In The Matter Of:

BRISTOL-MYERS SQUIBB COMPANY

v.

GENENTECH, INC., and CITY OF HOPE, et al.

DR. JEFFERSON D. FOOTE - Vol. 1

January 9, 2015

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SANOFI v. GENENTECH
IPR2015-01624
EXHIBIT 2010

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA
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BRISTOL-MYERS SQUIBB COMPANY,
Plaintiff/
Counter-Defendant,

vs.

Case No.:
2:13-cv-05400-MRP-JEM

GENENTECH, INC., and CITY OF HOPE,

Defendants/
Counter-Plaintiffs.
/

MEDAREX, L.L.C.,

Third Party Defendant/
Counter-Claimant.
/

VIDEOTAPED DEPOSITION OF
DR. JEFFERSON D. FOOTE

Friday, January 9, 2015

REPORTED BY: RACHEL FERRIER, CSR 6948
(NY-019567)

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BE IT REMEMBERED that, pursuant to the laws governing the taking and use of depositions, on Friday, January 9, 2015, commencing at 9:40 a.m. thereof, at the Sheraton on El Camino Real, 625 El Camino Real, Conference Room 1107, Palo Alto, California, before me, RACHEL FERRIER, a Certified Shorthand Reporter, personally appeared DR. JEFFERSON D. FOOTE, called as a witness by the Defendants, who, being by me first duly sworn, was thereupon examined as a witness in said action.

APPEARANCES OF COUNSEL

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APPEARANCES (Continued)

ALSO PRESENT: DAVID OSGOOD, Videographer
NEAL DAHIYA, Bristol-Myers Squibb and Medarex
---o0o---

PALO ALTO, CALIFORNIA
FRIDAY, JANUARY 9, 2015
9:40 A.M.
---o0o---
PROCEEDINGS

THE VIDEOGRAPHER: Good morning.
Here begins Video No. 1 in the deposition of Dr. Jefferson Foote in the matter of Bristol-Myers Squibb versus Genentech in the U.S. District Court, Central District of California, Case No. 2:13-cv-05400-MRP-JEM.
Today's date is January 9th, 2015, and the time on the video monitor is 9:40 a.m.
My name is David Osgood.
This video deposition is taking place at 625 El Camino Real in Palo Alto, California.
Counsel, would you please identify yourselves and state who you represent.
MS. DAVIS: Kira Davis -- Paul, Weiss, Rifkind, Wharton & Garrison -- for Genentech and City of Hope.
MS. LUCIER: Allison Lucier from Paul, Weiss, also for Genentech and City of Hope.
MR. McCORMICK: Richard McCormick from

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Mayer Brown for Bristol-Myers and Medarex.
MR. BROWN: Neal Dahiya from Bristol-Myers and Medarex.
THE VIDEOGRAPHER: Thank you very much.
The Court Reporter today is Rachel Ferrier of Merrill.
And would the Reporter please swear in the witness.

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DR. JEFFERSON D. FOOTE

called as a witness, having been first duly sworn, was examined and testified as follows:

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EXAMINATION

BY MS. DAVIS:

Q Good morning, Dr. Foote.

As you just heard, my name is Kira Davis, and I represent Genentech and City of Hope.

As we discussed a little bit before we started, I understand you are feeling somewhat under the weather today, so if at any point in time you need to take a break, please just let us know and we can take breaks as frequently as -- as needed.

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Does that make sense?

A Yes. Thank you.

MS. DAVIS: So we are going to start.

I want to hand you five documents, so let me put them on the record.

Exhibit 1 is the Expert Report of Jefferson Foote, Ph.D., in BMS v Genentech.

Exhibit 2 is the Rebuttal Expert Report of Jefferson Foote, Ph.D., also in this case.

Exhibit 3 is U.S. Patent 4,816,567.

Exhibit 4 is U.S. Patent 6,331,415.

And Exhibit 5 is U.S. Patent 7,923,221.

I'm handing you those documents.

THE WITNESS: Thank you.

(Exhibits 1 through 5 were marked for identification by the Reporter.)

BY MS. DAVIS:

Q So starting with -- they're -- they're all yours now.

Starting with Exhibit 1, do you recognize Exhibit 1 to be a report that you prepared in this case?

A Yes, this is.

Q And if you turn to the first page of that report.

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A Turn to the first page.

Q The first page of text.

A I'm on page 1 with the "1" at the bottom.

Q In the Introduction, this report says that you have been retained by Bristol-Myers Squibb and Medarex, LLC.

Do you see that?

A Yes.

Q And that is correct?

A That is correct.

Q If I refer to those two companies today jointly as "BMS," will you understand what I'm referring to?

A Yes.

Q You -- in your first opinion -- in your first paragraph in your report, you indicate that you are providing expert opinions and testimony in this matter concerning the invalidity of -- of two patents.

Do you see that?

A Yes.

Q And the first patent is the '415 patent?

A Right, or Cabilly II, yes.

Q And that was my question.

That -- that patent is commonly referred to

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as "Cabilly II"; correct?

A Mm-hmm.

Q And if you turn to your stack of documents, Exhibit 4 is a copy of Cabilly II.

Do you see that?

A '415, Cabilly II, yes.

Q And the -- the next patent that you opine on is the '221, or Cabilly III, patent; is that correct?

A That's correct.

Q And if I refer to that as "Cabilly III," we will all understand what -- what I'm referring to?

A I prefer calling it Cabilly III rather than whatever the number is, '221.

Q And Exhibit 5 in your stack of documents should be Cabilly III.

Do you have that?

A 5, Cabilly III, '221, yes.

Q So if at any point during the day you need to refer to those patents, you have them. Those copies are -- are for your use during this deposition.

The other exhibit we marked is Exhibit 3.

Do you have that?

A Exhibit 2 and Exhibit 3.

Q And Exhibit 3 is what's known as the

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"Cabilly I" patent; is that correct?
A Yes.
Q Okay. So you can set the patents aside for the moment; although, again, if at any point you need them --
A Mm-hmm.
Q -- they will stay with you.
A Are these in order, Exhibit 3, 4, 5; Cabilly I, II, III?
Q Yes, they are in order.
A That will help me. Thank you.
Q You have previously served as an expert, opining on the validity of the Cabilly II patent; is that correct?
A Yes.
Q You were retained in that case by GSK?
A Yes.
Q If you look in your report at paragraph 3 -- and this is, again, Exhibit 1.
In paragraph 3, you state, in part, that Defendants Genentech and/or City of Hope may have an expert respond to this report.
Do you see that?
A Yes.
Q That has since happened; correct?

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A Yes.
Q And you put in a second report, a rebuttal report?
A Yes.
Q And that is the document that is Exhibit 2 in front of you right now; is that correct?
A Yes.
Q So Exhibits 1 and 2, combined, are you -- your two reports in this case.
Do those two reports contain a complete summary of the opinions you are offering in this case?
A Yes.
Q Sitting here today, are you aware of any corrections that you would like to make to either of your reports?
A There was something in the first report. On page 5, there was a typo, line 4, where it says, "Moreover, anticipation does not require actual performance and/or suggestions in a disclosure." And instead of "and/or," it would be the -- better to say "performance of a suggestion in a disclosure."
Q So, for the record, the -- the corrected sentence would read:

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Moreover, anticipation does not require actual performance of a suggestion in a disclosure; it only requires that those suggestions teach a person skilled in the art how to implement the suggestion without undue experimentation.
A That's right.
Q Any other corrections that you are aware of, sitting here today?
A There was one that Dr. Fiddes pointed out. I don't remember where it is in my report, but it had to do with a quote from very early in the Cohen & Boyer patent, and -- well, we'll -- I don't remember how I'd correct it, but it may come up during the discussion.
Q Okay. And if at any point today we see the language you would like to correct, please let me know and we'll -- we'll note the correction on the record.
A Good. Thank you.
Q You've reviewed a report authored by Dr. Fiddes; is that correct?
A That is.
Q Have you reviewed any other expert reports

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submitted in this case?
A No.
Q Do you know that a report was submitted by a Dr. Silverstein?
A Yes.
Q Have you reviewed that report?
A No.
Q Are you aware that a report was submitted by a Dr. Casali (phonetic)?
A Yes.
Q Have you reviewed that report?
A No.
Q How about a report by Dr. Skerra?
(Telephonic interruption.)
THE WITNESS: Forgive me.
MS. DAVIS: Take as much time as you want to adjust the phone. These things happen.
THE WITNESS: It's from the husband of a Genentech employee. I certainly don't want to talk to him now.
BY MS. DAVIS:
Q Are you aware that a report was put in this case by Dr. Skerra?
A Yes.
Q Have you reviewed that report?

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A No.
Q Do you know Dr. Fiddes?
A No.
Q You have never met?
A Not that I can recall.
Q Turning to the second page of your report --
A Yes.
Q -- you describe, in this section, some of your own personal background; is that fair?
A Yes.
Q In paragraph 6, you indicate that your first research project in the laboratory of Professor David Dressler was an attempt to clone an antibody gene; is that correct?
A That's correct.
Q As I understand it, that project was not successful; correct?
A Correct.
Q You failed to clone an antibody gene?
A That's correct.
Q When did you first clone an antibody gene, if ever?
A First clone one. Well, that would have been in Winter's lab, and, again, it depends what's meant by "clone." The first antibody I worked with I made

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synthetically.
Q You worked with Sir Gregory Winter beginning in approximately 1985; is that correct?
A That's correct, yes.
Q So you believe you would have first cloned an antibody gene at some point in 1985 or subsequent to that?
A That's right.
Q You had -- you had mentioned that it might depend on what was meant by "cloning"; is that correct?
A Yes, but I'm -- I'm being too worried about my answer. I synthesized a gene and cloned that and expressed it.
Q What -- what, typically, do you understand the word "cloning" to mean in reference to a gene?
MR. McCORMICK: Objection; vague, ambiguous.
THE WITNESS: My understanding of cloning a gene is putting the DNA and coding something, such as an antibody, onto a replicable plasmid or other DNA vector.
BY MS. DAVIS:
Q And creating a synthetic gene would be included within that definition?
A Yes.

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Q There are other -- there are other ways to clone a gene other than by creating a synthetic version?
A Yes.
Q What other ways -- what -- what other types of methods fall within what you understand to be the definition of "cloning"?
MR. McCORMICK: Objection; vague, ambiguous.
THE WITNESS: Many methods. One can start from the genome of -- of the cell that's producing an antibody. One can isolate messenger RNA from a cell, reverse transcribe that in what's called "CDNA cloning." One can take a gene that someone else has isolated by one of these methods and you can transfer that to a vector. Sometimes we call that "subcloning," but that's a form of cloning as well.
BY MS. DAVIS:
Q Do you know when reverse transcriptase was discovered?
A I think that was in the late 1960s.
Q When did it become possible to create CDNA?
A I don't know the origin date. I know that in this early-antibody-cloning project, that was our approach, so by 1997, but I think before then, well before then.

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Q In paragraph 7 of your report, you describe a project you worked on under the direction of Professor Evan Kantrowitz?
A That's correct.
Q And the project you worked on was studying the structure and function of aspartate transcarbamylase; is that correct?
A That's correct.
Q Did I pronounce it correctly?
A "Aspartate transcarbamylase," yeah.
Q That particular protein is frequently referred to as "A-T Case"?
A "A-T-C ase."
Q "A-T-C ase"?
A Attorneys always say "A-T Case," but it's "A-T-C ase."
Q And "ATCase" --
A Yeah.
Q -- is a common way to refer to that particular protein?
A That's correct.
Q In this work from the 1979-to-1980 time period, you attempted to clone the gene encoding ATCase?
A I did.

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Q And that effort was not successful; correct?
A That's correct.
I should add. I don't want to mislead you. That wasn't the main area of work that I was doing. I was working on other projects and have papers from that period, and this was kind of a side light.
Q What was the main area of your work during that time period?
A The main area of work in that time period in Dr. Kantrowitz's lab had to do with isolating and studying mutations in the ATCase gene that were reintroduced in bacteria that would substitute new amino acids at so-called nonsense codons, its approach to studying protein structure that's not used any longer.
Q Was protein expression a focus of your work in Dr. Kantrowitz's lab?
A "Protein expression," do you mean "recombinant expression" by that question?
Q Let's just start with expression recombinant or not recombinant.
A Oh, well, the protein we worked with was expressed, was made in bacteria, but it was nonrecombinant.
Q Were you studying expression -- the

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expression aspect of that protein, or were you studying something else?
A We were mainly interested in how the protein's enzymatic activity is regulated, so we weren't studying how it was expressed.
Q And you said it was nonrecombinant?
A That's right.
Q When did you first work on a recombinant protein?
A Well, in Berkeley, when I started graduate school, I worked on a recombinant version of ATCase.
Q And when did you begin working on a recombinant version of ATCase?
A When?
Q When.
A That would be September of 1980. I don't know the exact date, but when I arrived in my first lab rotation, starting then.
Q Did you succeed in expressing a recombinant protein during your time at Berkeley?
A Oh, yes. Expression had already been worked out, and I used this plasmid that had been constructed repeatedly to prepare recombinant protein.
Q And that is -- was that the beta-lactamase

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protein?
A No, no. It was the -- it was ATCase. I worked on ATCase in three different labs.
Q You said the plasmid had been constructed by others that you were working with?
A That's right.
Q When did you first construct a plasmid for the re- -- for the expression of a recombinant protein?
A Did I construct. Well, that would have been in Winter's lab, beginning in 1985.
You mentioned "beta lactamase," and you have reminded me that, in Evan Kantrowitz's lab, I did do an experiment with recombinant beta lactamase, but that was not a recombinant construct that I had prepared. It was the beta lactamase on pBR322, a plasmid that had been constructed in Dr. Boyer's lab.
Q And you said the first time you prepared a plasmid for the expression of a recombinant protein was with Dr. Winter?
A That's right. I had worked with recombinant plasmids with -- in Dressler's lab.
And I might add. Dressler's lab was kind of a subsidiary of Walter Gilbert's lab. Dressler

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had -- was an assistant professor. He had been Gilbert's graduate student, and he was given a ten-year-track faculty job, but he was within the ambit of Gilbert. We had joint group meetings. We shared facility. There was a lot of interaction. I also --
Q Go ahead.
A Oh, no.
Q Were you finished with your answer?
A Yeah, I was going to say something not germane.
Oh, but let me just make sure I say it. I don't want to mislead you. I don't want to deprive you of information.
I, in Berkeley, in my first year, also worked with a recombinant protein called -- what's it called. It has several names. One is kanamycin phosphotransferase, and you've -- you've triggered my memory, and, in fact, that was my first successful attempt at making a expression construct, which I did my first year, beginning at the very end of 1980. That project was not continued.
Q And you said that was a recombinant protein?
A Yes.
Q And you constructed the vector used to

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express that protein?
A Yes. Yes. I had -- well, yes.
Q Did you achieve expression of the recombinant protein?
A I did. I could give you more deals so you -- I can speed things along.
The -- that gene had already been cloned, and so I took it from one vector that -- where it had been cloned, and I transferred that into something called a "runaway plasmid," which would -- supposed to exist in very high copy number. Would have many thousands of copies per E. coli cell and was thought to be better for high expression of recombinant proteins. I did get it transferred. Expression was rather ambiguous. It -- in retrospect, I probably just should have stuck with what I had and not try to overexpress it.
Q The phosphotransferase, what -- I'm sorry. What was the full name of that particular protein?
A Kanamycin, k-a-n-a-m-y-c-i-n.
Q And the kanamycin phoso- --
A Phosphotransferase, p-h-o-s-p-h-o-t-r-a-n-s-f-e-r-a-s-e.
Q The kanamycin phosphotransferase, what type of protein is that?

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A That's a drug-resistance protein. It modifies kanamycin, a drug. It modifies other similar drugs as well, and modifies them by transferring a phosphate group onto them, rendering them nontoxic to the cell that harbors this gene.
Q Is it a bacterial protein?
A It is, yes.
Q Is it a single-unit protein?
A Yes.
Q And you cloned it into another type of bacteria?
A I -- it was still E. coli. I put it into a new vector and transferred that into E. coli.
Q So it's an E. coli protein that you transvected into E. coli?
A I don't want to mislead you again. I'm not sure I would call it an "E. coli protein." It came originally from -- oh, I'm not sure where it came from originally. It was encoded on something called "Transposon 5," but I don't recall who first identified that. A transposon is a gene that can hop from bug to bug.
Q It is bacterial, though?
A It is bacterial.
Q You said someone else had cloned it first; is

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that correct?
A Yes.
Q Do you know who that was?
A I don't know. It was -- it was widely available.
Q When you say "widely available," do you mean you could order it?
A Not from a company. He would phone someone up and ask for it, though.
Q So phone someone up in another lab and ask --
A That's right.
Q -- for a copy?
A That's right.
Q You received your Ph.D. in 1985?
A That's right.
Q So in 1983, by definition, you did not have a Ph.D.?
A That's correct.
Q You then went to work for Sir Gregory Winter?
A That's correct.
Q If I refer to Sir Gregory Winter as "Dr. Winter," is that --
A That's fine.
Q That's acceptable?
A It's tough for me to say "Sir Gregory,"

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thinking of him as a knight.
Q And you were with Dr. Winter from 1985 to 1992?
A That's right. Although, during that time, I kind of had a -- I kind of had dual mentors, Greg and -- sorry, Dr. Winter and says Cesar Milstein.
Q Have you spoken to Dr. Winter recently?
A No.
Q Are you aware that there is a related case to this one in which Dr. Winter has issued an opinion?
A I was told that he had given an opinion, but I don't know much about the case. I thought it might be this case, but I didn't pay attention. I didn't read his opinion.
Q And you have not spoken to Dr. Winter about this case?
A No. My last -- I last spoke with him it must have been 2011, 2012. It was a 60th-birthday party for him that I went to.
Q When is the last time you spoke to Dr. Winter about -- when, if ever, is the last time you spoke to Dr. Winter about antibodies?
A That would have been that time.
Q The 60th-birthday party?
A That's right.

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Q And you have never spoken to him about this case?
A No.
Q A minute ago you had -- strike that.
Just to go back a little bit on -- in -- strike that.
You had said that the kanamycin phosphotransferase that you were working with, you would obtain from another lab; is that correct?
A The -- the gene for the phosphotransferase was from another lab.
Q And this is in what time frame?
A Might even have been the same lab, Schachman's lab. It really was very widespread. This was 1980.
Q At that time, was it normal for labs to share materials with other labs of -- of the type of this gene that you were working with?
A Yes.
MR. McCORMICK: Objection.
THE WITNESS: There was no material transfer agreement that we used back then.
BY MS. DAVIS:
Q You would -- how often did you have occasion to phone up another lab and ask for material?

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A I would guess once or twice a year, like that. Often -- I didn't have to phone another lab often. The material was within the same building.
In the case of the so-called runaway plasmid, I had to go downstairs. The person who made it was there.
Q Turning to page 3 of your report, in paragraph -- paragraph 12 of your report, you refer to the time you spent prosecuting a drug delivery patent.
Do you see that?
A Yes.
Q That is a patent application on which you are the inventor?
A One of two inventors.
Q Has that patent issued?
A Not yet.
Q How long have you been prosecuting that patent?
A I think the original provisional application would have been in 2004, so that's more than ten years.
Q Do you -- strike that.
I don't want to -- I'm not asking about any discussions with patent lawyers.

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Sitting here today, do you have any expectation as to when, if at all, that patent will issue?
A This year.
Q And for the record, you are literally fingers crossed.
So you are hoping that patent will issue in 2015?
A Yes. In fact, just this morning, I received word that we had put in a response to the most recent Office Action.
Q And if the patent issues in 2015, that would be approximately 11 years of prosecution?
A Yes.
Q In -- on page 4 of your report, there's a section called "Prior Testimony."
Do you see that?
A Page -- yes.
Q And this indicates that you gave deposition testimony in Glaxo Group Limited v. Genentech, Inc., et al.
Do you see that?
A Yes.
Q That is a case in which you opined on the validity of the Cabilly II patent?

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A That's right.
Q Have you reviewed your deposition transcript that is described in this "Prior Testimony" section?
A I've not gone back and reread the whole transcript.
Q Sitting here today, are you aware of anything in that deposition transcript that you believe was a misstatement?
MR. McCORMICK: Objection.
THE WITNESS: I can't think of a misstatement.
BY MS. DAVIS:
Q There is a second case listed under "Prior Testimony."
A Yes.
Q What does that case relate to, generally speaking?
A That's an employment law case. The plaintiff, Perez-Melgosa, was dismissed from the University of Washington with a allegation of scientific misconduct.
Q Were you an expert or a fact witness or something else?
A Expert, and I analyzed whether this was, indeed, misconduct.

