POSITA would understand the testing of Lin to suggest that the mol% of cationic lipid in nucleic acid-lipid particles using DOTAP/DOPC can impact transfection efficiency, and that for certain cationic lipids (*e.g.*, DOTAP) in systems with DOPC, transfection efficiency might continue to improve at a mol% above 50 percent. Janoff, ¶105 (another example in overlap is the DMRIE/DOPC formulations).

It would have been obvious for a POSITA to combine the disclosed ranges in either the '196 PCT or '189 publication with the teachings of Lin to increase the cationic lipid to the 50%-65% range in order to potentially increase the transfection efficiency. Janoff, ¶146. Lin tested helper lipids and cationic lipids to create carrier particles for nucleic acids, *i.e.*, "nucleic acid-lipid particles," the same general carrier

particles described in Patent Owner's prior disclosures. The goal of Lin was to increase transfection efficiency in *in vitro* applications by varying different parameters in cationic liposome, including the mol% of cationic lipid. Ex. 1006, 3307. Similarly, the '196 PCT and '189 publication both concern "efficiently deliver administer siRNA molecules" (Ex. 1003, [0045]; *see also* Ex. 1004, [0118]) in *in vitro* and *ex vivo* applications (Ex. 1003, [0017]; Ex. 1004, [0016]).

Patent Owner's prior disclosures specifically disclose cationic lipid proportions up to 60% and state that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *See, e.g.*, Ex. 1003, [0088]; *see also* Ex. 1004 [0152]. These disclosures also stress the importance of "efficiently deliver administer siRNA molecules." Ex. 1003, [0045]; *see also* Ex. 1004, [0118]. A POSITA would have looked to the prior art, including Lin, in order to determine the most appropriate proportions of, *e.g.*, cationic lipid. Janoff, ¶148. Given the success of generating nucleic acid-lipid particles with a cationic lipid proportion greater than 50% as described in Patent Owner's prior disclosures, a POSITA would have appreciated a reasonable expectation of doing so. *Id.*

A POSITA would understand the testing of Ahmad to support the proposition that for certain formulations, cationic lipids can increase transfection efficiency when they are incorporated above 50 mol%. *Id.*; Ex. 1007, 739-40; Fig. 3(a). In these formulations, transfection efficiency was reported to decrease above a certain

mol% cationic lipid (*e.g.*, around 70%). Ex. 1007, 739-40; Fig. 3(a). This was specifically applicable to formulations including DOTAP (also identified as a potential cationic lipid for use in the '069 patent) as well as for various "multivalent lipids." The '069 patent specifically discloses using multivalent lipids such as DOSPA and DOGS (18:10-11).

It would have been obvious for a POSITA to combine the disclosed ranges in either the '196 PCT or '189 publication with the teachings of Ahmad to increase the cationic lipid to the 50%-65% range in order to potentially increase the transfection efficiency. Janoff, ¶147. Ahmad tested helper lipids and cationic lipids to create carrier particles for nucleic acids, *i.e.*, "nucleic acid-lipid particles," the same general carrier particles described in Patent Owner's prior disclosures. Ahmad's goal was similarly to "identify the interactions between the CL-DNA complexes and the cells along the transfection pathway to overcome the biological impediments to optimal transfection" in *in vitro* applications. Ex. 1007, 740, 747 ("The presented transfection optimization strategy is directly relevant for gene therapy using *ex vivo* methods …."). Similarly, the '196 PCT and '189 publication both concern "efficiently deliver administer siRNA molecules" (Ex. 1003, [0045]; *see also* Ex. 1004, [0118]) in *in vitro* and *ex vivo* applications (Ex. 1003, [0017]; Ex. 1004, [0016]).

Patent Owner's prior disclosures specifically disclose cationic lipid

proportions up to 60% and state that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *See, e.g.*, Ex. 1003, [0088]; *see also* Ex. 1004 [0152]. These disclosures also stress the importance of "efficiently deliver administer siRNA molecules." Ex. 1003, [0045]; *see also* Ex. 1004, [0118]. A POSITA would have looked to the prior art, including Ahmad, in order to determine the most appropriate proportions of, *e.g.*, cationic lipid. Janoff, ¶148. Given the success of generating nucleic acid-lipid particles with a cationic lipid proportion greater than 50% as described in Patent Owner's prior disclosures, a POSITA would have appreciated a reasonable expectation of doing so. *Id.*

It would have been obvious for a POSITA to combine the disclosures in Lin and Ahmad. Four of the authors in the references overlap. Exs. 1006-1007. Ahmad builds on the work of Lin and references the findings of Lin explicitly. Ex. 1007, 743, 747; Janoff, ¶104. Given that, a POSITA would have been motivated to combine the references. *Id.*

2. CLAIM 8: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CATIONIC LIPID COMPRISES FROM 52 MOL% TO 62 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(c). For the reasons stated above, this range is obvious in view of Patent Owner's prior disclosures when combined with Lin and Ahmad. Janoff, ¶149. Again, Lin and Ahmad disclose that cationic mol% in the claimed range may increase transfection efficacy for certain lipid combinations.

C. GROUND 3: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '554 PUBLICATION

Claims 1-22 of the '069 patent are anticipated under 35 U.S.C. § 102(b) (pre-AIA) or obvious under 35 U.S.C. § 103 in view of the '554 publication. While the '554 publication does not disclose the exact same ranges of lipid components from claim 1 of the '069 patent explicitly, it discloses encompassing and overlapping ranges with sufficient specificity to anticipate. Janoff, ¶150. Moreover, the disclosed ranges establish obviousness and the testing in the '069 patent does not support alleged unexpected results for the claimed ranges. *Id.*

1. CLAIM 1

a) CLAIM 1(A): A NUCLEIC ACID-LIPID PARTICLE COMPRISING:

The '554 publication teaches "novel cationic lipids … and formulations thereof with biologically active molecules." Ex. 1005, [0019]. As one example, "the invention features a composition comprising a biologically active molecule (e.g., a polynucleotide such as a siNA, … [or] other nucleic acid molecule …), a cationic lipid, a neutral lipid, and a polyethyleneglycol conjugate, such as a PEG-diacylglycerol, PEG-diacylglycamide, PEG-cholesterol, or PEG-DMB conjugate." *Id.*, [0082]; Janoff, ¶151.

b) CLAIM 1(B): A NUCLEIC ACID

The '554 publication teaches "compositions … with biologically active molecules" including "nucleic acids." Ex. 1005, [0018-0019]. As one example, "the

invention features a composition comprising a biologically active molecule (e.g., a polynucleotide such as a siNA, antisense, aptamer, decoy, ribozyme, 2-5A, triplex forming oligonucleotide, [or] other nucleic acid molecule …)." *Id.*, [0082]; Janoff, ¶152.

c) CLAIM 1(C): A CATIONIC LIPID COMPRISING FROM 50 MOL% TO 65 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The '554 publication teaches "[c]ationic lipids that are useful in the present invention can be any of a number of lipid species which carry a net positive charge at a selected pH, such as physiological pH." Ex. 1005, [0454]; Janoff, ¶153. "[T]he cationic lipid component … comprises from about 2% to about 60% … or from about 40% to about 50% of the total lipid …." Ex. 1005, [0116]. In addition, the '554 publication also includes various specific formulations which include 50% or greater cationic lipid. *Id.*, Table 4 (*e.g.*, L054, L097, L109 (50% cationic lipid), L060-061, L098-103, L114, L116-117 (52%)).

The '554 publication also teaches particles "can transition from a stable lamellar structure adopted in circulation (i.e., in plasma or serum) at physiologic pH (about pH 7.4) to a less stable and more efficient delivery composition having an inverted hexagonal structure at pH 5.5-6.5, which is the pH found in the early endosome." *Id.*, [0137]. The cationic lipid is the active component in such the pH-dependent nucleic acid-lipid particles: "[s]uitable cationic lipid include those

cationic lipids which carry a net negative [*sic*] charge at a selected pH ….” *Id.*, [0083] (should refer to a net “positive” charge). A POSITA would understand that increasing the mol% of a cationic lipid with pH sensitivity in these particles might increase transfection efficiency since this event is fusion related and thought to occur as a result of the described phase shift. Janoff, ¶154.

Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. *Id.*, ¶155. For example, not only does the disclosed range substantially overlap with the claimed range, a preferred embodiment in the reference recites a narrower range that also partially overlaps and specific examples are provided within the claimed range for this lipid component. *Id.* In addition, a POSITA would be compelled to choose cationic lipid proportions at the top end of the recited range to increase the efficiency of the described phase shift. *Id.*

Additionally, the disclosed ranges establish *prima facie* obviousness which creates a presumption of obviousness. *E.I. Dupont*, No. 2017-1977, slip op. at *18-20; Janoff, ¶156. As discussed above, the testing in the ’069 patent does not support alleged unexpected results for the claimed ranges. *Id.*

d) CLAIM 1(D): A NON-CATIONIC LIPID COMPRISING A MIXTURE OF A PHOSPHOLIPID AND CHOLESTEROL OR A DERIVATIVE THEREOF, WHEREIN THE PHOSPHOLIPID COMPRISES FROM 4 MOL% TO 10 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE AND THE CHOLESTEROL OR DERIVATIVE THEREOF COMPRISES FROM 30 MOL% TO 40 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The '554 publication teaches "[t]he noncationic lipids used in the present invention can be any of a variety of neutral uncharged, zwitterionic or anionic lipids capable of producing a stable complex." Ex. 1005, [0455]. Neutral lipids are defined as "any lipophilic compound having non-cationic charge (e.g., anionic or neutral charge)." *Id.*, [0315]. "[T]he neutral lipid component … comprises … from about 20% to about 85% of the total lipid present in the formulation … the cholesterol component … comprises … from about 20% to about 45% of the total lipid present." *Id.*, [0313]. In addition, the '554 publication also includes various specific formulations which include cholesterol at a 30% proportion. *Id.*, Table 4 (*e.g.*, L106). Not only do the disclosed ranges encompass the claimed ranges, when the cationic lipid proportion is set at the maximum disclosed (*i.e.*, 60%), the '554 publication discloses the remaining 40% can be made up of cholesterol at 20-40%. *Id.*, [0313]. When the cholesterol is less than the full remaining 40%, another non-cationic lipid (*e.g.*, a phospholipid) may be added at up to 20% (unless a PEG conjugate is also added as described below for Claim 1(e), in which case this percentage is adjusted accordingly). *Id.* The following table compares the claimed

and disclosed lipid component percentages under this scenario:

	Cationic Lipid	Cholesterol	Phospholipid	PEG
'069 claims	50-65%	30-40%	4-10%	0.5-2%
'554 publication	60%	20-40%	0-19%	1-20%

Given the breadth of the claimed ranges for the phospholipid and cholesterol, these disclosures are sufficiently specific to anticipate the claimed ranges. Janoff, ¶157.

Given the explicit disclosure of encompassing ranges, this limitation is obvious and, as discussed above, the testing in the '069 patent does not support alleged unexpected results for the claimed ranges. Janoff, ¶158.

e) CLAIM 1(E): A CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISING FROM 0.5 MOL% TO 2 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE.

The '554 publication teaches "[i]n addition to cationic and neutral lipids, the formulated molecular compositions of the present invention comprise a polyethyleneglycol (PEG) conjugate." Ex. 1005, [0457]. The '554 publication further teaches "[i]t is often desirable to include other components that act in a manner similar to the DAG-PEG conjugates and that serve to prevent particle aggregation …." *Id.*, [0504]. "[T]he PEG conjugate … comprises from about 1% to about 20% … of the total lipid present." *Id.*, [0118]. Given the breadth of the claimed range for the conjugated lipid, these disclosures are sufficiently specific to

anticipate the claimed range. Janoff, ¶159.

This limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. A POSITA would have been aware that conjugated lipids stabilize carrier particles by inhibiting fusogenicity. *Id.*, ¶160. It would have been obvious for a POSITA to try to increase the fusogenicity, and hence potentially the transfection efficiency, by choosing a proportion of conjugated lipid in the 0.5%-2% range. *Id.* Moreover, given the explicit disclosure of encompassing ranges, this limitation is obvious and, as discussed above, the testing in the '069 patent does not support alleged unexpected results for the claimed ranges. *Id.*, ¶160.

2. CLAIM 2: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID COMPRISES A SMALL INTERFEREING RNA (SIRNA)

The '554 publication teaches "formulations for the delivery of chemically-modified synthetic short interfering nucleic acid (siNA) molecules that modulate target gene expression or activity in cells, tissues, such as in a subject or organism, by RNA interference (RNAi)." Ex. 1005, [0020]; Janoff, ¶161.

3. CLAIM 3: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN THE SIRNA COMPRISES FROM ABOUT 15 TO ABOUT 60 NUCLEOTIDES

The '554 publication teaches "[t]he siNA can be, for example, about 15 to about 40 nucleotides in length" or "about 38 to about 70 … nucleotides in length." Ex. 1005, [0209], [0240]. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Janoff, ¶162.

Given the explicit disclosure of encompassing ranges, this limitation is obvious. Janoff, ¶162.

4. CLAIM 4: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN THE SIRNA COMPRISES AT LEAST ONE MODIFIED NUCLEOTIDE

The '554 publication teaches "the siNA component of a formulated siNA composition of the invention is chemically modified so as not to stimulate an interferon response in a mammalian cell, subject, or organism." Ex. 1005, [0102]; Janoff, ¶163.

5. CLAIM 5: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN THE SIRNA COMPRISES AT LEAST ONE 2'-O-METHYL (2'OME) NUCLEOTIDE

The '554 publication teaches "examples of such chemical modifications include without limitation … 2′-O-methyl ribonucleotides …." Ex. 1005, [0194]; Janoff, ¶164.

6. CLAIM 6: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN SAID SIRNA IS ABOUT 19 TO ABOUT 25 BASE PAIRS IN LENGTH

The '554 publication teaches "the invention features a formulated siNA composition comprising a short interfering nucleic acid (siNA) molecule that down-regulates expression of a target gene, wherein said siNA molecule comprises about 15 to about 28 base pairs." Ex. 1005, [0178]. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. *Id*. Given the explicit disclosure of encompassing ranges, this limitation is obvious.

Janoff, ¶165.

7. CLAIM 7: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN SAID SIRNA COMPRISES 3' OVERHANGS

The '554 publication teaches "siNA molecules of the invention comprise duplex nucleic acid molecules with overhanging ends of about 1 to about 3 (e.g., about 1, 2, or 3) nucleotides, for example, about 21-nucleotide duplexes with about 19 base pairs and 3′-terminal mononucleotide, dinucleotide, or trinucleotide overhangs." Ex. 1005, [0193]; Janoff, ¶166.

8. CLAIM 8: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CATIONIC LIPID COMPRISES FROM 52 MOL% TO 62 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(c). For the reasons stated above, the '554 publication discloses this range with sufficient specificity to anticipate. Janoff, ¶167. In the alternative, this range is obvious given the overlapping range in the '554 publication. *Id.*

9. CLAIM 9: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE PHOSPHOLIPID COMPRISES DIPALMITOYLPHOSPHATIDYLCHOLINE (DPPC), DISTEAROYLPHOSPHATIDYLCHOLINE (DSPC), OR A MIXTURE THEREOF

The '554 publication teaches "suitable neutral lipids include … DSPC … DPPC … and/or a mixture thereof." Ex. 1005, [0085]; Janoff, ¶168.

10. CLAIM 10: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISES A POLYETHYLENEGLYCOL (PEG)-LIPID CONJUGATE

The '554 publication teaches "[i]n addition to cationic and neutral lipids, the

formulated molecular compositions of the present invention comprise a polyethyleneglycol (PEG) conjugate." Ex. 1005, [0457]; Janoff, ¶169.

11. CLAIM 11: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 10, WHEREIN THE PEG-LIPID CONJUGATE COMPRISES A PEG-DIACYLGLYCEROL (PEG-DAG) CONJUGATE, A PEG-DIALKYLOXYPROPYL (PEG-DAA) CONJUGATE, OR A MIXTURE THEREOF

The '554 publication teaches "[s]uitable polyethyleneglycol-diacylglycerol or polyethyleneglycol-diacylglycamide (PEG-DAG) conjugates …." Ex. 1005, [0086]. Because one of the listed species of PEG-lipid conjugates is disclosed, this element is anticipated. Janoff, ¶170.

12. CLAIM 12: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 11, WHEREIN THE PEG-DAA CONJUGATE COMPRISES A PEG-DIMYRISTYLOXYPROPYL (PEG-DMA) CONJUGATE, A PEG-DISTEARYLOXYPROPYL (PEG-DSA) CONJUGATE, OR A MIXTURE THEREOF

This limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. Janoff, ¶171. A POSITA would have been aware that PEG-dialkyloxypropyl (PEG-DAA) conjugates could be used in lieu of PEG-diacylglycerol (PEG-DAG) conjugates and that PEG-dialkyloxypropyl (PEG-DAA) conjugates can comprises a PEG-dimyristyloxypropyl (PEG-DMA) conjugate, a PEG-distearyloxypropyl (PEG-DSA) conjugate, or a mixture thereof. *Id.*, ¶171. Indeed, Patent Owner's prior disclosures from years before the '069 patent priority date address using PEG-DAA conjugates (*e.g.*, PEG-DMA or PEG-DSA) in lieu of PEG-DAG conjugates. *See, e.g.*, Ex. 1015, [0016].

13. CLAIM 13: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 12, WHEREIN THE PEG HAS AN AVERAGE MOLECULAR WEIGHT OF ABOUT 2,000 DALTONS

This limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. Janoff, ¶172. A POSITA would have been aware of PEG 2000 with an average molecular weight of about 2,000 daltons. *Id.* Indeed, Patent Owner's prior disclosures from years before the '069 patent priority date states: "PEGs are classified by their molecular weights; for example, PEG 2000 has an average molecular weight of about 2,000 daltons." *See, e.g.*, Ex. 1015, [0016].

14. CLAIM 14: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 10, WHEREIN THE NUCLEIC ACID-LIPID PARTICLE COMPRISES ABOUT 57.1 MOL% CATIONIC LIPID, ABOUT 7.1 MOL% PHOSPHOLIPID, ABOUT 34.3 MOL% CHOLESTEROL OR A DERIVATIVE THEREOF, AND ABOUT 1.4 MOL% PEG-LIPID CONJUGATE

See Claim 1(c). Janoff, ¶173. As noted above, the "about" language in this limitation encompasses amounts ±10, 20, 30 mol% from the amounts listed in Claim 14 that still fall within the ranges in Claim 1. For this reason, the claimed are invalid for the reasons presented above for Claim 1.

15. CLAIM 15: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLE COMPRISES FROM 1 MOL% TO 2 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(e). For the reasons stated above, the '554 publication discloses this range with sufficient specificity to anticipate. Janoff, ¶174. In the alternative,

this range is obvious given the overlapping range in the '554 publication. *Id.*

16. CLAIM 16: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID IN THE NUCLEIC ACID-LIPID PARTICLE IS NOT SUBSTANTIALLY DEGRADED AFTER INCUBATION OF THE PARTICLE IN SERUM AT 37°C FOR 30 MINUTES

The '554 publication teaches "[f]ormulated siNA compositions are complexed in EGM basal media (Bio Whittaker) at 37° C for 30 minutes in polystyrene tubes." Ex. 1005, [0588]. Moreover, the '554 publication is directed at "delivery agents that are serum stable, i.e. stable in circulation, that can undergo structural transformation, for example from lamellar phase to inverse hexagonal phase, under biological conditions." *Id.*, [0014]. Given these disclosures, a POSITA would have understood the limitation to be disclosed. Janoff, ¶175.

In the alternative, this limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. A POSITA would have been aware that the disclosed sample incubation parameters could have been used to establish serum stability as disclosed in the '554 publication. *Id.*, ¶176. It would have been obvious for a POSITA to incubate samples at 37°C for 30 min to establish serum stability. *Id.*

17. CLAIM 17: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS FULLY ENCAPSULATED IN THE NUCLEIC ACID-LIPID PARTICLE

The '554 publication teaches "[t]he encapsulation of anionic compounds using cationic lipids is essentially quantitative due to electrostatic interaction." Ex.

1005, [0011]. A POSITA would understand that full encapsulation requires only an excess of cationic lipid with regard to the nucleic acid for electrostatic interaction. Janoff, ¶177.

18. CLAIM 18: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID-LIPID PARTICLE HAS A LIPID:NUCLEIC ACID MASS RATIO OF FROM ABOUT 5 TO ABOUT 15

The '554 publication teaches "the siNA to lipid ratios (mass/mass ratios) in a formed formulated molecular composition range from about 0.01 to about 0.08." Ex. 1005, [0167]. This corresponds to a lipid:nucleic acid mass ratio of 12.5 to 100. Janoff, ¶178. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. *Id.*, ¶178.

This limitation would have been obvious in view of the '196 PCT in light of the knowledge of a POSITA. *Id.*, ¶179. A POSITA would have been aware that the total mass of the lipid frequently needs to exceed the mass of the nucleic acid to ensure that the negative charge on the nucleic acid is overcome by the positive cationic lipid charge.

Given the explicit disclosure of an overlapping range, this limitation is obvious. Janoff, ¶179.

19. CLAIM 19: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID-LIPID PARTICLE HAS A MEDIAN DIAMETER OF FROM ABOUT 40 NM TO ABOUT 150 NM

The '554 publication teaches "[n]anoparticles of the invention typically range

from about 1 to about 999 nm in diameter, and can include an encapsulated or enclosed biologically active molecule." Ex. 1005, [0317]. In addition, the '554 publication teaches "[t]he formulated particles made by the methods of this invention have a size of about 50 to about 600 nm or more, with certain of the particles being about 65 to 85 nm." *Id.*, [0463]. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Janoff, ¶180.

Given the explicit disclosure of an overlapping range, this limitation is obvious. Janoff, ¶180.

20. CLAIM 20: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE PHOSPHOLIPID COMPRISES FROM 5 MOL% TO 9 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(d). For the reasons stated above, the '554 publication discloses this range with sufficient specificity to anticipate. Janoff, ¶181. In the alternative, this range is obvious given the overlapping range in the '554 publication. *Id.*

21. CLAIM 21: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CHOLESTEROL OR DERIVATIVE THEREOF COMPRISES FROM 32 MOL% TO 36 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(d). For the reasons stated above, the '554 publication discloses this range with sufficient specificity to anticipate. Janoff, ¶182. In the alternative, this range is obvious given the overlapping range in the '554 publication. *Id.*

22. CLAIM 22: A PHARMACEUTICAL COMPOSITION COMPRISING A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1 AND A PHARMACEUTICALLY ACCEPTABLE CARRIER

The '554 publication teaches "[t]he pharmaceutical carrier is generally added following formulated siNA composition formation. Thus, after the formulated siNA composition is formed, the formulated siNA composition can be diluted into pharmaceutically acceptable carriers such as normal saline." Ex. 1005, [0502]; Janoff, ¶183.

Dated: January 9, 2019

Respectfully submitted,

By: /s/ *Michael R. Fleming*

Michael R. Fleming, Esq. (Reg. No. 67,933)
IRELL & MANELLA LLP
1800 Avenue of the Stars, Suite 900
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Attorneys for Petitioner

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24(d), I certify that the present paper contains 13,990 words as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, table of exhibits, mandatory notices, certificate of service, or this certificate of word count.

Dated: January 9, 2019

/s/ Michael R. Fleming
Michael R. Fleming

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. sections 42.6 and 42.105, that a complete copy of the Petition for Inter Partes Review of U.S. Patent No. 8,058,069 and Exhibits 1001 through 1019 are being served upon the patent prosecution counsel of record for Patent Owner via Express Mail at the address below on the 9th day of January, 2019, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board:

Kilpatrick Townsend & Strockton LLP
Mailstop: IP Docketing – 22
1100 Peachtree Street, Ste. 2800
Atlanta, GA 30309

/s/ Susan M. Langworthy
Susan M. Langworthy

JOINT APPENDIX 84

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

Moderna Therapeutics, Inc.

Petitioner

v.

Protiva Biotherapeutics, Inc.

Patent Owner

_____

U.S. Patent No. 8,058,069

Issued: November 15, 2011

Named Inventors: Edward Yaworski, Kieu Lam, Lloyd Jeffs, Lorne Palmer, Ian MacLachlan

Title: Lipid Formulations for Nucleic Acid Delivery

_____

DECLARATION OF ANDREW S. JANOFF, PH.D. IN SUPPORT OF MODERNA THERAPEUTICS, INC.'S PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,058,069

Mail Stop: PATENT BOARD
Patent Trial and Appeal Board
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Alexandria, VA 22313-1450

TABLE OF CONTENTS

I, Dr. Andrew S. Janoff, PhD, declare as follows:

I. INTRODUCTION

1. My name is Andrew S. Janoff. I am a consultant in biotechnology and drug delivery, primarily focusing on lipid and liposome technology.

2. I have been engaged by Moderna Therapeutics, Inc. ("Moderna") as an expert in connection with matters raised in the Petition for *Inter Partes* Review ("Petition") of U.S. Patent No. 8,058,069 (the "'069 patent") owned by Protiva Biotherapeutics, Inc. ("Patent Owner").

3. This declaration is based on the information currently available to me. To the extent that additional information becomes available, I reserve the right to continue my investigation and study, which may include a review of documents and information that may be produced, as well as testimony from depositions that have not yet been taken.

II. SUMMARY OF OPINIONS

4. The '069 patent is entitled "Lipid Formulations for Nucleic Acid Delivery." Ex. 1001. The '069 patent is directed to a composition of nucleic acid-lipid particles (*e.g.*, particles that can be used to deliver therapeutic nucleic acid payloads) comprising four lipid components (*i.e.*, cationic lipid, phospholipid, cholesterol, and conjugated lipid), each of which fall within a claimed proportion with regard to the total lipid in the particles. *See, e.g.*, Ex.

1001, cl. 1. The petition challenges claims 1-22 of the '069 patent.

5. Petitioner's Ground 1 challenges claims 1-22 of the '069 patent as anticipated by the Patent Owner's prior disclosures in PCT/CA2004/001051, Publication No. WO2005007196 A2 ("'196 PCT"), Ex. 1003, or U.S. Patent Publication No US2006/0134189 ("'189 publication"), Ex. 1004, under pre-AIA 35 U.S.C. § 102(b) or, in the alternative, as obvious under pre-AIA 35 U.S.C. § 103 in view of Patent Owner's prior disclosures. Based on studying the petition and the exhibits cited in the petition as well as other documents, it is my opinion that claims 1-22 of the '069 patent are anticipated by the Patent Owner's prior disclosures, including the '196 PCT or the '189 publication. In the alternative, it is my opinion that claims 1-22 of the '069 patent are obvious in view of the Patent Owner's prior disclosures.

6. Petitioner's Ground 2 challenges claims 1-22 of the '069 patent as obvious in view of the Patent Owner's prior disclosures in light of Lin, Ex. 1006, and Ahmad, Ex. 1007, under pre-AIA 35 U.S.C. § 103. Based on studying the petition and the exhibits cited in the Petition as well as other documents, it is my opinion that claims 1-22 of the '069 patent are obvious in view of the Patent Owner's prior disclosures in light of Lin and/or Ahmad.

7. Petitioner's Ground 3 challenges claims 1-22 of the '069 as anticipated by the disclosures in U.S. Patent Publication No. 2006/0240554 A1

("'554 publication"), Ex. 1005, under pre-AIA 35 U.S.C. §§ 102(b) or, in the alternative, as obvious under pre-AIA 35 U.S.C. § 103 in view of the '554 publication. Based on studying the petition and the exhibits cited in the petition as well as other documents, it is my opinion that claims 1-22 of the '069 patent are anticipated by the '554 publication. In the alternative, it is my opinion that claims 1-22 of the '069 patent are obvious in view of the '554 publication.

III. QUALIFICATION AND EXPERIENCE

8. I am formally trained as a membrane biophysicist. I obtained my Ph.D. degree in Biophysics from Michigan State University in 1980. Before that, I received my MS in Biophysics from Michigan State University in 1977, and my BS in Biology from The American University in 1971. I received postdoctoral training in Pharmacology at the Harvard Medical School and in Anesthesia at the Massachusetts General Hospital.

9. I have played leadership roles in the discipline of pharmaceutical liposomology from its inception in 1981.

10. After my post-doctoral work, I was recruited from Harvard by the industrialist, Jack Whitehead, and became the first senior founding scientist at the Liposome Company, Inc. I eventually became the Vice President of Research and Development at the Liposome Company. I led the team at the Liposome Company that discovered, formulated, and developed ABELCET, a

novel lipid structure that is approved worldwide for systemic fungal infections. I first published the physical chemical characterization of this structure, along with an explanation of why it would yield a less toxic alternative to the traditional micelle formulation in the *Proceedings of the National Academy of Sciences*.

11. I led the team at the Liposome Company that developed Staclot LA, a diagnostic reagent comprised of Hexagonal (II) lipid that is a standard practice for diagnosing lupus anticoagulant. The work leading to this product was also published in the *Proceedings of the National Academy of Sciences*.

12. In addition I lead teams at the Liposome Company that formulated and characterized Myocet (Liposomal Doxorubicn Injection). This product is currently approved in Canada and the European Union and is used to treat metastatic breast cancer.

13. From 2001-2002, I was Chairman, and from 2002-2005, I was Chairman and CEO, of Celator Technologies, Inc. I was involved in the creation of Celator's intellectual property platform and built the company from a Canadian start up into an international pharmaceutical corporation with research, manufacturing, clinical development, regulatory, commercial, and legal functions. From 2005-2008, I was Chairman and CEO of its successor, Celator Pharmaceuticals, Inc., a company using controlled-release liposomes to deliver

combinations of chemotherapeutic agents to tumors. Celator's drug Vxyeos was recently approved by the FDA for the treatment of leukemia.

14. From 2009-2011, I was CEO of TranslationUP, which was a consortium of authorities from academic research, drug development, policy, finance, public relations, and law seeking to create a new model to more effectively advance government funded late-stage discovery concepts into clinical development.

15. In my career, I have overseen the filing of eight INDs, two NDAs and one MAA in the areas of oncology, antiinfectives, and acute respiratory distress syndrome, all involving liposome or lipid-delivery systems.

16. I have worked and published in the area of pulmonary surfactants involving treatment modalities in which lamellar lipid for instilling into neonate lungs was constructed to rearrange into the Hexagonal II architecture at body temperature. An article that I published on this topic in *Science* was reviewed and highlighted in *Lancet*, a leading British Medical Journal.

17. I have lectured and have conducted Grand Rounds in the areas of liposomes, lipid physical chemistry and drug delivery at many prestigious medical centers in the United States and Canada, and have been invited to speak on these topics at major industry, financial, scientific and medical symposia worldwide.

18. I have also served on various government advisory committees. For example, I taught at the NATO Advanced Study Institute in Cape Sunion, Greece, participated in FDA symposia regarding the quality and performance of controlled release parenterals, served on the Committee of Science and the Arts at the Franklin Institute in Philadelphia, and was a founding member on the Scientific Advisory Board at Rider University. I have also advised the Centre for Drug Research and Development in Vancouver, Canada on liposomal delivery systems.

19. I have served as an Adjunct Professor in the Department of Pathology, Anatomy and Cell Biology at Thomas Jefferson University Medical School. I have also been a visiting Research Scholar at Princeton University and have held appointments in the Departments of Physics, Molecular Biology, and Chemical Engineering.

20. I am the Editor-in-Chief Emeritus of the *Journal of Liposome Research*. I served on the editorial board of this Journal from 1994-1997, and was the Editor-in-Chief from 1997-2008.

21. I am an editor of *Liposomes: Rational Design* (Marcel Dekker, New York, 1999), a volume of expert reviews in the field of liposomology.

22. I hold over 75 U.S. patents in lipid nanotechnology and drug delivery, and I have authored more than 90 scientific articles and reviews

principally related to nanotechnology, lipid supramolecular structure, liposomes, and drug delivery including fusogenic liposomes and triggerable lipid assemblies.

23. My *curriculum vitae* is attached as Exhibit 1018.

24. I am being compensated by Moderna for my time spent in developing this declaration at a rate of $750 per hour, and for any time spent testifying in connection with this declaration at a rate of $750 per hour. My compensation is not contingent upon the substance of my opinion, the content of this declaration or any testimony I may provide, or the outcome of the *inter partes* review or any other proceeding.

25. I have no financial interest in Moderna.

26. My opinion expressed in this declaration are based on the Petition and exhibits cited in the Petition, and other documents and materials identified in this declaration, including the ’069 patent (Ex. 1001) and its prosecution history (Ex. 1016), the prior art references and materials discussed in this declaration, and any other references specifically identified in this declaration.

27. I am aware of information generally available to, and relied upon by, persons of ordinary skill in the art at the relevant times, including technical dictionaries and technical reference materials (including, for example, textbooks, manuals, technical papers, articles, and relevant technical standards).

28. I reserve the right to supplement my opinions to address any information obtained, or positions taken, based on any new information that comes to light throughout this proceeding.

IV. LEVEL OF ORDINARY SKILL IN THE ART

29. It is my understanding that the '069 patent should be interpreted based on how it would be read by a person of ordinary skill in the art at the time of the effective filing date of the application. It is my understanding that factors such as the education level of those working in the field, the sophistication of the technology, the type of problems encountered in the art, the prior art solutions to those problems, and the speed at which innovations are made may help establish the level of skill in the art.

30. I am familiar with the technology at issue and the state of the art at the earliest priority date of the '069 patent.

31. It is my opinion, based upon a review of the '069 patent, its file history, and my knowledge of the field of the art, that a person of ordinary skill in the art for the field of the '069 patent would have specific experience with lipid particle formation and use in the context of delivering therapeutic payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience. This level of skill is representative of the

authors/inventors of prior art cited herein. *See* Exs. 1002-1006.

32. I have considered the issues discussed in the remainder of this declaration from the perspective of a person of ordinary skill in the art. Although I used this perspective, I do not believe that any of my opinions would change if a slightly higher or lower level of skill were adopted.

V. LEGAL PRINCIPLES

A. Claim construction

33. I am not a patent attorney and my opinions are limited to what I believe a person of ordinary skill in the art would have understood, based on the patent documents. I use the principles below, however, as a guide in formulating my opinions.

34. My understanding is that a primary step in determining validity of patent claims is to properly construe the claims to determine claim scope and meaning.

35. In an *inter partes* review proceeding, as I understand from Moderna counsel, claims used to be given their broadest reasonable interpretation in light of the patent's specification. 37 C.F.R. § 42.100(b). I understand that the current claim construction standard in *inter partes* review proceedings is now governed by *Phillips v. AWH Corp*., 415 F.3d 1303 (Fed. Cir. 2005) and that the claims are interpreted as one of ordinary skill in the art would understand the claim

terms at the time of the invention. I also understand that this analysis is focused primarily on the intrinsic record.

36. It is my understanding that in determining whether a patent claim is anticipated or obvious in view of the prior art, the patent office must construe the claim under the *Phillips* standard. For the purposes of this review, I have construed each claim term in accordance with its plain and ordinary meaning under the required *Phillips* standard.

B. Prior Art

37. I understand that a patent or other publication must first qualify as prior art before it can be used to invalidate a patent claim. I understand that a U.S. or foreign patent qualifies as prior art to an asserted patent if the date of issuance of the patent is prior to the invention of the asserted patent. I further understand that a printed publication, such as an article published in a magazine or trade publication, qualifies as prior art to an asserted patent if the date of publication is prior to the invention of the asserted patent.

38. I understand that a U.S. or foreign patent also qualifies as prior art to an asserted patent if the date of issuance of the patent is more than one year before the filing date of the asserted patent. I further understand that a printed publication, such as an article published in a magazine or trade publication, constitutes prior art to an asserted patent if the publication occurs more than one

year before the filing date of the asserted patent.

39. I understand that a U.S. patent qualifies as prior art to the asserted patent if the application for that patent was filed in the United Stated before the invention of the asserted patent.

40. I understand that documents and materials that qualify as prior art can be used to invalidate a patent claim via anticipation or obviousness.

C. Anticipation

41. I understand that, once the claims of a patent have been properly construed, the second step in determining anticipation of a patent claim requires a comparison of the properly construed claim language to the prior art on a limitation-by-limitation basis.

42. I understand that a prior art reference "anticipates" an asserted claim, and thus renders the claim invalid, if all elements of the claim are disclosed in that prior art reference, either explicitly or inherently (*i.e.*, necessarily present).

43. I understand that anticipation in an *inter partes* review must be shown by a preponderance of the evidence.

D. Obviousness

44. I understand that even if a patent is not anticipated, it is still invalid if the differences between the claimed subject matter and the prior art are such

that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the pertinent art.

45. I understand that a person of ordinary skill in the art at the time the invention was made provides a reference point from which the prior art and claimed invention should be viewed. This reference point prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

46. I also understand that an obviousness determination includes the consideration of various factors such as (1) the scope and content of the prior art, (2) the differences between the prior art and the asserted claims, (3) the level of ordinary skill in the pertinent art, and (4) the existence of secondary considerations such as commercial success, long-felt but unresolved needs, failure of others, etc.

47. I understand that an obviousness evaluation can be based on a combination of multiple prior art references. I understand that the prior art references themselves may provide a suggestion, motivation, or reason to combine, but other times the nexus linking two or more prior art references is simple common sense. I further understand that obviousness analysis recognizes that market demand, rather than scientific literature, often drives innovation, and that a motivation to combine references may be supplied by the direction of the marketplace.

48. I understand that if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

49. I also understand that practical and common sense considerations should guide a proper obviousness analysis, because familiar items may have obvious uses beyond their primary purposes. I further understand that a person of ordinary skill in the art looking to overcome a problem will often be able to fit together the teachings of multiple publications. I understand that obviousness analysis therefore takes into account the inferences and creative steps that a person of ordinary skill in the art would employ under the circumstances.

50. I understand that a particular combination may be proven obvious merely by showing that it was obvious to try the combination. For example, when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. The result is likely the product not of innovation but of ordinary skill in the art and common sense.

51. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. When

a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill in the art can implement a predictable variation, the patent claim is likely obvious.

52. It is further my understanding that a proper obviousness analysis focuses on what was known or obvious to a person of ordinary skill in the art, not just the patentee. Accordingly, I understand that any need or problem addressed by the patent that was known in the field of endeavor at the time of invention can provide a reason for combining the elements in the manner claimed.

53. I understand that a claim can be obvious in light of a single reference, without the need to combine references, if the elements of the claim that are not found explicitly or inherently in the reference can be supplied by the common sense of one of skill in the art.

54. I understand that the disclosure of overlapping ranges in the prior art establishes a *prima facie* case of obviousness under 35 U.S.C § 103, but that a petitioner still has the burden of demonstrating invalidity by the preponderance of the evidence.

55. I understand that secondary indicia of non-obviousness may include (1) a long felt but unmet need in the prior art that was satisfied by the invention

of the patent; (2) commercial success of processes covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) taking of licenses under the patent by others; (6) deliberate copying of the invention; (7) failure of others to find a solution to the long felt need; and (8) skepticism by experts.

56. I also understand that there must be a relationship between any such secondary considerations and the invention. I further understand that contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

57. I understand that unexpected results can support a nonobviousness determination but must show unexpected results for the entire claimed range. This can be done by demonstrating that an embodiment has an unexpected result and providing an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner.

58. In sum, my understanding is that prior art teachings are properly combined where a person of ordinary skill in the art having the understanding and knowledge reflected in the prior art and motivated by the general problem facing the inventor, would have been led to make the combination of elements recited in the claims. Under this analysis, the prior art references themselves, or any need or problem known in the field of endeavor at the time of the invention,

can provide a reason for combining the elements of multiple prior art references in the claimed manner.

59. I understand that obviousness in an *inter partes* review must be shown by a preponderance of the evidence.

VI. BACKGROUND

A. Lipid carrier particles for nucleic acid payloads

60. Gene therapy—addressing disease at the level of the genetic cause, typically with nucleic acids—is an area of intensive medical research. Therapeutic nucleic acids can be used for both nucleic acid delivery and gene silencing (*e.g.*, small interfering RNA ("siRNA")). *See* Ex. 1009 (Gao), E92; Ex. 1006 (Lin), 3307. Long before the '069 patent, it was known that systems comprised of combinations of different types of lipids with nucleic acids could result in lipid-nucleic acid particles, an accepted delivery strategy for nucleic acid therapeutics. *See* Ex. 1009 (Gao), E95.

61. The '069 patent specification describes nucleic acid-lipid carrier particles that the patentees refer to as "stable nucleic acid-lipid particles" or "SNALPs." Ex. 1001, 5:51-58. The '069 patent discloses four lipid components: a cationic lipid, two non-cationic lipids (a phospholipid and cholesterol), and a conjugated lipid (*e.g.*, a polyethylene glycol ("PEG") lipid). *See, e.g.*, Ex. 1001, cl. 1 (components). These lipid components were known to

be basic building blocks of nucleic acid-lipid particles long before the '069 patent. *See* Ex. 1007 (Ahmad), 740, 746 ("[cationic lipids] for transfection typically consist of a mixture of cationic and neutral (helper) lipid" and "strategies for optimization … could involve introducing … PEG –lipids …."); Ex. 1009 (Gao), E95, 97 (cationic lipid carrier particles "are often formulated with a noncharged phospholipid or cholesterol as a helper lipid … PEG-lipid conjugates have been incorporated … to minimize interaction with blood components ....").

62. Cationic lipids have been used in the construction of nucleic acid-lipid particles because they interact with the negative charge on nucleic acid payload facilitating formation of lipid-nucleic acid complexes. *See* Ex. 1009 (Gao), E95. Effective delivery of the nucleic acid (called the "transfection efficiency") is thought to require fusion between the lipid complex and a cell membrane. *See* Ex. 1010 (Bennett), 48; Ex. 1009 (Gao), E95; Ex. 1007 (Ahmad), 746. Since cationic lipids can also interact with negative charges on cell membranes (under appropriate conditions, depending on the specific mixture of lipids in the carrier particle), this has been believed to promote, in some cases, the fusion event necessary for the effective delivery of the nucleic acid. *See* Ex. 1007 (Ahmad), 745("[A]n overall positive [cationic lipid]-DNA charge is required to promote initial electrostatic interactions with cell

membranes.").

63. Moreover, it was known that non-cationic "helper" lipids, *e.g.*, certain phospholipids and/or cholesterols, can be combined with the cationic lipid to influence the ability of the particles to transfect cells. *See* Ex. 1009 (Gao), E95 (cationic lipids "are often formulated with a noncharged phospholipid or cholesterol as a helper lipid to form liposomes. …. Lipoplexes form spontaneously when cationic liposomes are mixed with DNA. The structure of lipoplexes is influenced by multiple factors…. [including]…. the method of preparation. Lipoplexes come in various forms, including…lipid-coated DNA arranged in an hexagonal lattice, or partially condensed DNA surrounded by a lipid bilayer."); Ex. 1010 (Bennett), 47 (use of helper lipids).

64. A "conjugated lipid" (*e.g.*, a PEG-lipid) can be added to increase *in vivo* circulation time by providing a neutral, hydrophilic coating to the particle's exterior. *See* Ex. 1009 (Gao), E97 ("PEG-lipid conjugates have been incorporated into the lipoplexes to minimize the nonspecific interaction of lipoplexes with blood components."); Ex. 1011 (Heyes), 277 ("PEG-lipids both stabilize the particle during the formulation process and shield the cationic bi-layer, preventing rapid systemic clearance.").

65. "The structure of lipoplexes is influenced by multiple factors, including the charge ratio, the concentration of individual lipids and DNA, the

structure of the cationic lipid and the helper lipid, [and] the physical aggregation state of the lipids ([*e.g.*,] multilamellar or unilamellar liposomes, or micelles) ….” Ex. 1009 (Gao), E95. Transfection efficacy is complex because “[a] large number of parameters [are] involved.” Ex. 1007 (Ahmad), 740. Different transfection mechanisms “may be facilitated by alterations in liposome formulation ….” Ex. 1010 (Bennet), 48.

66. The claims of the ’069 patent are not limited to a combination of specific lipids, formation protocols, or the type of nucleic acid payload and encompass broad ranges of lipids that have dramatically varying structures likely resulting in drastically different activities. Effective proportions of lipid components for one set of lipid species and payload may not be effective for alternative lipid species and payloads.

67. For example, it was well-established at the time of the ’069 patent that “[t]he chemical structure of the cationic lipid ha[d] a major impact on the transfection efficiency.” Ex. 1009 (Gao), E95; Ex. 1011 (Heyes), 286. References incorporated into the ’069 patent acknowledge that “alternative cationic lipids” to the one tested would have “different [transfection] efficiencies.” *See* Ex. 1012 (’613 patent), 1:26-28 (“[A]lternative cationic lipids that work in essentially the same manner but with different efficiencies.”). I note, however, that many cationic lipids, including those disclosed in the ’069

patent do not necessarily work in the same manner. For example, some are pH dependent and others are not.

68. Cationic lipid variables impacting transfection efficiency include "the chemical structure of the cationic lipid [and] … the charge ratio between the cationic lipid and the DNA …." Ex. 1009 (Gao), E95. One example is whether the cationic lipid is comprised of a tertiary (*e.g.*, ionizable) or quaternary (*e.g.*, fixed positively charged) amine. Cationic lipids comprised of ionizable tertiary amines with pKas around 7 possess substantially neutral charges at physiological pH. Ex. 1011 (Heyes), 284. A POSITA would have known that these and other variables could impact the proportion of cationic lipid that is most effective for a given lipid component combination.

69. Hundreds of cationic lipids both univalent and multivalent, ionizable or with fixed positive charges were known at the time of the '069 patent. Ex. 1009 (Gao), E95; Ex. 1011 (Heyes), 286 ("[H]undreds of new cationic lipids have been developed … [that] differ by the number of charges in their hydrophilic head group and by the detailed structure of their hydrophobic moiety."). Thus the charge density on the surface of a nucleic acid-lipid particle, at a fixed cationic lipid proportion, can be modulated by introducing cationic lipids of different valancies (*i.e.*, cationic lipids with a different number of positive charges) or ionizable cationic lipids with different pKas. *See, e.g.*, Ex.

1011 (Heyes), Abstract. This would have been expected to impact the ability of some particles to promote fusion events with target cell membranes. *See* Ex. 1007 (Ahmad), 740. Both Ahmad and Lin identified charge density as an important determinate of transfection efficacy in some of the systems studied. *Id.*, 744; Ex. 1006 (Lin), 3312.

70. It was also well-known at the time of the '069 patent that certain lipid component combinations favor having a 50% or greater proportion of cationic lipid. First, early researchers often chose a 50% proportion of cationic lipid as a default in evaluating particle transfection efficiency. *See, e.g.*, Ex. 1010 (Bennett), 49 (50% cationic lipid); Ex. 1013 (U.S. Patent 7,939,505), 44:61-65 (cationic lipid of "about 0.5% to about 70% (mol%) of the total amount of lipid"), 96:40-67 (Example 32 and Table 12) (formulations with 50% cationic lipid), 99:34-101:45 (Examples 34-35 and Tables 15-18) (same). Second, Researchers determined that, in some cases, increasing the cationic lipid proportion above 50% increased transfection efficiency. Ex. 1007 (Ahmad), 744; Ex. 1006 (Lin), 3312.

71. At the time of the '069 patent the number of species of non-cationic lipids that could be employed was large, and differences among such lipids had been reported to impact the structure of the resulting nucleic acid-lipid particles. Ex. 1009 (Gao), E95 (transfection efficiency varies with "the structure and

proportion of the helper lipid in the complexes"). For instance, in the blood, the non-cationic lipid cholesterol seemed to stabilize certain formulations, "while formulations containing DOPE [another non-cationic lipid] tend[ed] to fall apart more easily." *Id.*, E96. In addition, variations in the proportions of non-cationic lipids in certain formulations were reported to impact their ability to deliver nucleic acid payloads. Ex. 1010 (Bennett), 51; Ex. 1007 (Ahmad), 744. The selection of conjugated lipid was also known to potentially impact the particle's chemistry and efficacy. Ex. 1003 ('196 PCT), [0094] ("By controlling the composition and concentration of the bilayer stabilizing component, one can control … the rate at which the liposome becomes fusogenic.").

72. In addition, the claims of the '069 patent encompass various types of "nucleic acids." A POSITA at the time of the '069 patent would have known that the species of nucleic acid payload would impact the optimal LNP formulation. For example, there are well-understood chemical and structural differences between mRNA and siRNA in terms of length, stability, and charge density of the nucleic acid. Given these differences, a POSITA would not have expected a formulation optimized for siRNA to perform similarly for mRNA.

73. This is confirmed in relevant literature post-dating the '069 patent, including Kauffman, et al. ("Kaufman"). Ex. 1019. Kaufman confirms "differences in optimized formulation parameter design spaces [of LNPs] for

siRNA and mRNA" and, for one of the systems tested using mRNA and LNPs comprising the phospholipid DOPE, determined that a 35% concentration of cationic lipid was optimal for mRNA delivery. *Id.*, A. These findings are consistent with the variation in LNP performance with different nucleic acid payloads that a POSITA would have expected at the time of the '069 patent.

74. A POSITA at the time of the '069 patent would have known that varying the nucleic acid payload, the specific lipid species, or the lipid proportions could change the performance of the nucleic acid-lipid particle. The range of lipids falling under the scope of the claims of the '069 patent is immense and a POSITA would have had no way of knowing if lipid combinations at any given proportion would have resulted in formulations of superior therapeutic index to other formulations. *See* Ex. 1007 (Ahmad), 740 ("[I]n comparative studies, typically only one or two data points per lipid are evaluated, allowing the ideal lipid composition (the ratio of neutral to cationic lipid) or cationic lipid/DNA ratio to be overlooked.").

B. The '069 patent disclosure

75. The '069 patent is premised on an alleged "surprising discovery" that prior art lipid components in certain proportions perform better than expected *in vitro* and *in vivo*. Ex. 1001, 5:44-51 (lipids "comprising from about 50 mol% to about 85 mol% of a cationic lipid, from about 13 mol% to about

49.5 mol% of a non-cationic lipid, and from about 0.5 mol% to about 2 mol% of a lipid conjugate provide advantages ….”). According to the ’069 patent, using the claimed lipid proportions result in “increased activity of the encapsulated nucleic acid … and improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index ….” *Id.*, 5:51-58.

76. The ’069 patent acknowledges that the following was known to a POSITA before to its priority date:

- Nucleic acid-lipid particles comprising a nucleic acid, cationic lipid, non-cationic lipid, and a conjugated lipid that inhibits aggregation of particles. *See id.*, 11:24-26 (“SNALP and SPLP typically contain a cationic lipid, a non-cationic lipid, and a lipid conjugate (e.g., a PEG-lipid conjugate).”).
- Preparation of such nucleic acid-lipid particles. *See id.*, 11:44-48 (“Nucleic acid-lipid particles and their method of preparation are disclosed in, e.g., U.S. Patent Publication Nos. 20040142025 and 20070042031, the disclosures of which are herein incorporated by reference in their entirety for all purposes.”).
- In addition, the prior art cited in the ’069 patent discloses nucleic acid-lipid particles with the listed component lipids having overlapping ranges: a cationic lipid range of “about 2% to about 70%,” a non-

cationic lipid range of "about 5% to about 90%," a cholesterol range of "about 20% to about 55%," and a PEG-lipid conjugate range of "about 0.5% to about 20%." *See, e.g.*, Ex. 1014 ('031 publication), [0033].

Thus, nucleic acid-lipid particles with (1) the claimed nucleic acid payload and (2) the same lipid components in overlapping ranges were admittedly known in the art. The sole basis for alleged novelty of the '069 patent claims is that a nucleic acid-lipid particle comprising component lipids in the claimed proportions achieves unexpected efficacy making the claims patentably distinct from the prior art.

77. During the prosecution of the '069 patent, the examiner cited Patent Owner's earlier, unrelated US2006/0008910 publication ("'910 publication") (Ex. 1015) as prior art disclosing nucleic acid-lipid particles with the claimed components and overlapping ranges of those components. *See, e.g.*, Ex. 1016 ('069 file history excerpts), 7/30/2010 Rejection, 3-5. Patent Owner put forth the following chart illustrating the overlapping ranges:

78.

Lipid Component	Claim 1 as Amended	US 2006/0008910*
Cationic Lipid	50-65 mol %	"2-60, 5-50, 10-45, 20-40, 30 mol%"
Phospholipid	4-10 mol %	"5-90 mol%"
Cholesterol	30-40 mol %	"20-55 mol %"
Conjugated Lipid	0.5-2 mol %	"1-20 mol %"

Id., 8/11/2011 Amendment, 7-9.

79. In response to the rejection, Patent Owner argued that the specific claimed ranges in the '069 patent lead to "***new and unexpected results***" and cited to test results regarding the "1:57 SNALP" in the specification. *Id.*, 1/31/2011 Amendment, 11. Patent Owner argued that "[a]pplicants have found that SNALP formulations having increased amounts of cationic lipid, *e.g.*, one or more cationic lipids comprising from about 50 mol% to about 65 mol% of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent …." *Id.* Patent Owner relied on Examples 3-4 from the specification arguing that these examples demonstrated that the 1:57 SNALP formulation was "more efficacious as compared to a nucleic acid-lipid particle previously described ('2:30 SNALP') … [and] more effective at silencing the expression of a target gene as compared to nucleic acid-lipid particles previously described ('2:40 SNALP')." *Id.*

80. Patent Owner further argued that the "claimed narrower ranges are not disclosed with 'sufficient specificity' [in the '910 publication] to constitute an anticipation …." *Id.*, 8/11/2011 Amendment, 7-9. Thereafter, the examiner allowed the claims.

81. The '069 patent includes *in vitro* (Example 2) and *in vivo* (Examples 3-4) testing of various nucleic acid-lipid formulations and comparison of those formulations to the admitted prior art (*i.e.*, the 2:30 and 2:40 formulations). Ex. 1001, 68:50-73:67. In these examples, however, only the 1:57 SNALP contains lipid proportions within the ranges claimed in the '069 patent.

82. Example 2 is the *in vitro* test in the '069 patent. *Id.*, 68:50-70:50. It involved a siRNA payload targeting the Eg5 gene with various lipid components in various proportions. *Id.*, Table 2. Of the tested lipid formulations, only Sample 9 (the 1:57 SNALP) falls within the lipid ranges in claim 1 of the '069 patent. *Id.*, cl. 1. Other than the 1:57 SNALP, the '069 patent did not test any combinations of lipid components covered by the claims for comparison to the admitted prior art.

83. Samples 1 and 16 in Table 2 reflect the 2:40 SNALP that is admitted prior art. *Id.*, Table 2. Sample 12 is similar to the 2:40 formulation, but with slight variations in the lipid proportions. As can be seen from Figures (1)(a)-(b),

(1) Sample 9 (1:57 SNALP) appears to be no more effective at gene silencing than Sample 12 (a 2:40-type SNALP with 40.4% cationic lipid), which it overlaps at every data point, (2) Sample 9 (1:57 SNALP) outperforms the admitted 2:40 prior art formulation only at extremely low total siRNA amounts, and (3) Samples 9 (1:57 SNALP) and 12 (2:40-type SNALP) outperform Sample 10, which is also comprised of greater than 50% cationic lipid (*i.e.*, 53.3%). The takeaway being that there is no clear advantage of using the claimed formulations, nor is there data that the entire claimed range of nucleic acid-lipid particles is superior to particles with less than 50% cationic lipid.

84. Example 3 involved testing the silencing activity of an siRNA payload targeting the Apo B gene with various lipid components in various proportions. *Id.*, 70:51-72:55; Table 4. Of the tested lipid combinations, only Sample 11 (1:57 SNALP) falls within the lipid ranges claimed in the '069 patent. Samples 2, 4-5 and 7 reflect the 2:40 SNALP proportions (Samples 4-5 employ different species of certain lipid components than Samples 2 and 7).

85. As can be seen from Figure 2, the 1:57 SNALP (Group 11) is likely not statistically significantly more efficacious than Group 12 (which is comprised of only 40.4% cationic lipid (*see* Table 4 above)). On the other hand, Group 12 appears to be more efficacious than Groups 2 and 7 (both examples of the admitted prior art 2:40 SNALP formation) even though it varies only slightly

from this formulation in that it is comprised of 1 mol% rather than 2 mol% PEG-2000-C-DMA.

86. Example 4 compares the silencing activity of the 1:57 SNALP formulation with the 2:30 SNALP formulation. Both SNALPs were formulated with a siRNA payload targeting the Apo B gene. *Id.*, 72:60-74:4; Table 5. Of note, the phospholipid used in formulating the 2:30 SNALP (DSPC) was a different phospholipid than was used in formulating the 1:57 SNALP (DPPC). *Id.*, 73:18-49. A POSITA would have been aware that varying the phospholipid species could impact transfection efficacy separate and apart from varying the lipid component proportions. In addition, the dosing and lipid to drug ratios were different regarding the two formulations. *Id.*, 73:50-67. The results of testing are shown in Figure 3. At most, this testing established that the 1:57 SNALP comprised of the specific species of lipid components and nucleic acid to lipid ratio disclosed, dosed as disclosed, outperformed the 2:30 SNALP comprised of the lipid species disclosed and dosed as disclosed.

87. Several other examples in the '069 patent illustrate that transfection efficiency may be influenced by varying just the species of lipid components used. For instance, comparing Groups 2 & 6 to Group 4 in Example 5, in which DLinDMA was replaced with DODMA without changing the ratios of the components used (*see id.*, Table 6), it can be seen that Group 4 apparently

exhibited inferior results. Example 5 also shows by comparing Groups 2 & 6 (PEG(2000)-c-DMA) to Group 5 (PEG(5000)-c-DMA), that variation of the conjugated lipid apparently impacts efficacy. In this Example, Group 5 appears inferior.

C. Claim Construction

88. I understand that in the '435 patent IPR, the Board determined that under the broadest reasonable interpretation standard, the term "nucleic acid-lipid particle" in independent claim 1 was the only claim term needing construction and means "a particle that comprises a nucleic acid and lipids, in which the nucleic acid may be encapsulated in the lipid portion of the particle." IPR2018-00739, Paper 15, at 10-11. For purposes of this review only, I will assume (without conceding) that this is the only necessary construction.

D. Prior art

89. The '069 patent family is but one of many patent families with substantially overlapping disclosures. Because these unrelated patent families, with differing inventors, do not claim priority to one another, the earlier disclosures are prior art to the '069 patent. Ex. 1003 ('196 PCT); Ex. 1004 ('189 publication); Ex. 1015 ('910 publication relied on by examiner during prosecution).

90. Patent Owner filed the provisional applications leading to the

unrelated '196 PCT in 2003—five years before the priority date of the '069 patent. Ex. 1003. The '196 PCT inventors are Ian MacLachlan, Ellen Ambegia, and James Heyes, a different inventive entity from the '069 patent inventive entity. *Id.* The '196 PCT was published on Jan. 27, 2005. *Id.* Also, the '196 PCT and the '069 patent do not claim priority to one another. *See* Exs. 1001, 1003. The '196 PCT is therefore prior art to the '069 patent under 35 U.S.C. § 102(b) (pre-AIA).

91. The '196 PCT is titled "Lipid Encapsulated Interfering RNA" and discloses "a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." Ex. 1003, [0002]. The disclosed SNALPs comprise "a cationic lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles and a siRNA." *Id.*, [0011]. The non-cationic lipids may include a phospholipid, cholesterol, and a PEG-conjugated lipid. *Id.*, [0089].

92. The '196 PCT discloses not only the same lipid components as claimed in the '069 patent, but also overlapping ranges of those components. According to the '196 PCT, "[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle … [i]n other preferred embodiments, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle." *Id.*, [0088]. Enough cationic lipid is added

to "produce a charge ratio [cationic lipid to nucleic acid] … of about 2:1 to about 6:1." *Id.*, [0126].

93. "The non-cationic lipid typically comprises from about 5% to about 90% of the total lipid present … [and] [t]he nucleic acid-lipid particles … may further comprise cholesterol … from about 20% to about 45% of the total lipid present …." *Id.*, [0091]. "[T]he SNALP further comprises a bilayer stabilizing component (BSC) …. t]he BSC is a conjugated lipid that inhibits aggregation of the SNALPs … present from about 0.5% to about 25% of the total lipid …." *Id.*, [0092-0093].

94. The '196 PCT specifically discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.*, [0088]. In addition, the '196 PCT incorporates by reference U.S. Patent No. 5,264,618 (the "'618 patent"). *Id.*, [0087], [0146]. The '618 patent in turn discloses a nucleic acid-lipid complex with 56% cationic lipid, 14% phospholipid and 30% cholesterol, as well as various other formulations over 50% cationic lipid. Ex. 1017, 34:54-35:23.

95. Another example of Patent Owner's prior, unrelated disclosure is the '189 publication. Ex. 1004. Patent Owner filed the provisional applications leading to the '189 publication in 2004-2005—three years before the priority date of the '069 patent. *Id.* The '189 publication inventors are Ian MacLachlan,

Lloyd Jeffs, Adam Judge, Amy Lee, Lorne Palmer, and Vandana Sood, a different inventive entity from the '069 patent inventive entity. *Id.* The '189 publication was published on Jun. 22, 2006. *Id.* Also, the '189 publication and the '069 patent do not claim priority to one another. *See* Exs. 1001, 1004. The '189 publication is therefore prior art to the '069 patent under 35 U.S.C. § 102(b) (pre-AIA).

96. The '189 publication discloses SNALPs comprising overlapping ranges of the four lipid components similar to those discussed above for the '196 PCT. Ex. 1004, [0009-0012], [0014], [0148-0181]. In addition, the '189 publication discloses testing relating to the 2:40 formulation that the Patent Owned identified as a prior art formulation. *Id.*, [0350-0391]. This formulation includes 40% cationic lipid and 2% conjugated lipid, 10% phospholipid and 48% cholesterol. *Id.*, [0351]. According to the '189 publication, this formulation demonstrated efficacy *in vitro* and *in vivo.* *Id.*, [0016]. These additional disclosures confirm that formulations with high cationic lipid percentages (*e.g.*, 40%) and low conjugated lipid percentages (*e.g.*, 2%) were known.

97. The '554 publication was published on October 26, 2006. Ex. 1005, cover page. The '554 publication is therefore prior art to the '435 patent under 35 U.S.C. § 102(b) (pre-AIA).

98. The '554 publication is titled "Lipid Nanoparticle Based

Compositions and Methods for the Delivery of Biologically Active Molecules." Ex. 1005. The '554 publication discloses "novel cationic lipids, transfection agents, microparticles, nanoparticles, and short interfering nucleic acid (siNA) molecules." *Id.*, Abstract. The cationic LNPs disclosed are comprised of, for example, "(a) a cationic lipid … (b) a neutral lipid; (c) a polyethyleneglycol conjugate …; and (d) a short interfering nucleic acid (siNA) molecule …." *Id.*, 28:36-48. Of note, these are the same components and payload described in the '069 patent.

99. The '554 publication discloses various ranges for the lipid components that overlap or encompass the ranges disclosed in the '069 patent, including the cationic lipid (*e.g.*, about 2% to about 60%), the neutral, non-cationic lipid (about 5% to about 90%), cholesterol (about 20% to about 45%), and the PEG conjugate (about 1% to about 20%). The '554 publication also includes various specific formulations including 50% or greater cationic lipid. *Id.*, Table 4 (*e.g.*, L054 DMOBA/Chol/DSPC/PEG-n-DMG (50/20/28/2).

100. Lin et al. ("Lin") is a publication titled "Three-Dimensional Imaging of Lipid Gene-Carriers: Membrane Charge Density Controls Universal Transfection Behavior in Lamellar Cationic Liposome-DNA Complexes." Ex. 1006. It was published in *Biophysical Journal* in May 2003, in Volume 84, at pages 3307-16. *See id.* Lin is therefore prior art to the '069 patent under 35

U.S.C. § 102(b) (pre-AIA).

101. Lin studied the impact of cationic lipid mole fraction on the transfection efficiency of lipid particles with a DNA payload in *in vitro* experiments. Ex. 1006, 3307. Using the cationic lipids DOTAP, DMRIE and DOSPA and the helper lipid DOPC, Lin determined that transfection efficiency increased as the cationic lipid mole fraction increased. *Id.*, 3309. In Figure 4(a), Lin shows the transfection efficiency as a function of the mole fraction of neutral lipid (DOPC). *Id.*, Fig. 4. The mol% of cationic lipid (*e.g.*, DOTAP, DOSPA, DMRIE) is derived by deducting the mole fraction of neutral lipid from 1 and multiplying by 100.

102. As can be seen from the figure, for each formulation the transfection efficiency increased with the mole percentage of cationic lipid incorporated. Starting at about 35 mole percent, transfection efficiency increased monotonically with increasing mole percentage for DOTAP formulations. For DMRIE formulations, over the same range, there was a steep increase in transfection efficiency from about 45-55 mole percent. For formulations comprised of the multivalent lipid DOSPA, transfection efficiency seemed to be biphasic—it increased monotonically up to about 35 mole percent and then seemed to saturate.

