

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

MERRILL CORPORATION

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SANOFI v. GENENTECH

IPR2015-01624

EXHIBIT 2010

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA

---o0o---

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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<p>1 BE IT REMEMBERED that, pursuant to the laws</p> <p>2 governing the taking and use of depositions, on</p> <p>3 Friday, January 9, 2015, commencing at 9:40 a.m.</p> <p>4 thereof, at the Sheraton on El Camino Real,</p> <p>5 625 El Camino Real, Conference Room 1107, Palo Alto,</p> <p>6 California, before me, RACHEL FERRIER, a Certified</p> <p>7 Shorthand Reporter, personally appeared</p> <p>8 DR. JEFFERSON D. FOOTE, called as a witness by the</p> <p>9 Defendants, who, being by me first duly sworn, was</p> <p>10 thereupon examined as a witness in said action.</p> <p>11 APPEARANCES OF COUNSEL</p> <p>12 For the Plaintiff:</p> <p>13 MAYER BROWN LLP</p> <p>14 BY: RICHARD McCORMICK, Attorney at Law</p> <p>15 1675 Broadway</p> <p>16 New York, New York 10019</p> <p>17 Telephone: 212.506.2500</p> <p>18 Email: rmccormick@mayerbrown.com</p> <p>19</p> <p>20 For the Defendants:</p> <p>21 PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP</p> <p>22 BY: KIRA A. DAVIS, Attorney at Law</p> <p>23 ALLISON M. LUCIER, Attorney at Law</p> <p>24 1285 Avenue of the Americas</p> <p>25 New York, New York 10019</p> <p>Telephone: 212.373.3230</p> <p>Email: kdavis@paulweiss.com</p> <p>alucier@paulweiss.com</p>	<p>1 PALO ALTO, CALIFORNIA</p> <p>2 FRIDAY, JANUARY 9, 2015</p> <p>3 9:40 A.M.</p> <p>4 ---o0o---</p> <p>5 PROCEEDINGS</p> <p>6</p> <p>7 THE VIDEOGRAPHER: Good morning.</p> <p>8 Here begins Video No. 1 in the deposition of</p> <p>9 Dr. Jefferson Foote in the matter of Bristol-Myers</p> <p>10 Squibb versus Genentech in the U.S. District Court,</p> <p>11 Central District of California, Case No.</p> <p>12 2:13-cv-05400-MRP-JEM.</p> <p>13 Today's date is January 9th, 2015, and the</p> <p>14 time on the video monitor is 9:40 a.m.</p> <p>15 My name is David Osgood.</p> <p>16 This video deposition is taking place at</p> <p>17 625 El Camino Real in Palo Alto, California.</p> <p>18 Counsel, would you please identify yourselves</p> <p>19 and state who you represent.</p> <p>20 MS. DAVIS: Kira Davis -- Paul, Weiss,</p> <p>21 Rifkind, Wharton & Garrison -- for Genentech and</p> <p>22 City of Hope.</p> <p>23 MS. LUCIER: Allison Lucier from Paul, Weiss,</p> <p>24 also for Genentech and City of Hope.</p> <p>25 MR. McCORMICK: Richard McCormick from</p>

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1 Mayer Brown for Bristol-Myers and Medarex.
 2 MR. BROWN: Neal Dahiya from Bristol-Myers
 3 and Medarex.
 4 THE VIDEOGRAPHER: Thank you very much.
 5 The Court Reporter today is Rachel Ferrier of
 6 Merrill.
 7 And would the Reporter please swear in the
 8 witness.
 9 ---o0o---
 10 DR. JEFFERSON D. FOOTE
 11 _____
 12 called as a witness, having been
 13 first duly sworn, was examined and
 14 testified as follows:
 15 ---o0o---
 16 EXAMINATION
 17 BY MS. DAVIS:
 18 Q Good morning, Dr. Foote.
 19 As you just heard, my name is Kira Davis, and
 20 I represent Genentech and City of Hope.
 21 As we discussed a little bit before we
 22 started, I understand you are feeling somewhat under
 23 the weather today, so if at any point in time you
 24 need to take a break, please just let us know and we
 25 can take breaks as frequently as -- as needed.

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1 Does that make sense?
 2 A Yes. Thank you.
 3 MS. DAVIS: So we are going to start.
 4 I want to hand you five documents, so let me
 5 put them on the record.
 6 Exhibit 1 is the Expert Report of Jefferson
 7 Foote, Ph.D., in BMS v Genentech.
 8 Exhibit 2 is the Rebuttal Expert Report of
 9 Jefferson Foote, Ph.D., also in this case.
 10 Exhibit 3 is U.S. Patent 4,816,567.
 11 Exhibit 4 is U.S. Patent 6,331,415.
 12 And Exhibit 5 is U.S. Patent 7,923,221.
 13 I'm handing you those documents.
 14 THE WITNESS: Thank you.
 15 (Exhibits 1 through 5 were marked
 16 for identification by the Reporter.)
 17 BY MS. DAVIS:
 18 Q So starting with -- they're -- they're all
 19 yours now.
 20 Starting with Exhibit 1, do you recognize
 21 Exhibit 1 to be a report that you prepared in this
 22 case?
 23 A Yes, this is.
 24 Q And if you turn to the first page of that
 25 report.

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1 A Turn to the first page.
 2 Q The first page of text.
 3 A I'm on page 1 with the "1" at the bottom.
 4 Q In the Introduction, this report says that
 5 you have been retained by Bristol-Myers Squibb and
 6 Medarex, LLC.
 7 Do you see that?
 8 A Yes.
 9 Q And that is correct?
 10 A That is correct.
 11 Q If I refer to those two companies today
 12 jointly as "BMS," will you understand what I'm
 13 referring to?
 14 A Yes.
 15 Q You -- in your first opinion -- in your first
 16 paragraph in your report, you indicate that you are
 17 providing expert opinions and testimony in this
 18 matter concerning the invalidity of -- of two
 19 patents.
 20 Do you see that?
 21 A Yes.
 22 Q And the first patent is the '415 patent?
 23 A Right, or Cabilly II, yes.
 24 Q And that was my question.
 25 That -- that patent is commonly referred to

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1 as "Cabilly II"; correct?
 2 A Mm-hmm.
 3 Q And if you turn to your stack of documents,
 4 Exhibit 4 is a copy of Cabilly II.
 5 Do you see that?
 6 A '415, Cabilly II, yes.
 7 Q And the -- the next patent that you opine on
 8 is the '221, or Cabilly III, patent; is that
 9 correct?
 10 A That's correct.
 11 Q And if I refer to that as "Cabilly III," we
 12 will all understand what -- what I'm referring to?
 13 A I prefer calling it Cabilly III rather than
 14 whatever the number is, '221.
 15 Q And Exhibit 5 in your stack of documents
 16 should be Cabilly III.
 17 Do you have that?
 18 A 5, Cabilly III, '221, yes.
 19 Q So if at any point during the day you need to
 20 refer to those patents, you have them. Those copies
 21 are -- are for your use during this deposition.
 22 The other exhibit we marked is Exhibit 3.
 23 Do you have that?
 24 A Exhibit 2 and Exhibit 3.
 25 Q And Exhibit 3 is what's known as the

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

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

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

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1 submitted in this case?
 2 A No.
 3 Q Do you know that a report was submitted by a
 4 Dr. Silverstein?
 5 A Yes.
 6 Q Have you reviewed that report?
 7 A No.
 8 Q Are you aware that a report was submitted by
 9 a Dr. Casali (phonetic)?
 10 A Yes.
 11 Q Have you reviewed that report?
 12 A No.
 13 Q How about a report by Dr. Skerra?
 14 (Telephonic interruption.)
 15 THE WITNESS: Forgive me.
 16 MS. DAVIS: Take as much time as you want to
 17 adjust the phone. These things happen.
 18 THE WITNESS: It's from the husband of a
 19 Genentech employee. I certainly don't want to talk
 20 to him now.
 21 BY MS. DAVIS:
 22 Q Are you aware that a report was put in this
 23 case by Dr. Skerra?
 24 A Yes.
 25 Q Have you reviewed that report?

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1 A No.
 2 **Q Do you know Dr. Fiddes?**
 3 A No.
 4 **Q You have never met?**
 5 A Not that I can recall.
 6 **Q Turning to the second page of your report --**
 7 **A Yes.**
 8 **Q -- you describe, in this section, some of**
 9 **your own personal background; is that fair?**
 10 A Yes.
 11 **Q In paragraph 6, you indicate that your first**
 12 **research project in the laboratory of**
 13 **Professor David Dressler was an attempt to clone an**
 14 **antibody gene; is that correct?**
 15 A That's correct.
 16 **Q As I understand it, that project was not**
 17 **successful; correct?**
 18 A Correct.
 19 **Q You failed to clone an antibody gene?**
 20 A That's correct.
 21 **Q When did you first clone an antibody gene, if**
 22 **ever?**
 23 A First clone one. Well, that would have been
 24 in Winter's lab, and, again, it depends what's meant
 25 by "clone." The first antibody I worked with I made

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

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

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1 **Q In paragraph 7 of your report, you describe a**
 2 **project you worked on under the direction of**
 3 **Professor Evan Kantrowitz?**
 4 A That's correct.
 5 **Q And the project you worked on was studying**
 6 **the structure and function of aspartate**
 7 **transcarbamylase; is that correct?**
 8 A That's correct.
 9 **Q Did I pronounce it correctly?**
 10 A "Aspartate transcarbamylase," yeah.
 11 **Q That particular protein is frequently**
 12 **referred to as "A-T Case"?**
 13 A "A-T-C ase."
 14 **Q "A-T-C ase"?**
 15 A Attorneys always say "A-T Case," but it's
 16 "A-T-C ase."
 17 **Q And "ATCase" --**
 18 A Yeah.
 19 **Q -- is a common way to refer to that**
 20 **particular protein?**
 21 A That's correct.
 22 **Q In this work from the 1979-to-1980 time**
 23 **period, you attempted to clone the gene encoding**
 24 **ATCase?**
 25 A I did.