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Q Did not -- that case in no way relates to the Cabilly patents?
A No relation.
Q I want to turn now to Section IV of your report, "Legal Principles to be Applied."
A Yes.
Q The first section under that relates to anticipation; correct?
A Correct.
Q And you state:
"It is my understanding that for a patent claim to be invalid as anticipated, there must be clear and convincing evidence that all elements of the claim are disclosed in a single piece of prior art, either expressly or inherently."
Do you see that?
A Yes.
Q Are you aware of there being any other requirements in order to demonstrate anticipation, to your understanding?
A Well, I'm not a lawyer, but I -- I'm not aware of anything outside that. If it's all disclosed within one piece of prior art, then I

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believe that anticipates the patent in question.
Q In conducting your anticipation analysis, did you take into account whether all elements of the claim appeared in a single prior art reference arranged as in the claim?
MR. McCORMICK: Objection; vague, ambiguous.
THE WITNESS: I didn't really -- what do you mean "arranged"?
BY MS. DAVIS:
Q Do you have an understanding of what it means for all the elements of the claim to appear in a single prior art reference arranged as in the asserted claim?
A You have used "arranged" again, and I sense that there's a lot of legal precedent concerning that term, so I'm a little reluctant to give a definitive answer.
Q So my first question is: Do you use the concept of whether all of the elements of the claim appear on a single prior art reference arranged as in the claim -- so my first question is whether you used that concept?
MR. McCORMICK: Same objection.
THE WITNESS: Again, I'm getting hung up on "arranged."

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What I saw in the patents that I analyzed was that they were -- the elements all seemed to be thematically related. There was no sort of separate part to a patent -- or to one -- say the Boyer or Bujard patent that dealt with a different topic, and I didn't inappropriately, I think, combine something from any irrelevant part with the main part -- that wasn't in the main part.
BY MS. DAVIS:
Q In -- I'm sorry. Were you finished?
A In that it -- to that extent -- to that extent, I made sure that all the elements I was referring to were thematically linked together, thus arranged, yeah.
Q You mentioned combining elements; is that correct?
A Combining elements?
Q Was one aspect of your approach to combine elements of, let's say, the Cohen & Boyer patent?
A I wrote about combining elements of the Cohen & Boyer patent with a paper by Riggs & Itakura.
Q And that was in connection with your obviousness analysis?
A Yes.
Q Sticking to anticipation --

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A Right.
Q -- did you take into account whether all of the elements of the claim of the Cabilly II claim appeared in, let's start with, Cohen & Boyer, combined, as they were in Cabilly?
MR. McCORMICK: Objection; vague, ambiguous, and confusing.
THE WITNESS: I find the question kind of abstract. That's why I'm having trouble answering it.
BY MS. DAVIS:
Q Did you take into account, in conducting your anticipation analysis, whether the elements you observed in the prior art were combined in that prior art in the same way that they were combined in Cabilly?
A Yes, I did.
Q How did you take that into account?
A I saw that what was done in the prior art was the same as what was done in Cabilly, more or less, with the vectors and genes somewhat changed.
Q You indicate in your report that the disclosure can be either expressed or inherent; is that correct?
A That's right.

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Q Sticking to anticipation, does any of your anticipation opinion depend on a disclosure in one of the pieces of prior art being an inherent disclosure?
A Again, that seems very broad and kind of abstract for me to answer in a categorical way. If -- if we come to particular examples of inherency, I could maybe describe them or how I used them.
Q In the abstract, you don't know whether you relied exclusively on expressed disclosure; is that correct?
A Expressed disclosure. Well, no -- well, for example, Cohen & Boyer lists antibodies as a type of recombinant protein that could be made with their method, but they don't have an express example of that, if that's what you mean.
Q So my question right now is limited to -- strike that.
In your description of the law of anticipation --
A Right.
Q -- you describe what you understand to be an inherent disclosure.
Do you see that in this paragraph 18?

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A Paragraph 18, single -- expressly or inherently, yes.
Q And regarding inherent disclosure, you say:
"A claim element is inherent in the prior art if it is necessarily present in the prior art reference, even though a person of ordinary skill in the art (defined below) would not necessarily recognize or appreciate the presence of the inherent disclosure in the prior art at the time of the filing of the patent."
A Yes.
Q Do you see that?
A Yes, I do.
Q And that is your understanding of "inherent disclosure" in connection with the law of anticipation?
A Yes.
Q And in conducting your anticipation analysis, are you relying on any inherent disclosures in the Cohen & Boyer patent?
A I'm --
MR. McCORMICK: Objection; foundation.

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Go ahead.
THE WITNESS: Right. I'm just a little perplexed by what -- by "inherency," which I -- it's kind of a legal term, and it's alient to my scientific background.
If we have a -- if we have any paper, there are things in a paper that go unsaid but are assumed or widely known that people will use without them having been said in the paper, and I believe the same may be true here.
BY MS. DAVIS:
Q So we will go through Cohen & Boyer later --
A All right.
Q -- so, at that point, we can return and I will ask you more specifically whether some of the disclosures --
A Okay.
Q -- you understand to be inherent disclosures --
A Right.
Q -- is that fair?
A Okay. That's fair.
Q In the -- on page 5 --
A Yes.
Q -- you have the law of obviousness described;

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is that correct?
A Yes.
Q Paragraph 20 says:
"A prior art reference is pertinent to the obviousness analysis if it discloses information designed to solve the same problems faced by the patent's inventors," and then it goes on.
A Yes.
Q Do you see that?
A Yes.
Q What did you consider to be the problem faced by the patent's inventors?
A Which patent?
Q Cabilly II.
A The problem they faced was expression of recombinant antibodies, recombinant proteins.
Q So you just said, "expression of recombinant antibodies, recombinant proteins."
A Yes.
Q Was it both of those problems that they were faced with?
A That's a genus/species issue. They were expressing recombinant antibodies, which are

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proteins.
Q You understood the problem faced by the inventors of the Cabilly II patent to be the expression of recombinant antibodies which are proteins?
A A particular type of protein, yes.
Q And that is the problem that you had in your mind when conducting your obviousness analysis?
A Yes.
Q How did you determine that that was the problem faced by the inventors of the Cabilly II patent?
A That that was their problem, an expression of recombinant antibodies. That seemed to be what the whole patent was written about.
Q You go on in your description of the law of obviousness to say:
"A prior art reference is pertinent... if the reference discloses information that has obvious uses beyond its main purpose that a person of ordinary skill in the art would reasonably examine to solve the same problems faced by the inventors."

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Do you see that?
A Paragraph 20, yes.
Q What criteria did you use to decide what a person of ordinary skill in the art would examine trying to solve the problem of the expression of recombinant antibodies?
A That was a long question. Could we read that back.
(Record read by Reporter as follows:
"QUESTION: What criteria did you use to decide what a person of ordinary skill in the art would examine trying to solve the problem of the expression of recombinant antibodies?")
THE WITNESS: The criterion was thematic relatedness.
BY MS. DAVIS:
Q What do you mean by "thematic relatedness"?
A Someone who expresses Protein A and someone who expresses Protein B are both expressing a protein, even though A is not the same as B. That's thematic relatedness.
Q Did you consider -- strike that.
Are you saying that any art regarding the expression of a protein is art that you believe might have been used by a person of ordinary skill in the art trying to express a recombinant antibody?

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A Again, can I have that question again -- read back.
(Record read by Reporter as follows:
"QUESTION: Are you saying that any art regarding the expression of a protein is art that you believe might have been used by a person of ordinary skill in the art trying to express a recombinant antibody?")
THE WITNESS: Yes. Art pertaining to expression of proteins is potentially relevant to someone expressing a new protein.
BY MS. DAVIS:
Q Do you believe that art relating to the expression of prokaryotic proteins would be relevant to the person faced with the problem of the expression of a recombinant antibody?
A Yes.
MR. McCORMICK: Objection.
BY MS. DAVIS:
Q And why is that?
A They are both proteins. There's no real difference among proteins that come from bacteria and proteins that come from eukaryotes.

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Q In what ways is there no real difference among proteins that come from bacteria and proteins that come from eukaryotes?
A They are made of the same amino acids. They are encoded by genes using the same genetic code.
Q Are they expressed in similar ways?
MR. McCORMICK: Objection; vague, ambiguous.
THE WITNESS: Largely, yes, they are.
Can I get some water?
MS. DAVIS: Oh, sure. Let's -- we can go off the record for just a second to get a water refill.
THE WITNESS: Yeah.
THE VIDEOGRAPHER: Off the record at 10:26.
(Recess taken.)
THE VIDEOGRAPHER: Back on the record at 10:26.
BY MS. DAVIS:
Q Turning to page 6 of your report?
A Yes.
Q In paragraph 22, you state:
"I understand that I should also consider whether a reason existed at the time of the invention that would

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have prompted a person of ordinary skill in the art in the relevant field to combine the known elements in the way the patent claim does." Do you see that?
A Yes.
Q First -- strike that. We are still talking about obviousness; correct?
A Yes.
Q There's a reference to "relevant field" here. Do you see that?
A Yes.
Q What did you mean by "relevant field"?
A Relevant field. In this case, the set of technologies that relates to recombinant expression of proteins or even expression and isolation of nonrecombinant proteins. Much of protein biochemistry, much of gene expression and molecular biology is potentially relevant.
Q And you did not limit -- in conducting your analysis, you did not limit the relevant field to the expression of eukaryotic proteins?
A I didn't limit it to that, no.
Q And you didn't limit the relevant field to

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the expression of recombinant proteins?
A No.
Q You go on to say: "The reason could come from the prior art, the background knowledge of one of ordinary skill in the art, the nature of the problem to be solved, market demand, or common sense." Do you see that?
A Yes, I do.
Q Did you take into account market demand in conducting your obviousness analysis?
A It was at the back of my mind that antibodies could be a very important protein to be able to produce and manipulate.
Q How so?
A Antibodies have been used in therapy for more than a century and will continue to be used in therapy.
Q How did that factor into your obviousness analysis?
A Obvious -- my obviousness analysis, it was a background awareness of a very large number of people working on antibodies of great interest in

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continuing to use antibodies in therapy and being able to modify antibodies to improve their therapeutic potential.
Q Just to backtrack a minute, you had said that you did not exclude from your description of the relevant field the expression of nonrecombinant proteins; correct?
A That's right.
Q Why not?
A Oh, many biochemical techniques for working on proteins were devised and are still devised using proteins isolated directly from an organism or microorganism, and those you would use the same for recombinant or nonrecombinant proteins. As I said, I had worked on recombinant ATCase and nonrecombinant ATCase, but many of the techniques for working on the protein itself were the same.
Q You also said you did not exclude from the relevant field prokaryotic proteins?
A That's right.
Q Why not?
A Why did I not exclude prokaryotic proteins from -- I'm trying to understand your question.
Q In your obviousness analysis, you made use of the idea of there being a relevant field of art;

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correct?
A Yes.
Q And within that relevant field, you -- strike that. You considered the expression of prokaryotic proteins to be within that relevant field.
A Yes.
Q Why did you exclude the expression of prokaryotic proteins within the relevant field for purposes of your obviousness analysis?
A Why did I?
Q Why did you?
A Did I exclude -- did I just say that? I'm sorry.
Q Why did you include?
A Why did I include prokaryotic proteins. I don't make a distinction between pro- -- prokaryotic or eukaryotic; because, to me, proteins are proteins, many common properties.
Q Do you make a distinction between prokaryotic and eukaryotic host cells?
MR. McCORMICK: Objection; vague, ambiguous.
THE WITNESS: Well, technically, they are handled in a different way, but no. They're -- differences between them don't concern me.

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BY MS. DAVIS:
Q And so expression results achieved in a prokaryotic host cell are relevant to expression in the eukaryotic host cell?
A They are.
MR. McCORMICK: Objection; vague, ambiguous --
THE WITNESS: Yes --
MR. McCORMICK: -- incomplete hypothetical. Go ahead.
THE WITNESS: I've expressed the same protein in a prokaryotic cell and a eukaryotic cell.
BY MS. DAVIS:
Q In paragraph 23 of your report, you say: "In making the obviousness assessment, one must also consider certain other surrounding circumstances -- so-called 'secondary considerations' -- that I understand may be raised by the patentee in support of non-obviousness." Do you see that?
A Yes.
Q Do you understand that Genentech and City of Hope have raised secondary considerations in this case?
A I don't really -- I can't recall if I was told anything about that. I -- if they were, I don't know what they are.
Q Have you reviewed the report of a Dr. Fintan Walton?
A I may have looked at that. I don't even recall if I looked at that in the Glaxo case, but I didn't for this case.
Q In conducting your obviousness analysis, did you take into account any of the so-called secondary considerations, as that phrase is used in paragraph 23?
A Not in a very substantial way. They -- they didn't affect my opinion.
Q So you said "not in a very substantial way," which suggests to me you did consider them at least a little bit; is that correct?
A This is -- in my background knowledge, I'm aware that Genentech makes a lot of antibodies and sells them, and they do wonderful things for patients, and other companies make antibodies and they pay royalties to Genentech based on the Cabilly patent. I'm aware of that.

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Q And how, if at all, did you take those factors into account in conducting your obviousness analysis?
A I didn't really apply that to the obviousness issue, which, to me, was a scientific technical issue; whereas, what I mentioned, royalties, is more a business issue.
Q You mentioned that Genentech has many antibody products.
A Yes.
Q And BMS has an antibody product that's at issue in this case?
A That's right.
Q Do you know whether those antibodies -- well, strike that.
Let me start with the BMS antibody, Yervoy.
Do you know whether Yervoy is made in a eukaryotic host cell or a prokaryotic host cell?
A I believe it's made in a eukaryotic host cell.
Q Do you --
A I didn't study how it's made. I didn't talk with anyone at Bristol about how they were making this.
Q Do you understand that the process used to make Yervoy in a eukaryotic host cell is a process that is covered by the asserted claims of Cabilly II?
A Yes; otherwise, we wouldn't be here.
Q Do you know whether -- strike that.
Do you know whether BMS is contesting infringement?
A I believe BMS thinks that the allegation of infringement isn't valid because the underlying patent is invalid. The underlying claims are invalid.
Q And do you understand that BMS is not -- well, strike that.
A Yeah.
Q You are an inventor on several patents.
A Yes.
Q You understand the concept of infringement, generally speaking.
A Yes.
Q Do you know whether BMS is contesting whether Yervoy infringes the asserted claims of the Cabilly II patent, other than the argument that the patent claims are invalid?
A I'm not aware of what might have gone on between BMS and Genentech beyond the claims I was

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asked to look at.
Q Could you turn to page 7.
Paragraph 25 is the definition of a -- well, strike that.
Page 25 includes the definition of a person of ordinary skill in the art.
A Paragraph 25, yes.
Q And that definition you state that you believe a person of ordinary skill in the art would have a Ph.D. in molecular biology or a related discipline, such as biochemistry, with one or two years of post-doctoral experience or an equivalent amount of combined education and laboratory experience; is that correct?
A Yes.
Q As of April 1983, you did not have a Ph.D.?
A That is correct.
Q Do you believe you were -- do -- strike that.
Do you believe you are within the definition of a person of ordinary skill in the art as of April 1983?
A I don't meet this definition that I've set up. I would have been very close, though, so although I was only three years into my Ph.D., I did have this work experience in Walter Gilbert, David

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Dressler's lab, so I was close.
You are looking for a black and white?
Q No. I'm looking for your answer so that it -- it --
A Those were my skills at that time.
Q Continuing on in this paragraph, you say you base this opinion on the level of education and experience of persons actively working in the field at the time of the invention --
A Yes.
Q -- including the inventors of the Cabilly patents.
What field -- how are you defining "field" in this context?
A "Field" here is the expression of recombinant proteins.
Q In --
A Or if that's -- go ahead.
Q Please, if you are not done with your answer, please finish.
A Actively working in the field, you would stop there. Oh, there were additional parts to that, but maybe you were going to come to that.
Q We will come to that --
A Right.

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Q -- my first question is: For purposes of -- of figuring out who was working in the field, what definition of "field" did you use?
A Field, expression of recombinant proteins.
Q For purposes of figuring out who was a person of ordinary skill in the art, you limited the field to expression of recombinant as opposed to nonrecombinant proteins; is that correct?
THE WITNESS: Please read back.
MS. DAVIS: Go ahead.
(Record read by Reporter as follows:
"QUESTION: For purposes of figuring out who was a person of ordinary skill in the art, you limited the field to expression of recombinant as opposed to nonrecombinant proteins; is that correct?")
THE WITNESS: Oh, yes. The -- that's correct. The person expressing recombinant proteins would have all the facility for working with DNA; whereas, a pure protein biochemist would not.
BY MS. DAVIS:
Q A little bit earlier we were discussing, in connection with your obviousness analysis, that you had included, within the field of art that was

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relevant, the expression of nonrecombinant proteins.
Do you remember that?
A Yes.
Q Why is the field of art that the person of ordinary skill looking at broader -- strike that.
Why did you limit the field of persons of ordinary skill in the art to recombinant proteins when you did not limit the field for obviousness purposes to recombinant proteins?
A Oh, because many of the techniques the person skilled in the art would use come from outside that narrow field, such as gel electrophoresis of proteins, doesn't really have anything to do with whether the protein is recombinant or not, but it's a vital technique to know how to use for problems like recombinant expression of proteins.
Q Continuing on in paragraph 25, you refer to the types -- the type of problems encountered in the art and the prior art solutions to those problems.
Do you see that?
A Yes.
Q What types of problems encountered in the art did you have in mind in forming your definition of a person of ordinary skill in the art?
A Type of problems encountered in the art.

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Well, that would have to do with -- for example, the group that had expressed insulin had -- they expressed it as a fusion protein and needed to have a way to cut that protein after it was made to release the insulin chains. That's an example of a problem that could be relevant.

Proteins often, once they are made, are not in the ideal form, and biochemists have ways of treating them chemically. I've certainly done that, that type of considerations.

Q You go on in this paragraph to discuss the sophistication of the technology in the art at the time of the invention, including the rapidity with which innovations were made in the art at the time of the invention.

Do you see that?

A Yes.

Q What did you understand to be the level of sophistication of the technology in the art at the time of the invention?

A The sophistication of the technology -- now I've lost your question. Please read back.

Q Well, let me --

A Yeah.

Q -- actually, let me rephrase it.

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A Yeah.

Q What did you mean by "the sophistication of the technology in the art at the time of the invention"?

A I meant that these were very cutting-edge techniques at the time in recombinant expression, recombinant protein expression. Many people were working on that. The -- the field was moving very fast.

Q And how did you -- how did that factor into your analysis?

A Well, that had to do with what the -- that the person of ordinary skill would be taking in all this -- all these new developments, this flux in the field, and might have to use techniques that he or she hadn't used before but could find in the literature and apply, like that. There would be some self-education going on.

Q And finally in this paragraph, you refer to the rapidity with which innovations were made.

Do you see that?

A Yes.

Q Were innovations being rapidly made in approximately April 1983?

A Innovations were being made.

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Q How did that factor into your analysis?

A It didn't have anything to do with priority dates. I've always kept those in mind. Just the -- the same thing. This pertains to a person of ordinary skill who would -- who would be following these new developments, so you wouldn't have a static, unchanging body or mental knowledge at the beginning of try and do this, but would learn along the way.

MS. DAVIS: We are at a fairly good breaking point.

MR. McCORMICK: Sure.

MS. DAVIS: You want to take a break?

MR. McCORMICK: We've been going an hour. Thank you.

THE WITNESS: That's fine.

THE VIDEOGRAPHER: Off the record at 10:48.

(Recess taken.)

THE VIDEOGRAPHER: Back on the record at 11:02.

BY MS. DAVIS:

Q So if you could turn to page 7 of your report.

A Yes.

Q There's a section on page 7 entitled "Summary

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of Opinions."

Do you see that at the very bottom?

A Yes.

Q And then it goes on over to page 8?

A Yes.

Q My first question is: Is the "Summary of Opinions" section, in fact, a summary of -- a fair and complete summary of your opinions in this case?

A Yes.

Q Starting with the very bottom of page 7, you refer to the Cabilly II patent?

A Yes.

Q And there are three asserted claims from the Cabilly II patent at issue in this case?

A 15, 17, 33.

Q And with respect to those three claims, it is your opinion that those claims are anticipated both by the Cohen & Boyer patent and by the Bujard patent?

A Yes.

Q Sticking for the moment to anticipation, is it correct that there is no other art that you are contending anticipates claims 15, 17, and 33 of Cabilly II?

A No other art contained within Cohen & Boyer

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and Bujard.
Q Cohen & Boyer and Bujard are the only prior art references that you contend anticipate the asserted claims of Cabilly II?
A That's right. Just to be sure, there are other discoveries in the field about antibody genes, but these are what can be used for expression.
Q The first bullet is -- or strike that.
The very last line on page 7: "Claims 15, 17 and 33 are anticipated by the Bujard patent."
A Yes.
Thank you.
Q Did you take into account in your analysis whether the Bujard patent was enabled?
A I didn't -- I didn't take enablement into account. I wasn't asked to opine on enablement.
Q I think you might be answering a slightly different question than the one I asked --
A Oh.
Q -- although, that is helpful.
Let me start with what I think you were answering.
There -- you are aware that there's an invalidity doctrine known as enablement, in general terms?