103. A POSITA would understand the testing of Lin to suggest that the

mole percentage of cationic lipid in nucleic acid-lipid particles can impact transfection efficiency, and that for certain cationic lipids transfection efficiency might continue to improve at mole percentages above 50 percent. A POSITA would further understand that precisely how the mole percent of cationic lipid might impact transfection efficiency depends on both the cationic lipid species and neutral lipid species chosen.

104. Ahmad et al. ("Ahmad") is a publication titled "New multivalent cationic lipids reveal bell curve for transfection efficiency versus membrane charge density: lipid–DNA complexes for gene delivery." Ex. 1007. It was published in *The Journal of Gene Medicine* on January 31, 2005, in Volume 7, at pages 739-48. *See id.* Four of the authors in the references overlap. Exs. 1006-1007. Ahmad builds on the work of Lin and references the findings of Lin explicitly. Ex. 1007, 743, 747. Ahmad is therefore prior art to the '069 patent under 35 U.S.C. § 102(b) (pre-AIA).

105. Ahmad studied the impact of membrane charge density on the transfection efficiency of cationic liposome-DNA complexes comprised of cationic and neutral helper lipids. Ex. 1007, 739. Ahmad also contemplated adding cholesterol and PEG-lipids to these lipid complexes. *Id.*, 744 ("[C]holesterol, which leads to lamellar complexes, is increasingly used as a neutral lipid for *in vivo* applications."), 746 ("strategies for optimization …

could involve introducing PEG–lipids … to block … unspecific interactions ….”). Thus all four lipid components from the ’069 patent were disclosed.

106. Ahmad found that a variety of cationic lipids increased the transfection efficiency in the DOPC formulations he studied as shown on Figure 3(a). In Ahmad, cationic lipids with multiple charges were observed to provide higher transfection efficiencies. *Id.*, 740 (“Numerous lipids with varied chemical and physical properties have been synthesized to improve the transfection efficiencies …. These include multivalent lipids, which have been described as superior to their monovalent counterparts.”). More specifically, Ahmad determined that for the multivalent cationic lipids studied, a maximum transfection efficiency occurred at around 50 mole percent. Yet for the monovalent lipid DOTAP, transfection efficiency increased monotonically from a cationic lipid percentage of about 35 mole percent to a cationic percentage of about 90 mole percent. *Id.*, 744. Ahmad reported that the optimal transfection efficiency for MLV 5 (a multivalent cationic lipid) was at 55 mole percent when incorporated into DOPC formulations, whereas the maximal TE for DOTAP, incorporated into DOPC formulations was at 90 mole percent. *Id.*, 743. A POSITA would understand the testing of Ahmad to suggest that the mole percentage of cationic lipid in nucleic acid-lipid particles can impact transfection efficiency, and that for certain cationic lipids transfection efficiency might

continue to improve at mole percentages above 50 percent.

107. Ahmad includes a statement that "[m]inimizing the amount of cationic lipid is desirable to reduce cost as well as potential toxic effects of the cationic lipid." *Id.*, 745. But, Ahmad also noted that "with the amounts of cationic lipid employed in our *in vitro* experiments, we find no toxic effects on the cells as judged by cell morphology and the amount of total cellular protein." *Id.*, 746. Given that the disclosures in the '069 patent are not limited to *in vivo* applications, a POSITA would understand the insights of Ahmad could apply to the particles disclosed in the '069 patent. Moreover, a POSITA would be aware that a cationic lipid resulting in particles that are neutral at physiological pH could be used to limit toxicity. Ex. 1011 (Heyes), 284.

VII. THE CHALLENGED CLAIMS ARE INVALID

A. Ground 1: Claims 1-22 are anticipated by or obvious in view of the Patent Owner's Prior Disclosures

108. It is my opinion that claims 1-22 of the '069 patent are anticipated under § 102(b) (pre-AIA) or obvious under 35 U.S.C. § 103 in view of Patent Owner's prior disclosures in the '196 PCT or '189 publication. While Patent Owner's prior disclosures do not explicitly disclose the exact same range of lipid components from claim 1 of the '069 patent, it discloses encompassing and overlapping ranges with sufficient specificity to anticipate. Moreover, the disclosed ranges establish a *prima facie* case of obviousness and the testing in

the ’069 patent does not support alleged unexpected results for the claimed ranges.

109. The ’196 PCT and ’189 publication disclose encompassing and overlapping ranges with sufficient specificity to anticipate the range of lipid components recited in claim 1 of the ’069 patent. Ex. 1003, [0009-0012], [0014], [0148-0181]. In addition, the ’189 publication discloses testing relating to the 2:40 formulation that the Patent Owned identified as a prior art formulation. *Id.*, [0350-0391].

Claim 1[a]: A nucleic acid-lipid particle comprising:

110. Patent Owner’s prior disclosures teach “compositions and methods for silencing gene expression by delivering nucleic acid-lipid particles comprising a siRNA molecule to a cell.” Ex. 1003, (Abstract); Ex. 1004, (Abstract). From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 1[b]: A nucleic acid

111. Patent Owner’s prior disclosures teach “the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery.” Ex. 1003, [0002]; Ex. 1004, [0182]. siRNA is a nucleic acid. From these disclosures, a POSITA would appreciate that the claim limitation is expressly

disclosed.

Claim 1[c]: A cationic lipid comprising from 50 mol% to 65 mol% of the total lipid present in the particle

112. Patent Owner's prior disclosures teach"[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle … [i]n other preferred embodiments, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle." Ex. 1003, [0088]; Ex. 1004, [0152]. Patent Owner's prior disclosures disclose that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." Ex. 1003, [0088]; Ex. 1004, [0152]. In addition, Patent Owner's prior disclosures incorporate by reference ('196 PCT) or directly reference ('189 publication at [0155, 0157]) the '618 patent, which discloses nucleic acid-lipid complex with 56% cationic lipid, 14% phospholipid and 30% cholesterol, as well as various other formulations containing over 50% cationic lipid. Ex. 1017, 34:54-35:23. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. For example, not only does the disclosed range substantially overlap with the claimed range, a preferred embodiment in the reference recites a narrower preferred range that also partially overlaps. Moreover, given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious.

Moreover, determining the optimal proportion of cationic lipid for a given lipid combination would be a simple matter of varying the proportion using prior art methodologies.

113. As a preliminary matter, during prosecution the Patent Owner only asserts unexpected results vis-à-vis the 2:30 and 2:40 formulations (testing for the 2:40 formulation was disclosed in the '189 publication). For example, the Patent Owner ignores Group 12 in Figure 2 of the '069 patent that has a cationic lipid percentage of 40.4% and is clearly in the prior art given the admitted 2:40 formulation. Numerous other prior art formulations contain cationic lipid percentages over 50%. *See, e.g.*, Exs. 1006-1007. Patent Owner thus failed to address the entire scope of the prior art in asserting unexpected results.

114. In addition, given the disclosures in the '069 patent, a POSITA would not expect all alternative data points falling within the recited numeric range to perform like the 1:57 SNALP. The *in vivo* testing in Example 2 shows that even minor variations in lipid percentages appeared to impact efficacy. Sample 2 and Sample 12 from Table 4 contain the exact same lipid species in the respective ratios 2/40/10/48 and 1/40.4/10.1/48.5. Ex. 1001, Table 4. According to Figure 2, these slight variations in lipid proportions lead to apparently different transfection efficiencies. *Id.*, Fig. 2. A POSITA would expect that similar minor variations in lipid proportions within the claimed range

might lead to similar variations in transfection efficiency. *See* Ex. 1007 (Ahmad), 740 ("[I]n comparative studies, typically only one or two data points per lipid are evaluated, allowing the ideal lipid composition (the ratio of neutral to cationic lipid) or cationic lipid/DNA ratio to be overlooked.").

115. The '069 patent defines "cationic lipid" as "any of a number of lipid species that carry a net positive charge at a selected pH, such as a physiological pH (*e.g.*, pH of about 7.0)." Ex. 1001, 12:59-61. The '069 patent includes almost three dozen examples of cationic lipids. *Id.*, 47:44-50:3. At the time of the '069 patent, hundreds of additional lipids that are cationic at physiological pH were known in the art. Ex. 1009 (Gao), E95 ("[H]undreds of new cationic lipids have been developed ….). In addition, because claim 1 of the '069 patent does not contain any limitation to a specific pH, the additional lipids that are cationic at a certain pH would also meet the definition of the term.

116. The testing in the '069 patent compares only one cationic lipid, DLinDMA, to the admitted prior art formulations to illustrate alleged unexpected results. Ex. 1001, Tables 2, 4, 5. Example 5 in the '069 patent shows that variation of the cationic lipid impacts efficacy. *Id.*, Table 6 (Samples 2 & 6 (DLin-DMA) vs. Sample 4 (DODMA)). A POSITA would understand these results to suggest that a preferred proportion for one cationic lipid (*e.g.*, DLinDMA) does not necessarily apply to all other cationic lipids (*e.g.*,

DODMA).

117. It was well-known in the art that "[t]he chemical structure of the cationic lipid [had] a major impact on the transfection efficiency." Ex. 1009 (Gao), E95. Indeed the '613 patent incorporated by reference in the '069 patent acknowledges that "alternative cationic lipids" to the one tested would have "different [transfection] efficiencies." *See* Ex. 1012, 1:26-28 ("[A]lternative cationic lipids … with different efficiencies."). A POSITA would have no reason to believe that the alleged unexpected advantages of a 50-65% proportion of DLinDMA would be applicable to all cationic lipids.

Claim 1[d]: A non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from 4 mol% to 10 mol% of the total lipid present in the particle and the cholesterol or derivative thereof comprises from 30 mol% to 40 mol% of the total lipid present in the particle

118. Patent Owner's prior disclosures teach that the non-cationic lipids may include a phospholipid and cholesterol. Ex. 1003, [0089]; Ex. 1004, [0159]. "The non-cationic lipid typically comprises … preferably from about 20% to about 85% of the total lipid present in said particle … If present … preferably the cholesterol comprises from about 20% to about 45% of the total lipid." Ex. 1003, [0091]; Ex. 1004, [0152] (overlapping range). Patent Owner's prior disclosures disclose that "[d]epending on the intended use of the nucleic acid-

lipid particles, the proportions of the components are varied ….” Ex. 1003, [0088]; Ex. 1004, [0152]. In addition, Patent Owner’s prior disclosures incorporate by reference (’196 PCT) or directly reference (’189 publication) the ’618 patent, which discloses a nucleic acid-lipid complex with 56% cationic lipid, 14% phospholipid and 30% cholesterol. Ex. 1017, 34:54-35:23.

119. Not only do the disclosed ranges encompass the claimed ranges, when combined with a cationic lipid proportion of 60%, the available range for cholesterol is 20-40% and the range for the other non-cationic lipid (*e.g.*, a phospholipid) is decreased to 0%-20%. Given the breadth of the claimed ranges for the phospholipid and cholesterol, these disclosures are sufficiently specific to anticipate the claimed ranges. Moreover, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, the testing in the ’069 patent does not support alleged unexpected results for the claimed ranges.

Claim 1[e]: A conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol% to 2 mol% of the total lipid present in the particle

120. Patent Owner’s prior disclosures teach that “[t]he SNALP further comprises a bilayer stabilizing component (BSC). …. [T]he BSC is a conjugated lipid that inhibits aggregation of the SNALPs … present from about 0.5% to about 25% of the total lipid ….” Ex. 1003, [0092-0093]; Ex. 1004, [0152]

(overlapping range). Patent Owner's prior disclosures disclose that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." Ex. 1003, [0088]; Ex. 1004, [0152]. "By controlling the composition and concentration of the bilayer stabilizing component, one can control … the rate at which the liposome becomes fusogenic" impacting the transfection efficiency. Ex. 1003, [0094]; Ex. 1004, [0095]. Given the breadth of the claimed range for the conjugated lipid, these disclosures are sufficiently specific to anticipate the claimed range.

121. This limitation would also have been obvious in view of the '196 PCT in light of the knowledge of a POSITA. A POSITA would have been aware that conjugated lipids stabilize carrier particles by inhibiting fusogenicity. It would have been obvious for a POSITA to try to increase fusogenicity, and hence potentially transfection efficiency, by choosing a proportion of conjugated lipid in the 0.5%-2% range. Moreover, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious.

Claim 2: The nucleic acid-lipid particle of claim 1, wherein the nucleic acid comprises a small interfering RNA (siRNA)

122. Patent Owner's prior disclosures teach "the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." Ex.

1003, [0002]; Ex. 1004, [148] (siRNA). From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 3: the nucleic acid-lipid particle of claim 2, wherein the siRNA comprises from about 15 to about 60 nucleotides

123. Patent Owner's prior disclosures teach "[t]he siRNA molecule may comprise about 15 to about 60 nucleotides." Ex. 1003, [0011]; Ex. 1004, [0021]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 4: the nucleic acid-lipid particle of claim 2, wherein the siRNA comprises at least one modified nucleotide

124. Patent Owner's prior disclosures teach "a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated." Ex. 1003, [0062]; Ex. 1004, [0099]. Patent Owner's prior disclosures further teach that the term "nucleic acid" "encompasses nucleic acids containing … modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring …." Ex. 1003, [0076]; Ex. 1004, [0272] (modified siRNA). From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 5: the nucleic acid-lipid particle of claim 2, wherein the siRNA comprises at least one 2'-O-methyl (2'OMe) nucleotide

125. Patent Owner's prior disclosures teach that the term "nucleic acid" "encompasses nucleic acids containing … modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring …. Examples of such analogs include, without limitation … 2-O-methyl ribonucleotides …." Ex. 1003, [0076]; Ex. 1004, [0129]. A 2-O-methyl ribonucleotide is a 2'-O-methyl nucleotide. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 6: the nucleic acid-lipid particle of claim 2, wherein said siRNA is about 19 to about 25 base pairs in length

126. Patent Owner's prior disclosures teach "siRNA … of about … 19-25 (duplex) nucleotides in length." Ex. 1003, [0065]; Ex. 1004, [0057]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 7: the nucleic acid-lipid particle of claim 2, wherein said siRNA comprises 3' overhangs

127. Patent Owner's prior disclosures teach that "siRNA duplexes may comprise 3' overhangs of about 1 to about 4 nucleotides, preferably of about 2 to about 3 nucleotides and 5' phosphate termini." Ex. 1003, [0065]; Ex. 1004, [0057]. From these disclosures, a POSITA would appreciate that the claim

limitation is expressly disclosed.

Claim 8: the nucleic acid-lipid particle of claim 1, wherein the cationic lipid comprises from 52 mol% to 62 mol% of the total lipid present in the particle

128. *See* Claim 1(c). For the reasons stated above, the '196 PCT discloses this range with sufficient specificity to anticipate. Overlapping ranges of this narrower range also renders this limitation *prima facie* obvious.

Claim 9: the nucleic acid-lipid particle of claim 1, wherein the phospholipid comprises dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), or a mixture thereof

129. Patent Owner's prior disclosures teach that "[e]xamples of noncationic lipids useful in the present invention include: phospholipid-related materials, such as … DSPC … DPPC …." Ex. 1003, [0089]; Ex. 1004, [0159]. Patent Owner's prior disclosures also teach using more than one phospholipid. Ex. 1003, [0128]; Ex. 1004, [0159]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 10: the nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particles comprises a polyethyleneglycol (PEG)-lipid conjugate

130. Patent Owner's prior disclosures teach that "[b]ilayer stabilizing components include, but are not limited to, conjugated lipids that inhibit aggregation of the SNALPs, polyamide oligomers (*e.g.*, ATTA-lipid

derivatives), peptides, proteins, detergents, lipid-derivatives, PEG-lipid derivatives ….” Ex. 1003, [0052], *see also* [0013]; Ex. 1004, [0088]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 11: the nucleic acid-lipid particle of claim 10, wherein the PEG-lipid conjugate comprises a PEG-diacylglycerol (PEG-DAG) conjugate, a PEG-dialkyloxypropyl (PEG-DAA) conjugate, or a mixture thereof

131. Patent Owner’s prior disclosures teach that “[t]he PEG-lipid conjugate may be one or more of a PEG-dialkyloxypropyl (DAA), a PEG-diacylglycerol (DAG) … and combinations thereof.” Ex. 1003, [0013]; Ex. 1004, [0088]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 12: the nucleic acid-lipid particle of claim 11, wherein the PEG-DAA conjugate comprises a PEG-dimyristyloxypropyl (PEG-DMA) conjugate, a PEG-distearyloxypropyl (PEG-DSA) conjugate, or a mixture thereof

132. Patent Owner’s prior disclosures teach “three exemplary PEG-dialkyloxypropyl derivatives suitable for use in the present invention … PEG-C-DMA … PEG-A-DMA … and … PEG-S-DMA.” Ex. 1003, [0031]; Ex. 1004, [0292] (PEG-DMA). Patent Owner’s prior disclosures teach “[o]ther PEG DAAs suitable for use in the present invention can be synthesized using similar

protocols. For instance, PEG-A-DSA and PEG-C-DSA can be synthesized ….” Ex. 1003, [0242]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 13: the nucleic acid-lipid particle of claim 12, wherein the PEG has an average molecular weight of about 2,000 daltons

133. Patent Owner’s prior disclosures teach “[i]n a preferred embodiment, the PEG has an average molecular weight of from about 1000 to about 5000 daltons, more preferably, from about 1,000 to about 3,000 daltons and, even more preferably, of about 2,000 daltons.” Ex. 1003, [0097]; Ex. 1004, [0083]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 14: the nucleic acid-lipid particle of claim 10, wherein the nucleic acid-lipid particle comprises about 57.1 mol% cationic lipid, about 7.1 mol% phospholipid, about 34.3 mol% cholesterol or a derivative thereof, and about 1.4 mol% PEG-lipid conjugate

134. *See* Claim 1. As noted above, the “about” language in this limitation encompasses amounts ±10, 20, 30 mol% from the amounts listed in Claim 14 that still fall within the ranges in Claim 1. For this reason, the claimed are invalid for the reasons presented above for Claim 1.

Claim 15: the nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particle comprises from 1 mol% to 2 mol% of the total lipid present in the particle

135. *See* Claim 1(e). For the reasons stated above, the Patent Owner's prior disclosures disclose this range with sufficient specificity to anticipate. In the alternative, this range is *prima facie* obvious given the overlapping range in the Patent Owner's prior disclosures.

Claim 16: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid in the nucleic acid-lipid particle is not substantially degraded after incubation of the particle in serum at 37°C for 30 minutes

136. Patent Owner's prior disclosures teach "[i]n some embodiments … the nucleic acid in the nucleic acid-lipid particle is resistant in aqueous solution to degradation by a nuclease." Ex. 1003, [0011]; Ex. 1004, [0076]. Patent Owner's prior disclosures teach "'[s]erum-stable' in relation to nucleic acid-lipid particles means that the particle is not significantly degraded after exposure to a serum or nuclease assay that would significantly degrade free DNA." Ex. 1003, [0082]; Ex. 1004, [0105]. Patent Owner's prior disclosures teach "[s]amples are incubated at 37°C for 30 min …." Ex. 1003, [0204]; Ex. 1004, [0291-0292] (incubated). Given these disclosures, a POSITA would have understood the limitation to be disclosed.

137. In the alternative, this limitation would have been obvious in view

of Patent Owner's prior disclosures in light of the knowledge of a POSITA. A POSITA would have been aware that the disclosed sample incubation parameters could have been used to establish serum stability as disclosed in Patent Owner's prior disclosures. It would have been obvious for a POSITA to incubate samples at 37°C for 30 min to establish serum stability.

Claim 17: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid is fully encapsulated in the nucleic acid-lipid particle

138. Patent Owner's prior disclosures teach "[i]n some embodiments, the siRNA molecule is fully encapsulated within the lipid bilayer of the nucleic acid-lipid particle such that the nucleic acid in the nucleic acid-lipid particle is resistant in aqueous solution to degradation by a nuclease." Ex. 1003, [0011]; Ex. 1004, [0151]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 18: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid-lipid particle has a lipid:nucleic acid mass ratio of from about 5 to about 15

139. Patent Owner's prior disclosures teach "the nucleic acid to lipid ratios (mass/mass ratios) in a formed SNALP will range from about 0.01 to about 0.08 … and, more preferably, about 0.04 …." Ex. 1003, [0127]; Ex. 1004, [0198]. This corresponds to a lipid:nucleic acid mass ratio of 12.5 to 100. Given the breadth of the claimed range, these disclosures are sufficiently specific to

anticipate the claimed range.

140. This limitation would have been obvious in view of Patent Owner's prior disclosures in light of the knowledge of a POSITA. A POSITA would have been aware that the number of molecules of monovalent cationic lipid needs to exceed the number of charges on the nucleic to ensure that the negative charge on the nucleic acid is overcome by the positive cationic lipid charge. Moreover, given the explicit disclosure of an overlapping range, this limitation is *prima facie* obvious.

Claim 19: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid-lipid particle has a median diameter of from about 40 nm to about 150 nm

141. Patent Owner's prior disclosures teach "[t]he SNALPs made by the methods of this invention are typically about 50 to about 150 nm in diameter." Ex. 1003, [0120], [0139]; Ex. 1004, [0201]. Given the breadth of the claimed range, this disclosure is sufficiently specific to anticipate the claimed range. Moreover, given the explicit disclosure of an overlapping range, this limitation is *prima facie* obvious.

Claim 20: the nucleic acid-lipid particle of claim 1, wherein the phospholipid comprises from 5 mol% to 9 mol% of the total lipid present in the particle

142. *See* Claim 1(d). For the reasons stated above, Patent Owner's prior disclosures disclose this range with sufficient specificity to anticipate. In the

alternative, this range is *prima facie* obvious given the overlapping range in Patent Owner's prior disclosures.

Claim 21: the nucleic acid-lipid particle of claim 1, wherein the cholesterol or derivative thereof comprises from 32 mol% to 36 mol% of the total lipid present in the particle

143. *See* Claim 1(d). For the reasons stated above, Patent Owner's prior disclosures discloses this range with sufficient specificity to anticipate. In the alternative, this range is *prima facie* obvious given the overlapping range in Patent Owner's prior disclosures.

Claim 22: a pharmaceutical composition comprising a nucleic acid-lipid particle of claim 1 and a pharmaceutically acceptable carrier

144. Patent Owner's prior disclosures teach "[t]he invention also provides for pharmaceutically acceptable compositions comprising a nucleic acid-lipid particle." Ex. 1003, [0019]; Ex. 1004, [0018]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

B. Ground 2: Claims 1-22 are obvious in view of the Patent Owner's Prior Disclosures in light of Lin and Ahmad

145. To the extent that those disclosures alone are determined not to disclose a proportion of cationic lipid in the 50%-65% range, a POSITA would have understood from Lin and Ahmad that such proportions of cationic lipid may increase transfection efficacy and would have been motivated to combine those

disclosures with the system disclosed in the '196 PCT and '189 publication.

Claim 1[c]: A cationic lipid comprising from 50 mol% to 65 mol% of the total lipid present in the particle

146. To the extent that the disclosures above are determined not to disclose the claimed range for cationic lipids, this limitation would have been obvious in view of the '196 PCT in light of Lin and Ahmad. Exs. 1006-1007. As discussed above, a POSITA would understand the testing of Lin to suggest that the cationic lipid mol% of nucleic acid-lipid particles can impact transfection efficiency and that for certain lipid components a mol% greater than 50% may increase the transfection efficiency of the carrier particles. Ex. 1006 (Lin), Fig. 4(a). A POSITA would understand the testing of Ahmad to support the proposition that for certain formulations, cationic lipids can increase transfection efficiency when they are incorporated above 50 mol%. Ex. 1007 (Ahmad), 739–40; Fig. 3(a). In these formulations, transfection efficiency was reported to decrease above a certain mol% cationic lipid (*e.g.*, around 70%). *Id.* It would have been obvious for a POSITA to combine the disclosed ranges in Patent Owner's prior disclosures with the teaching of Lin and Ahmad to increase the cationic lipid to the 50%-65% range in order to potentially increase the transfection efficiency.

147. It would have been obvious for a POSITA to combine the disclosed

ranges in either the '196 PCT or '189 publication with the teachings of Ahmad to increase the cationic lipid to the 50%-65% range in order to potentially increase the transfection efficiency. Ahmad tested helper lipids and cationic lipids to create carrier particles for nucleic acids, *i.e.*, "nucleic acid-lipid particles," the same general carrier particles described in Patent Owner's prior disclosures. Ahmad's goal was similarly to "identify the interactions between the CL-DNA complexes and the cells along the transfection pathway to overcome the biological impediments to optimal transfection" *in vitro* and *ex vivo* applications. Ex. 1007, 740, 747 ("The presented transfection optimization strategy is directly relevant for gene therapy using *ex vivo* methods …."). Similarly, the '196 PCT and '189 publication both concern "efficiently deliver administer siRNA molecules" (Ex. 1003, [0045]; *see also* Ex. 1004, [0118]) in *in vitro* and *ex vivo* applications (Ex. 1003, [0017]; Ex. 1004, [0016]).

148. Patent Owner's prior disclosures specifically disclose cationic lipid proportions up to 60% and state that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *See, e.g.*, Ex. 1003, [0088]; *see also* Ex. 1004 [0152]. These disclosures also stress the importance of "efficiently deliver administer siRNA molecules." Ex. 1003, [0045]; *see also* Ex. 1004, [0118]. A POSITA would have looked to the prior art, including Ahmad, in order to determine the most appropriate

proportions of, *e.g.*, cationic lipid. Given the success of generating nucleic acid-lipid particles with a cationic lipid proportion greater than 50% as described in Patent Owner's prior disclosures, a POSITA would have appreciated a reasonable expectation of doing so.

Claim 8: the nucleic acid-lipid particle of claim 1, wherein the cationic lipid comprises from 52 mol% to 62 mol% of the total lipid present in the particle

149. *See* Claim 1(c). For the reasons stated above, this range is obvious in view of the Patent Owner's prior disclosures when combined with Lin and Ahmad. Again, Lin and Ahmad disclose that cationic mol% in the claimed range may increase transfection efficacy for certain lipid combinations.

E. Ground 3 Claims 1-22 are anticipated by or obvious in view of the '554 publication

150. It is my opinion that claims 1-22 of the '069 patent are anticipated under § 102(b) (pre-AIA) or obvious under 35 U.S.C. § 103 in view of the '554 publication. While the '554 publication does not disclose the exact same ranges of lipid components from claim 1 of the '069 patent explicitly, it discloses encompassing and overlapping ranges with sufficient specificity to anticipate. Moreover, the disclosed ranges establish a *prima facie* case of obviousness and the testing in the '069 patent does not support alleged unexpected results for the claimed ranges.

Claim 1[a]: A nucleic acid-lipid particle comprising:

151. The '554 publication teaches "novel cationic lipids … and formulations thereof with biologically active molecules." Ex. 1005, [0019]. As one example, "the invention features a composition comprising a biologically active molecule (e.g., a polynucleotide such as a siNA, … [or] other nucleic acid molecule …), a cationic lipid, a neutral lipid, and a polyethyleneglycol conjugate, such as a PEG-diacylglycerol, PEG-diacylglycamide, PEG-cholesterol, or PEG-DMB conjugate." *Id.*, [0082]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 1[b]: A nucleic acid

152. The '554 publication teaches "compositions … with biologically active molecules" including "nucleic acids." *Id.*, [0018-0019]. As one example, "the invention features a composition comprising a biologically active molecule (e.g., a polynucleotide such as a siNA, antisense, aptamer, decoy, ribozyme, 2-5A, triplex forming oligonucleotide, [or] other nucleic acid molecule …)." *Id.*, [0082]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 1[c]: A cationic lipid comprising from 50 mol% to 65 mol% of the total lipid present in the particle

153. The '554 publication teaches "[c]ationic lipids that are useful in the present invention can be any of a number of lipid species which carry a net

positive charge at a selected pH, such as physiological pH." *Id.*, [0454]. "[T]he cationic lipid component … comprises from about 2% to about 60% … or from about 40% to about 50% of the total lipid …." *Id.*, [0116]. In addition, the '554 publication also includes various specific formulations which include 50% or greater cationic lipid. *Id.*, Table 4 (*e.g.*, L054, L097, L109 (50% cationic lipid), L060-061, L098-103, L114, L116-117 (52%)).

154. The '554 publication also teaches particles "can transition from a stable lamellar structure adopted in circulation (i.e., in plasma or serum) at physiologic pH (about pH 7.4) to a less stable and more efficient delivery composition having an inverted hexagonal structure at pH 5.5-6.5, which is the pH found in the early endosome." *Id.*, [0137]. The cationic lipid is the active component in such the pH-dependent nucleic acid-lipid particles: "[s]uitable cationic lipid include those cationic lipids which carry a net negative [sic] charge at a selected pH …." *Id.*, [0083] (should refer to a net "positive" charge). A POSITA would understand that increasing the mol% of a cationic lipid with pH sensitivity in these particles might increase transfection efficiency since this event is fusion related and thought to occur as a result of the described phase shift.

155. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. For example, not only does

the disclosed range substantially overlap with the claimed range, a preferred embodiment in the reference recites a narrower range that also partially overlaps and specific examples are provided within the claimed range for this lipid component. In addition, a POSITA would be compelled to choose cationic lipid proportions at the top end of the recited range to increase the efficiency of the described phase shift.

156. Additionally, the disclosed ranges establish *prima facie* obviousness which creates a presumption of obviousness. As discussed above, the testing in the '069 patent does not support alleged unexpected results for the claimed ranges.

Claim 1[d]: A non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from 4 mol% to 10 mol% of the total lipid present in the particle and the cholesterol or derivative thereof comprises from 30 mol% to 40 mol% of the total lipid present in the particle

157. The '554 publication teaches "[t]he noncationic lipids used in the present invention can be any of a variety of neutral uncharged, zwitterionic or anionic lipids capable of producing a stable complex." Ex. 1005, [0455]. Neutral lipids are defined as "any lipophilic compound having non-cationic charge (e.g., anionic or neutral charge)." *Id.*, [0315]. "[T]he neutral lipid component … comprises … from about 20% to about 85% of the total lipid

present in the formulation … the cholesterol component … comprises … from about 20% to about 45% of the total lipid present." *Id.*, [0313]. In addition, the '554 publication also includes various specific formulations which include cholesterol at a 30% proportion. *Id.*, Table 4 (*e.g.*, L106). Not only do the disclosed ranges encompass the claimed ranges, when combined with a cationic lipid proportion at 60%, the available range for cholesterol is 20-40% and the range for the other non-cationic lipid (*e.g.*, a phospholipid) is decreased to 0%-20%. Given the breadth of the claimed ranges for the phospholipid and cholesterol, these disclosures are sufficiently specific to anticipate the claimed ranges.

158. Moreover, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, the testing in the '069 patent does not support alleged unexpected results for the claimed ranges.

Claim element 1[e]: A conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol% to 2 mol% of the total lipid present in the particle

159. The '554 publication teaches "[i]n addition to cationic and neutral lipids, the formulated molecular compositions of the present invention comprise a polyethyleneglycol (PEG) conjugate." *Id.*, [0457]. The '554 publication further teaches "[i]t is often desirable to include other components that act in a manner similar to the DAG-PEG conjugates and that serve to prevent particle

aggregation ….” *Id.*, [0504]. “[T]he PEG conjugate … comprises from about 1% to about 20% … of the total lipid present.” *Id.*, [0118]. Given the breadth of the claimed range for the conjugated lipid, these disclosures are sufficiently specific to anticipate the claimed range.

160. This limitation would have been obvious in view of the ’196 PCT in light of the knowledge of a POSITA. A POSITA would have been aware that conjugated lipids stabilize carrier particles by inhibiting fusogenicity. It would have been obvious for a POSITA to try to increase fusogenicity, and hence potentially transfection efficiency, by choosing a proportion of conjugated lipid in the 0.5%-2% range. Moreover, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, the testing in the ’069 patent does not support alleged unexpected results for the claimed ranges.

Claim 2: The nucleic acid-lipid particle of claim 1, wherein the nucleic acid comprises a small interfering RNA (siRNA)

161. The ’554 publication teaches “formulations for the delivery of chemically-modified synthetic short interfering nucleic acid (siNA) molecules that modulate target gene expression or activity in cells, tissues, such as in a subject or organism, by RNA interference (RNAi).” *Id.*, [0020]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly

disclosed.

Claim 3: the nucleic acid-lipid particle of claim 2, wherein the siRNA comprises from about 15 to about 60 nucleotides

162. The '554 publication teaches "[t]he siNA can be, for example, about 15 to about 40 nucleotides in length" or "about 38 to about 70 … nucleotides in length." *Id.*, [0209], [0240]. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Moreover, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious.

Claim 4: the nucleic acid-lipid particle of claim 2, wherein the siRNA comprises at least one modified nucleotide

163. The '554 publication teaches "the siNA component of a formulated siNA composition of the invention is chemically modified so as not to stimulate an interferon response in a mammalian cell, subject, or organism." *Id.*, [0102]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 5: the nucleic acid-lipid particle of claim 2, wherein the siRNA comprises at least one 2'-O-methyl (2'OMe) nucleotide

164. The '554 publication teaches "examples of such chemical modifications include without limitation … 2′-O-methyl ribonucleotides …."

Id., [0194]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 6: the nucleic acid-lipid particle of claim 2, wherein said siRNA is about 19 to about 25 base pairs in length

165. The '554 publication teaches "the invention features a formulated siNA composition comprising a short interfering nucleic acid (siNA) molecule that down-regulates expression of a target gene, wherein said siNA molecule comprises about 15 to about 28 base pairs." *Id.*, [0178]. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Moreover, given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious.

Claim 7: the nucleic acid-lipid particle of claim 2, wherein said siRNA comprises 3' overhangs

166. The '554 publication teaches "siNA molecules of the invention comprise duplex nucleic acid molecules with overhanging ends of about 1 to about 3 (e.g., about 1, 2, or 3) nucleotides, for example, about 21-nucleotide duplexes with about 19 base pairs and 3′-terminal mononucleotide, dinucleotide, or trinucleotide overhangs." *Id.*, [0193]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 8: the nucleic acid-lipid particle of claim 1, wherein the cationic lipid comprises from 52 mol% to 62 mol% of the total lipid present in the particle

167. *See* Claim 1(c). For the reasons stated above, the '554 publication discloses this range with sufficient specificity to anticipate. In the alternative, this range is *prima facie* obvious given the overlapping range in the '554 publication.

Claim 9: the nucleic acid-lipid particle of claim 1, wherein the phospholipid comprises dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), or a mixture thereof

168. The '554 publication teaches "suitable neutral lipids include … DSPC … DPPC … and/or a mixture thereof." Ex. 1004, [0085]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 10: the nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particles comprises a polyethyleneglycol (PEG)-lipid conjugate

169. The '554 publication teaches "[i]n addition to cationic and neutral lipids, the formulated molecular compositions of the present invention comprise a polyethyleneglycol (PEG) conjugate." *Id.*, [0457]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 11: the nucleic acid-lipid particle of claim 10, wherein the PEG-lipid conjugate comprises a PEG-diacylglycerol (PEG-DAG) conjugate, a PEG-dialkyloxypropyl (PEG-DAA) conjugate, or a mixture thereof

170. The '554 publication teaches "[s]uitable polyethyleneglycol-diacylglycerol or polyethyleneglycol-diacylglycamide (PEG-DAG) conjugates …." *Id.*, [0086]. Because one of the listed species of PEG-lipid conjugates is disclosed, this element is anticipated.

Claim 12: the nucleic acid-lipid particle of claim 11, wherein the PEG-DAA conjugate comprises a PEG-dimyristyloxypropyl (PEG-DMA) conjugate, a PEG-distearyloxypropyl (PEG-DSA) conjugate, or a mixture thereof

171. This limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. A POSITA would have been aware that PEG-dialkyloxypropyl (PEG-DAA) conjugates could be used in lieu of PEG-diacylglycerol (PEG-DAG) conjugates and that PEG-dialkyloxypropyl (PEG-DAA) conjugates can comprises a PEG-dimyristyloxypropyl (PEG-DMA) conjugate, a PEG-distearyloxypropyl (PEG-DSA) conjugate, or a mixture thereof. Indeed, the Patent Owner's prior disclosures from years before the '069 patent priority date address using PEG-DAA conjugates (*e.g.*, PEG-DMA or PEG-DSA) in lieu of PEG-DAG conjugates. *See, e.g.*, Ex. 1015 ('910 publication), [0016].

Claim 13: the nucleic acid-lipid particle of claim 12, wherein the PEG has an average molecular weight of about 2,000 daltons

172. This limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. A POSITA would have been aware of PEG 2000 with an average molecular weight of about 2,000 daltons. Indeed, the Patent Owner's prior disclosures from years before the '069 patent priority date states: "PEGs are classified by their molecular weights; for example, PEG 2000 has an average molecular weight of about 2,000 daltons." *See, e.g.*, Ex. 1015 ('910 publication), [0016].

Claim 14: the nucleic acid-lipid particle of claim 10, wherein the nucleic acid-lipid particle comprises about 57.1 mol% cationic lipid, about 7.1 mol% phospholipid, about 34.3 mol% cholesterol or a derivative thereof, and about 1.4 mol% PEG-lipid conjugate

173. *See* Claim 1(c). As noted above, the "about" language in this limitation encompasses amounts ±10, 20, 30 mol% from the amounts listed in Claim 14 that still fall within the ranges in Claim 1. For this reason, the claimed are invalid for the reasons presented above for Claim 1.

Claim 15: the nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particle comprises from 1 mol% to 2 mol% of the total lipid present in the particle

174. *See* Claim 1(e). For the reasons stated above, the '554 publication discloses this range with sufficient specificity to anticipate. In the alternative,

this range is *prima facie* obvious given the overlapping range in the '554 publication.

Claim 16: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid in the nucleic acid-lipid particle is not substantially degraded after incubation of the particle in serum at 37°C for 30 minutes

175. The '554 publication teaches "[f]ormulated siNA compositions are complexed in EGM basal media (Bio Whittaker) at 37° C for 30 minutes in polystyrene tubes." Ex. 1005, [0588]. Moreover, the '554 publication is directed at "delivery agents that are serum stable, i.e. stable in circulation, that can undergo structural transformation, for example from lamellar phase to inverse hexagonal phase, under biological conditions." *Id.*, [0014]. Given these disclosures, a POSITA would have understood the limitation to be disclosed.

176. In the alternative, this limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. A POSITA would have been aware that the disclosed sample incubation parameters could have been used to establish serum stability as disclosed in the '554 publication. It would have been obvious for a POSITA to incubate samples at 37°C for 30 min to establish serum stability.

Claim 17: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid is fully encapsulated in the nucleic acid-lipid particle

177. The '554 publication teaches "[t]he encapsulation of anionic

compounds using cationic lipids is essentially quantitative due to electrostatic interaction." *Id.*, [0011]. A POSITA would understand that full encapsulation requires only an excess of cationic lipid with regard to the nucleic acid for electrostatic interaction. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

Claim 18: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid-lipid particle has a lipid:nucleic acid mass ratio of from about 5 to about 15

178. The '554 publication teaches "the siNA to lipid ratios (mass/mass ratios) in a formed formulated molecular composition range from about 0.01 to about 0.08." *Id.*, [0167]. This corresponds to a lipid:nucleic acid mass ratio of 12.5 to 100. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range.

179. In the alternative, this limitation would have been obvious in view of the '196 PCT in light of the knowledge of a POSITA. A POSITA would have been aware that the total mass of the lipid frequently needs to exceed the mass of the nucleic acid to ensure that the negative charge on the nucleic acid is overcome by the positive cationic lipid charge. Moreover, given the explicit disclosure of an overlapping range, this limitation is *prima facie* obvious.

Claim 19: the nucleic acid-lipid particle of claim 1, wherein the nucleic acid-lipid particle has a median diameter of from about 40 nm to about 150 nm

180. The '554 publication teaches "[n]anoparticles of the invention typically range from about 1 to about 999 nm in diameter, and can include an encapsulated or enclosed biologically active molecule." *Id.*, [0317]. In addition, the '554 publication teaches "[t]he formulated particles made by the methods of this invention have a size of about 50 to about 600 nm or more, with certain of the particles being about 65 to 85 nm." *Id.*, [0463]. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Moreover, given the explicit disclosure of an overlapping range, this limitation is *prima facie* obvious.

Claim 20: the nucleic acid-lipid particle of claim 1, wherein the phospholipid comprises from 5 mol% to 9 mol% of the total lipid present in the particle

181. *See* Claim 1(d). For the reasons stated above, the '554 publication discloses this range with sufficient specificity to anticipate. In the alternative, this range is *prima facie* obvious given the overlapping range in the '554 publication.

Claim 21: the nucleic acid-lipid particle of claim 1, wherein the cholesterol or derivative thereof comprises from 32 mol% to 36 mol% of the total lipid present in the particle

182. *See* Claim 1(d). For the reasons stated above, the '554 publication

discloses this range with sufficient specificity to anticipate. In the alternative, this range is *prima facie* obvious given the overlapping range in the '554 publication.

Claim 22: a pharmaceutical composition comprising a nucleic acid-lipid particle of claim 1 and a pharmaceutically acceptable carrier

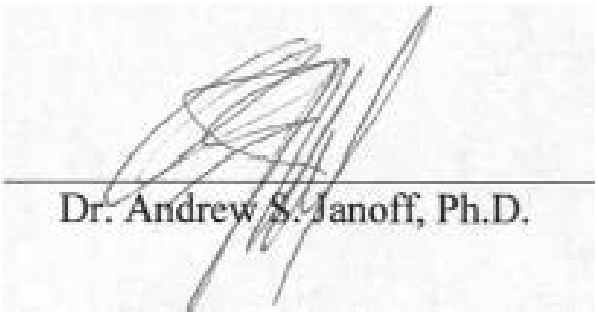
183. The '554 publication teaches "[t]he pharmaceutical carrier is generally added following formulated siNA composition formation. Thus, after the formulated siNA composition is formed, the formulated siNA composition can be diluted into pharmaceutically acceptable carriers such as normal saline." Ex. 1005, [0502]. From these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.

VIII. CONCLUSION

184. In sum, it is my opinion that Grounds 1-3 advanced in the Petition demonstrate that the challenged claims of the '069 patent are disclosed or rendered obvious by the cited prior art.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code.

Executed on January 2, 2019 in Princeton, NJ.



JOINT APPENDIX 85

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

Moderna Therapeutics, Inc.

Petitioner

v.

Protiva Biotherapeutics, Inc.

Patent Owner

_____

Case No. IPR2019-00554
U.S. Patent No. 8,058,069

_____

DECLARATION OF THOMAS J. ANCHORDOQUY, PH.D. IN SUPPORT OF PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

Mail Stop: PATENT BOARD
Patent Trial and Appeal Board
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P.O. Box 1450
Alexandria, VA 22313-1450

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I, Dr. Thomas J. Anchordoquy, PhD, declare as follows:

I. INTRODUCTION

1. I am a tenured Professor in the Department of Pharmaceutical Sciences at the University of Colorado Anschutz Medical Campus in Aurora, Colorado. I have been retained by counsel for ModernaTX, Inc. ("Moderna") as an expert in the relevant art.

2. I understand that Moderna formerly engaged Dr. Andrew Janoff as an expert in this matter and that he submitted a declaration dated January 2, 2019 ("Janoff Declaration") in support of Moderna's Petition for Inter Partes Review ("IPR") of U.S. Patent No. 8,058,069 (the "'069 patent") ("Petition"). EX1008. I understand that Dr. Janoff passed away in December 2019 and that I have been engaged to replace him as Moderna's expert in this proceeding.

3. I have reviewed Dr. Janoff's declaration and, while I may have emphasized different points or stated things differently, I agree with the general premises set-forth regarding the invalidity of the '069 patent as stated therein.

4. On November 13, 2019, Patent Owner Protiva Biotherapeutics, Inc. ("Patent Owner") filed its response to Moderna's Petition ("Response"). I have been asked to provide additional explanation regarding the prior art and the state of the art in response to Patent Owner's arguments in its Response.

While counsel for Moderna has assisted in the preparation of this declaration (*e.g.*, aiding in formatting and providing introductory language and legal standards), the substantive opinions discussed herein are my own.

5. This declaration is based on the information currently available to me. To the extent that additional information becomes available, I reserve the right to continue my investigation and study, which may include a review of documents and information that may be produced, as well as testimony from depositions.

II. SUMMARY OF OPINIONS

6. I understand that the Board ordered an IPR over the'069 patent with respect to the following grounds of unpatentability for claims 1-22:

A. Under §102 and §103 in view of either the '196 PCT and '189 publication;

B. Under §103 in view of each of the '196 PCT and '189 publication in view of Lin and/or Ahmad; and,

C. Under §102 or §103 in view of the '554 publication.

7. The '069 patent is directed to a nucleic acid-lipid particle comprising four lipid components (*i.e.*, a cationic lipid, cholesterol, a phospholipid and a conjugated lipid), each of which fall within a claimed proportion with regard to the total lipid in the particles. *See, e.g.*, EX1001, cl.

1. In my opinion, Moderna has shown that the cited prior art in Grounds 1-3 renders each of the claims in the '069 patent invalid by a preponderance of the evidence.

III. QUALIFICATION AND EXPERIENCE

8. I possess the knowledge, skills, experience, training and the education to form an expert opinion and testimony in this case.

9. I received a bachelor of science in biology from Oregon State University in 1982. I received my master's and doctoral degrees from the University of California Davis in Zoology in 1988 and 1989, respectively. I did my doctoral thesis work under the direction of Dr. John Crowe at the University of California Davis. Dr. Crowe is an expert in the stability of liposomes during freezing and drying, and this was the main topic of my thesis work.

10. I continued my studies at the University of Colorado as a post-doctoral researcher with Dr. John Carpenter in the University of Colorado School of Pharmacy, where I joined the faculty as an Assistant Professor in Pharmaceutical Sciences in 1998. I was promoted to Associate Professor in Pharmaceutical Sciences with Tenure in 2005, and then to Full Professor in 2011.

11. While my doctoral degree is in Zoology, my laboratory focused almost exclusively on liposomes as a model membrane system while I conducted my dissertation research. Accordingly, I have been working with liposomes since 1985. My initial work focused primarily on the physical stability of liposomes during freezing and drying. At that time, liposomes were being investigated as drug delivery vehicles, and our work on stabilization was of interest to the pharmaceutical industry.

12. One of the main measures of stability for a liposome at the time was the extent to which it retained encapsulated drugs, and I frequently conducted assays to determine the extent to which liposomes leaked contents during various stresses.

13. I began working on the ability of liposomes and lipid particles to facilitate the delivery of nucleic acids during my post-doctoral research. At that time, 1996, the interest in gene therapy was intense and many of the people who studied liposomes were now focusing on DNA delivery. This became my predominant focus after I took my faculty position in 1998. During this time, I was in regular communication with scientists at Ribozyme Pharmaceuticals, which ultimately transitioned into Sirna Therapeutics, Inc. (the assignee of the '554 publication (EX1005)) once the potential of siRNA technology became evident.

14. My first issued patent (filed in 2004, issued in 2011) described lipid encapsulation technology for use in delivering DNA and siRNA. In contrast to SNALP technology, my patent described a process by which lipid bilayers could be formed around a solution of nucleic acids, effectively surrounding the nucleic acids to achieve complete encapsulation within a lipid vesicle.

15. In addition, my laboratory focused on understanding the parameters that contributed to serum stability of lipid-nucleic acid particles as well as the mechanisms responsible for effective intracellular delivery. After two decades, my laboratory still focuses on understanding and optimizing lipid-mediated nucleic acid delivery.

16. As part of my faculty position in the Department of Pharmaceutical Sciences at the University of Colorado, I teach both pharmacy students and PhD students about the basics of pharmacy and drug development. Particularly relevant to the current proceeding, I train my PhD students and postdoctoral researchers in liposomes and lipid-mediated nucleic acid delivery. One of my main teachings in the PhD curriculum is a course I developed entitled “Liposome-based Drug Delivery” which reviews the genesis of many fundamental ideas in the field from their initial applications in liposomes

through their adaptation to gene delivery and up to their current use for siRNA delivery.

17. In addition to training half a dozen postdoctoral researchers, I have graduated seven PhD students in my career, all of whom work in the pharmaceutical industry. Of particular relevance to the current proceeding, my first PhD student, Dr. Ye Zhang, graduated from my lab the day before being hired at Sirna Therapeutics in nearby Boulder, CO. Dr. Zhang is an inventor listed on the '554 publication. EX1005.

18. Throughout my career, I have published over 100 manuscripts in peer-reviewed journals and books. The vast majority of these publications involve lipids and/or nucleic acids and focus on stability, formulation, and delivery. In addition, I have filed over a dozen patent applications mostly focused on the formulation of small molecule pharmaceuticals.

19. As mentioned previously, I am a recognized expert in the field of liposomes and lipid-mediated delivery, and I serve on the editorial/advisory board of several scientific journals including Pharmaceutics, Journal of Pharmaceutical Sciences, and Therapeutic Delivery. In addition to organizing symposia on gene and drug delivery for national meetings, I also frequently serve as a reviewer for the National Institutes of Health on study sections to

evaluate grant applications associated with nucleic acid delivery, *e.g.*, Gene and Drug Delivery, Nanotechnology, Biomaterials and Biointerfaces. My *curriculum vitae* is attached as EX1021.

20. I am being compensated by Moderna for my time spent in developing this declaration and for any time spent testifying in connection with this declaration at a rate of $750 per hour. My compensation is not contingent upon the substance of my opinion, the content of this declaration or any testimony I may provide, or the outcome of the *inter partes* review or any other proceeding. I have no financial interest in Moderna.

21. My opinions expressed in this declaration are in response to the Patent Owner's Response and the associated Declaration of Dr. Thompson (EX2031). I have specifically reviewed the Petition and exhibits cited in the Petition, the Patent Owner's Response and exhibits cited in the Response, and other documents and materials identified in this declaration, including the '069 patent (EX1001), the prior art references and materials discussed in this declaration, and any other references specifically identified in this declaration.

22. I am aware of information generally available to, and relied upon by, persons of ordinary skill in the art at the relevant times, including technical dictionaries and technical reference materials (including, for example,

textbooks, manuals, technical papers, articles, and relevant technical standards).

23. I am not a patent attorney or an expert in patent law. I have reviewed the legal section of the Janoff Declaration (¶¶33-59) and have used those legal standards to guide my analysis.

24. I reserve the right to supplement my opinions to address any information obtained, or positions taken, based on any new information that comes to light throughout this proceeding.

IV. Level Of Skill In The Art

25. I have reviewed Dr. Janoff's opinions regarding the level of skill in the art and the Board's determinations related thereto in the Institution Decision, Paper 8 ("ID"), in this case, and agree that a person of ordinary skill in the art ("POSITA") "would have specific experience with lipid particle formation and use in the context of delivering therapeutic nucleic acid payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience."

26. Based upon my education and experience, I am at least a POSITA. I also agree with the Board that the level of ordinary skill in that art in this field is "high." ID, 25.

V. Claim construction

27. In the related '435 patent IPR, the Board construed "Nucleic Acid Lipid Particle" as "a particle that comprises a nucleic acid and lipids, in which the nucleic acid may be encapsulated in the lipid portion of the particle." EX1022, 10-13. While I understand that the Board applied the "broadest reasonable interpretation" standard in the '435 patent IPR, it noted that it was "construing this claim term when read in light of the Specification of the '435 patent …." *Id.* I agree with the Board's reasoning therein and agree that this is also the appropriate construction given the disclosures in the '435 patent and file history as understood by a POSITA at the time.

28. Given the same specification and claim language in the instant proceeding, it is my opinion that the term should receive the same construction here. *See* EX1001, 11:4-12.

29. Patent Owner and Dr. Thompson argue for the same construction that the Board rejected in the '435 patent IPR. *See* Resp., 9 ("… necessarily including a nucleic acid encapsulated in the lipid portion of the particle,

thereby protecting it from enzymatic degradation."). The Board soundly rejected this argument (*see* EX1022, 11-13). I agree with the Board's rejection and the reasoning stated therein.

30. Patent Owner and Dr. Thompson argue that the Board's '435 patent construction of this term "would encompass an empty lipid particle." Resp., 10; EX2031, ¶¶32-33. This is not accurate as the claims also require a nucleic acid payload to be included as part of the particle. *See* EX1001, cl. 1.

31. In addition, the specification states "[t]he lipid particles and compositions of the present invention may be used for a variety of purposes, including the delivery of ***associated or encapsulated*** therapeutic agents to cells, both in vitro and in vivo." EX1001, 6:20-23 (emphasis added). A POSITA would understand that "associated" as quoted is different from "encapsulated" and encompasses particles in which the nucleic acid is not within the interior of the particle and/or surrounded by lipids.

32. For example, it was known in the art at the time of the '069 patent that the extent to which a nucleic acid is surrounded by lipids depends on the amount of nucleic acid and lipid used in the preparation, and the ratio of positive charges from the cationic lipids relative to anionic charges from the nucleic acid (the "N/P ratio"). For example, in many systems at low N/P ratios

containing comparatively less lipid, it was known that the probability of encasement of nucleic acids within a lipid barrier was reduced as compared to the situation at higher N/P ratios.

33. Furthermore, the term "encapsulation" is defined in the '069 patent as protection from degradation by nucleases (EX1001, 22:63-23:13), but it was well known that binding to many cations, *e.g.*, polylysine, resulted in nuclease resistance and reduced dye staining even though such polymers do not contain an internal volume and structure that would be capable of physically surrounding the nucleic acid.

34. Patent Owner relies on a passage of the '069 patent stating "nucleic acids, when present in the lipid particles of the present invention, are resistant in aqueous solution to degradation with a nuclease." *See* EX1001, 11:42-55. There are several methods of protecting different types of nucleic acids from degradation that were known in the art and do not involve encapsulation, including chemical synthesis with modifications to prevent degradation as described for ribozymes in the '069 patent. *Id.,* 44:33-35; *see also* EX1005, ¶20 ("The use of chemically-modified siNA improves various properties of native siRNA molecules through increased resistance to nuclease degradation in vivo, improved cellular uptake, and improved pharmacokinetic properties in vivo."). Patent Owner's arguments ignore these disclosures.

35. As the Board determined in the '435 patent Final Decision, the portions of the prosecution history cited by Dr. Thompson address ***a SNALP, which is but one example of a nucleic-acid lipid particle***. *See* EX1022, 12 ("For instance, the '435 patent identifies a 'stable nucleic acid-lipid particle' or SNALP as an example of a 'nucleic acid-lipid particle,' *see, e.g.*, Ex. 1001, 3:38–39 (stating 'nucleic acid-lipid particle (e.g., SNALP)'), 3:47–48, 3:57–58, 4:4–8, 4:12–13, 4:17–19, 27:43–45, and the term 'nucleic acid-lipid particle' is broader than a SNALP.'").

36. Patent Owner and Dr. Thompson's argument that the scope of the relevant art excludes references addressing lipoplexes (*see, e.g.,* Resp. at 5, 44, 56-57; EX2031, ¶¶153-157) is misplaced and ignores express disclosures in the '069 patent and prior art.

37. As discussed above, the '069 patent claims are not limited to SNALPs, which are identified as but one example of the claimed nucleic acid-lipid particles. *See, e.g.,* EX1001, 3:27-28 ("In certain embodiments, the nucleic acid-lipid particle (*e.g.*, SNALP) comprises ….". A POSITA would understand that lipoplex and liposomal structures existed at the time of the '069 patent that meet the additional claim limitations.

38. A POSITA at the time of the '069 patent working with SNALPs, liposomes, or lipoplexes, would also regularly look at research and publications regarding other types of lipid carrier particles to inform their work. Indeed, the '069 patent specifically references prior work done with types of carrier particles other than SNALPs. *See, e.g.*, EX1001, 59:28-32 ("One sizing method, used for liposomes and equally applicable to the present particles …."), 63:31-33 (referencing liposome sterilization techniques). The '069 patent also incorporates the '618 patent by reference. EX1001, 12:51-64. The '618 patent is directed at polynucleotide lipid complexes (*i.e.*, lipoplexes). *See* EX1017, 30:22-41.

39. Further, a 2005 article published by the inventors on their work with SNALPs specifically cites to prior work done with other types of carrier particles, including liposomes and lipoplexes. *See,* EX1011, 277 (citing to prior work with fusogenic phospholipids in lipoplexes to inform research on SNALPs), 286-287 (multiple lipoplex and liposome research papers cited in the references as supporting various informative propositions). This confirms my opinion.

40. My own work in the field also supports looking at research for different types of lipid carrier particles to help inform further particle development. My graduate course in liposome-mediated drug delivery traces

the origins of many of the lipid-carrier particle concepts described in the '069 patent (*i.e.*, three-dimensional structure, PEGylation, and endosomal escape) from their initial use in liposomes up to their use in cationic lipid nanoparticles for use in siRNA delivery. In my opinion, it is irrefutable that these fundamental phenomena were established in the 1980s (when I was in graduate school), later applied to gene delivery using liposomes and lipoplexes, and ultimately co-opted for the development of siRNA delivery vehicles.

41. I thus agree with Dr. Janoff that a POSITA would have been motivated to combine earlier teachings regarding liposomes and lipoplexes (*e.g.*, Lin (EX1006) and Ahmad (EX1007)) with the teachings of either the '189 publication (EX1004) or the '196 PCT (EX1003).

VI. THE INSTITUTED GROUNDS

42. Based upon the evidence presented, it is my opinion that Petitioner has demonstrated that claims 1-22 of the '069 patent are invalid by a preponderance of the evidence. Each of the cited prior art references discloses nucleic acid-lipid particles with the four claimed lipid components and formulated with overlapping ranges for each of the lipid components. *See* EXS1003-1005. Patent Owner and Dr. Thompson's arguments to the contrary do not change my opinion.

43. Patent Owner relies on arguments directed at the claimed range for the phospholipid and cholesterol components. Response, 14, 17. There does not appear to be anything special or critical about the claimed ranges for these components (*i.e.*, phospholipid 4-10 mol%, cholesterol 30-40 mol%). EX1001, cl. 1. The lipid components are generally added as a bilayer stabilizing component or to provide rigidity to the lipid carrier particle. Generally, the concentrations of these lipids can be varied within reason with less impact on particle performance. For example, a POSITA would not expect a particle with 11 mol% phospholipid versus 10 mol% in the claims or 41 mol% cholesterol versus 40 mol% as in the claims to behave differently in any impactful way.

A. An Overlapping Phospholipid Range Is Disclosed

44. Both prior art reference discloses a non-cationic lipid range of 5-90%. EX1003, [0091]; EX1004, [0152]; EX1005, [0313]. In addition, each reference discloses a narrower range for the non-cationic lipid that also overlaps with the claimed range. EX1003, [0091] (20-85%); EX1004, [0152] (30-70%); EX1005, [0313] (20-85%).

45. Each reference identifies a phospholipid as one of the species that can be used in the disclosed lipid-carrier particles. EX1003, [0089]; EX1004, [0159]; EX1005, [0455]. I agree with the Board's reasoning that an overlapping range of phospholipids is thus disclosed to a POSITA in the prior

art references. *See* ID, 22-24 (Phospholipid disclosed ('196 PCT/'189 publication)), 36-37 (same for '554 publication).

46. Patent Owner and Dr. Thompson argue that no range for a phospholipid is disclosed, because a phospholipid is just one type of potential non-cationic lipid. Response, 13-17; EX2031, ¶¶40-41. First, the prior art disclosures would have put a POSITA on notice that a phospholipid could be used in the disclosed carrier particles in the ranges cited above, even if it is only one potential non-cationic lipid species. Second, these arguments ignore the further disclosures in the working examples of each prior art reference discussed below.

47. In its Final Decision, the Board in the '435 patent IPR found that there was no "***particular*** range for the phospholipid [in the prior art] that overlaps the range required" in the '435 patent claims. EX1022, 35. Patent Owner and Dr. Thompson offer similar arguments here. *See, e.g.,* Resp. 2; EX2031, ¶¶38-58. I understand that the question is what a POSITA reading the reference would understand. Any argument that a POSITA would not be put on notice that a phospholipid could be used in the disclosed carrier particles in the ranges is contrary to the patentee's statements in the '069 patent file history (EX1016) and is not consistent with what a POSITA would understand having read the prior art and intrinsic record.

48. The prosecution history confirms the disclosure of overlapping ranges for each lipid component. During the prosecution of the '069 patent, the Examiner cited Protiva's earlier '910 publication as prior art. EX1016, 5-6. The Examiner pointed to ¶85 of the '910 publication to support disclosure of overlapping range for each of the four lipid components: "MacLachlan teaches particles formulated with ranges of amounts that overlap with the instantly claimed ranges…." *Id.*

49. Patentee did not dispute the Examiner's understanding and, indeed, put for the chart below identifying the prior art disclosed ranges for each lipid component (including the phospholipid):[1]

Lipid Component	Claim 1 as Amended	US 2006/0008910*
Cationic Lipid	50-65 mol %	"2-60, 5-50, 10-45, 20-40, 30 mol%"
Phospholipid	4-10 mol %	"5-90 mol%"
Cholesterol	30-40 mol %	"20-55 mol %"
Conjugated Lipid	0.5-2 mol %	"1-20 mol %"

As can be seen, a phospholipid range of 5-90 mol% is indicated.

50. The disclosures in the '910 publication at ¶85 are substantively identical to the disclosures in Protiva's later disclosures cited as prior art in this proceeding. *See, e.g.,* EX1004, ¶152. Reading the file history, a POSITA

[1] I note that the patentee did not decrease to the range of the phospholipid to accommodate the presence of cholesterol in the chart including in the file history.

would thus understand the cited prior art to disclose an overlapping range for the phospholipid (and the other lipid components as well).

B. The Same Four Lipid-Component Carrier Particles Are Disclosed

51. Patent Owner and Dr. Thompson's argument that "[t]he petition separately parses the claimed amounts of cationic lipids, conjugated lipids, and non-cationic lipids from the references, without regard to one another" (Response, 27) is misplaced.

52. Each prior art reference describes lipid carrier particles with the four lipid components claimed in the '069 patent (*i.e.*, a cationic lipid, phospholipid, cholesterol and conjugated lipid). EX1003 [0088]-[0093]; EX1004, [0152]; EX1005 [0313]. I agree with Dr. Janoff and the Board in its initial determination that EXS1003-1005 disclose overlapping ranges for each of these lipid components. ID, 16-18 ('196 PCT), 18 ('189 publication), 34-36 ('554 publication); Janoff Decl. ¶¶92-99. A chart is included below summarizing the disclosed ranges:

	Cationic Lipid	Non-Cationic Lipid	Conjugated Lipid
'196	2-60% [0088]	5-90% [0091]	0.5-25% [0093]
'189	2-60% [0152]	5-90% [0152]	0.5-20% [0152]
'554	2-60% [0313]	5-90% [0313]	1-20% [0313]

53. Each reference also specifically discloses that the non-cationic/neutral lipid can be a mixture of a phospholipid and cholesterol. EX1003, [0090], EX1004, [0159].EX1005, [0443]. A POSITA would understand the following ranges to apply when a phospholipid/cholesterol are present using simple math to deduce the low point of the disclosed cholesterol range (in each case 20%) from the highpoint and low points of the non-cationic lipid range to determine the range for the phospholipid:

	Cationic Lipid	Non-Cationic Lipid	Cholesterol	Conjugated Lipid
’196	2-60% [0088]	0-70% [0091]	20-45% [0091]	0.5-25% [0093]
’189	2-60% [0152]	0-70% [0152]	20-55% [0152]	0.5-20% [0152]
’554	2-60% [0313]	0-70% [0313]	20-45% [0313]	1-20% [0313]

54. A POSITA would understand that individual lipid components in the prior art references are meant to be combined in the ranges of concentrations disclosed for each lipid to create the carrier particles. In other words, as with the ’069 patent, a POSITA would consider it appropriate to combine lipid components, using a point in the disclosed range for each component, to create carrier particles. A POSITA would have understood that if you increase the percentage of one lipid component, the remaining components have to decrease accordingly. Thus, the mathematical analysis that

Dr. Janoff and the Board conducted in the ID to determine various lipid percentages was well within the understanding of a POSITA.