<p style="text-align: right;">Page 18</p> <p>1 Q And that effort was not successful; correct? 2 A That's correct. 3 I should add. I don't want to mislead you. 4 That wasn't the main area of work that I was doing. 5 I was working on other projects and have papers from 6 that period, and this was kind of a side light. 7 Q What was the main area of your work during 8 that time period? 9 A The main area of work in that time period in 10 Dr. Kantrowitz's lab had to do with isolating and 11 studying mutations in the ATCase gene that were 12 reintroduced in bacteria that would substitute new 13 amino acids at so-called nonsense codons, its 14 approach to studying protein structure that's not 15 used any longer. 16 Q Was protein expression a focus of your work 17 in Dr. Kantrowitz's lab? 18 A "Protein expression," do you mean 19 "recombinant expression" by that question? 20 Q Let's just start with expression recombinant 21 or not recombinant. 22 A Oh, well, the protein we worked with was 23 expressed, was made in bacteria, but it was 24 nonrecombinant. 25 Q Were you studying expression -- the</p>	<p style="text-align: right;">Page 20</p> <p>1 protein? 2 A No, no. It was the -- it was ATCase. I 3 worked on ATCase in three different labs. 4 Q You said the plasmid had been constructed by 5 others that you were working with? 6 A That's right. 7 Q When did you first construct a plasmid for 8 the re- -- for the expression of a recombinant 9 protein? 10 A Did I construct. Well, that would have been 11 in Winter's lab, beginning in 1985. 12 You mentioned "beta lactamase," and you have 13 reminded me that, in Evan Kantrowitz's lab, I did do 14 an experiment with recombinant beta lactamase, but 15 that was not a recombinant construct that I had 16 prepared. It was the beta lactamase on pBR322, a 17 plasmid that had been constructed in Dr. Boyer's 18 lab. 19 Q And you said the first time you prepared a 20 plasmid for the expression of a recombinant protein 21 was with Dr. Winter? 22 A That's right. I had worked with recombinant 23 plasmids with -- in Dressler's lab. 24 And I might add. Dressler's lab was kind of 25 a subsidiary of Walter Gilbert's lab. Dressler</p>
<p style="text-align: right;">Page 19</p> <p>1 expression aspect of that protein, or were you 2 studying something else? 3 A We were mainly interested in how the 4 protein's enzymatic activity is regulated, so we 5 weren't studying how it was expressed. 6 Q And you said it was nonrecombinant? 7 A That's right. 8 Q When did you first work on a recombinant 9 protein? 10 A Well, in Berkeley, when I started graduate 11 school, I worked on a recombinant version of ATCase. 12 Q And when did you begin working on a 13 recombinant version of ATCase? 14 A When? 15 Q When. 16 A That would be September of 1980. I don't 17 know the exact date, but when I arrived in my first 18 lab rotation, starting then. 19 Q Did you succeed in expressing a recombinant 20 protein during your time at Berkeley? 21 A Oh, yes. Expression had already been worked 22 out, and I used this plasmid that had been 23 constructed repeatedly to prepare recombinant 24 protein. 25 Q And that is -- was that the beta-lactamase</p>	<p style="text-align: right;">Page 21</p> <p>1 had -- was an assistant professor. He had been 2 Gilbert's graduate student, and he was given a 3 ten-year-track faculty job, but he was within the 4 ambit of Gilbert. We had joint group meetings. We 5 shared facility. There was a lot of interaction. I 6 also -- 7 Q Go ahead. 8 A Oh, no. 9 Q Were you finished with your answer? 10 A Yeah, I was going to say something not 11 germane. 12 Oh, but let me just make sure I say it. I 13 don't want to mislead you. I don't want to deprive 14 you of information. 15 I, in Berkeley, in my first year, also worked 16 with a recombinant protein called -- what's it 17 called. It has several names. One is kanamycin 18 phosphotransferase, and you've -- you've triggered 19 my memory, and, in fact, that was my first 20 successful attempt at making a expression construct, 21 which I did my first year, beginning at the very end 22 of 1980. That project was not continued. 23 Q And you said that was a recombinant protein? 24 A Yes. 25 Q And you constructed the vector used to</p>

6 (Pages 18 to 21)

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

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1 A That's a drug-resistance protein. It
 2 modifies kanamycin, a drug. It modifies other
 3 similar drugs as well, and modifies them by
 4 transferring a phosphate group onto them, rendering
 5 them nontoxic to the cell that harbors this gene.
 6 **Q Is it a bacterial protein?**
 7 A It is, yes.
 8 **Q Is it a single-unit protein?**
 9 A Yes.
 10 **Q And you cloned it into another type of**
 11 **bacteria?**
 12 A I -- it was still E. coli. I put it into a
 13 new vector and transferred that into E. coli.
 14 **Q So it's an E. coli protein that you**
 15 **transfected into E. coli?**
 16 A I don't want to mislead you again. I'm not
 17 sure I would call it an "E. coli protein." It came
 18 originally from -- oh, I'm not sure where it came
 19 from originally. It was encoded on something called
 20 "Transposon 5," but I don't recall who first
 21 identified that. A transposon is a gene that can
 22 hop from bug to bug.
 23 **Q It is bacterial, though?**
 24 A It is bacterial.
 25 **Q You said someone else had cloned it first; is**

Page 24

1 **that correct?**
 2 A Yes.
 3 **Q Do you know who that was?**
 4 A I don't know. It was -- it was widely
 5 available.
 6 **Q When you say "widely available," do you mean**
 7 **you could order it?**
 8 A Not from a company. He would phone someone
 9 up and ask for it, though.
 10 **Q So phone someone up in another lab and ask --**
 11 A That's right.
 12 **Q -- for a copy?**
 13 A That's right.
 14 **Q You received your Ph.D. in 1985?**
 15 A That's right.
 16 **Q So in 1983, by definition, you did not have a**
 17 **Ph.D.?**
 18 A That's correct.
 19 **Q You then went to work for Sir Gregory Winter?**
 20 A That's correct.
 21 **Q If I refer to Sir Gregory Winter as**
 22 **"Dr. Winter," is that --**
 23 A That's fine.
 24 **Q That's acceptable?**
 25 A It's tough for me to say "Sir Gregory,"

Page 25

1 thinking of him as a knight.
 2 **Q And you were with Dr. Winter from 1985 to**
 3 **1992?**
 4 A That's right. Although, during that time, I
 5 kind of had a -- I kind of had dual mentors, Greg
 6 and -- sorry, Dr. Winter and says Cesar Milstein.
 7 **Q Have you spoken to Dr. Winter recently?**
 8 A No.
 9 **Q Are you aware that there is a related case to**
 10 **this one in which Dr. Winter has issued an opinion?**
 11 A I was told that he had given an opinion, but
 12 I don't know much about the case. I thought it
 13 might be this case, but I didn't pay attention. I
 14 didn't read his opinion.
 15 **Q And you have not spoken to Dr. Winter about**
 16 **this case?**
 17 A No. My last -- I last spoke with him it must
 18 have been 2011, 2012. It was a 60th-birthday party
 19 for him that I went to.
 20 **Q When is the last time you spoke to Dr. Winter**
 21 **about -- when, if ever, is the last time you spoke**
 22 **to Dr. Winter about antibodies?**
 23 A That would have been that time.
 24 **Q The 60th-birthday party?**
 25 A That's right.

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1 **Q** And you have never spoken to him about this
 2 case?
 3 A No.
 4 **Q** A minute ago you had -- strike that.
 5 Just to go back a little bit on -- in --
 6 strike that.
 7 You had said that the kanamycin
 8 phosphotransferase that you were working with, you
 9 would obtain from another lab; is that correct?
 10 A The -- the gene for the phosphotransferase
 11 was from another lab.
 12 **Q** And this is in what time frame?
 13 A Might even have been the same lab,
 14 Schachman's lab. It really was very widespread.
 15 This was 1980.
 16 **Q** At that time, was it normal for labs to share
 17 materials with other labs of -- of the type of this
 18 gene that you were working with?
 19 A Yes.
 20 MR. McCORMICK: Objection.
 21 THE WITNESS: There was no material transfer
 22 agreement that we used back then.
 23 BY MS. DAVIS:
 24 **Q** You would -- how often did you have occasion
 25 to phone up another lab and ask for material?