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A When you -- the patent must work. It must be enabled. Okay. Yes.
Q And you have not been asked to opine as to whether the Cabilly II or the Cabilly III patents --
A Oh, that's right.
Q -- meet the enablement requirement.
That's what you were saying; is that correct?
A That's right. Yeah, that's right. I'm sorry.
Q The -- the question that -- that I would like to ask you now --
A Okay.
Q -- is whether the particular prior art that you used in your anticipation analysis -- whether you consider whether that prior art was enabled for the purpose that you used it for?
A Yes.
Q And you did consider whether the prior art was enabled?
A That's right.
Q Is that analysis contained in your opinion -- in your reports in this case?
A My analysis was the -- was that the Bujard patent and the Cohen & Boyer patent were enabled for -- yes.

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Q And that is --
A But aren't all patents presumed to be enabled? I believe they were enabled, yeah, okay, as written.
Q The analysis that goes along with your view that the Cohen & Boyer patent and the Bujard patent are enabled, that analysis is found within your two reports in this case?
A Yes.
Q Turning to page 8?
A Yes.
Q You say at the top: In the alternative, claim 33 is obvious, and in one bullet you have it in view of Bujard in combination with Riggs & Itakura, and in another bullet, you have it as obvious in view of Cohen & Boyer.
A Yes.
Q In combination with Riggs & Itakura.
So you -- you have -- strike that.
You are not contending that claims 15 and 17 of the Cabilly II patent are obvious; is that correct?
A Yes, apparently. Yes.
Q The only claim of Cabilly II that you are contending is obvious is claim 33?

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A That's right.
Q And with respect to claim 33, you have put forward two combinations of prior art?
A Correct.
Q You are not opining that there are other combinations of prior art that would make obvious claim 33 of the Cabilly II patent?
A I'm -- I'm not claiming that. I've focused on this Riggs & Itakura.
Q Riggs & Itakura, in combination with either Cohen & Boyer or in combination with Bujard?
A For claim 33, yes.
Q You would agree there is other art discussed in your reports?
A Other art, yes.
Q The other art that you discuss in your report that is not Cohen & Boyer, Bujard, and Riggs & Itakura, you are not opining that that art should be used in an obviousness combination?
MR. McCORMICK: Objection.
THE WITNESS: That's right, yes, because I talk about other recombinant proteins that have been expressed, but it's these that I've distilled down as the most germane methods to which to use for the argument about obviousness.

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BY MS. DAVIS:
Q These being Cohen & Boyer, Bujard, and Riggs & Itakura?
A That's right.
Q The next portion at the top of page 8 refers to the Cabilly III patent?
A Yes.
Q So in a minute I'm going to ask you about your obviousness-type double-patenting opinions with respect to Cabilly III.
A Right.
Q I first want to ask you: Is it correct that you are not opining that the asserted claims of Cabilly II are invalid due to obviousness-type double patenting?
A That's correct, only Cabilly III.
Q And with respect to Cabilly III, there are -- are you -- strike that.
If you turn to the next page, page 9, there's a section "Asserted Claims of the Cabilly III Patent"?
A Yes.
Q And there are, in fact, five asserted claims of the Cabilly III patent; is that correct?
A That's right.

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Q One of those claims is claim 34?
A That's right.
Q Now, if we go back to page 8 in your "Summary of Opinions," you are not opining that claim 34 of Cabilly III is invalid; is that correct?
A I'm leaving that one out of it -- or, sorry, please repeat.
Q You are not opining that claim 34 of Cabilly III is invalid?
A No, only the other four: 20, 27, 43, and 46.
Q So you have no opinion at all regarding claim 34 of Cabilly III?
A Leaving 34 alone.
Q With respect to the four Cabilly III claims that you do have an opinion on, is it correct that you are not opining that any of those four claims are anticipated?
A That's correct.
Q And you are also not opining that any of those four claims are obvious other than by way of obviousness-type double patenting?
A That's correct.
Q A minute ago we talked about invalidity opinions you are not making, specifically enablement.

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Do you recall that?
A Yes.
Q Are you familiar with an invalidity doctrine -- strike that.
Are you familiar with a validity requirement known as the "written description requirement"?
A Written description of an invention, also called an "enablement," or --
Q Whether -- go ahead.
A I'm aware of that. A written description of the invention must accompany the patent application.
Q You are not opining on the written description of the Cabilly II or Cabilly III patents; correct?
A Not opining on the written description -- no, I'm -- I see what you mean, I think. I'm not finding fault with the written description. I'm finding fault with the claims. That's where my focus is.
Q So you have not made an -- strike that.
You have no opinions regarding whether --
Let's go -- we have a microphone fail, so let's go briefly off the record just for a second.
THE VIDEOGRAPHER: Off the record at 11:13.
(Recess taken.)

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THE VIDEOGRAPHER: Back on the record at 11:13.
BY MS. DAVIS:
Q You don't have any opinions in this case regarding whether the Cabilly II or Cabilly III patents met the written description requirement for validity is that correct?
A That's correct.
Q Could you turn to page -- strike that -- page 10.
Page 10, at the bottom, there's a section referred to as "Prosecution History."
Do you see that?
A Yes.
Q You have looked at portions of the Cabilly II prosecution history; is that correct?
A That's correct.
Q Have you looked at the entire prosecution history of Cabilly II?
A My eyes passed over it, but please don't ask me to recall parts of it. I -- I did look at it.
Q In -- on page 11, paragraph 37 -- in paragraph 37 you refer to the fact that the PTO rejected the claims of the Cabilly II patent over the Axel patent and the Moore patent.

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Do you see that?
A Yes.
Q Have you compared Cohen & Boyer to the Axel patent?
A I've looked at both.
Q Have you considered whether the Cohen & Boyer patent defers from the Axel patent?
MR. McCORMICK: Objection; foundation.
THE WITNESS: I have considered. My -- yes.
BY MS. DAVIS:
Q What is your opinion?
A My understanding is that the -- the Patent Office construed the Axel patent as producing just one recombinant polypeptide chain; whereas, I believe that Boyer outlines production of more than one polypeptide chain.
Q Have you considered the Moore patent?
A I have looked at the Moore patent, but I don't recall much about it.
Q Have you compared Cohen & Boyer to the Moore patent?
A Not in a comprehensive way that I remember, but I did look at both of those.
Q Turning to page 12, could you look at paragraph 38?

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A Yes.
Q You say in paragraph 33 that you understand that Cohen & Boyer was cited by the applicants during the prosecution of the Cabilly II patent and Cabilly III patent but that it was not the subject of a rejection by the PTO during prosecution of those patents.
Do you see that?
A Yes.
Q What do you understand it to mean that Cohen & Boyer was not the subject of a rejection by the PTO?
A Oh, the PTO did not tell your client, "Oh, your patent was anticipated by Cohen & Boyer." Although -- yeah, that's my understanding.
Q Is it your understanding that Cohen & Boyer would have been considered by the PTO during the prosecution of the Cabilly II and Cabilly III patents?
A I notice- --
MR. McCORMICK: Objection.
THE WITNESS: I noticed that it was referenced in the -- somewhere in the file wrapper more than once, but -- sorry. What did you just ask?

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BY MS. DAVIS:
Q Is it your understanding that Cohen & Boyer would have been considered by the PTO during the prosecution of the Cabilly II and Cabilly III patents?
MR. McCORMICK: Objection; vague.
THE WITNESS: Considered. I don't know. I just know that it was part of the record. I don't know what the PTO did with it or if considered as a particular meaning. I don't know how it was treated.
BY MS. DAVIS:
Q The next section in your report is "Question Presented"?
A Yes.
Q So in paragraph 39 you state:
"I have been asked to express an opinion on whether the asserted claims of the Cabilly II Patents would have been anticipated or made obvious by the Cohen & Boyer patent and/or the Bujard patent, alone or in combination with Riggs & Itakura."
Do you see that?

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A Yes.
Q Sticking to that sentence about Cabilly II, my -- my question to you is: Were you asked specifically to consider whether those three art references anticipated or rendered obvious Cabilly II? Was that the question you were given?
A That was the question I was given, but we discussed quite a bit besides that. I've read quite a few references besides just these three.
Q Were you familiar with either the Cohen & Boyer patent or the Bujard patent prior to your work in connection with the GFK Cabilly case?
A I knew about the Cohen & Boyer patent. I did not know about the Bujard patent.
Q Were you asked -- strike that.
Did you find either of the Bujard patent or the Riggs & Itakura patent yourself?
A The Riggs & Itakura is not a patent.
Q Yes. Fair question.
You didn't find the art that you were asked to opine on yourself; is that correct?
A Well, I found -- Cohen & Boyer was well known, but Bujard and the Riggs & Ita- -- the Riggs & Itakura paper is a more obscure. I hadn't read that before.

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Q And those were provided to you by the attorneys?
A Yes.
Q Continuing on in paragraph 39, it says that you were asked to express an opinion on whether the asserted claims of the Cabilly III patents would have been obvious under ODP when certain claims of the Cabilly I patent were combined with the teachings of the Cohen & Boyer patent and/or the Bujard patent.
Do you see that?
A Yes.
Q Were you asked to consider those specific combinations?
A I was, yes.
Q You didn't come up with those combinations on your own?
A I hadn't heard of ODP before this case.
Q And a fair point is that ODP is shorthand for "obviousness-type double patenting."
Is that your understanding?
A Yes, that's my understanding. Sorry.
Q Could you turn to page 13.
A Yes.
Q You have a footnote, Footnote 5.

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Do you see that?
A Yes.
Q And in that footnote, you refer to a prior report written by an expert, E. Fintan Walton.
Do you see that?
A Yes.
Q You have not read Dr. Walton's report in this case; is that correct?
A That's right.
Q You note that Dr. Walton has made some statements about the Cohen & Boyer patents in the -- the report you did read; is that fair?
A In the report I did read? I read Walt- -- Dr. Walton's report in the GSK case, yeah --
Q And --
A -- that retained this language, yes.
Q -- in this footnote, you are referring to a report Dr. Walton prepared in a case that's referred to here as MedImmune.
Do you see that?
A That's -- MedImmune, yes.
Q Do you know what that's a reference to, the MedImmune case?
A That's the earlier case in which I -- oh, actually, no. That's not the case I worked on.

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That's the case before. That's right, yeah.
Q Is that the only report by Dr. Walton that you have reviewed, the MedImmune report?
A That's right.
Q In the footnote, you describe some statements that Dr. Walton has made previously about the Cohen & Boyer patents; correct?
A Yes.
Q Do you agree that the Cohen & Boyer invention was a fundamental one?
A Yes.
Q Are you familiar at all with the licensing of the Cohen & Boyer patent?
A I've heard a few things about it.
Q What --
A That it was -- they quite nobly wanted it to be applied as widely as possible and made it available to everyone. Didn't try to cut anyone out.
Q Are you aware that Dr. Walton has compared the licensing history of the Cabilly patents to the Cohen & Boyer licensing history?
A I -- I don't recall reading that, but I can't say that it's not true. I just don't recall.
Q Do you have any opinions on the licensing

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history of the Cabilly patents?
A I don't know much about the licensing history, so, no.
MS. DAVIS: If you turn to page 14, and, at this point, let me go ahead and mark Cohen & Boyer.
(Exhibit 6 was marked for identification by the Reporter.)
BY MS. DAVIS:
Q I have handed you what's been marked as Exhibit 6.
A Okay.
Q This is a U.S. Patent 4,237,224.
Do you see that?
A Yes.
Q And this is the Cohen & Boyer patent referred to in your report; is that correct?
A This is.
Q So in paragraph 44 on page 14, you have some statements from the Cohen & Boyer patent; correct?
A Yes.
Q And you begin with the -- strike that.
You first say that the Cohen & Boyer patent explicitly and repeatedly discloses insertion of multiple foreign genes, and then the first quote is: "DNA having at least one intact gene."

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Do you see that?
A Yes.
Q And your reference to Cohen & Boyer -- the first reference is column 1, line 58 through 59, so if you want to turn there.
Is it your understanding that the phrase in the Cohen & Boyer patent that you have excerpted, "DNA having at least one intact gene" -- would that refer to a single fragment of DNA, in your view?
A A sig- -- a sig- -- single fragment of DNA. Let me take a minute to read this.
Well, they don't -- their words are: "A plasmid or viral DNA is modified to form a linear segment," which, in practice, means it's cut with a restriction enzyme, "having ligatable termini which is joined to DNA having at least one intact gene," and that could be a single fragment of DNA or it could be more than one, as long as both fragments have complementary ligatable termini.
Q The next -- well, strike that.
Continuing on in paragraph 44, you have a reference that's from column 4 at line 29 to 30: "DNA containing the foreign gene(s)."
Do you want to turn to that?
A Four -- yes.

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Q And the full context of that phrase is:
"If production of cohesive termini is by restriction endonuclease cleavage, the DNA containing the foreign gene(s) to be bound to the plasmid vehicle will be cleaved in the same manner as the plasmid vehicle."
Do you see that?
A Yes.
Q Do you believe that that is a reference to a single fragment of DNA?
A I'm just taking a minute to read. I'm sorry for the delay.
I think it could be one fragment or two fragments. They -- they don't say one.
Q Do they say two fragments?
A No. They don't give a number. I think, in many cases, it might be one, but two is not ruled out by this.
The main condition is if production of cohesive termini is by restriction endonuclease cleavage, which could give more than one fragment, which -- and the -- the multiplicity of fragments are each capable of being inserted in this site

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that's been opened in the plasmid vehicle.
Q You would agree that a single fragment of DNA could contain one or more genes; correct?
A Yes.
Q It depends on how the DNA is cut?
A Yes.
Q And you agree that Cohen & Boyer are, in places, discussing using a single fragment of DNA that may contain one or more genes on that single fragment of DNA?
A They contemplate more than one gene on a single fragment of DNA. I don't see a departure from that, yeah.
Q Continuing on in paragraph 44, you quote a portion of Cohen & Boyer that refers to the DNA fragment may include one or more genes or one or more operons.
Do you see that?
A Yes.
Q And I just first want to ask you: What is an "operon"?
A An "operon" is a -- was a regulatory structure, an arrangement of segments of DNA that was first identified in prokaryotes. I don't think there's a strict definition. We don't really have

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strict definitions in molecular biology, but one of the typical ones is the lactose operon, which has multiple genes, a promoter. It also has a separate gene for a repressor molecule that has its own promoter, so it's a collection of genes and signal sequences that act as one unit.
Q You would agree that an operon is a contiguous set of co-regulated genes; right?
A The operons I know about are contiguous there, yes.
Q You can obtain an operon on a single fragment of DNA?
A Yes.
Q And, in fact, if you continue in paragraph 44, you have a quote from Cohen & Boyer in which they, in fact, obtained a complete operon on a single fragment; is that right?
A I'm not seeing it, but I think you are right; they did the tryptophan operon on a single fragment.
Q Is that the -- there is an indented portion of paragraph 44.
Do you see that?
A Oh, yes. Oh, I see, yes. Yes.
Q And so Cohen & Boyer, at this particular example that you have cited, is a single fragment of

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DNA containing a complete operon?
A Yes.
Q And the operon is bacterial?
A That's a bacterial operon, yes.
Q In paragraph 45, you state -- strike that.
A portion of paragraph 45 reads:
"... the Cohen & Boyer patent teaches co-expression of multiple distinct and separate polypeptides in a single microorganism host cell."
Do you see that?
A Yes.
Q Where are you getting from Cohen & Boyer "multiple distinct and separate polypeptides"?
A Multiple distinct and separate polypeptides. Well, that refers to all the previous references where Cohen & Boyer talk about gene or genes. Genes is inherently multiple.
Q What did you mean by "distinct and separate polypeptides"?
A Let's see. "Distinct and separate" meaning that there are two separate polypeptide chains; that the end of one does not connect to the beginning of the other.

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Q What teachings in Cohen & Boyer led you -- strike that.
What teachings in Cohen & Boyer refer to polypeptides where the end of one is not connected to the beginning of another?
A Well, the tryptophan operon is the best example where there are five polypeptides, each not connected end to end.
Q Are there other portions of Cohen & Boyer that refer to polypeptides that are not connected to one another?
MR. McCORMICK: Objection; asked and answered.
THE WITNESS: I'm reading into the statements of more than one gene, meaning that they would not be connected one to the other.
BY MS. DAVIS:
Q And why are you reading that into those statements?
A That's usually the way I interpret two distinct genes. One can contemplate a fusion protein, but I don't think that's what they are talking about, and certainly not in the tryptophan case, but.
Q What are you relying on to interpret two

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distinct genes to exclude a fusion protein?
A It's not that I'm excluding a fusion protein. A fusion protein is two genes fused together. Let's think of it simply like that. But two genes that aren't fused together would still fit this description, so both situations fit this language of two genes.
Q We discussed earlier the -- the concept of expressed disclosure for anticipation versus inherent disclosure for anticipation.
Do you recall that?
A Yes.
Q Is the fact that, in your opinion, Cohen & Boyer teaches co-expression of multiple and -- multiple distinct and separate polypeptides in a single microorganism host cell -- is that based on expressed disclosures, inherent disclosures, or both?
A Well, expressed disclosures, with the example of the tryptophan.
Q Please continue.
A Yeah.
Inherent disclosures, again, if they were -- yeah, I think -- well, tryptophan is an expressed disclosure. Again, inherently, just from

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understanding molecular biology, two independent genes not connected is a -- is a more natural state. That's inherently the way one would think about it. And if someone told me -- that's a fusion protein. That's the exception. It's the -- when the two separate genes -- I don't think of them as being -- forming a continuous polypeptide gene -- polypeptide chain.
Q Could you turn to page 15?
A Yes.
Q At the -- the top carry-over paragraph, you state, in part:
"... the invention encompasses distinct and separate polypeptide subunits that assemble to form a multimeric protein."
Do you see that?
A Yes.
Q What in Cohen & Boyer shows the assembly of distinct and separate polypeptides to form a multimeric protein?
A Well, they express the trp operon, which normally -- which encodes these genes that associate together.
Q Are other portions of Cohen & Boyer that

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disclose distinct and separate polypeptide subunits that assemble to form a multimeric protein?
A An expressed disclosure?
Q Let's -- let's start with an expressed disclosure.
A This is Cohen & Boyer. Let me just look at the examples. Well, the expressed disclosure is the tryptophan. The other examples aren't like that.
Q Are there -- strike that.
Just to be sure I understand your answer, are there other portions of Cohen & Boyer that you believe expressly disclose separate and distinct polypeptide subunits assembling to form a multimeric protein?
A Well, they -- okay. Cohen & Boyer lists proteins that are -- that could be made by their method, and that includes several examples of proteins that are heteromultimers, and those would be made in the cell. Whether they would assemble together in the cell isn't really discussed in Cohen & Boyer, except Cohen & Boyer allow the possibility of in vitro combination of these subunits, but definitely multimeric proteins can be made within one cell in their invention.
MS. DAVIS: So I'm not quite sure how long we

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have been going, but we are going to have to chain the tape soon.
THE WITNESS: Oh.
MS. DAVIS: Should we go ahead and take a quick break?
MR. McCORMICK: Yeah, that makes sense.
THE WITNESS: Quick break. Okay.
THE VIDEOGRAPHER: This concludes Video 1, Volume 1 in the deposition of Dr. Foote.
Going off the record at 11:43.
(Recess taken.)
THE VIDEOGRAPHER: This begins Video 2, Volume 1 in the deposition of Dr. Jefferson Foote.
Going back on the record, the time is 11:55.
BY MS. DAVIS:
Q Dr. Foote, you prepared a chart that is at the back of your report setting forth your comparison of the Cohen & Boyer patent and the asserted claims of the Cabilly II patent and then the Bujard and Cabilly II; is that correct?
A That's correct.
Q Let's go ahead and turn to that chart now.
A Yeah.
Q And the first page should be C-1.
A C-1.

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Q And this is labeled "Section 102 Invalidity Claim Chart" at the top?
A Right.
Q And this is the chart you prepared setting forth where in Cohen & Boyer and then Bujard the elements of the asserted Cabilly II claims can be found?
A Yes.
Q The first claim you have listed is claim 33?
A Yes.
Q And is it -- well, strike that.
What were you trying to convey in this chart?
A The chart's no different from the bulk of the report. It's just a summary.
Q So looking at the first box in the chart, you have a claim limitation from claim 33 of Cabilly II?
A Yes.
Q And that limitation is:
"A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell,

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comprising."
Is that correct?
A Yes.
Q I just want to talk right now about Cohen & Boyer.
A Okay.
Q So I'm going to set aside Bujard for the moment.
You state in your entry for Cohen that -- that corresponds to this limitation: Cohen discloses a process for producing an antibody in a unicellular organism.
Do you see that?
A Yes.
Q Now, the language that you cite next to antibody is section -- is column 1, line 39; column 9, lines 28 through 30; and column 16, 63 through 65.
A Yes.
Q So let's start with the first of those.
So column 1, line 39, that has the word "antibodies"?
A Yes.
Q And that's why you are citing it?
A Yes.