55. The four lipid component particles in each prior art reference including a cationic lipid, phospholipid, cholesterol and conjugated lipid are not theoretical. Each reference includes actual example formulations tested with such four-lipid component systems. For the four lipid component particles tested in the ’196 PCT, the formulation were 15/55/20/10 (cationic/phospholipid/cholesterol/conjugated). *See, e.g.,* EX1003, [0223]. For the four lipid component particles tested in the ’189 Publication, the formulation were 30/20/48/2 (cationic/phospholipid/cholesterol/conjugated) or 40/10/48/2. EX1004 (Examples 13-17). For the four lipid component particles tested in the ’554 Publication, the formulations were 48/40/10/2, 30/20/48/2, or 50/20/28/2. *See, e.g.,* EX1005, Table IV (L051, L053, L054, L069, L077, L080, L082, L083, L109). Each of these examples are consistent with the ranges that I outlined in the charts above for four lipid component particles. The prior art thus expressly spells out the lipid components combined as in the ’069 patent claims to a POSITA.

C. Lipid-Carrier Particles Are Amenable To Routine Optimization

56. Patent Owner and Dr. Thompson argue that the field involves complex technology and significant unpredictability. *See, e.g.*, Resp. 12, 19-24; EX2004, ¶¶57-59, 136. I do not disagree with this general statement. For example, the claims encompass ***all*** nucleic acid payloads, cationic lipids, non-cationic lipids, and conjugated lipids. A POSITA would expect significant changes to the particle formulations like varying the payload (*e.g.*, from a small siRNA to a large plasmid), the cationic lipid (*e.g.*, from an ionizable cationic lipid to a non-ionizable cationic lipid), or the phospholipid (*e.g.*, from a fusogenic phospholipid like DOPE to a stabilizing phospholipid like DSPC) would impact the effectiveness of a specific lipid composition. This is my understanding of what Dr. Janoff referred to in his declaration. *See* Janoff Decl. ¶¶65-66.

57. However, once a system has been defined (the payload, lipid species and method of particle formulation have been chosen) and shown to be effective, a POSITA would consider variation of the lipid percentages to determine the optimal lipid ranges a matter of routine optimization. *See* Janoff Decl. ¶108. For example, given the defined efficacious prior art systems discussed above (*e.g.*, the 2:40 formulation in the '189 publication), a POSITA would have used the general conditions of such systems as a starting point and been motivated to optimize the lipid formulations therein using routine

optimization. I thus agree with the Board's statement: "in view of the high level of ordinary skill in the art, that optimization of the ranges of components to achieve the claimed composition would be the 'normal desire of scientists or artisans to improve upon what is already generally known.'" ID, 25.

58. In my experience, one of the first variables that was typically optimized was the amount of cationic lipid as reflected in the N/P ratio. *See* EX1005, [0149]-[0155] (optimizing N/P ratios). In fact, many commercial kits today instruct users to vary the amount of cationic lipid as the primary optimization protocol.

59. In a research lab setting, it has been my experience that it was standard practice (and still is) to first optimize the amount of cationic lipid (using the N/P ratio as opposed to just the cationic lipid concentration). For *in vivo* applications, a PEGylated (conjugated) lipid has been typically employed to reduce interactions with serum and uptake by phagocytic cells in the liver, lung, and spleen. *See* EX1008, ¶64. However, it was demonstrated long before the '069 patent that PEGylation prevented uptake by phagocytic cells by reducing interactions with the cell surface. It was subsequently demonstrated (and well known to POSITA) that the reduced cellular interaction afforded by PEGylated lipids resulted in dramatic reductions in nucleic acid delivery once the particles reached the cells. EX1024, 241. Because of this, a POSITA would

minimize the amount of PEGylated lipid to allow interactions with the target cell for intracellular delivery of the nucleic acid. Thus, at the time of the '069 patent, researchers generally used low levels of PEG needing little optimization. Finally, researchers optimize the amount of neutral lipid (*e.g.*, cholesterol and phospholipid). This general ordering is confirmed in the '069 patent. EX1001, 68:35-48.

60. The need to optimize the concentrations of the various lipid components is confirmed by the '069 patent and prior art. The '069 patent states that "[i]t will be readily apparent to one of skill in the art that depending on the intended use of the particles, the proportions of the components can be varied…." EX1001, 49:62-65. The prior art similarly states that "[i]t will be readily apparent to one of skill in the art that the proportions of the components of the nucleic acid-lipid particles may be varied." EX1004, [0152]; *see also* EX1003, [0088] ("…the proportions of the components are varied…."); EX1024, 251.

61. The testing in the '069 patent illustrates just this practice. *See* EX1001, Examples 2-3 (Tables 2 and 4). As can be seen on Table 2 below, the payload and composition is defined and the N/P ratio and proportions of the lipids are varied to determine the optimal range:

TABLE 2

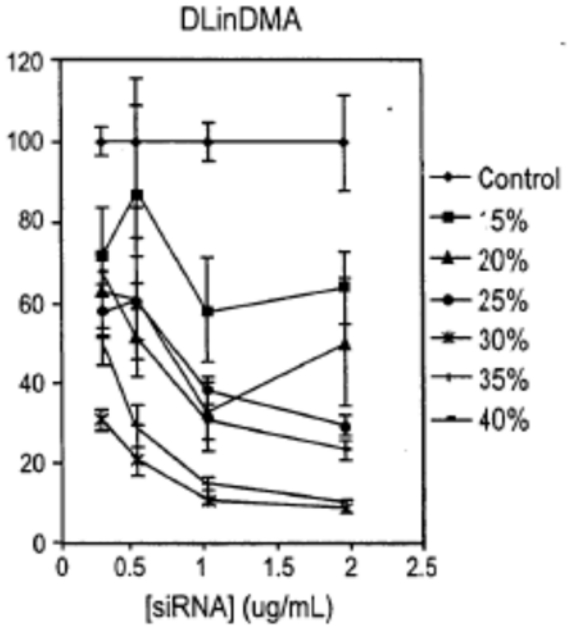
Characteristics of the SNALP formulations used in this study.

Sample No.	Formulation Composition, Mole % PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol	Lipid/Drug Ratio	Finished Product Characterization		
			Size (nm)	Polydispersity	% Encapsulation
1	2 | 40 | 10 | 48	12.4	57	0.07	90
2	1.8 | 36.4 | 18.2 | 43.6	14.0	72	0.12	89
3	1.4 | 27.0 | 6.8 | 64.9	16.5	70	0.12	92
4	1.3 | 25.3 | 12.7 | 60.8	18.1	76	0.07	93
5	3.9 | 39.2 | 9.8 | 47.1	13.5	53	0.27	86
6	3.6 | 35.7 | 17.9 | 42.9	15.1	58	0.18	87
7	2.7 | 26.7 | 6.7 | 64.0	17.6	56	0.17	92
8	2.5 | 25.0 | 12.5 | 60.0	19.2	61	0.13	92
9	1.4 | 57.1 | 7.1 | 34.3	17.8	84	0.10	88
10	1.3 | 53.3 | 13.3 | 32.0	19.5	83	0.10	89
11	1.1 | 42.6 | 5.3 | 51.1	22.0	80	0.10	93
12	1.0 | 40.4 | 10.1 | 48.5	23.6	78	0.11	88
13	2.8 | 56.3 | 7.0 | 33.8	19.0	62	0.14	80
14	2.6 | 52.6 | 13.2 | 31.6	20.6	66	0.14	82
15	2.1 | 42.1 | 5.3 | 50.5	23.1	71	0.16	91
16	2 | 40 | 10 | 48	24.7	67	0.14	92

62. It is worth noting that despite the wide range in lipid:drug ratios listed in Table 2, a calculation of the various amounts of actual cationic lipid as reflected in the N/P ratio in the different preparations reveals that samples 1-8 utilize the exact same N/P ratio of about 3. Similarly, samples 9-16 utilize a N/P ratio of exactly double that ratio, approximately 6. It is clear that despite the range of component percentages listed, the experimenters took great care to control the N/P ratio, as would be expected by POSITA.

63. This is confirmed by Patent Owner's '910 publication which discloses experiments with a SNALP with a siRNA payload with a cationic lipid concentration ranging from 5%-40%. EX1015, [0335]. As can be seen

from Figure 23, increasing concentrations of DLinDMA were tested to determine optimal knockdown levels.



64. This is also shown in Patent Owner's reference EX2014. Tables 1 and 2 of that reference show in detail testing of formulations for a wide variety of lipid percentages for each lipid component (*e.g.*, a cationic lipid range of 20-80mol%) to optimize formulations. *See also id.*, 116-120 (discussing optimization).

65. The file history is consistent with this means of optimization. During prosecution, the examiner specifically concluded that "MacLachlan teaches particles formulated with ranges of amounts that overlap with the instantly claimed ranges and teaches that the proportions of the components

can be varied by those of skill in the art. Thus, ***by routine experimentation towards optimization, one of skill in the art could arrive at the instantly claimed proportions***." EX1016, 6 (emphasis added).

66. Thus, I agree with Dr. Janoff that given the defined systems in the prior art, "determining the optimal proportion of cationic lipid for a given lipid combination would be a simple matter of varying the proportion using prior art methodologies." *See* Ex. 1008, ¶112.

67. Patent Owner argues that "[t]he petition does not identify a reason to select the claimed composition from the prior art references, nor does it address why there would be a reasonable expectation of success of arriving at the claimed compositions." Response, 27. I disagree. The '189 publication discloses effective transfection using a carrier particle with almost the exact same species of lipid components to carry the same nucleic payload as was tested in the '069 patent. Compare EX1004 (Examples 13-17) with EX1001, (Examples 2-4).[2] Given this defined system with demonstrated efficacy as shown in the '189 publication, a POSITA would not start from scratch, but use

[2] DPPC is used instead of DSPC in the '069 patent testing, but Dr. Thompson acknowledges that a POSITA would expect the two phospholipids to behave similarly. EX2031, ¶102; EX2005:158:20-159:4 ("I don't think it's going to have that much of an impact.").

the general conditions of this proven systems as a starting point and would have been motivated to use it, or a similar system, with an expectation that the system to be similarly efficacious at optimized lipid concentrations.

68. Patent Owner and Dr. Thompson argue that the prior art ranges are too broad to support routine optimization. *See, e.g.,* Response, 11. This argument ignores that: (1) the specification of each prior art reference discloses working examples disclosing narrower ranges of each lipid component that have been shown to work; and (2) POSITAs were aware of benefits of using the claimed ranges that would have motivated them to try such ranges with a reasonable expectation of success. I discuss each lipid component range in turn more detail below.

69. I have reviewed the Board's Final Decision in the '435 patent IPR. EX1022 (IPR2018-00739, Paper 51). I understand that the Board determined that Petitioner there did not carry its burden to establish obviousness. *Id.,* 35-36. I understand from my review of the materials that the Board did not find that the claims in the '435 patent could not be shown to be obvious in view of the prior art cited, but that in the Board's opinion the Petitioner had not made such a showing based upon the record in that proceeding. Given the references I have reviewed in this proceeding, the '069 patent claims would have been obvious to a POSITA at the time of the '069 patent.

(i) Optimization Of The Cationic Lipid

70. As a preliminary matter, Patent Owner and Dr. Thompson's repeated argument that there is no "motivation as to why a POSITA would increase the concentration of cationic lipid" (Response, 5-6, 16, 18, 25) beyond those reduced to practice in the prior art (*e.g.*, the 2:40 formulation in the '189 publication) reflects a basic misunderstanding regarding the role of cationic lipids in particle performance.

71. The parameter of interest is the amount of cationic lipid, not merely its concentration. The net amount of cationic lipid available to offset the negatively charged nucleic acid phosphate groups depends on (1) the cationic lipid concentration and (2) the lipid to drug ratio. A POSITA would have known that both these variables must be taken into account in determining the amount of cationic lipid. For example, if you double the cationic lipid concentration from 25% to 50%, but halve the lipid to drug ratio, there is no net impact on the amount of cationic lipid in the particle.[3]

[3] Of note, the claims of the '069 patent are silent on the lipid to drug ratio to use with any given cationic lipid concentration and I have seen no data in the '069 patent or cited art indicating a positive correlation of the cationic lipid concentration to transfection efficacy where the lipid to drug ratio is held constant.

72. While N/P ratios of the lipid particles of the '069 patent are not listed in the specification, a POSITA can calculate the ratio by using the lipid:drug mass ratio to determine the amount of total lipid used per phosphate on the nucleic acid, and then use the molar ratios of the lipid components to compute the moles of cationic lipid in the preparation. For example, on Table 4 of Example 3 all of the formulations listed have an N/P ratio of approximately 3 except Groups 11 and 12, which have a N/P ratio of double that, approximately 6:[4]

[4] Given the consistency of the N/P ratios, it appears that the inventors intentionally used the approximately 3 and 6 ratios as benchmarks. It is, however, unclear as to why this information was omitted from the specification.

TABLE 4

Characteristics of the SNALP formulations used in this study.

	Formulation Composition	Lipid/Drug	Finished Product Characterization		
Group	Lipid Name & Mole %	Ratio	Size (nm)	Polydispersity	% Encapsulation
2	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 2 | 40 | 10 | 48	12.4	59	0.15	93
3	PEG(2000)-C-DMA | DLinDMA | Cholesterol 2.2 | 44.4 | 53.3	10.7	55	0.17	91
4	PEG(2000)-C-DMA | DLinDMA | DOPC | Cholesterol 2 | 40 | 10 | 48	12.5	59	0.16	92
5	PEG(2000)-C-DMA | DLinDMA | DMPC | Cholesterol 2 | 40 | 10 | 48	12.2	56	0.11	92
6	PEG(2000)-C-DMA | DLinDMA | DPPE | Cholesterol 1.8 | 36.4 | 18.2 | 43.6	13.8	66	0.16	93
7	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholestanol 2 | 40 | 10 | 48	12.4	56	0.12	92
8	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.4 | 27.0 | 6.8 | 64.9	16.5	60	0.10	93
9	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.3 | 25.3 | 12.7 | 60.8	18.1	74	0.13	92
10	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 2.5 | 25.0 | 12.5 | 60.0	19.2	60	0.13	93
11	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.4 | 57.1 | 7.4 | 34.3	17.8	79	0.09	94
12	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.0 | 40.4 | 10.1 | 48.5	23.6	72	0.11	93
13	PEG(2000)-C-DMA | DLinDMA | DPPC 2 | 70 | 28	8.7	73	0.09	87
14	PEG(2000)-C-DMA | DLinDMA | DPPC 1.6 | 54.7 | 43.8	11.3	65	0.11	87

73. As discussed above, the ’189 publication discloses using substantially the same nucleic acid-lipid particles (same payload and substantially the same lipid components) as disclosed in the ’069 patent. Looking at Examples 13-17 in the ’189 publication, the N/P ratio tested in the ’189 publication was approximately 6—virtually the same as the N/P ratio tested in the ’069 patent. EX1004, [0350]-[0391]; *see also* EX1027, 3 (also tested at N/P ratio of 6).

74. Looking at the ’069 patent, for the formulations in Table 4 of Example 3, a POSITA would have known that by decreasing the lipid to drug

ratio in Group 11 compared to Group 12 (from 23.6 to 17.8) and correspondingly increasing the cationic lipid concentration (from 40.4 to 57.1 mol%), a consistent N/P ratio would be achieved. A POSITA would thus expect the resulting particles to perform similarly—exactly as shown by the data for Groups 11 and 12 in Example 3. This illustrates both a motivation to increase the cationic lipid percentage while decreasing the lipid:drug ratio to achieve the optimized N/P ratio, and a basis for expecting the particles to be effective.

75. The prior art also illustrates that a POSITA would have been motivated to increase the cationic lipid concentration in order to optimize the N/P ratio. It was known in the art that cationic lipids neutralize the "negative charge which is associated with the nucleic acids (or other polyanionic materials) present." EX1004, [0223]. Indeed, the '189 publication states that it is "more preferabl[e]" to have enough cationic lipid present to neutralize at least 90% of "the negative charge of the nucleic acid" (compared to 50% or 70% of the charge). A POSITA would understand this to favor increasing amount of cationic lipid sufficiently to achieve the identified level of charge negation.

76. Moreover, a POSITA would have known that an excess of positive charge promotes endosomal release of the payload once a target is

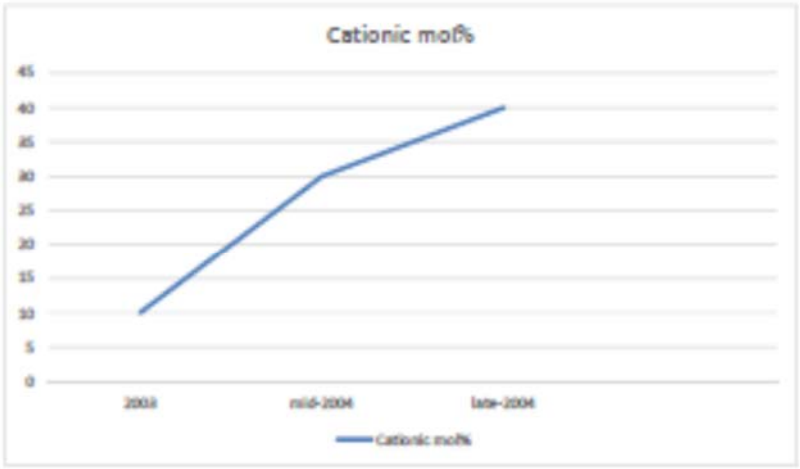
reached. EX1024, 230 ("Cationic lipids also function by providing the liposome with a net positive charge, which in turn enables binding of the NA complex to anionic cell surface molecules."). A POSITA would have been aware that having more cationic lipid can increase interactions with the cell surface promoting binding with the target.

77. One potential benefit of increasing the cationic lipid concentration while decreasing the lipid:drug ratio (thus maintain the N/P ratio) is a net decrease in the amount of helper lipids (*e.g.,* phospholipids, cholesterol, and PEG). Moreover, even if cationic lipid concentrations alone are considered a driver of efficacy (as opposed to the actual amount of cationic lipid), it is undisputed that each prior art reference discloses a cationic lipid range of 2-60%. *See* EX1003 [0088]; EX1004, [0152]; EX1005 [0313]. The upper end of this range overlaps with the claimed range in the '069 patent. In addition, each reference discloses a narrower range of 40-50% that also overlaps with the claimed range. *See id.* A POSITA would have understood these disclosures to describe potential cationic lipid concentration ranges (including the 50-60% range) for effective lipid-carrier particles. These disclosures would thus motivate a POSITA to create particles at the upper end of the disclosed ranges (*e.g.,* at 50% or above) with a reasonable expectation of success.

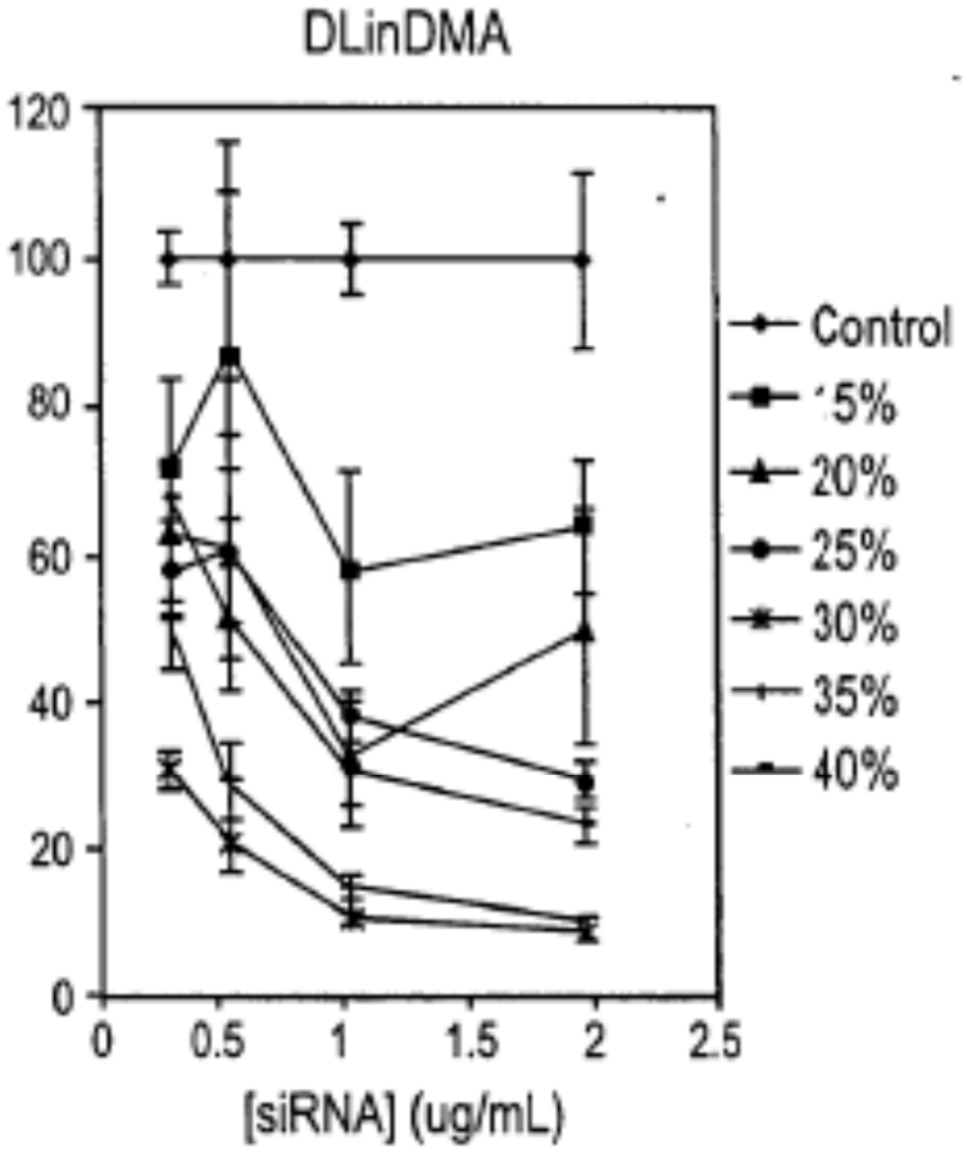
78. The Patent Owner's own disclosures illustrate a trend toward using higher cationic lipid concentrations. The '196 PCT claims priority to 2003 and discloses experiments with a SNALP with a siRNA payload and a four lipid component system with lipid percentages of 15/20/55/10 (cationic/phospholipid/ cholesterol/conjugated).

79. Patent Owner's U.S. Patent No. U.S. Patent No. 7,799,565 claims priority to mid-2004 and discloses experiments with a SNALP with a siRNA payload and a four lipid component system with lipid percentages of 30/20/48/2 (cationic/phospholipid/ cholesterol/conjugated). EX1028, 52:54-53:17.

80. Patent Owner's '189 publication claims priority to late 2004 and discloses experiments with a SNALP with a siRNA payload and a four lipid component system with lipid percentages of 40/10/48/2 (cationic/phospholipid/cholesterol/conjugated). EX1004, [0351]-[0385]. Over time, we thus see a consistent increase in the cationic lipid concentrations used in Patent Owner's prior disclosures.



81. This is confirmed by Patent Owner's '910 publication which claims priority to 2004 and discloses experiments with a SNALP with a siRNA payload with a cationic lipid concentration ranging from 5%-40%. EX1015, [0335]. As can be seen from the figure, increased concentrations of DLinDMA were disclosed as being associated with greater knockdown levels confirming the understanding described above.



82. These disclosures would further motivate a POSITA, using the 2:40 formulation as a starting point, to create particles with a cationic lipid in the claimed range with a reasonable expectation of success.

83. Patent Owner and Dr. Thompson argue that all cationic lipids are toxic and a POSITA would thus always have sought to decrease the cationic lipid concentration. *See, e.g.,* Response, 7. In so doing, Patent Owner again equates the cationic lipid concentration with the *amount* of cationic lipid used for delivery of a given payload.

84. As discussed above, a POSITA would have recognized that cationic lipid toxicity was largely determined by the N/P ratio. Moreover, a POSITA would have been aware that toxicity in nucleic acid-lipid particles is largely a function of such particles having a net positive charge at physiological pH.

85. To address potential toxicity issues, years before the ’069 patent priority date, ionizable cationic lipids had been developed whose charge was low at physiological pH, but became strongly cationic in the acidified environment of the endosome. EX1004 [0223] (using ionizable lipid DLinDMA); EX1011, 280 (same), Fig. 1 (showing substantially neutral charge at pH 7.4); EX1009, 6 (“Cationic lipids that are charged only at mildly acidic but not at neutral pH … may also be a potential solution to the toxicity issues ….”); EX1005, [0462] (same). This was confirmed by the lead inventor on the ’069 patent in a 2007 treatise. *See* EX1024, 239-240; *see also* EX2021, 173 (neutral particles at physiological pH preferred). This understanding still holds

true even today: "…such positively charged systems induce pronounced toxicity in vivo due to immune activation…[t]o circumvent this problem, we developed ionizable cationic lipids…." EX1026, 1085.

86. Because of the low charge of such cationic lipids at physiological pH, higher concentrations of cationic lipid could be used to increase the N/P ratio while maintaining a substantially neutral (non-toxic) charge in the resulting particles at physiological pH. It would have been routine to consider the pKa of the cationic lipid and the pH of the surrounding media in determining the extent to which the charge on the nucleic acid was neutralized. For example, as shown by EX1011, 281, the pKa of DLinDMA is 6.7. Having taken an undergraduate biochemisty course, POSITA would have been able to calculate that only one-sixth of the DLinDMA molecules thus possess a positive charge at physiological pH (the pH of blood is 7.4). Thus, a N/P ratio of approximately 6 would be required to fully neutralize the negative charges on the nucleic acid in the blood.

87. As stated in the '189 publication, it is important to neutralize approximately 90% of the negative charges on the nucleic acid. EX1004, [0062]. A POSITA would have recognized that an N/P ratio of 3 would only neutralize approximately half of the negative charges on an RNA payload in the blood, and thus be insufficient according to the prior art.

88. In fact, both the '069 patent and the prior art '189 publication demonstrate the use of high cationic lipid concentrations to achieve this optimal N/P ratio of 6. *See, e.g.,* EX1004 [0351-0391] (*in vivo* testing of 2:40 formulation using DLinDMA), [0076, 0151] (resulting particles "substantially non-toxic" and tested N/P ratio of approximately 6); EX1001, Example 3, Table 4 (N/P ratio of approximately 6 used for Groups 11-12).

89. Lin and Ahmad provide further support that a POSITA would have been motivated to employ greater amounts of cationic lipid. While Lin and Ahmad tested lipoplex formulations and the complicated nature of what affects transfection efficiencies of the CL-DNA complexes, the testing therein establishes that for certain cationic lipids, increasing the N/P ratio by elevating the cationic lipid concentrations above 50 mol% enhanced transfection efficiency. EXS1006-1007. I believe that this provides further impetus for a POSITA to increase the cationic lipid percentage in order to increase the N/P ratio.

90. Patent Owner argues that there was no motivation to combine Lin and Ahmad with the '189 publication or '196 PCT and no reasonable expectation of success in doing so. Response, 57. I disagree. First, the claims of the '069 patent are not limited to non-lipoplex particles. Moreover, the '189 publication is also directed at SNALPs and it specifically identifies liposomes

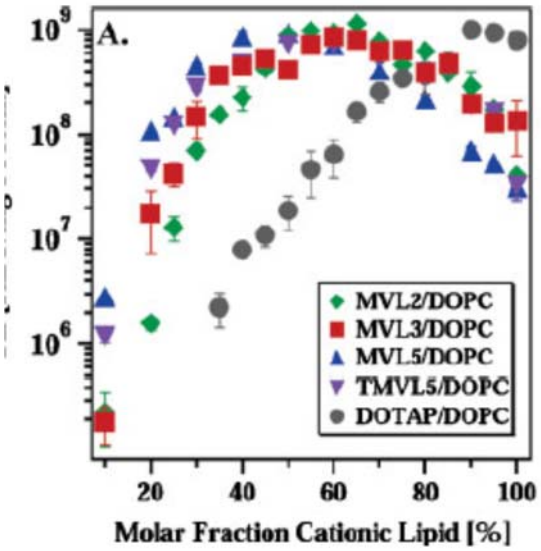
and lipoplexes as "alternative lipid-based carrier systems suitable for use with the present invention…." EX1004, [0149]. Second, as discussed above, in this field, it was common to look at prior research regarding various types of lipid carrier particles (*e.g.,* liposomes and lipoplexes) when developing lipid carrier particles. Both of the Patent Owner's prior art disclosures cite to prior work done on liposomes and lipoplexes. EX1003, [0132] (prior work with liposomes), [0175] (prior work with lipoplexes); EX1004, [0203] (liposome), [0156] (incorporating '618 patent by reference which is directed to lipoplexes).

91. A POSITA would have a had a reasonable likelihood of success in increasing the cationic lipid concentrations to bolster the N/P ratio given the express disclosures in the prior art of ranges up to 60%, the trend in the patent owner's prior disclosures of using higher cationic lipid proportions, and the availability of ionizable cationic lipids that are substantially charge neutral at physiological pH.

92. Patent Owner argues that Ahmad teaches away from increasing the cationic lipid concentration. Response, 59. While Ahmad mentions toxicity issues, Ahmad notes that the "toxic effects" are only a mere possibility: "minimizing the *amount* of cationic lipid is desirable to reduce cost as well as ***potential*** toxic effects of the cationic lipid." EX1006, 745 (emphasis added). Ahmad specifically noted that *in vitro*, the tested cationic lipid *amounts*

showed "no toxic effects on the cells as judged by cell morphology and the amount of total cellular protein." EX1006, 745-46. It is my understanding that claim 1 encompasses particles for *in vitro* use, In addition, a POSITA would have considered the findings of Ahmad informative in terms of needing to balance the increased delivery provided at high N/P ratios with the toxicity associated with increasing *amounts* of cationic lipid. Ahmad also utilized multivalent cationic lipids to achieve very high charge densities in order to test their hypothesis, and it was known by a POSITA that such extreme charge densities with multivalent cationic lipids were not suitable for *in vivo* use due to their toxicity.

93. Patent Owner also mischaracterizes Ahmad as reaching "saturation" at 50% cationic lipid. *See* Response, 58. Ahmad shows no such thing. As can be seen below, the monovalent cationic lipids do not level off until about 80% (EX1007, Fig. 3):



94. Patent Owner and Dr. Thompson point to accumulation in the plasma and immunogenicity as alternative sources of toxicity. Response, 29-30; EX2031, ¶86. Patent Owner confirmed, however, the lack of such toxicity issues for the 2:40 SNALP formulation in 2006. EX1027, 3. Patent Owner disclosed that its prior art 2:40 SNALP system resolved toxicity concerns: "[t]here was no evidence for complement activation, delayed coagulation, pro-inflammatory cytokine production (Supplementary Table 1) or changes in haematology parameters (data not shown), toxicities that have been observed previously with treatments using related approaches." *Id.*, 3. Thus, a POSITA would not have been dissuaded from using higher cationic lipid concentrations in such systems.

95. Patent Owner and Dr. Thompson also point to Moderna publications stating that toxicity issues with modern cationic lipids can be further minimized. Response, 29-30. That cationic lipids may be further improved does not negate their use at tolerable levels at the time of the '069 patent.

(ii) Optimization Of The Conjugated Lipid

96. Each prior art reference discloses an encompassing or overlapping range for the conjugated lipid. EX1003, [0093] (0.5-25%); EX1004, [0152] (0.5-20%); EX1005, [0313] (1-20%). In addition, the '189 publication discloses a narrower point for the conjugated lipid that also overlaps with the claimed range. EX1004, [0152] (2%).

97. Each prior art reference discloses four lipid component particles that are effective *in vivo* which contain a conjugated lipid at the lower end of the disclosed ranges. For the four lipid component particles tested in the early '196 PCT, the conjugated lipid was 10%. *See, e.g.,* EX1003, [0223]. For the four lipid component particles tested in the later '189 Publication, the conjugated lipid was down to 2%. *See, e.g.,* EX1004, [0289], [0369]. For the four lipid component particles tested in the '554 Publication, the conjugated lipid was also 2%. *See, e.g.,* EX1005, Table IV (L051, L053, L054, L069,

L077, L080, L082, L083, L109). This illustrates the trend in using minimal amounts of conjugated lipid.

98. As Dr. Janoff pointed out, it was known in the art that a conjugated lipid could be included to prevent particle aggregation in serum. Janoff Decl. ¶61. In addition, the following "PEG dilemma" was known in the art: including enough PEG to stabilize the particle, but not so much that the particle is unable to engage the target *in vivo*. EX1024, 241. In other words, it was known that the amount of conjugated lipid (*e.g.,* PEG) should be minimized to allow the nucleic acid payload to interact with the target cell to maximize delivery. *Id.*

99. Patent Owner's argument that "low levels of conjugated lipid (*i.e.*, 0.5 mol% to 2 mol%) would have been expected to result in unstable particles that aggregate and fail to effectively transfect cells" (Response, 30.) ignores the actual testing done in the prior art. A POSITA would have known that the presence of phospholipids also helps to maintain a bilayer structure, thereby allowing lower levels of conjugated lipid to be used.

100. The claimed range of 0.5-2% conjugated lipid is within the disclosed ranges for conjugated lipid in the prior art and consistent with the ranges actually tested in the prior art. Given the accepted reasoning in the field

regarding the use of conjugated lipid and effective four-lipid component systems using conjugated lipid in the claimed range, a POSITA would have been motivated to test such ranges in optimizing the prior art disclosed ranges and also had a reasonable likelihood of success.

101. Patent Owner and Dr. Thompson point to other systems that used 10% PEG. That other systems using higher PEG percentages may have existed does not negate that a POSITA would have been well aware of the examples above, in which lower levels of PEG were used.

102. Patent Owner and Dr. Thompson also argue that a high level of cationic lipid and a low level of PEG in tandem was contrary to the prevailing wisdom. Response, 18-19, 29; EX2031, ¶¶57-58, 77-78. This is not consistent with the disclosures in the '189 publication and '554 publication of high levels of cationic lipid and low levels of PEG. EX1004 [0351-0391] (40 mol% cationic lipid/2 mol% PEG); EX1005, [0408], Table IV (L077, L069, L080, L082, L083, L060, L061, and L051 with 48-52 mol% cationic lipid and 2-3 mol% PEG). While these specific formulations vary slightly from the claimed ranges, they do establish the falsity of Patent Owner's assertion that use of high cationic lipid concentrations coupled with low PEG concentrations *in vivo* was not known.

(iii) Optimization Of The Cholesterol

103. Each reference also discloses that the non-cationic lipid can comprise a mixture of cholesterol and another non-cationic lipid (*e.g.*, a phospholipid). Each reference discloses that cholesterol, when present, is in a certain range. EX1003 (20-45% [0091]); EX1004 (20-55% [0152]); EX1005 (20%-45% [0311]). Each reference also specifically discloses using cholesterol when a phospholipid is used. EX1003 [0158] ("The method is especially useful for vesicles made from phospholipids (which can contain cholesterol)…."); EX1004, [0238] (same); EX1005, [0499] (same).

104. Each prior art reference discloses four lipid component particles that are effective *in vivo* which contain a phospholipid and cholesterol. For the four lipid component particles tested in the '196 PCT, the formulation contained 20% cholesterol. *See, e.g.,* EX1003, [0223]. For the four lipid component particles tested in the '189 Publication, the formulations were 48% cholesterol for both the 2:30 and 2:40 formulations. *See, e.g.,* EX1004, [0289], [0369]. For the four lipid component particles tested in the '554 Publication, the formulations were 10-48% cholesterol. *See, e.g.,* EX1005, Table IV (L051, L053, L054, L069, L077, L080, L082, L083, L109).

105. It was known in the art that cholesterol could be added to a lipid carrier particle to provide rigidity to the particle. Janoff Decl., ¶71; EX1010, 6 (presence of cholesterol leads to higher transfection efficiency). A POSITA

would have been aware that a minimum amount of cholesterol was thought to be required to saturate the lipid mixtures and to provide stability (*e.g.*, in the 20-25% range). EX1003 (20-45% [0091]); EX1004 (20-55% [0152]); EX1005 (20%-45% [0311]). A POSITA would also have been aware of the risk of the cholesterol precipitating out of solution if too much was used. Upper limits of 40-55% were thus commonly used to avoid this risk. EX1003 (20-45% [0091]); EX1004 (20-55% [0152]); EX1005 (20%-45% [0311]).

106. The claimed range of 30-40% cholesterol is squarely within the disclosed ranges for cholesterol in the prior art and the generally acceptable ranges in the field. A POSITA would thus have been motivated to test such a range in optimizing particle formulations. Given the accepted reasoning in the field regarding the use of cholesterol and effective four-lipid component systems using cholesterol in the claimed range, a POSITA would have also had a reasonable likelihood of success.

(iv) Optimization Of The Phospholipid

107. A POSITA at the time of the ’069 patent would have been aware that phospholipids could be included as a bilayer stabilizing component. As discussed in the ’554 publication, it was desirable to design delivery systems to maintain the bilayer structure for stability in the blood, but to transition to the

fusogenic hexagonal phase inside the target cell. EX1005, [0137]; *see also* EX1024, 239-240.

108. Each prior art reference discloses four lipid component particles that are effective in vivo which contain a phospholipid. For the four lipid component particles tested in the '196 PCT, the formulations contained 55% phospholipid. *See, e.g.,* EX1003, [0223]. In the later disclosures of the'189 Publication, the four lipid component particles tested included 20% phospholipid or 10% phospholipid. *See, e.g.,* EX1004, [0289], [0369]. For the four lipid component particles tested in the '554 publication, the phospholipid ranged from 20-40%. *See, e.g.,* EX1005, Table IV (L051, L053, L054, L069, L077, L080, L082, L083, L109). The disclosed phospholipid range is thus not theoretical.

109. This balance required the use of components that served to promote the bilayer structure, and a POSITA would have understood that most phospholipids (including DSPC, DPPC) would serve this purpose. As with the conjugated lipid, a POSITA would have been aware that having some amount of phospholipid can provide structural stability to the resulting particles, but having too much will inhibit release of the payload upon contact with the endosome. Thus, a POSITA would have been motivated to test phospholipid concentrations at the lower end of the disclosed ranges, especially when a

conjugated lipid is also used. This is confirmed by the use of 10% phospholipid in the closest prior art—the 2/40 formulation tested in the '189 publication.

D. Dependent claims

110. Claim 8 specifies that the cationic lipid comprises from 52 mol% to 62mol%. Given the disclosures above in the prior art regarding the disclosed range for the cationic lipid, the tested range for the cationic lipid and the motivation for a POSITA to optimize the claimed range with a reasonable likelihood of success, this slightly narrower range reflects routine optimization (52 mol% -62 mol% vs. 50 mol% - 65 mol%) that would have been obvious to a POSITA.

111. Claim 14 specifies that the particles have "about 57.1 mol% cationic lipid, about 7.1 mol% phospholipid, about 34.3 mol% cholesterol…and about 1.4 mol % PEG-lipid conjugate." While Patent Owner argues that "this claim is drawn to a 1:57 particle" (Response, 61), Patent Owner does not explain what "about" encompasses. During prosecution, the examiner stated in this context that "'comprising about' could embrace an amount ±10, 20, 30 mol% of a lipid component." Ex. 1016, 5/12/11 Rejection, 2. This would result in ranges far wider than those addressed above. Moreover, even at the narrowest, a POSITA would understand these limitations to encompass at least the variability in particle formulation described in the

specification: "typically, in the 1:57 formulation, the amount of cationic lipid will be 57 mol% +- 5 mol%, and the amount of lipid conjugate will be 1.5 mol% +- 0.5 mol%." EX1001, 68:39-41. The resulting ranges of 52.1-62.1 mol% cationic lipid and 0.9-1.9 mol% conjugated lipid are only slightly different than the ranges in claims 1 and 8 addressed above. While the specification is silent on the variability in the phospholipid and cholesterol, a POSITA would expect some variability as they make up the remaining lipid in the particle.

112. Given the disclosures above in the prior art regarding the disclosed ranges for the lipid components, the tested range for the lipid components and the motivation for a POSITA to optimize the claimed ranges with a reasonable likelihood of success, these slightly narrower ranges reflects routine optimization that would have been obvious to a POSITA.

113. Claim 15 specifies that the conjugated lipid comprises from 1 mol% to 2 mol% of the total lipid present in the particle. Given the disclosures above in the prior art regarding the disclosed range for the conjugated lipid, the tested range for the conjugated lipid and the motivation for a POSITA to optimize the claimed range with a reasonable likelihood of success, this slightly narrower range reflects routine optimization that would have been obvious to a POSITA.

114. Claim 16 specifies that the nucleic acid in the nucleic acid-lipid particle is not substantially degraded after incubation of the particle in serum at 37°C for 30 minutes. As Dr. Janoff explained, each prior art reference discloses that the described lipid-carrier particles are serum stable (as defined therein in an equivalent fashion to the claim limitation). Janoff Decl. ¶¶136-137, 175-176. Patent Owner argues that these descriptions refer to "the ability to test" for degradation. Response, 62. That is not accurate. The disclosures describe the resulting particles and map similar disclosures in the '069 patent. EX1001, 22:50-53. Given these disclosures and the successful *in vivo* testing described in the prior art, a POSITA would have both a motivation to create serum stable particles and reasonable expectation of success of achieving such particles.

115. Claim 17 specifies that the nucleic acid is fully encapsulated in the nucleic acid-lipid particle. Fully encapsulated is defined at EX1001, 22:63-23:6 as being "not significantly degraded" in serum. A POSITA would understand that this is tested as described above in claim 16 and is demonstrated by *in vivo* effectiveness. Claim 17 specifies that the nucleic acid is fully encapsulated in the nucleic acid-lipid particle. Fully encapsulated is defined at EX1001, 22:63-23:6 as being "not significantly degraded" in serum (*e.g.*, "less than about 25% of the active agent or therapeutic agent in the particle is degraded"). Patent Owner's own publications from 2006 regarding the 2:40 formulation

confirmed "[n]ucleic acid encapsulation efficiencies were 92-97%." EX1027, 2-3.

116. Given the disclosures above for Claim 16, the additional disclosures described by Dr. Janoff (Janoff Decl. ¶¶138, 177) and the disclosure of successful *in vivo* testing described in the prior art, a POSITA would have both a motivation to create particles with the described encapsulation and reasonable expectation of success of achieving such particles.

117. Claim 18 specifies that the nucleic acid-lipid particle has a lipid:nucleic acid mass ratio of from about 5 to about 15. A POSITA would have known that the lipid:nucleic acid mass ratio would impact the N/P ratio. As Dr. Janoff explained, a "POSITA would have been aware that the total mass of the lipid frequently needs to exceed the mass of the nucleic acid to ensure that the negative charge on the nucleic acid is overcome by the positive cationic lipid charge." Janoff Decl. ¶179. As discussed above, adjusting the N/P ratio was typically the first step in carrier particle optimization. This is reflected in the prior art: "the nucleic acid to lipid ratios (mass/mass ratios) in a formed nucleic acid-lipid particle will range from about 0.01 to about 0.2, from about 0.03 to about 0.01 or from about 0.01 to about 0.08." EX1004, [0198]; EX1003, [0127] (same); EX1005, [0167], [0468] (same). A nucleic acid:lipid

ratio of .08 is equivalent to a lipid:nucleic acid ratio of 12.5 and optimization of the mass ratios would be obvious given the impact on the N/P ratio and the requirement for different N/P ratios depending on the pKa of cationic lipid used and the nucleic acid payload.

118. Claim 20 specifies that the phospholipid comprises from 5 mol% to 9 mol% of the total lipid present in the particle. Given the disclosures above in the prior art regarding the disclosed range for the phospholipid, the tested range for the phospholipid and the motivation for a POSITA to optimize the claimed range with a reasonable likelihood of success, this slightly narrower range reflects routine optimization that would have been obvious to a POSITA.

119. Claim 21 specifies that the cholesterol or derivative thereof comprises from 32 mol% to 36 mol% of the total lipid present in the particle. Given the disclosures above in the prior art regarding the disclosed range for cholesterol, the tested range for cholesterol and the motivation for a POSITA to optimize the claimed range with a reasonable likelihood of success, this slightly narrower range reflects routine optimization that would have been obvious to a POSITA.

120. Claim 22 specifies a "pharmaceutical composition comprising a nucleic acid-lipid particle of claim 1 and a pharmaceutically acceptable

carrier." Patent Owner does not dispute that the payloads in the prior art were typically siRNA and the goal was to develop particles for therapeutic treatment. The prior art discloses using "pharmaceutically acceptable carriers" like saline. EX1008, ¶183; EX1005, [502]; EX1004, 242 (same); EX1003, [0175]. A POSITA would thus understand these additional limitation to be obvious in view of the prior art.

VII. SECONDARY CONSIDERATIONS CANNOT OVERCOME PETITIONER'S OBVIOUSNESS SHOWING

A. The Test Data Is Not Commensurate With The Scope Of The Claims

121. I have reviewed Dr. Janoff's analysis of the test data presented in the '069 patent and agree that it fails to demonstrate unexpected results. EX1008, ¶¶81-87. Patent Owner relies on test data that covers only a small portion of the potential numeric ranges in the claims, and an even smaller portion of the potential lipid components and payloads claimed. A POSITA would be aware that changes to the payload, identity of lipid components, or production techniques can impact efficacy. The '069 patent test data compares only a single data point, the 1:57 formulation, to the closest prior art 2:40 formulation. *See* EX1001, Fig. 2. Moreover, the claims cover all lipid species for the identified genus—given the limited subset of payloads, lipid

components, and production techniques tested, there is no reason to believe the 1:57 test data would apply to all other claimed particles.

B. Test Data Does Not Show Unexpected Results

122. Patent Owner mischaracterizes the results of Figure 1. Response, 33-34. Figure 1B shows prior art formulations (*e.g.,* Sample 12 (2:40 type SNALP)) possessing the same efficacy as the 1:57 SNALP. Patent Owner's assertion that the data illustrate increased potency is thus not supported. Most of the other data points perform similarly as well. This is not surprising given the same N/P ratio was used for Samples 9-16.

123. Patent Owner's arguments regarding Example 3 of the '069 patent are also unsupported. *See* Response, 4-5. As discussed above, Groups 11-12 on Table IV are the only two samples tested at a N/P ratio of 6. That such samples outperform samples formulated at a N/P ratio of 3 would have been expected when using an ionizable cationic lipid. EX1004, Fig. 2.

124. Patent Owner argues that Sample 12 may have performed marginally better than Sample 11. Response, 43; EX2031, ¶100. My review of the data indicates that the samples appear to behave similarly as would be expected from such similar formulations possessing the same N/P ratio. Any assessment of differences between formulations would require a statistical test

which was not presented. However, my visual inspection indicates that the performance of Sample 11 was not significantly different than Sample 12.

125. Patent Owner and Dr. Thompson argue that the bar for evaluating unexpected results should not be the demonstrated performance of the known 2:40 type SNALPs, but any apparent efficacy versus a PBS standard. Response, 32 (expect "little, if any, efficacy"); EX2004, ¶¶66-67. This does not reflect the understandings of a POSITA in evaluating unexpected results given the prior performance of the 2:40 SNALP.

126. Patent Owner also relies on testing in Example 4 regarding the prior art 2:30 formulation. Response, 35. First, the 2:30 formulation is not the closest cited prior art, the 2:40 is—and Example 3 shows the 2:40 formulation performing substantially similarly to the 1:57 formulation. Second, different dosing regimes were used between samples in the testing in Example 4 and there was no dose response data presented. It is unclear how the 2:30 would have performed at the same dosing regime as the 1:57 formulation.

127. It is also important to point out that all the formulations in Examples 4 and 5 were performed at the non-optimized N/P ratio of 3. Comparisons of formulations at the non-optimized N/P ratio are difficult to justify and are of minimal value.

128. I understand that Dr. Thompson at his deposition argued that the results in Example 3 are relevant because he expects the 2:30 and 2:40 formulations to behave comparably based upon data reported in Figures 9 and 13 of the '189 publication. Ex. 1025, 183:23-191:10 ("…My opinion is that the 2-to-40 formulation is not substantially better than the 2-to-30…."). A POSITA would not consider this a scientifically supported position. The data from these figures is from two separate tests involving different dosing regimes, different lipid species and different durations. EX1004, [0326]-[0333], [0360]-[0367]. Given this variability, drawing such parallels is not scientifically valid.

129. Patent Owner also points to Examples 5 and 7-11 from the '069 patent, but these examples do not contain any comparison in performance to the prior art and hence are merely showing some effectiveness with regard to a PBS standard. Response, 35-37. At most, these examples illustrate variability in particle performance with different lipid species. EX1001, Fig. 4. I note that these formulations were also done at a suboptimal N/P ratio.

130. Patent Owner and Dr. Thompson also cite to later testing as alleged evidence of unexpected results. Response, 37-42; EX2031, ¶¶99-112. These data fail to demonstrate unexpected results for at least three reasons: (1) the data is not commensurate with the scope of the claims; (2) the data only shows efficacy of certain formulations, not unexpected results when compared

to the closest prior art; (3) data in the cited references shows variability by lipid species used and (4) and, many of these experiments were conducted at a suboptimal N/P ratio.

131. Patent Owner provides a chart of formulations falling within the claims tested after the filing of the '069 patent. EX2008. As can be seen from the chart, for most of the formulations tested, there is only a single data point for a given combination of lipid species. Moreover, the numeric ranges tested include no data points over 60% mol% cationic lipid. *Id.* Given these limitations, a POSITA would not consider this data to illustrate efficacy over the numeric range, let alone unexpected results when compared to the 2:40 formulation. A POSITA would also understand that the later-tested formulations fail to demonstrate efficacy of the broad range of nucleic acid and lipid species covered by the claims. Noticeably lacking are any references to non-ionizable cationic lipids, fusogenic phospholipids (*e.g.,* DOPE), or DNA payloads. EX2008.

132. I understand that results must be unexpected when compared to the closest prior art. Patent Owner and Dr. Thompson ignore this standard and instead argue that any efficacy is unexpected. *See, e.g.,* Response, 38 ("Each of these formulations demonstrated potent gene silencing activity *in vivo*."). But, without actual comparisons to the 2:40 formulation from the prior art, there is

no way to judge whether these formulations performed better or worse than the prior art.

133. Patent Owner also fails to inform the Board that this testing showed that several formulations falling within the scope of the claims did not perform any better than the PBS standard. EX2010, Fig. 2 (DLinMorph shows no efficacy); EX2011, Fig. 3 (DPetroDMA shows no efficacy); (EX2006, 393:21-394:24 (1:57 formulation with DLinMorph shows no efficacy); EX2011, Fig. 3 (DPetroDMA shows no efficacy); EX2006, 401:6-21 (other cationic lipids using 1:57 formulation "have similar knockdown levels as--as PBS.").

134. Finally, Patent Owner and Dr. Thompson point post-filing data showing that particles with higher levels of conjugated lipid (3.5-5% range) performed worse. Response, 36-37 (citing EX2014, Fig. 12). As discussed above, minimizing the conjugated lipid to increase particle performance was well-known in the art at the time of the '069 patent. These results are in no way surprising.

C. Other Secondary Considerations Lack The Required Nexus Or Are Attributable To The Prior Art

135. Patent Owner argues that there was an unresolved long felt need for lipid-carrier particles, but cites to articles from the 2003 timeframe.

Response, 45-46 (citing EX2016, EX2018). This ignores the disclosures in the cited prior art (EXS1003-1005) dating from 2003-2005 and other work in the industry up until 2008. Indeed, Patent Owner cites to an article from 2012 detailing investments in lipid nanoparticles in the early 2000s that discusses "a seminal paper on systemic small interfering RNA (siRNA) delivery." EX2019, 1, n. 5. This paper, authored by the named inventors on the '069 patent, details experiments done with the prior art 2:40 formulation and was published in 2006. EX1027, 3.

136. Patent Owner also erroneously points to a "$2.5-3.5 billion in investment," but that investment related to the therapeutic siRNA, not just lipid-carrier particles. Response, 45 (citing EX2020, 10). Patent Owner also cites to an article from 2010, but the article discusses Patent Owner's "SNALP" solution and notes ongoing challenges and alternatives. EX2020, 5. In addition, neither article differentiates Patent Owner's prior SNALP disclosures, *e.g.,* EXS1003-1004, from the '069 patent.

137. Patent Owner erroneously points to its "500 person-years and $200M" investments in "SNALP technology." Response, 46. But a significant portion of the investment could be attributable to the work leading to the Patent Owner's prior art SNALP disclosures (*e.g.*, EX1003-1004, EX1011). As another example, Patent Owner points to Roche switching to "[Patent Owner's]

SNALP liposome." EX2019, 10. But there is no indication that Roche used the SNALPs of the '069 patent as opposed to prior art SNALP systems.

138. Regarding failure of others and skepticism, Patent Owner repeats its mistaken argument that toxicity favored teaching away. Response, 47. Patent Owner ignores that prior art cationic lipids were developed that were substantially non-toxic, *e.g.*, DLinDMA, and that these ionizable cationic lipid were used *in vivo*. EX1004, [0351]-[0391]. In the "seminal paper" discussed above dating from 2006, Patent Owner disclosed that its prior art 2:40 SNALP system resolved toxicity concerns: "There was no evidence for complement activation, delayed coagulation, pro-inflammatory cytokine production (Supplementary Table 1) or changes in haematology parameters (data not shown), toxicities that have been observed previously with treatments using related approaches." EX1027, 3.

139. For commercial success, Patent Owner points to the commercial product Onpattro. Response, 49-50. First, Onpattro does not use the 1:57 formulation detailed in the '069 patent. Second, Dr. Thompson asserts that Onpattro is has the following mass ratios (mg) 2.0 (siRNA), 12.7 (cationic lipid), 5.9 (cholesterol), 3.1 (phospholipid), 1.5 (conjugated lipid). EX2031, ¶136. This is not accurate. The label for Onpattro from the FDA (EX1023, Section 11), indicates the following mass ratios (mg) 2.0 (siRNA), 13.0

(cationic lipid – Dlin-MC3-DMA), 6.2 (cholesterol), 3.3 (phospholipid - DSPC), 1.6 (conjugated lipid – PEG-C-DMG). This equates to the following molar ratios 49.3 mol% cationic lipid, 39.0% cholesterol, 10.2% phospholipid, and 1.6% (conjugated lipid). Thus, the lipid components in Onpattro do not fall within the claimed ranges.

140. Moreover, the developers of Onpattro identify the development of the second-generation cationic lipid DLin-MC3-DMA as the breakthrough leading to Onpattro's clinical development: "A first breakthrough was reached with the development of the ionizable lipid DLinKC2DMA." EX1026, 1085. In addition, much of the alleged evidence of secondary considerations relates to the siRNA payload, not the delivery vehicle. EX2023-2024 (first in class siRNA therapeutic), EX2038 (same).

141. Patent Owner asserts that there is a nexus between the commercial success of Onpattro and the '069 patent citing a 2016 article. Response, 50 (citing EX2023). The article just mentions using SNALPs, which would include the prior art 2:40 formulation. EX2023, 50. The article also mentions technologies like chemical modification of the siRNA payload. *Id.* But each of the cited prior art references disclose particles with lipid ranges including these concentrations.

142. Given the lack of sufficient nexus to the claimed ranges and scope of the prior art, I conclude that a POSITA would consider Patent Owner's evidence of non-obviousness to be insufficient to overcome the strong obviousness showing.

VIII. CONCLUSION

143. In sum, it is my opinion that Petitioner has demonstrated that the challenged claims of the '069 patent are rendered obvious by the cited prior art by a preponderance of the evidence.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code.

Executed on March 2, 2020 in Denver, Colorado.

Dr. Thomas J. Anchordoquy

JOINT APPENDIX 86

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Appeal no. T0505/20-3.3.08
EP 2 279 254 / 09 731 866.1
Patentee: Arbutus Biopharma Corporation
On behalf of Opponent-Appellant 2
Our Ref.: 200 312 m10/ohu

We provide further observations on behalf of Opponent-Appellant 2 (OA2), in response to the arguments and five claim requests filed on 18 September 2020 by the Patentee (P) in reply to the appeals.

Contents

1 Summary

OA2 maintains that the Opponents' Appeals should be allowed, and the Opposed Patent revoked. In particular, OA2 will argue that:

1. The amendments in AR1, AR1a, AR2 and AR3 **are late-filed** without justification **and should not be admitted**.

2. We agree with Opponent Appellant 1 (OA1) that the OD **failed to base its decision on the wording of the claims** and that this **materially affected the OD's decision** resulting in the erroneous findings that the Opposed Patent satisfied both Art 54 EPC and Art 56 EPC.

3. The non-specific **"*for use*" amendment** introduced by P **contravenes Rule 80 EPC** because the language employed is non-limiting in the technical context of a claim to a "nucleic acid-lipid particle". The case law cited by P under Rule 80 EPC applies expressly only to limiting features.

4. The subject matter of claim 1 of the MR and at least AR1, AR1a and AR2 are based upon **multiple selections** of individual, non-linked features in the application as filed, such that the combination of features in amended claim 1 cannot be derived directly and unambiguously from the original disclosure for the Opposed Patent. The ARs contain further added matter, and AR2 and AR3 moreover contravene Article 123(3) EPC due to the deletion of a limitation.

5. **The claims** of the MR and at least AR1, AR1a and AR2 **lack novelty over D1** due to the significant overlap of the claimed ranges with endpoints and ranges disclosed in paragraph [0354] of D1.

6. Alternatively, the **subject matter of the claims cannot be inventive**:

7. In the experimental Examples, the **Opposed Patent does not support any unexpected technical effect** achieved over the whole nucleic acid genus, lipid genera and molar percentage ranges claimed. In particular, the Opposed Patent neither discloses nor experimentally supports any technical effect associated with the claimed ranges for the proportions of phospholipid and cholesterol.

8. **P cannot rely on specific effects** such as "serum stability" at any stage of the problem-solution approach to exclude prior art formulations from the analysis under Article 56 EPC or to overcome them, **because P does not limit claim 1** by such an

effect. **Further, even if** any specific effect were implied into the claims, it must also be assumed to be **present in the prior art particles**.

9. In that context, it is emphasized that the Opposed Patent makes **no conceptual contribution to the art that warrants genus claims broadly covering nucleic acid-lipid particles**. Nucleic acid-lipid particles with the four lipid components were already common general knowledge at the priority date, and a large number of exemplary particles were already disclosed in the art.

10. **No feasible starting point in D1 may be ignored**, including the "50:20:28:2 SNALPs".

11. **Claim 1 merely recites arbitrary alternatives**. The skilled person solving the problem of providing merely any alternative, without a requirement to achieve any specific effect beyond what was already commonplace in the art at least to the non-specific standard according to the claim wording, would have arrived at these alternatives by **routine experimentation**, working entirely within the teaching of D1. The motivation of the skilled person to pursue routine experiments is emphasized, because the Opposed Patent lacks any technical contribution that is commensurate with the scope of the claims and because the objective technical problem is the non-ambitious provision of any alternative.

12. In particular, formulations with **phospholipid in the claimed range** – the only difference, e.g., to L109 of D1 – were also **known and obvious** to the skilled person. Starting from any formulation that differs in this feature, such a phospholipid content cannot support an inventive step in view of the teachings in D1.

13. These deficiencies apply to all claim requests. No claim request defines a technical contribution involving an inventive step over the state of the art.

14. No claim request meets the requirements of the EPC.

15. We also maintain all submissions filed previously. We expressly agree with, support and fully adopt all submissions made by OA1.

2 Admissibility

2.1 New AR1, AR1a, AR2 and AR3 inadmissible in view of first-instance proceedings

16. We request that new auxiliary requests AR1, AR1a, AR2 and AR3 be held inadmissible.

17. AR1, AR1a, AR2 and AR3 are not the same as Auxiliary Requests 2, 2a, 3 and 4 (the **OD Auxiliary Requests**) filed on 9 August 2019; they contain additional amendments and are to be considered a new set of requests. These new requests are late filed and moreover P could and should have filed the requests during the oral proceedings at first instance.

2.1.1 Late removal of "*for use*" wording from dependent claims (Article 84 EPC)

18. Regarding the "*for use*" language in dependent claims, P had two opportunities to bring the OD Auxiliary Requests into compliance with Article 84 EPC, once the OD had made clear that this was an issue under Article 84 EPC:

- firstly, after the break between 11:03 and 11:12 when making the same amendments to the claim set then designated AR1 (i.e. the current MR) for all claims except claim 11; and

- when the OD specifically gave P a second opportunity to make this amendment to all claims (i.e., including claim 11 in AR1 (current MR)), having re-confirmed that this was required, immediately before the break between 11:35 and 11:40. See the Minutes of the oral proceedings, p.2 (upper part).

19. P took neither opportunity to make the required amendments, despite the fact that P clearly knew that the presence of the "for use" wording in the claims was a problem in relation to all relevant claims under Article 84 EPC, and given the amendments made to AR1 (current MR), recognized what amendment was required to resolve this issue. P had ample opportunity to act accordingly.

20. Nevertheless, P opted to submit amendments to overcome the issue only in then AR1 (current MR), and not to its other ARs. P thus positively elected to define the format of the claims of its fall-back ARs so that those claims included the "for use" feature in the dependent claims, despite the clear objections of the OD to that format.

21. In the circumstances, P should not be allowed to reverse that election by filing new claims now. AR1, AR1a, AR2 and AR3 and the additional amendments they contain are thus late-filed without justification and should thus not be admitted into the appeal proceedings.

2.1.2 New AR1: wording further polished without justification or mention

22. Moreover, contrary to P's allegations, claim 1 of AR1 does not correspond to claim 1 of OD AR2 as filed on 9 August 2019, in that the word "*comprises*" has been added with regard to the cholesterol component range compared to OD AR2 of 9 August 2019. That term "*comprises*" had specifically been removed from the claim in OD AR2 of 9 August 2019 compared to claim 1 as granted and replaced by the newly introduced term "*of*", which was not present in granted claim 1. The term "*of*" remains present in current new AR1 as filed on appeal.

23. This addition of "*comprises*" to the amended claim language of OD AR2 in present new AR1 has not been explained or even mentioned in P's reply. It appears to have been made for reasons of clarity (Article 84 EPC), but this cannot justify the late filing of the amendment. Firstly, as in the case of the inappropriate addition of "*for use*" language in dependent claims of P's claim requests, a clear request could and should have been filed before the OD. Secondly, the claim language is not even improved by the addition of the word "*comprises*" as in present new AR1, because it is introduced in a manner that results in the phrase "*…derivative thereof of comprises from…*". This phrase requires interpretation and *prima facie* introduces new clarity issues (Article 84 EPC), at least because the significance and relationship of the terms "*of*" and "*comprises*" side by side in the new context need to be determined. Appeal proceedings are not a further opportunity for P to attempt to further "polish" the wordings of their previous ARs under Article 84 EPC, and much less so when the result of such "polishing" is itself dubious under Article 84 EPC. Moreover, the amendment to introduce the word "*of*" compared to the claims as granted does not appear to comply with Rule 80 EPC.

2.1.3 New AR1: established added matter present in claim 10

24. New AR1 is, in any case, also necessarily unallowable, because AR1 contains dependent claim 10 as granted and thus cannot possibly be conducive to the appeal proceedings.

25. The OD decided that dependent claim 10 as granted contains added matter (section 2.1.3.1 of the decision), a sub-aspect of the decision with which we agree, for at least the reasons given in section 2.1.3.1 of the decision. **P withdrew their appeal** against the OD's decision that the MR before the OD contained added matter, inter alia due to claim 10. Thus, that sub-aspect of the OD's decision cannot be reversed in the present appeal proceedings. Any claim request such as new AR1, which re-introduces dependent claim 10 as granted into the proceedings is bound to fail for that reason alone.

26. Thus, new AR1 should also not be admitted because it foreseeably cannot be conducive to the appeal proceedings for this additional reason.

2.1.4 AR2 and AR3: evident contravention of Article 123(3) EPC

27. We also immediately point out that AR2 and AR3 evidently contravene Article 123(3) EPC, because the limitation "*non-cationic*" has been deleted from claim 1 of these requests compared to claim 1, part (c). AR2 and AR3 thus also evidently cannot be conducive to P's response in the appeal proceedings.

28. We discuss this deficiency under Article 123(3) EPC in more detail in section 8 below.

2.2 The Patentee's further requests

29. P also requests:

- that D35 is admitted into the proceedings (§ 6, Section C); and
- that D38 is not admitted into the proceedings (§ 7, Section F).

D35

30. D35 is an experimental report filed by P. We do not accept P's arguments as to the relevance of D35 to the issues in the appeal. However, in any case, it is not open to P to challenge the OD's decision on admissibility. P withdrew their Notice of Appeal on 28 April 2020 and has thus acknowledged the decision of the Opposition Division. P's request for admission of D35 is therefore without basis and should be refused.

31. We also note that P alleges, in essence, that, if only it had been asked, it would have "*supplied information about how the results presented in D35 were obtained*". Even

in their submission alleging this, however, P still does not provide that information, which is extremely odd given the issues at hand.