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

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1 Sitting here today, do you have any
 2 expectation as to when, if at all, that patent will
 3 issue?
 4 A This year.
 5 **Q** And for the record, you are literally fingers
 6 crossed.
 7 So you are hoping that patent will issue in
 8 2015?
 9 A Yes. In fact, just this morning, I received
 10 word that we had put in a response to the most
 11 recent Office Action.
 12 **Q** And if the patent issues in 2015, that would
 13 be approximately 11 years of prosecution?
 14 A Yes.
 15 **Q** In -- on page 4 of your report, there's a
 16 section called "Prior Testimony."
 17 Do you see that?
 18 A Page -- yes.
 19 **Q** And this indicates that you gave deposition
 20 testimony in Glaxo Group Limited v. Genentech, Inc.,
 21 et al.
 22 Do you see that?
 23 A Yes.
 24 **Q** That is a case in which you opined on the
 25 validity of the Cabilly II patent?

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1 A That's right.
 2 **Q** Have you reviewed your deposition transcript
 3 that is described in this "Prior Testimony" section?
 4 A I've not gone back and reread the whole
 5 transcript.
 6 **Q** Sitting here today, are you aware of anything
 7 in that deposition transcript that you believe was a
 8 misstatement?
 9 MR. McCORMICK: Objection.
 10 THE WITNESS: I can't think of a
 11 misstatement.
 12 BY MS. DAVIS:
 13 **Q** There is a second case listed under "Prior
 14 Testimony."
 15 A Yes.
 16 **Q** What does that case relate to, generally
 17 speaking?
 18 A That's an employment law case. The
 19 plaintiff, Perez-Melgosa, was dismissed from the
 20 University of Washington with an allegation of
 21 scientific misconduct.
 22 **Q** Were you an expert or a fact witness or
 23 something else?
 24 A Expert, and I analyzed whether this was,
 25 indeed, misconduct.

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1 **Q Did not -- that case in no way relates to the**
 2 **Cabilly patents?**
 3 A No relation.
 4 **Q I want to turn now to Section IV of your**
 5 **report, "Legal Principles to be Applied."**
 6 A Yes.
 7 **Q The first section under that relates to**
 8 **anticipation; correct?**
 9 A Correct.
 10 **Q And you state:**
 11 **"It is my understanding that for a**
 12 **patent claim to be invalid as**
 13 **anticipated, there must be clear and**
 14 **convincing evidence that all**
 15 **elements of the claim are disclosed**
 16 **in a single piece of prior art,**
 17 **either expressly or inherently."**
 18 **Do you see that?**
 19 A Yes.
 20 **Q Are you aware of there being any other**
 21 **requirements in order to demonstrate anticipation,**
 22 **to your understanding?**
 23 A Well, I'm not a lawyer, but I -- I'm not
 24 aware of anything outside that. If it's all
 25 disclosed within one piece of prior art, then I

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1 believe that anticipates the patent in question.
 2 **Q In conducting your anticipation analysis, did**
 3 **you take into account whether all elements of the**
 4 **claim appeared in a single prior art reference**
 5 **arranged as in the claim?**
 6 MR. McCORMICK: Objection; vague, ambiguous.
 7 THE WITNESS: I didn't really -- what do you
 8 mean "arranged"?
 9 BY MS. DAVIS:
 10 **Q Do you have an understanding of what it means**
 11 **for all the elements of the claim to appear in a**
 12 **single prior art reference arranged as in the**
 13 **asserted claim?**
 14 A You have used "arranged" again, and I sense
 15 that there's a lot of legal precedent concerning
 16 that term, so I'm a little reluctant to give a
 17 definitive answer.
 18 **Q So my first question is: Do you use the**
 19 **concept of whether all of the elements of the claim**
 20 **appear on a single prior art reference arranged as**
 21 **in the claim -- so my first question is whether you**
 22 **used that concept?**
 23 MR. McCORMICK: Same objection.
 24 THE WITNESS: Again, I'm getting hung up on
 25 "arranged."

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1 What I saw in the patents that I analyzed was
 2 that they were -- the elements all seemed to be
 3 thematically related. There was no sort of separate
 4 part to a patent -- or to one -- say the Boyer or
 5 Bujard patent that dealt with a different topic, and
 6 I didn't inappropriately, I think, combine something
 7 from any irrelevant part with the main part -- that
 8 wasn't in the main part.
 9 BY MS. DAVIS:
 10 **Q In -- I'm sorry. Were you finished?**
 11 A In that it -- to that extent -- to that
 12 extent, I made sure that all the elements I was
 13 referring to were thematically linked together, thus
 14 arranged, yeah.
 15 **Q You mentioned combining elements; is that**
 16 **correct?**
 17 A Combining elements?
 18 **Q Was one aspect of your approach to combine**
 19 **elements of, let's say, the Cohen & Boyer patent?**
 20 A I wrote about combining elements of the Cohen
 21 & Boyer patent with a paper by Riggs & Itakura.
 22 **Q And that was in connection with your**
 23 **obviousness analysis?**
 24 A Yes.
 25 **Q Sticking to anticipation --**

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1 A Right.
 2 **Q -- did you take into account whether all of**
 3 **the elements of the claim of the Cabilly II claim**
 4 **appeared in, let's start with, Cohen & Boyer,**
 5 **combined, as they were in Cabilly?**
 6 MR. McCORMICK: Objection; vague, ambiguous,
 7 and confusing.
 8 THE WITNESS: I find the question kind of
 9 abstract. That's why I'm having trouble answering
 10 it.
 11 BY MS. DAVIS:
 12 **Q Did you take into account, in conducting your**
 13 **anticipation analysis, whether the elements you**
 14 **observed in the prior art were combined in that**
 15 **prior art in the same way that they were combined in**
 16 **Cabilly?**
 17 A Yes, I did.
 18 **Q How did you take that into account?**
 19 A I saw that what was done in the prior art was
 20 the same as what was done in Cabilly, more or less,
 21 with the vectors and genes somewhat changed.
 22 **Q You indicate in your report that the**
 23 **disclosure can be either expressed or inherent; is**
 24 **that correct?**
 25 A That's right.

<p style="text-align: right;">Page 34</p> <p>1 Q Sticking to anticipation, does any of your 2 anticipation opinion depend on a disclosure in one 3 of the pieces of prior art being an inherent 4 disclosure? 5 A Again, that seems very broad and kind of 6 abstract for me to answer in a categorical way. 7 If -- if we come to particular examples of 8 inherency, I could maybe describe them or how I used 9 them. 10 Q In the abstract, you don't know whether you 11 relied exclusively on expressed disclosure; is that 12 correct? 13 A Expressed disclosure. Well, no -- well, for 14 example, Cohen & Boyer lists antibodies as a type of 15 recombinant protein that could be made with their 16 method, but they don't have an express example of 17 that, if that's what you mean. 18 Q So my question right now is limited 19 to -- strike that. 20 In your description of the law of 21 anticipation -- 22 A Right. 23 Q -- you describe what you understand to be an 24 inherent disclosure. 25 Do you see that in this paragraph 18?</p>	<p style="text-align: right;">Page 36</p> <p>1 Go ahead. 2 THE WITNESS: Right. I'm just a little 3 perplexed by what -- by "inherency," which I -- it's 4 kind of a legal term, and it's alien to my 5 scientific background. 6 If we have a -- if we have any paper, there 7 are things in a paper that go unsaid but are assumed 8 or widely known that people will use without them 9 having been said in the paper, and I believe the 10 same may be true here. 11 BY MS. DAVIS: 12 Q So we will go through Cohen & Boyer later -- 13 A All right. 14 Q -- so, at that point, we can return and I 15 will ask you more specifically whether some of the 16 disclosures -- 17 A Okay. 18 Q -- you understand to be inherent 19 disclosures -- 20 A Right. 21 Q -- is that fair? 22 A Okay. That's fair. 23 Q In the -- on page 5 -- 24 A Yes. 25 Q -- you have the law of obviousness described;</p>
<p style="text-align: right;">Page 35</p> <p>1 A Paragraph 18, single -- expressly or 2 inherently, yes. 3 Q And regarding inherent disclosure, you say: 4 "A claim element is inherent in the 5 prior art if it is necessarily 6 present in the prior art reference, 7 even though a person of ordinary 8 skill in the art (defined below) 9 would not necessarily recognize or 10 appreciate the presence of the 11 inherent disclosure in the prior art 12 at the time of the filing of the 13 patent." 14 A Yes. 15 Q Do you see that? 16 A Yes, I do. 17 Q And that is your understanding of "inherent 18 disclosure" in connection with the law of 19 anticipation? 20 A Yes. 21 Q And in conducting your anticipation analysis, 22 are you relying on any inherent disclosures in the 23 Cohen & Boyer patent? 24 A I'm -- 25 MR. McCORMICK: Objection; foundation.</p>	<p style="text-align: right;">Page 37</p> <p>1 is that correct? 2 A Yes. 3 Q Paragraph 20 says: 4 "A prior art reference is pertinent 5 to the obviousness analysis if it 6 discloses information designed to 7 solve the same problems faced by the 8 patent's inventors," and then it 9 goes on. 10 A Yes. 11 Q Do you see that? 12 A Yes. 13 Q What did you consider to be the problem faced 14 by the patent's inventors? 15 A Which patent? 16 Q Cabilly II. 17 A The problem they faced was expression of 18 recombinant antibodies, recombinant proteins. 19 Q So you just said, "expression of recombinant 20 antibodies, recombinant proteins." 21 A Yes. 22 Q Was it both of those problems that they were 23 faced with? 24 A That's a genus/species issue. They were 25 expressing recombinant antibodies, which are</p>

10 (Pages 34 to 37)

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1 proteins.