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Q Now that line in column 1 is not talking about a process to produce antibodies; is that correct?
A Well, isn't it. One -- one sec, please.
I believe it is talking about a process to produce antibodies. You are talking about it at a very high-level, but it's about a process.
Q Does the language in column 1, around line 39, discuss the production of antibodies?
A Right around 39, it lists antibodies as an example of what could be made, but talks about other things that could be made, one of which is antibodies.
Q Now, the -- the sentence that that language appears in is: "Thus, it becomes practical to introduce into a particular microorganism, genes specifying..."
A Yes.
Q Do you see that?
A Yes.
Q Is this section discussing introducing genes into an organism?
A It's definitely talking about introducing genes.
Q Do --

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A But I'm not -- let me finish, though.
MR. McCORMICK: Read as much as you need --
THE WITNESS: Right.
MR. McCORMICK: -- to finish answering the question.
THE WITNESS: But it later talks about functions, which are indigenous to other classes of organisms, so.
BY MS. DAVIS:
Q Do you understand the function language to be a reference to producing antibodies?
A Yeah. The function is -- that refers to what is produced, not just the gene itself. The gene itself is just DNA, like lots of other DNA. It's -- the function refers to the product of the gene doing something.
Q Is there a difference -- strike that.
A Yeah.
Q We discussed earlier some of your work prior to 1983.
Do you recall that?
A Yes.
Q Was there a difference in the work that you did between introducing a gene into an organism and having that organism express the gene?

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A A difference between those. Well, the genes I introduced were expressed, so one led to the other.
Q Is it always the case that you will get expression of a gene that you have introduced into an organism?
A You could have a dead gene. I -- I accept that.
Q What do you mean by a "dead gene"?
A A gene that's not transcribed, let's say. It never produces a protein.
Q What types of genes would not be transcribed?
MR. McCORMICK: Objection.
THE WITNESS: That's hard to answer. There's not really a -- a property that would keep a gene from being transcribed. They are just little aspects of its structure, whether it has a promoter nearby, whether it's in a cell that supplies functions to transcribe it, things like that.
BY MS. DAVIS:
Q Do you believe that once that -- strike that.
How difficult is it to ensure that a gene you have introduced into a cell is expressed?
A Difficult. That's -- that's tough to quantify. I'm looking -- always looking to quantify

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things. I think most genes can be expressed. Sometimes it takes a little work. Sometimes the level of detection is such that it's being expressed and you don't know it, but genes can be expressed.
Q So in this particular passage of Cohen & Boyer, is it fair to say that you believe that they are discussing the production of antibodies -- well, strike that.
What language is it again in this section of Cohen & Boyer that you believe refers to the production of antibodies?
A When they use the word "function."
Q And that is because one function of the organism into which the gene has been introduced is to express the gene?
A One sec, please.
This is very high-level language, but the use of the word "function" means these processes; nitrogen fixation, photosynthesis, enzymes and antibodies. These functions refers to the gene product doing something. So they are not really interested in just putting the DNA there per se. Putting the DNA there becomes interesting because of the functions it confers on the microbe that's received it.

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Q In this particular language in column 1, do Cohen -- Cohen & Boyer describe expression of an antibody gene?
A Describe it. They -- they describe it as a -- at a high-level. They don't say how to describe it. They just say introducing these genes will be part introducing of a function.
Q In the -- in your chart, the next line you had quoted was in column 9, line 28.
So can we turn to that?
A Line 28.
Q And the language that you were citing --
A Right.
Q -- is the sentence that "other poly (amino acids) of interest include serum proteins," and then it goes on to include globulin, e.g., gamma-globulin -- globulins or antibodies.
Is that the language you are referring to?
A That's right.
Q So this section is saying, in your opinion, that antibodies are a protein of interest to Cohen & Boyer?
A Yes.
Q You would agree that this language does not discuss a process for producing antibodies?

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A It doesn't specifically refer to a process for antibodies; that's right.
Q Does it generally refer to a process for antibodies?
A Well, first, your process for expressing a whole cornucopia of recombinant proteins, that's part of the power of this patent. It (sic) useful for just about everything.
Q Does the language in column 9 at lines 28 through 30, does that language refer to a process, either generally or specifically, for producing antibodies?
A Let me look at this again. One sec.
There is a process. By introducing one or more exogenous genes into a unicellular organism, the organism will be able to produce polypeptides and proteins.
Q And then --
A And then it gives this list of things it could be applied to.
Q And you were referring to the language at column 9, lines 12 --
A 12, yeah.
Q In your chart, you see -- so you -- you have the language in column 9, lines 12 through 14 --

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A Right.
Q -- appearing shortly -- shortly after the section we have been discussing?
A Yes.
Q Before we get to that, I want to go to column 16, lines 63 through 65.
A 53 through -- but you may want 63. Okay.
Q In your chart, do you see that the first reference --
A Oh, 63.
Q 63.
A Oh, right. I see, yeah.
Q And that states:
"Besides enzymes, other proteins can be produced such as antibodies, antigens, albumins, globulins, glycoproteins, and the like"?
A Yes.
Q Does this language describe a process for producing antibodies?
A It refers to the overall process disclosed in the patent, but not a specific process for how to make an antibody. Antibodies are grouped in this very general process -- or they are grouped together with other proteins that can be made in this very

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general process.
Q Do you know what section of the patent this language appears in?
A Section. It appears to be --
MR. McCORMICK: The document speaks for itself.
THE WITNESS: Right. The -- there are a series of examples, but this seemed like a more general discussion.
So the real -- more general discussion than just somatostatin in the last example. So this is the experimental section. Or is that -- I'm sorry. I'm confused by their organization. The various section heads are "Experimental" and "Example V." It's in the specification.
BY MS. DAVIS:
Q And this is in the "Example V" section.
Is that your understanding?
A That was the last header, but by column 16, they cease to discuss somatostatin and shifted to a more general discussion.
For example, at the end of the last paragraph of column 15:
"It is evident from the above results, that both DNA from a

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eukaryotic source and RNA transcribed from the eukaryotic DNA can be formed in a bacterial cell and isolated," etc.

Q In conducting your anticipation analysis, with respect to Cohen & Boyer, did you take into account what sections the various phrases you've pulled out -- what sections those appear in?

A I paid attention to what --

MR. McCORMICK: Object; characterization. But go ahead.

THE WITNESS: I paid attention to whether they were in the specification or the claims.

BY MS. DAVIS:

Q Did you take into account anything else regarding what sections they appeared in?

A I paid attention to what was trying to be said, so I know the difference between an abstract and background and summary. I took into account that, but -- but, you know, to me the section head is just part of the -- part of the explanation. It helps guide the reader to what's contained below, but there's a distinct difference between claims and specification, and that's the one I paid the most attention to.

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Q In the three examples we have discussed so far that are in your -- your sort of first two lines regarding the Cohen & Boyer patent --

A Yes.

Q -- have -- have we seen any reference to heavy chains or light chains?

A In those three lines, it just says antibodies.

Q And Cohen -- please finish.

A Which -- which inherently have heavy chains or light chains, but they don't use the words "heavy" and "light."

Q And, in fact, at no point in Cohen & Boyer is there a reference to either a heavy chain or a light chain; is that correct?

A I'm not aware of a -- I would have to -- it would take too long to check, but I'm not aware of a specific use of heavy chain or light chain.

Q Did any of the three passages that we have discussed -- did those refer to the concept of a single host cell?

A Let's see. So 1:39: "Thus, it becomes practical to introduce into a particular microorganism," that would be a single host cell.

Line 28 refers back to that first full

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paragraph of column 9: "By introducing one or more exogenous genes into a unicellular organism," that's a single cell.

And then 16:63, let me take a look. I'm sorry to go through this so laboriously.

"In addition, the products" -- I'm now reading from line 60 on column 16.

"In addition, the products of the enzymic reactions may be more readily isolated and more efficiently produced by a transformant than by the original host."

So a transformant, again, is singular. The antibody reference follows that. So, again, it would seem to be a single host cell.

Q Are you familiar with -- well, strike that.

In your reports, you have referred to the early work producing insulin; correct?

A Yes.

Q And you are aware that, early on, insulin was produced by putting one of the insulin chains in one cell and the other insulin chain in another cell; correct?

A The City of Hope and Genentech group did

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that, yes. Mm-hmm.

Q In the passages we have just discussed in Cohen & Boyer, do you understand those passages to exclude the type of process that the Genentech and City of Hope individuals used in producing insulin with one chain in one cell and the other chain in another cell?

A Exclude that. I think Cohen & Boyer is completely compatible with expressing a single polypeptide.

Q So let's --

A Yeah.

Q -- let's start with column 1, the first section we looked at.

A Right.

Q And you had said that the language in column 1 you understood to refer to a single host cell.

A Yes.

Q Could the language in column 1 also refer to a method like the method used by Genentech and City of Hope to produce insulin with each of the chains in a separate cell?

A That could be. I could see that, yes.

Q And is the same true of the other passages of

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Cohen & Boyer that we have discussed that -- that you opine refer to a single host cell?
A Refer to a single host cell. I think with Cohen & Boyer, you can always express one chain in a single host cell, yes.
Q Does Cohen & Boyer -- strike that.
So insulin is a multimeric protein; correct?
A It has two chains, yes.
Q Cohen & Boyer does not insist that you put both of those two chains in a single cell; is that correct?
A Does not insist; it allows, yes.
Q And so the passages of Cohen & Boyer that we have been looking at don't specify that -- if you have a multimeric protein, they don't specify that you must put the chains all into one cell?
A Let's see.
MR. McCORMICK: I'm going to object as asked and answered.
THE WITNESS: It's a good question. I'll start with the first one.
Well, in some cases -- in some cases, you would have to put everything into one cell, so if we take -- I'm going to start in column 1, 34, and the sentence:

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"Thus, it becomes practical to introduce into a particular microorganism, genes specifying such metabolic or synthetic functions as nitrogen fixation, photosynthesis, antibiotic production, hormone synthesis, protein synthesis... enzymes or antibodies, or the like..."
For -- some of those processes are -- are complex and require several -- several actors to work in -- in series, like the -- well, you know, photosynthesis, nitrogen fixation, antibiotic production -- that's a metabolic pathway -- you would need the machinery, multiple genes present within the same cell for that to work.
BY MS. DAVIS:
Q So in the example of nitrogen fixation --
A Yes.
Q -- the goal in nitrogen fixation is not to produce a protein that is harvested, it's to transform the organism into one that fixes nitrogen?
A Can live off the air, yes.
Q And so in a case like that, it's not the -- the project isn't a success unless the single

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organism at the conclusion is able to fix nitrogen --
A In that case, yes.
Q -- is that correct?
In the context of a protein that is being harvested, like insulin, does Cohen & Boyer require that the chains -- the composite chains be put into a single cell?
MR. McCORMICK: Objection; again, asked and answered.
THE WITNESS: I don't think it requires that they be put into a single cell. They could make it as two fusion proteins, the way you have described.
BY MS. DAVIS:
Q And the reference to the way I described is with reference to the Genentech and City of Hope prior to 1983?
A That's right.
Q As of -- well, strike that.
Do you understand that the priority date for Cohen & Boyer is 1974?
A Yes.
Q As of 1974, CDNA had not yet come into use; right?
A I don't recall. I didn't study that issue.

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Q When was the first time you used CDNA?
A That would have been 1977.
Q How difficult would it have been in 1974 to put both the heavy chain and light chain of an antibody into a single host cell?
A In 1974, the first antibody chains had not even been cloned, so that would have made it very hard in 1974.
Q If, in 1974, someone succeeded in cloning them, would there be other difficulties in getting both the antibody heavy chain gene and antibody light chain gene into a single cell?
MR. McCORMICK: Objection --
THE WITNESS: If someone --
MR. McCORMICK: -- incomplete hypothetical.
THE WITNESS: -- had cloned them, I -- I see much less problem. The big problem was cloning them in the first place. I should add. That was true for a lot of proteins. There were not very many cloned proteins in 1974.
MS. DAVIS: I had promised half an hour, so -- we can keep going?
MR. McCORMICK: If -- you mean another 15 minutes? Whatever the witness --
MS. DAVIS: Okay.

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MR. McCORMICK: -- he --
MS. DAVIS: Sure.
MR. McCORMICK: -- he needs the breaks more than we do.
MS. DAVIS: All right.
THE WITNESS: No, we are fine.
MS. DAVIS: We can keep going? All right. We will go a little further.
Q So in the same box, there's the language -- the Cohen & Boyer box, you had referred earlier to the passage on column 9, lines 12 through 14.
Do you want to turn to that?
A Oh, sorry. Where are we in the table?
Q Still in the first Cohen & Boyer box --
A Yeah.
Q -- the sentence beginning: "See, e.g." --
A Oh, "See, e.g., 9:12 to 14."
Q And that language is the sentence beginning: "By introducing one or more exogenous genes"; correct?
A Let me -- I'm on the wrong column. Sorry. Where did it go. There. By introducing one or more exogenous genes, yes.
Q The language that you have quoted in your chart at column 9, lines 12 through 14, does not say

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which specific genes are going into the unicellular organism; is that correct?
A 12 to 14 --
MR. McCORMICK: Objection.
THE WITNESS: -- does not say which. That follows later. Mm-hmm.
BY MS. DAVIS:
Q Continuing in your chart, now you have the reference to column 16, lines beginning at line 53.
Do you see that?
A Yes.
Q And that is -- strike that.
That section begins: "In addition, the subject method provides means for preparing enzymes, enzymic products from bacteria," and then it goes on.
Is that the language you were referring to?
A Yes.
Q That particular language does not say anything about which specific genes are being introduced into the cell, does it?
A Doesn't it say other proteins can be produced; antibodies, antigens, albumins, globulins? Or am I looking in the wrong place or misunderstanding your question?

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Q Well, let me ask it this way: It's --
A Yeah.
Q -- your understanding that the language at the end of that paragraph -- that those are the genes that are being introduced?
A Means for preparing these, so these are introduced, yes.
Q And as we have discussed earlier, there's no mention anywhere in Cohen & Boyer that you are aware of of heavy chain or light chain; correct?
A Not specific language for heavy chain and light chain.
Q And this language in particular does not include a reference to either a heavy chain or a light chain, then?
A It doesn't break antibodies down into heavy chain or light chain. And I might point out, an antibody is a globulin. It is a glycoprotein, so it's included multiple times, but not broken down into heavy chain or light chain.
Q Is there any reference in the Cohen & Boyer patent to the variable domain of a heavy chain or a light chain?
A It's not broken down that far either. Again, someone knowing the structure of antibodies in 1974

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would know there are heavy chains and light chains and variable domains and constant domains. That was all known then from the protein-level analysis, even in advance of the study of antibody genes.
Q You said a few minutes ago that, as of 1974, antibody genes had not been cloned; correct?
A That's right.
Q Do you believe that it is a predicate to be able to use the Cohen & Boyer method to produce an antibody that you have cloned the antibody genes?
MR. McCORMICK: Hold on. Let me read this. I'll just object as ambiguous to time frame. But you can answer.
THE WITNESS: Can I have that again?
MS. DAVIS: Sure.
THE WITNESS: Yeah.
BY MS. DAVIS:
Q Do you believe that it is a predicate to be able to use the Cohen & Boyer method to produce an antibody that you have cloned the antibody genes?
A Well, part of Cohen & Boyer is about cloning genes, so many of these other things hadn't been cloned either. This was the start of cloning. This is what it would be good for. So you don't need to have them in hand right in 1974, if that's what you

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were asking.
Q When did it become possible, in your opinion, to produce an antibody using the method of Cohen & Boyer?
A Possible. There's some complexity to that question because it would have been possible in 1974 if you had the right pieces of DNA there. Those pieces of DNA started emerging later in the 1970s, so by 1977, we were making a serious effort in Dressler's lab. Of course, Tamagawa, who got the Nobel Prize, was making an even more serious effort. Other people were working on that by late '70s, in that region.
Q You believe -- for purposes of your opinion in this case, you believe that there is a point, a time in which using the Cohen & Boyer method, a person of ordinary skill in the art would be able to produce an antibody; correct?
A A point in time or region in time. I couldn't name a day, an hour, minute, but.
Q What is the region of time?
A Region of time: 1978, '79, '80, '81, in there, maybe '82, but in that region, it became possible.
Q What are you basing that opinion on?

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A I'm basing that, I confess, on my own experience, having tried to do that as a technician in the lab. I thought it was possible then. But other papers began to appear with parts of antibodies cloned. The genes themselves appeared, the -- the first constant region clones by Tamagawa. The mechanisms of antibody rearrangement were understood.
So basing it on those factors, a kind of wave of understanding of antibody genes as they existed in humans and animals, and the dynamics they would go through and what their DNA sequences were; how they were -- their expression was controlled; what cells they would appear in. This was a body of knowledge that was developing then.
Q How much work was being done with the genes for human antibodies in the range of time period you have identified?
A I would say --
MR. McCORMICK: Objection. Just outside the scope of his report.
THE WITNESS: Right.
I did not study human antibodies for this report, but my impression is that not much work was being done on human antibodies at that time. The

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big focus was on hybridomas, which had appeared in 1975.
BY MS. DAVIS:
Q Is there a point in time, in your mind, in which the focus switched away from hybridomas?
A The focus switched away from hybridomas. I used the word "focus," but I might have better said "foci." There were different groups. There were some groups interested in how expression of these genes are controlled; other groups were interested in therapeutic use.
You asked about a period of time where it shifted away from hybridomas. I think hybridomas are still of interest, but the beginning of -- well, I couldn't really identify a point in time where interest shifted away from hybridomas.
Q Are you equating hybridomas with murine hybridomas?
A Yes.
Q Are you familiar at all with human-murine hybridomas?
A I'm dimly aware that people have tried hard to make human hybridomas and did not have much success.
Q Are you aware of some reports of success

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with -- well, first, I want to start with human-murine hybridomas.
MR. McCORMICK: Objection; time frame, vague, ambiguous.
THE WITNESS: Right.
I didn't study this. I don't recall specific reports, so I can't answer that with any confidence.
BY MS. DAVIS:
Q You mentioned hearing reports of individuals having difficulties with human-human hybridomas; was that correct?
A I -- I did not follow that literature well at the time, and I haven't followed it since. I can't really give an informed answer there.
Q Do you know if there's any difference between -- strike that.
Do you know if the -- the difficulties you are vaguely recalling related to human-human hybridomas or humine (sic) -- human-murine hybridomas?
A I would barely be aware the difference. I couldn't -- I couldn't say.
Q If you could turn to page C-2.
A C-2.
Q And in the top of this is a carry-over box

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from --
A Right.
Q -- your first Cohen & Boyer --
A C-1.
Q -- limitation.
A Okay.
Q The last sentence is:
"The one or more genes include antibodies having at least the variable region of the heavy and light chains."
Do you see that?
A Yes.
Q And you agree, as we've discussed a couple times, that heavy and light chains -- those don't appear anywhere in Cohen & Boyer; right?
A Right. Those -- those words don't appear, but I did mention earlier that antibodies were understood to have separate heavy and light chains. That much was well known.
Q The next limitation of the Cabilly II patent is the second box on the -- the left:
"Independently expressing a first DNA sequence encoding at least the variable domain of the

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immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain so that said immunoglobulin heavy and light chains are produced as separate molecules in said single host cell transformed with said first and second DNA sequences."
A Yes.
Q Do you see that?
A Yes.
Q And in your box on Cohen & Boyer, you say:
"The transformed microorganism is capable of independently expressing the DNA sequences encoding the heavy and light chains," and then you quote some language in the patents.
A That's right.
I was wondering: Are we going to start something pretty long or would now -- now be a good time for a break?
MS. DAVIS: Let's go ahead and --
THE WITNESS: Okay.
MS. DAVIS: -- break for lunch.

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MR. McCORMICK: Was there a question pending? I just want to --
MS. DAVIS: I --
THE WITNESS: It seemed like we moved to a -- I'm sorry to --
MS. DAVIS: If there was a question pending --
MR. McCORMICK: You'll withdraw it --
MS. DAVIS: -- I will withdraw it.
THE WITNESS: Thanks.
MS. DAVIS: It might have been: Are those words on the page? So --
THE VIDEOGRAPHER: Off the record at 12:40.
(Lunch recess taken.)
---o0o---

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AFTERNOON SESSION 1:28 P.M.