32. The OD was, in any case, correct to hold D35 inadmissible, as it must be self-evident to P that any experimental data filed in good faith in proceedings before the EPO must comply with normal scientific and legal standards of repeatability.

D36

33. We have set out in our statement of grounds of appeal why the OD's finding that D35 was inadmissible did not automatically imply that D36 should also be held inadmissible. We have, further, justified why the OD's decision on D36 should be overturned and D36 should be held admissible on appeal.

34. P has vaguely criticised variation in the experimental data of D36, but such normal experimental variation does not *prima facie* cast any doubt on the credibility of the overall implications of the data in D36. In particular, P has not presented any complete and reproducible data of their own that would be capable of casting doubt on D36. Data that is subject to normal experimental variation is still significantly more meaningful and thus carries significantly more weight than P's approach of filing a document such as D35 that purports to show data supporting a particular conclusion, but withholds key information such that it cannot be evaluated or repeated.

D38

35. D38 as filed by OA1 in response to the decision of the OD should in any case be admitted, because it has been filed to address details of discussions that arose mainly during and shortly before the oral proceedings, and to demonstrate why the decision of the OD is incorrect.

36. Once again, P has vaguely criticised variation in the experimental data of D38. But such normal experimental variation does not *prima facie* cast any doubt on the credibility of the overall conclusions from the data in D38. In particular, P has not presented any completely described and repeatable experiments of their own that are even capable of casting doubt on D38. D38's data are still significantly more meaningful and therefore should carry more weight than the incomplete and unrepeatable data in P's D35 that withholds key information.

2.3 Documents D39 and D40

37. D39 (PCT/US93/07149, EP appln no. 93 918 499.0) is the patent application underlying T 1241/03, and is filed in direct response to P's citation of T 1241/03 in their reply to the appeal. D39 shows that P's citation of T 1241/03 under the heading of added subject matter was inappropriate, because the circumstances in T 1241/03 were not comparable, and that, in fact, T 1241/03 does not support P's position.

38. D40 is reference [15] (Zimmermann et al.) in the handbook chapter D20, and is enclosed herewith as evidence of the skilled person's common general knowledge for the information of the Board in response to P's arguments in paragraphs 109-118 and particularly 114-117 of the reply. D40 underlines the fact that siRNA-lipid particles with a phospholipid content of, e.g., 10 % for use *in vivo* were part of the skilled person's common general knowledge before the priority date. That formulation is mentioned in Handbook chapter D20 precisely because it was one of the many formulations that were already commonly known and available to the skilled person at the time of D20 and the relevant date of the Opposed Patent.

39. We note that the fact that siRNA particles including "formulation 67" of Zimmermann et al. were commonly known was already in the proceedings due to the citation of that formulation in handbook chapter D20. D40 merely confirms the molar ratios of the lipids, which were not amongst the representative details of the commonly known formulations that were reproduced as such in D20.

40. D40 thus merely provides a better understanding of the state of the art, is obviously relevant, its submission is reasonable, and its consideration will not delay the proceedings in any way. For such reasons, even a completely new piece of evidence (which D40 is not, for the reasons just given) filed during an appeal was taken into account in T 274/99. See also T 106/97 (Reason 3.5), and T 1076/00 (Reason 1), in which documents filed during the appeal were taken into account on the grounds that they were relevant evidence of common general knowledge (each cited in the Case Law book, 9th ed., 2019, section V-A, 4.13.1 (c)).

3 Substantial procedural violation (OD's reliance on "*systemically*")

41. We agree with the analysis by OA1 that the OD's failure to base its decision on the wording of the claims materially affected the OD's decision, and contributed to the OD arriving at an incorrect decision under Article 100(a) EPC.

42. This failure to base the decision on the wording of the claims and the material consequences of this error are evident from

(i) the misquoting of the final feature of Claim 1, AR1 (now MR) to include the non-existent feature "*comprising systemically administrating*" in both sections 4.2 (p.10) and 4.5.1 (p.12) of the decision under appeal, instead of the actual claim wording "*comprising administering*":

> for use in a method for the in vivo delivery of a nucleic acid, the method comprising systemically administering said nucleic acid-lipid particle to a mammalian subject.

(the text reproduced here is, e.g., from section 4.2, p.10);

(ii) the arbitrary inclusion of this feature in the formulation of the objective technical problem (last paragraph of section 4.10.4, p.17);

(iii) the discussion in section 4.10.5 of the decision under appeal (pp.17-18), in which the OD appears to have relied on this feature in an arbitrary theory of non-obviousness, under which according to the OD claim 1 overcame the prior art.

43. P relies on section 4.10.4 of the decision to allege that nothing turns on this clear error of the OD. That is incorrect.

44. In section 4.10.4 (pages 16 and 17), the OD stated that, although "*effective systemic delivery … is not an explicit feature of claim 1*", it was an implicit feature of the particles of Claim 1. However, the OD equally considered this to be an implicit feature of certain particles from D1. Further, in the beginning of this section (page 16), the OD was merely rebutting P's incorrect arguments that the claimed subject matter was allegedly characterized by a particularly "*efficient*" level of systemic delivery. Accordingly, the OD recognized – in this aspect correctly – that a particular, "*efficient*" level of systemic delivery is neither a requirement of the claim nor, in any case, would it be a distinction from the prior art.

45. Despite stating that the "*for use*" language does not imply *inter alia* systemic delivery (10.4.2) and is not a distinguishing feature (see also the discussion of section 4.10.5 below under Rule 80 EPC), it is evident that the OD in fact mistakenly gave this feature a technical meaning in its assessment of Article 56 EPC, which materially affected its decision.

46. Initially, it was inappropriate, and indeed misleading for the remainder of the problem-solution approach, for the OD to include the feature "*systemic*" in the formulation of the objective technical problem (last paragraph of section 4.10.4, p.17), considering that the scope of claim 1 is not limited to particles that are suitable particularly for "*systemic*" administration. The feature "*systemic*" is neither an explicit nor an implied limitation of claim 1.

47. Subsequently, the OD particularly fell into error when comparing the Patent to D1. The OD (in section 4.10.5 on page 17) developed a theory according to which it would not be obvious from D1 "*which compositions … would be suitable for systemic delivery*".[1] The OD reasoned that it is "*unlikely*" that all particles in D1 "*will be suitable for systemic delivery*". That theory is entirely baseless and moreover fundamentally relies on purely imagined and unjustifiable implications of the non-existent feature "*systemic*".

48. The OD read the feature "*systemic*" into claim 1 arbitrarily, and then proceeded to give it undue material weight and meaning, in a way that the OD considered to support a finding of non-obviousness in the final stages of the problem-solution approach. That finding was incorrect in any case (see section 7 on Article 56 EPC below). But it is also apparent from the wordings and general direction taken toward the end of the decision that the OD's error of reading "*systemic*" into claim 1 must have made a central, material contribution to the incorrect final outcome under Article 56 EPC.

49. A further aspect under which the OD's error of reading "*systemically*" into the amended claim language in claim 1 appears to have materially affected the decision is with respect to Rule 80 EPC. The reason given by the OD rejecting OA2's objection under Rule 80 EPC was that

> *"the opposition division understands that the feature of claim 13 has been introduced into claim 1 in relation to inventive step.*
>
> *Auxiliary request 1 therefore meets the requirements of Rule 80 EPC."*
>
> (Section 4.3, on p.10 of the decision.)

[1] This is further expanded when the OD imagines the further implications of this alleged lack of teaching for alternative range values (discussed on page 18), in the final stage of the problem-solution approach

50. As discussed above, the way in which the OD "understood" the amendment to "relate to inventive step", in line with this statement, becomes clear from the fact that, when the question of inventive step arose, the OD incorrectly read "*systemically*" into amended claim 1, causing further errors in the decision under Art. 56 EPC.

51. As we explain in more detail in the next section below, however, on a correct interpretation of the phrase "*for use in a method for the in vivo delivery …*", i.e., without reading in the term "*systemic*", this "*for use*" language is entirely non-limiting in the technical context of the claimed subject matter. By that interpretation, it was thus clear from the outset that it could not even potentially play a part in the assessment of the grounds of opposition.

52. Thus, had the OD not read the term "*systemic*" into the "*for use*" language of claim 1, all claim requests containing the amendment to introduce the "*for use*" language into claim 1 should have been rejected under Rule 80 EPC. Accordingly, the OD's failure to base the decision on the wording of the claims also materially affected the decision under that heading.

4 The Main Request contravenes Rule 80 EPC

53. As already outlined above and in our grounds of appeal, the OD should have rejected the MR and other claims containing the "*for use*" amendment under Rule 80 EPC.

54. P argues that the addition of the phrase "*for use in a method for the in vivo delivery of a nucleic acid, the method comprising administering said nucleic acid lipid particle to a mammalian subject*" to the end of claim 1 "*was a serious attempt to overcome a ground of opposition*". On a correct interpretation of the claim language resulting from the amendment, it is immediately apparent that this is not the case. The "*for use*" phrase is evidently non-limiting in the context of claim 1.

4.1 National law is irrelevant

55. P further makes an incoherent and unsubstantiated argument that the wording of AR1 might be differently interpreted under the national law of the Contracting States (see § 40 of P's reply). Since the present proceedings are proceedings under the EPC, such national interpretation has no relevance to Rule 80 EPC, and P's arguments

in this regard can be disregarded. What is relevant is whether the amendment was occasioned by a ground for opposition under Art. 100 EPC.

4.2 The case law of the Boards of Appeal underlines the deficiency under Rule 80

56. In principle an amendment may pass the threshold of Rule 80 EPC without necessarily ultimately overcoming the ground of opposition. As stated by the Board in T 750/11, though, the amendment must still be at least a "*serious attempt*" to overcome a ground. Further, the amendment must "*further limit the subject matter*" of the claims ("*eine Änderung, die den Gegenstand eines unabhängigen Anspruches weiter einschränkt*", T 750/11, point 2.3.2 of the reasons). The latter requirement is also included in the case summary in the Case Law book cited by P. Neither threshold is met by the present amendment.

4.3 No serious attempt

57. The amendment introducing the present "*for use*" language is evidently not a serious attempt to overcome a ground of opposition, because it is immediately evident that the added feature contributes no technically meaningful information to the claim that further limits its subject matter beyond the particle according to the claim as granted. In particular, despite its "*for use*" format, it adds no new, technically meaningful suitability, purpose or effect that the particle did not already have according to claim 1 as granted. The scope of claim 1 remains the same.

58. As we explain further below, the non-specific wording of the "*for use*" amendment in claim 1 does not single out any distinct subset of nucleic acid-lipid particles from the group of nucleic acid-lipid particles that is simply defined as having lipid components within the claimed ranges of proportions. In substance, both before and after the amendment introducing the "*for use*" feature, claim 1 requires nothing more than a nucleic acid-lipid particle, as defined by the structural claim features.

4.4 No limiting feature

59. In the context of the technical subject matter of claim 1, the purposes of "*in vivo delivery of a nucleic acid*" and "*administering said nucleic acid lipid particle*" are entirely non-specific. These additions to claim 1 as granted do not require a specific suitability for achieving any particular technical effect that pertains only to a subset of particles and thus limits the claim further. Thus, the amendment is not the kind of "limiting feature" that the Board referred to in T 750/11, point 2.3.2 of the reasons.

60. Certainly, any lipid-nucleic acid particle as defined by the broad structural features in the claim as granted can be "*administered*" and thus at least "*delivered*" into a living body (i.e., "*in vivo*"). Whether it is technically meaningful or desirable to do so for any purpose is an entirely separate question. To illustrate the issue further, these non-specific purposes also do not imply that any other particular property limits the claimed particles, e.g., non-toxicity.

61. For example, the claim including this wording still encompasses all of the lipid-nucleic acid particles that have the structural features of the claim as granted, regardless of whether, after the administration / delivery *in vivo*, according to the amendment, they would demonstrate:

- a therapeutic effect,
- no technical effect at all,
- harmful or otherwise purely disadvantageous effects (e.g., such that no inventive step is conceivable for that reason alone), or
- a lethal effect, e.g. as a toxin / poison.

Any such particle is, in any case, "suitable for" at least the entirely non-specific "use" that has been added to claim 1.

62. Therefore, we also emphasise that the "*for use*" language of amended claim 1 cannot even theoretically assume the role of a functional "catch-all" feature, e.g., of the kind that is typically used to limit a claim that defines a variety of structures only to embodiments that are suitable for achieving a particular technical effect and to exclude "non-working" or otherwise "non-patentable" embodiments (with a view to any of Articles 83, 54, 56, 52 and 53 EPC). It is immediately evident that the present "*for use*" amendment contributes no technical information going beyond the structural features that were already present in the claim as granted.

63. For these reasons, in response to § 39 of P's reply, we strongly contest P's argument that the "*for use*" amendment could affect which formulations of D1 or D25 may be considered to be the closest prior art. As discussed above, any nucleic acid-lipid particle can be administered/delivered *in vivo* within the meaning of the non-specific "*for use*" language chosen by P. Certainly that applies to each and every formulation that is disclosed in D1 and D25. The mere introduction of such non-specific and non-limiting "for use" language cannot influence the choice of starting point for the problem-solution approach under Article 56 EPC.

64. As is also reflected in the reasoning of the Board of Appeal in T 750/11 (point 2.3.2 of the reasons), an amendment that, as in the present case, does not further limit a claim in any technically meaningful way cannot, by its very nature, overcome any ground of opposition, because the subject matter of a claim, its patentability and its enablement are all assessed based only on the technical limitations to the claim.

65. Therefore, precisely in view of the principles mentioned in T 750/11 (point 2.3.2 of the reasons), P's suggestion that this non-limiting feature could pass under Rule 80 EPC but then be effectively ignored when considering substantive patentability issues (because it is not a limiting amendment) is plainly incorrect.

66. Thus, the MR contravenes Rule 80 EPC and is to be rejected.

4.5 All Auxiliary Requests also contravene Rule 80 EPC

67. Claim 1 in each of AR1, AR1a, AR2 and AR3 has also been amended to contain the same non-limiting *"for use"* language.

68. Each of AR1, AR1a, AR2 and AR3 must thus also fail under Rule 80 EPC.

5 Added subject matter (Art. 100(c) EPC)

5.1 Summary of added matter issues

69. As we have set out in §§ 20-34 of our statement of grounds of appeal, the subject matter of claim 1 is not directly and ambiguously derivable from the application as filed, A0, at least because it results from multiple independent selections.

70. Firstly, the definition of the range of amounts of cationic lipid in subsection (b) of claim 1 is a selection from various distinct options that are presented as equally preferable in A0 (cf., e.g., at least paragraphs [0113], [0114], [0118], original claims 8 or 9).

71. Secondly, the feature "*mixture of phospholipid and cholesterol or a derivative thereof*" in subsection (c) of claim 1 and, thirdly, the range of amounts applied to those lipids of subsection (c) are each the result of various further independent selections. This follows from the list of different alternatives relating to one or more of the features in subsection (c) that are presented in various ways, but all as being preferred, in paragraphs such as [0119], [0129], [0130], [0131], [0143], and [0144],

and in at least original claims 10-13, 15 and 16 of A0. In this context, we note that the alternatives according to original claims 27 and 33, also need to be taken into account. These latter original claims highlight only different feature combinations, not those now claimed by P according to the MR.

72. As we have also pointed out, besides the fundamental issue of the multiple selections, original claim 15 as such cannot provide basis for the amounts of "*phospholipid and cholesterol or a derivative thereof*" in feature 1(c), because original claim 15 only refers to "*the cholesterol*", and not to the alternative of the "*derivative thereof*". This corresponds to the way some other passages of A0, such as paragraphs [0253] and [0254], also refer only to "*cholesterol*".

73. No pointer toward the specific combination of features in claim 1 of the MR can be found in A0.

74. Further, if the "*for use*" language were afforded limiting weight as a technical feature of the claim despite the considerations discussed above under Rule 80 (and further below under Art. 56 EPC), then we agree with OA1 that this would further contribute to the generation of added matter by multiple independent selections. As pointed out by OA1, the "*for use*" language is found, e.g., in original claim 43, and it is expressly presented in A0 on the same level as an alternative "*for use*" definition, namely "*for introducing an nucleic acid into a cell*" (original claim 41). In this case, the inclusion of the "*for use*" language in the claim would represent a yet further (fourth) selection.

5.2 Specific responses to P's reply

5.2.1 Original claims 13 and 15 cannot provide basis for claim 1 per se

75. P relies selectively on claims 13 and 15 as basis, and has argued that the use of the definite article "*the*" in the phrase "*the cholesterol*" original claim 15 means that this phrase in claim 15 "*directly and unambiguously*" also refers to "*a derivative thereof*" in original claim 13 (§§ 47, 49 of the reply). That is clearly incorrect. By the disclosure standard that applies under the EPC, which takes account only of <u>direct and unambiguous</u> disclosure, this phrase precisely does <u>not</u> refer to the "*derivative*". It only refers to "*the cholesterol*".

76. P also alleges that "*the skilled person would see from paragraph [0119] of the* [A0] *that cholesterol and cholesterol derivatives are interchangeable*" and further that this

supports their reliance on claim 15 (§ 48 of the reply). But nothing in paragraph [0119] discloses directly and unambiguously that "*cholesterol*" and "*cholesterol derivative*" are necessarily and in all cases interchangeable in any sense that could be relevant under the normal standard of disclosure for assessing claim amendments.

77. The distinction between cholesterol and derivatives thereof as reflected in a comparison of original claims 13 and 15 is significant in the assessment under Article 100 (c) EPC under the normal standard of disclosure.

78. Firstly, "*cholesterol*" on the one hand and a "*cholesterol derivative*" on the other are directly and unambiguously distinct subject matter.

79. Secondly, merely for further illustration, A0 itself demonstrates that a choice between a cholesterol derivative and cholesterol can generally make a technical difference. For example, in Figure 2 and Table 4 (A0, p.94), the formulations "Group 2" and "Group 7" differ only in that Group 2 contains cholesterol and Group 7 contains a cholesterol derivative, namely cholestanol (in which one double bond is saturated compared to cholesterol). Otherwise, Groups 2 and 7 are identical, i.e., in terms of both lipid species (see A0, p.94, Table 4) and lipid proportions (i.e., "2|40|10|48"). Nevertheless, the performance of Group 2 in knocking down liver ApoB is appreciably inferior to Group 7. This apparently results from the selection of a different lipid species, namely the selection of a cholesterol derivative instead of cholesterol (see section 6.4, § 62 of our statement of opposition, Appendix A to our statement of grounds of appeal).

80. Moreover, it is evident and illustrated by practical examples in the technical documents on file that the subject matter "*cholesterol derivative*" can also fall within a different lipid class according to claim 1 and the disclosure of A0, thus fulfilling a different technical role as well as clearly being a "*cholesterol derivative*". This fact is illustrated by particles such as "L109" in D1, which contain both cholesterol and the cholesterol derivative 2KPEG-cholesterol in a combined molar proportion of 30%, wherein the cholesterol derivative 2KPEG-cholesterol also falls into the lipid class "*conjugated lipid*". We emphasise that there is no basis for an arbitrary exclusion of such a lipid from the scope of the term "*cholesterol derivative*". Thus, a "*cholesterol derivative*" and "*cholesterol*" can have technically very distinct roles.

81. All of the above underlines that, even if a cholesterol derivative and cholesterol may in some cases play similar functional roles, under the legal standard for assessing

added subject matter, it is not direct and unambiguous that the skilled person would read the disclosure of A0 as implying necessarily that "*cholesterol*" and "*cholesterol derivative*" are interchangeable in all respects. They remain technically distinct subject matter.

82. It is, thus, not direct and unambiguous that a reference to "*cholesterol*" can simply be read as a reference to a "*cholesterol derivative*", merely because, with hindsight, P considers this to be advantageous when amending the claims. The distinctions between these terms and the content of the application as filed cannot be ignored. In fact, by the established standard of disclosure, P has amended the claim without basis.

5.2.2 P relies on multiple independent selections from lists of alternatives and new combinations of features

83. P also relies particularly on the beginning of paragraph [0130] of A0. That subject matter, however, is presented in between paragraphs [0129] and [0131], which disclose equally preferred subject matter on the same level. Paragraph [0129] states that phospholipid-free particles are preferred, and paragraph [0131] states that particles with a higher content of phospholipid and a lower content of cholesterol or derivative thereof are preferred (cf. also the alternative to claim 15 in claim 16, albeit each without reference to the cholesterol derivative).

84. We also note that claim 1(c) imposes an upper limit of 49.5 mol % of non-cationic lipid in total as in original claim 1. But each of paragraphs [0129], [0130] and [0131] are not directly and unambiguously disclosed in that context. Rather, they are disclosed on A0, page 27, in the context of the preceding passage of A0 on page 26, which lists options according to which the upper limit of total non-cationic lipid is, e.g.:

- 60 mol % – paragraph [0122]
- 49.5 mol % – paragraph [0123]
- 45 mol % – paragraph [0124]
- 40 mol % – paragraph [0125]

85. Each of those upper limits is entirely compatible with each of paragraphs [0129], [0130] and [0131].

86. The upper limits for phospholipid (10%) and cholesterol or a derivative thereof (40%) according to claim 1 of the MR add up to more than the 49.5 mol % of paragraph [0123] and original claim 1. This merely implies that, in some embodiments, the presence of an amount at the upper end of the claimed range of one lipid may have the result that not the entire claimed range of another lipid is then covered by the claim, or may imply a certain, new upper limit, if certain other features are selected. This corresponds entirely to P's own argument according to which the lower limit of 13 % for non-cationic lipid according to original claim 1 becomes redundant due to the selection of particular other claim limitations (§ 51 of the reply). For example, according to the claim, at 10% phospholipid, the content of cholesterol derivative cannot be more than 39.5%.

87. Thus, if any of paragraphs [0129], [0130] and [0131] are combined with paragraph [0123] in this manner, as proposed by P, there is no reason not also to combine any of them with any of paragraphs, e.g., [0123], [0124] or [0125].

88. This further highlights that multiple independent selections have been made and combined in claim 1 vis-à-vis the content of the application as filed.

5.2.3 The combination in claim 1 is not disclosed in the original claims

89. With reference to §§ 50, 52, 54 and 55 of P's reply, original claims 13 and 15 of A0 do not change this assessment. Firstly, as mentioned above, the definition in claim 15 does not directly and unambiguously extend to the cholesterol derivative. Secondly, even if claim 15 did contain the wording of claim 1(a) of the MR, the issue is that, just as the description, the original claims of A0 equally highlight other alternatives as being preferred. For example, claim 16 refers to a higher content of phospholipid and a lower content of cholesterol, similarly to paragraph [0131]. Claim 27 refers to a particle that is phospholipid-free, similarly to paragraph [0129].

90. Moreover, contrary to § 55 of P's reply, it is incorrect for P to argue that "*there is a disclosure of the subject matter of claims 13 and 15*", when that subject matter is the result of a selection from equally highlighted alternatives, further combined with other selections, e.g., the range for amounts of cationic lipid.

91. In particular, also within the original claims that depend from original claim 1, we re-emphasise that there is initially a first selection to be made in order even to arrive at the "*mixture of a phospholipid and cholesterol or a derivative thereof*" according to claim 13.

92. Original claim 10 merely requires the presence of "*cholesterol or a derivative thereof*". For illustration, we note immediately that this is consistent with the phospholipid-free particles that also feature throughout the application and the examples. See also original claim 27; "*Group 3*" in Example 5, Table 6, Fig. 4; or "*Group 2*" and "*Group 15*" in Example 6, Table 7, Fig. 5 which are particularly highlighted as being potent in paragraph [0362] of A0. The content of conjugated lipid, cationic lipid and cholesterol of these phospholipid-free formulations – "1.5 | 61.5 | 36.9" (see Table 7) – is also entirely consistent with the corresponding mol % ranges for those lipid classes according to original claim 1.

93. Original claim 12, which depends only on claim 1 and not on claim 10, requires only the presence of phospholipid. That is consistent with the cholesterol-free particles that are also disclosed in the application; cf. Example 3, Table 4, Groups 13 and 14, Example 5, Table 6, Group 8. The contents of conjugated lipid, cationic lipid and cholesterol of exemplified formulations in A0 are entirely consistent with the corresponding mol % ranges for those lipid classes according to original claim 1 (cf. Table 6, Group 8: "1.8 | 70.2 | 28.1"; Table 4, Group 13: "2 | 70 | 28", Group 14: "1.6 | 54.7 | 43.8";

94. In any case, nothing in the original claims directly and unambiguously discloses the combination of any of the lists of alternatives in dependent original claims 10-16 with the specific range for the cationic lipid of 50-65% as in claim 1 of the MR, which is itself selected from alternatives in the description as discussed previously, e.g.:

- the range of 55 mol % to 65 mol % of paragraph [0114];
- the range of 52 mol % to 62 mol % of original claim 9;
- any of the values preceding 65% in paragraph [0118], either as lower or as upper limits of a range, or the values as such.

95. In that regard, P has not denied the existence of these alternatives. But P has argued that they involve not only an alternative upper limit, but also an alternative lower limit, and further that it is allegedly relevant to "*explain why there should be a change to the lower limit of 50 mol % which was in claim 1 of the OA*" (§ 67 of the reply). That argument does not address the point at issue, however. The issue is that the other alternatives are, in any case, present in A0, and that A0 does not provide any indication as to why any one of them, as opposed to another, should be

combined with the further selections made from the various options for defining phospholipid, cholesterol and/or derivative content, as discussed above.

96. If a range in original claim 1 is amended in any way, a choice from different alternatives in the application that are presented on an equivalent level must be made. The issue is the legal principle that in such circumstances the combination of multiple independent selections from alternatives generates added subject matter (Case Law book, 9th ed., 2019, p.459, II-E, 1.6: e.g., 1.6.1: '*the application as filed is not a "reservoir"*'). This principle applies regardless of whether the selections relate to the upper limit, the lower limit, or both.

97. We note the reliance that P places specifically on alternatives that are recited in original claims. However, compared to claim 1of the MR, original dependent claims 8 and 9 recite only different, alternative ranges for the cationic lipid, i.e.,

- Claim 8: "*about 56.5 mol % to about 66.5 mol %*" or
- Claim 9: "*about 52 mol % to about 62 mol %*".

98. We note immediately that, in the context of assessing multiple selections from lists of alternatives within the original claims, the alternative of 56.5-66.5 mol % according to claim 8 is on no account automatically excluded as a possible alternative by selections of further definitions according to which the total of non-cationic and conjugated lipids would amount to at least 34.5 mol % as in claim 1 of the MR. If combined with original claim 8 as opposed to claim 9, such a selection would merely imply a modification of the effective upper endpoint in the range of original claim 8 down to **65.5** mol %. The lower endpoint of 56.5 mol % would remain unchanged in principle. Once again, this corresponds simply to the principle underlying to P's own argument according to which the lower limit of 13 % for non-cationic lipid according to original claim 1 becomes redundant due to the selection of particular other claim limitations (§ 51 of the reply).

99. Thus, each of the ranges of original claims 8 and 9 is certainly available as a possible alternative for defining the amount of cationic lipid. Any such definition regarding the cationic lipid is selected and combined independently with any of the alternative options for defining components and amounts of a non-cationic lipid according to, e.g., original claims 10-16 or similar portions of the description.

100. Each of the alternative range definitions for the cationic lipid in the original claims – including that of claim 9 – is, in any case, different from the definition that is recited by P in claim 1 of the MR, which is not highlighted according to the original disclosure in A0 at all.

5.2.4 The combination in claim 1 is not derivable from the examples of A0

101. P, e.g., in § 54 of the reply, argues that the combinations of features found in claim 1 can be made taking into account the skilled person's reading of "*the description and its examples*". But that argument is incorrect.

102. The case law has in some cases, when appropriate, recognised "implicit pointers" toward particular feature combinations in view of clearly advantageous embodiments in the experimental examples. But further consideration of the example section in A0 under this aspect also cannot help P to demonstrate basis for claim 1, because, just as the original claims, the experimental examples in A0 do not provide any pointer toward the particular combination of selected features in claim 1 of the MR.

103. We have already discussed the disclosure in the examples of A0 in general in section 6 of our opposition (Appendix A to our statement of grounds of appeal). In view of P's reply to the appeal, we will discuss aspects of the experimental examples of A0 once again from the perspective of Art. 100(c) EPC.

5.2.4.1 The generalised statements in Example 1 provide no relevant pointer

104. If the skilled person can glean any generalizable information regarding generic range definitions from the examples of A0, then this relates only to the ranges of cationic lipid that are also disclosed, e.g., in original claims 8 and 9 and various more specific claims,[2] and not the combinations of particular ranges as claimed.

105. Example 1 of A0 is entitled "*Materials and Methods*" and in paragraphs [0338] and [0339] (pages 91-92) provides an overview of the formulations used in the remaining examples. In particular, Example 1 also provides disclosure that is generalised to a certain degree, because it summarises what, according to the application as filed, was considered to be the focus of the supposed invention, according to the experimental examples.

[2] In original claims 27 and 33 these ranges are combined with other features, but those features are also distinct from present claim 1 of the MR.

106. With regard to the identities and amounts of lipid components, paragraph [0339] underlines initially only that any focus of the supposed invention according to A0 resided only in certain amounts for the cationic lipid, namely in the specific values of "*57.1 mol %*" or "*61.5 mol %*" (as recited, e.g., in original claims 31, 38 and 39). A certain degree of generalisation relates only to specific ranges that are centered around those values and do not deviate from them by more than 5 mol %. Those are the ranges of original dependent claims 8 and 9, and they are also found in original claims 27 and 33.

107. Beyond that, the examples section only confirms that even either of these alternative ranges for the cationic lipid do not directly and unambiguously imply any particular further choices with regard to the non-cationic lipid component(s) and their amounts. This is clear from the somewhat generalised summary disclosure in Example 1.

108. See, e.g., paragraph [0339], p.91, lines 28-29, in Example 1:

> *"Typically, in the 1:57 formulation, the amount of cationic lipid will be 57 mol % ± 5 mol % [this would imply **52-62 mol %**, as in original claim 9] and the amount of lipid conjugate will be 1.5 mol % with the balance of the 1:57 formulation being made up of non-cationic lipid (e.g., phospholipid, cholesterol, or a mixture of the two)."*

109. In this statement, the various choices that remain to be made for the non-cationic lipid expressly remain completely open: first between the three options "*e.g., phospholipid, cholesterol, **or** a mixture of the two*", and then, secondly, between various further options for amounts or ranges of any non-cationic lipid that is selected.

110. Alternatively, see, e.g., paragraph [0339], p.91, line 31, to p.92, line 2, in Example 1:[3]

> *"Similarly, in the 1:62 formulation, the amount of cationic lipid will be 62 mol % ± 5 mol % [as the actual value of reference compositions is 61.5%, this leads to the range **56.5-66.5** mol % of claim 8], and the amount of lipid conjugate will be 1.5 mol % ± 0.5 mol %, with the balance of the 1:62 formulation being made up of the non-cationic lipid (e.g., cholesterol).*

[3]

111. Also in this alternative definition of the cationic component, the various choices that remain to be made for the non-cationic lipid remain completely open: firstly between various options for the non-cationic lipid ("*cholesterol*" alone is recited here, though expressly only as an example) and secondly between various further options for amounts or ranges for any non-cationic lipid that is selected.

112. This central disclosure in A0, in conjunction with the original claims, strongly underlines that claim 1 of the MR extends to added subject matter compared to the disclosure of A0. As mentioned, the summary of the experimental focus of A0 in Example 1 must be assumed to be representative of subject matter that was contemplated to characterise an invention according to the application as originally filed. But this central disclosure precisely does not point directly and unambiguously toward the combinations of components and ranges as in claim 1 of the MR. To the contrary, it underlines that claim 1 is based on multiple selections:

- Firstly, A0 requires choices to be made regarding range definitions for the content of cationic lipid, and

- Secondly, whichever choice is made for the cationic lipid, further choices remain to be made regarding the non-cationic lipid(s) (i.e., both the specific combinations of lipids to be used, and their relative components).

113. In view of the above, it is clear that the range P has selected for the cationic lipid is not even a one of the various alternative highlighted ranges according to A0. Further, the specific definition and ranges for the phospholipid and cholesterol or derivative thereof needs to be selected and remodelled from the various alternatives as disclosed, e.g., in original dependent claims 10-13 and 15-16, and other expressly disclosed range combinations such as in original claim 33, and phospholipid free embodiments such as original claim 27.

114. This disclosure reflects choices that need to be made from various alternative compositions and ranges, much as in the original claim set, with a view at least to original claims 8, 9, 10, 11, 12, 13, 15, 16, 27 and 33.

115. The phospholipid-free alternative of original claim 27 also contains the range for cationic lipid of original claim 8. Further, it significantly overlaps with the range of, e.g., claim 9. Further its weight in A0 is underlined by Example 1 and paragraph [0339]. Thus, to the skilled person considering the disclosure of A0 as a whole, and

starting from original claim 1 as does P in the reply to the appeals, phospholipid-free embodiments did present themselves as true, equally weighted alternatives to embodiments having a mixture of phospholipid and cholesterol or a derivative thereof. This is fully line with dependent original claim 10, which also selects only cholesterol or a derivative thereof as a claim limitation and does not require phospholipid to be present at all.

116. Original claim 33 also contains the range for cationic lipid of original claim 9 (and the above cited portion of A0 paragraph [0339]), 52-62 mol %, now in express combination with further definitions, regarding the non-cationic lipid components and their amounts. But those further definitions are different from those that have been selected individually for incorporation into claim 1 of the MR alongside other selections . Original claim 33 recites 36-47 mol %, for phospholipid and cholesterol only (again, not a derivative thereof), and moreover a different definition for the conjugated lipid (PEG-lipid only, and only 1-2 %).

5.2.4.2 The comparative data in the Examples provide no relevant pointer

117. Continuing beyond the summary of the experimental focus of A0 in Example 1, the data in the remaining experimental examples also do not provide any pointer towards the particular combination of ranges and definitions in claim 1 of the MR.

118. The experimental data as a whole once again point only toward definitions involving the ranges for cationic lipid according to claims 8, 9, 27 and 33 and Example 1, paragraph [0339] as mentioned above, or to formulations having the specific combination of values that are singled out in original claims 31, 38 and 39. Thus, the experimental data as a whole also do not change the fact that multiple independent selections are required to arrive at the combination of ranges in claim one of the MR.

119. Formulations according to original claims 27 and 33 and Example 1, paragraph [0339] are referred to in A0 as “1:57” and “1:62” formulations. We note, however, that, in terms of comparative performance, even “1:57” and “1:62” formulations are merely placed as alternatives on the same level in A0 in view of the experimental examples as a whole. Thus, a selection has to be made even between “1:57” and “1:62” formulations and their characteristics as alternatives that are disclosed on the same level – as can be seen, e.g., in original claims 8 and 9.

120. In more detail, A0, [0358] in combination with Table 6 and the experimental comparative data in Fig. 4 (cf. Groups 2 and 3) expressly show that performance is

equal with particles with 57.1 mol % and with 61.5 mol % cationic lipid ("1:57" and "1:62" formulations, respectively). Note that, particularly "1:62" formulations do not necessarily contain any phospholipid at all, as is highlighted, e.g., by original claim 27. As mentioned, Example 6 (Table 7 and Fig. 5) is dedicated entirely to phospholipid-free "1:62 SNALP" formulations. Thus, starting from original claim 1, not only the definition of the limits of the range for cationic lipid, but also the choice of whether to include phospholipid in the particle represented significant selections.

121. Further, if the skilled person attempted to determine from A0 whether either of the "1:57" and/or "1:62" formulations were, as a matter of fact, advantageous compared to the state of the art, the skilled person would find that they are not. For example, A0 clearly discloses that, in the comparative assays performed in the examples, their performance is merely equal to "2:40" formulations of the prior art. See the essentially equal performance of "2:40" formulation Group 12 in each of Fig. 1 / Table 2 and Fig. 2 / Table 4 compared to the "1.57" formulations Group 9 in Fig. 1 / Table 2 and Group 11 in Fig. 2 / Table 4, as has been discussed in detail in section 6 2 of our opposition (Appendix A of the statement of grounds of appeal).

122. In particular, as explained in section 6.3.2 of our opposition (Appendix A of the statement of grounds), the "2:30" formulation of Example 4, Table 5, and Fig. 3 was clearly not a relevant reference for comparison within the disclosure of A0, merely considering that, as mentioned, A0 itself shows that prior-art "2:40" formulations perform equally well to "1:57" formulations.

123. Thus, even the "1:57" or "1:62" formulations that A0 highlights by comparison to others are not truly advantageous and within the meaning of certain case law on "implicit pointers". To the extent that certain features of such specific "1:57" or "1:62" formulations are nevertheless highlighted in comparison to alternative definitions such as those used in claim 1, they in any event do not point toward the particular selection and combination of features and ranges in claim 1 of the MR. At most, they only point toward a combination of the specific proportions and lipids as used in the "1:57" formulation of Group 9 in Fig. 1 / Table 2 and Group 11 in Fig. 2 / Table 4, or the "1:62" formulation of Group 3 of Table 6 and Fig. 4 as such.

124. This subject matter may be reflected by definitions and express feature combinations as in original claims 27, 31, 33, 38 and 39. But the distinct definition that is found in claim 1 of MR is assembled from features that are presented separately, and in a disjunct manner in various lists of definitions and embodiments in A0. Their

selection and combination in claim 1 extends beyond the content of the application as filed.

5.2.4.3 The feature combinations in the examples all include siRNA

125. Finally, if P proposes to rely on the examples as in § 54 of the reply, then it should also be noted that, unlike claim 1 of the MR, all feature combinations "pointed to" by the examples would necessarily include siRNA.

126. The feature "*siRNA*" undergoes significant technical interactions with other components of the nucleic acid-lipid particles that are defined overall by the feature combinations used in the examples. Thus, no claimed subject matter may be considered to be "pointed to" by the examples without a limitation to "*siRNA*".

127. In particular, the well-known and centrally important electrostatic interactions between the negatively charged backbone of the formulated nucleic acid and the cationic lipid[4] demonstrate *prima facie* a strong technical relationship between the particular structure and physico-chemical properties of the nucleic acid on the one hand and those of the cationic lipid in the formulated particle on the other hand. Further, the physico-chemical properties of the cationic lipid in the nucleic acid-lipid particles evidently cannot be separated from its amounts.

128. The physico-chemical properties of "*siRNA*", as used in all the examples in A0, *prima facie* differ significantly from those of a wide range of other types of "*nucleic acid*" structures that are potentially encompassed by the term "*nucleic acid*" according to claim 1 part (a).

129. siRNA is a short, double-stranded structure of typically approximately 20-22 base pairs. The length of one siRNA molecule thus corresponds to two turns of a regular double helix. In such a double helix, the charged phosphate backbones of the two strands are highly ordered and aligned with each other, in the well-known, characteristic, antiparallel and helical manner. siRNAs are thus a quite special type of

[4] See, e.g.: **D21** (declaration by Janoff), § 62: "*Cationic lipids have been used in the construction of nucleic acid-lipid particles because **they interact with the negative charges on nucleic acid payloads** facilitating the formation of such particles…*"; **D20**, p.239: "*9.2.1 Cationic lipids … Cationic lipids play two roles in liposomal NA* [nucleic acid] *formulations. In the first case, they encourage **interaction between the lipid bilayer and the negatively charged NA**…*"; **D19**:, p.440, rhc, last paragraph: "*COMPONENTS … Cationic Lipids … A multivalent cation is the essential component to **condense negatively charged nucleic acid by charge-charge interaction** into a small particle. For most of the NP* [nanoparticles] *cationic lipids are the key element used to package the DNA.*"

molecule within the broad genus "*nucleic acid*". These small "rods" of RNA double helix are completely different in their structure and overall physico-chemical properties compared to other types of "*nucleic acid*". Relevant physico-chemical properties include, e.g., surface-charge distribution.

130. Other types of "*nucleic acid*" may encompass either RNA or DNA, which of course has a fundamentally different sugar backbone lacking the 2'OH (and has a different form of double helix when double-stranded). Other types of "*nucleic acid*" may evidently also be, e.g., much longer than siRNA, and they may be single-stranded, leading to larger, irregular tertiary structures and/or flexible, "unstructured" regions, as in mRNA. Such other types of "*nucleic acid*" will *prima facie* interact significantly differently with the other components of the claimed of nucleic acid-lipid particles, compared to the short, uniform, double-helical siRNA "rods" – e.g., in terms of the above-mentioned electrostatic interactions with the cationic lipid via backbone phosphates.

131. Accordingly, the technical properties of the claimed particles overall, including their properties as a function of cationic lipid content, would *prima facie* also be expected to differ materially, depending on whether "*siRNA*" or an entirely different "*nucleic acid*" structure interacts with the cationic lipid within such formulations.

132. Starting from the summary of the materials and methods on which the entire experimental section is based in Example 1 (paragraphs [0338] and [0339]) and, accordingly, likewise in all individual experimental examples, the formulations having feature combinations that were contemplated to represent an invention in A0 were studied and disclosed only in the context of siRNA.

133. Accordingly, this technical context is also reflected in those original claims that recite feature combinations that the skilled person would recognise as being based upon the focus of the experimental examples, i.e., original claims 27, 31, 33, 38 and 39.

134. All such original disclosures of feature combinations according to the core teaching of the application also require an siRNA. Such feature combinations were not presented in the context of nucleic acids in general, as in claim 1 of the MR.

5.2.5 The case law does not support P's arguments

135. P has referred to case T 1241/03, selectively referring only to point 7 of the reasons and superficially citing only the summary of the case in the Case Law book. But this

decision does not in fact support P's position, because the Board's decision in T 1241/03 was based on a completely different kind of disclosure in the application as filed. We enclose the application as filed underlying T 1241/03 as D39 (PCT/US93/07149, EP appln no. 93 918 499.0), for the present Board's ease of reference.

136. The claims at issue in T 1241/03 were based on features that followed directly and unambiguously from straightforward and unambiguous statements of preference in D39 (see particularly p.5, line 33, and p.6, lines 16-17, as discussed expressly by the board in point 6 of the reasons). The optionality and expressly contemplated absence of one ingredient (glycine) that was at issue with regard to one independent claim was specifically disclosed and highlighted (D39, p.5, lines 20-22). Moreover, D39 at p.6, line 36 to page 7, line 7 disclosed a single preferred embodiment and in Example 1 a further, very similar formulation that was tested. Both the preferred embodiment of page 6-7 and the tested embodiment of Example 1 were unambiguously consistent with and confirmed the combination of features according to claim 1. These pointers were unambiguous in the sense that, unlike the present case, both the preferred embodiment of page 6-7 and the tested embodiment of Example 1 supported the claimed features rather than providing support for alternative definitions that were disclosed in the application as filed but not selected in the independent claims at issue.

137. Thus, the claims at issue in T 1241/03 did not involve multiple independent selections from lists of alternatives as in the present case.

138. Instead of T 1241/03, it would be more pertinent in the present case to consider the principle emphasised by the Board of Appeal in T 389/13, reason 3.5:

> *"It is pointed out in G 2/10 (see point 4.5.3 of the reasons for the decision) that it cannot be considered a principle that where an application discloses a general teaching and specific embodiments, groups thereof or areas, all other potential embodiments or intermediate generalisations falling within the ambit of the general teaching (but not as such disclosed in the application as filed) would thereby, by implication, inevitably also be disclosed. Whether the subject-matter defined now in claim 1 of the main request, which represents a restriction of the subject-matter of claim 1 as filed or a generalisation of a more specific embodiment thereof disclosed in the application as filed is directly and unambiguously derivable from the application as filed can only be*

> *decided on a case by case basis having due regard to the technical circumstances of the present case."*

139. T 389/13 is also referenced in the Case Law book, 9th ed., 2019, p.459, in the section II-E, 1.6.1 which is entitled "*Combination of features pertaining to separate embodiments; 'the application as filed is not a "reservoir"'*.

140. T 389/13 related to a composition that had been defined rather broadly in original claim 1 of the application as filed. That original definition including some structural features, as well as two initial ranges of parametric values ("*molecular weight distribution , MWD^L of less than about 8*" and "*transition temperature … of less than -20°C*"). Other passages of the application indicated a preference for the structural features, as well as a definition of additional parameters which might be used to characterise the composition, and corresponding ranges of values. The original, broad definition in original claim 1 had been amended by introducing certain limitations based on such statements of preference or the additional parameters and corresponding ranges of values (including "*from 35 to 65 weight percent of … a component*"; "*having a density of from 0.905 to 0.955 g/cm³*"; "*molecular weight distribution … of 30 or less…*"). See also Case Law book, 9th ed., 2019, p.459, in the section II-E, 1.6.1.

141. The Board noted that the Patentee had not indicated any explicit passage of the application as filed defining in a single place the claimed combination of features (reason 3.2). The Board explained that:

> *"The Board has no doubt that each of the amended features listed above is as such, i.e. when read in isolation, disclosed in the application as filed to constitute a possible limitation of the subject-matter of claim 1 as filed. This, however, does not allow it to be concluded that the skilled person would implicitly derive the combination of those limitations directly and unambiguously, using common general knowledge, from the application as filed. In this context "implicitly" means that the skilled person would have found this disclosure as necessarily implied by the content of the application as originally filed as a whole."*
>
> (Reason 3.2)

142. The Board further explained that

"The opinion of the appellant [Patentee] that it would be usual practice to consider allowable under Article 123(2) EPC the amendment consisting of the incorporation of several dependent claims into the independent claim they refer to cannot be adhered to by the Board without any reservation. Even if it may be said that a practitioner in the patent field might need to consider combining several dependent claims referring directly or indirectly to an independent claim in order to provide a suitable limitation of the independent claim they refer to, as each of those dependent claims is a priori meant to provide a possible fall-back position (e.g. in case the independent claim they refer to needs to be limited in view of the prior art), the question whether the subject-matter resulting from those various restriction of said independent claim fulfills the requirements of Article 123(2) EPC can nevertheless not be decided schematically, based legally speaking on the mere purpose of those dependent claims. This also is independent of the question whether the dependent claims possess single or multiple dependencies."

(Reason 3.3)

143. The Board held that the amendments at issue lacked basis in the original disclosure by the applicable legal standard, reasoning as follows in point 3.5 of the Reasons, before pointing out the above-cited aspect of the Enlarged Board's reasoning in G 2/10 (see point 4.5.3 of the reasons for the decision):

"In the present case (i) the density of the HMW component, (ii) the polydispersity (Mw/Mn) of the polyethylene composition with the HMW component being characterized as having a substantially uniform comonomer distribution or a reverse comonomer distribution and (iii) the Tdb being less than -25°C are defined in dependent claims, the sole link between those features being that they are preferred embodiment of the composition of claim 1, which does not necessarily mean that they all pertain to the same preferred embodiment."

(Reason 3.4)

144. The Board also reasoned (points 3.6 and 3.7 of the Reasons):

"3.6 The appellant, however, failed to show that the application as filed discloses implicitly or explicitly that the values defined for each of those

*parameters are meant in the application as filed to be obtained **in combination** to the extent defined now in claim 1, …*
… so that the Board could not conclude that the subject-matter of amended claim 1 would emerge in a direct and unambiguous manner from the application as filed when reading its claim 1 in the light of the application as a whole."

"3.7 Submissions made starting from a more specific embodiment of the application as filed and explaining as to why a generalisation of that specific embodiment would result into the subject-matter of claim 1 in a direct and unambiguous manner in the light of the technical information contained in the application as filed were not provided either. It was also not shown that the examples as a whole would provide a pointer to the above definition of features. The appellant [Patentee] *indicated in this respect that examples 1 to 8 and 11 would disclose compositions falling within the ambit of claim 1 as amended. Assuming to the benefit of the appellant that this is true, the Board notes that **each of those examples are defined not only by the features defined in amended claim 1, but also by additional parametric features** such as melt indices and density of the overall composition, and that the values obtained in the examples for each of the parameters defined in claim 1 are not representative of the numerical ranges defined in claim 1. Hence, in view of the examples of the application as filed, it is also not apparent that the subject-matter **as defined in claim 1** was contemplated by the inventor of the present application."*

145. Likewise, it is submitted that each of the formulations in the examples of the present case are also defined by additional features such as the presence of an **siRNA**. Further, as discussed above in detail, the skilled person reading A0 as a whole would conclude that any generalisation of the specific embodiments according to the Examples would, in accordance with the generalising statements in Example 1, involve at least one of the specific ranges for the cationic according to original claims 8 or 9. The skilled person would also note that these ranges are also present in the features that were disclosed in combination in original claims 27 and 33. In contrast, the skilled person would not necessarily and directly and unambiguously, derive a combination of ranges having limits as in amended claim 1 of the present MR, and moreover lacking the siRNA component of the specific Examples.

146. As was also emphasised by the Board in T 389/13:

> *"3.8 The underlying idea of Article 123(2) EPC is that an applicant or patent proprietor shall not be allowed to improve his position by defining subject-matter not disclosed in the application as filed, since so doing would give him an unwarranted advantage and could be damaging to the legal security of third parties relying on the content of the original application (G 1/93, OJ EPO, 1994, 541, point 9 of the reasons for the decision)."*

and

> *"3.10 Allowing those various restrictions without there being any - even implicit - indication in the application as filed that the **specific** combination of newly introduced parametric ranges and of amended restricted ranges was envisaged would be unfair to third parties. It would give an applicant or a patentee who filed a broad speculative claim an unwarranted advantage over other applicants who were the first to attribute any significance to a specific combination of parameters and their ranges of values encompassed by said broad original claim, as such type of selection invention is in principle patentable and even rather usual in the present field of technology. The underlying principle is that any invention for which protection is sought, i.e. in the specific form claimed, and which therefore is meant to provide a contribution to the art justifying a patent monopoly must have been made at the date of filing the application and be properly disclosed therein. As indicated in point 2.3.3 of the reasons for G 1/03 (OJ EPO, 2004, 413) "applicants deal with the state of the art of which they are aware (see Rule 27(1)(b) EPC)" (now Rule 43(1)(b) EPC) "and try to delimit the invention against it. For any further state of the art of which they are not aware, they draft fall-back positions for preferred (and more preferred) embodiments. In this way the invention as set out in the specification may appear like the skins of an onion and it becomes clear where the core of the invention is."*

147. In the present case, it is submitted that, compared to the very broadly drafted original claim 1 of A0, the fall-back positions that correspond to what was recognisable as the "*core of the invention*" within the meaning of the Board's comments above were, in particular, the ranges of original claims 8 and 9 when combined with other features including siRNA as in original claims 27 and 33 and the corresponding combinations of values, siRNA, and lipid species as in original claims

31, 38 and 39. Other combinations of ranges, in contrast, and as found in claim 1 of the MR, are based on multiple selections and selective generalisations and omissions. Thus, in essence the same conclusions apply to claim 1 of the MR as were drawn by the Board of Appeal in T 389/13.

148. Claim 1 of the MR thus contravenes Art 123(2) EPC.

5.3 No Auxiliary Request complies with Art 123 EPC

5.3.1 AR1: dependent claim 10 adds matter

149. AR1 contains added matter for various reasons, including the presence of dependent claim 10. The OD decided that this dependent claim contains added matter, for at least the reasons given in section 2.1.3.1 of the decision:

> *"Originally filed claim 38 as dependent on claim 33 cannot provide the basis for granted claim 10. Originally filed claim 33 does not contain the feature "noncationic' 1 in (c) and does not contain the feature "that inhibits aggregation of particles" in (d). Originally filed claim 38 is therefore not directed to the same embodiment as granted claim 10. Claim 10 therefore contains added matter."*

150. We agree with that sub-aspect of the decision.

151. In more detail, as discussed before the OD, regarding the initial aspect of the reasoning cited above, phospholipids and cholesterol derivatives can be either cationic or non-cationic. The OD in section 2.1.3.1 of the decision acknowledged this broader scope of the classes "*phospholipid*" and "*cholesterol derivative*" as such as one of the reasons for which granted claim 10 contained added matter. For this reason, amongst others, the basis in original claim 1 of A0 for granted claim 1, relating only to "*non-cationic*" lipids in feature (c), was directed to a different embodiment than the basis in original claims 33 and 38 of A0 for the features of granted claim 10, which related to <u>all</u> phospholipids and cholesterol derivatives (including cationic species). Added matter thus arose in view of this technically significant difference between the two embodiments when definitions according to original claims 33 and 38 were combined with features from other embodiments including the "*non-cationic*" limitation of granted claim 1, as in granted claim 10. Such combinations mixing selected aspects of both separate original embodiments were not originally disclosed.

152. **P withdrew their appeal** against the OD's decision that the MR before the OD contained added matter inter alia due to claim 10. Thus, that sub-aspect of the OD's decision cannot be reversed.

153. Accordingly, AR1 also contravenes Article 123(2) EPC for this additional reason.

5.3.2 AR1 and AR1a: claim 1 adds matter

Undisclosed combination of features

154. In each of AR1 and AR1a, claim 1 recites the range of original PCT claim 9. But this does not alter the fact that, overall, the claim still relates to a combination of selected features that were not disclosed directly and unambiguously in the claimed combination in A0.

155. The range of original PCT claim 9 is also selection, for example, initially vis-à-vis at least the range of original claim 8 which is disclosed on exactly the same level in a dependent claim, and still needs to be combined with the other features in claim 1 of AR1 and AR1a, e.g., with the amounts of phospholipid, cholesterol or derivative thereof. Those combinations were not disclosed in the application as filed.

156. The only directly and unambiguously disclosed combinations of features involving the ranges or original claims 8 and 9 are found in original claims 27 and 33. Those feature combinations, e.g., in claim 33, differ from the combinations in claim 1 in AR1 and AR1a in multiple aspects, including

- different requirements and range endpoints for a phospholipid, cholesterol or derivative thereof,
- a lack of a limitation of the phospholipid or cholesterol derivative to be "*non-cationic*",
- a limitation to a PEG-lipid conjugate,
- but no limitation to a conjugated lipid *"that inhibits the aggregation of particles*",
- a different lower limit for the PEG-lipid conjugate (1 mol %), and
- only an siRNA as the formulated nucleic acid.

157. The definitions of the amounts of phospholipid and cholesterol or derivative thereof in feature (c) from paragraph [0130] of A0 were also not originally disclosed in combination with the new upper limit of 47.5%.

158. As for the MR, the "*for use*" language, if considered limiting at all despite the considerations discussed above under Rule 80 (and further below under Art. 56 EPC), represents a further selection between alternatives disclosed on the same level, i.e., at least between the alternatives of original claims 41 and 43.

The value of 47.5 % as such adds matter

159. The value of 47.5 % as such also adds matter. This value is not originally disclosed. A decrease of the originally disclosed value of 49.5% to 47.5% in claim 1 of AR1 and AR1a also does not follow directly and unambiguously from the selection of the range for cationic lipid of original claim 9. In claim 1 of AR1 and AR1a, other lipid components have also been specified further in comparison to original claim 1, but it is not direct and unambiguously derivable that all other lipid amounts in the formulation apart from the cationic lipid are also to be selected as claimed.

160. An increase of 2 % in minimum cationic lipid content according to original claim 9 could likewise lead to an adjustment in amounts for the conjugated lipid such that the maximum amount of non-cationic lipid is not 47.5 % but a different value, or the selection of a different range definition for the non-cationic lipids (phospholipid, cholesterol or derivative thereof) as such may lead to a different value than 47.5 %.

161. Indeed, for example, in original claim 33, the only actual disclosure of a further combination of features involving the range of "*about 52 mol % to about 62 mol %*" as in original claim 9 and a "*mixture of phospholipid, cholesterol or derivative thereof*", the upper limit of those components is "***47 mol %***", not 47.5 %. That direct and unambiguous disclosure also requires a "***PEG-lipid conjugate***" in an amount of at least "***1%***". Thus, the adjustment of the amount of cationic lipid as in claim 1 in AR1 and AR1a, when also adjusting the ranges for a phospholipid, cholesterol or derivative thereof, was originally indeed also associated with a different adjustment of those latter amounts, and witih an adjustment of the amounts for a conjugated lipid, such that 47.5 % does not result directly and unambiguously.

162. The value 47.5 % thus represents added matter.

163. Thus, claim 1 in AR1 and AR1a contravenes Article 123(2) EPC.

5.3.3 AR2: claim 1 adds matter

164. AR2 also relates to added matter, because the amounts for cationic lipid and noncationic lipid mixture (both phospholipid and cholesterol or derivative thereof) and other features according to original claim 33 have been combined with both

- the selected embodiment for other range amounts for these features of paragraph [0130] of A0 and
- features of the embodiment of original claim 1 of A0, including the limitation in part (d) "*that inhibits aggregation of particles*".

165. The feature combination of claim in AR2 was not originally disclosed.

166. Regarding the second point above, as was also recognised by the OD, the embodiments of original claims 1 and 33 were separate embodiments, and the various features of those embodiments cannot simply be mixed, matched and recombined at will. For this latter reason, granted claim 10 related to added matter. P has not appealed against that decision.

167. Thus, claim 1 of AR2 also contravenes Article 123(2) EPC.

168. In this context, we also immediately note AR2 clearly contravenes Article 123(3) EPC due to the deletion of the limitation "*non-cationic*" from claim 1, part (c) compared to granted claim 1. The same applies to AR3. For completeness, this deficiency is fully discussed separately in section 8 below.

5.3.4 Conclusions under Articles 100(c) and 123 EPC

No AR overcomes the deficiencies of the MR under Article 100(c) EPC

6 Lack of novelty (Art. 100(a) and 54 EPC)

169. We agree with the analysis presented by OA1 demonstrating that the MR also lacks novelty over, e.g., paragraph [0354] of D1 and thus also paragraph [0312] of D25. The amendment in the MR to recite 4-10 mol % of non-cationic phospholipid content does not establish novelty over at least paragraph [0354] of D1 (paragraph [0312] of D25).

170. This analysis is fully consistent with our analysis under Article 54 EPC and the applicable case law regarding the overlap of the claimed ranges with the disclosure in

D1 and D25 as set forth in our opposition statement (see section 7; §§ 73-118 in Appendix A of the Statement of Grounds of Appeal, including in § 112 against the phospholipid range of granted claim 7(b) that is now recited in claim 1) and in our submissions of 9 August 2019 (section 3; §§ 11-31 in Appendix C of the Statement of Grounds of Appeal).

171. P attempts to derive from the minutes of oral proceedings before the OD that the lack of novelty could be ignored under Article 12(6) RPBA EPC. That is simply incorrect.

172. D1 is cited in respect of Article 54 EPC in the grounds of opposition, and, notwithstanding the amendment of the claim set during the oral hearing, the Opponents never abandoned these objections; neither can this be derived from minutes of the oral proceedings. The Opponents merely did not add anything <u>further</u> to their written submissions in the context of the oral proceedings before the OD. Those submissions had explained in detail, e.g., the significance of overlapping ranges, both generally (as discussed in OA1's statement of grounds) and specifically against the phospholipid range of claim 7(b) as granted that is now recited in claim 1. Objections under Article 54 EPC based on D1 are not newly raised in this appeal.

173. In any case, the OD addressed the claims of the present MR under Article 54 EPC in view of D1 and D25. It is clear, however, that the OD was <u>wrong</u> in sections 4.9.1 and 4.9.2 of the decision under appeal to hold that no disclosure in D1 or D25 is relevant to the novelty of the present claims. In view of the endpoints and overlap of the ranges concerned and the established criteria of the case law as set out in detail in the most recent submissions by OA1 (see particularly section 4.1.3), the lack of novelty over D1, e.g., in [0354] (or D25, e.g., in [0312]) is overwhelmingly clear and must not be ignored in the circumstances.

174. In summary, the disclosure of endpoints and ranges in combination in D1, paragraph [0354] destroys the novelty of claim 1 of the MR at least because:

- **endpoint 60%** for the D1 cationic lipid falls in the corresponding claimed range, and moreover there is a significant overlap at 50-60%, i.e., with a substantially broad upper portion of the known range that extends to 60%;

- **endpoint 5%** for the D1 neutral lipid falls in the corresponding claimed range for the non-cationic phospholipid, and it is directly and unambiguously derivable from

D1, paragraph [0354], that the term "neutral lipid" applies to a "non-cationic phospholipid"; particularly, this is inevitably so in the typical embodiments in which both phospholipid and cholesterol are present and cholesterol and its content are specified separately;

- **endpoint 1%** for a conjugated lipid of D1 falls in the relevant claimed range;
- the claimed range of **30-40%** cholesterol is

  (a) **not sufficiently narrow** to establish novelty in the circumstances compared to the known ranges mentioned in D1, paragraph [0354] (**10-60%** or, especially, **20-45%**)[5]; and

  (b) **not far removed** from any specific examples disclosed in the prior art and from the end-points of the known range (cf. the range **20-45%** and the examples in D1 that employ, e.g., **28%** cholesterol).

175. In view of the disclosure of D1 as a whole (rather than the narrow embodiment the OD focussed on), and considering how the general disclosure of D1 is summarised with all relevant features combined in a single paragraph of D1 [0354], the skilled person would certainly seriously contemplate carrying out this disclosure within the ranges claimed by P, within the meaning of the established case law.

176. In particular, the skilled person working within these ranges based on D1 would seriously contemplate working in an area in which the combined amounts of phospholipid and cholesterol do not exceed 49.5%. Just as the other values, this simply represents a normal and indeed representative area for the skilled person to work in based on D1, paragraph [0354]. P's arguments beginning in § 81 of their submission are thus incorrect.

177. For example, consider the singled-out endpoint **5%** for phospholipid, in combination with the **entire mid-range** of the D1 ranges 10-60% or 20-45% for cholesterol, i.e., covering approximately 30-40% – just as claimed by P. The skilled person would certainly seriously contemplate working, *inter alia*, in the mid-range of a known generic range, just as they would *prima facie* particularly take into account the singled out endpoints. In the mid-range around 30-40% cholesterol, the skilled

[5] The endpoints 30 and 40 simply define the entire midrange of the D1 cholesterol ranges, and correspond in essence to an approximately equally spaced logical continuation within the endpoints of the D1 ranges, i.e., 10, 20, 45, 60.

person following D1 would comfortably be working within the 49.5% limit for total non-cationic lipid of P's claim 1.

178. More specifically, and taking into account other components, for nearly half this range, i.e., up to 34.5% cholesterol, the cationic lipid could be included precisely at 60% - the endpoint. We note that 34.5% cholesterol is very close to the middle of the D1 ranges - 10-60% (35%) and 20-45% (32.5%). Further, the claimed range for cationic lipid also overlaps not only with the endpoint in D1 paragraph [0345] but also to a significant extent with the upper portion (50-60%) of the known D1 range for cationic lipid. The skilled person would also seriously contemplate working in this part of the D1 disclosure. Certainly, they would seriously contemplate working in the subrange extending from the specific endpoint 60% down to 50%, considering, e.g., the Examples using 50% cationic lipid in D1. In this area of generic overlap regarding the cationic lipid (50-60%), the cholesterol content according to D1 can of course also be higher than 34.5% and still correspond to what P claims. Thus, the entire mid-range of the D1 cholesterol ranges – approximately 30-40% – is a relevant and novelty-destroying area of overlap with claim 1.

179. Of course, since the skilled person would seriously contemplate working within the entire ranges of 30-40% cholesterol and 50-60% cationic lipid, higher percentages than 5% for the phospholipid according to the disclosure of D1 would also be compatible and relevant for the claim, such that the relevant area of overlap in respect of the phospholipid is also broader than just the highlighted endpoint. Considering 30% cholesterol and 50% cationic lipid, for example, up to 19% phospholipid would be compatible with the teaching of D1, paragraph [0354] (so as to allow for 1% conjugated lipid). Thus, based on D1, paragraph [0354], the skilled person would also seriously contemplate working in the area 5-19% phospholipid. The claimed area of 4-10% phospholipid is clearly not a novel selection over that range, considering that (a) it is not a sufficiently narrow range compared to the known range to establish novelty, and (b) its proximity to the specifically disclosed endpoint of 5% in D1. For the reasons discussed above, the skilled person following D1, paragraph [0354], would also seriously contemplate using it in combination with the remaining claimed ranges.

180. Thus, the combination of the claimed ranges is not a novel selection over D1, paragraph [0354].

181. In summary, P is incorrect to allege that D1, paragraph [0354], does not make available particles having no more than 49.5% non-cationic lipid in conjunction with the other claim features:

- The skilled person following the disclosure of D1 would seriously contemplate working in the area of 30-40% for cholesterol, which is a broad range centered approximately on the middle of the ranges that D1, paragraph [0354], discloses for cholesterol.

- The use of that range would also be seriously contemplated in combination with other points and ranges disclosed in D1 in ways that meet all the requirements of claim 1, including the requirement for no more than 49.5% non-cationic lipid.

- Thus, the overlap of the generic disclosure of D1, paragraph [0354], with claim 1 is such that it is plainly novelty-destroying.