2 **Q You understood the problem faced by the**

3 **inventors of the Cabilly II patent to be the**

4 **expression of recombinant antibodies which are**

5 **proteins?**

6 A A particular type of protein, yes.

7 **Q And that is the problem that you had in your**

8 **mind when conducting your obviousness analysis?**

9 A Yes.

10 **Q How did you determine that that was the**

11 **problem faced by the inventors of the Cabilly II**

12 **patent?**

13 A That that was their problem, an expression of

14 recombinant antibodies. That seemed to be what the

15 whole patent was written about.

16 **Q You go on in your description of the law of**

17 **obviousness to say:**

18 "A prior art reference is

19 pertinent... if the reference

20 discloses information that has

21 obvious uses beyond its main purpose

22 that a person of ordinary skill in

23 the art would reasonably examine to

24 solve the same problems faced by the

25 inventors."

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1 **Do you see that?**

2 A Paragraph 20, yes.

3 **Q What criteria did you use to decide what a**

4 **person of ordinary skill in the art would examine**

5 **trying to solve the problem of the expression of**

6 **recombinant antibodies?**

7 A That was a long question. Could we read that

8 back.

9 (Record read by Reporter as follows:

10 "QUESTION: What criteria did you

11 use to decide what a person of

12 ordinary skill in the art would

13 examine trying to solve the problem

14 of the expression of recombinant

15 antibodies?")

16 THE WITNESS: The criterion was thematic

17 relatedness.

18 BY MS. DAVIS:

19 **Q What do you mean by "thematic relatedness"?**

20 A Someone who expresses Protein A and someone

21 who expresses Protein B are both expressing a

22 protein, even though A is not the same as B. That's

23 thematic relatedness.

24 **Q Did you consider -- strike that.**

25 **Are you saying that any art regarding the**

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1 **expression of a protein is art that you believe**

2 **might have been used by a person of ordinary skill**

3 **in the art trying to express a recombinant antibody?**

4 A Again, can I have that question again -- read

5 back.

6 (Record read by Reporter as follows:

7 "QUESTION: Are you saying that any

8 art regarding the expression of a

9 protein is art that you believe

10 might have been used by a person of

11 ordinary skill in the art trying to

12 express a recombinant antibody?")

13 THE WITNESS: Yes. Art pertaining to

14 expression of proteins is potentially relevant to

15 someone expressing a new protein.

16 BY MS. DAVIS:

17 **Q Do you believe that art relating to the**

18 **expression of prokaryotic proteins would be relevant**

19 **to the person faced with the problem of the**

20 **expression of a recombinant antibody?**

21 A Yes.

22 MR. McCORMICK: Objection.

23 BY MS. DAVIS:

24 **Q And why is that?**

25 A They are both proteins. There's no real

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1 difference among proteins that come from bacteria

2 and proteins that come from eukaryotes.

3 **Q In what ways is there no real difference**

4 **among proteins that come from bacteria and proteins**

5 **that come from eukaryotes?**

6 A They are made of the same amino acids. They

7 are encoded by genes using the same genetic code.

8 **Q Are they expressed in similar ways?**

9 MR. McCORMICK: Objection; vague, ambiguous.

10 THE WITNESS: Largely, yes, they are.

11 Can I get some water?

12 MS. DAVIS: Oh, sure. Let's -- we can go off

13 the record for just a second to get a water refill.

14 THE WITNESS: Yeah.

15 THE VIDEOGRAPHER: Off the record at 10:26.

16 (Recess taken.)

17 THE VIDEOGRAPHER: Back on the record at

18 10:26.

19 BY MS. DAVIS:

20 **Q Turning to page 6 of your report?**

21 A Yes.

22 **Q In paragraph 22, you state:**

23 **"I understand that I should also**

24 **consider whether a reason existed at**

25 **the time of the invention that would**

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1 **have prompted a person of ordinary**
 2 **skill in the art in the relevant**
 3 **field to combine the known elements**
 4 **in the way the patent claim does."**
 5 **Do you see that?**
 6 A Yes.
 7 **Q First -- strike that.**
 8 **We are still talking about obviousness;**
 9 **correct?**
 10 A Yes.
 11 **Q There's a reference to "relevant field" here.**
 12 **Do you see that?**
 13 A Yes.
 14 **Q What did you mean by "relevant field"?**
 15 A Relevant field. In this case, the set of
 16 technologies that relates to recombinant expression
 17 of proteins or even expression and isolation of
 18 nonrecombinant proteins. Much of protein
 19 biochemistry, much of gene expression and molecular
 20 biology is potentially relevant.
 21 **Q And you did not limit -- in conducting your**
 22 **analysis, you did not limit the relevant field to**
 23 **the expression of eukaryotic proteins?**
 24 A I didn't limit it to that, no.
 25 **Q And you didn't limit the relevant field to**

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1 **the expression of recombinant proteins?**
 2 A No.
 3 **Q You go on to say:**
 4 **"The reason could come from the**
 5 **prior art, the background knowledge**
 6 **of one of ordinary skill in the art,**
 7 **the nature of the problem to be**
 8 **solved, market demand, or common**
 9 **sense."**
 10 **Do you see that?**
 11 A Yes, I do.
 12 **Q Did you take into account market demand in**
 13 **conducting your obviousness analysis?**
 14 A It was at the back of my mind that antibodies
 15 could be a very important protein to be able to
 16 produce and manipulate.
 17 **Q How so?**
 18 A Antibodies have been used in therapy for more
 19 than a century and will continue to be used in
 20 therapy.
 21 **Q How did that factor into your obviousness**
 22 **analysis?**
 23 A Obvious -- my obviousness analysis, it was a
 24 background awareness of a very large number of
 25 people working on antibodies of great interest in

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1 continuing to use antibodies in therapy and being
 2 able to modify antibodies to improve their
 3 therapeutic potential.
 4 **Q Just to backtrack a minute, you had said that**
 5 **you did not exclude from your description of the**
 6 **relevant field the expression of nonrecombinant**
 7 **proteins; correct?**
 8 A That's right.
 9 **Q Why not?**
 10 A Oh, many biochemical techniques for working
 11 on proteins were devised and are still devised using
 12 proteins isolated directly from an organism or
 13 microorganism, and those you would use the same for
 14 recombinant or nonrecombinant proteins. As I said,
 15 I had worked on recombinant ATCase and
 16 nonrecombinant ATCase, but many of the techniques
 17 for working on the protein itself were the same.
 18 **Q You also said you did not exclude from the**
 19 **relevant field prokaryotic proteins?**
 20 A That's right.
 21 **Q Why not?**
 22 A Why did I not exclude prokaryotic proteins
 23 from -- I'm trying to understand your question.
 24 **Q In your obviousness analysis, you made use of**
 25 **the idea of there being a relevant field of art;**

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1 **correct?**
 2 A Yes.
 3 **Q And within that relevant field, you -- strike**
 4 **that.**
 5 **You considered the expression of prokaryotic**
 6 **proteins to be within that relevant field.**
 7 A Yes.
 8 **Q Why did you exclude the expression of**
 9 **prokaryotic proteins within the relevant field for**
 10 **purposes of your obviousness analysis?**
 11 A Why did I?
 12 **Q Why did you?**
 13 A Did I exclude -- did I just say that? I'm
 14 sorry.
 15 **Q Why did you include?**
 16 A Why did I include prokaryotic proteins. I
 17 don't make a distinction between pro- -- prokaryotic
 18 or eukaryotic; because, to me, proteins are
 19 proteins, many common properties.
 20 **Q Do you make a distinction between prokaryotic**
 21 **and eukaryotic host cells?**
 22 MR. McCORMICK: Objection; vague, ambiguous.
 23 THE WITNESS: Well, technically, they are
 24 handled in a different way, but no. They're --
 25 differences between them don't concern me.