THE VIDEOGRAPHER: Back on the record at 1:28.
BY MS. DAVIS:
Q So, Dr. Foote, I want to start with C-2 of your report, which is still the chart.
A Yes.
Q And I want to talk about the portions of Cohen that you have listed as corresponding to the Cabilly II claim 33 limitation that begins "independently expressing."
Are you there?
A Yes.
Q And you indicate in your report that the transformed microorganism of the Cohen & Boyer patent is capable of independently expressing the DNA sequences encoding the heavy and light chains.
Do you see that?
A Yes.
Q And the portion that you -- the first portion you cite is column 5, line 64 to 65.
A That's right.
Q So can we go there.
And the sentence in question, which you have

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also quoted in the chart, is:
"The DNA fragment may include one or more genes or one or more operons";
is that correct?
A Yes.
Q Does that language refer to independent expression?
A Yes, more than one gene expressed.
Q Are you equating the expression of more than one gene with independent expression?
A Yes.
Q And why is that?
A Because the alternate is a fusion protein, and I think that's a very special case, so my -- I think the default is that if you express two genes, you get two polypeptides.
Q Continuing on in your chart --
A Yes.
Q -- you have a reference to column 6, lines 1 through 3?
A Yes.
Q And you say that, in your chart:
"(the foreign DNA fragment should have 'an intact promoter and base sequences coding for the initiation

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and termination sites... for gene expression.'")
A Yes.
Q Is it your opinion that so long as you have an intact promoter and initiation and termination sequences, you will get at least some expression of the gene you've inserted into the microorganism?
A Yes -- oh.
MR. McCORMICK: Objection; incomplete hypothetical.
Go ahead.
THE WITNESS: You would need those, promoter and terminator.
BY MS. DAVIS:
Q Is it your opinion that so long as you have the promoter and terminator in -- that you have inserted into the microorganism, that you will get at least some expression of the gene of interest?
A I can think of ways that would go wrong, but, in most cases, it would work.
Q In what ways could it go wrong?
A Well, if you had a -- like a nonsense code on -- in your reading frame, that might mess you up, or, you know, some other structure that would interfere with transcription or translation. But in

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most -- those are exceptional cases.
Q In most cases, so long as you have an intact promoter and initiation and termination sequences, you would expect to get at least some expression?
A Yes.
Q What else would you need, if anything, in order to get at least some expression?
A Those are all you would need, really. Those are the minimum.
Q Is one promoter sufficient to get expression of both heavy and light chain?
MR. McCORMICK: Objection; incomplete hypothetical.
THE WITNESS: Yes. You need at least one.
What I'm thinking is that if you had one promoter, you could have a construct, like in the genes for ATCase where you have a intracistronic region where one chain stops being translated, you go along a bit, and then the new one starts. So you wouldn't -- you don't need two promoters. You can get by with one promoter.
BY MS. DAVIS:
Q Would you be concerned at all -- strike that.
As of 1983, if you were constructing a -- a plasmid according to Cohen & Boyer, would you be

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concerned at all about the possibility that you would get uneven expression of the heavy chain and the light chain with your vector?
A Uneven expression. So more of one than the other?
Q Yes.
A You could well get that. I'm not at all sure that would be a problem though.
Q Why do you say you are not at all sure that would be a problem?
A I don't know why it would be a problem if you get an unequal expression, unless you had almost none of one.
Q Would you be able to recover intact antibody if you had a vector that resulted in uneven expression of the heavy and light chain?
MR. McCORMICK: Objection; vague, ambiguous.
THE WITNESS: I think you would. You would end up throwing part of it away because there wasn't a partner for the chain that was in excess.
BY MS. DAVIS:
Q You would agree that Cohen & Boyer does not say that heavy and light chains would be produced as separate molecules?
A Could I have that again? I would agree

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that --
Q Cohen & Boyer does not say that heavy and light chains would be produced as separate molecules?
A Cohen & Boyer doesn't mention the words "heavy" and "light chains."
Q And with respect to other multimeric proteins, Cohen & Boyer also doesn't specify that any of those multimeric proteins, their component chains, would be produced independently?
A Which multimeric proteins do you mean? because there are several appearances of that throughout.
Q Are there any multimeric proteins discussed in Cohen & Boyer in which you believe Cohen & Boyer describes the constituent chains being expressed independently?
A I don't recall, no.
Q Is it fair to say that you believe Cohen & Boyer should be read to call for the production of heavy and light chains as separate molecule because you believe that's the better option as compared to a fusion protein?
A The better option. I don't know what's meant by "better option," but I would like to learn more,

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and maybe I could help you then.
Q You had said a little while ago that you didn't believe that a fusion protein was what coin -- Cohen & Boyer meant; is that fair?
A Cohen & Boyer could accommodate a fusion protein, but they don't insist on it, yes. I remember the discussion, I think, and for a fusion protein, you need a very precise joining. If you are doing it with restriction enzyme sequences, that has to match just perfectly for -- to make your polypeptide sequence be translated in frame.
Okay. Let me stop there. I'm getting off track.
Q Let me just ask it this way: Can you explain to me again why you are assuming that the proteins produced, according to Cohen & Boyer, are produced as separate molecules as opposed to, for example, a fusion protein?
A Oh, I'm saying that they would be produced as separate molecules as the kind of default; that if Cohen & Boyer wanted to talk about a fusion protein or if someone wanted to describe making a fusion protein, you need to have more precise language, more precise instructions.
So if I were reading Cohen & Boyer and it

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says "express two genes," I wouldn't assume that those two genes would be fused in frame unless there had been a deliberate effort to fuse them in frame.
Q Why, in that example, would you assume that they would be produced as separate molecules?
MR. McCORMICK: Objection; asked and answered.
THE WITNESS: Because if their -- if two genes are juxtaposed, having been cut on fragments with restrict- -- restriction sequences, it would be -- it would be a tremendous coincidence if they lined up exactly in frame flush right together. One goes out to its end and immediately the next one starts. There would have -- there has to be a very concerted effort to achieve that.
So if one talks about just two genes, there's no way those would form a fusion protein unless there was a deliberate effort to -- to fuse them.
BY MS. DAVIS:
Q Is there any particular type of cellular machinery that would be required such that two genes would be produced as separate molecules?
A Cellular machinery. Well, you are right; someone has to stop translating the first one and start translating the second one, or a new ribosome

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can start translating the second one, but you do need the ribosome to stop adding polypeptide, and the termination codon would usually do that.
Q And to get the ribosome to start on the second chain or a new ribosome to start on the second chain, is machinery required for that?
A There's a ribosomes start site usually, yeah.
Q Were those types of machinery known in 1983?
A Yes.
Q Do you believe that there's any other type of cellular machinery other than what we have just discussed that would be required to get two genes within the same cell produced as separate molecules?
A That's the -- that's the chief requirement that the -- there's an independent start site for ribosome to start translating the second one. You do need the thing to be transcribed, but that would be for making -- transcribing one gene or two, you need a promoter in there somewhere. You need a promoter before the first thing you want transcribed, not just somewhere. In a particular place.
Q Were promoters known in 1983?
A Oh, yes.
Q How many promoters were known in 1983?

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A I couldn't give a precise number. I would guess between ten and a hundred.
Known, you mean the sequence known and the function identified? So that had been a very active area of research for 20 years at the molecular level for ten years. Walter Gilbert worked a lot on the lactose operon, so did Arthur Riggs, the inventor on the Cabilly patents.
Q Are there different promoters for eukaryotic versus prokaryotic genes?
A Yes, there are.
Q Were promoters that were suitable for use with eukaryotic genes known in April of 1983?
MR. McCORMICK: Objection; outside the scope of his expert report.
THE WITNESS: There were promoters known for eukaryotic expression in 1983. It is outside my expertise, but, yes, eukaryotic promoters were known. The -- several promoters in SV40 in particular.
BY MS. DAVIS:
Q You mentioned "SV40." That's a eukaryotic -- strike that.
SV40 is a promoter suitable for use with eukaryotic genes?

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A SV40 is a virus that infects mammalian cells, and there are promoters within the virus that have been used for expression of eukaryotic genes and were being used at the time. I -- another rotation project in Berkeley in my first year of graduate school was with Robert Tijan's -- in Robert Tijan's lab, and we worked with SV40 promoters.
Q In your own experience, did you work with any promoters suitable for use with eukaryotic genes other than SV40?
A At what time?
Q Prior to April 1983.
A That was the only one I worked with, eukaryotic promoter.
Q Did you have success using the SV40 promoter with eukaryotic genes?
A Yes.
Q Continuing in your chart regarding Cohen & Boyer, still in the -- the column -- or the box corresponding to the independent -- independently expressing limitation --
A Yes.
Q -- you have a reference towards the bottom to column 6, line 6, through column 9, line 34. So let's start with that.

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Is that a reference to the section of --
A I'm lost. Eight --
Q Column 8, beginning at line 6.
A Column 8, line 6. Okay.
Q That is a reference to the section "Replication and Transcription of the Plasmid"?
A Yes.
Q And then you also refer to column 16, lines 8 through 12?
A Yes.
Q And in that section, the language you are referring to, as quoted in your report, is:
"... and entire operon can be introduced into a bacterial cell and the cell becomes capable of transcription, translation, and production of a functional gene product."
Do you see that?
A 12. Yes, I do.
Q You would agree that an operon -- in an operon, the genes are contiguous?
A The genes are contiguous, separated by small bits of DNA, yes.
Q And you would also agree that this portion of

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Cohen & Boyer does not include reference to antibodies?
A I'm looking at 16, 8 to 12?
Q Yes.
A Well, doesn't use the word "antibody," but if we back up a few lines at 16, line 2:
"The employment of DNA for production of ribosomal RNA is merely illustrative of using a genome from a eukaryotic cell for formation of a recombinant plasmid," dah, dah, dah. "Genomes from a eukaryotic cell for formation of genotypical properties, such as the production of enzymes" -- see, it doesn't mention -- they don't mention antibodies, but they could have -- "could have equivalently been used."
Q And it is your opinion that those references to enzymes could include antibodies?
A That's right. It says "such as production of enzymes." That's one example.
In some of these lists of proteins that can be produced, they talk about antibodies and enzymes.

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Q Could you turn to page C-3 of your report.
A Okay.
Q This corresponds to claim 15 of Cabilly II, this page?
A Okay.
Q And you see that, on the left, claim 15 is set forth?
A Yes.
Q And then you have a box setting forth the portions of Cohen & Boyer that you believe correspond?
A Yes.
Q The middle paragraph of your Cohen & Boyer column states:
"Cohen does not explicitly disclose whether the one or more genes are located at different insertion sites (non-contiguous). However, Example III teaches transcription of 18S and 28S" RNA -- "rRNA in E. coli."
Do you see that?
A Yes, I do.
Q You agree that, as you have stated, Cohen & Boyer does not explicitly disclose whether the one or more genes are located at different insertion

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sites?
A Yes.
Q Does Cohen & Boyer describe 18S and 28S as being non-contiguous?
A Well, these were known to be non-contiguous in the -- at the time the application was written. I don't know whether they used that word. I can look for it if you like.
Q Well, I don't want to limit you specifically to the word "non-contiguous."
Do you know whether Cohen & Boyer describes 18S and 28S, in words or substance, as non-contiguous?
A I would have to look to be sure.
Would you like me to read it and look for "non-contiguous" or?
Q Let me ask it this way: Are you aware, sitting here now, of a place in Cohen & Boyer in which they describe those two genes as being non-contiguous, in words or substance?
A I can't remember a passage with that in it. I haven't memorized it. I'm sorry.
Q You then say -- strike that.
Your reference to "18S" and "28S" is a reference to transcription of those two genes; is

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that correct?
A Yes.
Q Does Cohen & Boyer have an example of both the transcription and translation of two non-contiguous genes?
A Oh, well, in the tryptophan operon, any two genes in a room might be next to each other, but, you know, the first gene is not contiguous with the third gene, let's say.
Q In the tryptophan operon, the thing separating the third gene from the first gene in your description is the second gene --
A That's correct --
Q -- correct?
A -- yes.
Q Other than in that context, does Cohen & Boyer describe both a description and translation of non-contiguous genes?
MR. McCORMICK: Objection.
THE WITNESS: Sorry. In -- in that context?
BY MS. DAVIS:
Q Other than --
A Other than --
Q -- strike that.
You have explained that in the -- the --

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A Tryptophan.
Q -- tryptophan context, because there are more than two genes, the, for example, first and third are not contiguous to each other. They are separated by the second gene; correct?
A That's right.
Q And so my question is: Other than in that context, does Cohen & Boyer disclose one or more genes that are not contiguous being both transcribed and translated?
MR. McCORMICK: Objection.
THE WITNESS: I don't think he does. I could look at the examples, but I don't think there's one. The others are -- the other examples are one product at a time, I think. But then he does have this -- those are the specific examples.
BY MS. DAVIS:
Q In the third paragraph of your Cohen box on page C-3 --
A Yes.
Q -- you say:
"Furthermore, in order to express separate heavy chain and light chain subunits that could assemble into an immunoglobulin, the genes would

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necessarily have to be non-contiguous, i.e., separated in the vector by sufficient non-coding DNA sequence to ensure that they are produced as separate molecules and not as a" sig- -- "single heavy chain/light chain fusion." Do you see that?

A Yes.

Q A minute ago you had said it would be difficult to get expression as a fusion protein; is that correct?

A You would have to take specific steps to do it; although, not always. To have the end of one protein exactly coincide with the beginning of the next is very hard. Sometimes you can clone into a preexisting gene, so I think in cloning insulin, by Gilbert's group, not by Genentech group, they cloned into the middle of a beta-lactamase gene, and their insulin was fused to that, so that wasn't so hard. It was just -- but it wasn't the same kind of thing as having two independent genes. The beta-lactamase gene was destroyed.

Q In the language in -- in your report, you're -- you indicate that you would need the genes

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to be non-contiguous to ensure that they are not produced as a fusion chain; is that correct?

A Let's see. Sorry. My head's pounding. Can you repeat, please.

Q Sure.

A Yeah.

Q In the language in your report --

A Yes.

Q -- you indicate that you would need the genes to be non-contiguous to ensure that they are not produced as a fuse -- fusion chain; is that correct?

A The genes would be non-contiguous. They would not -- that is, the genes would be separated by some piece of DNA that wasn't translated.

Q And you believe that's necessary because, otherwise, they would be produced as a fusion protein?

A They -- I'm using this to rule out a fusion protein in this case. If they are separated by a little piece of DNA, they are not a fusion protein.

Q In your report, you have said that the reason you assume that they are separated by at least some DNA --

A All right.

Q -- is to ensure that they are produced as

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separate molecules and not as a single heavy chain/light chain fusion. Do you see that?

A Please point it out to me. I believe you, but --

Q In the box corresponding to claim 15.

A Oh.

Q The carry-over paragraph.

A Okay. Oh, so there's more to it. "... in order to express separate heavy chain and light chain" subu- -- "subunits that could assemble into an immunoglobulin, the genes would... have to be non-contiguous..."

And that relies on knowledge that was -- been known for many years by then; that the end terminal of the light chain and the end terminal of the heavy chain are relatively close to each other. That is, the variable domains of the heavy chain and light chain in three-dimensional space line up next to each other, but if you did one of these fusions, let's say a light chain followed by heavy chain, that would physically move the heavy chain very far from the light chain and could never get back in

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three-dimensional space to form a -- an association that would be capable of binding antigen. That's why they would have to be separate.

Q Do you have a particular reference in mind that you were referring to in the answer you just gave?

A A particular reference that shows what?

Q In the answer you just gave, you described the -- the reasons why you wouldn't want a fusion protein if you wanted the heavy and light chain to assemble correctly; is that correct?

A Why you wouldn't want them as a fusion protein, yeah.

Q Do -- is there a particular article or patent or other reference that you have in mind?

A That deal specifically with the fusion problem and the impossibility of having a fusion between heavy and light chains?

Q Yes.

A I don't have one in mind that was present in 1983. I'm relying kind of on -- not kind of. I'm relying on common sense and also what was known about antibody structure.

Q Was it known, prior to April 1983, that the -- that a fusion protein of an antibody heavy

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chain and light chain would be -- would present difficulties in terms of getting a functional antibody?

MR. McCORMICK: Objection; asked and answered.

THE WITNESS: Was it known in the sense of had it been proven or -- I don't think that had been addressed. But the structure of antibodies was known, even the three-dimensional structure. And just knowing about what the parts of the antibody do, it -- it wouldn't make sense. It would be like having a cat with two, you know, feet going down and two more feet going up. You just wouldn't make a construct like that.

BY MS. DAVIS:

Q Are you familiar with instances in the prior art, prior to April of 1983, in which proteins, other than antibodies, were expressed as fusion proteins and then later recombined?

A Well, the insulin chains were expressed as fusion proteins and recombined.

Q Would it be possible, in your view, prior to April of 1983, to express the antibody heavy and light chains as a fuse- -- fusion protein and then later recombine them?

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A Could they be expressed --

MR. McCORMICK: Objection; vague, ambiguous, confusing.

THE WITNESS: So they would be expressed as a fusion protein and then perhaps cut away from the thing they were fused to and then recombined.

I forgot your original question, but if I -- I'm not aware of that having been done by 1983, but it sounds to me like it could be done or -- in 1983, you could have done it that way.

BY MS. DAVIS:

Q Were fusion proteins always -- strike that.

Prior to April of 1983, are you aware of proteins, other than insulin, that were expressed as fusion proteins intentionally?

A I didn't study the list of fusion proteins, but insulin is the main example that comes to mind by several labs. The somatostatin in the Cohen & Boyer paper was another one. I think the same group made human growth hormone. But I don't -- I didn't read the human growth hormone papers. I can't be sure of that.

Q Did you read the somatostatin papers?

A No. My knowledge on somatostatin comes from Cohen & Boyer, their example.

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Q Was somatostatin expressed as a fusion protein?

A I believe it was. Let me -- so we are looking at "Example V: Cloning of Synthetic Somatostatin Gene."

"Because of the failure to detect somatostatin activity from cultures carrying plasmid" -- I'm reading column 15, line about -- starting about 17.

"Because of the failure to detect somatostatin activity from cultures carrying plasmid pSOM1, a plasmid was constructed in which the somatostatin gene could be located at the COOH-terminus of the beta-galactosidase gene, keeping the translation in phase."

So that's a fusion protein, yes.

Q Would the method described in Cohen & Boyer for producing somatostatin as a fusion protein -- would that have worked to produce an antibody heavy and light chain as a fusion protein?

MR. McCORMICK: Objection.

THE WITNESS: So do you mean that if we took

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a light chain gene and used that the way they used somatostatin, fused that, and then separately made a heavy chain fused with beta-galactosidase and fused that, would that -- would that have produced these separate chains.

It would have produced fusion polypeptides, but part of the trick here with somatostatin was that -- I don't recall the somatostatin sequence offhand, but with insulin, there was a reliance on particular chemical reaction to cleave the fused polypeptide chain right at a specific place that would free up the insulin part, independent of the thing it had fused to. And I don't think the same technique could be applied to an antibody, which is much longer than these short peptide hormones.

BY MS. DAVIS:

Q With respect to insulin, you are referring to cleavage at the methionine?

A That's right.

Q Do you know whether somatostatin -- whether it was cleaved at methionine?

MR. McCORMICK: Objection; foundation.

THE WITNESS: Cleaved at a methionine in this paper?

MS. DAVIS: Correct.

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THE WITNESS: I don't recall offhand, but I can look and tell you.
Looks like they didn't do that chemical workup.
BY MS. DAVIS:
Q Can you tell from Cohen & Boyer how the somatostatin protein was cleaved?
MR. McCORMICK: Objection; foundation.
THE WITNESS: I don't see a cleavage reaction here.
BY MS. DAVIS:
Q Are you able to tell whether the fusion protein method used for somatostatin in Cohen & Boyer would have worked to produce antibody and -- antibody heavy and light chains?
MR. McCORMICK: Objection.
THE WITNESS: Well, it wouldn't have given antibody heavy chain and light chains, it would have given a fusion to something else. I'm sorry I hadn't read this more carefully before, but it's detailed biochemistry here I'm trying to understand on the fly.
BY MS. DAVIS:
Q Are you still reviewing?
A It's okay.

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Q It's fine if you are. I just want to make sure --
A Let's try the next question.
Q Are you aware of any reason why, following Cohen & Boyer, a person of ordinary skill in the art could not express antibody heavy and light chain in a manner similar to the somatostatin experiments and then reconstitute those chains into a functional antibody?
A I -- I don't see an impediment.
Q The chains in that hypothetical would be expressed attached to another protein?
A Well, if you make a fusion, you have to get rid of the thing it's fused to.
Q And you see no impediment to producing antibody heavy and light chains, according to Cohen & Boyer, where each heavy and light chain -- each of the heavy and light chain is fused to another protein?
A I -- I see potential problems in getting rid of the thing it's fused to.
Q You would need to identify a method to cleave away the fusion partner?
A That's right.
Q You don't know what method was used to cleave away the fusion partner in the somatostatin example?
A No, I don't.
MR. McCORMICK: Objection.
THE WITNESS: I haven't been able to figure it out just here.
MS. DAVIS: Okay. I want to move on to a new topic.
THE WITNESS: Okay.
MS. DAVIS: Do we -- is -- does anyone need a break?
THE WITNESS: Time flies. I don't need a break.
MS. DAVIS: Okay. Then let's mark the next exhibit. This is Exhibit 7, the Bujard patent, U.S. Patent 4,495,280.
(Exhibit 7 was marked for identification by the Reporter.)
BY MS. DAVIS:
Q Do you have that in front of you?
A I do.
Q So if you could turn in your report back to page 15, you see that you have a section labeled "Bujard."
A Yes.
Q My first question is about paragraph 48,

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which carries over onto page 16. In that paragraph, you state:
"The invention is an elaboration of the recombinant expression method of the Cohen & Boyer patent."
Do you see that?
A Yes.
Q Is it a fair statement that Bujard is an elaboration of Cohen & Boyer as opposed to being an entirely separate invention?
A An elaboration --
MR. McCORMICK: Objection.
THE WITNESS: Scientifically speaking, it's an elaboration. I don't know about a legal term, but, yes.
BY MS. DAVIS:
Q For purposes of your anticipation analysis, did you view that Bujard and Cohen & Boy- -- Boyer references as similar?
MR. McCORMICK: Objection.
THE WITNESS: Yes, they were similar.
BY MS. DAVIS:
Q In your opinion, they anticipate the asserted claims of the Cabilly II patent for similar reasons; fair?