182. For completeness, although this has already been pointed out by OA1, we add that, as already discussed above under Rule 80 EPC, the non-specific "*for use*" language is not relevant for any analysis under Article 100(a) EPC, because it is not limiting in substance. It does not provide any further limitation to the claim beyond the structural features already included and discussed above, because any nucleic acid-lipid particle can be administered/delivered *in vivo*, and claim 1 does not require a suitability for any further, more specific effect or purpose.

183. It is also directly and unambiguously derivable from D1 that the "*formulated molecular composition*" (or, interchangeably, "*lipid nanoparticle*", etc.) according to D1, paragraph [0354] is disclosed for the formulation of siRNA (see, e.g., D1, paragraph [0353]), i.e., a nucleic acid.

184. D25, paragraph [0312], is novelty-destroying for the same reasons.

185. In conclusion, the MR lacks novelty.

186. AR1, AR1a and AR2 are affected by the same significant overlap of lipid ranges and thus lack novelty for the same reasons.

7 Lack of inventive step (Art. 100(a) and 56 EPC)

187. In the unlikely event that the Board were to find the MR novel over D1, particularly considering paragraph [0354], the claimed compositions would nevertheless lack an inventive step. We focus on D1 for brevity, but corresponding observations apply based on the corresponding portions of D25.

7.1 Starting point: the "50:20:28:2 formulations"

7.1.1 P's arguments are flawed as they are not based on claim limitations

188. P relies on a strategy of arguing that the "*for use*" language in the claim influences the choice of closest prior art, the formulation of the objective technical problem and the obviousness analysis, allegedly because not all formulations in D1 were specifically tested for a suitability for specific uses such as "*systemic*" or "*serum stable*" *in vivo* delivery. Those arguments are incorrect, and P's strategy is flawed, for various reasons.

189. Each step in the objective problem-solution analysis under Article 56 EPC must be based on the features of the claims. Only the features of the claim define the subject matter for which a patent applicant or patentee seeks protection and purports to have made a contribution to the art. If a feature is not included in the claim as a claim limitation,[6] or is not associated with an asserted effect across the whole scope of the claim, then a patentee cannot rely on that feature or effect to influence the problem-solution approach in any way.

190. Therefore, the "*for use*" language in present claim 1 – being non-limiting – does not provide any basis for functional differentiation between different formulations in D1 as starting points for the problem-solution approach, as alleged by P. As already discussed in detail under Rule 80 EPC, that non-specific "*for use*" language simply refers to any administration / delivery *in vivo*, regardless of whether any further effect or purpose is thereby achieved.[7]

191. P's arguments rely, much like those of the OD in the flawed decision under appeal, on aspects of "***systemic***" administration as though this were a feature of claim 1 (see,

[6] For example, it may not be possible to recite a desired claim limitation because it was not originally disclosed and would therefore lack basis if included, or a patentee may choose not to recite a limitation due to a desire to achieve a broader claim scope.

e.g., P's citation from section 4.10.5 of the decision in § 93 of P's reply)[8]. In addition, P also relies heavily on the yet more specific criterion of whether a formulation is "***serum stable***" (§§ 94, 99, 100, 101, 102, 104, 105, 106 of P's reply).

192. P's approach is clearly incorrect under the problem-solution approach, because in reality it is immediately evident that the scope of the non-specific "*for use*" language in claim 1 also encompasses *in vivo* delivery that is, e.g., "**local**" or "**topical**", i.e. the opposite of "*systemic*".

193. Thus, much like the OD in section 4.10.5 of the decision under appeal though to an even greater extent, P thus falls into the error of engaging in a discussion under Article 56 EPC that is not based on limitations of the claims. Neither feature can correctly play a part in the assessment of obviousness.

7.1.2 P's arguments do not correctly identify the perspective of the skilled person

194. P (§ 95) alleges that the Opponent-Appellants have not performed the analysis from the perspective of the skilled person. However, with all due respect, it is P who errs in that regard. Under Article 56 EPC, the skilled person's intentions and criteria are defined by the subject matter of the claim at issue, particularly its purpose and effects, to the extent that such purpose and effects are derivable from and achieved across the scope of the claim features.

195. Merely as an illustration, in the distinct case of a specific medical use claim under Article 54(5) EPC, the skilled person at the outset of the problem-solution approach is generally assumed to desire to treat the disease that is specified in the claim. Accordingly, that specified disease and the skilled person's assumed desire to treat it may thus generally affect the choice of starting point and on that basis prior art that is not concerned with that specific treatment effect might be excluded.

196. In view of the wording of present claim 1 of the MR, the skilled person does not need to achieve any specific property, effect or purpose to work within the scope of claim, because the claim does not require any such effect. P thus again cannot rely on any specific property, effect or purpose to exclude parts of the prior art. This conclusion follows, precisely, from the skilled person's perspective, in view of the non-specific scope of the claim language.

[8] See also the erroneous inclusion by the OD of this feature in the wording of claim 1.

197. As set out above, any formulation – in D1 or elsewhere – can be delivered *in vivo* at least to the trivial standard that follows from the non-specific "*for use*" wording that P uses in claim 1. No further motivation is required than, e.g., to find out what happens after such delivery, or to deliver the nucleic acid regardless of extent, localization, efficiency, side effects, or other effects. Thus, to the skilled person starting from D1, due to the absence of any requirement for a particular effect in claim 1, it is strictly irrelevant whether a formulation of D1 has been tested *in vivo* or otherwise, and further whether any specific effect such as "serum stability" was tested.

198. Thus, in accordance with the established case law, any of particles L054, L073, L097 and L109, which have a lipid component ratio of "50:20:28:2", are highly relevant starting points, because they:

- are conceived for the same purpose as the claimed subject matter (at the level defined in claim 1, i.e., *in vivo* delivery regardless of any further effect), and
- have the most relevant technical features in common, i.e., require only a minimum of structural modifications to arrive within the claim (e.g., the Case Law book, 9th ed. 2019, I-D, 3.1).

199. As pointed out in our statement of grounds, compared to formulation L109, claim 1 has only a single difference, i.e., a lower phospholipid content, because L109 has a total content of 30% in cholesterol or a derivative thereof (28% cholesterol and 2% 2KPEG-conjugated cholesterol), 50% cationic lipid and 2% 2KPEG-conjugated cholesterol. See §§ 48-57 of our statement of grounds of appeal.

200. We emphasise once again with reference to §§ 48-57 of our statement of grounds that there is no basis for giving the term "*or*" in the phrase "*cholesterol or a derivative thereof*" an arbitrarily narrow meaning in the sense of an exclusive "*or*", as the OD contemplated at first instance. The existence in the prior art of particles such as D1, L073 further illustrates the fact that more than one lipid can contribute to any of the lipid classes recited in claim 1. In L073, for example, the role of the "*cationic lipid*" feature is performed by two different cationic lipids side-by-side (each at 25 mol %). There is no rational basis for discriminating between different lipid classes arbitrarily and interpreting claim 1 in a manner that would exclude, e.g., formulations in which the feature "*cholesterol or a derivative thereof*" is satisfied by multiple different cholesterol derivatives side-by-side. Likewise, there is no rational basis for

interpreting claim 1 in a manner that would exclude formulations in which the feature "*cholesterol or a derivative thereof*" is satisfied by cholesterol and a cholesterol derivative side-by-side, as in the case of D1, L109.

201. P argues in § 102 that citation of L109 as a starting point "*rings especially hollow as the skilled person is not even taught by D1 that L109 is serum stable*". As set out above, serum stability is not a relevant consideration for the skilled person because "serum stability" is not a feature of the claim, nor is it implied by "*for use*". This argument must therefore fail.

202. Moreover, as discussed further below, L109 has the same 50:20:28:2 molar lipid ratios of formulation L073, which was in fact flagged as being of interest for practical use by its representative testing in Examples 7 and 8 of D1. L073 and L109 differ only in the choice of specific lipid in each of the classes that are recited in claim 1, and not in the general type of "four-lipid" formulation or their relative amounts. L109 would therefore be of significant interest to the skilled person.

7.1.3 The identity of specific lipid components is irrelevant to inventive step

203. P cannot rely on differences in the specific chemical identity of lipid components, because claim 1 does not recite a specific nucleic acid lipid particle defined by its specific lipid components, but instead recites classes of lipid molecules. These classes are defined by nothing more than broad ranges of relative amounts in combination with an unspecified nucleic acid.

204. Although we discuss the specific content of Examples 7 and 8 further below, the initial point to note is that it is not even relevant which specific effects were tested in Examples 7 and 8, because P does not limit claim 1 by any specific effect. Any formulation that has been made can also be delivered at least without further effect, in the non-specific scope of claim 1.

205. In conclusion, P cannot influence the problem-solution approach to its own advantage by reading features into the claim that are neither recited nor implied, to differentiate between different formulations in D1 and exclude certain prior art formulations from the analysis under Article 56 EPC. P would be reading features into the claim only for the purposes of achieving a supposed advantage in the assessment under Article 56 EPC, whereas thereafter and for all other purposes they would not be limiting, because they are simply not present in the claim.

206. That approach would be fundamentally incompatible with European patent law.

7.1.4 D1 teaches that 50:20:28:2 compositions are serum-stable

207. Moreover, even if "serum stability" were a criterion (which is strongly denied), then P's arguments would also fail, and the "50:20:28:2" formulations would still be an appropriate starting point. D1 in any case provides a substantiated and plausibly generalized teaching that a particles of the specific type "50:20:28:2" are serum stable.

208. This teaching is provided specifically for 50:20:28:2 formulations L054, L073 and L097 in paragraphs [0182], [0184], and [0192], respectively, with supporting data in Example 7 (paragraphs [0644], [0645], Fig. 11) for L073 as a representative example.

209. As mentioned, P attempts to avoid L109 additionally by arguing that "*the skilled person is not even taught by D1 that L109 is serum stable*" (§ 102 of the reply). But just as L054 and L097, formulation L109 also shares the 50:20:28:2 lipid ratios with formulation L073, which is tested in Example 7. L054, L073, L097 and L109 differ only in the choice of specific lipid in each class, not their general types or relative amounts. P cannot rely on differences in the specific chemical identity of lipid components, because claim 1 does not recite the specific chemical identity of the lipid components, but only recites broad ranges of molar percentages.

210. P further alleges that the skilled person would distrust and ignore the data for L073 of Example 7 due to the type of test employed (§ 100 of the reply), but provides no evidence to support that allegation. In fact, there is no reason for the skilled person to doubt the teaching in D1 that L054, L073, L097 and L109 are suitable to be administered to a living animal, at least for testing purposes. P's arguments in that regard must thus fail.

211. Further, we note that Example 8 (paragraphs [0646], [0647], Fig. 12) also characterizes L073 favorably in terms of transfection delivery efficiency at physiologically relevant pH, assessed by determining the pH-dependent phase transition of the formulated composition.

212. P alleges that, e.g., L051 should be favoured as the "closest prior art" (see § 109 of P's reply) to the exclusion of L073 and other 50:20:28:2 formulations. We note, however, that D1 interprets the data of both Example 7 (Fig. 11) and Example 8 (Fig. 12) such that its conclusions and teaching for L073 and L051 in terms of its projected

in vivo utility in terms of serum stability and transfection delivery efficiency at physiological pH are simply the same as for L051. See in paragraphs [0645] and [0647], as well as paragraphs [0346] and [0347] (last sentences). Figures 11 and 12 indeed show that both L073 and L051 perform effectively equally within the error margins of the assay in terms of both serum stability and transfection delivery efficiency. Thus, there is no basis for P's suggestion that the skilled person would conclude that L073 and other 50:20:28:2 formulations were to be "disregarded" and only L051 was of interest. This is a synthetic attempt by P to exclude the most relevant compositions of the prior art from consideration by using an ex post facto analysis (see also the discussion of the case law prohibiting such patentee-biased ex post facto approaches to the selection of the starting point below, in section 7.1.5).

213. The skilled person would understand, that, particularly for the purposes of a patent application such as D1, if data such as those of Examples 7 and 8 and Figs 11 and 12 render plausible that various formulations have desirable properties for some kinds of in vivo uses, it is sufficient and normal if only a subset of particles is subjected for further testing. In the absence of concrete, substantiated reasons, the skilled person would not merely for this reason doubt the clear teaching in D1 that 50:20:28:2 formulations such as L073 are expected to be equally useful in vivo as L051.

As mentioned, P has not provided evidence to substantiate any such concrete reasons for the skilled person to doubt and ignore the generalized teaching of D1 regarding L073 and other 50:20:28:2 formulations. Rather, P has simply asserted without evidence that the skilled person would ignore the teaching in D1 regarding 50:20:28:2 formulations. P's arguments are insufficient to discharge the burden of proof for making such an assertion.

7.1.5 "50:20:28:2 formulations" cannot be ignored as feasible starting points

214. As alluded to above, even if other formulations within D1 were also considered as starting points,[9] 50:20:28:2 formulations such as L054, L073, L097 and L109 cannot be ignored.

215. Each is in any case a feasible starting point, from which the claimed subject matter does lack an inventive step. The practice in such cases of multiple feasible starting points is well-established and is summarised in the EPO Guidelines for Examination

[9] Indeed, claim 1 is also not inventive over other formulations in D1.

(G-VII, 5.1) as follows, particularly with reference to T 1742/12, (Reasons 6.5); T 824/05, (Reasons 6.2), and the remaining cited case law:[10]

> *"In the event of refusal or revocation, it is sufficient to show on the basis of one relevant piece of prior art that the claimed subject-matter lacks an inventive step: there is no need to discuss which document is "closest" to the invention; the only relevant question is whether the document used is a feasible starting point for assessing inventive step (see T 967/97, T 558/00, T 21/08, T 308/09 and T 1289/09). This is valid even if the problem identified in a problem-solution reasoning may be different from the one identified by the applicant/patentee.*
>
> *As a consequence the applicant or proprietor cannot refute the argument that the claimed subject-matter lacks inventive step by submitting that a more promising springboard is available: a piece of prior art on the basis of which the claimed invention is considered non-obvious cannot be "closer" than a document on the basis of which the claimed invention appears obvious, because it is evident in this situation that the former does not represent the most promising springboard from which to arrive at the invention (T 1742/12, Reasons 6.5; T 824/05, Reasons 6.2)."*

216. Thus, even if the claimed subject matter were ever found not to be obvious starting from a starting point preferred by P, other starting points in D1, such as the 50:20:28:2 formulations, may not be ignored and would also have to be assessed as starting points.

217. The general statements by the Boards Of Appeal in T 405/14, reason 19, and T 694/15, reason 13 also support this view. In T 405/14, reason 19, the Board stated

> *"all items of prior art considered as starting points which allow the elaboration of a **realistic** attack under Article 56 EPC may be considered to qualify as "closest prior art", although this currently accepted terminology is somewhat misleading. The approach thus excludes any abstract notion of metric. It follows that every objection of lack of inventive step has to be assessed on its own merits and that a document selected as starting point cannot be excluded only because some seemingly more promising item of prior art is available."*

[10] These principles evidently apply equally regardless of whether the multiple starting points are in different documents or in the same document, as in the case of D1.

218. In T 694/15, reason 13, the Board stated

> *"It can be economical to start from prior art that is in some sense close to the invention, in the hope that the consideration of this single starting point will be enough to establish whether the claimed subject matter would have been obvious. However, if this fails, before arriving at the conclusion that the subject matter would not have been obvious, it is necessary to consider other possible starting points, to see whether there are any other paths leading to the invention, that the skilled person would have taken when searching for solutions to technical problems pertinent to that starting point. If such a path exists, then the invention would have been obvious. …"*

219. In T 1087/15, reason 1.1.1, the Board followed T 855/15 and T 2057/12 and emphasised that a principal consideration in choosing the starting point for the problem-solution approach is simply how easily it leads in an obvious way to the invention:

> *"To be overly restrictive as regards possible starting documents for an inventive step attack is unnecessary since less promising starting points would anyway make an obvious modification thereof (in order to reach the claimed subject-matter) more difficult than when starting from a more promising document. Therefore, rather than the 'appropriateness' of a document being analysed in too great detail in advance of the formulation of an inventive step attack, less promising starting documents will ultimately be exposed by resulting in unsuccessful inventive step attacks. In this regard it should be remembered that 'closest' prior art is merely a label given to the piece of prior art from which an inventive step attack starts and which is considered to be the most promising. In many cases it may indeed not be possible to identify whether one piece of prior art is necessarily 'closer' than another piece of prior art, and doing so may well artificially restrict inventive step considerations using the problem/solution approach."*

220. Thus, P's arguments in reply to the appeals striving to influence the outcome of the problem-solution approach via its starting point are futile in view of the legally correct approach reflected in the case law-cited above.

221. The above case law dictates that, if ever the Board were to conclude that the features of claim 1 were not obvious starting from P's preferred starting point in D1

(which we also deny), then this would merely mean that this starting point is not the "closest", i.e., is not the most relevant, promising springboard. The features of claim 1 are certainly mere obvious alternatives starting from the 50:20:28:2 formulations in D1.

7.2 Objective technical problem vis-à-vis 50:20:28:2 formulations

222. As indicated in our statement of grounds of appeal, compared to L054, L073 or L097 there are two differences (very slightly higher cholesterol and 10% lower phospholipid), and compared to L109 there is only one structural difference (only 10% lower phospholipid).

223. The one or more differences are not associated with any technical effect compared to D1 formulations such as L054, L073, L097 or L109. This was, in principle, correctly concluded by the OD (4.10.3 of the decision of the OD. Nevertheless, the OD incorrectly included the aspect of suitability for "*systemic*" delivery in the objective technical problem (last paragraph of 4.10.4). in view of the non-specific claim features, however, no specific property such as suitability for "*systemic*" delivery, "serum stability" or the like can be included in the formulation of the objective technical problem.

224. P has now omitted "*systemic*" at least from the formal formulation of the objective technical problem in § 110 of their reply. P still includes the phrase "*suitable for in vivo delivery*". But that phrase also has no place in the objective technical problem, because the corresponding non-specific "for use" language in claim one is not a technically meaningful or limiting property. As discussed in detail under various aspects above, any formulation that has been made can also be delivered *in vivo* at least without further effect, i.e., at least to the trivial standard that follows from the non-specific "*for use*" wording that P uses in claim 1.

225. Thus, the objective technical problem vis-à-vis D1 is simply the minimal problem of providing any alternative to the particles of D1.

7.3 Obviousness starting from the 50:20:28:2 formulations

226. As acknowledged by the OD, it would have been obvious to raise cholesterol from 28% into the range 30-40% when providing an alternative. For example, this simply encompasses the middle of the range "20-45%" as taught by the express generic teaching in D1 in both paragraphs [0160] and [0354].

227. In the starting point of 50:20:28:2 formulations, the ratio of cationic lipid to total neutral lipid is 50:50.

228. The OD in section 4.10.5 of the decision (page 18) assumed that:

> *"… the skilled person would be inclined to maintain a ratio of cationic lipid versus total neutral lipid of approximately 1".*

229. The OD then fell increasingly into error in logical and quantitative aspects, becoming self-contradictory and inconsistent. In particular, despite initially assuming a tendency on the part of the skilled person to maintain "*a ratio of cationic lipid versus total neutral lipid of approximately 1*" (i.e., approximately around 50:50), the OD conversely went on to reason that, when "*increasing the amount of cholesterol*" the skilled person would "*not be inclined*" to decrease the amount of phospholipid.

230. This reasoning is arbitrary and illogical: it does not even appear to be mathematically possible on the one hand "*to maintain a ratio of cationic lipid versus total neutral lipid of approximately 1*" while on the other hand "*increasing the amount of cholesterol*" and not decreasing the amount of phospholipid. To the contrary, if one assumes, as did the OD, that the skilled person would obviously and conservatively be inclined "to *maintain a ratio of cationic lipid versus total neutral lipid of approximately 1*", it follows automatically to reduce the amount of phospholipid as a consequence of increasing the cholesterol content. To do otherwise would result in the ratio of cationic lipid versus total neutral lipid no longer remaining around 1.

231. The skilled person taking that approach would, therefore, not only maintain the content of both cationic lipid and the total content of neutral lipid approximately the same, but would also take the obvious step of compensating for an increase in cholesterol content by a concomitant decrease in phospholipid content.

232. This would have made perfect technical sense because the skilled person would have been aware that phospholipid and cholesterol have similar "fusogenic" roles. D1 expressly refers to both components "fusogenic lipids" in Fig 6. This common functional role would have provided the skilled person with a reasonable expectation that the cholesterol and phospholipid components would be interchangeable to a significant extent, and accordingly with motivation to decrease phospholipid when increasing cholesterol.

233. Therefore, when making an alternative to a 50:20:28:2 formulation, just as it was obvious to raise cholesterol by, e.g., 10% or 12% (i.e., to 38% or 40%), it was also obvious simultaneously to lower the phospholipid content by 10% or 12% (i.e., to 10% or 8%), while leaving the amount of cationic lipid static at 50%. The skilled person modifying a 50:20:28:2 formulation to provide an alternative particle would thereby have arrived in an obvious manner within the scope of claim 1 (e.g.: 50:10:38:2). Again, there is no technical improvement in the claimed formulation and the OD agreed it was a mere alternative. That mere alternative would be readily derived by the skilled person.

234. Further considering that D1 also expressly contained a generalized teaching pointing toward a cationic lipid content of up to 60% (cf. [0157] and [0354]), it was all the more obvious to reduce the amount of phospholipid while increasing the cholesterol content, to implement the teaching of D1 overall when working in the middle of the range "20-45%" as expressly taught in paragraphs [0160] and [0354].

235. Further, directly after the disclosure of cholesterol in the range of up to 45% in paragraph [0160], D1 paragraph [0161] also discloses a generic teaching including particles with:

- cationic lipid at 50 % (as in the 50:20:28:2 starting formulations such as L073);
- "*neutral lipid*" amounting to 30-50%", and
- 0-10% PEG conjugate.

236. For the PEG conjugate, the starting value of 2% is consistent with this range and was entirely commonplace (see, e.g., Table IV). By way of further example, we note that, e.g., prior art document D12 (also in the name of the precursor of P, Protiva) expressly describes the routine modification of PEG-lipid content in SNALPS at [0159] as follows:

> *"The bilayer stabilizing component (e.g., PEG-lipid) typically comprises from about 0 mol % to about 20 mol %, from about 0.5 mol % to about 20 mol %, from about 1.5 mol % to about 18 mol %, from about 4 mol % to about 15 mol %, from about 5 mol % to about 12 mol %, or about 2 mol % of the total lipid present in the particle. One of ordinary skill in the art will appreciate that the concentration of the bilayer stabilizing component can be varied depending on the bilayer stabilizing*

component employed and the rate at which the nucleic acid-lipid particle is to become fusogenic." (emphasis added)

237. When thus, within the scope of that teaching, the skilled person employs cholesterol in the "mid-range" 30-40% as an obvious (and in fact individually not even novel) implementation of the range 20-45% from the immediately preceding paragraph [0160], then certainly at the upper end of that obvious cholesterol range (40%,), e.g., a phospholipid content of 8% inevitably results. This therefore represents a further path through which the skilled person starting from D1 would arrive at subject matter matching all features of claim 1 in an obvious manner.

238. We also emphasise that the skilled person starting from the 50:20:28:2 formulations of D1 would not have hesitated to reduce the amount of the phospholipid component downwards by at least 10% and to screen formulations with amounts of phospholipid of below 10% in a routine manner. The skilled person would also generally not have expected a content of phospholipid above 10% to be important for good performance of "SNALP" formulations, e.g., in medical in-vivo applications for siRNA delivery. This is in view of:

- the 20% difference in phospholipid between L051 and L073 particles, which are the equally effective in Examples 7 and 8 as discussed above, and
- Fig. 29 in D1 which shows that even phospholipid-free particles L060 and L061 were also very effective, e.g., at delivering siRNA for HBV.

Both of these aspects of the D1 disclosure provide clear further pointers toward formulations with low phospholipid content.

239. D1 does not disclose the existence of a technical prejudice against lowering the phospholipid component by e.g. 10% or more. Neither does any other cited prior art document. Also, P has not submitted proof of common general knowledge that such a technical hindrance indeed existed in the art. In addition, P has also not submitted evidence of common general knowledge of technical hindrances against the use of certain molar percentages of cationic lipid, cholesterol or conjugated lipids. Hence, the skilled person would not feel restricted in modifying molar percentages of said components, and would thus without any restriction perform routine experimentation to arrive at a particle within the claims.

240. SNALPs with a phospholipid content of, e.g., 10 % for use *in vivo* were part of the skilled person's common general knowledge before the priority date. For example,

the handbook review chapter D20, lists well-known SNALPs on page 246. Formulation no. 67 (D20 reference [15], i.e., Zimmermann et al., published in the highly visible journal Nature), e.g., refers to a SNALP containing 10% phospholipid (DSPC) for use *in vivo*.

241. D20 reference [15] (Zimmermann et al.) is enclosed herewith for the information of the Board as D40, as evidence of the molar ratios of formulation no. 67 in the D20 review, because D20 mentions many details of the known formulations such as that of Zimmermann et al., but not the molar ratios of lipids. We note, however, that these molar ratios of lipids were, in any case, inherent to "formulation 67" of Zimmermann et al. That formulation is mentioned in Handbook chapter D20 precisely because it was one of the many formulations that were already commonly known and available to the skilled person at the time of D20 and the relevant date of the Opposed Patent.

242. In that case, the 10% phospholipid were used alongside 40% cationic lipid and 48% cholesterol. But D1 itself taught the skilled person that more cationic lipid (e.g., 50% or up to 60%) and less cholesterol (e.g. 28% as in the starting point or anywhere in the range of 20 to 45%, of which 30-40% is an obvious implementation), could also be used.

243. Thus, the ranges of **4-10% phospholipid in combination with 50-60% cationic lipid and 30-40% cholesterol** lack an inventive step in view of D1, or D1 in combination with common general knowledge as evidenced by D20, or D1 combined specifically with formulation 67 of D20. That formulation, for example, would have provided yet further encouragement to the skilled person to use phospholipid at 10% instead of 20% as in the starting point. The skilled person would immediately have realised that this was fully in line with the teaching of D1, e.g., because it would compensate in an obvious manner for, e.g., the 10 % increase in cholesterol that also would have been obvious in view of D1.

7.4 No inventive step in singling out a known embodiment

244. As pointed out by OA1, no inventive step is generated in simply picking a specific embodiment out of a more general disclosure of the prior art (T 133/01, reasons 4.4-4.7). Further, P cannot rely on any unexpected effect to support a claim to inventive step, since it has not demonstrated any particular effect shared by the particles defined by claim 1. In view of this it is important to keep in mind that an arbitrary choice from several possibilities, all of which were obvious to the skilled person, also

cannot confer an inventive step (T 1544/07, reasons 6.7.2, and T 964/92, reasons 2.10).

245. This legal principle is general, and is also reflected, e.g, in the EPO Guidelines G-VII in the Annex, in the section "3.1 *Obvious … selection among a number of known possibilities*", and in T 1045/12 (see reasons 4.7.7), where the appellant (applicant) argued that, in the presence of several, equally likely options, the board had to provide a reason why the skilled person would have selected the claimed option. The board disagreed and explained that the fact that there were other options had no bearing on the obviousness of one specific option. Furthermore, if all options were equally likely, then the invention merely resulted in an obvious and consequently non-inventive selection among a number of known possibilities (the Board referred to the above-cited section of the Guidelines, in the edition of November 2018). See also the Case Law, 9th ed. 2019, I-D. 9.19.10, citing T 1045/12 (see reasons 4.7.7).

246. In view of all of the above arguments, the skilled person would have had a reasonable expectation of success of providing any alternative SNALP to a SNALP of D1. For the avoidance of doubt, though, we also note the legal implications of the minimal objective technical problem of providing a mere alternative to a SNALP of D1.

7.5 Consequences of "mere alternative" as objective technical problem

247. The Boards of Appeal have pointed out that such a non-ambitious objective technical problem means that the skilled person more readily has a reasonable expectation of success, i.e., in any case, less prompting by the prior art is required to render the claimed alternative obvious. As summarised in the Case Law book, section I-D, 7.1:

> *"In T 2168/11 the board referred to the case law, according to which the expectation of success depended on the complexity of the technical problem to be solved. While for very ambitious problems requiring the consideration of all the features relied on by the respondent (patent proprietor) but not contained in claim 1, important difficulties might be expected a priori, less ambitious problems might normally be associated with higher expectation of success (see T 192/06, T 782/07)."*

248. Moreover, this case also falls into the case group in which a finding of obviousness must follow because there is a "try and see situation", in which the concept of a reasonable expectation of success does not even apply.

249. According to the established case law, a "try and see" situation applies when the skilled person, in view of the teaching in the prior art, had already clearly envisaged a group of compounds or a compound and then can determine by routine tests whether such compound/s had the desired effect (T 889/02, T 542/03, T 1241/03, T 1599/06, T 1364/08

250. In the present case, a plethora of SNALPs of the general claimed type with various relative lipid proportions were already known and had also already been used in vivo for various purposes (e.g.: D1, D20). Further, as already discussed under Rule 80, Art 54 and Art 56 above, absolutely no specific "in vivo" purpose or effect is even required (i.e., due to the non-specific wording employed, the claim covers SNALPs that could be "delivered in vivo", but would, in fact, e.g., be toxic or otherwise disadvantageous). Thus, it would be straightforward for the skilled person to identify "the desired effect", because it is an effect that can be attributed to every SNALP. Accordingly, the skilled person could thus clearly envisage one or more compounds and could then determine by routine tests whether such compound/s had the desired effect – a try and see situation clearly applies.

251. That this approach was standard for the skilled person is confirmed by the comments in Handbook reference D20 (§9.3, p. 251) relating to SNALP formulation:

> *"Similar to detergent dialysis, SNALP formation by ethanol dilution is optimized by balancing ionic strength, cationic lipid, and PEG lipid content." (emphasis added)*

252. It can plainly be seen that the skilled person therefore appreciated from their common general knowledge (as recorded in D20) that that SNALP formation can be optimized by varying the cationic lipid and PEG lipid content of particles, which means that they are optimizable and result-effective parameters. The skilled person would thus routinely modify these parameters until the desired results are obtained, and would thus naturally arrive within the scope of the claimed formulations without inventive skill.

253. In conclusion, the claimed formulations are not inventive over the 50:20:28:2 formulations of D1.

7.6 Lack of inventive step also starting from "48:40:10:2" formulations such as L051

254. The claimed subject matter is, in any case, also obvious starting from "48:40:10:2" formulations such as L051 (see Table IV), which P proposes as a starting point (§ 109 of the reply).

255. Starting from L051, the skilled person would have noted that, e.g., Examples 7 and 8 of D1 expressly taught that both L051 and L073 performed similarly in terms of at least serum stability and transfection delivery efficiency at physiologically relevant pH (Examples 7 and 8 and Figs 11 and 12; paragraphs [0346] and [0347], last sentences, and [0645], [0647]).

256. The skilled person desiring to solve the objective technical problem by modifying the teaching of D1 to provide any alternative to L051 would also have noted that L073, while performing just as well as L051 in the assays of Examples 7 and 8, had

- a higher content of cationic lipid (50% in total),
- a much lower content of phospholipid (20%), and
- a much higher content of cholesterol (28%), whereas
- the content of PEG-conjugated lipid was the same (2%).

257. It would thus have been entirely obvious, with a reasonable expectation of success, for to the skilled person starting from L051 to provide an alternative by

- increasing the content of cationic lipid;
- decreasing the content of phospholipid;
- increasing the content of cholesterol; and
- keeping the content of PEG-conjugated lipid constant, at the usual value of 2%.

258. L073 would thus have had an obvious role as a "motivator" formulation, leading the skilled person to provide alternatives in the presently claimed ranges without inventive skill.

259. In light of these evident differences and the trends indicated by the juxtaposition of L051 and L073 in Examples 7 and 8, it would also have been entirely obvious for the skilled person, motivated by L073, to

- increase the content of the cationic lipid from 48% to at least the 50% value that worked in L073 or beyond (i.e., certainly into the range of 50-60% involved no inventive skill), and
- decrease the phospholipid and increase the cholesterol content beyond the values of L073 into the ranges of 4-10% or less and 30-40%, respectively.

260. This is all the more so considering that the objective technical problem is only to provide an alternative (rather than an improvement, since no advantageous effect is associated with the distinguishing claim features).

261. D1 already disclosed 50:20:28:2 formulations such as L073 as such, and in view of the objective technical problem the skilled person by definition seeks for any alternative, i.e., any non-inventive modification to the teaching D1. Considering that P cannot rely on any unexpected technical effect, it would not have involved any inventive skill for the skilled person modifying D1 to find any alternative and following the trends indicated by "motivator formulation" L073 also to go beyond the values of L073, e.g., to 10% or below for the phospholipid and into the 30-40% range for cholesterol.

262. The range for phospholipid as claimed is somewhat further removed from the L073 values than the very close or overlapping claimed ranges of the other components. However, the OD, for example, has held that the skilled person, in view of D1, would have been inclined to maintain a ratio of cationic versus total neutral lipid of approximately "50:50".

263. Considering that some room for modification of the cationic lipid and cholesterol beyond the already known L073 values must be allowed within the upwards trend indicated by L073 for these two components when starting from L051, e.g., on a most conservative basis at least a +10% margin must be allowed for as being obvious, leading the skilled person without invention to the alternative ranges 50-60% for cationic lipid and 30-40% for cholesterol.

264. We note that D1 in any case provides a further pointer and confirmation that for the cationic lipid the range up to 60% is of interest, in view of the express generic teaching regarding that value as an upper endpoint, e.g., in paragraphs [0354] and [0157]. Simultaneously, D1 also provides a pointer and confirmation that, for the cholesterol component, ranges that were much higher than the 10% of L051 and higher than the 28% of L073 would be of interest, in view of the express generic teaching of the range extending up to 45% in paragraphs [0354] and [0160].

265. Then, however, the content of phospholipid must automatically be adjusted to at least 10% lower than in L073 – i.e., at 10% or less – whenever at least one of the obviously-modified cationic lipid and cholesterol ranges exceeds the L073 values such that they approach, e.g., 60% and/or 40%, respectively. Thus, the range 4-10% was also obvious.

266. Once again, we also emphasise that P has not demonstrated any unexpected technical effect for the claimed range. Thus, as only alternatives with no particular advantage need to be provided, and L073 expressly sets the general directions for modifications when starting from L051, all such modifications are entirely obvious and would have been carried out by the skilled person without inventive skill.

267. We also emphasise that:

- the skilled person would not have hesitated to vary the amount of the phospholipid component downwards on a scale of at least, 10-20% and to and screen also formulations with amounts of phospholipid of below 10% in a routine manner, and

- the skilled person would generally not have expected a high content of phospholipid to be important for good performance of "SNALP" formulations, e.g., in medical in-vivo applications for siRNA delivery.

268. This is in view of:

- the 20% difference in phospholipid between the equally effective L051 and L073 particles, and
- Fig. 29 in D1 which shows that phospholipid-free particles L060 and L061 were also very effective, e.g., at delivering siRNA for HBV,

Both of these aspects of the D1 disclosure provide clear pointers toward formulations with low phospholipid content.

269. Moreover, SNALPs with phospholipid content of, e.g., 10 % for use *in vivo* were commonly known to the skilled person before the priority date. For example, the handbook review chapter D20, lists well-known SNALPs on page 246. Formulation no. 67 (D20 reference [15], i.e., Zimmermann et al., published in the highly visible journal Nature), e.g., refers to a SNALP containing 10% phospholipid (DSPC) for use *in vivo*.

270. D20 reference [15] (Zimmermann et al.) is enclosed herewith for the information of the Board as D40, as evidence of the molar ratios of lipids in this formulation that is referenced in the review. D20 reviews many details of the known formulations but does not mention the molar ratios of lipids. We note, however, that these molar ratios of lipids were, in any case, inherent to the formulation of D40. That formulation is mentioned in handbook chapter D20 precisely because it was one of the many formulations that were already commonly known and available to the skilled person at the time of D20.

271. In that case, the 10% phospholipid were used alongside 40% cationic lipid and 48% cholesterol. But D1 itself taught the skilled person that more cationic lipid (e.g., 50% or more) and less cholesterol (e.g. down to 28%) could also be used. Thus, the ranges of 4-10% phospholipid in combination with 50-60% cationic lipid and 30-40% cholesterol do not involve an inventive step over D1, or D1 in combination with common knowledge, or D1 combined specifically with either of D20 or D40.

272. Moreover, as has been emphasised previously by both Opponents, in any case, all of the claimed ranges remained entirely within the teaching of D1, e.g., particularly in paragraph [0354].

273. In conclusion, regardless of which of the discussed starting points within D1 or D25 is chosen, the claimed subject matter lacks an inventive step.

7.7 No inventive contribution warranting broad claims

274. In addition to the above, we also particularly emphasize that, with respect to the state-of-the-art, the Opposed Patent does not make a technical contribution that supports an inventive step across the whole claimed area. The Opposed Patent provides no inventive solution to a technical problem that could justify a broad scope of protection.

275. Particularly when considered against the background of the skilled person's common general knowledge of the general type of formulation that is claimed (e.g.: D20), this lack of any significant contribution beyond what was already known is clear from a comparison of the experimental data in, e.g., D1 and in the Opposed Patent[11]. Even for the single formulation that is tested in the Opposed Patent and falls within the scope of the present claims (a particular "siRNA:57.1:7.4:34.3:1.4" formulation

[11] See section 6 of our opposition, i.e., Appendix A to our statement of grounds of appeal.

employing specific lipid species), no objective contribution to the art in the form of any unexpected effect can be derived from the Opposed Patent. Let alone can any generalizable inventive contribution be derived.

276. P's arguments contain various serious flaws and inconsistencies in this regard. In the reply to the appeal, P applies double standards. When it comes to the prior art, P argues that the skilled person has blinders on and only considers relevant specific examples of nucleic acid lipid particles that are shown to have certain characteristics such as being "serum stable". However, when it comes to the Opposed Patent and claim 1 of each claim request, by P's approach, allegedly significant functional characteristics do not need to be included in the wording of claim 1 as claim features but instead can be read into claim 1 arbitrarily, i.e., regardless of the fact that P's "*for use*" phrasing is much broader[12], and regardless of the fact that the definitions of the structural characteristics of the claimed particles allow for such broad variation that they evidently cannot be assumed to imply the functional features on which P relies across their whole scope.

277. This strategy of P is clearly intended to mask the fact that the Opposed Patent does not make a contribution to the art that warrants broad claims, let alone claims in which all particle components are left unspecified both as to their chemical identity and, to a large extent, their molar percentage. It is emphasized that the contribution of the Opposed Patent to the art does not reside in the general idea of providing four-component nucleic acid-lipid particles. These particles in various forms and compositions were already part of the skilled person's common general knowledge before the priority date, as evidenced, e.g., by D20, Chapter 9 of a handbook authored by one of the inventors of the Patent (see D20, p.246 in Table 9.1, four-component siRNA formulations 63-68; routine preparation according to, e.g., D20, section 9.3.5).

278. Besides in D20 and its references, many more exemplary embodiments of four-component nucleic acid-lipid particles are disclosed in other prior art references such as D1 and D25 and many other documents cited in the opposition.[13] Hence, the

[12] As discussed in detail elsewhere herein, the "for use" phrasing is so broad that it is not limiting at all in the technical context of the claim.

[13] We refer also to the review of the state of the art in the Introduction to our opposition, i.e., section 4 of Appendix A to our statement of grounds of appeal, in which the citations were subsequently renumbered according to the first-instance concordance table.

conceptual idea to use four-component siRNA-lipid particles was already commonplace, as were many different individual embodiments of such articles.

279. The Opposed Patent does not provide any further conceptual breakthrough in nucleic acid-lipid particle formulation. Rather, the Opposed Patent merely tests individual siRNA-lipid particles (defined by their specific chemical constituents and their specific molar percentages), and ultimately narrows down in the Examples to a single, specific nucleic acid-lipid particle in which lipid components have specified chemical identities and molar percentages, and the formulated "*nucleic acid*" is the very particular species "siRNA": the "siRNA:57.1:7.4:34.3:1.4" formulation of Group 11, Example 3, Table 4, which is composed of DLinDMA, DPPC, cholesterol and PEG(2000)-C-DMA. But even for this specific siRNA-lipid particle, which is infinitely narrower in scope than claim 1 of the MR, no unexpected effect (let alone any improvement) over the siRNA-lipid particles of, e.g., D1 could be established by P.

280. In Example 4, the specific "Group 11" siRNA-lipid particle is compared to a "2:30 SNALP" formulation according to the prior art and is thereby made to look "advantageous" at least in one experiment in the Opposed Patent. However, this comparison is completely irrelevant for any assessment under Article 56 EPC, because "Group 11" was not advantageous over other, structurally closer prior art formulations, and indeed no unexpected effect at all has been demonstrated for "Group 11" over such other formulations as were known from D1.[14]

281. Furthermore, the Opposed Patent does not provide any rationale or general theory as to why the individual siRNA-lipid particles tested should be generalized at all, let alone to the excessive extent of claim 1. More specifically, in Example 3 of the Patent, only the above-mentioned specific siRNA formulation of Group 11 satisfies the limitations of claim 1 of the MR (see Table 4). In Example 4, the same particle is tested again. In Example 5, siRNA lipid particles having exactly the same molar percentages but now with different lipid species were tested (Table 6, groups 2, 4, 5, 6 and 7). Figure 4, belonging to Example 5, evidences a variability between siRNA-lipid particles as regards gene silencing activity when the chemical identity of the

[14] See particularly sections 6.2 and 6.3.2 in our opposition, i.e., in Appendix A to our statement of grounds of appeal.

lipid components is changed.[15] Examples 7-12 again test only the same siRNA-lipid particle that was already tested as Group 11 in Example 3.

282. Thus, the Opposed Patent does not remotely attempt to provide a technical contribution that could correspond to the breadth of claim 1 in each of P's claim requests. In fact, all the Opposed Patent discloses is, in essence, the routine preparation and application of a specific siRNA-lipid particle, "Group 11", that is nothing more than a further, arbitrary and thus non-inventive embodiment of the state-of-the-art. The Opposed Patent used only components, and amounts thereof, that were commonly known as such to the skilled person (i.e., already reflected even in handbooks such as D20) and accessible in combination by routine workshop modifications without any technical hindrance. No evidence of any unexpected effect vis-à-vis the prior art was produced.

283. What is more, in blatant inconsistency with the breadth of claim that P seeks to achieve, Figure 4 in Example 5 of the Opposed Patent actually shows that the use of lipids in the same class but having different chemical structures impacts the biological activity of the particle. This renders null and void P's proposition that the Opposed Patent may have made a broad conceptual contribution warranting the claimed scope of protection.

284. In reality, and in conclusion, as discussed herein above in the context of the problem-solution approach, the features of claim 1 of the MR relate to arbitrary, non-inventive embodiments, based at most on selections from among a number of readily available possibilities, which all formed part of the state-of-the-art. A relatively low mole % of phospholipid as claimed also cannot specifically support an inventive step, for the reasons discussed in sections 7.3-7.6 above.

7.8 No Auxiliary Request involves an inventive step

285. If admitted into the proceedings, none of the ARs overcome the deficiencies under Article 56 EPC.

286. All the observations above apply likewise to claim 1 in each of AR1, AR1a and AR2. In these claim requests, generic ranges for lipids are altered compared to the MR. But

[15] For further details and discussion, see also section 6.4 of our opposition, i.e., of Appendix A to our statement of grounds of appeal.

the claimed ranges are still broad, arbitrary and non-inventive vis-à-vis D1, for all the reasons given above for the MR.

287. AR2 additionally recites an siRNA, rather than also covering other nucleic acids, but formulation of siRNA is disclosed in D1. Thus, siRNA is not a relevant distinction over D1.

288. Claim 1 in AR3 is limited to the specific amounts of lipids that are used in the formulation of "Group 11" in D1. The chemical species of lipids are still entirely undefined, however. In any case, the specific recited amounts also lacked an inventive step before the claimed priority date. Initially, the use of the four lipid classes in the general ranges of the recited values lacked an inventive step for all the reasons discussed above for the MR. Further, the specific recited values, which are all near the mid-points of these non-inventive ranges, were merely arbitrary further embodiments that were already available to the skilled person without inventive skill, based on the state-of-the-art.

289. Thus, all claim requests fail, and the Opposed Patent is to be revoked.

8 Auxiliary Requests: AR2 and AR3 contravene Article 123(3) EPC

290. Under the various headings of the EPC above, we have already explained why P's Auxiliary Requests 1) should be held inadmissible and 2), if admitted into the proceedings, do not overcome the deficiencies of the MR (Rule 80, Art 100(c), Article 100(a) under the aspects of Articles 54 and 56 EPC).

291. AR2 and AR3 also contravene Article 123(3) EPC, because, in contrast to claim 1 as granted, AR2 and AR3 do not limit the phospholipid and cholesterol derivatives of feature (c) to be "*non-cationic*".

292. As discussed before the OD in the context of the added matter in granted claim 10 (section 2.1.3.1 of the decision), phospholipids and cholesterol derivatives can be either cationic or non-cationic. The OD acknowledged this broader scope of the classes "*phospholipid*" and "*cholesterol derivative*" as such as one of the reasons for which granted claim 10 contained added matter. For this reason, amongst others, the basis in original claim 1 of A0 for granted claim 1, relating only to "*non-cationic*" lipids in feature (c), was directed to a different embodiment than the basis in original claims 33 and 38 of A0 for the features of granted claim 10, which related to <u>all</u> phospholipids and cholesterol derivatives (including cationic species). Added matter thus arose in view of this technically significant difference between the two embodiments when definitions according to original claims 33 and 38 were combined with features from other embodiments including the "*non-cationic*" limitation of granted claim 1 as in granted claim 10. Such combinations mixing selected aspects of both separate original embodiments were not originally disclosed. <u>P did not appeal that decision</u>.

293. In amended versions of claim 1 in AR2 and AR3, the "*non-cationic*" limitation of granted claim 1 has been deleted, and the definitions for phospholipids and cholesterol derivatives has been extended beyond the granted claim scope to <u>all</u> phospholipids and cholesterol derivatives in the broader sense that includes cationic species. In that respect, claim 1 in each of AR2 and AR3 corresponds to the distinctly defined embodiments of original claims 33 and 38, respectively, as acknowledged in section 2.1.3.1 of the OD's decision.

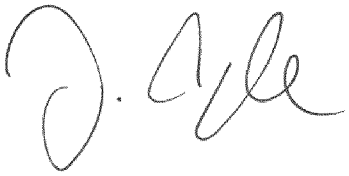
294. The scope of claim 1 in AR2 and AR3 thus extends to subject matter not covered by claim 1 as granted, in contravention of Article 123(3) EPC.

9 Conclusions

295. In conclusion and summary, the MR contravenes the EPC under Rule 80, Article 100(c), and Article 100(a) under the aspects of Articles 54 and 56 EPC.

296. If admitted into the proceedings, none of P's new ARs overcomes the deficiencies of the MR. Each new AR also introduce new deficiencies beyond those of the MR.

297. The decision of the OD to maintain the Opposed Patent in amended form is thus to be overturned, and the Opposed Patent is to be revoked.·



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Enc.:

D39 Application as filed in T 1241/03 (PCT/US93/07149, EP 93 918 499.0)

D40 Ref 15 of D20 (Zimmerman *et al.*)

JOINT APPENDIX 87

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Patentanwälte Rechtsanwälte mbB

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European Patent Office

80298 M U N I C H

Opposition against EP-B1-2 279 254 (09 73 1866.1)
Patentee: Protiva Biotherapeutics Inc.
Opposition by: Merck, Sharp & Dohme Corp.
Vossius Ref.: AB1140 EP/OPP S3

München, April 5, 2018
JAE/OSW/ELH

GROUNDS FOR OPPOSITION AGAINST EP 2 279 254 B1

We herewith file an opposition in the name and on behalf of

Merck, Sharp & Dohme Corp.
126 East Lincoln Avenue
Rahway, New Jersey 07065
USA

against European patent EP 2 279 254 B1 entitled "Novel lipid formulations for nucleic acid delivery".

The proprietor of the patent is: Protiva Biotherapeutics Inc., 100-8900 Glenlyon Parkway, Burnaby, British Columbia V5J 5J8, Canada.

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1. REQUESTS

The EPO is requested to debit our deposit account no. 2800.0321 with the opposition fee (EUR 785.00). The corresponding debit order is also included in the concurrently filed EPO Form 2300E.

We request that the patent be revoked in its entirety for all contracting states on the grounds of Art. 100(a) EPC in conjunction with Art. 54 EPC for lack of novelty, Art. 100(a) EPC in conjunction with Art. 56 EPC for lack of inventive step, Art. 100(b) EPC for insufficiency of disclosure, and Art. 100(c) EPC as extending beyond the content of the original application.

As an auxiliary measure, oral proceedings in accordance with Art. 116(1) EPC are requested.

2. CITED DOCUMENTS

The following documents are cited in this opposition:

D1: US 2008/0020058 (publication date: January 24, 2008)
D2: WO 2006/053430 (publication date: May 26, 2006)
D3: Lin AJ et al., *Biophys J*, 2003; 84(5):3307-16 (publication date: May 2003)
D4: Ahmad A et al., *J Gene Med*, 2005; 7(6):739-48 (publication date: January 31, 2005)
D5: Gao X et al., *AAPS J*, 2007; 9(1):E92-104 (publication date: March 23, 2007)
D6: Filing receipt for the priority application US 61/045,228 of the opposed patent
D7: Excerpt from the USPTO register on US 61/045,228
D8: PCT request for the application WO 2009/127060 underlying the opposed patent

We furthermore reserve the right to rely on the documents referenced in the opposed patent as well as the documents cited during the examination proceedings of the opposed patent in the present opposition.

3. INADMISSIBLE EXTENSION

3.1 The feature of granted claim 1 requiring the presence of "a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle" extends beyond the content of the original application

3.1.1 Granted claim 1 of the opposed patent relates to a nucleic acid-lipid particle and is based on original claim 1 of the underlying application (i.e., WO 2009/127060).

Compared to original claim 1, however, granted claim 1 of the patent requires that the "non-cationic lipid" contained in the claimed nucleic acid-lipid particle comprises "a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle". This feature was introduced in the course of the examination proceedings. The patentee (then applicant) initially referred to pages 27 to 28, paragraph [0130] of the original application as support for this added feature (in the applicant's submission of May 7, 2013), and then to page 68, paragraph [0253] of the application (in its subsequent submission of September 13, 2013). Yet, none of these paragraphs [0130] and [0253] nor any other passage of the original application provide a basis for this added feature.

3.1.2 To begin with, paragraph [0130] on pages 27 to 28 of the application underlying the opposed patent discloses "certain other preferred embodiments", in which the non-cationic lipid comprises a mixture of a phospholipid and cholesterol or a derivative thereof, and wherein both the phospholipid and the cholesterol or a derivative thereof must be present in specific amounts, as shown in the following:

> **[0130]** In certain other preferred embodiments, the non-cationic lipid comprises a mixture of: (i) a phospholipid of from about 4 mol % to about 10 mol % of the total lipid present in the particle; and (ii) cholesterol or a derivative thereof of from about 30 mol % to about 40 mol % of the total lipid present in the particle. As a non-limiting example, a lipid particle comprising a mixture of a phospholipid and cholesterol may comprise DPPC at about 7 mol % and cholesterol at about 34 mol % of the total lipid present in the particle. In other embodiments, the non-cationic lipid comprises a mixture of: (i) a phospholipid of from about 3 mol % to about 15 mol %, from about 4 mol % to about 15 mol %, from about 4 mol % to about 12 mol %, from about 4 mol % to about 10 mol %, from about 4 mol % to about 8 mol %, from about 5 mol % to about 12 mol %, from about 5 mol % to about 9 mol %, from about 6 mol % to about 12 mol %, from about 6 mol % to about 10 mol %, or about 3, 4, 5, 6,

7, 8, 9, 10, 11, 12, 13, 14, or 15 mol % (or any fraction thereof or range therein) of the total lipid present in the particle; and (ii) cholesterol or a derivative thereof of from about 25 mol % to about 45 mol %, from about 30 mol % to about 45 mol %, from about 25 mol % to about 40 mol %, from about 30 mol % to about 40 mol %, from about 25 mol % to about 35 mol %, from about 30 mol % to about 35 mol %, from about 35 mol % to about 45 mol %, from about 40 mol % to about 45 mol %, from about 28 mol % to about 40 mol %, from about 28 mol % to about 38 mol %, from about 30 mol % to about 38 mol %, from about 32 mol % to about 36 mol %, or about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 mol % (or any fraction thereof or range therein) of the total lipid present in the particle.

(page 27, paragraph [0130] of the original application; underlining added)

As can be seen, paragraph [0130] necessarily requires a specific content of the phospholipid, namely a content of "about 4 mol % to about 10 mol %" (in the "other preferred embodiments" disclosed in the first sentence of paragraph [0130]), or a content of "about 3 mol % to about 15 mol %" or various subranges thereof (in the "other embodiments" disclosed in the third sentence of paragraph [0130]).

Granted claim 1 of the opposed patent, however, does not include a corresponding limitation of the content of the phospholipid. While it requires the presence of a phospholipid, it does not specify any particular minimum content of the phospholipid at all, and it does not impose the same upper limit for the content of the phospholipid as required in paragraph [0130] of the original application either. Granted claim 1 would thus allow the presence of, e.g., 1 mol-% or 18 mol-% of a phospholipid – neither of which would be possible in the embodiments disclosed in paragraph [0130] of the application. For this reason alone, paragraph [0130] of the original application fails to provide a direct and unambiguous disclosure of the above-mentioned feature in granted claim 1 of the patent. The recitation of this feature in granted claim 1 thus constitutes an inadmissible intermediate generalization.

3.1.3 With respect to page 68, paragraph [0253] of the original application, we note that this passage refers to "lipid particles containing a mixture of phospholipid and cholesterol" and specifies the content of cholesterol in such particles, as highlighted in the following:

[0253] In certain other embodiments, the cholesterol present in lipid particles containing a mixture of phospholipid and cholesterol comprises from about 30 mol % to about 40 mol %, from about 30 mol % to about 35 mol %, or from about 35 mol % to about 40 mol % of the total lipid present in the particle. As a non-limiting example, a lipid particle comprising a mixture of phospholipid and cholesterol may comprise cholesterol at about 34 mol % of the total lipid present in the particle.

(page 68, paragraph [0253] of the original application; underlining added)

Notably, however, paragraph [0253] of the original application does not relate to any derivatives of cholesterol, and particularly fails to disclose any specific content of cholesterol derivatives.

For this reason alone, paragraph [0253] of the underlying application fails to support the above-mentioned feature of granted claim 1 of the patent, requiring that "the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle" (emphasis added).

3.1.4 Thus, for the reasons explained above, neither paragraph [0130] nor paragraph [0253] of the original application provide a basis for the feature of granted claim 1 of the patent specifying that the non-cationic lipid comprises "a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle". This feature is not directly and unambiguously derivable from any other passage of the original application, either. It follows that granted claim 1 is inadmissibly extended, in violation of the requirements of Art. 123(2) EPC.

3.2 The original application fails to disclose the specific content of cationic lipid recited in item (b) of granted claim 1 *in combination* with the specific content of cholesterol or a derivative thereof recited in item (c) of granted claim 1

Compared to original claim 1 of the underlying application, granted claim 1 of the opposed patent has been amended by (i) limiting the content of the cationic lipid to "50 mol % to 65 mol %", and by (ii) reciting that the non-cationic lipid comprises "a mixture of a phospholipid and cholesterol or a derivative thereof" and further limiting the content of the cholesterol or derivative thereof to "30 mol % to 40 mol %".

3.2.1 When the patentee (then applicant) made the above-mentioned first amendment in the course of the examination proceedings, i.e. the restriction of the content of cationic lipid in claim 1 to "50 mol % to 65 mol %", they referred to page 24, paragraph [0113] of the original application as support.

However, even if, *arguendo*, paragraph [0113] of the original application were accepted to provide a basis for the cationic lipid content of 50 to 65 mol-% recited in granted

claim 1, it would still be necessary to arbitrarily select this specific range for the cationic lipid content from a host of possible ranges disclosed in the original application.

For ease of reference, the relevant passages of the original application disclosing different possible cationic lipid contents, i.e. paragraphs [0113] to [0118] on pages 24 to 25, are reproduced in the following:

> **[0113]** In some embodiments, the cationic lipid may comprise from about 50 mol % to about 90 mol %, from about 50 mol % to about 85 mol %, from about 50 mol % to about 80 mol %, from about 50 mol % to about 75 mol %, from about 50 mol % to about 70 mol %, from about 50 mol % to about 65 mol %, or from about 50 mol % to about 60 mol % of the total lipid present in the particle.
>
> **[0114]** In other embodiments, the cationic lipid may comprise from about 55 mol % to about 90 mol %, from about 55 mol % to about 85 mol %, from about 55 mol % to about 80 mol %, from about 55 mol % to about 75 mol %, from about 55 mol % to about 70 mol %, or from about 55 mol % to about 65 mol % of the total lipid present in the particle.
>
> **[0115]** In yet other embodiments, the cationic lipid may comprise from about 60 mol % to about 90 mol %, from about 60 mol % to about 85 mol %, from about 60 mol % to about 80 mol %, from about 60 mol % to about 75 mol %, or from about 60 mol % to about 70 mol % of the total lipid present in the particle.
>
> **[0116]** In still yet other embodiments, the cationic lipid may comprise from about 65 mol % to about 90 mol %, from about 65 mol % to about 85 mol %, from about 65 mol % to about 80 mol %, or from about 65 mol % to about 75 mol % of the total lipid present in the particle.
>
> **[0117]** In further embodiments, the cationic lipid may comprise from about 70 mol % to about 90 mol %, from about 70 mol % to about 85 mol %, from about 70 mol % to about 80 mol %, from about 75 mol % to about 90 mol %, from about 75 mol % to about 85 mol %, or from about 80 mol % to about 90 mol % of the total lipid present in the particle.
>
> **[0118]** In additional embodiments, the cationic lipid may comprise (at least) about 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 mol % (or any fraction thereof or range therein) of the total lipid present in the particle.

(pages 24 to 25, paragraphs [0113] to [0118] of the original application; underlining added)

As shown above, the original application underlying the opposed patent provides an extensive number of different definitions for the content of the cationic lipid. These different definitions are all disclosed as equally suitable alternatives, as also reflected by the use of the expressions "in some embodiments", "in other embodiments", "in yet other embodiments", "in still yet other embodiments", "in further embodiments", and "in additional embodiments".

The specific range of 50 mol-% to 65 mol-% for the content of cationic lipid, which is now recited in granted claim 1, is not disclosed to be preferred over the many other alternative ranges disclosed in the original application. The incorporation of this specific range of 50 mol-% to 65 mol-% into claim 1 thus amounts to an arbitrary first selection.

3.2.2 As concerns the above-mentioned second amendment made in claim 1, i.e. the limitation to a non-cationic lipid comprising "a mixture of a phospholipid and cholesterol or a derivative thereof" and the limitation of the content of the cholesterol or derivative thereof to "30 mol % to 40 mol %", we emphasize that this amendment is not directly and unambiguously derivable from the original application at all, as already explained in section 3.1 above.

However, even if, *arguendo*, it were assumed that these features would be derivable from page 68, paragraph [0253] of the original application (which we contest), their incorporation into claim 1 would still amount to two further arbitrary selections. This becomes directly apparent when looking at paragraphs [0252] to [0254] on pages 68 to 69 of the application:

> **[0252]** In certain embodiments, the cholesterol present in phospholipid-free lipid particles comprises from about 30 mol % to about 45 mol %, from about 30 mol % to about 40 mol %, from about 35 mol % to about 45 mol %, or from about 35 mol % to about 40 mol % of the total lipid present in the particle. As a non-limiting example, a phospholipid-free lipid particle may comprise cholesterol at about 37 mol % of the total lipid present in the particle.
>
> **[0253]** In certain other embodiments, the cholesterol present in lipid particles containing a mixture of phospholipid and cholesterol comprises from about 30 mol % to about 40 mol %, from about 30 mol % to about 35 mol %, or from about 35 mol % to about 40 mol % of the total lipid present in the particle. As a non-limiting example, a lipid particle comprising a mixture of phospholipid and cholesterol may comprise cholesterol at about 34 mol % of the total lipid present in the particle.
>
> **[0254]** In further embodiments, the cholesterol present in lipid particles containing a mixture of phospholipid and cholesterol comprises from about 10 mol % to about 30 mol %, from about 15 mol % to about 25 mol %, or from about 17 mol % to about 23 mol % of the total lipid present in the particle. As a non-limiting example, a lipid particle comprising a mixture of phospholipid and cholesterol may comprise cholesterol at about 20 mol % of the total lipid present in the particle.

(pages 68 to 69, paragraphs [0252] to [0254] of the original application; underlining added)

In order to derive the above-mentioned features from this passage of the original application, it would be necessary to select the possibility that the lipid particles contain

"a mixture of phospholipid and cholesterol". This possibility is not disclosed to be preferred over other possibilities described in the original application, such as the embodiments in which the lipid particles are "phospholipid-free" (as disclosed in paragraph [0252] on page 68). The incorporation of the feature requiring "a mixture of phospholipid and cholesterol" into claim 1 thus constitutes a further arbitrary selection.

In addition thereto, following the above-mentioned selection of a mixture of phospholipid and cholesterol, the original application continues to disclose a number of different alternative ranges for the content of cholesterol. Thus, the application lists the ranges of (i) about 30 mol-% to about 40 mol-%, (ii) about 30 mol-% to about 35 mol-%, (iii) about 35 mol-% to about 40 mol-%, (iv) about 10 mol-% to about 30 mol-%, (v) about 15 mol-% to about 25 mol-%, and (vi) about 17 mol-% to about 23 mol-% of cholesterol in paragraphs [0253] and [0254]. All these different ranges are disclosed as equally suitable alternatives. Importantly, there is no indication that the specific range of 30 mol-% to 40 mol-% of cholesterol would be preferred over the other ranges disclosed in paragraphs [0253] and [0254]. The amendment made to claim 1, limiting the content of cholesterol to "30 mol % to 40 mol %", therefore amounts to yet another arbitrary selection.

3.2.3 As explained above, the definitions of the cationic lipid in item (b) and of the non-cationic lipid in item (c) of granted claim 1 of the opposed patent are the result of at least three arbitrary selections, namely (i) the selection of the specific range of 50 mol-% to 65 mol-% for the content of the cationic lipid, (ii) the selection of a non-cationic lipid comprising "a mixture of phospholipid and cholesterol", and (iii) the selection of the specific range of 30 mol-% to 40 mol-% for the content of cholesterol. The combination of these arbitrarily selected features can, however, not be derived directly and unambiguously from the original application and therefore constitutes an inadmissible extension.

This conclusion is in accordance with established case law of the boards of appeal, which have consistently emphasized that a specific combination requiring a selection from at least two lists of alternatives must normally be regarded as "novel", i.e. as not disclosed in the corresponding document. This principle has been acknowledged and summarized, e.g., in decisions T 87/08 and T 727/00 as follows:

> "*It is established jurisprudence of the Boards of Appeal that subject-matter resulting from a specific combination requiring the selection of elements from at least two lists is normally regarded as novel (see e.g. T 12/81, point 13 of the reasons, OJ EPO 1982, 296).*" (T 87/08, reasons 3.2, last paragraph; emphasis added)

> "*Aus dieser Kombination jeweils eines Mitglieds aus zwei Listen von Merkmalen, welche durch keinen Hinweis in der ursprünglich eingereichten Anmeldung gestützt ist, resultiert ein Anspruchsgegenstand, der zwar denkgesetzlich von der ursprünglichen Anmeldung umfasst, aber in dieser individualisierten Form dort nicht offenbart war. Anspruch 1 des Hauptantrages hat daher allein aus diesem Grunde keine Stütze in der Beschreibung. (...) Anspruch 1 verstößt dementsprechend gegen Artikel 123 (2) EPÜ*" (T 727/00, reasons 1.1.4; emphasis added)

While the above-cited decision T 87/08 was concerned with the question of novelty, the fundamental principle regarding selections from at least two lists acknowledged in this decision must also be applied for assessing the admissibility of amendments under Art. 123(2) EPC. This is because the same standards must be applied when determining the disclosure-content of a document, whether it is a prior art document or the application or patent under consideration (as affirmed, e.g., in G 1/03, reasons 2.2.2, last paragraph, and T 5/08, reasons 9).

Thus, granted claim 1 of the opposed patent is inadmissibly extended because the definition of the cationic lipid and the non-cationic lipid in items (b) and (c) in claim 1 is the result of an inadmissible singling-out of features which have been arbitrarily selected and have not been disclosed in combination in the original application. This deficiency also applies to the further granted claims of the patent, which directly or indirectly refer back to granted claim 1. The opposed patent should thus be revoked under Arts. 100(c) and 123(2) EPC.