<p style="text-align: right;">Page 46</p> <p>1 BY MS. DAVIS: 2 Q And so expression results achieved in a 3 prokaryotic host cell are relevant to expression in 4 the eukaryotic host cell? 5 A They are. 6 MR. McCORMICK: Objection; vague, 7 ambiguous -- 8 THE WITNESS: Yes -- 9 MR. McCORMICK: -- incomplete hypothetical. 10 Go ahead. 11 THE WITNESS: I've expressed the same protein 12 in a prokaryotic cell and a eukaryotic cell. 13 BY MS. DAVIS: 14 Q In paragraph 23 of your report, you say: 15 "In making the obviousness 16 assessment, one must also consider 17 certain other surrounding 18 circumstances -- so-called 19 'secondary considerations' -- that I 20 understand may be raised by the 21 patentee in support of 22 non-obviousness." 23 Do you see that? 24 A Yes. 25 Q Do you understand that Genentech and City of</p>	<p style="text-align: right;">Page 48</p> <p>1 Q And how, if at all, did you take those 2 factors into account in conducting your obviousness 3 analysis? 4 A I didn't really apply that to the obviousness 5 issue, which, to me, was a scientific technical 6 issue; whereas, what I mentioned, royalties, is more 7 a business issue. 8 Q You mentioned that Genentech has many 9 antibody products. 10 A Yes. 11 Q And BMS has an antibody product that's at 12 issue in this case? 13 A That's right. 14 Q Do you know whether those antibodies -- well, 15 strike that. 16 Let me start with the BMS antibody, Yervoy. 17 Do you know whether Yervoy is made in a 18 eukaryotic host cell or a prokaryotic host cell? 19 A I believe it's made in a eukaryotic host 20 cell. 21 Q Do you -- 22 A I didn't study how it's made. I didn't talk 23 with anyone at Bristol about how they were making 24 this. 25 Q Do you understand that the process used to</p>
<p style="text-align: right;">Page 47</p> <p>1 Hope have raised secondary considerations in this 2 case? 3 A I don't really -- I can't recall if I was 4 told anything about that. I -- if they were, I 5 don't know what they are. 6 Q Have you reviewed the report of a Dr. Fintan 7 Walton? 8 A I may have looked at that. I don't even 9 recall if I looked at that in the Glaxo case, but I 10 didn't for this case. 11 Q In conducting your obviousness analysis, did 12 you take into account any of the so-called secondary 13 considerations, as that phrase is used in 14 paragraph 23? 15 A Not in a very substantial way. They -- they 16 didn't affect my opinion. 17 Q So you said "not in a very substantial way," 18 which suggests to me you did consider them at least 19 a little bit; is that correct? 20 A This is -- in my background knowledge, I'm 21 aware that Genentech makes a lot of antibodies and 22 sells them, and they do wonderful things for 23 patients, and other companies make antibodies and 24 they pay royalties to Genentech based on the Cabilly 25 patent. I'm aware of that.</p>	<p style="text-align: right;">Page 49</p> <p>1 make Yervoy in a eukaryotic host cell is a process 2 that is covered by the asserted claims of 3 Cabilly II? 4 A Yes; otherwise, we wouldn't be here. 5 Q Do you know whether -- strike that. 6 Do you know whether BMS is contesting 7 infringement? 8 A I believe BMS thinks that the allegation of 9 infringement isn't valid because the underlying 10 patent is invalid. The underlying claims are 11 invalid. 12 Q And do you understand that BMS is not -- 13 well, strike that. 14 A Yeah. 15 Q You are an inventor on several patents. 16 A Yes. 17 Q You understand the concept of infringement, 18 generally speaking. 19 A Yes. 20 Q Do you know whether BMS is contesting whether 21 Yervoy infringes the asserted claims of the 22 Cabilly II patent, other than the argument that the 23 patent claims are invalid? 24 A I'm not aware of what might have gone on 25 between BMS and Genentech beyond the claims I was</p>

13 (Pages 46 to 49)

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

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1 Dressler's lab, so I was close.
 2 You are looking for a black and white?
 3 **Q** No. I'm looking for your answer so that
 4 it -- it --
 5 A Those were my skills at that time.
 6 **Q** Continuing on in this paragraph, you say you
 7 base this opinion on the level of education and
 8 experience of persons actively working in the field
 9 at the time of the invention --
 10 A Yes.
 11 **Q** -- including the inventors of the Cabilly
 12 patents.
 13 What field -- how are you defining "field" in
 14 this context?
 15 A "Field" here is the expression of recombinant
 16 proteins.
 17 **Q** In --
 18 A Or if that's -- go ahead.
 19 **Q** Please, if you are not done with your answer,
 20 please finish.
 21 A Actively working in the field, you would stop
 22 there. Oh, there were additional parts to that, but
 23 maybe you were going to come to that.
 24 **Q** We will come to that --
 25 A Right.

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1 **Q** -- my first question is: For purposes of --
 2 of figuring out who was working in the field, what
 3 definition of "field" did you use?
 4 A Field, expression of recombinant proteins.
 5 **Q** For purposes of figuring out who was a person
 6 of ordinary skill in the art, you limited the field
 7 to expression of recombinant as opposed to
 8 nonrecombinant proteins; is that correct?
 9 THE WITNESS: Please read back.
 10 MS. DAVIS: Go ahead.
 11 (Record read by Reporter as follows:
 12 "QUESTION: For purposes of figuring
 13 out who was a person of ordinary
 14 skill in the art, you limited the
 15 field to expression of recombinant
 16 as opposed to nonrecombinant
 17 proteins; is that correct?")
 18 THE WITNESS: Oh, yes. The -- that's
 19 correct. The person expressing recombinant proteins
 20 would have all the facility for working with DNA;
 21 whereas, a pure protein biochemist would not.
 22 BY MS. DAVIS:
 23 **Q** A little bit earlier we were discussing, in
 24 connection with your obviousness analysis, that you
 25 had included, within the field of art that was

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1 relevant, the expression of nonrecombinant proteins.
 2 Do you remember that?
 3 A Yes.
 4 **Q** Why is the field of art that the person of
 5 ordinary skill looking at broader -- strike that.
 6 Why did you limit the field of persons of
 7 ordinary skill in the art to recombinant proteins
 8 when you did not limit the field for obviousness
 9 purposes to recombinant proteins?
 10 A Oh, because many of the techniques the person
 11 skilled in the art would use come from outside that
 12 narrow field, such as gel electrophoresis of
 13 proteins, doesn't really have anything to do with
 14 whether the protein is recombinant or not, but it's
 15 a vital technique to know how to use for problems
 16 like recombinant expression of proteins.
 17 **Q** Continuing on in paragraph 25, you refer to
 18 the types -- the type of problems encountered in the
 19 art and the prior art solutions to those problems.
 20 Do you see that?
 21 A Yes.
 22 **Q** What types of problems encountered in the art
 23 did you have in mind in forming your definition of a
 24 person of ordinary skill in the art?
 25 A Type of problems encountered in the art.

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1 Well, that would have to do with -- for example, the
 2 group that had expressed insulin had -- they
 3 expressed it as a fusion protein and needed to have
 4 a way to cut that protein after it was made to
 5 release the insulin chains. That's an example of a
 6 problem that could be relevant.
 7 Proteins often, once they are made, are not
 8 in the ideal form, and biochemists have ways of
 9 treating them chemically. I've certainly done that,
 10 that type of considerations.
 11 **Q You go on in this paragraph to discuss the**
 12 **sophistication of the technology in the art at the**
 13 **time of the invention, including the rapidity with**
 14 **which innovations were made in the art at the time**
 15 **of the invention.**
 16 **Do you see that?**
 17 A Yes.
 18 **Q What did you understand to be the level of**
 19 **sophistication of the technology in the art at the**
 20 **time of the invention?**
 21 A The sophistication of the technology -- now
 22 I've lost your question. Please read back.
 23 **Q Well, let me --**
 24 A Yeah.
 25 **Q -- actually, let me rephrase it.**

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1 A Yeah.
 2 **Q What did you mean by "the sophistication of**
 3 **the technology in the art at the time of the**
 4 **invention"?**
 5 A I meant that these were very cutting-edge
 6 techniques at the time in recombinant expression,
 7 recombinant protein expression. Many people were
 8 working on that. The -- the field was moving very
 9 fast.
 10 **Q And how did you -- how did that factor into**
 11 **your analysis?**
 12 A Well, that had to do with what the -- that
 13 the person of ordinary skill would be taking in all
 14 this -- all these new developments, this flux in the
 15 field, and might have to use techniques that he or
 16 she hadn't used before but could find in the
 17 literature and apply, like that. There would be
 18 some self-education going on.
 19 **Q And finally in this paragraph, you refer to**
 20 **the rapidity with which innovations were made.**
 21 **Do you see that?**
 22 A Yes.
 23 **Q Were innovations being rapidly made in**
 24 **approximately April 1983?**
 25 A Innovations were being made.