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A Yes.
Q In paragraph 49, you say that:
"The Bujard patent generally relates to methods and compositions for preparing and cloning strong promoters and terminator regulatory signals, and utilizing the strong regulatory sequences in the transcription and expression of a gene or genes of interest."
Do you see that?
A Yes.
Q You agree that the thrust of the Bujard patent is the strong promoter and terminator combination?
MR. McCORMICK: Objection.
THE WITNESS: That's why Bujard made a plasmid with these properties, yes. The thrust, yes.
BY MS. DAVIS:
Q At a very high-level, what does a promoter do?
A A promoter causes an enzyme called RNA polymerase to begin transcription of a strand of DNA near the promoter.

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Q We discussed earlier that you had done some work with the SV40 promoter; correct?
A That's right.
Q Had you, personally, done work with other promoters prior to April of 1983?
A "Other promoters," you mean eukaryotic promoters or any promoters?
Q Any promoters.
A No, I hadn't.
Q Approximately how much had you worked with the SV40 promoter?
A I worked for at least two quarters while taking classes, but that was maybe six months.
Q And this is prior to 1983?
A That's right. This is 1981.
Q Could you turn to page 17 of your report.
A Yes.
Q In paragraph 51, you state, in part:
"The overall goal of the invention is to optimize production of recombinant proteins encoded by the DNA sequence of interest."
Do you see that?
A Yes.
Q What did -- what did you mean by "optimize"?

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A Optimize. That -- that term basically means getting the most of what you want for the least expenditure of resources. So if you are growing up a cell, having the cell make more protein.
Q Is it fair to say that, prior to 1983, expression levels could vary in terms of the gene of interest being expressed?
A It could vary depending on what other factor, depended on promoter or cell type, other factors could -- yes.
Q One of the goals of Bujard was a particular way in which to optimize levels of expression.
A That's right.
Q Could you turn to paragraph 54.
A Yes. Ah, yes.
Q This paragraph you refer to Bujard's use of the term "multimer"?
A Yes.
Q You have a number of references in here that are references to "multimeric proteins"; is that fair?
A That is.
Q You would agree that Bujard was not using "multimer" to refer to a protein. It was, instead, using "multimer" to refer to a gene?

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A I think he was using -- he was referring to gene or genes coding a multimeric protein.
Q Does Bujard use "multimeric protein," the term?
A Does he use it in the patent at all? I know we are talking about this one line. He uses the term "multimer." What's the quote? "Plurality of genes, including multimers and operons."
Q In that quote, the multimer is genes; correct, not proteins?
A His usage is a little awkward, and I interpreted it as genes encoding for multimers, but it's genes, plurality of genes, yes.
Q What led you -- what are you relying on to conclude that his reference to "multimer" was referring to genes encoding multimeric proteins?
A Because an alternative of just repeated genes in a row wouldn't make sense. I -- I know he says "a plurality of genes, including multimers and operons." Well, you know, an operon is not a gene either. It's more complex, so I think his language was a little sloppy here.
Q In your report at paragraph 54, you have a number of uses of "multimer" and "multimeric"; correct?

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A That's right.
Q Those are in the context of the use of the term "multimer" referring to a protein; correct?
A That's correct.
Q Do you have any similar examples of the use of the word "multimer" in which it is referring to a gene?
A Do I have any. You mean, did I put any in my report or can I think of any?
Q Both.
A I didn't put that into my report.
Back to Dressler's lab. After working with this antibody project, the other one ongoing in the lab that I joined was looking at recombination between plasmids. This is not in vitro recombination the way Cohen & Boyer is, but natural recombination.
And if you think about it, if a plasmid is two circles and two circles recombine -- for the audio record, I'm making two circles with my fingers. If they recombine, you get one big circle, and we would call those "multimers." They could be the size of two little circles or three little circles or four little circles. So that was a usage, but, again, that's not repeated genes.

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"Multimer" is an English word, and in biochemistry it has the specific meaning about proteins with multiple subunits, or I may have quoted the Oxford English dictionary. There was a specific technical meaning. Usually refers to that.
Q Is it your understanding that "multimer" usually refers to multiples of the same gene?
A Multi- -- sorry. Multiper -- "multimer" refers to multiples of?
Q The same gene.
A In this case, it would be the same protein or -- I'm confused by the question. Maybe we should try it again.
Q My question is whether it is your understanding that "multimer" usually refers to multiples of the same gene.
A No. "Multimer" refers to multiples of the same protein subunit.
Q Could you turn to page 19?
A Yes.
Q Paragraph 57?
A Yes.
Q You note in here that the Bujard patent inventors themselves -- well, strike that, because there's a -- the reference will not be clear.

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Beginning a little higher up:
"A person of ordinary skill in the art would have known in 1983 that antibodies are assembled from multiple, discrete polypeptides (four - two heavy chains and two light chains) encoded for by two different genes. The Bujard patent inventors themselves recognized this when they identified the structure of each type of immunoglobulin that can be produced according to their method. For instance, they recognized that IgG has the molecular formula of gamma 2 kappa 2 and gamma 2 lambda 2 (two heavy chains and two light chains)."
Do you see that?
A Yes.
Q Turning to Bujard, you were referring to column 5?
A Yes.
Q If you could turn back to column 4, do you see, at column 4, line 35, in the same list of proteins, "immunoglobulins, e.g., IgA, IgD, IgE, IgG

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and IgM and fragments thereof"?
A Yes.
Q You would agree that Bujard lists the different types of antibodies twice?
A He lists them here, and then he lists them in column 5, yes.
Q In column 5, he lists them with their molecular formula?
A Yes.
Q In column 4, he does not list them with their molecular formula?
A Gives just their name, yes.
Q What do you make of the fact that Bujard lists the different types of antibodies twice?
MR. McCORMICK: Objection; foundation.
THE WITNESS: Well, he's giving a kind of -- he's just being redundant. He's giving a kind of paragraph list, and then he's taking more care and listing things one by one, one protein per line -- or per several lines, but he's saying the same thing for antibodies.
BY MS. DAVIS:
Q Do you --
A And also -- I'm sor- -- sorry to interrupt -- I notice, at the top, he says "and fragments

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thereof." So this is a more -- sorry.
In column 4, after IgA, 'D, 'E, 'G, and fragments thereof, so this is a kind of summary in one line. And then he spells it out in two lines: immunoglobulin G, IgG, or gamma G-globulin, molecular formula, like that. So summary -- summary statement and then a verbose statement.
Q You mentioned the antibody fragments are mentioned.
A Yes.
Q Does Bujard describe what is meant by "fragments of immunoglobulins"?
A I don't recall if he has a description outside that statement. I don't know that he has a specific description.
Q In 1983, would it -- strike that.
An IgG antibody can be conceived of as having three fragments; is that fair?
A Three fragments?
Q Yes.
A I'm just trying to count them. You are thinking Fv fragments, FAB fragments. There's an Fd fragment. Several fragments, yes.
Q An IgG antibody can be broken into two fab fragments and one Fc fragment; is that correct?

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A That's right, yes.
Q Would it have been known, in 1983, that an IgG antibody could be broken into two fab fragments and one Fc fragment?
A Yes.
Q The Fc fragment, that's the fraction crystallizable fragment?
A That's the common knowledge, but I don't think that's what it stands for.
Q What -- what do you think it stands for?
A Milstein told me this story. His very close friend -- his closest friend, Rodney Porter, is the one who did this fractionation, and in undergraduate courses, you hear FAB stands for fragment antigen binding, and Fc stands for fraction crystallizable, or fragment crystallizable.
But this wasn't true; that Porter did these digestions of IgG with proteolytic enzymes, and he would run them on chromatography columns, and he would elude peaks off these columns, and he got one peak, two peaks, three peaks, and he called them Peak A, Peak B, and Peak C.
And then, later, he took Peak A, thinking it was different from Peak B, and he ran it again, and he got two peaks again, and he found that Peak A and

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Peak B were the same thing, and he couldn't figure out what the difference was, so he started calling them FAB, and I thought this was just some weird story until I did it myself, and I got three peaks off a column, and I ran one and it split into two more peaks.
But Fc, I know what you mean.
Q That was in Dr. Milstein's lab?
A I -- that was after I left his lab, and I was at Fred Hutchinson when I did that experiment, with a very modern HPLC column, and it still split into three peaks.
Q The Fc fragment of an IgG antibody is composed entirely of heavy chain; is that correct?
A That's correct.
Q It's the second and third constant domains of the heavy chain joined to each other?
A That's correct.
Q There's no light chain in the Fc fragment; correct?
A That's correct.
Q Do you have an opinion as to whether an Fc fragment would be included in the fragments thereof that Bujard describes as being a protein that could be produced by this method?

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A Right. In his verbose list, he doesn't -- he doesn't mention Fc, so it's ambiguous. In the short summary list, he says "fragments," and Fc was certainly a -- a well-known fragment. For that reason, I would be inclined to believe that an Fc would be produced by his method.
Q Do you believe that Bujard anticipates the production of an IgA or an IgM antibody?
MR. McCORMICK: Objection.
THE WITNESS: Yes. He says this can be used to make IgA or IgM.
BY MS. DAVIS:
Q To your mind, is there any difference in how a person of ordinary skill in the art, in 1983, would go about producing an IgA or an IgM as opposed to an IgG antibody, according to the method of Bujard?
A Well, these have an extra chain that ties the end of the heavy chains together, the J chain, most well known for IgM. But you can still make IgAs lacking a J chain, and they assemble.
Q How about -- oh, please finish your answer.
A Yeah. And they are considered IgAs.
Q How about IgM; do you believe a person of ordinary skill in the art would have been able to

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make an IgM antibody, according to the method of Bujard, prior to 1983?
A IgM could have been made. Again, he -- you know, he gives the subunit substructure and doesn't mention the J chain, but could be made.
Q Could you make an IgM without a J chain?
A Well, you could certainly make the polypeptides inside a cell, and you could probably assemble them either in the cell or by in vitro methods.
Q In the answer you just gave, were you contemplating that the J chain would be made in a different cell?
A No. I mean, you could make it without having the gene for the J chain there.
Q Would that still be considered -- strike that.
Would the end product of that still be considered an IgM?
A I think it would.
Q In 1983?
A Yes.
MR. McCORMICK: We have been going about --
MS. DAVIS: Yeah.
MR. McCORMICK: -- an hour, more than one

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hour, so --
MS. DAVIS: And we need to change the tape, so --
MR. McCORMICK: Okay. Good timing, then.
MS. DAVIS: So let's go ahead and take a break.
THE VIDEOGRAPHER: This concludes Videotape No. 2, Volume 1 in the deposition of Dr. Foote.
Going off the record, the time is 2:33.
(Recess taken.)
THE VIDEOGRAPHER: This begins Video 3, Volume 1 in the deposition of Dr. Jefferson Foote.
Going back on the record, it's 2:50.
BY MS. DAVIS:
Q Dr. Foote, could you look at paragraph 58 of your report?
A I have it.
Q You refer, in paragraph 58, to -- the reference in Bujard to "free light chain"; correct?
A Yes.
Q Are there uses for free light chain, apart from as a part of an assembled antibody?
A Uses for free light chain. I'm trying to think of any that are more than trivial. Usually they go together with heavy chains.

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Q Have you considered whether there are reasons a researcher might have wanted free light chain in 1983?
A I didn't consider -- I'm considering now, but can't come up with much. They are a bit simpler than heavy chains.
Q Are you aware of any uses of free light chain as reagents?
A Light chains. Something called Bence Jones proteins are light-chain dimers, and those were studied for a time because they were easily obtained from cancer patients.
Q Are you familiar with any other instances in which -- well, strike that.
A light-chain dimer is two light chains; correct?
A That's correct.
Q Are you familiar with any other instances of light-chain dimers being intentionally produced?
A I can't think of any.
Q In paragraph 59, you say:
"In short, the inclusion of immunoglobulins (as well as the other multi-subunit proteins mentioned above) as an exemplar

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protein that could be produced by the Bujard method would have indicated to one ordinarily skilled in the art that the plasmid vehicle could, and necessarily must in the case of immunoglobulins, contain more than one foreign gene -- one each for the heavy and light chains."
Do you see that?
A Yes.
Q You say must contain the genes for the heavy and light chains in the case of an antibody; is that correct?
A "Neccssarily must," yes.
Q What is the basis for saying that if you were producing an antibody by the Bujard method, you must include both the heavy and light chain gene in the same plasmid?
A Well, that comes from the previous paragraph; that just reading through Bujard for -- reading that list, I would see, oh, free light chains, but -- but here he doesn't say free heavy chains. I can't find it anywhere. So that, to me, as someone skilled in the art reading that in 1983 would think, oh, well,

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there must be something wrong with making free heavy chains, so I'll make them together; I won't try to make them separately and later recombine them.

Q Is free light chain considered a contaminant?

A A contaminant of?

Q In an antibody production. If you were producing antibodies, do you sometimes end up with free light chain?

MR. McCORMICK: Objection; incomplete hypothetical.

THE WITNESS: Not usually. I haven't had that problem.

BY MS. DAVIS:

Q A minute ago you had said that the reason -- your basis for saying necessarily must include both a heavy and light chain is the absence of an entry for free heavy chain --

A That's right.

Q -- correct?

Do you have any other basis for saying that when producing an antibody by the method of Bujard, one of skill in the art necessarily must include the heavy and light chain in the same cell?

A No. I'm referring to that argument right there.

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Q You agree that an antibody could be produced by the method of Bujard by way of having the heavy chain in one cell, the light chain in another cell, followed by in vitro reconstitution?

A I think it could; although, Bujard seems to be warning me not to try to produce heavy chains.

Q You said -- oh, please finish.

A He didn't -- that's right. I might try anyway, but that would be a disincentive for me to try producing heavy chains separately. A disincentive doesn't mean it absolutely won't work.

Q You said you might try it anyway.

A Yes.

Q Why might you try that?

A Well, if I needed to make an antibody, I would probably try making the two chains together, but as I said before, it's a disincentive but not an absolute prohibition, so I have to make the heavy chain some way, and this would direct me to make it together with the light chain in the same cell.

Q Do you have any opinion as to why, in your view, the -- Bujard chose to express this concept by listing light chain but not listing heavy chain as opposed to vice versa?

A I don't know what was in his mind.

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Q If Bujard had said free heavy chain but did not list light chain, would your opinion be the same?

A If he listed free heavy chain but not free light chain, that would suggest to me, just from this patent alone, that it might be hard to make light chains by his method, and that would make me more inclined to try and express them together, the two chains.

Q Do you interpret the Bujard patent to be suggesting that it is difficult to make heavy chains alone?

A There's a suggestion there by its absence in that list, yes.

Q How, if at all, do you reconcile that with the fact that Bujard contemplates producing fragments of antibodies which could include the all-heavy-chain Fc fragment?

A Well, he doesn't list the Fc would make me think again about whether he meant to include that, but also, the Fc is not a heavy chain, it's a smaller part. Maybe it's okay to make Fc.

Q Is it, in fact, true that it is harder to make a heavy chain than it is to make a light chain?

A There's some lore that it's harder, and there

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was this precedent of finding a lot of these Bence Jones proteins in cancer patients, because it would come out in the urine. That's how it would be isolated.

My old professor talked about being in Wisconsin where it was so cold all the time. You could just take the stuff and -- the urine and leave it on the roof, and the next day you would have your Bence Jones protein.

So there was more experience with light-chain dimers.

Q The potential difficulty with producing heavy chain, how, if at all, in your opinion, is that overcome by producing it in the same cell with a light chain?

A In -- I don't think that gets you much of advantage, unless -- if they are made as separate polypeptides -- let's say in E. coli -- and they're not assembled, I don't think that buys you much advantage. If you could get to the stage of an assembled immunoglobulin, an IgG in assembled immunoglobulin tends to be very stable. It's not necessarily true of a isolated heavy chain.

Q Is it your opinion that in vivo -- well, strike that.

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In vivo assembly is assembly of the antibody heavy and light chains into an antibody within the cell; fair?
A Within the cell, in vivo assembly, yes.
Q Is it your opinion that in vivo assembly is easier than in vitro assembly?
MR. McCORMICK: Objection -- hold on -- it's outside the scope of his expert report and incomplete hypothetical.
THE WITNESS: I haven't considered assembly for this report, the feasibility, the enablement aspects. It's hard to say whether one would be easier.
BY MS. DAVIS:
Q A minute ago you had said that the -- the fact that, in your opinion, Bujard is discouraging you from producing free heavy chain would suggest to you to put the heavy and light chain in the same cell.
A That's right.
Q And I am trying to understand what is it about putting them both in the same cell that overcomes whatever it is that you see as the problem being flagged with respect to producing heavy chains? Do you have something in mind?

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A There're -- there are sort of two roots to that. Just that the reading of Bujard, the Bujard patent all by itself, says make free light chains, but it doesn't say make free heavy chains, but it does say make IgG, so I infer from that we will put both chains in the same cell.
From my knowledge of antibody biochemistry, I don't see the advantage of putting them in the same cell unless they are going to assemble, so I -- but, again, that's outside the areas I've considered for this report.
Q In the answer you just gave, you -- you said you don't see the advantage of putting them in the same cell unless they are going to assemble.
Were you referring to assembling in the cell?
A That's right. But, again, that's my personal scientific opinion that's influenced by -- by what I learned after, you know, over the years, and it's not my reading of Bujard.
My reading of Bujard says make light chains, but don't make standalone heavy chains, so put both in the same cell.
Q A person of ordinary skill in the art could make an antibody by expressing the heavy chain in one cell and the light chain in another cell in

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1983; correct?
MR. McCORMICK: Objection; incomplete hypothetical.
THE WITNESS: I believe a person skilled in the art could.
BY MS. DAVIS:
Q If that person proceeded to make the heavy chain in one cell and the light chain in another cell and then combined those two chains to make an antibody, would you expect to refer to the constituent heavy and light chains as "free light chains" and "free heavy chains"?
A Free light chains and free heavy chains. That would be -- you could call them that.
Q In your experience, does "free light chain" more commonly refer to light chain that will not go on to be combined with heavy chain to form an antibody?
A In my experience, free light chain can -- well, this is outside of the Bujard patent, but free light chain, by itself, when it associates with itself, can associate with itself as a dimer, and that structure is fairly stable.
Q Are you familiar with any uses of the term "free light chain" other than in the Bujard patent?

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A I don't have specific instances, but it -- it's a commonly understood term. It's a -- I wouldn't call it straight English, but it's common parlance in biochemistry.
Q Is it your understanding that, in common parlance, it is acceptable to refer to a light chain that is then joined with a heavy chain to form an antibody as a free light chain?
A A free light chain that's joined with a heavy chain is not -- no longer a free light chain.
Q Could you turn to page -- strike that.
Could you turn to page 22.
A Yes.
Q There is a section on Riggs & Itakura?
A Yes.
Q So my question is about the carry-over sentence, and you say that Dr. Riggs and Dr. Itakura were among the first scientists to use recombinant DNA technology and synthetic DNA to express mammalian polypeptides in bacteria.
Do you see that?
A Yes.
Q Is that correct?
A Yes. They were leaders, yes.
Q What is the significance of being among the

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first scientists to express a mammalian polypeptide in bacteria?
A The significance? Oh, just, in general, it's a good thing to be first, to be first than to be second.
Q Why is it significant that they were among the first to express a mammalian polypeptide in bacteria?
MR. McCORMICK: Objection; foundation.
THE WITNESS: Is it significant. This is just a kind of benign compliment. There's no deeper meaning to that. I'm showing that these are leaders in the field who have written this article that I'm going to quote from.
BY MS. DAVIS:
Q Prior to the work of Dr. Riggs and Dr. Itakura, scientists had expressed bacterial proteins in bacteria; fair?
A Yes.
Q And Dr. Riggs and Dr. Itakura are among the first to express a mammalian protein in bacteria; correct?
A That's right.
Q What significance, if any, do you ascribe to the mammalian aspect of their work?