3.3 Granted dependent claim 8 is inadmissibly extended

Granted claim 8 recites two alternative features, namely that "(a) the cholesterol or derivative thereof comprises from 30 mol % to 35 mol % of the total lipid present in the particle", or "(b) the cholesterol or derivative thereof comprises from 32 mol % to 36 mol % of the total lipid present in the particle and the phospholipid comprises from 3 mol % to 15 mol % of the total lipid present in the particle". Both of these alternative features (a) and (b) were added in the course of the examination proceedings and do not have any counterpart in the original claims of the underlying application.

The original application fails to provide any basis for the content of 30 mol-% to 35 mol-% of cholesterol or a derivative thereof, which is recited in alternative (a) of granted claim 8. In particular, this feature is not directly and unambiguously derivable from paragraph [0130] or [0253] of the original application for the same reasons as discussed in connection with granted claim 1 in section 3.1 above.

Moreover, the original application likewise fails to disclose the feature defined in alternative (b) of granted claim 8. In this regard, we note that paragraph [0130] on pages 27 to 28 of the application discloses an extensive number of different ranges for the content of cholesterol or a derivative thereof, and also for the content of the phospholipid. However, this passage fails to disclose the specific range of 32 mol-% to 36 mol-% for cholesterol or a derivative thereof in combination with the specific range of 3 mol-% to 15 mol-% for the phospholipid, which has been inadmissibly singled out from paragraph [0130] of the original application. It follows that granted dependent claim 8 contravenes the requirements of Art. 123(2) EPC for these additional reasons.

3.4 Granted dependent claim 10 is inadmissibly extended

The features recited in granted dependent claim 10 seem to be based on original independent claim 33 combined with original dependent claim 38 of the application underlying the opposed patent. However, due to the back-reference to granted claim 1, the subject-matter of granted dependent claim 10 is different from that of original claims 33 and 38, as explained in the following, and therefore inadmissibly extends beyond the content of the original application.

Specifically, granted claim 1 requires the presence of a "non-cationic lipid (...) comprising a mixture of a phospholipid and cholesterol or a derivative thereof". It follows from this wording that the phospholipid as well as the derivative of cholesterol must be non-cationic lipids. This is a relevant distinction because phospholipids and cholesterol derivatives can, in principal, be cationic or non-cationic. Since granted claim 10 is dependent on granted claim 1, this requirement also applies to the phospholipid and the derivative of cholesterol recited in granted claim 10.

In contrast thereto, original independent claim 33 of the underlying application recites as component (c) "a mixture of a phospholipid and cholesterol or a derivative thereof" –

without requiring the phospholipid or the derivative of cholesterol to be non-cationic lipids. Original dependent claim 38 recites specific contents of these lipid components but does not require the phospholipid or the derivative of cholesterol to be non-cationic lipids, either.

Consequently, granted dependent claim 10 does not relate to the same subject-matter as original claims 33 and 38. The other passages of the original application likewise fail to provide a basis for the specific subject-matter of granted claim 10, which is therefore inadmissibly extended.

4. PRIORITY

4.1 The priority claim of the opposed patent is invalid

The granted claims of the opposed patent are not entitled to the priority of US 61/045,228 filed on April 15, 2008, as explained in the following.

The priority application US 61/045,228 was filed in the name of three joint applicants, i.e. (i) Ian MacLachlan, (ii) Edward Yaworski, and (iii) Kieu Lam. This is evidenced by the enclosed filing receipt for the priority application (D6). Moreover, the official register of the USPTO indicates that this priority application has not been assigned to any successor in title (cf. the corresponding register excerpt enclosed as D7).

In contrast to the priority application, the PCT application underlying the opposed patent (i.e., WO 2009/127060) was filed in the name of "Protiva Biotherapeutics, Inc." as the sole applicant (for all designated states except US), which is evidenced by the enclosed PCT request (D8).

The applicant of the PCT application underlying the opposed patent is thus different from the joint applicants of the priority application, and there is no evidence on file that the priority right would have been transferred from the joint applicants of the priority application to the applicant of the PCT application underlying the opposed patent before the latter's filing date. For at least this reason, the priority claim of the opposed patent is invalid. The effective date for the assessment of patentability of all granted claims is therefore the filing date of the opposed patent, i.e. April 15, 2009.

5. NOVELTY

5.1 Granted claim 1 of the patent lacks novelty over US 2008/0020058 (D1)

5.1.1 US 2008/0020058 (D1) relates to lipid nanoparticle-based compositions for the delivery of biologically active molecules (cf. title of D1).

A number of exemplary lipid nanoparticle (LNP) formulations are disclosed in Table IV on pages 101 to 102 of D1, including the specific formulation "L109":

TABLE IV

Lipid Nanoparticle (LNP) Formulations

Formulation #	Composition	Molar Ratio
L109	DMOBA/DSPC/Cholesterol/2KPEG-Chol, N/P ratio of 2	50/20/28/2

N/P ratio = Nitrogen:Phosphorous ratio between cationic lipid and nucleic acid

(excerpt from Table IV on pages 101 to 102 of D1)

As disclosed in Table IV, the lipid nanoparticle formulation L109 contains the lipids DMOBA, DSPC, cholesterol and 2KPEG-Chol at a molar ratio of 50/20/28/2. The molar contents of these lipids add up to 100 parts and thus reflect the percent molar content (mol-%) of each lipid with respect to the total lipid in the formulation.

D1 explains that a "biologically active molecule", specifically a "nucleic acid molecule", can be formulated as L109 (cf. page 16, paragraph [0123] of D1). In this regard, D1 further indicates in Table IV that the formulation L109 has an "N/P ratio of 2", which refers to the nitrogen (N) to phosphorus (P) ratio between cationic lipid and nucleic acid (cf. page 102, bottom of Table IV in D1), and thereby confirms that the corresponding lipid nanoparticle contains a nucleic acid.

D1 thus discloses a lipid nanoparticle L109 which contains:

- a nucleic acid;
- 50 mol-% of DMOBA (i.e., N,N-dimethyl-3,4-dioleyloxybenzylamine; structure depicted on page 104 of D1), which is a cationic lipid (as explicitly mentioned, e.g.,

on page 16, paragraph [0119] of D1, and also on page 12, line 50 of the opposed patent);

- 20 mol-% of DSPC (i.e., distearoylphosphatidylcholine; structure depicted on page 104 of D1), which is a neutral (non-cationic) phospholipid (as acknowledged, e.g., on page 16, paragraph [0121] of D1, and also on page 13, line 30 and page 32, lines 20 to 21 of the opposed patent);
- 28 mol-% of cholesterol; and
- 2 mol-% of 2KPEG-Chol, which is PEG 2000 (2KPEG) conjugated to cholesterol (cf. page 16, paragraph [0122] and the structure depicted on page 104 of D1).

This lipid nanoparticle L109 disclosed in D1 anticipates granted claim 1 of the opposed patent, as will be explained in the following.

5.1.2 The lipid nanoparticle L109 of D1 comprises a nucleic acid, as explained in section 5.1.1 above, and thus fulfills the requirement specified in item (a) of granted claim 1 of the patent. It also comprises 50 mol-% of the cationic lipid DMOBA, so that the feature defined in item (b) of granted claim 1 is likewise fulfilled.

The lipid nanoparticle L109 further comprises 2 mol-% of "2KPEG-Chol", i.e. PEG 2000 (2KPEG) conjugated to cholesterol. Notably, this lipid is both a "conjugated lipid that inhibits aggregation of particles", as referred to in item (d) of granted claim 1 (which is explicitly acknowledged on page 8, line 58 of the opposed patent itself), and a derivative of cholesterol. As a consequence, the amount of 2 mol-% of 2KPEG-Chol contained in L109 can be notionally split into 0.5 mol-% of a "conjugated lipid" (2KPEG-Chol), whereby the feature defined in item (d) of granted claim 1 is fulfilled, and 1.5 mol-% of a "cholesterol derivative" (2KPEG-Chol). These 1.5 mol-% of a cholesterol derivative (2KPEG-Chol) together with the 28 mol-% of cholesterol contained in the lipid nanoparticle L109 result in a total of 29.5 mol-% of cholesterol and cholesterol derivative.

While granted claim 1 of the opposed patent requires from 30 mol-% to 40 mol-% of cholesterol or a derivative thereof, the lower limit of 30 mol-% fails to distinguish the claimed particle from the lipid nanoparticle L109 of D1 which contains 29.5 mol-% of cholesterol and cholesterol derivative. This is because granted claim 1 does not require

"30.0" mol-% of cholesterol or a derivative thereof, but merely "30" mol-% (without any decimal places).

In this regard, we wish to emphasize that the degree of precision defined by the value of 30 mol-% (without decimal places), which the patentee deliberately chose to recite in granted claim 1, has to be taken into account when interpreting this claim. This holds true all the more when considering that the opposed patent does, in fact, use a different (higher) degree of precision when specifying the cholesterol content in other passages; cf., e.g., page 44, Table 2 of the patent where samples 7, 8 and 10 are disclosed to have cholesterol contents of 64.0 mol-%, 60.0 mol-% and 32.0 mol-%, respectively. Moreover, even the granted claims of the patent use decimal places where it is intended to express a corresponding degree of precision, as reflected, e.g., in granted claim 10 which recites values of 57.1, 7.1, 34.3 and 1.4 mol-% for the contents of the different lipid components. It is thus evident that values such as 30 mol-% and 30.0 mol-% for the content of a lipid component in the opposed patent indicate different degrees of precision and thus have a different technical meaning.

In order to compare the above-mentioned value of 29.5 mol-% (for the combined content of cholesterol and cholesterol derivative in the lipid nanoparticle L109 of D1) with the corresponding lower limit of 30 mol-% recited in granted claim 1, the level of precision of this lower limit of 30 mol-% must hence be taken into account. If the same level of precision is applied to the content of 29.5 mol-% of cholesterol and cholesterol derivative in the lipid nanoparticle L109 of D1, the value of 29.5 mol-% must be rounded to the next integer for the purpose of comparison to granted claim 1. In accordance with regular rules for the rounding of numbers, the value of 29.5 mol-% is thus to be rounded up to 30 mol-%. It follows that the lipid nanoparticle L109 of D1 does, in fact, also fulfill the feature of granted claim 1 requiring 30 mol-% to 40 mol-% of cholesterol or a derivative thereof.

We further wish to remark that this reasoning is fully in accordance with established case law of the boards of appeal. In an exemplary manner only, we refer to the following explanations of the competent boards in decisions T 871/08 (of 8 December 2011), T 2203/14, T 1186/05, T 770/00, T 1735/09, T 234/09 and T 83/13:

"*The respondent [patentee] argued that the claimed subject-matter was novel, because the value 2.996 was lower than the lower limit of 3:1 defined in claim 1 at issue.*
This argumentation is not accepted by the board. When comparing a value from the state of the art (in the present case the value "2.996") – with those claimed (here the range of values of "from 3:1 to 9:1"), the state of the art value has to be given the same accuracy as the one claimed. In the case at issue, the values in the claims have been quoted without any digit after the comma, which means that for comparison purposes, the value 2.996 has to be rounded up to 3, which thus falls into the range of the claimed values. This judgement is in agreement with the jurisprudence of the boards of appeal (in particular T 1186/05, points 3.6.1 to 3.6.5 of the reasons; T 0708/05, point 3 of the reasons)." (T 871/08 of 8 December 2011, reasons 2.3; emphasis added)

"*It is accepted jurisprudence that when comparing a value from the state of the art with a claimed value, the state of the art value has to be given the same accuracy as the one claimed (T 871/08, Reasons 2.3 and decisions cited therein). Applying this teaching mutatis mutandis to the present case means that prior art disclosing a value of 5.2 would be considered relevant for novelty with respect to the upper end value of 5 as present in the claim as filed, but not with respect to the value of 5.0 as present in claim 1 as granted. Therefore, "approximately 5.0" and "approximately 5" can – in the present context – not have the same meaning. This is also in line with T 175/97 (Reasons 2.7), where it is indicated that the value of 0.8 mol present in the claim has to be interpreted as 0.75 to 0.84 mol.*" (T 2203/14, reasons 1.2.1; emphasis added)

"*For the definition of the density range the Respondent [Patentee] has chosen to use only two decimal places. This implies that a comparison with the prior art identifying three decimal places can only be made if the prior art values are also reduced to two decimals, that is to say rounded. The skilled person reading D1 would thus be obliged to round the disclosed value up to 0.89 for comparison (see decision T 0708/05 of 14 February 2007, not published in OJ EPO, under point 3 of the Reasons).*" (T 1186/05, reasons 3.6.5; emphasis added)

"*The Board considers that (...) calculations using 60% as value lead to total amounts for the emulsifier system of 0.403 (see table 3 ...). The percentages given in claim 1 give only the first decimal place and so are less precise than when figures with three decimal places are used. Accordingly, when the values obtained by adding specific figures turn out to have three decimal places, 0.403 for example, they have to be rounded down, ie 0.403% equates approximately to 0.4% and hence it cannot be concluded that this figure is not encompassed in the range from 0.1 to 0.4 wt.% as stated in claim 1. The Board is satisfied that the amount of emulsifier system employed in formulations D and E of Example 1 and F and G of Example 2 fall within*

the claimed scope." (T 770/00, reasons 2, eighth-to-last paragraph; emphasis added)

"*It has not been challenged by the appellant [patentee] that example 3 of document D5 (EP A 1 043 064) discloses (...). The molar ratio of ethylene to acetic acid obtained is 1.42:1 (...), and hence falls within the claimed range, since 1.42 shall read 1.4 when rounded to a significant figure less (see decision T 871/08, point 2.3 of the reasons, not published in the Official Journal of the EPO).*" (T 1735/09, reasons 3; emphasis added)

"*Le document (...) divulgue la préparation de laines minérales bio-solubles. Plus particulièrement, l'exemple 3 de ce document décrit la préparation d'une laine minérale ayant la composition suivante (...).*
Selon la requérante [titulaire], cette laine minérale se distingue de la laine minérale revendiquée par sa teneur en MgO de 5,2 %, qui serait supérieure à la teneur maximale en MgO prescrite par la revendication 1 en cause, à savoir supérieure à 5 %. Elle n'a pas fait valoir d'autres différences.
La chambre ne partage pas l'avis de la requérante [titulaire] pour les raisons suivantes :
D'une part, force est de constater que dans les revendications en cause ainsi que dans les revendications telles que délivrées, la composition des fibres est définie au moyen de plages numériques de pourcentages pondéraux des composants. Il est incontesté que ces compositions peuvent sans problème être définies de façon plus précise, voir par exemple les résultats d'analyse indiqués dans les tableaux 1 et 2 du brevet. La requérante/titulaire du brevet a cependant choisi d'exprimer la plupart des bornes desdites plages par des nombres entiers. Cependant, certaines desdites bornes sont exprimées sous forme de nombres décimaux avec un chiffre après la virgule (cf. revendications 2 à 4 en cause), et ceci même pour des cas où ledit chiffre après la virgule est un zéro. Dans le cadre des revendications, la requérante fait donc expressément une distinction entre un nombre entier N et le nombre décimal N,0.
Au vu de ce qui précède, la chambre considère que dans le contexte du brevet en cause, l'homme du métier comprendrait que les nombres entiers définissant les bornes des plages numériques dans la revendication 1 ne sont pas à comprendre comme des nombres entiers au sens mathématique, c'est-à-dire pouvant être exprimés sous forme de nombres décimaux du type N,000..., tel qu'affirmé par la requérante. Sinon, les bornes des plages de la revendication 1 auraient toutes été exprimées sous la forme N,0.
Lesdits nombres entiers sont donc à considérer, au contraire, comme des bornes exprimées délibérément sous une forme ayant un degré de précision inférieur à celui des nombres décimaux mentionnés dans le brevet. Par conséquent, lesdits nombres entiers couvrent également les valeurs décimales qui résultent en lesdits nombres entiers lors de l'application des règles de l'arrondi.

Une approche analogue a déjà été suivie par les chambres dans des cas comparables, voir par exemple T 1186/05 du 6 décembre 2007, points 3.6.5 et 3.6.6 des motifs. (...).
Sur la base des réflexions précédentes, la chambre conclut que le pourcentage pondéral de 5,2 % de MgO indiqué dans l'exemple 3 du document D3, arrondi afin de permettre la comparaison, ne peut pas être distingué de la borne supérieure de 5 % de MgO prescrit par la revendication 1.
Ceci revient à dire que ledit exemple 3 divulgue une laine minérale présentant toutes les caractéristiques de la revendication 1. L'objet de la revendication 1 n'est donc pas nouveau (Articles 52(1) et 54(1)(2) CBE)." (T 234/09, reasons 4.1 to 4.4; emphasis added)

In English translation: "*The document (...) discloses the preparation of bio-soluble mineral wools. In particular, example 3 of this document describes the preparation of a mineral wool having the following composition (...).*
According to the appellant [patentee], this mineral wool differs from the claimed mineral wool by its MgO content of 5.2%, which is greater than the maximum value of MgO defined in claim 1 at issue, i.e. greater than 5%. It has not asserted any other differences.
The board does not share the opinion of the appellant [patentee], for the following reasons:
To begin with, it has to be noted that in the claims under consideration as well as in the claims as granted the composition of the fibers is defined by means of numerical ranges of weight percent of the components. It is uncontested that these compositions can easily be defined in a more precise manner, see for example the results of the analysis indicated in tables 1 and 2 of the patent. The appellant/patentee has nevertheless chosen to express most of the boundaries of said ranges by integers. However, some boundaries are expressed in the form of decimal numbers with a figure after the decimal point (cf. claims 2 to 4 under consideration), and this even in cases where the figure after the decimal point is a zero. In the context of the claims, the appellant thus expressly makes a distinction between an integer N and the decimal number N.0.
In view of the foregoing, the board considers that in the context of the patent under consideration the skilled person would understand that the integers defining the boundaries of the numerical ranges in claim 1 are not to be understood as integers in the mathematical sense, i.e. as numbers which can be expressed in the form of decimal numbers of the type N.000..., as asserted by the appellant. Otherwise, the boundaries of the ranges of claim 1 would all have been expressed in the form N.0.
Said integers are thus to be considered, to the contrary, as boundaries that have deliberately been expressed in a form having a lower degree of precision than the decimal numbers mentioned in the patent. In consequence, said integers also cover the decimal values that result in said integers when applying the rules of rounding.

An analogous approach has already been applied by the boards in similar cases, see for example T 1186/05 of 6 December 2007, points 3.6.5 and 3.6.6 of the reasons. (...)
Based on the above considerations, the board concludes that the weight percentage of 5.2% of MgO indicated in example 3 of document D3, when rounded in order to allow a comparison, cannot be distinguished from the upper limit of 5% of MgO prescribed in claim 1.
This means that said example 3 discloses a mineral wool having all the features of claim 1. The subject-matter of claim 1 is thus not novel (Articles 52(1) and 54(1)(2) EPC)." (courtesy translation of T 234/09, reasons 4.1 to 4.4; emphasis added)

"*Le terme "une quantité inférieure à 15% en poids" comprend ainsi également des valeurs de concentration avec une décimale ou plus à partir de laquelle la précision des techniques de mesure ou la simple application des règles de l'arrondi des nombres donneraient comme valeur la valeur entière de "15% en poids"*." (T 83/13, reasons 1.2, last paragraph; emphasis added)

In English translation: "*The term "an amount of less than 15% by weight" thus also comprises concentration values with one or more decimal places from which the accuracy of the measurement techniques or the simple application of the rules of rounding of numbers would give as value the integer of "15% by weight"*." (courtesy translation of T 83/13, reasons 1.2, last paragraph; emphasis added)

The above-cited case law of the boards of appeal clearly confirms that it is appropriate, and indeed necessary, to consider the degree of precision of the lower limit of 30 mol-% of cholesterol or a derivative thereof, which is recited in granted claim 1 of the opposed patent, and – in consequence – to round the value of 29.5 mol-% (for the content of cholesterol and cholesterol derivative in the lipid nanoparticle L109 disclosed in D1) to the same level of precision, i.e. to 30 mol-%, for a meaningful comparison with claim 1. The feature of granted claim 1 requiring the presence of 30 mol-% to 40 mol-% of cholesterol or a derivative thereof thus fails to distinguish this claim from the lipid nanoparticle L109 of D1.

Finally, we note that the lipid nanoparticle L109 of D1 contains 29.5 mol-% of cholesterol and cholesterol derivative (2KPEG-Chol) as well as 20 mol-% of the phospholipid DSPC, which results in a total of 49.5 mol-% of non-cationic lipid. This is within the range of "up to 49.5 mol-%" of non-cationic lipid, as required in item (c) of granted claim 1. Moreover, these components of the lipid nanoparticle L109 of D1 also constitute a "mixture of a phospholipid and cholesterol or a derivative thereof" in

accordance with item (c) of granted claim 1. All of the features defined in item (c) of claim 1 of the patent are hence fulfilled.

In view of the above explanations, it is evident that granted claim 1 of the opposed patent lacks novelty in view of D1.

5.2 Granted claims 2 to 8 and 11 to 15 lack novelty over US 2008/0020058 (D1)

Granted claims 2 to 8 and 11 to 15 of the opposed patent all refer directly or indirectly back to claim 1 and likewise lack novelty over US 2008/0020058 (D1), particularly in view of the disclosure relating to the lipid nanoparticle L109 in D1. We refer to the corresponding explanations in section 5.1 above, and will discuss the additional features specified in granted claims 2 to 8 and 11 to 15 in the following.

5.2.1 Granted dependent claim 2 of the opposed patent requires that the nucleic acid in the claimed particle comprises a small interfering RNA (siRNA).

The lipid nanoparticle L109 of D1 contains a nucleic acid, as discussed in section 5.1.1 above. D1 specifically mentions "a siNA" as an example in this connection (cf. page 16, paragraph [0123] of D1). Moreover, D1 explicitly teaches that short interfering nucleic acids (siNA) include short interfering RNAs (siRNAs), and that these nucleic acids can be delivered across cellular membranes in accordance with the invention of D1 (cf. paragraph [0017], first full sentence on page 4 of D1). Granted claim 2 of the patent is therefore anticipated by D1.

5.2.2 Granted dependent claim 3 of the patent refers back to claim 2 (cf. section 5.2.1 above) and further recites in alternative (b) that the siRNA comprises at least one modified nucleotide.

D1 likewise discloses that "siNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically-modified nucleotides" (cf. paragraph [0363] on page 52, left-hand column of D1). Granted claim 3 of the opposed patent thus likewise lacks novelty in view of D1.

5.2.3 Granted dependent claim 4 recites in alternative (c) that the cationic lipid comprises from 50 mol-% to 60 mol-% of the total lipid present in the claimed particle.

The lipid nanoparticle L109 disclosed in D1 comprises 50 mol-% of the cationic lipid DMOBA, as explained in section 5.1.1 above, which falls within the range of 50 mol-% to 60 mol-% required in alternative (c) of granted claim 4 of the opposed patent. Also this claim is consequently anticipated by D1.

5.2.4 Granted dependent claim 5 requires in alternative (a) that the "conjugated lipid that inhibits aggregation of particles" comprises a polyethyleneglycol (PEG)-lipid conjugate.

The lipid nanoparticle L109 of D1 comprises "2KPEG-Chol" which is a PEG-lipid conjugate, as discussed in section 5.1.2 above. D1 consequently destroys the novelty of granted claim 5 of the patent.

5.2.5 Granted dependent claim 6 recites a functional feature in alternative (a), namely that "the nucleic acid in the nucleic acid-lipid particle is not substantially degraded after incubation of the particle in serum at 37°C for 30 minutes".

We note that this functional feature is either a necessary consequence of the structural features defined in granted claim 1, in which case it will also be fulfilled by the lipid nanoparticle L109 of D1 (which falls within the scope of granted claim 1), or else it is a mere desideratum defining a result to be achieved, in which case the claim would be insufficiently disclosed or lack inventive step (cf., e.g., T 661/09, catchword) in view of the teaching relating to serum stability in D1 (cf. page 3, paragraph [0015] and page 23, paragraph [0179]). Also granted claim 6 thus lacks patentability.

5.2.6 Granted dependent claim 7 requires in alternative (a) that the phospholipid comprises DPPC, DSPC or a mixture thereof. The lipid nanoparticle L109 of D1 contains the phospholipid DSPC and thus also anticipates granted claim 7.

5.2.7 Granted dependent claim 8 specifies in alternative (a) that the claimed particle comprises 30 to 35 mol-% of cholesterol or a derivative thereof. This feature is anticipated by the lipid nanoparticle L109 of D1 for the same reasons as detailed in section 5.1.2 above.

5.2.8 Granted claim 11 relates to a pharmaceutical composition comprising the nucleic acid-lipid particle of any one of the preceding claims and a pharmaceutically acceptable carrier. This claim likewise lacks novelty in view of D1 (cf., e.g., page 47, paragraph [0339] and page 79, paragraph [0596] of D1).

5.2.9 Granted claim 12 is directed to a method for introducing a nucleic acid into a cell, comprising contacting the cell *in vitro* with the nucleic acid-lipid particle of any one of granted claims 1 to 10. This method is anticipated, e.g., by page 25, paragraph [0200] and page 74, paragraph [0560] of D1.

5.2.10 Granted claim 13 refers to the nucleic acid-lipid particle of any one of granted claims 1 to 10 "for use in a method for the *in vivo* delivery of a nucleic acid, the method comprising administering said nucleic acid-lipid particle to a mammalian subject".

While this claim is drafted in the format of a medical use claim, it does not actually recite any therapeutic use. The nucleic acid comprised is the corresponding particle is not specified to be a *therapeutic* nucleic acid, and the *in vivo* delivery of any (undefined) nucleic acid does not necessarily constitute a *therapeutic* treatment. The recited use "for the *in vivo* delivery of a nucleic acid" must therefore be interpreted as merely requiring that the claimed particle has to be suitable for *in vivo* delivery, which is fulfilled by the lipid nanoparticle L109 of D1.

Notwithstanding the above, D1 also discloses a corresponding *in vivo* delivery, e.g., on page 74, paragraph [0560] and page 79, paragraph [0598], and thus anticipates granted claim 13 for this further reason.

5.2.11 Granted dependent claim 14 refers back to granted claim 13 and further specifies the route of administration. Corresponding routes of administration are also disclosed in D1 (cf. page 79, paragraph [0598] of D1), so that this claim lacks novelty as well.

5.2.12 Granted claim 15 relates to the nucleic acid-lipid particle of any one of granted claims 1 to 10 for use in a method for treating a disease or disorder in a mammalian subject. This claim lacks novelty, e.g., in view of page 79, paragraphs [0596] and [0598] of D1.

6. INVENTIVE STEP

6.1 Granted claim 1 is obvious in view of US 2008/0020058 (D1), optionally in combination with WO 2006/053430 (D2), Lin 2003 (D3) or Ahmad 2005 (D4)

Further to our explanations in section 5.1 above, concerning the lack of novelty of granted claim 1 of the opposed patent over D1, we will explain in the following why granted claim 1 is also obvious in view of D1 alone, and in view of D1 in combination with any of D2, D3 or D4.

6.1.1 For the assessment of inventive step, the problem-solution-approach requires as a first step the identification of the closest prior art document. In accordance with established case law of the boards of appeal, the closest prior art is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (cf., e.g., T 1492/09, reasons 31).

The opposed patent aims at providing nucleic acid-lipid particles as a delivery system for introducing nucleic acids such as siRNA into cells (cf. page 2, paragraph [0009] and page 3, paragraph [0015] of the patent).

US 2008/0020058 (D1) relates to lipid nanoparticle-based compositions for the delivery of biologically active molecules into cells, including nucleic acids such as siRNA (cf. title, page 1, paragraph [0003], and pages 3 to 4, paragraphs [0017] to [0020] of D1). The compositions taught in this document are reported to have an improved efficiency of delivery and to be stable in circulation (cf. page 3, paragraph [0015], page 4, paragraph [0017], and page 23, paragraph [0179] of D1). Document D1 thus relates to the same basic objective as the opposed patent and, consequently, qualifies as closest prior art for the assessment of inventive step.

6.1.2 The closest prior art document D1 discloses and exemplifies lipid nanoparticle compositions that are indistinguishable (cf. section 5.1 above) or extremely similar to the nucleic acid-lipid particle defined in granted claim 1 of the opposed patent, as they contain the same lipid components in the same or almost the same amounts as required in granted claim 1.

In particular, D1 describes the lipid nanoparticle formulations L054, L073, L097 and L109, which are most similar to the nucleic acid-lipid particle of granted claim 1 of the opposed patent and therefore constitute the relevant point of reference for the analysis of inventive step (cf., e.g., T 675/11, reasons 2.4 to 2.5).

These formulations contain "a biologically active molecule (e.g. a polynucleotide such as a siNA, miRNA, … or other nucleic acid molecule)" as well as a specific cationic lipid, neutral lipid, cholesterol, and PEG-conjugated lipid in a defined molar ratio (cf. page 16, paragraph [0123] and pages 101 to 102, Table IV of D1). The specific lipid composition of these formulations is summarized in the following:

TABLE IV

Lipid Nanoparticle (LNP) Formulations

Formulation #	Composition	Molar Ratio
L054	DMOBA/DSPC/Chol/2KPEG-DMG	50/20/28/2
L073	pCLinDMA or CLin DMA/DMOBA/DSPC/ Chol/2KPEG-DMG	25/25/20/ 28/2
L097	DMLBA/DSPC/Cholesterol/2KPEG-DMG	50/20/28
L109	DMOBA/DSPC/Cholesterol/2KPEG-Chol, N/P ratio of 2	50/20/28/2

N/P ratio = Nitrogen:Phosphorous ratio between cationic lipid and nucleic acid

(excerpt from Table IV on pages 101 to 102 of D1)

The molar ratios of the lipids in each formulation described in Table IV of D1 add up to 100 parts and thus indicate the percent molar content (mol-%) of each lipid with respect to the total lipid in the formulation. This is in conformance with the general description of D1, which indicates the amounts of each lipid component as "% of the total lipid present in the formulation" (cf., e.g., page 21, paragraphs [0157] to [0161] of D1), and is also confirmed by the indication of percentages in Figures 25 to 28 of D1 (which relate to exemplary formulations of Table IV). While the molar content of "2KPEG-DMG" in L097 is accidentally missing in Table IV, it is directly apparent that this lipid component is present in formulation L097 in an amount of 2 mol-% (molar ratio of 50/20/28/2), which is the amount resulting in a total of 100%.

Thus, formulation L054 disclosed in D1 contains:

- a biologically active molecule, which is specifically a nucleic acid molecule;
- 50 mol-% of the cationic lipid DMOBA (N,N-dimethyl-3,4-dioleyloxybenzylamine; cf. page 104 of D1);
- 20 mol-% of the neutral (non-cationic) phospholipid DSPC (distearoylphosphatidyl-choline; cf. page 104 of D1);
- 28 mol-% of cholesterol ("Chol"); and
- 2 mol-% of the conjugated lipid 2KPEG-DMG (2KPEG-n-dimyristylglycerol; cf. page 105 of D1)

(cf. page 16, paragraph [0123], page 17, paragraph [0128], page 23, paragraph [0182], and page 101, Table IV of D1).

As can be seen, the lipid nanoparticle formulation L054 of D1 contains all the components required in granted claim 1 of the opposed patent. For completeness, we note that the opposed patent itself refers to DMOBA as an exemplary cationic lipid (cf. page 12, line 50 of the patent), to DSPC as an exemplary non-cationic phospholipid (cf. page 13, line 30 and page 32, lines 20 to 21 of the patent), and to 2KPEG-DMG as an exemplary PEG-lipid conjugate, i.e. a "conjugated lipid that inhibits aggregation of particles" (cf. page 15, lines 4 to 5 and page 33, line 28 of the patent). Moreover, these components of the lipid nanoparticle L054 also fulfill all of the quantitative requirements recited in granted claim 1 of the patent, with the sole exception that granted claim 1 requires 30 mol-% to 40 mol-% of cholesterol or a derivative thereof, whereas the lipid nanoparticle L054 of D1 contains 28 mol-% of cholesterol.

Formulation L073 of D1 contains:

- a biologically active molecule, which is specifically a nucleic acid molecule;
- 25 mol-% of the cationic lipid CLinDMA (3-dimethylamino-2-(cholest-5-en-3-beta-oxybutan-4-oxy)-1-(cis,cis-9,12-octadecadienoxy)propane; cf. page 102 of D1) or pCLinDMA (cf. page 103 of D1);
- 25 mol-% of the cationic lipid DMOBA;
- 20 mol-% of the neutral (non-cationic) phospholipid DSPC;
- 28 mol-% of cholesterol ("Chol"); and
- 2 mol-% of the conjugated lipid 2KPEG-DMG

(cf. page 16, paragraph [0123], page 17, paragraph [0129], page 23, paragraph [0184], page 101, Table IV, and Figure 9 of D1).

The lipid nanoparticle formulation L073 of D1 likewise contains all the components required in granted claim 1 of the patent. We note that CLinDMA is mentioned as an exemplary cationic lipid in the opposed patent (cf. page 12, lines 49 to 50, page 13, line 1, and page 30, lines 39 to 40), and that the total content of the cationic lipids CLinDMA and DMOBA in L073 is 50 mol-%. The lipid components of the nanoparticle L073 thus also fulfill all the corresponding quantitative requirements of granted claim 1 of the patent, with the sole exception that granted claim 1 requires 30 mol-% to 40 mol-% of cholesterol or a derivative thereof, whereas the lipid nanoparticle L073 of D1 contains 28 mol-% of cholesterol.

Formulation L097 of D1 contains:

- a biologically active molecule, which is specifically a nucleic acid molecule;
- 50 mol-% of the cationic lipid DMLBA (cf. page 104 of D1);
- 20 mol-% of the neutral (non-cationic) phospholipid DSPC;
- 28 mol-% of cholesterol; and
- 2 mol-% of the conjugated lipid 2KPEG-DMG

(cf. page 16, paragraph [0123], page 24, paragraph [0192] and page 101, Table IV of D1).

Also the lipid nanoparticle formulation L097 of D1 contains all the components required in granted claim 1 of the patent, in the specific amounts required in claim 1, with the only exception that granted claim 1 requires 30 mol-% to 40 mol-% of cholesterol or a derivative thereof, while the lipid nanoparticle L097 of D1 contains 28 mol-% of cholesterol.

Formulation L109 of D1 has already been discussed in detail in connection with novelty. To avoid unnecessary repetitions, we refer to our corresponding explanations in section 5.1 above.

6.1.3 The nucleic acid-lipid particle of granted claim 1 of the opposed patent is thus distinguished from the lipid nanoparticles L054, L073 and L097 taught in D1 merely in that it requires 30 mol-% to 40 mol-% of cholesterol or a derivative thereof, while the lipid nanoparticles L054, L073 and L097 of D1 each contain 28 mol-% of cholesterol.

This difference does not result in any particular technical effect, let alone any advantageous effect or any improvement.

To begin with, we would like to stress that the opposed patent completely fails to provide any disclosure, let alone any experimental results or other tangible evidence, which would demonstrate any particular technical effect resulting from this slight difference in the content of cholesterol. Indeed, the patent does not even make any corresponding allegation.

In the absence of any tangible evidence to the contrary, however, it must be assumed that the minuscule difference between the minimum content of cholesterol required in granted claim 1 of the patent (30 mol-%) and the content of cholesterol in the above-mentioned lipid nanoparticles of D1 (28 mol-%) does not result in any particular technical effect.

In this respect, it must be kept in mind that, as a general rule, each party to opposition proceedings carries the burden of proof for the facts it alleges. Therefore, if the patentee were to allege that the above-mentioned distinguishing feature resulted in any advantageous effect or any kind of improvement (which we contest), they would bear the burden of proof.

This principle has been consistently acknowledged in the case law of the boards of appeal, including in particular the notion that the burden of proof for an alleged advantageous effect or improvement falls on the patentee if they wish to rely on any such effect or improvement in the discussion of inventive step. We refer to the following explanations in decisions T 1392/04, T 355/97, T 75/02, T 2034/09 and T 603/05 in this regard:

> "*However, where the proprietor alleges that the problem to be solved by the subject matter claimed over the closest prior art is to obtain an improvement of some particular property of this closest prior art, the legal burden of proof that there is an improvement is on the proprietor. A mere allegation that there is an improvement is not sufficient, there should be at least some experimental evidence that the particular property of the prior art is improved, when this closest prior art is modified in the minimum way necessary to fall under the subject matter now claimed. Experimental evidence is required to show that the improvement is necessarily attributable to the difference between the claimed subject matter and the closest prior art. The instances of the EPO should also be satisfied that this evidence makes it plausible that the problem has been solved over the whole range of the subject matter claimed.*" (T 1392/04, reasons 20; emphasis added)

"*Each of the parties to the opposition-appeal proceedings carries the burden of proof for the facts it alleges (following T 270/90, OJ EPO 1993, 725). If the Proprietor of the patent alleges the fact that the claimed invention improves a technical effect, then the burden of proof for that fact rests upon him. The unverifiable statement in the specification of the patent in suit that the technical effect is improved which is devoid of any corroborating evidence, does not discharge the Proprietor from his burden of proof with the consequence that the unsubstantiated allegation is not to be taken into account (point 2.5.1 of the reasons).*" (T 355/97, catchword; emphasis added)

"*Indessen trägt gemäß ständiger Rechtsprechung der Beschwerdekammern jede am Verfahren beteiligte Partei die Beweislast für die von ihr geltend gemachten Tatsachenbehauptungen. Wenn eine Partei, deren Sachvortrag auf der behaupteten Tatsache beruht, dieser Beweislast nicht genügt, so unterliegt sie insoweit (siehe...). Im vorliegenden Fall behauptet der Beschwerdegegner [Patentinhaber] die Tatsache, dass die beanspruchte Erfindung die Selektivität des Herstellungsverfahrens verbessere. Daher liegt die Beweislast für die Glaubhaftigkeit dieser Tatsachenbehauptung auch bei ihm.*" (T 75/02, reasons 3.4.1; emphasis added)

"*According to the jurisprudence of the Boards of Appeal, alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underlying the invention (see e.g. decision T 20/81, OJ EPO 1982, 217, point 3, last paragraph of the reasons).*" (T 2034/09, reasons 5.4.4; emphasis added)

"*According to the established case law of the Boards of Appeal, alleged advantages to which the Patent Proprietor merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step.*" (T 603/05, reasons 17)

Moreover, any hypothetical advantage or improvement would have to be obtained within the full scope of granted claim 1. This, however, seems highly implausible in view of the broad definitions of the different lipid components in granted claim 1 and the fact that the efficiency of nucleic acid-lipid nanoparticles was known to be dependent on the specific lipids used. This is also reflected in Lin 2003 (D3), Ahmad 2005 (D4) and Gao 2007 (D5), which highlight the relevance of the membrane charge density and lipid/DNA charge ratio for the transfection efficiency of liposome–DNA complexes and illustrate that lipids having different structures can yield decidedly different results (cf., in particular, pages 3309 to 3313 and Figure 4 of D3; page 743, left-hand column, second to

fourth paragraphs, page 744, Figures 3 and 5, and page 745, right-hand column, last paragraph of D4; and page E95, left-hand column, second paragraph of D5).

In view of the above, it must be concluded that the feature distinguishing granted claim 1 of the patent from the lipid nanoparticles L054, L073 and L097 of D1, i.e. the slightly higher cholesterol content, does not result in any particular technical effect.

6.1.4 Consequently, the objective technical problem underlying the opposed patent is merely the provision of a further (alternative) lipid nanoparticle for the delivery of nucleic acids.

6.1.5 A skilled person starting from the structurally closest lipid nanoparticles of D1 and attempting to solve the above problem would naturally have contemplated making slight modifications to the contents of the lipid components of these nanoparticles.

The modification required to arrive at a lipid nanoparticle falling within the scope of granted claim 1, i.e. slightly increasing the content of cholesterol in the lipid nanoparticles L054, L073 or L097 of D1 from 28 mol-% to 30 mol-%, is a completely ordinary measure that the skilled person would have easily considered. In particular, there is nothing in D1 which could possibly have prevented the skilled person from considering and implementing such a modification.

This is further confirmed by the fact that lipid nanoparticles containing cholesterol in the amount required in granted claim 1 were commonly known and used in the art at the priority date of the opposed patent. For example, the document WO 2006/053430 (D2), which is concerned with siRNA-containing nucleic acid-lipid nanoparticles and thus relates to similar particles for the same purpose as taught in D1, exemplifies an siRNA-containing lipid nanoparticle ("2:30:20 + 10% DODAC") having the following lipid composition: "DSPC:Cholesterol:PEG-C-DMA:DLinDMA:DODAC, 20:38:2:30:10 % molar composition" (cf. page 73, lines 22 to 25 of D2). This lipid nanoparticle contains 38 mol-% of cholesterol, which falls within the range of 30 mol-% to 40 mol-% required in granted claim 1 of the patent, in addition to cationic lipid (DLinDMA and DODAC; cf. page 2, lines 27 to 33 of D2), a non-cationic phospholipid (DSPC), and a conjugated lipid (PEG-C-DMA), which are the same types of lipid components as also contained in the particles of D1 and as required in the opposed patent. This finding confirms that the skilled person starting from D1 and trying to solve the above problem would have readily

contemplated raising the cholesterol content of the lipid nanoparticles L054, L073 and L097.

When doing so, the skilled person would have proceeded cautiously and would have attempted to raise the content of the neutral lipid cholesterol in the nanoparticles L054, L073 or L097 of D1 while retaining the molar ratios of the other classes of lipid components, i.e. the cationic lipid and the conjugated lipid. Thus, when raising the content of the neutral lipid cholesterol (e.g., by 2 mol-%), the skilled person would have reduced the content of the other neutral lipid DSPC contained in the nanoparticles of D1 accordingly (i.e., by 2 mol-%), which is a simple and straightforward approach for retaining the molar ratios between neutral lipid, cationic lipid and conjugated lipid. The skilled person would thereby have arrived at particles embraced by granted claim 1 of the opposed patent without any inventive ingenuity.

It should also be appreciated that the choice of this particular modification (over other possible modifications which might not have resulted in a lipid nanoparticle according to granted claim 1) can not in itself justify the presence of an inventive step because it is merely an arbitrary choice from several possibilities which would all have been obvious to the skilled person. This is in accordance with established case law of the boards of appeal, as reflected by the following decisions T 1544/07 and T 964/92:

> "*However, the simple number of alternatives which a skilled person had at his disposition when looking for alternative stabilisers has no impact on the assessment of obviousness, since a mere arbitrary choice from a host of possible solutions does not in itself involve inventive ingenuity*" (T 1544/07, reasons 6.7.2)

> "*During the oral proceedings the Appellant [Patentee] further submitted that on the above basis the skilled person would have had to consider a host of possible alternatives, and that in the absence of any hint in the prior art towards the suitability of the relative small group of compounds defined in the present Claim 1, the selection of this group was not obvious, since the skilled person would not have chosen just this group. However, this submission must be dismissed, since if, as in the present case, a number of reasonable structural modifications was obvious, all compounds resulting from such modifications, irrespective of their number, are equally suitable candidates for solving that technical problem and would therefore all be "suggested" to the skilled person. Any arbitrary choice among them does therefore not involve an inventive step (see e.g. T 220/84 of 18 March 1986, No. 7 of the reasons).*" (T 964/92, reasons 2.10)

In consequence, a skilled person starting from the lipid nanoparticles L054, L073 or L097 of D1 and tackling the problem of providing further lipid nanoparticles would have been motivated to modify these lipid nanoparticles by slightly increasing their cholesterol content and reducing their DSPC content accordingly. In doing so, the skilled person would easily have arrived at lipid nanoparticles falling within granted claim 1 of the opposed patent without any inventive activity. Granted claim 1 is thus obvious in view of D1 alone, and also in view of D1 in combination with any of D2, D3 or D4.

6.2 Granted claims 2 to 15 are obvious in view of US 2008/0020058 (D1), optionally in combination with WO 2006/053430 (D2), Lin 2003 (D3) or Ahmad 2005 (D4)

All of the further granted claims 2 to 15 of the patent refer directly or indirectly back to granted claim 1. The additional features recited in these further claims are already disclosed in D1 (as discussed in section 5.2 above) or constitute mere routine variations which do not result in any particular technical effect. Granted claims 2 to 15 are therefore likewise obvious to a skilled person in view of D1, optionally in combination with D2, D3 or D4.

7. SUFFICIENCY OF DISCLOSURE

7.1 The opposed patent does not sufficiently disclose the preparation of the claimed nucleic acid-lipid particles comprising any "derivative" of cholesterol

Granted claim 1 of the opposed patent is a product claim directed to a nucleic acid-lipid particle comprising, *inter alia*, a "derivative" of cholesterol.

For the assessment of patentability, the terms in a claim have to be given their broadest technically sensible meaning (cf., e.g., T 1086/99, reasons 4.2, penultimate paragraph). In accordance with this principle, a "derivative" of cholesterol may be understood as relating to any chemical substance that can be derived from cholesterol, e.g., by modifying or replacing any moiety of cholesterol with any other chemical moiety.

The opposed patent, however, fails to enable a skilled person to prepare each and every conceivable derivative of cholesterol. This is self-evident in view of the fact that

chemical substances can be conceived, which a skilled person cannot prepare on the basis of his/her common general knowledge (which is also reflected in the Guidelines for Examination; cf. chapter G-VI, 4). Yet, the expression "derivative" of cholesterol also encompasses cholesterol conjugated to such chemical substances which the skilled person cannot prepare without undue burden, using only the opposed patent and his/her common general knowledge. The opposed patent consequently fails to enable a skilled person to prepare nucleic acid-lipid particles as defined in granted claim 1, comprising *any* conceivable derivative of cholesterol. It follows that granted claim 1 is not sufficiently disclosed within its full scope and should hence be revoked.

Since all further granted claims 2 to 15 likewise embrace any conceivable derivative of cholesterol, these claims are insufficiently disclosed for this same reason.

8. CONCLUSION

The request to revoke European patent EP-B-2 279 254 in its entirety for all contracting states for a lack of novelty (Arts. 100(a) and 54 EPC), a lack of inventive step (Arts. 100(a) and 56 EPC), a lack of sufficient disclosure (Arts. 100(b) and 83 EPC), and an inadmissible extension beyond the content of the original application (Arts. 100(c) and 123(2) EPC) is thus justified.

Oswin Ridderbusch

Oswin Ridderbusch
European Patent Attorney

Encl.:
Notice of opposition (EPO Form 2300E)
Documents D1 to D8 (as listed in section 2 above)

JOINT APPENDIX 88

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
Civil Action No. 22-252-MSG

ARBUTUS BIOPHARMA CORPORATION and GENEVANT SCIENCES GMBH,	:
Plaintiffs,	:
v.	:
MODERNA, INC. and MODERNATX, INC.,	:
Defendants.	:
MODERNA, INC. and MODERNATX, INC.,	:
Counterclaim-Plaintiffs,	:
v.	:
ARBUTUS BIOPHARMA CORPORATION and GENEVANT SCIENCES GMBH,	:
Counterclaim-Defendants.	:

VIDEOTAPED DEPOSITION OF DAVID H. THOMPSON, PH.D.

Tuesday, November 14, 2023

Reported by:

SUSAN ASHE, CSR, RMR, CRR

Job No.: SY008234

Videotaped deposition of DAVID H. THOMPSON, PH.D., taken on behalf of the Defendants, beginning at 9:04 a.m. Eastern Standard Time, on Tuesday, November 14, 2023, at the law offices of Williams & Connolly, 680 Maine Avenue, Southwest, Washington, D.C., before Susan Ashe, CSR, RMR, CRR.

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Law Clerk
Williams & Connolly

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Videographer
TransPerfect Legal Solutions

CONTENTS

EXHIBITS

TUESDAY, NOVEMBER 14, 2023;
9:04 A.M. EASTERN STANDARD TIME

--o0o--

VIDEOGRAPHER: Good morning.

This is Video No. 1 of the videotape-recorded deposition of Dr. David Thompson in the matter of Arbutus Biopharma, Inc. et al. versus Moderna, Inc., et al. filed in the U.S. District Court for the District of Delaware, Case No. 22-252-MSG.

This deposition is being held at Williams & Connolly LLP on November 14, 2023 at approximately 9:04 a.m.

My name is Orson Braithwaite, from the firm of TransPerfect Legal Solutions, and I'm the legal video specialist.

The court reporter is Susan Ashe, in association with TransPerfect Legal Solutions.

Counsel will now state their appearances for the record.

MR. McLENNAN: Mark McLennan, for Moderna defendants.

I've got -- with me today is my colleague Kaye Horstman.

MR. SHEH: This is Tony Sheh, from Williams & Connolly, on behalf of Genevant.

I'm joined today by Shaun Mahaffy and Falicia Elenberg, also from Williams & Connolly.

And also on the line is Peter Zorn from Genevant.

VIDEOGRAPHER: Thank you.

Will the court reporter please swear in the witness.

Whereupon,

DAVID H. THOMPSON, PH.D.

having been first duly sworn, was examined and testified as follows:

MR. McLENNAN: And just before we get started, could we have counsel for Arbutus announce themselves.

MR. BRAUSA: Sure. This is Adam Brausa, from the Morrison Foerster firm, on behalf of Arbutus.

I'm joined by Elizabeth Howard, consultant for Arbutus.

We're both remote.

EXAMINATION

BY MR. McLENNAN:

Q. Good morning, Dr. Thompson.

A. Good morning.

Q. Could you please state your full name for the record.

A. David H. Thompson.

Q. Where do you currently work?

A. Purdue University.

Q. And is that your only employer?

A. That is my only employer.

Q. What is your title at Purdue?

A. I'm a professor of chemistry.

Q. You submitted a declaration in this case. Correct?

A. Please restate the question.

Q. You prepared a declaration?

A. Yes.

MR. McLENNAN: We'll mark that as Exhibit 1.

(Whereupon, Thompson Exhibit 1 was marked for identification.)

MR. McLENNAN: And this is Joint Appendix 7, Declaration of Dr. Thompson.

BY MR. McLENNAN:
Q. Is this the declaration you prepared in this matter?
(Witness reading.)
Q. Dr. Thompson, are you -- you're comparing it against another document I see you've got there.
It's not an exhibit. Is that another copy of your declaration?
A. I have my declaration.
Q. Okay.
A. I'm just assuring myself that this document meets -- is the same as what I've -- what I have confidence in.
Q. Okay. Take as much time as you need.
(Witness reading.)
Q. Dr. Thompson, it's been about ten minutes.
Are you going line by line, or what's your review process like?
A. I'm reviewing the document that I've been given before I give my answer.
(Witness reading.)
Q. You can skip the CV, Dr. Thompson. I'll let you know if I ask about it.
A. Okay.
Q. So 13 minutes later, is that the

declaration in Exhibit 1 that you prepared in this matter?
MR. SHEH: Counsel, I just want to note that you asked him to verify if a document was an accurate copy.
That could take 13 minutes.
MR. McLENNAN: I asked if it was the declaration he prepared.
BY MR. McLENNAN:
Q. Dr. Thompson --
A. Yeah. What is the question, please?
Q. Is Exhibit 1 the declaration you prepared in this matter?
A. Yes. I've confirmed that it's an authentic copy of what I've prepared.
Q. Okay. And are you aware of any mistakes in your declaration in Exhibit 1?
A. I'm not aware of any substantive mistakes.
There may be typographical errors that I missed.
Q. Okay. On the face of the document, it's dated September 25, 2022.
Is that meant to be September 25, 2023?
A. That would be an example of a typographical error.

Q. But no other typographical errors you're aware of sitting here right now?
A. The -- I'm not aware of other typographical errors in the document.
Q. How long did you spend preparing your declaration?
A. Many hours.
Q. Can you give an estimate of how many hours?
A. More than ten, less than 100.
Q. More than 50?
A. I can't recall.
Q. When did you start working on the declaration?
A. Well, my declaration cites to work that was done -- published in 1992. So I don't know if that's what you're asking.
Q. I'm interested in the work that you did in putting together the declaration.
When did that work start, not the references cited.
A. I don't recall.
Q. You realize you're under oath today and you're required to tell the truth?
A. Yes, I understand that.

Q. Is there any reason that you can't give full, accurate, and complete testimony today?
A. No.
Q. You understand that some of the documents you've been given access to in this case include Moderna's confidential information?
A. Yes, I understand that I've received privileged documents.
Q. And there are certain people on the Zoom link to the deposition today that don't have access to that information.
So I will let you know if I'm going to refer to Moderna's confidential information so that we can ask those people to drop off the Zoom link.
But I would ask that you also let me know if any of your answers are going to reveal anything from Moderna's documents.
Is that okay?
MR. SHEH: I'll just note that I will also be policing it.
And, Doctor, if you need to refer to Moderna internal documents to make your answer complete, you can feel free to do that. That's counsel's job to place a protective order.

Q. And Dr. Thompson --
A. Understood.
Q. Okay. And you will let me know before you give an answer that reveals Moderna confidential information?
A. I will do my very best to not violate other's property.
Q. Okay. Thank you.
What did you do to prepare for your deposition today?
MR. SHEH: I'll just object and just caution the witness not to reveal any substantive communication with counsel.
THE WITNESS: That was....
Thank you for that.
A. I read a lot and thought through the work that I've -- or the document that has been presented.
Q. Your declaration?
A. My declaration, yes.
Q. You spent a lot of time reviewing your declaration, in other words?
A. I spent time reviewing my declaration, reviewing patents, reviewing other documents relevant to the -- my positions in this case.

Q. And since signing your declaration September 25, 2023, did you review any documents that are not cited in your declaration that you thought were relevant to your opinions?
MR. SHEH: Object to form.
A. I read the literature regularly. And collectively, that informs my opinion, so that the question actually is vague for me.
Q. Are there any documents that come to mind that you think are relevant to your opinions that you've learned about since September 25, 2023?
MR. SHEH: Object to form, mischaracterizes.
A. I don't know.
Q. In preparing for your deposition, did you review any documents that were not cited in your declaration?
VIDEOGRAPHER: Counsel, can you bring your microphone up.
A. Please repeat the question.
Q. In preparing for your deposition, did you review any documents that were not cited in your declaration?
A. I don't know.
Q. Did you review any of your prior testimony

from the previous proceedings between Moderna and Arbutus?
A. I reviewed some of that, some of those proceedings.
Q. And that included some of your prior testimony?
A. Yes.
Q. In reviewing the materials from those prior proceedings, did you notice any opinions that you gave in that prior proceeding that you want to correct or clarify?
MR. SHEH: I'll just object, and again caution the witness not to reveal the substance of any communication with counsel.
Go ahead.
A. The prior testimony was truthful. There's nothing that -- other than some unfortunate word choice that needs correction.
Q. Any particular unfortunate word choice that comes to mind?
A. One where the word "formed" should have been used.
Q. Okay. We might come to that.
So going back to your declaration in this

case, Exhibit 1, did you identify all the references that ended up in the declaration?
MR. SHEH: Object to form.
A. Can you clarify the question, please.
Q. What I'm trying to get at is: Did all of the references that ended up in your report come from you, or was it a mixture of some came from counsel and some came from you?
A. It was a collaborative process where there were citations to the open literature.
Those were largely provided by myself.
The legal citations were...the -- were part of my collaborative group's work effort.
Q. Did you conduct a literature search yourself, specifically for the declaration?
A. I've -- I conduct literature researches on nearly a daily basis.
It would be -- and so, yes, I've conducted literature searches.
Q. And did you conduct literature searches specifically for this declaration?
A. To be clear, the searches that I did were to find specific citations to work that I knew had been published and had previously been in hard copy form, but I went back to retrieve in electronic

form.
Q. So in other words, you were familiar with some of the references; you just needed to pinpoint them or locate a copy?
A. I wanted to correctly -- that's correct. I wanted to assure that I had the right citations.
Q. Okay. If you go to paragraph 15 of your report -- it's on page 5.
Do you see there there's some previous proceedings referred to before the Patent Trial and Appeal Board?
A. Yes, I see the description of -- or paragraph 15 describes my statement that I've submitted declarations and was deposed in IPR cases.
Q. And the previous proceedings between Moderna and Arbutus that we referred to earlier, those are the ones described in paragraph 15. Right?
A. Let me make sure that I can answer your question accurately.
(Witness reading.)
A. Please repeat the question.
Q. The prior proceedings between Moderna and Arbutus that we referred to earlier, those prior proceedings are described in paragraph 15. Correct?

A. This is describing proceedings for IPR~2018-00739 and IPR 2019-00554.
Q. And so when I asked earlier if you were reviewing -- strike that.
When I asked earlier if you had reviewed testimony from those prior proceedings, it was testimony from the proceedings in paragraph 15 that you recall reviewing. Correct?
A. When I reviewed IPR proceedings, I was focused on the statements and the content.
Which actual document it traces to is not something I remember right now.
Q. Okay. Going back to the preparation for your deposition, did you meet with anyone to prepare for your deposition?
MR. SHEH: I just caution the witness again not to reveal the contents of any communication with counsel.
A. I met with members of the Wilson [sic] & Connolly group.
Q. Was anyone else present at those meetings?
A. There were outside counsel from the -- at least one of the individuals online right now.
Q. Is that Peter Zorn?
MR. SHEH: I'll just cut right

through this.
It was Adam Brausa.
MR. McLENNAN: Okay. Thanks.
BY MR. McLENNAN:
Q. And apart from the one individual -- Mr. Brausa -- was there anyone else in attendance?
A. Not that I'm aware of.
Q. And was it just one meeting or several meetings?
A. Can you clarify the question, please.
Q. So I'm asking about your preparation for the deposition.
Did you meet just one time or more than one time?
A. I met with the team more than one time.
Q. How many times did you meet?
A. Several times in person, phone calls, videoconference.
I'm not sure -- not exactly sure of the number of meetings.
Q. Well, let's just start with the in-person meetings.
How many in-person meetings did you have to prepare?
A. I recall three in-person meetings.

Q. Three full days?
A. Some of those meetings were full days.
Q. And what about the Zoom meetings; how long were they for?
A. I can't recall.
Q. And when was the first meeting to prepare for the deposition?
A. Which meeting are you referring to?
Q. The meetings to prepare for your deposition.
A. I explained a moment ago there were different types of meetings. I'm asking which sort of meeting you're referring to.
Q. Oh, are you talking about Zoom versus in person?
When was the first in-person meeting?
A. To the best of my recollection, it was in the summer.
Q. Okay.
A. Of 2023.
MR. McLENNAN: Thanks.
If you could please turn to paragraph 56 of your declaration.
And Dr. Thompson, before we look at 56, I'll give you a copy of the patent.

This is Exhibit 2. It's U.S. Patent 8,058,069.

(Whereupon, Thompson Exhibit 2 was marked for identification.)

BY MR. McLENNAN:

Q. And will you understand today if I talk about it as the "'069 patent," Exhibit 2?

A. Oh, I will understand it as '069, the '069 patent.

Q. Great. I don't have to read out all the patent numbers. Thanks.

A. I heard "'062."

Q. Oh.

A. That's why I said....

Q. Okay. So in paragraph 56, from this section onwards, this is about your opinions about the -- if we can call it the "mol % ranges" in the claims of the '069 patent and related family members. Right?

(Witness reading.)

A. Paragraph 56 is describing the use of significant figures and rounding in the Lipid Composition Patents.

Q. And in paragraph 56, you state that -- this is the second sentence:

With respect to the recited mol % ranges, the POSA would have known that lipid concentrations could be experimentally determined, for example, using high-performance liquid chromatography ("HPLC").

Do you see that?

A. Yes.

Q. In the '069 patent, is there any description of a method for determining lipid concentration?

(Witness reading.)

Q. Dr. Thompson, are you going page by page through the patent?

A. I'm trying to answer your question.

Q. Okay. Why don't you skip ahead to the examples in Column 68.

MR. SHEH: Dr. Thompson, you're free to look at as much or little of this document as you need to to answer Mr. McLennan's question.

Q. Yeah, Dr. Thompson, if you like, I can limit my question to the examples.

If you do want to go through the entire

document, you're welcome to, though.

(Witness reading.)

A. Please restate the question.

Q. So the question from 12 minutes ago was whether in the examples of the '069 patent there is any description of the method you used to measure lipid content.

A. There's no expressed description of an HPLC method, which is what triggered the question, as I understand, from paragraph 56.

There is a description of a so-called "kit" that is mixture of lipids.

It's not -- it's unclear to me whether there was any testing done at that point.

Q. And could you point out where the "kit" is that you're referring to?

(Witness reading.)

A. So Column 60, line 46 is a section describing kits. It's essentially, as I understand, a way to expedite formulation studies.

Q. If sorry. Was that Column "60" or "16"?

A. "6-0."

Q. "6-0."

And so, what do the kits have to do with the method of measuring lipid content?

A. The previous statement about the analysis of the lipids, as I said, does not -- HPLC method does not appear.

But typically when you are preparing -- in this case, the kit may comprise a container which is compartmentalized for holding the various elements of the lipid particles, the active agents, the individual lipid components of the particles.

The kit typically contains the lipid particle compositions of the present invention, preferably in dehydrated form.

So what I'm speaking to is that there may -- there typically is some type of quantitation when you're preparing a sample that is going to be used broadly.

Q. And for the kit example you pointed to, would the quantification be before or after the lipid particle is formed?

A. Ideally, one would analyze before and after the particle is formed.

Q. Can you tell from the kit description here in Column 60 whether they measured lipid content before or after the particle was formed?

A. There's no explicit description of an analytical method in this section.

It's a -- just a -- what one would presume when the kit is made is that there's a -- some type of analysis so that you are certain of the composition you're beginning with.

Q. So in other words, the amount of lipids that are used at the start of the formulation process?

A. In the '069, the -- and at the time of this disclosure, the most common procedure was to use either a phosphate assay or cholesterol assay to look at composition before particle formation.

Q. And when you say using a phosphate assay or a cholesterol assay, that would measure the amount of those components individually. Right?

A. Correct. Those techniques are specific for those components of the sample.

Q. So after going through the examples, you said that there was no explicit reference to an analytical method for determining lipid content.

Are there any implicit descriptions of analytical methods?

MR. SHEH: Object to form.

A. There are -- this document describes many analytical methods.

Most of the methods are focused on

particle size analysis, on biological performance.

There are many analytical methods here. It's just not describing in this document the analysis of the lipid formulation components.

Q. And when you say "in this document," just for the record you're talking about the '069 patent. Right?

A. I'm -- yes, I'm referring to '069.

Q. So in your declaration, you're talking about HPLC methods.

If there's no disclosure in the '069 patent to use HPLC, why did you decide to include descriptions here about HPLC in particular -- as opposed to any other method?

A. Well, as I say, with respect to recited mol % ranges, a person of skill in the art would have known that lipid concentrations could be experimentally determined.

For example, using HPL- -- High Performance Liquid Chromatography, HPLC.

So a moment ago, I mentioned other chemical methods that can be used.

But in paragraph 56, I'm speaking about a more -- a technique that will -- that is capable, if one has a validated method, of detecting multiple

components in a formulation.

Q. You mentioned that there were the other chemical methods that you spoke about earlier.

Were they methods for determining individual lipid components and their concentrations alone, right -- not mixtures?

MR. SHEH: Object to form.

A. I believe what the testimony shows is that they are capable of detecting those individual components.

And to be clear, they are -- they can detect those components within a mixture of lipids or other materials.

Q. Sorry. Was that can or can't detect?

A. They can --

Q. "Can."

A. -- detect.

Q. And so, are you talking about the kits or are you talking about the phospholipid and cholesterol assays?

A. My previous two statements on this topic are referring to the phosphate analysis and the cholesterol analysis in a sample of lipid formulation.

Q. And is there a --

A. Not a -- not a -- not the kit.

Q. Okay. And is there a name for the analytical techniques used in those phosphate and cholesterol analyses?

A. The phosphate analysis is based on phosphomolybdic acid. So it's a perchloric acid digestion of the sample and measurement of the inorganic phosphate in a colorimetric assay.

The cholesterol assay is based on a cholesterol oxidase, enzymatic-based assay.

Q. And those two methods, those aren't described in the '069 patent in the example section we were just looking at. Right?

A. These methods are historical.

The phosphomolybdic acid assay traces back to, I believe, 1954. So it's -- widely used technique.

Similarly, the cholesterol assay is a standard method. Kits exist for that.

And so, there's no specific citation to those methods, I presume, because they're widely understood.