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1 **Q How did that factor into your analysis?**
 2 A It didn't have anything to do with priority
 3 dates. I've always kept those in mind. Just the --
 4 the same thing. This pertains to a person of
 5 ordinary skill who would -- who would be following
 6 these new developments, so you wouldn't have a
 7 static, unchanging body or mental knowledge at the
 8 beginning of try and do this, but would learn along
 9 the way.
 10 MS. DAVIS: We are at a fairly good breaking
 11 point.
 12 MR. McCORMICK: Sure.
 13 MS. DAVIS: You want to take a break?
 14 MR. McCORMICK: We've been going an hour.
 15 Thank you.
 16 THE WITNESS: That's fine.
 17 THE VIDEOGRAPHER: Off the record at 10:48.
 18 (Recess taken.)
 19 THE VIDEOGRAPHER: Back on the record at
 20 11:02.
 21 BY MS. DAVIS:
 22 **Q So if you could turn to page 7 of your**
 23 **report.**
 24 A Yes.
 25 **Q There's a section on page 7 entitled "Summary**

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1 **of Opinions."**
 2 **Do you see that at the very bottom?**
 3 A Yes.
 4 **Q And then it goes on over to page 8?**
 5 A Yes.
 6 **Q My first question is: Is the "Summary of**
 7 **Opinions" section, in fact, a summary of -- a fair**
 8 **and complete summary of your opinions in this case?**
 9 A Yes.
 10 **Q Starting with the very bottom of page 7, you**
 11 **refer to the Cabilly II patent?**
 12 A Yes.
 13 **Q And there are three asserted claims from the**
 14 **Cabilly II patent at issue in this case?**
 15 A 15, 17, 33.
 16 **Q And with respect to those three claims, it is**
 17 **your opinion that those claims are anticipated both**
 18 **by the Cohen & Boyer patent and by the Bujard**
 19 **patent?**
 20 A Yes.
 21 **Q Sticking for the moment to anticipation, is**
 22 **it correct that there is no other art that you are**
 23 **contending anticipates claims 15, 17, and 33 of**
 24 **Cabilly II?**
 25 A No other art contained within Cohen & Boyer

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

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1 A When you -- the patent must work. It must be
 2 enabled. Okay. Yes.
 3 **Q And you have not been asked to opine as to**
 4 **whether the Cabilly II or the Cabilly III patents --**
 5 A Oh, that's right.
 6 **Q -- meet the enablement requirement.**
 7 **That's what you were saying; is that correct?**
 8 A That's right. Yeah, that's right. I'm
 9 sorry.
 10 **Q The -- the question that -- that I would like**
 11 **to ask you now --**
 12 A Okay.
 13 **Q -- is whether the particular prior art that**
 14 **you used in your anticipation analysis -- whether**
 15 **you consider whether that prior art was enabled for**
 16 **the purpose that you used it for?**
 17 A Yes.
 18 **Q And you did consider whether the prior art**
 19 **was enabled?**
 20 A That's right.
 21 **Q Is that analysis contained in your opinion --**
 22 **in your reports in this case?**
 23 A My analysis was the -- was that the Bujard
 24 patent and the Cohen & Boyer patent were enabled for
 25 -- yes.

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1 **Q And that is --**
 2 A But aren't all patents presumed to be
 3 enabled? I believe they were enabled, yeah, okay,
 4 as written.
 5 **Q The analysis that goes along with your view**
 6 **that the Cohen & Boyer patent and the Bujard patent**
 7 **are enabled, that analysis is found within your two**
 8 **reports in this case?**
 9 A Yes.
 10 **Q Turning to page 8?**
 11 A Yes.
 12 **Q You say at the top: In the alternative,**
 13 **claim 33 is obvious, and in one bullet you have it**
 14 **in view of Bujard in combination with Riggs &**
 15 **Itakura, and in another bullet, you have it as**
 16 **obvious in view of Cohen & Boyer.**
 17 A Yes.
 18 **Q In combination with Riggs & Itakura.**
 19 **So you -- you have -- strike that.**
 20 **You are not contending that claims 15 and 17**
 21 **of the Cabilly II patent are obvious; is that**
 22 **correct?**
 23 A Yes, apparently. Yes.
 24 **Q The only claim of Cabilly II that you are**
 25 **contending is obvious is claim 33?**

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1 A That's right.
 2 **Q And with respect to claim 33, you have put**
 3 **forward two combinations of prior art?**
 4 A Correct.
 5 **Q You are not opining that there are other**
 6 **combinations of prior art that would make obvious**
 7 **claim 33 of the Cabilly II patent?**
 8 A I'm -- I'm not claiming that. I've focused
 9 on this Riggs & Itakura.
 10 **Q Riggs & Itakura, in combination with either**
 11 **Cohen & Boyer or in combination with Bujard?**
 12 A For claim 33, yes.
 13 **Q You would agree there is other art discussed**
 14 **in your reports?**
 15 A Other art, yes.
 16 **Q The other art that you discuss in your report**
 17 **that is not Cohen & Boyer, Bujard, and Riggs &**
 18 **Itakura, you are not opining that that art should be**
 19 **used in an obviousness combination?**
 20 MR. McCORMICK: Objection.
 21 THE WITNESS: That's right, yes, because I
 22 talk about other recombinant proteins that have been
 23 expressed, but it's these that I've distilled down
 24 as the most germane methods to which to use for the
 25 argument about obviousness.

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1 BY MS. DAVIS:
 2 **Q** These being Cohen & Boyer, Bujard, and Riggs
 3 & Itakura?
 4 A That's right.
 5 **Q** The next portion at the top of page 8 refers
 6 to the Cabilly III patent?
 7 A Yes.
 8 **Q** So in a minute I'm going to ask you about
 9 your obviousness-type double-patenting opinions with
 10 respect to Cabilly III.
 11 A Right.
 12 **Q** I first want to ask you: Is it correct that
 13 you are not opining that the asserted claims of
 14 Cabilly II are invalid due to obviousness-type
 15 double patenting?
 16 A That's correct, only Cabilly III.
 17 **Q** And with respect to Cabilly III, there are --
 18 are you -- strike that.
 19 If you turn to the next page, page 9, there's
 20 a section "Asserted Claims of the Cabilly III
 21 Patent"?
 22 A Yes.
 23 **Q** And there are, in fact, five asserted claims
 24 of the Cabilly III patent; is that correct?
 25 A That's right.

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

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

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1 THE VIDEOGRAPHER: Back on the record at
 2 11:13.
 3 BY MS. DAVIS:
 4 **Q** You don't have any opinions in this case
 5 regarding whether the Cabilly II or Cabilly III
 6 patents met the written description requirement for
 7 validity is that correct?
 8 A That's correct.
 9 **Q** Could you turn to page -- strike that --
 10 page 10.
 11 Page 10, at the bottom, there's a section
 12 referred to as "Prosecution History."
 13 Do you see that?
 14 A Yes.
 15 **Q** You have looked at portions of the Cabilly II
 16 prosecution history; is that correct?
 17 A That's correct.
 18 **Q** Have you looked at the entire prosecution
 19 history of Cabilly II?
 20 A My eyes passed over it, but please don't ask
 21 me to recall parts of it. I -- I did look at it.
 22 **Q** In -- on page 11, paragraph 37 -- in
 23 paragraph 37 you refer to the fact that the PTO
 24 rejected the claims of the Cabilly II patent over
 25 the Axel patent and the Moore patent.

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1 Do you see that?
 2 A Yes.
 3 Q Have you compared Cohen & Boyer to the Axel
 4 patent?
 5 A I've looked at both.
 6 Q Have you considered whether the Cohen & Boyer
 7 patent defers from the Axel patent?
 8 MR. McCORMICK: Objection; foundation.
 9 THE WITNESS: I have considered. My -- yes.
 10 BY MS. DAVIS:
 11 Q What is your opinion?
 12 A My understanding is that the -- the Patent
 13 Office construed the Axel patent as producing just
 14 one recombinant polypeptide chain; whereas, I
 15 believe that Boyer outlines production of more than
 16 one polypeptide chain.
 17 Q Have you considered the Moore patent?
 18 A I have looked at the Moore patent, but I
 19 don't recall much about it.
 20 Q Have you compared Cohen & Boyer to the Moore
 21 patent?
 22 A Not in a comprehensive way that I remember,
 23 but I did look at both of those.
 24 Q Turning to page 12, could you look at
 25 paragraph 38?

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1 A Yes.
 2 Q You say in paragraph 33 that you understand
 3 that Cohen & Boyer was cited by the applicants
 4 during the prosecution of the Cabilly II patent and
 5 Cabilly III patent but that it was not the subject
 6 of a rejection by the PTO during prosecution of
 7 those patents.
 8 Do you see that?
 9 A Yes.
 10 Q What do you understand it to mean that Cohen
 11 & Boyer was not the subject of a rejection by the
 12 PTO?
 13 A Oh, the PTO did not tell your client, "Oh,
 14 your patent was anticipated by Cohen & Boyer."
 15 Although -- yeah, that's my understanding.
 16 Q Is it your understanding that Cohen & Boyer
 17 would have been considered by the PTO during the
 18 prosecution of the Cabilly II and Cabilly III
 19 patents?
 20 A I notice--
 21 MR. McCORMICK: Objection.
 22 THE WITNESS: I noticed that it was
 23 referenced in the -- somewhere in the file wrapper
 24 more than once, but -- sorry. What did you just
 25 ask?

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1 BY MS. DAVIS:
 2 Q Is it your understanding that Cohen & Boyer
 3 would have been considered by the PTO during the
 4 prosecution of the Cabilly II and Cabilly III
 5 patents?
 6 MR. McCORMICK: Objection; vague.
 7 THE WITNESS: Considered. I don't know. I
 8 just know that it was part of the record. I don't
 9 know what the PTO did with it or if considered as a
 10 particular meaning. I don't know how it was
 11 treated.
 12 BY MS. DAVIS:
 13 Q The next section in your report is "Question
 14 Presented"?
 15 A Yes.
 16 Q So in paragraph 39 you state:
 17 "I have been asked to express an
 18 opinion on whether the asserted
 19 claims of the Cabilly II Patents
 20 would have been anticipated or made
 21 obvious by the Cohen & Boyer patent
 22 and/or the Bujard patent, alone or
 23 in combination with Riggs &
 24 Itakura."
 25 Do you see that?