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A The fact that it was mammalian -- nothing really special. They weren't even the first. I mean, Gilbert expressed insulin in bacteria before them. It just happened to be red insulin.
Q Not specific to Dr. Riggs and Itakura, but with respect to the scientists who first expressed a mammalian protein in bacteria, what significance, if any, do you ascribe to their success in expressing a mammalian protein in bacteria as opposed to a bacterial protein in bacteria?
A I think, at the time, it showed that -- well, there really was a universal genetic code that -- you know, here you could take something from a human or a mouse or a monkey or a rabbit and put it in bacteria, and it would make the same protein, essentially, in bacteria as was being made in the higher organism.
Q You believe that --
A That, and there was also a -- it was, in a way, kind of technical triumph in that mammalian DNA, the DNA in one mammalian genome, the DNA within one cell, is many, many times larger -- or longer, containing more nucleotides, than in a bacterium. So, in this case, they are taking a much smaller part of a big mass and cloning that.

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For example, when my group in Berkeley cloned that ATCase gene, they didn't even take it from a bacterium, they took it from a bacteria-phage. So it represented much of -- a fair amount of -- a significant amount of that bacteria-phage was the gene of interest, so they had to separate it from a much smaller mass than if they had to take that from a huge eukaryotic genome. So there was a technical triumph to expressing mammalian genes in bacteria, having to do with isolation of the gene itself, not really that the proteins were too different.
Q In this paragraph, you describe the -- the insulin production process at a high-level; is that correct?
A Yes.
Q You agree that Dr. Riggs and Dr. Itakura used separate cells for each of the two insulin chains?
A Separate transformation of E. coli cells, yes.
Q Was that a significant result?
MR. McCORMICK: Objection.
THE WITNESS: Significant. Not really. That seems like the easiest way to do it.
BY MS. DAVIS:
Q Do you remember hearing about Dr. Riggs and

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Dr. Itakura's work --
A I do.
Q -- at around the time?
A I do. Very much.
Q Do you remember what you thought when you heard about their production of insulin?
A I remember what I thought about it, because it was, at that time, that I was working in the Gilbert group, which was the rival, and I thought, oh, Gilbert lost, and I wasn't feeling kindly to him -- toward Gilbert, at that time, so it was, ah, Gilbert lost, but I -- I liked the audacity of using synthetic DNA.
Gilbert's group had not really invested in organic chemistry. They took the purely biological approach of making cDNA clones, and they had gone on a kind of pretentious expedition to this biohazard facility in Britain to try and clone a human gene, and I was -- I found that a pleasing result; that Itakura is the one who gave the talk that I heard that he had done it by this way. I thought, you know, good for chemistry.
Q Do you recall having any reaction to the -- the fact that Dr. Riggs and Dr. Itakura put each of the two insulin chains in separate cells?

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A No real reaction to that, no.
Q You said a little while ago that using one chain per cell seemed to you to be the easiest way to do it.
Is that -- was that your testimony?
A That's right.
Q Why is that?
A Well, I'm thinking here of putting two plasmids in the same cell. If you had put them in the same cell, they might -- there's a possibility they would be unstable, but I haven't really thought through that issue of what would be the best way to make insulin.
Q In general, is one gene per cell easier than two genes per cell?
MR. McCORMICK: Objection.
THE WITNESS: It may depend on the system, but you -- if you are making one gene, you have to clone less. Your construct might be smaller. You would -- if you were using an intercistronic-type construct -- like for ATCase, you would have to make sure that intercistronic region with the ribosome restart site would be there. Not -- not greatly more difficult, but there's a sort of nuisance value to putting in two genes.

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BY MS. DAVIS:
Q Are smaller constructs -- well, strike that.
In 1983, would a smaller construct be easier to work with than a larger construct?
MR. McCORMICK: Objection.
THE WITNESS: That would be -- that would depend on small and large. Something that was 5,000 basis would be easier to work with than something that was 15,000, but 5,000 versus 6,000, you might -- you wouldn't notice the difference.
BY MS. DAVIS:
Q Could you turn to page 26 of your report.
A Okay.
Q Paragraph 74, are you there?
A Yes.
Q In that paragraph, you say -- well, strike that.
This is referring to Bujard; correct?
A Right.
Q You say:
"The region between the promoter and terminator in the plasmid vector can have a plurality of restriction sites to allow insertion and removal of regulatory signals and genes.

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When two or more genes of interest are present in this region, the insertion of one or more regulatory signals before each gene will result in expression of both gene and separate production of the encoded-for polypeptide."
Do you see that?
A Yes.
Q Is it always true that when you have two or more genes of interest in the coding region with one or more regulatory signals before each gene, you will achieve expression of both genes and separate production of the encoded-for polypeptide?
A If they are appropriate signals and regulatory sequences, yes.
Q What would you need to know in order to figure out what would be the appropriate signals and regulatory sequences?
A Well, let's say I was making one of these intercistronic constructs. I would like to know that the region between the two polypeptide genes would include this ribosome restart site.
At the upstream end, I would want to know that the promoter is going to be functional in that

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particular cell type.
Q In 1983, do you believe a person of ordinary skill in the art would have been able to select appropriate promoters for use in expressing the antibody heavy and light chain gene?
A Yes.
MR. McCORMICK: Objection.
BY MS. DAVIS:
Q What types of promoters do you believe a person of ordinary skill in the art could have selected in 1983 to express antibody heavy and light chain genes?
A Are these --
MR. McCORMICK: Same objection.
Go ahead.
THE WITNESS: Are these using Bujard's method?
MS. DAVIS: Yes, using Bujard's method.
THE WITNESS: Well, could use some of the genes that Bujard himself found from the T5 phage. One could use lack promoters. There have been quite a few promoters active in E. coli identified by then.
BY MS. DAVIS:
Q Would a lack promoter work to express an

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antibody heavy or light chain gene?
A I think it could be used to do that.
Q Could you turn to page 29.
A 29, yes.
Q And so on page 29, you have a section entitled "Obviousness of Asserted Claim 33 in the Cabilly II Patent."
A Yes.
Q This section addresses obviousness.
A Yes.
Q Paragraph 84 on the next page, are you there?
A Yes.
Q You state: "Cohen & Boyer and Riggs & Itakura" -- strike that.
You say:
"Cohen & Boyer and Riggs & Itakura are all publications in the same general field of research: the production of eukaryotic proteins in heterologous host cell systems, specifically microorganisms."
Do you see that?
A Yes.
Q What is the significance to your analysis that Cohen & Boyer and Riggs & Itakura are in the

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field of the production of eukaryotic proteins in heterologous host cell systems?
A The significance of that? Common goals.
Q Is that the field in which you believe a person of ordinary skill in the art in 1983 faced with the problem of producing a recombinant antibody, the field in which that person would be looking to?
A Yes.
Q Could you turn to page 32.
Page 32 you have a heading "Invalidity of the Asserted Claims of the Cabilly III Patent under ODP"; correct?
A Yes. Uh-huh.
Q As discussed earlier, that's obviousness-type double patenting?
A Yes.
Q For purposes of your opinion that certain claims of Cabilly III are invalid for obviousness-type double patenting, did you consider the Cabilly II file history?
A I looked at the file history here and there. I didn't master it, so it didn't enter tremendously into my analysis.
Q Are you aware that the PTO considered

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arguments that certain claims of Cabilly II were invalid for obviousness-type double patenting?
A I believe I did see that.
Q Do you know what the resolution of that issue was?
A The patent was issued, so they must have decided against it.
Q Did you consider the arguments made in connection with the -- in the file history regarding the obviousness-type double-patenting argument raised with respect to Cabilly II?
A I'm sorry. Was --
Q Let me rephrase.
A Yeah.
Q In conducting your analysis of whether Cabilly III is invalid for obviousness-type double patenting, did you examine the arguments that were rejected by the Patent Office with respect to Cabilly II?
A I -- I did have a look, but I don't really remember what they are as we sit here, and mostly my analysis was -- rested on looking at this Cabilly claim -- or this claim 2 from Cabilly I and the Cabilly II and III in light of Cohen & Boyer and Bujard, and Mr. McCormick explained the concept of

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obvious-type double patenting. That's mostly where -- that's where most of my information came from to reach this conclusion, this opinion.
Q Did you compare the arguments that you are making with respect to double patenting of Cabilly III to the arguments made before the PTO about the alleged obviousness-type double patenting of Cabilly II?
A I didn't compare. I didn't write my piece and then go back and compare. I did -- again, vaguely looked at the old file history, but I wouldn't say that it was influential.
Q Do you know whether the PTO considered, in connection with Cabilly II, combinations of a claim of Cabilly I with particular art references?
A I don't recall what they put together. My recollection of the action between your client and the PTO is very vague.
Q Do you know what art references had been combined with Cabilly I claims in the context of the Cabilly II ODP arguments?
A I don't recall, no.
Q Do you know whether any of the arguments that you are making with respect to the alleged double patenting of Cabilly III are similar to the

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arguments that have been raised with respect to alleged double patenting of Cabilly II?
A As we sit here, I don't, offhand, know the relation of my arguments to what happened before the PTO.
Q Could you turn to page 34.
A Mm-hmm.
Q You have a footnote on page 34.
Do you see that?
A Yes.
Q You say in the footnote:
"... once it was known that non-chimeric heavy and light chains could be successfully co-expressed (i.e., transcribed and translated) in a single host cell and that a chimeric heavy or light chain could also be successfully expressed (i.e., transcribed and translated) in a single host cell, a person of ordinary skill in the art would have been confident that chimeric heavy and light chains could be successfully co-expressed (i.e., transcribed and translated) in a single host cell."
Do you see that?
A Yes.
Q That statement is true?
A Let me read that.
Yes, and this -- this jogs my memory; that one result of the action between your client and the PTO was the emphasis that, in Cabilly I, a chimeric light chain or a chimeric heavy chain could be expressed, but not both. It was "or" not "and/or."
Q Do you -- strike that.
A Right.
Q I -- I appreciate the clarification.
A Yeah. Mm-hmm.
Q I want to ask you about the statement just in isolation.
A Right.
Q Not necessarily --
A Okay.
Q -- with respect to Cabilly I.
A Right.
Q Do you agree with the statement you made in Footnote 10?
A Right. So let me read it again.
Yes, I agree with that.

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Q In this footnote, do you distinguish -- well, strike that.
I don't see in this footnote any particular type of DNA that you are describing as being expressed, whether it be murine or rabbit or something else; is that fair?
A It just says "chimeric" or "non-chimeric," mm-hmm.
Q One option for -- for chimeric DNA would be part murine, part human; is that fair?
A That's -- that's chimeric.
Q Did you -- do you believe the -- well, strike that.
A murine-human chimeric antibody is within what you are discussing in Footnote 10?
A Yes.
Q What significance, if any, do you ascribe to the fact that in a murine-human chimeric antibody, a portion of the DNA is human?
A What effect do I describe -- ascribe to that?
MR. McCORMICK: Objection; foundation.
THE WITNESS: Effect from the point of view of a molecular biologist expressing, because they will have different functions in vivo, but just in terms of expression, what effect does that have. No particular effect comes to mind.
BY MS. DAVIS:
Q Are human antibody heavy and light chain genes expressed in a fashion similar to murine antibody heavy and light chain genes?
MR. McCORMICK: Objection; incomplete hypothetical.
THE WITNESS: Do you mean in humans and in mice?
MS. DAVIS: Recombinantly.
THE WITNESS: Recombinantly.
MR. McCORMICK: Same objection.
THE WITNESS: They are expressed the same way.
BY MS. DAVIS:
Q Would you -- well, strike that.
A Yeah.
Q You say in this that once it was known that non-chimeric heavy and light chains could be successfully co-expressed and then a chimeric heavy or light chain could also be expressed, a person of ordinary skill in the art would be confident that chimeric heavy and light chains could be successfully co-expressed.
And my question is: In that statement, did

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you have in mind a particular type of non-chimeric heavy or light chain, whether it be murine or some other type of chain?
A I didn't have a particular one in mind, but most were murine at that point.
Q Would a person of ordinary skill in the art, having seen a non-chimeric murine and a heavy light chain being successfully co-expressed, be confident that a human-murine chimeric heavy and light chain could be successfully co-expressed?
A That is --
MR. McCORMICK: Hold on.
Objection; incomplete hypothetical and to the extent it's outside the scope of his expert report.
THE WITNESS: So you mean a murine variable region attached to a human constant region?
MS. DAVIS: Yes.
THE WITNESS: Yes. There would be confident -- confidence that that could be expressed.
BY MS. DAVIS:
Q What would be the basis of the confidence with respect to expression of the human constant region?
A The confidence is not so much positive as a

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lack of negatives: Why couldn't it be expressed. Other constant regions are expressed, so why not the human one. I don't see a specific block there.
Q You can set that aside, and I want to ask you some questions about Exhibit 2, which is your rebuttal report.
A Oh, yes.
Q First, a general question. I had read your rebuttal report. I did not see in your rebuttal report any rebuttal specific to the question of obviousness-type double patenting.
Do you agree that that is not contained within your rebuttal report?
A That's not contained. It was sort of kicked down the road.
Q What do you mean "kicked down the road"?
A I think I reserved the right to respond to it later, but I didn't respond at this time.
Q Sitting here today, do you have any response to Dr. Fiddes' arguments on the subject of obviousness-type double patenting?
MR. McCORMICK: Object to foundation.
THE WITNESS: I remember not agreeing with them. If you would like to discuss them, maybe we -- we could.

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BY MS. DAVIS:
Q My first question is --
A Yeah.
Q -- just whether you have any concrete responses to Dr. Fiddes that you can think of right now on the issue of obviousness-type double patenting, which, as we discussed, are not included in this report?
A No. I just didn't treat it in this report. I don't have anything to tell you right now.
Q Could you turn to page 3 of your rebuttal report.
A Yes.
Q In paragraph 9, you are referring to the creation of a single vector containing the heavy and light chain genes according to the methods of either Cohen & Boyer and Bujard; is that correct?
A Yes.
Q You then say:
"Moreover, such a vector could be generated from the teachings of these prior art patents, coupled with a person of ordinary skill in the art's knowledge of recombinant DNA techniques for the creation of

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expression vectors, without undue experimentation."
Correct?
A Correct.
Q Is it your opinion that, in 1974, following the methods of Cohen & Boyer, a vector could have been created without undue experimentation that contained the antibody heavy and light chain genes?
A There would have been undue experimentation to isolate those genes.
Q In 1974?
A In 1974.
Q At what point between 1974 and 1983 do you believe that the vector containing the heavy and light chain genes could be created without undue experimentation?
A Oh, I think by around 1980. What was missing in 1974 were the genes themselves. The antibody genes had never been cloned by anyone, and introns hadn't been discovered. The genomic gene structure of the antibodies was unknown at that time.
That's what would have made it very hard for, you know, a second-year post-doc to do it in 1974. It would have been more possible in '80, '81, '82, '83.

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Q You mentioned just now 1981, '82, '83. Among those years, is there a particular year you have in mind?
A It gets easier and easier with each year.
Q Just so that I'm sure I understand your testimony --
A Yes.
Q -- is there one year that you believe is the best candidate among those four, or does your answer include all four years?
A I think '83 would be better than '82, but I think it could have been done in all four years.
Q Other than cloning of the genes, what was available in the later years that would have been very difficult in 1974?
A The tools were much better. We had oligonucleotide-directed mutagenesis. If we didn't have a restriction site in the right place, we could put one there. We had many, many more restriction enzymes to choose from. We had CDNA cloning from kits, commercial material technology. The tools were much better in '83.
Q You said that, in 1974, it would have been very difficult to make a vector containing the heavy chain gene and the light chain gene aco- --

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according to Cohen & Boyer?
A Yes.
Q Would it have been possible at all to make a heavy chain gene and a light chain -- strike that. Would it have been possible at all in 1974 to create a single vector containing the heavy chain gene and the light chain gene?
A In 1974, possible at all. And leaving out the idea of undue experimentation.
Q Correct.
A I think it would have been.
Q Could you have made, in 1974, a vector containing the heavy chain gene and the light chain gene both in the form of genomic DNA?
A Genomic DNA. It would have been split into exons, and that wasn't known in 1974, and it would have -- it would have taken a genomic gene and put it into a bacterium. You wouldn't have gotten a polypeptide, so that would have prevented it. So, no, it would not have been possible with genomic.
Q Was there another option in 1974 other than the use of genomic DNA that would have let you put both a heavy chain gene and a light chain gene in a single vector?
A I'm thinking more of fragments thereof. That

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would have been easier. Even though DNA sequencing was just beginning right around then, there's extensive protein sequencing, so we knew what the -- we knew what variable domains looked like. We knew the amino acid sequence of many of them.
So if someone had been able to clone a variable domain from a cancer cell, let's say, one could have -- one could have expressed that gene, that variable domain gene, would have known what the boundaries were, and it could have been expressed. Not elegantly, not without great difficulty, but it could have been done.
Q In your answer --
A Yeah.
Q -- are you limiting expression to the variable domain only?
A Well, we knew what the constant domains were too, but I don't think we could have synthesized a complete -- let's just focus on the heavy chain. I don't think, by synthetic methods, we could have made one that was, whatever, hundreds of basis long. It was just not feasible with the organic chemistry technology for making synthetic oligonucleotides, so we would have had to take pieces from the genome, and we would have run into this problem of exons.

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There may have been an expectation that genes were contiguous then, but we found out that was wrong. We found out that was wrong the first time someone sequenced an antibody gene.
Q That happened after 1974?
A That did.
Q You mentioned variable domains and constant domains were known in 1974.
A Yes.
Q Was the boundary between the constant domain and the variable domain of an antibody known in 1974?
A Yes.
Q When did that become known, do you know?
A Oh, that was defined by protein sequencing and was known, I would say, by 1971. In 1971, Cabot published a compilation of amino acid sequences, and he got the boundaries about right.
Q You did some early work attempting to clone an antibody gene; correct?
A That's right.
Q That was in the late 1970s?
A 1977.
Q Did you know, at that time, the boundary between the variable domain and the constant domain?

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A Yes.
Q Do you think, essentially, everyone in the field working with antibodies knew where the boundary between the variable domain and the constant domain was?
MR. McCORMICK: Objection.
THE WITNESS: Yes.
BY MS. DAVIS:
Q Do you believe that Drs. Cohen & Boyer believed an antibody could be produced using their methods in 1974?
A Yes.
Q Why do you think they believed an antibody could be produced using their methods in 1974?
A Even though those genes weren't -- oh, produced using their method in 1974. That's the question.
I don't know what they, personally, believed. The impression I get from reading the patent is that all these problems of expressing proteins would fall into place, and they would fall into place using this method, and there will be difficulties on the way, but those will be overcome, and so I think that they believed the problem could be overcome using their method, even if there were difficulties along

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the way.
Again, there hadn't -- it was at the dawn of cloning. This was the key cloning patent, but they had envisioned that these problems would be solved; you know, antibodies, nitrogen fixation, photosynthesis. Complicated things could be slotted into the -- into a restriction plasmid and would function in vivo.
Q Could you turn to pages 4 and 5.
A Yes.
Q The paragraph 12 at the bottom of page 4?
A Yes.
Q You state:
"... a person of ordinary skill in the art in April 1983 was able to create a vector capable of expressing both the heavy and light chain genes, including the necessary regulatory elements, without undue experimentation. Although a step-by-step methodology for creating this vector is not explicitly recited in the prior art patents, a workable route could be devised from a reading of the patent

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specifications, combined with a scientific literature of the day, and the 'ordinary' experimenter's years of training, and common sense."
Do you see that?
A Yes.
Q What scientific literature of the day did you have in mind when you wrote this sentence?
A Let me read this again. One sec.
And you asked about what's the relative scientific literature of the day?
Q Yes.
A Oh, well, that's -- literature of the day is all about the knowledge of the different antibody genes and where the pieces were.
The -- the problem that Boyer & Cohen faced was that the antibody genes were kind of a black box. We didn't really know what they looked like, but, in a way, solving that was a research problem that was outside of the Cohen & Boyer method. If someone had handed Cohen & Boyer, you know, restriction fragments with heavy chain and the light chain, they could have put them in their plasmid and made antibody protein.