Q. Have you ever conducted a cholesterol assay of that type?

A. Yes.

Q. And what was the context in which you conducted that assay?
A. I've prepared liposome formulations for small molecule drug delivery in the '90s. And often, those formulations had blends of different lipid components.
And one of the ways to monitor the fidelity of your formulation was by doing these analytical assays after preparing the particles.
So phosphate assay and cholesterol assay are things that I've done.
Q. And when you say the fidelity of the liposome, are you talking about stability?
A. No.
Q. What are you referring to?
A. What -- that word -- the intent of that word is to reflect that the material in, i.e., the dry powders of lipid or other components that are being -- that are being weighed into the sample vial.
And then under -- treated with some dispersion method, some way to disperse them into the aqueous phase, that the composition of the dispersed material is reflective of what was the ratio materials that went into the -- as dry

powders.
MR. SHEH: Mark, it's been about an hour. Do you want to take a break?
MR. McLENNAN: Sure.
MR. SHEH: Thanks.
VIDEOGRAPHER: The time is 10:07 a.m. This ends Unit 1.
We're off the record.
(Whereupon, a recess was taken.)
VIDEOGRAPHER: The time is 10:23 a.m. This begins Unit No. 2.
We're on the record.
BY MR. McLENNAN:
Q. Dr. Thompson, earlier we were talking about the colorimetric test method and the enzymatic test method for cholesterol and phospholipids. Right?
A. Yes.
Q. Are there similar test methods to determine the concentration of cationic lipid or conjugated lipid?
MR. SHEH: Objection to scope.
A. At the time of the '069, I'm not aware of a method for chemical testing, other than HPLC analysis.

And for the polyethylene glycol lipid conjugates, I'm not aware of -- at the time, of other methods, other than HPLC.
Q. Okay. And just to clarify your answer, you said at the time of the '069 you're not aware of a method for chemical testing, other than HPLC.
Were you referring to quantifying the cationic lipid?
A. So at the time of the '069, the -- what I was referring to was the analysis of the cationic lipid for authenticity.
Q. And when you say "authenticity," does that include quantification of the lipid concentration?
A. Could you clarify what you mean by "lipid concentration."
Q. I think I might have -- maybe it's easier -- I asked them together. Maybe we'll just separate them.
Are you aware of any test method to measure the lipid concentration of a cationic lipid that existed at the time of the '069 patent, other than HPLC?
MR. SHEH: Objection; scope.
A. I can't recall any general method.
Q. Okay. And in some of your answers to the

previous questions, you said "at the time of the '069 patent."
Are you talking about the priority date?
A. I was referring to the filing date --
Q. Filing date?
A. -- when the document was created and submitted.
Q. And in your report at paragraph 25, you say that the family of the '069 patent claimed priority to an application filed in 2008, another one in 2009.
Is it fair to say you're talking about the 2008, 2009 time frame?
A. Yes, that's the time frame I'm referring to.
Q. Okay. And in your report, if we go back to paragraph 56.
(Pause.)
Q. You stated earlier that you were including HPLC as an example of a method to experimentally determine lipid concentration.
Is that right?
A. With respect to the recited mol % ranges, the person of skill in the art would have known that lipid concentrations could be experimentally

determined -- for example, using High Performance Lipid Chromatography.

Q. And are there any other methods -- strike that.

Are there any methods, other than HPLC, to experimentally determine lipid concentration?

MR. SHEH: Objection; scope.

A. There are many different methods and many different types of lipids.

There may be other methods that are more compound-specific that would not require HPLC.

Q. Did the specific method you're calling out here, HPLC -- did that impact your opinions about the mol % ranges and use of significant figures?

MR. SHEH: Object to form.

A. Please restate the question. I didn't catch part of it.

Q. Did the specific method you're calling out here at paragraph 56, HPLC -- did that impact your opinions about the mol % ranges and the use of significant figures?

MR. SHEH: The same objection to form.

A. What I'm describing in this paragraph is an -- a method that could be used.

And it's a -- simply a way to describe what lipid is -- or one of the techniques that can be used to describe what's been dispersed into a particle, a lipid particle.

Q. Did you consider the degree of precision of HPLC in providing your opinions on the mol % ranges?

A. I'm well aware of precision and the need for calibration and standards and a -- particularly, in work related to -- that's ultimately going to be regulated, that there be validated methods that -- with known retention times, limits of detection, etc.

Q. And were those relevant to your opinions about the application of significant figures to the mol % ranges?

A. Actually, what -- that's a separate issue that -- it's conflating two different concepts.

One is speaking to how one measures lipid concentrations. The other is scientific convention and guidance from the USP and pharmaceutical standards.

Q. So those are distinct concepts?

A. Measuring lipid concentrations by HPLC or some other method is telling you what is in your

disperse sample.

The numbers that one obtains any sort of experimental quantity, you then apply the USP and Remington guidances.

Q. Would your application of the USP and Remington guidances be affected at all by what analytical method you're using to measure lipid content?

MR. SHEH: Object to form.

A. Please restate the question.

Q. Okay. So in paragraph 56, you've noted that HPLC is one method of determining lipid content. Correct?

A. Yes.

Q. And in general, you have opinions about this claim term -- that a person of skill in the art would apply to significant figures. Correct?

MR. SHEH: Object to form.

A. So as I say in the section above paragraph~56 significant figures and rounding are standard scientific conventions that the person of skill in the art would have been aware of and would have applied in interpreting the claims of the Lipid Composition Patents with respect to the recited mol % ranges.

The person of skill in the art would have known that lipid concentrations could be permanently determined.

And so, the leading statement there is that what's governing is the accepted rules for significant figures and rounding for scientific measurements.

And HPLC is one type of scientific measurement.

Q. And would your application of significant figures and rounding -- would that vary, based on what analytical method was being used, or would it always be the same?

MR. SHEH: Object to form.

A. You would uniformly apply the rules of significant figures and rounding to a scientific measurement -- that's what my previous answer clearly stated.

And it's agnostic about the technique that's being used to make that measurement.

So you're applying a uniform set of rules and -- to whatever measure that's being made.

Q. Thanks, Dr. Thompson. That was what I was getting at.

And so going back to HPLC as the example

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you gave, did you consider the precision of the HPLC method?

MR. SHEH: Object to form, foundation.

A. The HPLC chromatograph can be configured in many ways with different types of detectors, each with their own dynamic range, sensitivity.

And so, that is a feature that you would take into consideration when looking at a specific protocol to understand what the...what the precision sensitivity of the method is.

Q. And does the precision or sensitivity of the analytical method affect your opinions at all about the scope that the mol % range is?

MR. SHEH: Objection; asked and answered.

A. You make an HPLC -- in this specific case, an HPLC measurement. And the precision of that measurement will be a function of the detector that is chosen.

Q. If you go to paragraph 60 of your report, please.

Do you see in paragraph 60 you've got a table with the ranges of the '069 patent?

A. Yes, I see this.

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Q. And in the right-hand two columns, the "Lower Limit" and "Upper Limit," you have provided the numerical scope of the range that you think applies based on significant figures and rounding. Correct?

A. I'm listing in this table the -- applying the standard rules of rounding significant figures to indicate that the recited range of 50 mol % would be using those guidances would indicate that 49.5 mol % would be the lower limit of satisfying the 50~mol % range, and that the upper limit 65.4 mol % -- I'm speaking now of the cationic -- in both of these, 49.5 mol % of the cationic lipid or as much as 65.4 mol % of the cationic lipid would be within the recited range.

And that comes from applying the rules of rounding and significant figures.

Q. And so, the lower and upper limits that you've come up with in paragraph 60 based on the application of significant figures and rounding, are they also agnostic to the precision of whatever analytical instrument you're using to measure lipid content?

A. These numbers are -- that I'm citing are the limits that follow those USP and Remington

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guidances.

And the way that one determines the actual concentrations in a sample are a matter of the analytical method chosen.

Q. The limits that you've chosen in paragraph~60 based on significant figures and rounding, are they agnostic to the precision of the analytical instrument you're using to measure lipid content?

MR. SHEH: Objection; asked and answered.

A. As I said, the precision of the analytical method is something that would be considered when comparing lower and upper limits.

Q. And how would they be considered, specifically?

A. If they...if the analytical method is producing a value that falls within or outside these lower limit and upper limit ranges that I've specified here, that arise from their recited ranges and what that -- what is allowable based on the rules of rounding and significant figures.

Q. Would you agree with me that any -- analytical instruments could have a spectrum of precision, so you could have one method that is very

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precise and then another method that is less precise?

MR. SHEH: Objection; scope, incomplete hypothetical.

A. There are many different analytical methods. They have different types of precision that are -- that they're capable of informing the scientist of.

Q. And the numbers you have here in the table you made in paragraph 60 in the columns "Lower Limit" and "Upper Limit," were those numbers that you included there -- would they change based on the precision of the analytical instrument?

MR. SHEH: Objection; asked and answered.

A. The lower limit and upper limit that is listed here would not change.

Q. Now, the conventions you talk about from USP and Remington's, are they internationally recognized conventions?

MR. SHEH: Objection to scope.

A. The Remington reference is a, essentially, a textbook.

The USP is a -- the "US" standing for "United States Pharmacopeia" -- is an entity that

is -- essentially collects and produces -- collects samples, produces monographs for validated -- or ways to perform validated analyses and limits of detection analyses.

So to the extent that they are internationally recognized, I don't know who buys the Remington textbook, but USP is often used for guidance by other entities.

Q. And the principles of significant figures and rounding, you were aware of them before your involvement in this case. Correct?

A. Yes -- yes.

Q. And is it fair to say, you've been familiar with those conventions throughout your career?

MR. SHEH: Objection to the form.

A. As an educator, this is something that -- significant figures is -- and rounding are matters that come up regularly.

So -- and as an active researcher, it's something that my colleagues and my students are considering on a regular basis.

Q. And you've been a visiting professor overseas at various institutions. Right?

A. Yes. I've been a visiting professor at University of British Columbia, Chulalongkorn University, Technical University of Denmark.

Q. And are you aware through those --

A. Pardon me.

Q. Sorry.

A. Those are the international examples.

I've also visited domestic institutions as a visiting faculty member.

Q. And through those international visiting professorships, were you aware of any alternative conventions of significant figures and rounding?

MR. SHEH: Objection; scope.

A. I...in my experiences outside my Purdue laboratory and Purdue University environment, those institutions that I visited, I don't recall other conventions for rounding and significant figures being used.

Q. Okay. Now, if we go back to the '069 patent, which is Exhibit 2.

Earlier we were talking about whether there are any methods described in the '069 patent for measuring lipid content.

Are you aware -- and if we could just start with off the top of your head. And if you

want to go review it, I can ask that.

But are you aware of whether the '069 patent actually reports any measured lipid content values?

MR. SHEH: Object to form.

A. Can you clarify the question, please.

Q. Okay. So the '069 patent contains information about molar ratios. Correct?

A. Yes.

Q. And do you know whether it contains measured values of lipid content as opposed to descriptions of the starting content?

A. In my review of the document, I did not see a -- of the '069 document, I did not see a specific description of a method for analyzing the dispersed lipid in a formulation.

Q. Okay. So if you go to Table 2 -- this is in Column 69 of the '069 patent.

Are you there, Doctor?

A. Yes. Pardon me.

Yes, I'm -- I see Table 2.

Q. Great. And this -- the title of this is "Characteristics of the SNALP formulations used in the study." Right?

A. Yes.

Q. And there's a heading "Formulation Composition, Mole %."

Do you see that?

A. Yes.

Q. And what is your understanding of what the numbers in those columns represent?

A. These are reporting formulation composition mol % of the -- what's referred to as the "conjugate lipid" the PEG(2000)-C-DMA and the DLinDMA, as well as the DPPC and cholesterol content in the -- in 16 different formulations.

Q. And the "DLinDMA" is the cationic lipid in that example. Right?

A. "DLinDMA" is the ionizable lipid.

It's the agent that is protonated to become cationic under the conditions of formulation.

Q. Okay. And when you say that this column refers to the formulation composition, do you understand that represents the amount of lipids before the particles are formed?

A. This table is -- since there's -- it's not specified whether there was a HPLC analysis, I anticipate that these are nominal concentrations of the different lipid components.

Q. And what do you understand "nominal

concentrations" to be?
A. Actually, I spoke to this extensively in previous cases.
What "nominal" means is: The composition that you are writing into your notebook and you are metering out, whether it's the polymetric or weight measurement to produce a mixture of the lipid components before you treat them with the dispersion method.
Q. So is it akin to a recipe: It's the amounts that are going in?
A. I think that's a reasonable description.
It's an intended proportion -- set of proportions.
Q. In Table 2, the lipid amounts listed here, they're listed in mol %. Correct?
A. Yes. That's the header at the top of the second column, "Formulation Composition, Mole %."
Q. And the numbers that appear in those columns, they have varying numbers of significant figures. Correct?
A. Yes. Applying them, the conventions, the USP conventions, they are of varying significant figures.
Q. And do you have any understanding of why

the inventors would have chosen to include varying numbers of significant figures?
A. I don't know. That is a -- it could be limitations on reagent. It could be a question that they're trying to interrogate. There may --
I don't know what their purpose was, but these are the values that they went for.
MR. SHEH: Mark, he's just adjusting the --
MR. McLENNAN: Oh, no problem.
MR. SHEH: Thanks.
(Pause.)
BY MR. McLENNAN:
Q. If you go over to Column 78, Example 8, let me know when you get there.
A. The '069?
Q. Yeah, of the '069.
And in Example 8, there's a description of SNALP formulations, the 1:57 SNALP formulation.
Do you see that?
A. Yes.
Q. And at Column 78 around line 17, there's a description of an "input lipid to drug ratio"?
A. Column 78, line --
Q. Around 17.

A. -- 17? Okay.
Yeah, so:
This study illustrates comparison of the tolerability and efficacy of the 1:57 SNALP formulation with ApoB-targeting siRNA as prepared by...direct dilution or in-line dilution process....
Is that the...yeah.
Q. Yeah, that's the section.
And so, do you see in that first paragraph it refers to the "input lipid to drug ratio"?
A. I'm sorry. I don't see "input."
Q. At about -- Line 18.
A. Okay. Yeah, so:
...direct dilution or in-line dilution process at an input lipid to drug ratio of 6:1 to 9:1.
Q. And the "lipid to drug ratio," is that referring to the ratio in like absolute weight or is that another calculation that's performed with -- based on the molecular weight?
MR. SHEH: Objection; beyond the

scope.
A. Typically, these are -- the lipids are determined by molar ratios.
And once you know the composition of the ionizable form of the lipid, you're often tying your ratios to that part of the formulation.
Q. And the lipid to drug ratio there, that's referring to total lipid -- not just the ionizable lipid, though. Right?
MR. SHEH: Same objection.
A. The -- it's describing a -- the 1:57 composition and the input lipid.
Q. Just to be clear, the input lipid is all of the lipids -- not just one particular lipid?
A. That is the expectation.
Q. If you go over to Column 79 of the '069 patent, at around line 8 there's a formulation summary and a table that doesn't have a title.
A. Yes.
Q. And in the last column, it says, "Final L:D" Ratio "(mg:mg)."
Do you see that?
A. Yes.
Q. Is that the final lipid to drug ratio?
MR. SHEH: Objection; beyond the

scope.
A. So what is being described here is the final lipid to drug ratio in milligrams to milligrams for the formulations that are being tested.
Q. And what is the "final" in "final lipid to drug" referring to?
A. It's referring to the particles that were made.
Q. And if you look through Example 1, the lipid particles were administered to animals. Correct?
A. Example 1. So....
Q. Sorry. This is still Example -- I think we're in Example 8.
A. Okay. Example 8.
Q. And it has -- just below that table we're looking at in Column 79, there's a description.
A. Um-hum. Yes, I see that description of Procedures, the Treatment, Endpoint, Groups, etc.
Q. And so, the lipid particles in Example 8 were administered to animals?
MR. SHEH: Objection; beyond the scope.
A. Some....

It appears the formulation was administered to animals.
Q. And so, the final lipid to drug ratio that's referred to in the table in Column 79, do you expect that that was the lipid to drug ratio of the particle that was administered to the animals?
MR. SHEH: Same objection to scope.
A. The...it's unclear, actually.
The methods used to collect particle size data and to do a lipid to drug ratio measurement may be different than what was actually administered to the animals.
Q. So in other words, you're saying that there could be a different lipid to drug ratio at the composition that was administered to the animals than what's reported in that table?
A. No -- no, that's not what I'm saying.
What I'm saying is that the sample, the particles that were generated to make the particle size measurement and lipid to drug ratio measurement do not require sterile filtration.
But before administration -- it can be the same inflammation, the same set of particles. But before administering to animals, you'd have to do a

sterile filtration.
And so, the -- that's what I'm referring to.
Q. Would you expect the lipid to drug ratio to change as a result of the filtration?
A. It depends on the operation.
Q. Are there any other processing steps that might be carried out from the final lipid to drug ratio before it's administered?
MR. SHEH: Objection; scope.
A. I can't speak for -- to such a general question.
Q. Okay. If you look at Column 78, do you see that there's a calculation of dosages there in both lipid content and encapsulated siRNA?
A. I'm on Column 78. There are three tables here. Can you help me?
Q. So for any of them, do you see in all of them they have a heading "IV Dosage" and there's a column that says "Total Lipid"?
A. Yes, I see that.
Q. And there's also a column that says "Encap. siRNA"?
A. Yes, I see that.
Q. And so, would those two columns be used to

calculate the -- oh, sorry. Shoot, they're dosages.
Those are describing the amount of lipid per kilogram of the mammal that's administered.
Is that right?
MR. SHEH: Objection; beyond the scope.
A. The total lipid is -- in these tables is -- appears to be referring to the amount of lipid that's present in the formulation and the amount that was -- total amount dosed per kilogram in the animal.
Q. And so from those two columns, could you calculate the lipid to drug ratio that was administered to the mammal?
MR. SHEH: Objection; beyond the scope.
A. Yeah, I -- I would not -- I would need to take some time to study that and evaluate their -- how they're producing these numbers.
Q. Okay. We might come back to that.
In -- if you look at Column 80, there is a description next to Figure 12 around line 28.
Just let me know when you get there.
(Witness reading.)
A. Yes, I see it.

Q. And that description refers to both an input lipid to drug ratio and a final ratio of lipid to drug. Correct?
A. (Reading:)
Figure 12 shows that ApoB protein and the total cholesterol levels were reduced to a similar extent by the 1:57 SNALP at a 6:1 input lipid to drug ratio (final ratio of 7:1) and the 1:57 SNALP at a 9:1 input L:D ratio (final ratio of 10:1).
Q. Was it a convention in the field to report both the input lipid to drug ratio and the final ratio?
MR. SHEH: Objection; beyond the scope.
A. Actually, this whole series of questions are not part of my declaration.
Can you direct me to where this is relevant to what --
Q. Sure.
A. -- I'm here to clarify for you?
Q. Sure.

You provide opinions about whether or not -- or, sorry, strike that.
You provide opinions about the meaning of the term "lipid particle" and whether it is a finished lipid particle. Correct?
A. Yes.
Q. And you considered the disclosures of the '069 patent in coming to that opinion?
A. That's one of a family of patents that I refer to.
Q. And it's your opinion that the lipid particle claimed in the '069 patent is not a final lipid particle. Correct?
MR. SHEH: Object to form.
A. What I'm saying in my declaration is that the claim describes formation of a particle, and that particle can be -- is a particle -- once it's formulated is a particle, regardless of where the position in the lifecycle of that -- until it's born, until you dispose of the sample, it's still a particle. That's the point I'm making.
Q. And you agree, though, that the claims of the '069 patent do not claim the amounts of lipids in terms of input components. Correct?
MR. SHEH: Object to form. It

calls for a legal conclusion.
A. What I'm speaking to -- paragraph 60 of my declaration, page 29, these are the recited ranges that are in Claim 1.
That's what I'm speaking to.
Q. Okay. So if we stick on paragraph 60.
(Pause.)
A. Okay. Yes, I'm there.
Q. And if you look at the "Upper Limit" column.
If you have a sample that you would say falls within the claims that is at the very top of the upper limit for each of the four components, would you agree with me that that would add up to more than 100 percent?
MR. SHEH: I'm sorry, Mark. Where are you looking?
MR. McLENNAN: Paragraph 60.
MR. SHEH: Paragraph 60 -- I see, in his declaration.
Okay. Thank you.
A. Yeah, so summing -- I believe I understand.
Please restate the question, just to make sure I understand.

Q. So the four upper limits you provided --
A. Yes.
Q. -- in paragraph 60.
A. Yes.
Q. If you add the four of those together, that would sum up to more than 100 percent correct?
A. Yes.
Q. And does that affect your opinions in any way about the ranges of each of these?
A. Well, the -- since it's a percentage, there is no -- there's no way that they can add up to more than 100.
So if they're high in one portion of a formulation, it's going to be lower in another portion of the formulation.
That's what a percentage is. That's a percent of 100 percent.
Q. So in other words, it has to add up to 100 percent?
A. Yes.
MR. SHEH: Objection.
A. It --
MR. SHEH: Let me deal with my objections, Doctor.
Object to form.

A. The mol % of the four components that are listed -- if those are the only components in the mixture are these four components, then you would expect that they are -- that in the experiment, that they would -- they should add up to 100 percent within experimental error.

Q. Okay. And do you know what the experimental error is for, say, for example, HPLC?

MR. SHEH: Objection; beyond the scope.

A. I think we've already plowed this field. I've answered that question I think at least three times -- that it depends on the instrument and the type of detector that the instrument is configured with.

Q. Okay. If you go over to paragraph 66 of your declaration, this is where you talk about the file history of the '069 patent.

MR. SHEH: Mark, if you're going to start on this section, do you mind if we take a break?

MR. McLENNAN: Yeah, sure.

MR. SHEH: It's been about an hour.

MR. McLENNAN: Sounds good.

MR. SHEH: Thank you.

VIDEOGRAPHER: The time is 11:15 a.m. This ends Unit 2. We're off the record.

(Whereupon, a recess was taken.)

VIDEOGRAPHER: The time is 11:30 a.m. This begins Unit No. 3. We're on the record.

BY MR. McLENNAN:

Q. Dr. Thompson, we started talking about the -- or I just pointed you to paragraph 66 in your declaration about the file history of the '069 patent.

A. Yes, I see it.

Q. Now, you're aware in prosecution of the '069 patent that the claims originally included the word "about" before the mol % ranges. Right?

A. Right, I understand the patentee amended the claims to remove the term "comprising about" -- "composing about," in quotations, from the pending claims -- then-pending claims.

Q. And in paragraph 66, you refer to the examiner's construction of "comprising about" to mean "an amount +/- 10, 20, or 30 mol % of a lipid component."

Do you see that?

A. Yes.

Q. Is that your understanding of what "about" means in the context of the '069 patent?

MR. SHEH: Object to form, scope.

A. I'm -- what I'm saying here is that I'm basing my statements on the examiner's construction.

Q. Do you have --

A. They're the ones that use this -- "an amount +/- 10, 20, 30 mol % of a lipid component."

Q. And do you have your own view of what "about" means in context of the '069 patent?

A. No.

Q. The term "comprising about" is not in the final claims that issued as the '069 patent. Correct?

A. Right. So paragraph 67 is what was -- contained the language "comprising from about" for the cationic lipid molar ratios.

And the paragraph 69 shows the striking of the word -- in Claim 1, striking of the word "about" in each of the lipid components -- so struck from the cationic lipid, the noncationic lipid, and the conjugated lipid.

Q. And so for the claim language in paragraph~69, you've provided what you believe is a numerical scope of each of the ranges in paragraph~60, applying significant figures and rounding. Correct?

A. That's a...I don't quite understand the question.

Q. Okay.

A. Can you please restate.

Q. Let me take you back to paragraph 60.

A. Um-hum.

Q. This table you have here in paragraph 60, it's about the issued claims. Right?

A. These are -- right, the recited range that I'm listing in this table are based on the claims that appeared in --

Q. Paragraph 69?

A. -- the allowed claims in 69.

Q. Okay. And the allowed claims do not have the word "about." Correct?

A. In Claim 1 -- the allowed Claim 1 does not have -- that, that was struck from Claim 1.

Q. Okay. So considering the table you have in paragraph 60 -- the lower and upper limit, can we refer to that as the numerical scope of the range?

A. So the paragraph in 60, this table --
Q. Um-hum.
A. -- you're asking if that is the numerical scope of the range?
Q. Yeah, I want to ask you questions about the lower and upper limit, and just -- if you have a particular phrase for it.
I would call it the "numerical scope."
A. Right. So I'm -- that -- I now know the term that you're using.
As I said earlier, these numbers that are derived based on the allowed claims -- or the allowed language in Claim 1, and applying the guidelines for rounding and significant figures.
Q. If we start with the cationic lipid limitation, what would be the lower and upper limit for the claim when it recited "about" during prosecution?
MR. SHEH: Object to form.
A. That's...that can mean many things, and actually depend highly on the specific lipid we're talking about.
So I'm not -- I'm unable to answer that question, actually. There are too many variables at play.

Q. So if we limit it just to the cationic lipid, you don't know what the numerical range would be if it recited "about 50 percent to about 65~mol %," as it did during prosecution?
MR. SHEH: Object to form.
A. So the analysis that I've -- I'm presenting here is based on what the examiner put forward of 10, 20 mol %, +/-.
And in terms of a hypothetical meaning of "about," that's...I would need to give that more thought.
Q. Did you consider the meaning of "about" as it existed during prosecution in these claims, in preparing your declaration?
MR. SHEH: Objection; asked and answered.
A. I applied the guidance of -- or the statement of the examiner to what "about" meant and did not go beyond that.
Q. And do you agree with the examiner's construction of "about" to mean "+/- 10, 20, or 30 mol %"?
MR. SHEH: Objection; scope.
A. Repeat the question, please.
Q. Do you agree with the examiner's

construction of "about" to mean "+/- 10, 20, or 30 mol %"?
A. That's not --
MR. SHEH: Objection; scope.
A. -- not my judgment to make.
Q. Did you consider the meaning of "about" during prosecution?
MR. SHEH: Objection --
Q. Strike that.
Did you consider the meaning of the term "about" as it existed in the claims during prosecution?
MR. SHEH: Objection; asked and answered three times.
A. I considered the examiner to be the gatekeeper and that their applied meaning of "about" is the relevant meaning that I should use in my -- in producing my opinion.
Q. Do you have an alternate meaning for the word "about" in this context?
A. As I said, I don't have a meaning of "about." It's -- would require a great deal of reflection.
Q. And what would you have to reflect on?
MR. SHEH: Objection; scope.

A. Essentially, every element of the process and the materials used -- as you put it earlier -- in the recipe.
The specific lipids; their proportions; their method of making a particle, as is specified in Claim 1 -- that...those are all factors that would -- and others that I'm probably forgetting in this moment -- that would be bundled into consideration of what "about" might mean.
Q. When the applicant removed the word "about," do you think that the scope of the claims changed?
MR. SHEH: Objection to scope.
A. The question is: Do I believe that the scope of the claims changed?
Q. Yes.
(Witness reading.)
A. That strikes me as more of a legal question than a scientific one.
Q. Did you consider the impact of removing the word "about" during prosecution?
A. I considered the sequence that -- or the -- and read through the record of how that back-and-forth between the examiner and Dr. Heyes, followed that decision.

I have not given thought to how -- what the impact of those changes are.
Q. So there's no impact that you can think of right now of deleting the word "about"?
A. From a scientist's perspective, the deletion of that word is -- makes it more defined that the -- in the case of the cationic lipid of Claim 1, now there are two significant figures: 50 mol % and 65 mol %. As the recited range, that's -- that's the -- I guess, to me, what the impact is.
Q. Okay. And so looking back at the table you have this paragraph 60, if that's the more defined version after the deletion of the word "about," what is the less defined version?
MR. SHEH: Objection; scope.
A. I can't say.
Q. When the claims recited "about," did the claims allow for variability in the mol %?
MR. SHEH: Objection to the scope, asked and answered.
A. There's a time element here.
Can you please repeat the question.
Q. So the claims in....
Let's have a look at paragraph 67. This is the claims when they recited "about."

And if we take the specific example of the cationic lipid, at this stage in January 2011 the claim recited:
> Cationic lipid comprising from about 50 mol % to about 65 mol %.

Do you see that?
A. Yes.
Q. Does the phrase "about 50 mol %" allow for variability below 50 mol %?
A. It allows for variability above or below 50 percent in an indeterminate amount.
Q. You can't quantify how much variability above or below 50 percent?
MR. SHEH: Objection to scope.
A. I think this is what the examiner was calling out, is the -- is that it required....
The uncertainty could be as large as +/- 10 percent -- 20, 30 mol % -- that that "about" term allowed for a large range of deviation from...specifically, it would -- applying the examiner's terms, it could be as low as 20 mol % or...and as high as 95 mol %, if you apply the examiner's stated +/- ranges.
So it -- it's a -- was established -- or

that...that +/- range that the examiner was specifying was, I think, the point that they were pushing to have more clarity.
Q. And you don't have your own interpretation of what percentage variability applied with the use of the word "about," right -- you're unable to know what the examiner thought?
A. I'm relying on the examiner's expertise and their role of playing referee in defining what are allowable claims.
Q. And you've offered no definition of your own of "about"?
A. My only definition is, as I've stated, paragraph 66:
> ...I understand that the patentee amended the claims to remove the term "comprising about" from then-pending claims based on the Examiner's construction of "comprising about" to mean "an amount +/- 10, 20, 30 mol % of a lipid component."

I think that states it clearly.
Q. Is that your own definition, or is that

the examiner's definition?
A. The examiner is the one. That's why it's a quotation.
But I'm applying that construction in my opinions in this matter.
Q. And are you offering your opinions as a person of skill in the art?
A. Yes.
Q. And so, what is the definition that a person of skill in the art would apply to the word "about"?
MR. SHEH: Objection; scope, form, foundation.
A. I don't know.
Q. And you can't provide a numerical scope of any of these claim limitations as they existed when they had the word "about" in them. Correct?
MR. SHEH: Objection; asked and answered -- five times.
A. As I said, I have applied this guidance to my opinions that I've established.
Q. So there's no numerical scope that you could offer as a person of skill in the art as to what these claims allowed for when they recited "about"?

MR. SHEH: Objection; mischaracterizes.
A. I've answered the question.
Q. There's no -- you can't put numbers to it. Correct?
A. No further response.
Q. Okay. Do you believe that when the applicant deleted the word "about," that they narrowed the scope of the claims?
A. When they deleted the word "about," did they narrow the scope of the claims -- that's the question?
Q. Yes.
MR. SHEH: Objection to scope.
A. I think this has also been answered.
Applying the "+/- 10, 20, 30 mol %," that is...is what the examiner was driving -- or was essentially speaking to, is that it was -- that the "about" allowed for a wider range of mol percentages.
Q. And as a person of skill in the art, do you believe that when the applicant deleted the word "about" they narrowed the scope of the claims?
MR. SHEH: Objection; asked and answered, scope.

A. Repeat the question, please.
Q. As a person of ordinary skill in the art, do you believe that when the applicant deleted the word "about" they narrowed the scope of the claims?
A. I've answered that question.
The use of the word "about" was a way to remove the uncertainty or the -- yeah, the uncertainty about what range was allowable.
Q. And would the "about" limitation, when it was in the claims, have allowed for variation?
MR. SHEH: Objection; scope.
A. As I say, the term "about" is what -- I'm relying on the examiner's interpretation. And they've spelled out what they view as the scope of what was a potential uncertainty.
Q. And so, you keep referring to what the examiner stated.
But I'm asking what your opinion is as a person of skill in the art who's offering opinions about the prosecution history.
MR. SHEH: Objection to scope, asked and answered.
A. I may not like driving 55, but that's what the sign says. And if I get ticketed, I'm -- have to obey the law.

This is the voice of an entity that sets the boundaries.
That's the basis that I used for my evaluation.
Q. So is that the meaning that you're applying to the word "about"?
MR. SHEH: Object to form.
A. I need a better question.
Q. Okay. So you've said that the examiner is the voice of an entity that sets the boundaries.
And I've asked: Is the definition -- "an amount +/- 10, 20, 30 mol %," is that the definition of "about" that you've applied in providing your opinions as a person of ordinary skill in the art?
A. That "+/- 10, 20, 30 mol %" is the -- is what I've taken to understand is -- as the meaning of "comprising about."
Q. If you go over to the '069 patent and if you look at the claims in Columns 91 and 92 -- and if you look at Claim 14, do you see that Claim 14 recites mol % of the four lipid components, and it recites them as about a certain mol %?
A. Right -- Claim 14, particle....
(Reading:)
Nucleic acid-lipid

particle of claim 10, wherein the nucleic acid-lipid particle comprises about 57.1 mol % cationic lipid, about 7.1 mol % phospholipid, about 34.3 mol % cholesterol or a derivative thereof, and about 1.4 mol % PEG-lipid conjugate.
Q. And did you consider this claim in forming your opinions in your declaration?
A. Yes.
Q. So if we start with the cationic lipid, it's recited as about 57.1 mol %. Correct?
A. Yes.
Q. What is the numerical scope that that claim allows for in terms of the mol % of the cationic lipid?
MR. SHEH: Objection; beyond the scope.
A. The way I read it, it maps to Claim 10. Claim 10 maps to Claim 1.
Claim 1 spells out 50 to 65 mol % cationic lipid.
So ultimately, that "about" in this case is more bounded.

Q. So --
A. It means that it's -- can be as low as 50. It can be as high as -- well, it can be as low as 49.5. It can be as high as 65.4.
That's what "about" means in this case.
Q. So is there any difference between Claim 14 and Claim 1?
MR. SHEH: Objection; scope.
A. The language is different. Of course there are differences.
Q. Okay. So if we just stick with the mol % of the cationic lipid, is there a difference in the numerical scope of that particular limitation between Claim 14 and Claim 1?
MR. SHEH: Objection; asked and answered, scope.
A. Because they're...Claim 14 is mapping back to Claim 1, the...I'm...I'm seeing that the...the -- what's the right word here? -- the about 57.1 mol % cationic lipid is a -- is a more precise description of a -- or at least three significant digits instead of the two significant digits of Claim 1.
Q. So in your mind, for Claim 14, a composition with 49 percent -- sorry 49.5 mol % cationic lipid would meet the limitation in Claim 14

of about 57.1 mol % cationic lipid?
MR. SHEH: Objection; scope.
A. Actually, I believe I've answered this question that since it maps back to Claim 1 -- and I've spelled out in my declaration what those lower and upper limits are for the cationic lipid in Claim 1 -- I think it's clear.
Q. Okay. I think you might have it backwards.
I'm asking if 50 mol % or 49.5 mol % would meet Claim 14, which recites 57.1 -- sorry, let me start again.
I'm asking whether 49.5 mol % cationic lipid would meet the requirements of Claim 14, which recites about 57.1 mol % cationic lipid.
MR. SHEH: Objection; scope.
A. It is a -- it is a -- one of many possible mol percentages that would fit within the confines of Claim 1.
Q. Okay. But I'm actually asking about Claim 14. Would it fit within the confines of Claim 14?
MR. SHEH: Objection; form, scope.
A. The -- if I apply the -- the rules --

well, actually "about" -- as I've said before, I'm -- I don't have a position on the word -- or I don't have a definition of "about" in my declaration that goes beyond my understanding of the examiner's definition.
Q. So sitting here today, can you answer whether or not 49.5 mol % cationic lipid would fall within the scope of Claim 14, which recites about 57.1 mol % cationic lipid?
MR. SHEH: Objection; asked and answered, scope.
A. I believe I've stated that now at least twice, that because of the connected -- because 14 maps to 10, Claim 10, Claim 10 maps to Claim 1 and Claim 1 -- as I state in paragraph 60, the -- for the cationic lipid the lower range, 49.5 mol % and the upper range 65.4 mol %.
Q. Okay. And you keep referring back to Claim 1. But I'm really trying to find out what is the scope of Claim 14, which recites "about."
So yes or no, would a composition with 49.5 mol % cationic lipid fall within the scope of Claim 14?
MR. SHEH: Objection; asked and answered now three times. And....

A. Can we --
MR. SHEH: Wait, wait, wait. Let me finish my objection, Doctor.
THE WITNESS: Okay.
MR. SHEH: Scope. Sorry.
MR. McLENNAN: And, yeah, Tony, I'll have to ask you to stop with the coaching objections too. Thank you.
MR. SHEH: I don't think they're coaching objections. But I think you're going way beyond the scope -- that's the problem with your questions.
A. I can't remember exactly how far we need to go back, but I did speak to this 49.5 percent.
Can we read back earlier questions -- or my responses to earlier questions?
I think my answer is unchanged from what I've already stated.
Q. So every one of your answers, you've referred back to Claim 1. But I've asked you about -- I want to know about the scope of Claim 14, which recites "about."
A. And I've said multiple times, now, that the word "about" is not something that I've defined in my declaration beyond what the examiner stated,

+/- 10 percent -- plus 10, 20, 30 mol %.
That's...you know.
Q. So setting aside what the examiner defined it as, you are not able to answer about the scope of Claim 14 because you don't have your own definition of the word "about."
Is that correct?
A. I'm applying the guidance of the examiner.
Q. And you're applying that without considering whether a person of ordinary skill in the art would think it's correct or not.
Is that right?
A. I'm applying it because those are the rules.
There are plenty of...of....
People have all sorts of opinions in this case. I'm referring back to and relying on the language of the examiner.
Q. Okay. And this deposition is about you explaining your opinions.
So do you have an opinion on the meaning of the word "about"?
MR. SHEH: Objection; form, asked and answered.
(Witness reading.)

Q. Dr. Thompson, to answer the question I asked several minutes ago, you're reviewing your declaration.
Is that right?
MR. SHEH: You did ask whether he has an opinion, and those opinions are in his declaration.
MR. McLENNAN: Thanks, Tony, for answering for the witness.
MR. SHEH: Well, you're just badgering the witness. So....
A. Please restate the question.
Q. Do you have an opinion on the meaning of the word "about" in the context of the '069 patent from the perspective of a person of ordinary skill in the art?
A. The language that seems most relevant to my opinion is stated in paragraph 66.
Q. Okay. And is that your opinion, that the examiner's construction is the correct meaning of "about" in this context?
A. The word "about" is indeterminate.
That's not what I was asked to opine on. I've not opined on that specific word, other than the context that I've spelled out here in my

declaration, and now multiple times in questioning, what I applied as what "about" means.
Q. Okay. So other than pointing to what the examiner stated during prosecution, you don't have any opinions of your own about the meaning of the word "about" from the perspective of a person of ordinary skill in the art -- yes or no?
MR. SHEH: You're free to answer the question however you wish, Doctor.
A. I've stated my position --
Q. Okay.
A. -- of how I interpret the word "about" for this case.
Q. And can you spell out what is your interpretation of the word "about"?
A. "About" -- this is paragraph 70 -- "about to mean +/- 10, 20, 30 mol % of a lipid component."
That language appears multiple times in the document. That's...I don't know what's so hard to understand about that.
Q. But is that your interpretation of the word "about"?
MR. SHEH: Objection; scope, asked and answered.
A. I'm under oath. I've put forth my

beliefs.
I've stated now, multiple times, what I believe, for purposes of this question, what I mean by -- or what I've used as my applicable definition of "about" with respect to the molar ratio claims.
Q. And you've just repeatedly referred to what the examiner said.
But you still haven't answered my question about what your interpretation is from the perspective of a person of ordinary skill in the art.
What does "about" mean in the context of the '069 patent?
MR. SHEH: Objection; scope, answered now like six times.
A. "About" -- "interpretation of about to mean +/- 10, 20, 30 mol % of a lipid component."
That's what I mean.
Q. Okay. Thank you.
Now, paragraph 71 -- in the second sentence, you've said:
...the prosecution history shows that the Examiner construed "about" to mean "+/- 10, 20, 30 mol %," and the

applicant's amendment addressed that construction.

Can you explain what you mean by "the applicant's amendment addressed that construction"?

A. Paragraph 71. Correct?

Q. Yes.

(Witness reading.)

A. Okay. So repeat the question, please.

Q. Okay. In your report, you stated at paragraph 71 "the applicant's amendment addressed that construction" -- referring to the examiner's construction there.

What are you referring to?

A. So (reading):

> The "Person Of Skill in the Art" reading the file history of the Lipid Composition Patents would therefore not understand the applicant's amendment to have disclaimed the application of significant figures and rounding to the claims.

So they're saying that the rules of the USP -- the guidance of the USP and Remington are

still relevant.

(Continued reading:)

> Rather, the prosecution history shows that the Examiner construed "about" to mean "+/- 10, 20, 30 mol %," and the applicant's amendment addressed that construction. The prosecution history...thus makes clear that the meaning of "about" as "+/- 10, 20, 30 mol %" is unconnected to whether the "Person Of Skill in the Art" would have interpreted the claim mol % ranges using the ordinary rules of significant figures and rounding.

Again, meaning that Remington and USP are still relevant.

(Continued reading:)

> The prosecution history does not at all support that the applicant intended the claimed ranges to be infinitely

precise under Moderna's position that ranges would be understood to be "exact." I...disagree with Moderna's construction.

Q. And so, the second sentence in that paragraph stating that the applicant's amendment addressed that construction, is that referring to the amendment to remove the word "about"?

A. So the prosecution history showing that "about" had this broad range of +/-.

And the applicant's amendment addressed that construction. So that's where the amendments are in paragraph 69, where the words "about" in Claim 1 had been stricken.

Q. Okay. If you look in your paragraph -- your table in paragraph 60, this is where you set out the limits of Claim 1 of '069 patent.

Now, according to you, there's different significant figures, depending on which lipid is being recited. Correct?

A. So the recited ranges that are in Column 2 of my table cite, in some cases, to two significant digits and, in other cases, one significant digit.

Q. And so, for example, for the conjugated

lipid, the lower limit is -- how many significant figures is that?

A. That would be one significant digit.

Q. The conjugated lipid, the 0.5 mol %?

A. 0.5 is one significant digit, one digit to the right of the decimal place.

Q. And so, you've only allowed 0.05 mol % variation in the lower limit.

Is that correct?

A. So the lower limit is a statement about -- is applying the rounding rules.

Q. Um-hum.

A. And so, 0.45 is -- would round up to 0.5.

If the -- well, a number 5 or greater in the hundredths decimal place would round up to 0.5.

That's what I'm saying here.

Q. Okay. And if you compare the recited range to the lower limit that you ascribed by applying significant figures and rounding, the difference there is 0.05 mol %. Right?

A. Yes. In this case it's 0.05 mol % difference.

Q. And for each of the other lower limits in your table in paragraph 60, the difference is 0.5 mol % -- compared to the recited ranges. Correct?

MR. SHEH: Object to form.
A. So because these are rounding -- a question about rounding, it's stating lower limits that, when rounded to two significant figures, the lower limit for cationic lipid 49.5 mol % would round up to 50 mol %.
Similarly for the phospholipid and cholesterol.
Q. And so for each of those -- cationic, phospholipid, and cholesterol -- applying rounding and significant figures, the lower limit is 0.5 mol % less than the numbers that appear in the recited range?
A. They're a reflection of the lower limit that would appropriately round to the relevant significant digits that are established by the -- or governed by the significant figures and convention.
Q. Is there any convention that, where you have four components and there's an amount recited for each of them, that you should apply the same number of significant figures?
MR. SHEH: Objection; form, scope.
A. I'm not clear on the question.
Can you please reframe it.

Q. So the conjugated lipid we went through earlier has a difference in the recited range compared to the lower limit, where you ascribed, you know, application of significant figures and rounding. And the difference was 0.05 mol %.
And then for the others recited in the claim, it's a difference of 0.5 mol %. Right?
MR. SHEH: Objection; mischaracterizes.
A. I believe what you're pointing to is the fact that when you're dealing with a smaller number, it may appear that there are more significant figures.
The point is: You are -- your lower limit is going to round to the recited range to establish whether it's in range or out of range.
So the specific arithmetic is not the point. It's the point that the lower limit rounds to the appropriate significant number of significant figures.
Q. Okay. I think I see what you're saying.
So you're saying the fact that the conjugated lipid is a lower percent doesn't mean that you have to apply the same degree of, for want of a better word, variation to the other lipid

components?
MR. SHEH: Object to form.
A. I'm saying that the -- whether it's the upper limit or lower limit, what's being applied is a boundary for the molar -- mol %s that would fall within the recited ranges.
Q. And you're applying rounding and significant figures conventions to each individual number in the claim. Correct?
A. I'm applying that -- those rules consistently for each of these four components.
Q. And you're applying them to each number in the claim individually. Correct?
A. I'm applying those same guidelines.
The upper limit is -- as you can see, they're all at the .4 level.
That's because if it were .5, it would round -- they could round up to a number that is outside the range.
So that's establishing the ceiling.
And the lower limits are applying those same -- consistently, the same set of guidelines are what are being uniformly applied to establish the floor and the ceiling.
Q. If you turn back to the '069 patent at

paragraph 68 and look back at Example 1.
Oh, sorry, Column 68.
A. Yes, I see it.
Q. If you look at paragraph 40 -- sorry, line~40 of Column 68, do you see there a sentence starting with the word "Typically"?
A. Yes, I see that.
Q. And it says:
> Typically, in the 1:57 formulation, the amount of cationic lipid will be 57 mol % +/- 5 mol %, and the amount of lipid conjugate will be 1.5 mol % +/- 5 mol %....

Do you see that?
MR. SHEH: Objection; form.
A. Yes, I see those statements.
Q. And what concept do you think the inventors are conveying with the "+/- 5 mol %"?
MR. SHEH: I'm sorry, Mark, which -- can you specify which "+/-" you're looking at?
MR. McLENNAN: It's Column 68, line 40.
MR. SHEH: Got it. Thank you.

A. So for -- in line 48 [sic] where they're referring to the "ionizable lipid" -- typically, in the 1:57 formulation, the lipid, ionizable lipid, will be -- well, actually, what it says is "cationic lipid." But that's always...these are most often ionizable lipids.

...the amount of cationic lipid will be 57 mol % +/- 5 mol %....

So the meaning of that to me is: It can be as high as 62 mol %. It can be as low as 52 mol %.

Q. And do you have an understanding of what the inventors are trying to convey with that?

Is that allowing for variability?

MR. SHEH: Objection; scope.

A. I think the keyword here is "typically."

So since this is in the "Materials and Methods" section of the document and it's covering a whole range of experiments, I think what they're trying to achieve here is just an economy of describing the methods.

In one formulation, they may want to use 52 mol %.

In another, they may want 62. And they're

simply trying to -- for the purposes of the reader, for the experimentalist, to just say that the formulations can be within this set of -- within this range.

Q. And with your application of significant figures and rounding, would you apply significant figures and rounding on top of this +/- 5 mol % range?

So in other words, you've said that the limit was 52 to 62 percent for the cationic lipid. Would you then apply significant figures and rounding to 52 and 62 percent?

MR. SHEH: Objection; scope.

A. As I say, this is part of an experimental method.

And so, that +/- is just telling the experimentalist that the range can fall there, within -- between 52 and 62 mol % for the specific case of a specific cationic lipid.

But for a given case, the rules of rounding and significant figures will apply.

Q. So they would apply to the 62 and 52 percent outer limits?

A. If an experiment is done at 62 mol % -- or set up at 62 mol %, that would be two significant

digits.

And the rules of rounding and -- would then apply around that figure.

So anything that might measure 62.4 or 61.5 would be the same set of rounding convention -- or it would use the same rounding convention for that specific case.

Q. So in other words, 61.5 mol % would meet 57 mol % +/- 5 mol %?

MR. SHEH: Objection; asked and answered.

A. I think you've taken my statement out of context.

What I'm -- what I -- the specific example that I gave of a hypothetical 62 mol % -- if the measured value is 61.5, that would round to 62. That's the point I was trying to make.

Q. And if the inventors have described a formulation with 57 mol %, +/- 5 mol %, would 61.5~mol % with application of significant figures and rounding principles -- would it fall within the range of 62 to -- or, sorry, 52 to 62 mol %?

A. That boundary of 57 +/- 5 would include a measured value of 61.5 --

Q. Okay.

A. -- mol %.

MR. McLENNAN: Is now a good time for a lunch break?

MR. SHEH: Yeah. Doctor, do you have a preference on time -- oh, go ahead, please.

VIDEOGRAPHER: The time is 12:29 p.m. This ends Unit 3.

We're off the record.

(Whereupon, the deposition recessed for lunch at 12:29 p.m.)

- - -

AFTERNOON SESSION
(1:10 p.m.)
VIDEOGRAPHER: The time is 1:10 p.m. This begins Unit No. 4.
We're on the record.
BY MR. McLENNAN:
Q. Dr. Thompson, on any of the breaks today did you discuss the substance of your testimony with counsel?
A. No.
Q. All right. So I think you'll be relieved to know I'm going to move past rounding to talk about your opinions about the finished lipid particle on...starting in paragraph 40 of your declaration.
And at paragraph -- if you go ahead to 48 in this section, paragraph 48.
A. Yes.
Q. In this paragraph, you're describing further processing steps that the particles could be subject to.
(Witness reading.)
A. Yes. In paragraph 48, I'm referring to other treatments that can occur after the initial particle formation, where homogenization,

sonication, or extrusion might be techniques that the sample is exposed to.
Q. And is it your opinion that each of those three processing conditions -- homogenization, sonication, and extrusion -- can affect the lipid molar ratio?
A. Yes. Each of these methods -- homogenization, sonication, extrusion -- they're high-energy input methods, and that -- although the details can be dependent on the method applied, they -- essentially, the materials in the sample can resort and alter molar ratios of the -- or the composition of the SNALP.
Q. And when you say the materials can resorb, you're talking about the lipids leaving the particle and going back into solution.
Is that correct?
A. The -- pardon me -- the word I used was "resort."
So in other words --
Q. Oh, "resort."
A. -- each of the -- of these particles are self-assemblies. They're held together with a variety of forces.
And once you apply high energy, the

materials can exchange from -- between particles, from the particle into bulk.
There's essentially a reorganization or resortment that can happen.
Q. Is the particle still intact during that process?
MR. SHEH: I'm sorry, Mark. I missed....
Q. Is the particle still intact?
A. That's a great question.
The...man, I'm -- I'm -- don't know that this has been studied in detail, looking at, you know, capturing the states, organization states, as these methods are being used.
But the expectation is that they're -- that they are -- the particle remains. It's just altered exchange rates, on/off rates, of the materials that comprise the particle that are -- is what I envision.
But as I say, I'm not aware of a rigorous study that focuses on this particular question.
Q. In the section of the patent that you point to -- and I think we might need to give you a different patent.
Let me just --

MR. McLENNAN: Since you have cites here to the '378 patent, I'll give you a copy of that too.
So we'll mark this as Exhibit 3.
(Whereupon, Thompson Exhibit 3 was marked for identification.)
MR. McLENNAN: And Exhibit 3 is Joint Appendix 6, which is the '378 patent or U.S. Patent No. 11,141,378.
BY MR. McLENNAN:
Q. So this is the patent that you're referring to in the paragraph that we were just on, paragraph 48 of your declaration?
A. Yes. I see at the bottom of 48, such as...abbreviation...'378 patent -- the second line from the bottom of page 21.
Q. And if you pull up the '378 patent and go to paragraph -- oh, sorry, page -- let me start again.
If you look at Exhibit 3, the '378 patent, and you go to Column 61.
And in paragraph 48 of your report, you're reciting -- or you're citing to Column 61 from lines~4, through to 62/27.
And if you look over the patent, it looks

like this is where it's describing the sizing of the SNALPs.
Is that right?
(Witness reading.)
A. Yes. It's -- this is the description of the methods that I'm referring to in my declaration -- in paragraph 48.
Q. And the three techniques -- so sizing -- oh, sorry, let me start again.
The three techniques -- homogenization, sonication, and extrusion -- those are referred to in this section of the '378 as methods to size the particles to a desired size.
Is that right?
A. Yes. In this section of the '378, it's -- pardon me -- referring to the initial particle formation -- and then if a change in particle size is needed for whatever reason, that one of these three methods can be used to, for example, break up aggregates or otherwise break down large -- larger parts of the dispersion into smaller -- smaller particles.
Q. And in this section of the patent here, Column 61, it doesn't refer to any change in lipid content or lipid molar ratios, right -- it just

refers to a change in size as a result of these processes?
A. At Column 61, lines 4 through 32 are simply talking about the changes in the sizing of the particles.
Q. And there's no mention of change in lipid content or lipid molar ratios?
A. This section is not describing that -- describing change in molar ratios.
Q. And in paragraph 48 of your declaration, you haven't mentioned anywhere in the patent where there is a reference to lipid content changing as a result of homogenization, sonication, or extrusion?
MR. SHEH: Objection; form.
A. Where there is existing data, those are examples that I reviewed while preparing my remarks. And it's actually the basis for my opinion that these techniques can -- that these high-energy techniques can impact molar ratios of the sample.
Q. And that's based on your knowledge in the field, not based on anything explicit in the patent.
Is that right?
A. That's based on my knowledge of working in the lipid field for a long time.
Q. If you look at the -- we could look at the

claims of the '378 patent as an example.
Do any of the claims recite anything about sonication, homogenization, or extrusion?
(Witness reading.)
A. Just to make sure I haven't lost the thread of the question, can you please restate the question.
Q. Do any of the claims recite anything about lipid particles that have been sonicated, homogenized, or processed through extrusion?
A. No. After reviewing the 30 claims, no.
Q. Okay. If you could go to Table 4 of the '378 patent that appears in Columns 73 and 74.
A. Okay.
Q. And under the heading "Finished Product Characterization," do you see it lists the size there?
A. Yes, I see that header, that column header -- and the "Size," "Polydispersity," "% Encapsulation."
Q. And the size is referring to the size of the particles?
A. Pardon me. It's referring -- it's -- the metric is nanometers. So that's the average particle diameter.

Q. Okay. And if the -- strike that.
For the size that's listed here in Table 4 under "Finished Product Characterization," would you expect that if these particles went through any of those sizing techniques that we just spoke about, that the size would be the post-sizing measurement?
MR. SHEH: Objection; form, scope.
A. I don't know.
Q. Would it make sense to refer to it as the "finished product" if it was still subject to further processing steps?
A. The term "finished" I take to relate to whatever objectives there are for the experiment.
The data that are shown here are size and percent encapsulation measurements. And so, they're "finished" from that perspective.
I don't know -- I have no idea what other experiments might have been intended for the SNALP formulations in Table 4.
Q. Do you think it would make sense if the inventors listed a size there for finished product and then it was subject to further processing steps to change the size?
A. I think the use of the -- in this case,

sizing experiment is -- in one view, can be finished in the sense that if the only goal of the experiment was to find out how different compositions might impact drug to lipid ratio and size and percent encapsulation -- that's the goal of the experiment.

But if there's additional intent to test them in cells or animals, then an additional sterilization step would need to be taken.

Q. And aside from sterilization, just focusing on the sizing techniques you are talking about in paragraph 48 of your report, do you think that the inventors could have listed this size here under finished product and then have those particles subject to some sort of sizing after that?

MR. SHEH: Objection; asked and answered.

A. By taking Table 4 literally, "Finished Product Characterization," this is reporting the size, drug to lipid ratio, polydispersity, and percent encapsulation for these formulations.

I have -- I don't know what else -- there's nothing else reported here. So it's not possible to tell whether there were additional steps taken with these samples.

Q. In paragraph 49 of your report --

actually, sorry, paragraph 50 -- you refer to a potential addition of salts.

(Witness reading.)

A. Right. The invention may include "adding nonlipid polycations which are useful to affect the liquefaction of cells using the present compositions," and that "addition of these salts is preferably after the particles have been formed."

Q. And those "nonlipid polycations" -- because they're not lipids, they wouldn't count towards the lipid molar ratio in, for example, Claim 1 of the '378 patent?

A. The nonlipid polycations would not impact the lipid -- calculated or measured molar ratio of the lipids.

Q. If you go ahead to paragraph 55, please, of your declaration -- just let me know when you get there.

A. Yes, I'm here.

Q. And in paragraph 55, you're referring back to your opinions from the IPR proceedings.

Is that right?

A. Yes. It's describing that I'm forming this opinion based on the IPR declaration and materials that cite my declaration.

Q. And if you go over the page, still on paragraph 55, starting on page 26, do you see the sentence starting at "But so too..."?

And I'll just read it into the record:

> But so too are particles formed during the manufacturing process that are subject to further manufacturing or processing steps; those particles are likewise formed or finished particles, as distinguished from starting materials that can have a different lipid composition "or" ratio.

A. Yes, I see that statement.

Q. So for a particle like the one you're referring to here that is still subject to further manufacturing or processing steps -- in your opinion as a person of ordinary skill in the art, would you still refer to that as a "final particle"?

A. I would refer to it --

MR. SHEH: Object to form. Sorry, Doctor.

THE WITNESS: Sorry.

A. I would refer to it as a "particle."

Q. Would you refer to it as a "finished particle," if it's still subject to further manufacturing steps?

MR. SHEH: Same objection; form.

A. As I was trying to clarify in the discussion about Table 4 in the '378 patent, that "finished" in my mind means you're at the end of your intended experimental agenda.

And so, the -- if your intent, as in Table 4, is to learn about the impact of variations in formulation on all the different metrics that are reported here -- the lipid ratio, size, polydispersity, percent encapsulation -- from that perspective, if that's the end of the experiment, those are "finished particles."

But if the intent is for those same particles to then be brought into some other evaluation, then the particles are...they're not finished in that sense. They're just "particles."

Q. Okay. We've been looking at the examples in the '378 or the '069 patent.

All of these examples are with lipid particles containing siRNA. Correct?

A. Can you -- I'm sorry, can you direct me to

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the -- because we're now talking about two different patents.
Q. Sorry. Dr. Thompson, do you understand that the '378 patent and the '069 patent are related and they share a specification?
A. Yes.
Q. So just because you have the '378 in front of you just for ease of reference, the examples starting in Columns 69 through 90 -- and I believe you looked through these earlier in the '069 patent, so the text should be the same but you can look through again if you need to -- all of those examples relate to lipid particles with siRNA as the nucleic acid. Correct?
MR. SHEH: Objection; scope.
(Witness reading.)
A. So Examples 2 through 11 refer to siRNA. Example 1 is "Materials and Methods" section. Example 12 is a synthetic description of a synthesis procedure.
Q. And before we leave off this patent family, today we've spoken about two patents in this family -- the '378 patent and the '069.
But you also reviewed other family members within that same patent family. Correct?

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I can orient you to paragraph 26 of your declaration.
A. Yes.
Q. And so for our discussion about the '378 and the '069 patent, is it fair to say that applies to the other patents in the family too?
A. I need you to restate the question, please.
Q. We pulled out as exhibits two specific examples, the '069 patent and the '378.
Do you see three other family members listed?
A. Yes.
Q. And you reviewed those in preparing your declaration. Right?
A. Yes.
Q. And if you didn't specifically call out those other family members as having some sort of different claims, is it fair to say our discussion today about the '378 and the '069 patent applies equally to those other patents that you've listed here?
A. I believe so, yes.
Q. At paragraph 21 of your declaration, you talk about the structure of the LNPs at issue in

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this case.
Is that right?
A. Yes.
...LNPs at issue in this case generally are formed by...self-assembly of...lipids and the nucleic acids into particles.
Q. And as far as you know -- we'll just take this one step at a time.
Do you know if the '069 patent refers to lipid particles as "lipid nanoparticles"?
MR. SHEH: Objection; form.
A. I would have to review.
Q. Is the term "SNALP" the same thing as a lipid nanoparticle, or is it different?
MR. SHEH: Objection; scope.
A. As this field was finding its way and was receiving contributions from dozens of research groups that were out in the world, there were many abbreviations that were used.
"SNALP" was one of those abbreviations.
Q. And have you referred to "SNALP" as a brand name before?
A. I am -- actually, I don't know. I don't

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know if that is a brand name or not.
Q. Based on your understanding of the term "SNALP" in the context of the '069 patent, how does that relate to the term "lipid nanoparticle"?
MR. SHEH: Objection; scope.
A. So the abbreviation for "SNALP," "Stabilized Nucleic Acid Lipid Particle," is describing stabilization.
The fact that it is a particle containing nucleic acid and is a particle that contains lipid and an LNP -- at least the formulations that are described in the...in the -- in my declaration and are summarized in -- we've looked at the ranges earlier where there are four lipid components, so it's lipid and nucleic acid in a lipid nanoparticle.
Q. You've got a diagram on page 9 of your report from a journal article from 2020.
Do you see that?
A. Yes.
Q. That's a computer-generated drawing, correct -- it's not like an image?
A. The graphical -- or what's labeled here "Samaridou 2020, Graphical Abstract" is a -- it's an artist's rendering. It's not -- it's not experimental data.

Q. Okay. Yeah, that's what I was getting at.
The artist rendering or graphical abstract, do you know whether the SNALPs of the '069 patent would look like that if you had some sort of experimental data characterizing the structure?
MR. SHEH: Objection; incomplete hypothetical, scope.
A. I don't know.
Q. Do you know if a person of skill in the art would have had....
Actually, let me start somewhere else. Withdrawn.
This graphical abstract is from an article in 2020. Right?
A. Correct.
Q. And it's setting forth what a person of skill in the art would understand about a lipid nanoparticle in 2020. Correct?
A. The graphical abstract drawing here is a -- I guess, a -- I would call it a -- kind of a summation of a number of different kinds of experiments that -- that -- of very different types, that are kind of summarized in this picture.
Q. Do you think a person of ordinary skill in the art would have had this understanding of the

structure of a lipid nanoparticle depicted in page 9 of your declaration in 2008?
MR. SHEH: Objection; scope.
A. I think there are some skilled artisans that may have had some sense. But it was a....
It was a struggle at this time to really understand what was being produced, because there -- the methods were only available -- a few labs that could give -- render this kind of pictorial image.
Q. And when you say "render this type of pictorial image," are you talking about based on experimental data or just generating this computer diagram?
A. I'm referring to the actual experimental data that underlies this summary or this easier-to-understand depiction of what is produced in a -- when generating an LNP.
Q. Do you think you would have had this understanding of the structure of an LNP in 2008?
A. In 2008 I was aware of images of a core of what we now call "lipid nanoparticles," and that that core was -- in the images was, I'll call it, "nonuniform."
In other words, the core was very textured. But the resolution at the time --

available at the time made it hard to really tell what the organization, the true organization was.
Q. And this diagram on page 9 of your declaration, it distinguishes the location of each of the four lipid components and the nucleic acid. Correct?
MR. SHEH: Objection; form.
A. It's an attempt to show that the PEG lipid or "conjugate lipid," as we've been referring to it today, the -- unfortunately, the typo, the amino lipid being the ionizable lipid or as is -- we've been referring to today, the "cationic lipid" -- structural lipid, the -- as we've been referring to it today, the "phospholipid" component, and the cholesterol component and the nucleic acid, where they -- what their likely organization is in the LNP.
Q. And in 2008, would you have known the likely organization of each of the four lipid components of the nucleic acid as depicted here in page 9?
A. That is a cartoon that is attempting to describe -- produce a rational, chemically sensible organization of the components of the mixture.
And we were operating with the same

expectations in 2008, that there are four components that are organized in forming the structure.
The tools to resolve at a molecular level, as is implied in this cartoon, still doesn't exist. That's why this is a cartoon.
Q. In 2008 would you have been able to determine where in this structure each of the four lipids would be located?
MR. SHEH: Objection; scope.
A. Actually, I think I answered that in the last question: We can't tell now. We couldn't tell in 2008.
MR. McLENNAN: Okay. So we can switch gears to the '651 patent.
I think we're up to Exhibit 4.
(Whereupon, Thompson Exhibit 4 was marked for identification.)
MR. McLENNAN: Exhibit 4 is U.S. Patent No. 9,504,651.
BY MR. McLENNAN:
Q. Is it okay if we refer to this one as the '651 patent?
A. Yes.
Q. If you go to the claims of the '651 patent -- it starts in Column 19.

Let me know when you're there.
A. Yes, I'm there.
Q. Does Claim 1 require a formulation that was made by any specific method?
MR. SHEH: Objection; scope.
A. Claim 1 describes:
A lipid vesicle formulation comprising:
(a) a plurality of lipid vesicles, wherein each lipid vesicle comprises:
a cationic lipid;
an amphipathic lipid; and
a polyethyleneglycol...lipid; and,
(b) messenger RNA (mRNA), wherein at least 70% of the mRNA in the formulation is fully encapsulated in the lipid vesicles.
So it's....
I read that to mean that the method of forming the lipid vesicles is not yet specified.
Q. Okay. So the lipid vesicle formulation

could be made by any method, as long as it meets the criteria that you just read out from the text of Claim 1?
MR. SHEH: Objection; scope.
A. It is speaking to lipid vesicle formulation that's producing a plurality of lipid vesicles with these components and having that at least 70 percent of the mRNA in the formulation is fully encapsulated in the lipid vesicles.
Q. And in your declaration, you opine that a POSA would understand the phrase you just read out as referring to "encapsulation efficiency."
Is that right?
A. Yeah -- actually, there are a number of paragraphs --
Q. Yeah, let's go to....
A. -- I was referring to that.
For example, paragraph 92, I speak -- I state:
A "Person Of Skill in the Art" would further understand that the full claim limitations "wherein at least 70%, at least 80%, about 90% of the mRNA in the formulation is fully

encapsulated in the lipid vesicles" also limit the invention of the '651 patent based on where the mRNA is located, i.e., the mRNA must be contained inside the vesicle.
Q. So you're just reading from paragraph 92.
Is that right?
A. Yeah.
Q. Is it your opinion that Claim 1 requires any sort of level of encapsulation efficiency?
MR. SHEH: Object to form.
A. As this section of my declaration is describing, that encapsulation efficiency is an experimental measure, I describe the measure in the bottom of paragraph 91 where it's the ratio of the fluorescence intensity after you destroy the formulation with detergent, minus the intensity before you destroyed the structure, divided by the after-lipid vesicles are broken.
So that -- that's what we calculate in the lab when we've made a formulation. And the interpretation, the -- what it's speaking to is how accessible the dye is to the nucleic acid before you burst the vesicles.