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1 A Yes.
 2 Q Sticking to that sentence about Cabilly II,
 3 my -- my question to you is: Were you asked
 4 specifically to consider whether those three art
 5 references anticipated or rendered obvious
 6 Cabilly II? Was that the question you were given?
 7 A That was the question I was given, but we
 8 discussed quite a bit besides that. I've read quite
 9 a few references besides just these three.
 10 Q Were you familiar with either the Cohen &
 11 Boyer patent or the Bujard patent prior to your work
 12 in connection with the GFK Cabilly case?
 13 A I knew about the Cohen & Boyer patent. I did
 14 not know about the Bujard patent.
 15 Q Were you asked -- strike that.
 16 Did you find either of the Bujard patent or
 17 the Riggs & Itakura patent yourself?
 18 A The Riggs & Itakura is not a patent.
 19 Q Yes. Fair question.
 20 You didn't find the art that you were asked
 21 to opine on yourself; is that correct?
 22 A Well, I found -- Cohen & Boyer was well
 23 known, but Bujard and the Riggs & Ita-- the Riggs
 24 & Itakura paper is a more obscure. I hadn't read
 25 that before.

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

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1 Do you see that?
 2 A Yes.
 3 **Q** And in that footnote, you refer to a prior
 4 report written by an expert, E. Fintan Walton.
 5 Do you see that?
 6 A Yes.
 7 **Q** You have not read Dr. Walton's report in this
 8 case; is that correct?
 9 A That's right.
 10 **Q** You note that Dr. Walton has made some
 11 statements about the Cohen & Boyer patents in the --
 12 the report you did read; is that fair?
 13 A In the report I did read? I read Walt- --
 14 Dr. Walton's report in the GSK case, yeah --
 15 **Q** And --
 16 A -- that retained this language, yes.
 17 **Q** -- in this footnote, you are referring to a
 18 report Dr. Walton prepared in a case that's referred
 19 to here as MedImmune.
 20 Do you see that?
 21 A That's -- MedImmune, yes.
 22 **Q** Do you know what that's a reference to, the
 23 MedImmune case?
 24 A That's the earlier case in which I -- oh,
 25 actually, no. That's not the case I worked on.

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1 That's the case before. That's right, yeah.
 2 **Q** Is that the only report by Dr. Walton that
 3 you have reviewed, the MedImmune report?
 4 A That's right.
 5 **Q** In the footnote, you describe some statements
 6 that Dr. Walton has made previously about the Cohen
 7 & Boyer patents; correct?
 8 A Yes.
 9 **Q** Do you agree that the Cohen & Boyer invention
 10 was a fundamental one?
 11 A Yes.
 12 **Q** Are you familiar at all with the licensing of
 13 the Cohen & Boyer patent?
 14 A I've heard a few things about it.
 15 **Q** What --
 16 A That it was -- they quite nobly wanted it to
 17 be applied as widely as possible and made it
 18 available to everyone. Didn't try to cut anyone
 19 out.
 20 **Q** Are you aware that Dr. Walton has compared
 21 the licensing history of the Cabilly patents to the
 22 Cohen & Boyer licensing history?
 23 A I -- I don't recall reading that, but I can't
 24 say that it's not true. I just don't recall.
 25 **Q** Do you have any opinions on the licensing

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

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

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1 **Q And the full context of that phrase is:**
 2 **"If production of cohesive termini**
 3 **is by restriction endonuclease**
 4 **cleavage, the DNA containing the**
 5 **foreign gene(s) to be bound to the**
 6 **plasmid vehicle will be cleaved in**
 7 **the same manner as the plasmid**
 8 **vehicle."**
 9 **Do you see that?**
 10 A Yes.
 11 **Q Do you believe that that is a reference to a**
 12 **single fragment of DNA?**
 13 A I'm just taking a minute to read. I'm sorry
 14 for the delay.
 15 I think it could be one fragment or two
 16 fragments. They -- they don't say one.
 17 **Q Do they say two fragments?**
 18 A No. They don't give a number. I think, in
 19 many cases, it might be one, but two is not ruled
 20 out by this.
 21 The main condition is if production of
 22 cohesive termini is by restriction endonuclease
 23 cleavage, which could give more than one fragment,
 24 which -- and the -- the multiplicity of fragments
 25 are each capable of being inserted in this site

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1 that's been opened in the plasmid vehicle.
 2 **Q You would agree that a single fragment of DNA**
 3 **could contain one or more genes; correct?**
 4 A Yes.
 5 **Q It depends on how the DNA is cut?**
 6 A Yes.
 7 **Q And you agree that Cohen & Boyer are, in**
 8 **places, discussing using a single fragment of DNA**
 9 **that may contain one or more genes on that single**
 10 **fragment of DNA?**
 11 A They contemplate more than one gene on a
 12 single fragment of DNA. I don't see a departure
 13 from that, yeah.
 14 **Q Continuing on in paragraph 44, you quote a**
 15 **portion of Cohen & Boyer that refers to the DNA**
 16 **fragment may include one or more genes or one or**
 17 **more operons.**
 18 **Do you see that?**
 19 A Yes.
 20 **Q And I just first want to ask you: What is an**
 21 **"operon"?**
 22 A An "operon" is a -- was a regulatory
 23 structure, an arrangement of segments of DNA that
 24 was first identified in prokaryotes. I don't think
 25 there's a strict definition. We don't really have

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

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1 **DNA containing a complete operon?**
 2 A Yes.
 3 **Q And the operon is bacterial?**
 4 A That's a bacterial operon, yes.
 5 **Q In paragraph 45, you state -- strike that.**
 6 **A portion of paragraph 45 reads:**
 7 **"... the Cohen & Boyer patent**
 8 **teaches co-expression of multiple**
 9 **distinct and separate polypeptides**
 10 **in a single microorganism host**
 11 **cell."**
 12 **Do you see that?**
 13 A Yes.
 14 **Q Where are you getting from Cohen & Boyer**
 15 **"multiple distinct and separate polypeptides"?**
 16 A Multiple distinct and separate polypeptides.
 17 Well, that refers to all the previous references
 18 where Cohen & Boyer talk about gene or genes. Genes
 19 is inherently multiple.
 20 **Q What did you mean by "distinct and separate**
 21 **polypeptides"?**
 22 A Let's see. "Distinct and separate" meaning
 23 that there are two separate polypeptide chains; that
 24 the end of one does not connect to the beginning of
 25 the other.

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1 **Q What teachings in Cohen & Boyer led**
 2 **you -- strike that.**
 3 **What teachings in Cohen & Boyer refer to**
 4 **polypeptides where the end of one is not connected**
 5 **to the beginning of another?**
 6 A Well, the tryptophan operon is the best
 7 example where there are five polypeptides, each not
 8 connected end to end.
 9 **Q Are there other portions of Cohen & Boyer**
 10 **that refer to polypeptides that are not connected to**
 11 **one another?**
 12 MR. McCORMICK: Objection; asked and
 13 answered.
 14 THE WITNESS: I'm reading into the statements
 15 of more than one gene, meaning that they would not
 16 be connected one to the other.
 17 BY MS. DAVIS:
 18 **Q And why are you reading that into those**
 19 **statements?**
 20 A That's usually the way I interpret two
 21 distinct genes. One can contemplate a fusion
 22 protein, but I don't think that's what they are
 23 talking about, and certainly not in the tryptophan
 24 case, but.
 25 **Q What are you relying on to interpret two**

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1 **distinct genes to exclude a fusion protein?**
 2 A It's not that I'm excluding a fusion protein.
 3 A fusion protein is two genes fused together. Let's
 4 think of it simply like that. But two genes that
 5 aren't fused together would still fit this
 6 description, so both situations fit this language of
 7 two genes.
 8 **Q We discussed earlier the -- the concept of**
 9 **expressed disclosure for anticipation versus**
 10 **inherent disclosure for anticipation.**
 11 **Do you recall that?**
 12 A Yes.
 13 **Q Is the fact that, in your opinion, Cohen &**
 14 **Boyer teaches co-expression of multiple and --**
 15 **multiple distinct and separate polypeptides in a**
 16 **single microorganism host cell -- is that based on**
 17 **expressed disclosures, inherent disclosures, or**
 18 **both?**
 19 A Well, expressed disclosures, with the example
 20 of the tryptophan.
 21 **Q Please continue.**
 22 A Yeah.
 23 Inherent disclosures, again, if they were --
 24 yeah, I think -- well, tryptophan is an expressed
 25 disclosure. Again, inherently, just from