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By 1983, all those problems had been cleared up. We had ways of making antibodies with predetermined specificity. Milstein had done that. Human and mouse constant region genes had been cloned. We knew about the gene rearrangements.
So all that scientific knowledge that had accumulated made the problem much easier.
Q Are there any specific pieces of literature that you have in mind by name that you were referring to in this sentence regarding the scientific literature of the day?
A Oh, well, the -- we can start with the genes, per se, from the -- from the -- for the constant regions. Those were known in '83.
Q Is there a particular reference you have in mind that you would look to for the constant region genes of an antibody?
A Well, I think Phil Leder may have been the first one to clone a human kappa gene. That might have -- I think that was published by 1983. That's where I got mine from.
Leroy Hood had papers on constant region genes. Hanjo, Japanese group, had papers on constant region genes. Those are some.
Q Is there any other literature that you have

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in mind by name that you were referring to in the sentence regarding the scientific literature of the day?
A Papers by Tamagawa showing the rearrangement of variable and constant region genes during formation of a lymphocyte.
Q Anything else?
A Those are what spring to mind.
Q Continuing on in that paragraph, you have a list of -- of techniques that you opine would have been within the skill set of the ordinarily skilled genetic engineer.
Do you see that?
A Oh, yes. Uh-huh.
Q In addition to the techniques that you have listed here, would you have needed to incorporate into the vector features to control the proper ratio of the amounts of each immunoglobulin chain?
MR. McCORMICK: Objection.
THE WITNESS: That's more like fine-tuning. That's more optimization rather than creating an antibody in the first place.
BY MS. DAVIS:
Q Was controlling the ratio the amount of each immunoglobulin chain critical to being able to

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create a functional antibody in 1983?
A I don't think it was critical. I wouldn't say so, no.
Q You would expect to get some antibody regardless of whether you controlled the ratio of the amounts of each immunoglobulin chain?
A Yes.
MR. McCORMICK: Objection.
BY MS. DAVIS:
Q Could you turn to page 6.
MR. McCORMICK: Are we at a good breaking point?
MS. DAVIS: Sure.
MR. McCORMICK: We have been going about an hour and ten.
THE WITNESS: Yeah.
THE VIDEOGRAPHER: Off the record at 3:52.
(Recess taken.)
THE VIDEOGRAPHER: Back on the record at 4:07.
BY MS. DAVIS:
Q Dr. Foote, could you turn to page 9 of your rebuttal report, which is Exhibit 2.
A Yes.
Q In paragraph 20 on page 9, you refer to

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certain papers on the subject of the ATCase protein.
A That's right.
Q You are not arguing that these references anticipate the claims of the Cabilly II or Cabilly III patents; correct?
A That's right. I'm not using them as prior art.
Q You are not using them for either anticipation --
A Right, for anticipation, yes.
Q Are -- you are also not using these references in combination with other references to argue that any claim in Cabilly II or Cabilly III is obvious; correct?
A That's right.
Q When did you become aware of the ATCase papers that are listed in paragraph 20?
A Papers. So the thesis, when it was written, that was someone in the lab. The paper Pauza, et al., before it was published, it's very similar to the thesis.
The other papers, Wild, et al., Roof, Turnbough, I became aware of when they were published, or sometime slightly before. Let's just say when they were published. I don't -- yeah.

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MS. DAVIS: Let me mark, as the next exhibit, the PNAS Pauza paper.
(Exhibit 8 was marked for identification by the Reporter.)
MS. DAVIS: For the record, Exhibit 8 is -- strike that.
Exhibit 8 I'm handing to you.
THE WITNESS: Thank you.
MS. DAVIS: And for the record, Exhibit 8 is a PNAS paper, cites 79, 4020 through 4024.
Q Do you have that?
A Yes.
Q This is the PNAS Pauza paper referred to in your paragraph 20?
A Yes.
Q The title of the paper, "Genes encoding E. coli aspartate transcarbamoylase: The pyrB-pyrI operon."
A "pyrB-pyrI operon."
Q The genes encoding the ATCase, these are bacterial genes?
A They are.
Q In this particular work, there are references to E. coli genes and Salmonella genes; is that correct?

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A In this work, yes. Are there? And Salmonella?
Q My first question to you is --
A Yes.
Q -- are the gene -- the ATCase gene that the -- that Pauza was working with, are those --
A E. coli.
Q E. coli?
A Yes.
Q What host cell are they being expressed in?
A Let's see.
I think mostly they were expressed in E. coli. At some point they were -- people in the lab also expressed them in Salmonella. Was it this paper or a later paper? I -- I think I mention that in my report, but let's see.
No, it should be in here. Oh, you wanted me to find that; is that right, or --
Q We don't have to find the specific reference.
A Yeah.
Q It's your recollection that the ATCase genes were expressed in Salmonella?
A Yes.
Q Salmonella is a bacteria?
A That's right.

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Q So this work is the expression of a bacterial gene in a bacteria?
A That's right.
Q Do you know the percentage of homology between E. coli and Salmonella?
A Not offhand, no.
Q Do you have any guess as to the degree of homology?
A The homology, no. The number that sticks in mind is that there are about -- they diverged in evolution a hundred million years ago.
Q How closely related are E. coli and Salmonella for purposes of using the two as host cells?
MR. McCORMICK: Objection; foundation.
THE WITNESS: Well, let's see. I'm trying to remember the hierarchy. They might be the same class or order, not the same genous, obviously. But the E. coli genes were expressed in Salmonella, though. They -- so the control sequences, which were also from E. coli, worked in Salmonella.
BY MS. DAVIS:
Q Would you agree that the goal of the Pauza work was not protein synthesis?
A Pauza himself was interested in gene regulation. Others in the lab were interested in protein expression.
Q Is the focus of the Pauza paper gene regulation?
A It is, yes.
Q You would agree that the Pauza paper that is Exhibit 8 is not in the field of the expression of eukaryotic genes?
A It's -- doesn't concern eukaryotic genes; that's right.
Q As we discussed earlier, the ATCase gene is an operon?
A pyrB-pyrI operon, yes.
Q The genes are contiguous to one another?
A They are.
Q They are, therefore, necessarily on the same chromosome?
A They are.
Q The heavy chain gene of an antibody and the light chain gene of an antibody are on different chromosomes; correct?
A That's correct.
Q You said that -- that E. coli ATCase or -- was expressed in Salmonella; correct?
A Yes.

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Q Salmonella itself expresses ATCase; correct?
A Its own, yes.
Q ATCase is a protein that is naturally expressed in Salmonella?
A That's right.
Q Do you consider the expression of E. coli ATCase in Salmonella to be the expression of a heterologous protein?
A Yes.
Q Why is that?
A It's a different species.
Q Do you consider there to be any significance to the fact that Salmonella expresses ATCase on its own?
A We all -- you and I express ATCase.
Q Does it make it easier to have Salmonella express E. coli ATCase that Salmonella itself expresses ATCase?
MR. McCORMICK: Objection.
THE WITNESS: It's not so much that Salmonella expresses ATCase, it's that the control signals from the E. coli gene are active in Salmonella.
BY MS. DAVIS:
Q Why are the control signals from the E. coli

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gene active in Salmonella?
A Why are they. I would have to speculate on that. I would guess they are -- they have some similarity to signals in Salmonella.
Q Could you turn to page 10 of your rebuttal report.
A Yes.
Q You discuss, in paragraph 22, the size of the ATCase protein; correct?
A Correct.
Q It is -- strike that.
In the first sentence, you take issue with Dr. Fiddes' statement that the size and complexity of an intact antibody was a significant advance in the art?
A Sorry. Please repeat the --
Q Sure.
A Yeah. In the size --
Q In paragraph 52 --
A Yes.
Q -- you are taking issue with Dr. Fiddes' statement regarding the size and complexity of an antibody --
A Yes.
Q -- reflecting a significant advance in

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achieving its expression.
A That's right.
MS. DAVIS: Let me mark the next exhibit.
(Exhibit 9 was marked for identification by the Reporter.)
BY MS. DAVIS:
Q You have been handed Exhibit 9, the expert report of Dr. Skerra?
A Yes.
Q You have not seen this report; correct?
A That's correct.
Q Could you turn to page 13.
A I'm there.
Q Paragraph 46?
A Yes.
Q Dr. Skerra states:
"By April of 1983, insulin was the only multimeric (i.e., hetero-dimeric) protein produced using recombinant DNA expression."
Do you see that?
A Yes.
Q Do you agree with that statement?
A Well, ATCase is an exception, so I think he may have left out the word "eukaryotic," or -- or

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something like that, but I don't agree with it as he has written it right here. What we have just been talking about conflicts with that.
Q If Dr. Skerra had insed sted (sic) -- had instead said: By April of 1983, insulin was the only multimeric eukaryotic protein produced using recombinant DNA expression, would you agree with that statement?
A I -- I haven't studied that issue. I'm not sure if I could inform you whether other proteins were being expressed then.
Q Are you aware of any multimeric eukaryotic proteins produced using recombinant DNA expression prior to April of 1983 other than insulin?
A Not offhand, but my memory is imperfect.
Q Could you look at paragraph 47.
A Yes.
Q Dr. Skerra states:
"Many heterologous proteins were expressed as fusion proteins, i.e., the eukaryotic protein was fused with a portion of an unrelated bacterial protein. This strategy took advantage of the host cell machinery for transcription and

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translation."
Do you see that?
A Yes.
Q Do you agree with Dr. Skerra that, by April of 1983, many heterologous proteins were being expressed as fusion proteins?
A I don't know enough about expression of fusion proteins. I haven't studied that issue.
Q Dr. Skerra states:
"... fusion proteins are often more stable in bacteria than the native eukaryotic protein."
Do you see that?
A I see that.
Q Do you agree with that statement?
A Again, my -- I haven't studied that. I don't know enough to agree or disagree.
Q Could you turn to page 14, paragraph 49. Are you there?
A Yes.
Q Dr. Skerra states:
"None of the proteins expressed in 1983 compare in size and complexity to an immunoglobulin molecule."
Do you see that?

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A I do.
Q Do you agree with that statement?
A Well, he seems to have overlooked ATCase, and I wonder, again, if he's qualifying this with some subset like eukaryotic or -- I don't know what, but because of the ATCase exception, which I think was a large complex molecule, I would disagree. My testimony is opposite of his, yes.
Q If Dr. Skerra had stated: None of the proteins expressed in 1983 -- strike that.
If this said: None of the eukaryotic proteins expressed in 1983 compare in size and complexity to immunoglobulin molecule, would you agree with that statement?
A I don't know enough to say whether I would agree with that or not, but that would -- that would exempt ATCase. That might explain our disagreement there.
Q Could you turn to page 15?
A Yes.
Q Paragraph 51?
A Yes.
Q In the middle, there is a sentence that begins: "Moreover, as of April."
A Yes.

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Q Dr. Skerra states:
"Moreover, as of April 1983, neither I, nor Genentech's previous experts Drs. Harris and McKnight, were aware of any reported example of expression of a recombinant multimeric protein, let alone an immunoglobulin tetramer, in a single bacterial host cell."
Do you see that?
A Yes.
Q Do you agree that there was no reported example of an -- of expression of a recombinant in a single bacterial host cell as of April 1983?
A No, I don't. There's the ATCase example, as we have discussed.
Q Are there any other examples that you are aware of?
A I think the nitrogenase may have been expressed before April 1983, and that's a multimeric protein.
Q What was the protein again?
A Nitrogenase.
Q What type of protein is nitrogenase?
A In the particular case, it was a bacterial protein I'm thinking of. That's in my rebuttal report.
Q Is that one of the nitrogen-fixing proteins?
A That's right, yes.
Q You can set aside Exhibit 9.
A Wow, this exhibit's long. He's very thorough.
Q Back to your rebuttal report, Exhibit 2. Could you turn to page 11?
A Yes.
Q In paragraph 23, you are discussing nitrogen fixation?
A Yes. Yes.
Q The goal of nitrogen fixation is to take an organism that does not fix nitrogen and get it to fix nitrogen; correct?
A That's correct.
Q The goal of nitrogen fixation is not protein synthesis; is that correct?
A Well, that depends how you break the project down. What's key to success is expression of -- or other -- well, expression of these nitrogen-fixation gene proteins, and the overall goal is to extract nitrogen from the air and put it into organic form, such as proteins.

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Q Is the goal of the nitrogen-fixation work the recovery of the protein expressed by the nitrogen-fixation genes?
A The -- that's an intermediate goal. The long-term goal is to take nitrogen out of the atmosphere. Expression of the nitrogen-fixation genes -- in one project, you would just be content to have the nit- -- nitrogenase expressed in the cell, not isolated, and I think that's the one I was writing about here.
Q You were writing about the project in which it was expressed but not isolated?
A It may have been isolated, but it was not going to be isolated and used medically, if that's -- yeah.
Q What field of work would you say the nitrogen fixation papers fall into?
A I would say gene expression. And although the initial work was with prokaryotic genes, would not necessarily be -- well, let me just say -- let me go back to my first statement.
It was -- the field is protein expression.
Q Is the field protein expression or gene expression?
A Sorry. Gene expression, expression of

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recombinant proteins.
Q The -- strike that.
You refer to a number of papers in these pages in your report on nitrogen fixation; correct?
A Yes. Yes.
Q You are not relying on those papers to argue that the claims of the Cabilly II or III patents are anticipated; correct?
A That's correct.
Q You are not relying on those papers to argue that the claims of the Cabilly II and III patents are obvious; correct?
A That's correct.
Q The nitrogen-fixation genes that you describe in these paragraphs in your report are all bacterial in origin; correct?
A That's right.
Q If you look at paragraph 24?
A Yes.
Q You refer to the mapping of the "(nif) genes of Klebsiella pneumoniae"?
A Yes. That's probably what I have right now, yeah.
Q That's a type of bacteria?
A That is.

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Q Do you know the degree of identity between that pneumonia bacteria and E. coli?
A I think they are not very closely related, but I -- I don't know exactly. Not the same class. They diverge higher up in the chain of phylum order, whatever.
Q Are they more closely related to each other or less closely related to each other than would be E. coli and Salmonella, if you know?
A I think Klebsiella is less closely related than Salmonella.
Q Could you turn to page 12.
A Yes.
Q The -- you have a reference in paragraph 25 to a paper by Fuhrmann & Hennecke.
Do you see that?
A Yes.
(Exhibit 10 was marked for identification by the Reporter.)
MS. DAVIS: I'm handing you Exhibit 10.
THE WITNESS: Thank you.
BY MS. DAVIS:
Q Is Exhibit 10 the Fuhrmann & Hennecke paper you refer to?
A Let's see. 187, 419. Yes, this is.

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Q This paper reports on the recombinant expression of E. coli nitrogen-fixing genes; is that correct?
A Rhizobium nitrogen-fixing genes, and they are expressed in E. coli.
Q Rhizobium is a type of bacteria?
A Yes.
Q Do you know how closely related Rhizobium is to E. coli?
A I know that it's not very closely related.
Q Is Rhizobium more or less closely related to E. coli than E. coli is to Salmonella?
A Less closely related than Salmonella and E. coli.
Q You are not relying on the -- this work for purposes of arguing that the Cabilly II or III patents are anticipated or obvious; correct?
A That's correct.
Q When did you become aware of the Fuhrmann & Hennecke paper?
A Fuhrmann & Hennecke. After Dr. Fiddes' report appeared, I made an investigation of nitrogen-fixation chains. I had been aware of that work going on. One of the people in my lab went to do that as a post-doc, and some of the early work

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had happened in Berkeley, but it's recent -- the end of last year that I bore down and read some of these papers. Even at Harvard, someone in Walter Gilbert's lab was trying to clone these genes.
Q In what field of work is the Fuhrmann & Hennecke paper?
A Expression of recombinant proteins.
Q Is this in the same field of work as papers on the expression of recombinant eukaryotic proteins?
A I would put it in the same field, yes.
Q Why is that?
A That the eukaryotic part is just a kind of technicality. Here they say that, oh, these Rhizobium genes haven't been expressed in E. coli before, so they are -- they are taking a difficult expression project and they are taking genes they want, putting them in E. coli to make recombinant proteins.
Q Does E. coli carry any nitrogen-fixation genes?
A No.
Q The -- are the proteins that are expressed as a result of the Fuhrmann paper -- were those isolated, do you know?

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A I don't recall offhand.
Q Is the ultimate goal of the work described in the Fuhrmann paper the creation of E. coli that fixes nitrogen?
A I think that's a stage that the -- the project passes through. I think this is more investigational still, cloning the genes, learning about their expression, and E. coli might be the host of choice to work with in the short-term.
In the longer term, these genes might, in turn, be put into transgenic plants, let's say, so that the plants wouldn't have to rely on nitrogen-fixing microbes in the soil, though. You could have plants that essentially would fertilize themselves.
Q Could you turn to page 14 of your report?
A Yes.
Q Beginning at page 14 and continuing on through the next several pages, you make reference to a number of different U.S. patents; is that correct?
A Yes.
Q Are you relying on any of those U.S. patents to argue that the claim of the Cabilly II or III patent are anticipated?

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A No.
Q Are you relying on any of those patents to argue that the claims of the Cabilly II or III patent are obvious?
A No. These are arguing against Dr. Fiddes' claim about the prevailing mindset.
Q Could you turn to page 18.
A 18.
Q And this is referring to a reference called "George"?
A Yes.
Q In the middle of the paragraph, there's a sentence that begins: "For example"?
A Yes.
Q And you say that the inventors approach recombinant protein production by co-expreshing (sic) -- co-expressing a fusion protocol, i.e., the gene for the protein of interest fused to a carrier protein, and the unfused protein of interest.
Do you see that?
A Yes, I do.
Q Do you agree that fusion proteins would sometimes be desired end product of work in the late '70s and early 1980s?

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A Sometimes the end product. That's -- would -- would I agree. Usually you don't want the fusion protein; you want to get rid of the things it's fused to. But I can't say categorically that you never want the fusion protein, and they seem to be making use of it here as a -- as a way of getting the protein of interest.
Q Let me rephrase my question.
A Yes.
Q I -- I phrased it poorly.
Would you agree that, in the late 1970s and early 1980s, fusion proteins were sometimes an intended product of the recombinant expression process to then be later reconstituted?
A Fusion protein was the -- sorry. Was it the --
Q An intended -- an intended product in the process.
A Yes, it was made intentionally.
Q You agree that, in the late 1970s and early 1980s, persons of ordinary skill in the art sometimes set out to intentionally make a fusion protein?
A Yes, but I haven't studied that issue. I don't know specific examples. I know that usually

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it's not the fusion partner you want but the unfused protein.
Q Could you turn to page 20.
A Yes.
Q You refer, in paragraph 40, to a patent relating to the production of cholera toxins?
A Yes.
MS. DAVIS: If you will bear with me one moment --
THE WITNESS: Sure.
MS. DAVIS: We will attempt to find my copy.
(Exhibit 11 was marked for identification by the Reporter.)
MS. DAVIS: I'm marking, as Exhibit 11, U.S. Patent 4,666,837.
THE WITNESS: Okay.
BY MS. DAVIS:
Q Exhibit 11 is the patent you are discussing in paragraph 40?
A Paragraph 40, '837, yes.
Q When did you become aware of this patent?
A During my work on the rebuttal report in November and early December.
Q Do you see that the assignee on this patent is a SmithKline entity?

A Yes.
Q Do you have an understanding as to how that entity is related to GlaxoSmithKline?
A I don't have specific knowledge. I vaguely recall that Glaxo used to be separate from SmithKline and other ent- -- entities.
Q Were you aware of this patent when you prepared a report in connection with the prior Cabilly litigation in which you were hired by Glaxo?
A I don't recall seeing this then.
Q In what field is the '837 patent?
A This is in expression of recombinant proteins.
Q The cholera toxin proteins, what type of proteins are there -- are those?
A What type of proteins. You mean their bacterial proteins?
Q Let's start there.
They are bacterial proteins, yes?
A Bacterial proteins. They encode a medically significant molecule, and even the cholera toxin is toxic. I believe they were going to use this as a -- as part of a vaccine.
Q The specific bacteria that these -- the cholera strain in question is vibrio cholera?

A That's right.
Q Do you know the degree of hemology between that and E. coli?
A Not offhand.
Q Do you know, generally, how closely related those two species are?
A I don't know.
Q It is fair to say, at least, that they are both bacteria?
A They are both bacteria. They grow in the gut.
Q You are not relying on the '837 patent to argue that the claims of the Cabilly II and III patents are anticipated; correct?
A That's right.
Q You are not relying on the '837 patent to argue that the claims of the Cabilly II or III patents are obvious; correct?
A That's correct.
MS. DAVIS: Can we take a break --
MR. McCORMICK: Sure.
MS. DAVIS: -- just to hopefully wrap up shortly thereafter?
MR. McCORMICK: Oh, okay. Great. Thanks.
THE VIDEOGRAPHER: Off the record at 4:44.

(Recess taken.)
THE VIDEOGRAPHER: Back on the record at 4:56.
MS. DAVIS: No further questions.
MR. McCORMICK: Thank you.
THE WITNESS: Thank you.
THE VIDEOGRAPHER: Here marks the end of Volume 1, Video No. 3 in the deposition of Dr. Foote.
Going off the record, the time is 4:56.
(Whereupon, the deposition was concluded at 4:56 p.m.)
---o0o---
I declare under penalty of perjury that the foregoing is true and correct. Subscribed at _____, California, this _____ day of _____, 2015.

_____
Signature of the witness

CERTIFICATE OF REPORTER
I, RACHEL FERRIER, a Certified Shorthand Reporter, hereby certify that the witness in the foregoing deposition was by me duly sworn to tell the truth, the whole truth, and nothing but the truth in the within-entitled cause;
That said deposition was taken down in shorthand by me, a disinterested person, at the time and place therein stated, and that the testimony was thereafter reduced to typewriting by computer under my direction and supervision and is a true record of the testimony given by the witness;
That before completion of the deposition, review of the transcript [X] was [ ] was not requested. If requested, any changes made by the deponent (and provided to the reporter) during the period allowed are appended hereto.
I further certify that I am not of counsel or attorney for either or any of the parties to the said deposition, nor in any way interested in the event of this cause, and that I am not related to any of the parties thereto.
DATED:

_____
RACHEL FERRIER, CSR No. 6948