So if you have exposed nucleic acid, it will contribute to that.
At the bottom of page 41, three lines from the bottom:
Encapsulation efficiency is equal to....
Within that parenthetical statement, it's the "I" without -- the intensity without the subscript, that's what you're measuring before you destroy the structure. That's giving you a readout of the amount of exposed nucleic acid -- i.e., nonencapsulated.
Q. And the experimental method you were just referring to about fluorescent dyes, those aren't described in the '651 patent. Correct?
Thankfully, this is a much shorter patent.
MR. SHEH: There are good things in life.
(Witness reading.)
A. So the methods that -- actually, please repeat the question.
Q. The experimental methods you have referred to about the use of fluorescent dyes, those are not described in the '651 patent. Correct?
A. This patent does not describe the

fluorescence method. It's using a filtration method as a way to assess encapsulation efficiency -- so a different technique, but the same goal of determining encapsulation efficiency.

Q. And where is the filtration technique referred to?

A. The clearest example is in Table I, where the -- at the bottom of the table, there's a double asterisk:

> Assume that 75% of pDNA is encapsulated and all free DNA is removed. Estimate 5% loss...on anion exchange cartridge.

So it appears to me that that's a....

I refer to it as "filtration," but it's a -- essentially, a polishing step to remove the nucleic acid that's outside the particle -- that's not encapsulated in the particle -- not fully encapsulated.

Q. With the part you just pointed to, the double asterisk in Table I, it says:

> Assume that 75% of the "plasmid DNA" is encapsulated....

So is -- are all of those calculations based on an assumption that it started with 75 percent encapsulated plasmid DNA?

A. I would need to study this more fully.

I've -- you know, in -- I'm trying to respond to your questions fully and honestly.

This is -- this specific question I had not taken up before. This is my best effort to answer your question.

So, no, I don't know what the basis of that -- where that number comes from, and it's something I would need to read more fully.

Q. So the "fluorescent dye" you refer to in paragraph 91 of your declaration, that particular assay for determining percentage encapsulation is not mentioned in the '651 patent?

A. As far as I can tell from revisiting '651, there's no description of the -- the fluorescence-based assay.

Q. And the "filtration" steps you refer to at Table I, does that actually describe the analytical technique used to quantify percentage encapsulation?

MR. SHEH: Objection; scope.

A. To my best understanding in looking over this document in this moment, the descriptions of

the amount of pDNA that's recovered, the amount of lipid that's recovered, are being reported.

And how those numbers are generated, I would need to look at more carefully.

Q. Okay. There's no specific analytical technique that you can determine at this stage. Right?

MR. SHEH: Object to form.

A. I have ideas how that might be -- how that might be determined. But I don't want to speculate.

Q. In paragraph 91 of your report where you refer to the fluorescent dye method, would that include the RiboGreen assay?

A. Yes, that's the most common method for detecting RNA that's not fully encapsulated.

Q. Now, you mentioned that RiboGreen would be the most common method for detecting RNA.

Would it also be capable of quantifying percentage encapsulation of plasmid DNA?

MR. SHEH: Objection; scope.

A. I would need to refamiliarize myself with the crosstalk that may or may not exist between RNA versus DNA detection by that probe.

Q. Do different fluorescent probes exist for different types of nucleic acids?

MR. SHEH: Objection; scope.

A. There are many different probes that are used that are -- that have greater or lesser specificity for the anolytes you're focused on.

Q. And apart from fluorescent dyes, are there other methods of determining percentage encapsulation?

MR. SHEH: Objection; scope.

A. There are other methods. Most are heavier from an experimental burden perspective, and one uses/selects the assay that allows for informed decision-making on the -- either at speed, if you're -- if it's a business. Or if you're trying to publish a paper, you'll have some sense of what kind of accuracy will be needed.

There's some that I'm aware of that use radioactive phosphorus as a detection method. So -- but that has a whole -- you have to be set up for that. So you choose the right tool for the job.

Q. Is another way to measure a percentage encapsulation measuring the degree of enzymatic degradation of nucleic acids?

MR. SHEH: Objection; scope.

A. As I say, there are -- there are many different methods that can be used.

Q. Is measuring enzymatic degradation one of those methods?
MR. SHEH: Objection; scope.
A. There have been reports of using nuclease sensitivity -- or nuclease exposure as a measure of encapsulation.
Q. And are you familiar with that method yourself?
A. I've not used that method myself.
Q. But you've seen it described in the literature?
A. Yes.
MR. SHEH: Mark, is now a good time for a break?
MR. McLENNAN: Sure.
VIDEOGRAPHER: The time is 2:17 p.m. This ends Unit 4.
We're off the record.
(Whereupon, a recess was taken.)
VIDEOGRAPHER: The time is 2:35~p.m. This begins Unit No. 5.
We're on the record.
BY MR. McLENNAN:
Q. So before we broke, we were talking about methods of measuring percentage encapsulation, and

we covered the fluorescent dyes and enzymatic degradation.
Are there any other methods that you're aware of?
MR. SHEH: Objection; scope, beyond the scope.
A. You left out a couple of others that I mentioned. And they all have their own strengths and weaknesses.
So it's the fluorescence method that is the -- kind of the gold standard, in my view.
Q. Okay. And the other one, sorry, was that the radioactive phosphorus -- was that one of the other methods you mentioned?
A. Radioactive phosphorus, the method that's -- that we reviewed here of ion exchange -- just different techniques.
The one that is most valuable, in my view, and least prone to artifacts is the fluorescence method.
Q. Claim 1 of the '651 patent doesn't require someone to measure percentage encapsulation by any particular method. Correct?
MR. SHEH: Objection; scope.
A. So the key phrase of Claim 1, in my view,

is the -- is 1(b):
...mRNA, wherein at least 70% of the mRNA in the formulation is fully encapsulated in the lipid vesicles.
So that's a statement of what is measured and what the interpretation of that number means -- 70 percent inside the lipid vesicle, fully encapsulated in the lipid vesicle; 30 percent in not fully encapsulated.
VIDEOGRAPHER: Counsel, can we go off the record for one moment?
MR. McLENNAN: Sure.
VIDEOGRAPHER: The time is 2:38 p.m. We're off the record.
(Whereupon, a recess was taken.)
VIDEOGRAPHER: The time is 2:39 p.m. We're on the record.
BY MR. McLENNAN:
Q. If you go to your declaration at -- well, actually, sorry -- sorry, just to follow up that answer.
So Claim 1 of the '651 patent, there's no specific method you have to use to determine

percentage encapsulation, correct -- you just have to meet the percentage claimed?
MR. SHEH: Objection; scope.
A. It's a statement of what the -- what the '651 is describing as fully encapsulated in the lipid vesicles, at least 70 percent. Those are the key metrics.
The other 30 percent of the mRNA would be understood to not be fully encapsulated.
Q. And so, the analytical technique of determining those metrics, as you refer to them, is not set out in the claim. Correct?
MR. SHEH: Same objection, beyond the scope.
A. In Claim 1, it's not dictating a particular method.
Q. In paragraphs 81 and 82 of your report, you refer to this concept of "encapsulation efficiency."
(Witness reading.)
A. Your question again, please.
Q. You're referring to the concept of "encapsulation efficiency" in these paragraphs of your report. Correct?
A. In paragraphs -- in multiple paragraphs.

But, specifically, 81 and 82 are referring to the -- line 3 of 81:

> ...inclusion of disclosures of specific percentages of encapsulation efficiency that are tied to specific claimed percentages of fully encapsulated mRNA, and the figures in the specification, the POSA would understand the numerical values in...percentage terms to refer to encapsulation efficiency percentages.

Q. Okay. And you were just reading from paragraph 81. Correct?

A. Correct.

Q. So do the claims of the '651 patent recite a certain level of encapsulation efficiency?

A. We reviewed a moment ago in the '651 Claim 1(b), wherein at least 70 percent of the mRNA in the formulation is fully encapsulated in the lipid vesicles.

That's -- that's -- 70 percent is the encapsulation efficiency.

It's 70 percent fully encapsulated. That's what that term means.

Q. And is that synonymous, percentage encapsulation within encapsulation efficiency?

MR. SHEH: Objection; asked and answered.

A. That's what I'm trying to explain in my declaration in this section.

Q. So if you think about Claim 1 of the '651 patent -- you've got it in front of you. Right?

A. Um-hum.

Q. If you start with a composition that was made by a process that has relatively poor encapsulation efficiency, say it led to 50 percent of the starting content of mRNA being encapsulated -- but then a filtration process was applied to remove free mRNA, leaving 99 percent of the mRNA in the formulation fully encapsulated -- would that still meet Claim 1, despite originally being made by a process with poorer encapsulation efficiency?

MR. SHEH: Objection; beyond the scope of the declaration.

A. It's a hypothetical. And the....

I think my description here stands, that

the notion is that in -- when '651 is executed, that process, you are -- what will be observed is at least 70 percent mRNA in the formulation being fully encapsulated.

Q. And so, what process are you referring to?

(Witness reading.)

A. So there....

So there are processes described in Figures 1 through 4, different ways to make -- to execute this -- to achieve this standard.

Q. But the claims of the '651 patent don't require any particular method to be used. Correct?

MR. SHEH: Objection to scope.

A. I've actually answered that earlier question, that the...the -- Claim 1 is spelling out the lipids that are present, the mRNA, and the -- at least 70 percent of the mRNA in the formulation being fully encapsulated.

Q. Sorry. I'm asking about this concept of "encapsulation efficiency" that you keep referring to.

If you use a process that has less than 70 percent encapsulation efficiency, you eventually remove the free RNA from the formulation that's claimed, would that meet Claim 1?

MR. SHEH: Objection; beyond the scope of the declaration, asked and answered.

A. There....

I understand the question, and that's basically mopping up a bad process. That's not -- that's not of value.

Q. Only a bad process would include a step to remove free RNA?

MR. SHEH: Objection to scope.

A. The....

(Witness reading.)

A. So in paragraph 95, I'm speaking to the consequences of not having full encapsulation:

> The mRNA's location can have substantial practical effect, as when nucleic acid is not contained inside a lipid vesicle, it can result in toxic side effects, degradation...rapid clearance. See Wheeler 1999 at "page" 271. ("In the case of nonviral systems such as plasmid DNA-cationic lipid complexes

(lipoplexes) the large size and positively charged character of these aggregates also result in rapid clearance, and the highest expression levels are again observed in "the" first-pass organs, particularly...lung. Plasmid DNA-cationic lipid complexes can also result in toxic side-effects both in vitro and in vivo.")

Q. So you just read out the entirety of paragraph 95 from your declaration?

A. Not the entirety --

Q. Okay.

A. -- actually.

Q. Half of it.

So going back to the hypothetical question I posed, you said you understood the question and that was essentially mopping up a bad process.

But I'm really interested to know whether it would meet Claim 1's requirement that at least 70 percent of the mRNA in the formulation is fully encapsulated.

MR. SHEH: Objection; beyond the scope, asked and answered.

A. I don't know what I haven't answered.

And if there is something that is not clear, then I'm going to need to understand and think about it more.

Q. Okay. So the limitation that you opined about is in Claim 1, wherein at least 70 percent of the mRNA in the formulation is fully encapsulated in the lipid vesicles.

Do you see that?

A. Yes.

Q. So that's distinguishing between two proportions of mRNA -- this mRNA in the formulation is fully encapsulated, and mRNA in the formulation that is not fully encapsulated in the lipid vesicles.

Is that right?

A. 70 percent is fully encapsulated in the lipid vesicle. 30 percent is not fully encapsulated.

Q. And so if you start out with less than 70 percent but you remove the free mRNA from the formulation, you'd agree with me that that would increase the percentage of mRNA in the formulation

that is fully encapsulated. Correct?

MR. SHEH: Objection; beyond the scope.

A. From my perspective, you've -- whatever is unencapsulated is -- as I describe in paragraph 95, may trigger undesired biological events.

From a process perspective, you're wasting drug. It's simply -- it's a silly argument.

Q. Well, I'm not so interested in whether it's silly. I'm just interested in a yes or no answer, or I don't know.

A. I don't know, then.

Q. You don't know? Okay.

Before looking at the '651 patent in the context of this case, did you have an understanding of what "partially encapsulated nucleic acids" referred to?

A. That's what I am representing on page 7 of my declaration, this cartoon showing different kinds of assembly states.

Q. And so to answer my question, you were or were not familiar with these before starting work on this case?

A. I was aware before starting on this case.

Q. So how would you describe the meaning of

"partially encapsulated nucleic acids"?

MR. SHEH: Objection.

A. "Partially" means "not fully," in my view.

Q. And --

A. "Fully encapsulated" is very clear: The nucleic acid is within a lipid vesicle.

If it's not in that state, it can be any number of different states.

Q. And so, I think you defined what "fully encapsulated" is.

But what does "partially encapsulated" mean?

A. I've....

It means "not fully encapsulated."

And this diagram is attempting to point to different possible states of nonencapsulation or partial encapsulation.

The measure is accessibility of the nucleic acid to a small-molecule probe dye. That's the most reliable method.

And if the dye can access, it will appear as nonencapsulated or partially encapsulated.

Q. So the dye would pick up on the parts of the nucleic acid that are not encapsulated.

Is that right?

A. The dye would pick up on the parts of the -- the nucleic acid that are not fully encapsulated.
Q. Would parts of the nucleic acid be -- sorry, let me strike that.
Would parts of the nucleic acid that is partially encapsulated be inaccessible to the dye?
A. These dye measures are population measurements.
It's...you're assessing the global status of the nucleic acid and the -- the minimal experimental interpretation is that the signal, the fluorescent signal, is arising from nucleic acid that is exposed, that is not fully encapsulated within that collection of -- that constellation of particles.
Q. And the diagram on page 7 of your declaration that you've pointed to, can you show me where in this diagram "partially encapsulated nucleic acid" is depicted?
A. So, actually, each of the cartoons here are rendering or attempt to describe different kinds of partial encapsulation.
In each case, whether it's the liposome DNA aggregate or this spaghetti and meatball part of

the cartoon or the spaghetti part of the cartoon, the nucleic acid has a water-accessible, water-exposed channel that the dye can diffuse into -- so permeate between the liposomes and the liposome DNA aggregate, the end of the spaghetti and the spaghetti part of the cartoon, between the different spaghetti and meatball portions of the assembly. They're --as long as the nucleic acid is exposed, it will render a fluoroscent signal with the fluoroscent dye.
Q. In this spaghetti and meatball example, are the meatballs on their own -- are they considered liposomes?
MR. SHEH: Objection to form.
A. They began as liposomes.
All right. So that's the whole -- you notice the directionality of the arrows.
So the sample was initially produced by making a liposome population, mixing it with the nucleic acid.
Once that encounter occurs, these are self-assembled structures, and there's a mixture of states that can result.
That's what this lower part of the cartoon, the spaghetti and meatballs part of the

cartoon, is trying to depict.
Q. Have you heard of the concept of "surface-adhered nucleic acid"?
A. Repeat the question.
Q. Have you heard of the concept of "surface-adhered nucleic acid"?
A. Yes.
Q. Is that concept depicted in the figure on page 7?
A. Some of these states involve surface-adhered, if the drawing is rendering some surface-adhered states.
Q. Would a surface-adhered nucleic acid be considered "partially encapsulated nucleic acid"?
A. No.
Q. Would it be considered "unencapsulated nucleic acid"?
A. I wouldn't consider it unencapsulated, simply physisorbed to the surface.
Q. And with the diagram on page 7, all of the nucleic acids are depicted as outside of the liposomes.
Have you ever heard of a concept where the nucleic acid is poking through the liposome shell so part of it is within the liposome, part of it is

outside?
MR. SHEH: Objection; beyond the scope.
A. That -- I'm not familiar with a literature that describes that state as a -- as an endpoint or a stable state of the formulation.
Q. But you've heard of it as a concept that it could exist, maybe just not as a defined endpoint?
A. There are plenty of ideas. Only some of them are correct ideas.
Q. Have you written about that concept before?
A. I've authored 170 papers. I can't say right now whether I've written about that before. I would have to look.
Q. Would you consider a nucleic acid in that state as "partially encapsulated"?
MR. SHEH: Object to form.
A. I think I already addressed this question in the sense that you're making -- your assay reports on a population, and there may be six-legged individuals in that population.
It's going to be a pretty rare occurrence, but -- realize that's a silly metaphor. But what

I'm getting at is that your measure is of a population, and what you're recording is the fluorescence that switches on when it binds to exposed nucleic acid.

That's the limit of the measure.

Where that is coming from, the careful scientist says it is not fully encapsulated within a lipid vesicle. That's the limit of prudent interpretation of the information.

Q. And when you refer to a "population," you mean there's many nucleic acids in a formulation and that's the population you're referring to. Right?

A. It means that there are many particles and many nucleic acids --

Q. And --

A. -- within those particles.

Q. And you're just looking at the overall fluorescence to determine the percentage encapsulation?

A. You're measuring -- it -- the fluorescence measurement is looking at the report from that entire population, correct.

Q. And so for the state where the nucleic acid is partially poking outside the liposome and part of it is inside the liposome, part of the

nucleic acid will be accessible to the fluoroscent dye. Correct?

A. In that six-legged individual example, then the part that is exposed will be dye-accessible.

The other part that is not the part that somehow is entrapped, retained inside the membrane vesicle, will be dye -- should be dye-inaccessible.

The details of that interface will be important to -- or where I think it's a -- an absurd model.

Q. And is there another way to describe that scenario, other than a nucleic acid poking through the shell?

A. I don't know. I'd have to think about it.

Certainly, it's not the way I think of these formulations where they are driven by electrostatic and hydrophobic -- minimizing those hydrophobic interactions with polar solvent.

Q. Going back to the example of the partially encapsulated nucleic acid in page 7 of your declaration, if you were using the enzymatic degradation analytical technique, would you be able to -- withdrawn.

Looking at the depiction of partially

encapsulated nucleic acids in page 7, would the enzymatic degradation analytical method we talked about earlier -- would that detect the nucleic acids that are partially encapsulated here?

MR. SHEH: Objection; beyond the scope, incomplete hypothetical.

A. I don't know.

Q. Throughout the '651 patent with all the reported degrees of percentage encapsulation -- oh, sorry, let me just start again.

Throughout the '651 patent, there are reported values of percentage encapsulation. Correct?

(Witness reading.)

A. So the figures are reporting -- Figure 5, 6, 7, and 8 are referring to DNA encapsulation.

Other two small molecule experiments reported. Figure 10 is safranine.

COURT REPORTER: Is what?

THE WITNESS: S-a-f-r-a-n-i-n-e.

A. And the description on -- in Figure 11 is for one of the standards, long-standing standards in the field, calcein, c-a-l-c-e-i-n. That's an easily measured fluoroscent dye.

Q. So for Figure 10, are you saying this

shows there are measuring encapsulation efficiency with the safranine dye?

COURT REPORTER: Excuse me. Could you repeat that.

Q. For Figure 10 of the '651 patent, you pointed out a dye, safranine?

A. Yes. Figure 10 is reporting a dye to -- on the y-axis, a dye-to-lipid ratio under different formulation conditions, different buffer concentrations, different pH, different buffer type, and a similar experiment described in Figure 11.

I think the take-home from this set of experiments is that it shows that the method will be successful for small molecules like calcein or safranine, and also for large molecules like plasmid DNA, that it's....

I'm struggling to find the word I want. But it's capable of encapsulating high molecular weight and low molecular weight cargo.

Q. The two fluorescent dyes you just mentioned, safranine and calcein, could they be used to detect nucleic acids?

A. Calcein is a calcium-sensitive dye. Safranine, I don't know.

Q. Okay. So if you look back at Example --

Examples 1 and 2, Examples 1 and 2 relate to encapsulation of plasmid DNA. Correct?
A. At the '651?
Q. '651.
A. Yeah.
Q. Columns 14 and 15.
(Witness reading.)
A. Yes. Examples 1 and 2 are pDNA experiments.
Q. Okay. And those two experiments, do they describe whether the percentage encapsulation is percentage fully encapsulated or percentage partially encapsulated?
MR. SHEH: Objection; beyond the scope.
A. As we discussed earlier, this double asterisk refers to encapsulation with a -- I would need to read the -- refresh my memory to read the full document in detail to answer your question precisely.
Q. But it doesn't say in those examples -- it doesn't differentiate between full and partial encapsulation, does it?
MR. SHEH: Objection; beyond the scope.

A. It is -- Table I is reporting pDNA recovery. That's at this point what we have to go on.
Q. If you look at Column 5 of the '651 patent, there's a definition column.
Just let me know when you get there.
(Pause.)
Q. And do you see the definition on line 38 of Column 5 for the term "lipid encapsulated"?
A. Yes.
Q. And it refers to:
> ...a lipid formulation which provides a compound with full encapsulation, partial encapsulation, or both.

(Witness reading.)
Q. Are you looking through your report, Dr. Thompson?
A. I'm looking through my document, because I've opined on this. If you have the paragraph number --
Q. I'll take a look.
A. -- I'd be happy to listen.
Q. You can look at paragraph 94.
A. It begins with, actually, paragraph 93,

where the '651 patent describes some of these locations in lipid vesicle systems -- one, which the "vesicle of lipids coating an interior comprising a nucleic acid such as a plasmid with a reduced aqueous interior."
That's the language that's in the Column 5 section that you just pointed us to.
> ...liposomes, wherein an aqueous volume is encapsulated by an amphipathic lipid bilayer; or wherein the lipids coat an interior comprising a large molecular component, such as a plasmid, with a reduced aqueous "material" [sic]; "and" lipid aggregates or micelles, wherein the encapsulated component is contained within a relatively disordered...mixture.

So these different locations were well understood to the POSA at the time of the invention.
And then I give that -- the spaghetti and meatballs example again, and that the POSA would understand -- this is now paragraph 94:

> The POSA would understand that this reference to "full" and "partial" encapsulation was in reference to the different potential locations of the encapsulated nucleic acid..."within a relatively disordered mixture" or in the "interior."

Q. So if we start at paragraph 93 of your declaration, you've taken the definition from the '651 patent of "lipid vesicle" appearing at Column 5, lines 30 to 37, and you've broken it up into three parts.
And in your declaration, you've assigned it numbers 1, 2, and 3 for the different parts.
Is that right?
A. The '651 patent describes some of these locations, and then it's trying to describe what some of those possible locations could be.
Q. And then you've broken up and numbered those three locations appearing in that definition?
MR. SHEH: Objection; asked and answered.
A. 1 and 2 are essentially, I think,

describing the same concept, that both 1 and 2 are -- have the nucleic acid -- the plasmid, in this case -- within a membrane-bounded vesicle compartment.

Whether you call it an "SPLP" or you call it a "liposome," they're talking about the same thing: The nucleic acid is inside a membrane bound or membrane shell.

And 3, the lipid aggregates or micelles are what are describing -- attempting to describe states that would be more similar to the spaghetti and meatballs cartoon.

Q. So the -- you've given it number 3 in paragraph 93.

A. Um-hum.

Q. That is the spaghetti and meatballs example that we discussed earlier?

A. If we continue here, these different locations in nucleic acid and the various lipid systems were well understood. Spaghetti and meatballs comes up again.

Q. Sorry, just -- on that, you mentioned spaghetti and meatballs --

MR. SHEH: Sorry. Can you let him finish your answer?

Q. Sure. Do you want to finish, Dr. Thompson?

A. Yeah. And then we go on in paragraph 94:

> ...understand that this "means" "full" and "partial" encapsulation was in reference to the different potential locations of the encapsulated nucleic acid..."within a relatively disordered lipid mixture"....
>
> That's one category.
>
> ...or in the "interior."
>
> That's the fully encapsulated.

Q. And so in paragraph 93, you refer to the "spaghetti and meatballs" arrangement.

Which of the three types -- oh, sorry, which of the three locations in the lipid vesicle systems is that referring to? Is that just No. 3?

A. Repeat the question. Sorry.

Q. So you mentioned "meatballs and spaghetti" in paragraph 93. Right?

A. Yes, I mentioned "spaghetti and meatballs" in paragraph 93.

Q. And so, which of the locations that you've

listed in that paragraph does the spaghetti and meatballs arrangement correlate to?

A. It...the...Case 1 and Case 2 that are outlined in 93 are defining the "fully encapsulated."

3, "wherein the encapsulated component is contained within a relatively disordered mixture," that is referring to this more disordered or spaghetti and meatballs-type configuration.

That's the...the conclusion that you would make from a dye-exclusion experiment.

Q. So are you saying that only within the third location are there partially encapsulated nucleic acids?

MR. SHEH: Objection; mischaracterizes.

A. I'm saying that when you do a dye-exclusion experiment, what you are reporting -- what you're detecting are the nucleic acids of the type that are described here in paragraph 93, No. 1 and No. 2, where the nucleic acids were inside, not dye-accessible, until you added detergent and destroyed the sample and destroyed the vesicle structure so that now the nucleic acids are available.

What type or what state the unencapsulated material is in is -- is actually not -- is -- is -- the spaghetti and meatballs is -- is one of other -- is just one of the possibilities.

Q. Okay. Can the concept of "partial encapsulation" exist in the lipid vesicle systems that you've numbered 1 and 2?

MR. SHEH: Objection; beyond the scope.

A. I think my statement here is clear, in which, A, "vesicle of lipids coating an interior comprising a nucleic acid such as a plasmid with a reduced aqueous interior."

That is a bounded -- I understand that to mean a fully encapsulated plasmid.

And Item 2, liposomes, "wherein" -- "wherein an aqueous volume is encapsulated by an amphipathic lipid bilayer, or wherein the lipids coat an interior comprising a large molecular component, such as a plasmid, with a reduced aqueous interior."

They're describing a bounded -- membrane-bounded object. If it's nucleic acid, they're fully encapsulated. That's what that language means.

Q. In your numbered list, No. 1 in your paragraph, you've labeled it "SPLPs." But actually in the definition, it just refers to it as "lipids."
Is that right?
A. "In the definition," can you -- what are you referring to?
Q. We're still at paragraph 5.
A. Okay.
Q. Between lines 30 and 40.
MR. SHEH: Column 5, Mark?
MR. McLENNAN: Yes.
A. Right. Column 5 of the '651 at line 30 is pretty clear:
"Lipid vesicle" refers to any lipid composition that can be used to deliver a compound...not limited to liposomes....
That's Item 2 in my declaration in page -- or, pardon me, paragraph 93:
...or wherein the lipids coat an interior, comprising a large molecular component....
That's also essentially what's being described by 1 and 2.

Q. I think I'm just not seeing -- I think there might be some typos. I'm just not seeing where 2 actually appears in the patent. I think that's where my confusion is.
A. So line --
Q. Oh, sorry -- I'm sorry. I'm not seeing No. 1.
A. The abbreviation -- which, actually, you're highlighting.
Part of the struggle in the field is the nonuniform notation that would often be used.
So the -- the "SPLP" is a -- just a label, in which -- the key point here, in my mind, is that -- beginning with the parenthetical statement, "vesicle of lipids coating an interior comprising nucleic acid, such as plasmid."
Q. Okay. And the Example No. 1 that you've listed there, is that also considered a "liposome"?
A. Well, the '651, Column 5, beginning at line 41, actually defines it. We don't have to guess. It defines it for us.
The term here "SPLP":
...refers to a stable plasmid lipid particle. "And" SPLP represents a vesicle of

lipids coating an interior comprising a nucleic acid such as a plasmid with a reduced aqueous interior."
Q. Oh, I see. That's where you're -- that's where your quote in paragraph 93 is coming from, got it.
And so for that particular example, No. 1, the SPLPs, could you still have some partially encapsulated nucleic acid with an SPLP?
MR. SHEH: Objection; beyond the scope, incomplete hypothetical.
A. "Vesicle of lipids coating an interior comprising a nucleic acid...."
I think that to me is the key phrase.
Q. So it has to be fully coating it. It's not -- it can't be the example we spoke about earlier where it's protruding through the shell?
A. If it's protruding through the shell or it's a nonuniform coating, it's going to respond to the dye.
It will report as un -- or as a not fully encapsulated. That's the point.
Q. Okay.
MR. SHEH: Mark, if you're

switching lines of questioning, it's almost been an hour, I think.
MR. McLENNAN: Yeah, now is a good time for a break.
MR. SHEH: Okay.
VIDEOGRAPHER: The time is 3:34 p.m. This ends Unit 5.
We are off the record.
(Whereupon, a recess was taken.)
VIDEOGRAPHER: The time is 3:55 p.m. This begins Unit No. 6.
We are on the record.
BY MR. McLENNAN:
Q. So Dr. Thompson, earlier we were looking at the definitions in Column 5 of the '651 patent.
Have you still got that open?
A. Yes.
Q. So the definition of "lipid encapsulated" at lines 38 onwards, is that distinguishing between "full encapsulation" and "partial encapsulation"?
(Witness reading.)
A. As I understand this language, there...since the preceding paragraph is describing "encapsulated components," I think what they're trying to express here is that the method of

production can generate a mixture of states and that that mixture of states can result in full encapsulation, partial encapsulation, or both.

I guess, the -- so they're just trying to say you can get this ensemble of states.

Q. And the "both" in that definition that we just looked at, that's referring to a lipid vesicle or a population of lipid vesicles with nucleic acids that are both fully and partially encapsulated.

It's not referring to a single nucleic acid that is both fully and partially encapsulated. Right?

MR. SHEH: Object to form.

A. The way I heard the question, there were really two ideas.

Can we try --

Q. Yeah, maybe we'll just do it one by one.

That definition is not talking about a nucleic acid that could be both fully and partially encapsulated. Right?

A. Right. The lipid encapsulated is referring to the different types of states that were described above -- the liposome state, the lipids coating an interior of a large molecular compartment, or lipid aggregates or micelles where

the encapsulated component is contained within a relatively disordered lipid mixture.

I think that's -- that's what this following paragraph is trying to describe.

That "lipid encapsulation" means that set of possibilities.

Q. If you look at paragraph 72 of your report, in your declaration on page 34 -- just let me know when you get there.

A. Yes, sir.

Q. So the two competing constructions are set out there about paragraph 72. Right?

A. Yes, I see them -- plaintiffs' construction, Moderna's construction.

Q. And your -- or plaintiffs' proposed construction that the mRNA in the formulation is contained inside the lipid vesicles.

Does "contained inside" exclude partial encapsulation?

A. The 70, 80, 90 percent of the formulation is referring to that mRNA that is fully encapsulated, that the other -- if it's 70 percent, then the other 30 percent; 80, there would be 20 percent; or 90, there would be 10 percent that is not fully contained inside.

Q. And that remaining percent -- and if we use the 70 percent fully encapsulated as an example, that 30 percent could include unencapsulated mRNA and partially encapsulated mRNA?

A. That's my interpretation as well.

Q. Okay.

A. Just to be clear, that 30 percent is dye-accessible. So it's -- what its status is, is not revealed by the dye-exclusion experiment itself.

Q. And when you say "status," that could be the location of the mRNA?

A. It means that the mRNA, some portion of the population of particles -- in the case of 70 percent of fully encapsulated, the other 30 percent has dye accessibility.

Q. Okay. If you go to paragraph 46 of your declaration, please, on page 20.

A. Okay.

Q. Okay. And so, just so there's no confusion -- so this is within the section of your declaration where you're talking about the other patent family we discussed earlier. This is in the context of the '435 patent.

But I want to draw your attention to a sentence about halfway down, starting with, "The

POSA."

So it says:

> The POSA would understand the claims at issue in the Lipid Composition Patents are product claims that do not require any particular manufacturing process or that any manufacturing process be completed in order to constitute a "particle" within the meaning of the claims.

Do you see that?

A. Yes, I see that.

Q. And is the same statement equally true for the '651 patent, which claims lipid vesicles?

MR. SHEH: Objection; beyond the scope.

A. I don't believe I was asked to form an opinion on that.

Q. Did you understand this opinion you've got in 46 when you wrote your report?

A. Did I understand the -- I'm sorry. I missed that.

Q. The sentence here, is that an opinion that

you have -- that we just read out?
A. Yes, of course. This is my declaration, so I stand behind by declaration.
Q. And so, that's an opinion based on the fact that the Lipid Composition Patents have product claims. Right?
A. The language you just read, yeah, is:
> The "Person Of Skill in the Art" would understand the claims at issue in the Lipid Composition Patents are product claims that do not require any particular manufacturing process or that any manufacturing process be completed in order to constitute a "particle" within the meaning of the claims.

What I'm really saying is that the Lipid Composition Patents are about making particles, and that that's -- period. It's about making particles.
Q. And so, the '651 patent, would you agree those are also product claims?
MR. SHEH: Objection; form, beyond the scope.

A. I don't know.
Q. You don't know, okay.
So Dr. Thompson, I'm going to ask you about your qualifications and experience briefly.
Do you have experience in formulating mRNA LNP compositions?
MR. SHEH: Object to form.
A. I have experience in plasmid formulations, siRNA formulations.
We are currently investigating other RNA forms in the vehicles that we're developing.
Q. Does that include mRNA?
A. At present, no.
Q. So, so far, you've not had any experience formulating mRNA LNP formulations?
A. My lab does not currently have experience with mRNA formulations.
Q. And then outside of your lab, have you had any professional experience relating to mRNA LNP formulations?
A. I would answer yes.
I frequently attend conferences and other events where the findings of researchers describe their work with message RNA, both naturally expressed, chemically modified -- the various forms

that are under investigation.
Q. And have you ever conducted your own research into mRNA LNP formulations?
A. That -- I think I've answered that.
My lab has not executed experiments with message RNA. We've worked with both longer and shorter sequences than mRNA sequences.
Q. Okay. And when was the last time you worked on a plasmid --
A. Actually, I -- sorry, please.
Q. No, no. I'm sorry. Go ahead.
A. I realize I misspoke a moment ago.
So, worked with shorter RNA sequences and longer DNA sequences. Plasmid DNA, is what I meant to say.
Q. And so, where would siRNA fall in that -- would that be in the shorter RNA sequences?
A. Yes.
Q. And when was the last time you worked on a plasmid DNA lipid formulation?
(Witness reading.)
A. So the -- among the published evidence would be Reference 151 in my CV.
It's on page 14 of the CV, entitled "Development and In Vitro Characterization of

Bladder Tumor Cells Targeted" -- "Bladder Tumor Cell Targeted Lipid-Coated Polyplex for Dual Delivery of Plasmids in Small Molecules."
So that's 2019.
The work reported in -- on the next page, Citation 169.
The Oncotarget paper in 2022 is reporting the use of polypeptide fusion proteins that were actually produced by lipid transfection of the plasmid and coating elastin like polypeptides.
COURT REPORTER: What was that last word -- the last before "polypeptides."
THE WITNESS: "Elastin."
COURT REPORTER: Thank you.
THE WITNESS: Like "polypeptides."
MR. SHEH: E-l-a-s- -- okay. Sorry.
BY MR. McLENNAN:
Q. Throughout your career, have you ever worked on a commercial-scale formulation of LNPs?
MR. SHEH: Object to form.
A. I didn't catch the first part.
Q. Let me rephrase.

Throughout your career, have you ever been involved in the development of a commercial-scale LNP formulation?

A. I've consulted organizations that are involved in that kind of work, but not -- I don't have hands-on commercial-scale LNP formulation work. That would be....

So in that context, no.

Q. And are all the consultancy positions that you've held listed in your CV?

And this is in Appendix A to your declaration.

A. The form of the CV that I've provided here does not appear to show organizations that I've consulted for.

Q. Do you keep another CV that shows your consultancy relationships?

A. Generally not.

That seems like privileged information to me. So I tend to not put it on a document that is subject to being public.

Q. So when you say "consultancy," you're talking about litigation consultancy?

A. No, not "just."

I consulted for --

MR. SHEH: I just caution the witness -- besides privileged communications with counsel, if you have obligations of confidentiality to these third parties that you're consulting with, I just want you to be cognizant of that.

And to the extent there's an issue, we can talk about it -- well, Mark and I will meet-and-confer -- Mr. McLennan and I can meet-and-confer to see how necessary it is to delve into these third-party confidential information.

THE WITNESS: Thank you for that heads-up.

A. I have signed confidentiality agreements. So I think I'm --

Q. Okay.

A. -- I'll leave it at that I did.

Q. I could narrow it down, or you could just give me a yes or no answer.

But have you ever consulted for any of the parties to this litigation, outside of this current proceeding and the previous IPR proceedings?

A. So for Arbutus and Genevant -- I guess that's what you're referring to specifically -- I've not consulted with -- for those organizations.

Q. Earlier we touched on analytical methods for measuring lipid content, and you said -- we spoke about HPLC.

Have you personally ran HPLC experiments to measure lipid content in lipid compositions?

A. Yes.

Q. Okay. During any of the breaks today, did you discuss the substance of your testimony with counsel?

A. No.

MR. McLENNAN: Okay. Pending any questions from counsel for the plaintiffs, I have no further questions.

Thank you for your time, Dr. Thompson.

MR. SHEH: Can we go off the record?

VIDEOGRAPHER: The time is 4:18 p.m.

We're off the record.

(Whereupon, a recess was taken.)

VIDEOGRAPHER: The time is 4:27 p.m.

We're on the record.

MR. SHEH: This is Tony Sheh from Williams & Connolly. Thank you for your time today, Dr. Thompson. Plaintiffs have no questions.

We can go off the record.

VIDEOGRAPHER: The time is 4:27 p.m.

We're off the record.

(Whereupon the deposition concluded at 4:27 p.m.)

DEPONENT'S SIGNATURE

Please be advised I have read the foregoing deposition, pages 1 through 165, inclusive. I hereby state there are:

(Check one)

_____ No corrections

_____ Corrections per attached

_____
DAVID H. THOMPSON, PH.D.

( ) Reading and signing was requested.

( ) Reading and signing was waived.

(X) Reading and signing was not requested.

Should the signature of the witness not be affixed to the deposition, the witness shall not have availed himself of the opportunity to sign or the signature has been waived.

--oOo--

ERRATA SHEET

NAME OF CASE: Arbutus Biopharma Corporation, et al. v. Moderna, Inc., et al.

DATE OF DEPOSITION: November 14, 2023

NAME OF WITNESS: DAVID H. THOMPSON, PH.D.

Reason Codes:

1: To clarify the record.

2: To conform to the facts.

3: To correct transcription error.

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DECLARATION UNDER PENALTY OF PERJURY

I am the witness in the foregoing deposition.

I have read the foregoing deposition or have had read to me the foregoing deposition, and having made such changes and corrections as I desired, I certify that the same is true in my own knowledge.

I hereby declare under penalty of perjury that the foregoing is true and correct.

In witness whereof, I hereby subscribe my name this _____ day of _____, 2023.

_____
DAVID H. THOMPSON, PH.D.

CERTIFICATE

I, SUSAN ASHE, a Registered Merit Reporter and Notary Public, hereby certify that the foregoing is a true and accurate transcript of the deposition of said witness, who was first duly sworn by me on the date and place hereinbefore set forth.

I FURTHER CERTIFY that I am neither attorney nor counsel, nor related to or employed by any of the parties to the action in which this deposition was taken, and further that I am not a relative or employee of any attorney or counsel employed in this action, nor am I financially interested in this case.

Dated this 16th day of November 2023.

_____
Susan Ashe, Notary Public
of the District of Columbia
My commission expires: May 14, 2028.

JOINT APPENDIX 89

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,	)	
Petitioner,	)	NO. IPR2019-00554
vs.	)	PATENT NO. 8,058,069
ARBUTUS BIOPHARMA CORPORATION,	)	
Patent Owner.	)	

DEPOSITION UPON ORAL EXAMINATION OF
DAVID H. THOMPSON, Ph.D.

WEDNESDAY, JANUARY 15, 2020
9:04 A.M.
701 5TH AVENUE, SUITE 5100
SEATTLE, WASHINGTON

REPORTED BY: VICKY L. PINSON, RPR-CCR Washington 2559
California No. 9845; Oregon No. 16-0442
JOB NO. 3835178
PAGES 1 - 211

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INDEX

Seattle, Washington; January 15, 2020
9:04 a.m.
* * *

DAVID H. THOMPSON, Ph.D.,
sworn as a witness by the Certified Court Reporter, testified as follows:

EXAMINATION
BY MR. WELLS:

Q. Good morning, Dr. Thompson. Welcome back. We've been through this a couple of times. Do you remember the general rules of a deposition?
A. Yes.
Q. You understand that you're under oath and obligated to tell the truth and the whole truth?
A. Yes.
Q. And if you'll allow me to finish my questions before you answer, I'll try to make sure that you can finish your answers before I begin the next question and make sure we don't talk over each other.
A. Yes.
Q. And if you don't understand any of my questions, I'll see if I can clarify them. Any reason you can't give your best testimony here today?

A. No.
Q. Now, you submitted a declaration in the IPR relating to the '069 Patent. Is that correct?
A. Yes.
Q. And when I said '069 Patent, you understand that I'm referring to U.S. Patent No. 8.058,069?
A. Yes.
MR. WELLS: And so let's go ahead and mark as Exhibit 1 a copy of your Declaration.
(Exhibit 1 was marked for identification.)
MR. ROSATO: It's Exhibit 23 already entered.
MR. WELLS: And let's go ahead and mark as Exhibit 2 to your deposition, which is Exhibit 2032 to the IPR, a copy of your CV.
(Exhibit 2 was marked for identification.)
Q. Okay. And is your CV current and up-to-date?
A. I'm just checking that. Yes.
Q. Now, when I was looking through your CV, I think I noticed that you had published nine additional articles since you had provided testimony previously in the IPR relating to the '435 and the '127 patents. Does that sound right?
A. Let me get the timeline here. I'm sorry, could you repeat the question? I want to make sure I

have it.
Q. When I was looking through your CV, it appeared that you had published nine additional articles since we had previously spoken at your deposition in the '435 and '127 IPRs. Does that sound right to you?
A. So my recollection is that the last time we had spoken was in January of 2019, and so it would have been, by that time it would be publications of 146. So by my account that would be two, four, five publications that appeared. There are a number that are still in process that are described here as in preparation.
Q. And do these additional publications relate to your work with polymer carrier chemicals?
A. These are -- one of those five is dealing with polymer carrier particles, yes.
Q. Do any of those five additional publications deal with cationic lipid carrier particles?
A. Since our last meeting these five that have appeared are focused on high throughputs. This is high throughputs screening machine learning. And the development of a polymer carrier system. So none of these that have yet, that have appeared are actually describing the use of cationic lipids.

Q. And so regarding your publications, you haven't published on cationic lipid -- cationic LNPs. Correct?
A. That actually is incorrect. I have published on cationic lipid particles. Just not since our last, since our last meeting.
Q. And do you have any additional patents that you've obtained since our last meeting?
A. So on page 15 the item that is listed No. 8, that actually is now issued, and that would be the only change.
Q. And does your patent work -- since our last meeting, do any of those patents relate to cationic LNPs?
A. The patents that are listed here are focused on polymer carriers for delivery. Both synthetic polymer and biopolymer, trying to advance the field of beyond cationic lipid particles.
Q. And the focus of your work is on polymer lipid carrier particles. Correct?
A. At present our focus is on polymer carriers. At the time of the '069, we were very actively involved in lipid particle, specifically bioresponsive lipid particles that would degrade in a program manner. But that is a theory that at present we typically use lipid

nanoparticles more or less as a benchmark for comparing our polymer carrier systems.
Q. And regarding your prior work at the time of the '069 Patent, just so we're clear as to the time we're talking about, what time frame are you referring to?
A. So this would be in, with respect to our work beginning in 1994 and extending actually actively in the lipid delivery area through the citation 110. So 2014 is where our, where the heart of the paper, the subject is focused on cationic lipid formulation.
Q. Did you say Publication 110?
A. Yes. Actually, yes, 110, entitled "DNA-Epitope Vaccine Provided Efficient Protection to Mice Against Lethal Dose of Influenza A Virus H1N1." So that's a paper describing a cationic lipid that we had developed that was degradable, and we were evaluating it as a potential vaccine in a mouse model.
Q. Now, I think that you mentioned earlier that you had done some research relating to degradable lipid particles. Correct?
A. Yes.
Q. Were those all cationic lipid particles or --
A. Not all cationic. There were some degradable phospholipids, actually natural products, so-called

plasmid coating lipids that are found predominantly in brain sarcoplasm as only malate (phonetic) source. It was kind of a natural choice because being natural products, they would have an intrinsic metabolic pathway, not only for their synthesis, but also for their degradation. And so it seemed like a natural family of materials to explore for nucleic acid delivery applications, since it got right to the heart of what the problem was from the very first cationic lipid publication, was their toxicity.
So that was really where we first established our efforts. We then -- so that's for phospholipid. That work, as I mentioned, the first publication appeared in '92, actually. That would be in the citation or publication listed here on page 3, Nos. 16 and 17, plasmalogen liposomes, and then extending into the mid 2000s where we were essentially using the same platform -- or I should say the same chemistry, to be more precise, the same phenyl ether, also called vinyl ether chemistry. But repositioning it to the position between a polyethylene glycol and a lipid anchoring group.
And so it, from a chemical reaction point of view it displayed the same kinds of reactivity profiles. But it was, instead, a non-cationic

MR. ROSATO: Objection to form and scope.
A. Actually, that's speculative. Some might actually say that -- look at the data and say, Gosh, 2 to 40 is the sweet spot. What I want to do is use my cationic lipid and see if I can push at 40 percent and push the performance. Maybe I want to vary some other, one of the many other variables that contribute to the efficacy of these particles.
It's not a -- these are multi-variant formulations. And it's as when we met a year ago, this was one of the key points, is that there were so many variables. It was unclear even if someone reports a positive result. Unclear what was truly positive. You're measuring. You have a readout. That readout is coming. It's downstream from so many events. The cargo has to get in. It has to be -- has to engage its target. It has to either not engage or nontarget or at least hopefully not contribute to toxicity. It needs to get into the cell. It needs to get under wrap. It needs to get to the target tissue. It needs to not be recognized by the immune system.
There are so many factors, that when you're using a measure of function that is so far downstream, at the time of the '069 and our level of understanding of how these complexes actually performed, you have no

clue about where, which of those steps, multiple steps -- and I've only touched on some of them -- which of those steps has been productive or how many of the steps have been productive or to what extent step No. 3 has gotten slightly better and that now increases the likelihood of step No. 4. It is rocket science. People didn't know what was at the root of enhanced function.
MR. ROSATO: Maybe it would be a good time to take a break, based on the length of time.
(Recess 2:57 p.m. - 3:10 p.m.)
Q. (By Mr. Wells) So we're still talking about the 189 Publication and the disclosures therein. So going from the 2 to 30 formulation to the 2 to 40 formulation, the cationic lipid was increased by 10 percent. Correct?
MR. ROSATO: Objection to form.
A. Right. Of those formulations, it's the cationic lipid and the other component. The other components of the formulation have to be adjusted accordingly.
Q. And in this case they adjusted the phospholipid down by 10 percent. Correct?
MR. ROSATO: Objection to form and foundation.

A. So in Example 12, the, it's the DSPC cholesterol 20 to 48. And in Example 14, DSPC cholesterol is 10 to 48.
So, right. As the cationic lipid concentration is increased, it's being, they're holding cholesterol constant and lowering the phospholipid concentration.
Q. And that's because you've still got to equal hundred percent. So you've got to figure out where your 10 percent is coming from. Correct?
A. Correct.
Q. And in your opinion was adjusting the phospholipid an obvious choice among the lipid components to change?
MR. ROSATO: Objection to form. Scope.
A. Um, as I've said multiple times now, it's an ensemble property. That's one way. At least to their credit they didn't change more than two variables. So they're at least keeping the conjugate lipid and the cholesterol constant. But one could -- since you're trying to explore unknown space, other choices are possible.
Q. One of skill in the art at the time if they were trying to find the sweet spot for these different things, they very well might have adjusted the

phospholipid to accommodate an increase in cationic lipid and test it in order to figure out whether that's the sweet spot. Is that right?
MR. ROSATO: Objection to form and scope.
A. There were many variables that could be changed. I don't want to speculate on what -- or presume to guess what one investigator versus another might choose.
Q. Are you aware of any reason why one of skill in the art at the time would not have wanted to change the phospholipid from 20 to 10 and would have said, Oh, that's a horrible idea?
MR. ROSATO: Objection to form and scope.
A. I think your own statements earlier about cholesterol content and the possibility for precipitation might be actually one of the reasons to hold the phospholipid constant and change the cholesterol composition.
It just, it's speculative and it is not what -- it's not an assumption that a careful scientist would be comfortable making. You do the experiment, you look at the data that come from that experiment, and then you make your information-base decision. You don't -- you can guess, but it's more searching in the darkness.

Q. And when they were switching from the 20-to-30 formulation to the 2-to-40 formulation, is that the kind of titration approach or optimization that we were talking about earlier where you're testing different variables to see where the sweet spot is?
MR. ROSATO: Objection to form. Scope. Misstates.
A. As you're developing a safe and efficacious formulation, you are, you're trying to design your experiments in a way that hopefully shed some insight into what parameters might be more important than others. So you, it's really a body of data that you're generating to guide you to the best formulation.
Q. Now, if a researcher is using similar building blocks, meaning similar lipids like DLin DMA, cholesterol, the phospholipid and the conjugated lipid, and wanted to find out where the sweet spot was for that combination, and we've already tested the 2-to-30 and the 2-to-40, is there any reason why the researchers wouldn't try the 2-to-50?
MR. ROSATO: Objection. Form. Scope. Incomplete hypothetical.
A. Without looking at other formulation aspects, what ions are present during the formulation? What is the formulation methodology? There are multiple

paths -- I should say multiple variables that could be explored. One you mentioned is just one of many possible avenues to explore.
Q. But a person of skill in the art if they've already shown increased efficacy moving from 2-to-30 to 2-to-40, it would have been obvious for them to try the 2-to-50. That's not something that would be out of the box?
MR. ROSATO: Objection to form. Scope. Foundation.
A. I think that's incorrect because you are someone -- a person of skill in the art at this time looking at just body weight as the measure of toxicity is, one, is being careful particularly in a corporate setting. You don't -- you get burned by your assumptions. That's one of the first lessons you learn in graduate school is to avoid assumptions. Certainly never trust them. And so of the set of parameters that one can vary, varying cationic lipid is just one of many choices that can be made.
Q. So looking at the move from the 2-to-30 formulation to the 2-to-40 formulation in the 189 Publication, if you wanted to further test what the sweet spot or the optimal range was, varying the cationic lipid is one potential variable that you could

vary among them to try to determine that?
MR. ROSATO: Objection to form. Foundation. Scope.
A. You know, I allude to this in essentially the heart of your question. I allude to in my declaration, saying that the rules were not known and the steps were not -- you could write on the board, but you did not know where the, where the leverage was. And if it was that obvious, why didn't it happen before '069? It's, that was a pivotal teaching that happens to be borne out by all that follows. Petitioner's own data, the fact that there's a FDA-approved product that falls in that specification, multiple independent laboratories.
You know, they could have made the assumptions that you're asserting. They didn't. It wasn't obvious. It's because it was multi-variant.
Q. Now, you keep mentioning Patisiran. And you did in your declaration an actual calculation of the molar weight associated with Patisiran. Is that correct?
A. 50 mol percent.
Q. Was it 50 exact or did you round it?
A. It's a rounded number.
Q. Do you know whether it was below 50 or above 50?

A. I, that was work that I had done sometime ago, so I can't recall.
Q. So if it was below -- are you done?
A. I can't recall how it was rounded. I'm sure that Alnylam, if it was lower than 50, would be looking for some way to steal this property.
Q. Steal this property, what are you talking about?
A. '069. It's the formulation that covers their property.
Q. You understand that the '069, the minimum amount of cationic lipid in that range is 50 percent. Correct?
A. Um-hmm.
Q. And when you calculated the molar percentages, you calculated the percentage for Patisiran at 50 percent. Correct?
A. Um-hmm.
Q. And that's a rounded number. Correct?
A. That is my recollection, yes.
Q. That's, sitting here today you don't know whether you rounded up to 50 percent or down to 50 percent. Right?
A. At this moment without the calculation in front of me, I, what I'm saying is that it's two

significant digits. Five-zero.
Q. And is it your understanding that the range of the claims would cover 49.95 because of the significant digits?
MR. ROSATO: Objection to form.
Q. (By Mr. Wells) And let me clarify that because I didn't say what part of the range. Is it your understanding that the claimed range of 50 to 65 percent cationic lipid would cover 49.95 percent cationic lipid?
MR. ROSATO: Objection to form.
A. It would be tied to the precision of the measurement. So whether it's mass-based or HPLC-based or whatever other measurement tool that's being used.
Q. Now, the carrier particles used in the Patisiran, the target is 50 percent. Is that correct? According to your calculation for the cationic lipid percentage.
A. 50 percent, yes.
Q. But that's the target; right? There's some plus-or-minus variability allowed. Correct?
MR. ROSATO: Objection to form. Foundation.
A. I haven't read the FDA insert with the product to see what that precision is. I didn't speak to that

in my declaration. The precision of that particular value, what I stated was 50 percent.
Q. But you would expect there to be some measure of variability allowed in the percentage of cationic lipid in the carrier particle for Patisiran, allowed by the FDA. Correct? It doesn't have to have 50.0000 percent exactly, to be properly formulated?
MR. ROSATO: Objection to form.
A. What I'm saying is that there's a precision of the measurement. I have not read and I am not prepared to comment on what the FDA insert or specifications allow. But one is -- one would expect that there is some batch variation or other variations in the product.
Q. And, in fact, we've talked about it before, how when you have these target percentages for your molar proportions, there's usually a bell-shaped curve where your target is somewhere in the large portion of the particles. But as we get to the shoulders, you're going to vary one way or the other. Correct?
A. What the number is indicative of is the average. The mean of the formulation. And they're within that distribution of particle sizes and compositions. There may be variations of, one, a particle may have a slightly different composition than

another particle in the composition. Globally or since you're measuring an ensemble property like concentration, you're looking at the overall lipid concentration in that, in that sample.
Q. So when it says a mol percentage in the '069 Patent, it's your understanding that that's an average molar percentage over the particle population?
MR. ROSATO: Objection to form. Foundation.
A. The expectation is that any approved product, there will be a well-defined range of concentrations and accepted tolerances.
Q. Looking at the '069 Patent, is it your understanding that where it says a cationic lipid comprising 50 mol percent to 65 mol percent of the total lipid present in the particle, that that's an average of all the particles in the population? Or do you have a different understanding?
MR. ROSATO: Objection to form. Foundation and scope.
A. It is guiding the field to the place where active formulations that are well tolerated can be expected. It's citing two significant digits in this -- in that example. And so that's the level of precision.

Q. And the claim from the '069 Patent is directed to a nucleic acid lipid particle. Correct?
A. A nucleic acid lipid particle comprised.
Q. And that's not a population of particles. It's a particle. Correct?
A. Well, a particle, if we could make just a particle and had that level of control, we may not be having this conversation. That's referring to a way of making a particle. And a position of skill in the art knows that what's being described is a population. A formulation of particles that has that composition.
Q. And so for Patisiran, since the target is 50 mol percent cationic lipid, according to your own calculations, and there's some level of variability expected in those particles, a proportion of the particles in the Patisiran are outside of the range for the '069 patent. Presumably, correct?
MR. ROSATO: Objection to form.
A. That's your presumption. Not mine.
Q. Would you presume that all of the particles in Patisiran are at 50 percent or over cationic lipid, based upon your experience as an expert in this field?
A. I would, in the absence of data to evaluate, I would expect that a FDA-approved product would have the kind of rigor of analysis that would have that

composition well mapped out. So it's, it's just based on multiple experiences with other kinds of FDA disclosures of whether it's a small molecule drug or, in this case, a formulation.
Q. Back to my question. Would you presume as an expert in the field that all of the particles in Patisiran have over 50 percent cationic lipid, based upon familiarity and experience with this technology?
MR. ROSATO: Objection to form. Asked and answered.
A. Since I'm not being informed of any of the data or the method of formulation or any of the other parameters that I've laid out that I've said now multiple times, it's multifactorial. It's simply wrong to speculate. That's wrong-minded.
Q. So you don't know one way or the other whether the particles in Patisiran are all over 50 percent cationic or whether some are below?
MR. ROSATO: Objection.
A. That's your statement, not mine. What I've said now three times already is that I expect that because it's achieved FDA approval, that there has been a, that there's an underlying analysis of that product. Otherwise they likely would not have achieved the approval that they received.

You have to show your composition, you have to show that there are no genotoxic components in that formulation. You need to show that it's reproducible so that batch-to-batch uniformity is appropriate for human therapeutics. So there's a whole underlying, I guess, trust that there are, that FDA is doing its job. And defining that. You're making an assumption and I've just spelled out what my expectation is in terms of composition.
Q. Well --
A. And it's mapped out.
Q. You've told me it's mapped out and the FDA has rigor, but I'm asking you whether you have an opinion as to whether all the particles in Patisiran have over 50 percent cationic lipid?
MR. ROSATO: Objection. Asked and answered.
A. I'll just say "all" is an absurd word in this context. It's a distribution, as I've said multiple times. How narrow that distribution is? To use your numbers, 49.95 percent to 50.05 percent? Or is it broader than that? I have no idea. But it is a expectation that that is -- that the mean value is 50 percent.
Q. Do you know what the cationic lipid used in

Patisiran is?
A. I don't recall the -- I believe I know, but I'm, I would want to review that, the product insert, to be certain.
Q. Does MC3 sound familiar?
A. That is, that is the species that I was inclined to remember.
Q. Do you know when MC3 was introduced into the market?
A. Into the market is when Patisiran was approved, which was 2018. Specifically, August 19 of 2018. I was at the Gordon Conference where that announcement was made.
Q. Do you know when MC3 was made available in the industry?
A. It -- actually, it's among the family of compounds that I spoke about earlier. It's part of the discovery of Steve Ansell and the lipid chemistry team. So there was a whole family of those compounds that the MC3 -- pardon me -- the MC family, where they walked the cation effectively away from the surface and evaluated their efficacy.
Q. MC3 is not an ionized cationic lipid. Correct?
A. It's an ionized cationic lipid.

Q. And the '069 Patent doesn't disclose MC3 specifically as an example of a cationic lipid that can be used with the patent technology. Correct?
MR. ROSATO: Objection to form.
A. It's stating a cationic lipid.
Q. It doesn't mention MC3 specifically without -- anywhere in the specification to your recollection. Is that correct?
MR. ROSATO: Objection. Asked and answered.
A. It is -- claim 1 is a cationic lipid.
Q. Right. But the '069 Patent gives examples of cationic lipids. Do you recall those discussions in the '069 Patent? We talked about them earlier today.
MR. ROSATO: Objection to form. Foundation.
A. Right. There are, just as we've reviewed in the other documents, there are other cationic lipids that were commonly part of an evaluation package. The family that is -- at least the notation that's being used here, this is column 18, the K2-C2 or otherwise known as XTC 2 is just members of that same family of lipids where they're cationic lipids, where they're manipulating the hydrolyze ability, the Acyl chain unsaturation degree, and the position of the ionizable

group relative to what's presumed to be the membrane surface.
Q. But MC3 is not one of the listed cationic lipids as examples in the '069 Patent. Correct?
MR. ROSATO: Objection. Asked and answered.
A. MC3 was a later member of this family of lipids that is being reported here.
Q. And when you say a later member of the family, a later developed member of the family than the ones reported in the '069 Patent. Correct?
A. Later from finding their way in this document? What I'm uncertain of is whether MC3 existed on the planet. Was it actually coming out of the synthesis pot at the time of the filing of the '069, and was it simply the dataset that may have existed that wasn't mature enough to find its way into this disclosure? It's presumptive. Your question is presumptive.
Q. If we can look at your declaration, please, at paragraph 27? You say it was widely understood. Read the second sentence and let me know when you're done reading it.
A. Yes.
Q. How do you reconcile your assertion that the amount of cationic lipid needed to be kept as low as

possible with the disclosures in the 189 Publication? That the cationic lipid could be increased to 30 percent and then increased even further to 40 percent?
MR. ROSATO: Objection to form. Misstates.
A. The statement here is pointing to the fact that the collective understanding of the field at the time was as it says: Keep the amount of systemic -- particles for systemic use, the amount of cationic lipid and the formulation should be kept as low as possible because of concerns over the toxic effects.
And so that's what was guiding people's thinking, was to keep cationic lipid concentration low. Here are publications showing that you can go from 15 percent cationic to 30, to even 40 in these specific formulations with toxicity measures of body weight.
So it's not changing the collective understanding. The whole body of knowledge was pointing to the toxicity of cationic lipids. And still points to their, the liabilities that they represent.
Q. Do you think that the disclosures in the '189 Patent, that you can go from 15 percent up to 30 percent and then to 40 percent cationic lipid are inconsistent with the collective understanding that

you're referring to at the time?
MR. ROSATO: Objection to form. Misstates.
A. What I'm saying is that this is a dataset. There were other datasets that we're not looking at that were very clearly pointing out the toxicity of high cationic lipid. So to cherry-pick one set of results is, you do at your own peril.
Q. But you would agree that if I look at the disclosures in the 196 Publication and the 189 Publication, that indicates that increasing the cationic lipid is not necessarily a bad thing.
MR. ROSATO: Objection to form.
A. From the perspective of the time of the '069, where it's clearly laid out, the collective understanding is that these are, this is a set of findings. And it has to fit with other findings where, in fact, high cationic lipids were shown to be very toxic. So it's just a, it's a retrospective point of view. Once you know what the answer is, you now know where to go. That's essentially a retrospective analysis. At the time there was no assurance that this was the right direction to go.
Q. But there was certainly an indication that it might be. Wasn't there? I mean, Protiva's own

disclosures showing that you can increase the cationic lipid from 15 percent to 30 percent to 40 percent. If one of skill in the art was aware of those disclosures, wouldn't it have been reasonable for them to try an even higher cationic percentage?
MR. ROSATO: Objection to form. Argumentative. Asked and answered.
A. As I've said multiple times, it's not just the composition. What lipids we're talking about, how the particles are formed, there are multiple measures. That is retrospective analysis.
Q. In your declaration you discuss the appropriate claim construction of nucleic acid lipid particle. Do you recall that discussion? It begins on paragraph 30 of your declaration, if that's helpful to you.
A. Yeah, it's helpful. Thank you.
Q. I'm not asking you to read the whole thing. Do you recall the general discussion?
A. Yeah. Yeah, I do.
Q. And then in the paragraph 31 it says: You've been informed by counsel that claim term should be construed based upon how they would be understood by a person of ordinary skill when read in light of the specification and the prosecution history.

I, DAVID H. THOMPSON, Ph.D., do hereby declare under penalty of perjury that I have read the foregoing transcript of my deposition; that I have made such corrections as noted herein, in ink, initialed by me, or attached hereto; that my testimony as contained herein, as corrected, is true and correct.

EXECUTED this _____ day of _____, _____, at _____, _____.

(City) (State)

_____

DAVID H. THOMPSON, Ph.D.

REPORTER'S CERTIFICATE

I VICKY L. PINSON, RPR-CCR, the undersigned Certified Court Reporter, pursuant to RCW 5.28.010 authorized to administer oaths and affirmations in and for the State of Washington, do hereby certify that the sworn testimony and/or proceedings, a transcript of which is attached, was given before me at the time and place stated therein; that any and/or all witness(es) were duly sworn to testify to the truth; that the sworn testimony and/or proceedings were stenographically recorded by me and transcribed under my supervision; that the foregoing transcript contains a full, true, and accurate record of all the sworn testimony and/or proceedings given and occurring at the time and place stated in the transcript; that a review of which was requested; that I am in no way related to any party to the matter, nor to any counsel. Nor do I have any financial interest in the event of the cause.

WITNESS MY HAND this 29th day of January, 2020.

VICKY L. PINSON, RPR-CCR

Washington Certified Court Reporter, CCR 2559