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

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

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

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1 **Q And this is labeled "Section 102 Invalidity**
 2 **Claim Chart" at the top?**
 3 A Right.
 4 **Q And this is the chart you prepared setting**
 5 **forth where in Cohen & Boyer and then Bujard the**
 6 **elements of the asserted Cabilly II claims can be**
 7 **found?**
 8 A Yes.
 9 **Q The first claim you have listed is claim 33?**
 10 A Yes.
 11 **Q And is it -- well, strike that.**
 12 **What were you trying to convey in this chart?**
 13 A The chart's no different from the bulk of the
 14 report. It's just a summary.
 15 **Q So looking at the first box in the chart, you**
 16 **have a claim limitation from claim 33 of Cabilly II?**
 17 A Yes.
 18 **Q And that limitation is:**
 19 **"A process for producing an**
 20 **immunoglobulin molecule or an**
 21 **immunologically functional**
 22 **immunoglobulin fragment comprising**
 23 **at least the variable domains of the**
 24 **immunoglobulin heavy and light**
 25 **chains, in a single host cell,**

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1 **comprising."**
 2 **Is that correct?**
 3 A Yes.
 4 **Q I just want to talk right now about Cohen &**
 5 **Boyer.**
 6 A Okay.
 7 **Q So I'm going to set aside Bujard for the**
 8 **moment.**
 9 **You state in your entry for Cohen that --**
 10 **that corresponds to this limitation: Cohen**
 11 **discloses a process for producing an antibody in a**
 12 **unicellular organism.**
 13 **Do you see that?**
 14 A Yes.
 15 **Q Now, the language that you cite next to**
 16 **antibody is section -- is column 1, line 39;**
 17 **column 9, lines 28 through 30; and column 16, 63**
 18 **through 65.**
 19 A Yes.
 20 **Q So let's start with the first of those.**
 21 **So column 1, line 39, that has the word**
 22 **"antibodies"?**
 23 A Yes.
 24 **Q And that's why you are citing it?**
 25 A Yes.

<p style="text-align: right;">Page 86</p> <p>1 Q Now that line in column 1 is not talking 2 about a process to produce antibodies; is that 3 correct? 4 A Well, isn't it. One -- one sec, please. 5 I believe it is talking about a process to 6 produce antibodies. You are talking about it at a 7 very high-level, but it's about a process. 8 Q Does the language in column 1, around 9 line 39, discuss the production of antibodies? 10 A Right around 39, it lists antibodies as an 11 example of what could be made, but talks about other 12 things that could be made, one of which is 13 antibodies. 14 Q Now, the -- the sentence that that language 15 appears in is: "Thus, it becomes practical to 16 introduce into a particular microorganism, genes 17 specifying..." 18 A Yes. 19 Q Do you see that? 20 A Yes. 21 Q Is this section discussing introducing genes 22 into an organism? 23 A It's definitely talking about introducing 24 genes. 25 Q Do --</p>	<p style="text-align: right;">Page 88</p> <p>1 A A difference between those. Well, the genes 2 I introduced were expressed, so one led to the 3 other. 4 Q Is it always the case that you will get 5 expression of a gene that you have introduced into 6 an organism? 7 A You could have a dead gene. I -- I accept 8 that. 9 Q What do you mean by a "dead gene"? 10 A A gene that's not transcribed, let's say. It 11 never produces a protein. 12 Q What types of genes would not be transcribed? 13 MR. McCORMICK: Objection. 14 THE WITNESS: That's hard to answer. There's 15 not really a -- a property that would keep a gene 16 from being transcribed. They are just little 17 aspects of its structure, whether it has a promoter 18 nearby, whether it's in a cell that supplies 19 functions to transcribe it, things like that. 20 BY MS. DAVIS: 21 Q Do you believe that once that -- strike that. 22 How difficult is it to ensure that a gene you 23 have introduced into a cell is expressed? 24 A Difficult. That's -- that's tough to 25 quantify. I'm looking -- always looking to quantify</p>
<p style="text-align: right;">Page 87</p> <p>1 A But I'm not -- let me finish, though. 2 MR. McCORMICK: Read as much as you need -- 3 THE WITNESS: Right. 4 MR. McCORMICK: -- to finish answering the 5 question. 6 THE WITNESS: But it later talks about 7 functions, which are indigenous to other classes of 8 organisms, so. 9 BY MS. DAVIS: 10 Q Do you understand the function language to be 11 a reference to producing antibodies? 12 A Yeah. The function is -- that refers to what 13 is produced, not just the gene itself. The gene 14 itself is just DNA, like lots of other DNA. It's -- 15 the function refers to the product of the gene doing 16 something. 17 Q Is there a difference -- strike that. 18 A Yeah. 19 Q We discussed earlier some of your work prior 20 to 1983. 21 Do you recall that? 22 A Yes. 23 Q Was there a difference in the work that you 24 did between introducing a gene into an organism and 25 having that organism express the gene?</p>	<p style="text-align: right;">Page 89</p> <p>1 things. I think most genes can be expressed. 2 Sometimes it takes a little work. Sometimes the 3 level of detection is such that it's being expressed 4 and you don't know it, but genes can be expressed. 5 Q So in this particular passage of Cohen & 6 Boyer, is it fair to say that you believe that they 7 are discussing the production of antibodies -- well, 8 strike that. 9 What language is it again in this section of 10 Cohen & Boyer that you believe refers to the 11 production of antibodies? 12 A When they use the word "function." 13 Q And that is because one function of the 14 organism into which the gene has been introduced is 15 to express the gene? 16 A One sec, please. 17 This is very high-level language, but the use 18 of the word "function" means these processes; 19 nitrogen fixation, photosynthesis, enzymes and 20 antibodies. These functions refers to the gene 21 product doing something. So they are not really 22 interested in just putting the DNA there per se. 23 Putting the DNA there becomes interesting because of 24 the functions it confers on the microbe that's 25 received it.</p>

23 (Pages 86 to 89)

<p style="text-align: right;">Page 90</p> <p>1 Q In this particular language in column 1, do 2 Cohen -- Cohen & Boyer describe expression of an 3 antibody gene? 4 A Describe it. They -- they describe it as 5 a -- at a high-level. They don't say how to 6 describe it. They just say introducing these genes 7 will be part introducing of a function. 8 Q In the -- in your chart, the next line you 9 had quoted was in column 9, line 28. 10 So can we turn to that? 11 A Line 28. 12 Q And the language that you were citing -- 13 A Right. 14 Q -- is the sentence that "other poly (amino 15 acids) of interest include serum proteins," and then 16 it goes on to include globulin, e.g., 17 gamma-globulin -- globulins or antibodies. 18 Is that the language you are referring to? 19 A That's right. 20 Q So this section is saying, in your opinion, 21 that antibodies are a protein of interest to Cohen & 22 Boyer? 23 A Yes. 24 Q You would agree that this language does not 25 discuss a process for producing antibodies?</p>	<p style="text-align: right;">Page 92</p> <p>1 A Right. 2 Q -- appearing shortly -- shortly after the 3 section we have been discussing? 4 A Yes. 5 Q Before we get to that, I want to go to 6 column 16, lines 63 through 65. 7 A 53 through -- but you may want 63. Okay. 8 Q In your chart, do you see that the first 9 reference -- 10 A Oh, 63. 11 Q 63. 12 A Oh, right. I see, yeah. 13 Q And that states: 14 "Besides enzymes, other proteins can 15 be produced such as antibodies, 16 antigens, albumins, globulins, 17 glycoproteins, and the like"? 18 A Yes. 19 Q Does this language describe a process for 20 producing antibodies? 21 A It refers to the overall process disclosed in 22 the patent, but not a specific process for how to 23 make an antibody. Antibodies are grouped in this 24 very general process -- or they are grouped together 25 with other proteins that can be made in this very</p>
<p style="text-align: right;">Page 91</p> <p>1 A It doesn't specifically refer to a process 2 for antibodies; that's right. 3 Q Does it generally refer to a process for 4 antibodies? 5 A Well, first, your process for expressing a 6 whole cornucopia of recombinant proteins, that's 7 part of the power of this patent. It (sic) useful 8 for just about everything. 9 Q Does the language in column 9 at lines 28 10 through 30, does that language refer to a process, 11 either generally or specifically, for producing 12 antibodies? 13 A Let me look at this again. One sec. 14 There is a process. By introducing one or 15 more exogenous genes into a unicellular organism, 16 the organism will be able to produce polypeptides 17 and proteins. 18 Q And then -- 19 A And then it gives this list of things it 20 could be applied to. 21 Q And you were referring to the language at 22 column 9, lines 12 -- 23 A 12, yeah. 24 Q In your chart, you see -- so you -- you have 25 the language in column 9, lines 12 through 14 --</p>	<p style="text-align: right;">Page 93</p> <p>1 general process. 2 Q Do you know what section of the patent this 3 language appears in? 4 A Section. It appears to be -- 5 MR. McCORMICK: The document speaks for 6 itself. 7 THE WITNESS: Right. The -- there are a 8 series of examples, but this seemed like a more 9 general discussion. 10 So the real -- more general discussion than 11 just somatostatin in the last example. So this is 12 the experimental section. Or is that -- I'm sorry. 13 I'm confused by their organization. The various 14 section heads are "Experimental" and "Example V." 15 It's in the specification. 16 BY MS. DAVIS: 17 Q And this is in the "Example V" section. 18 Is that your understanding? 19 A That was the last header, but by column 16, 20 they cease to discuss somatostatin and shifted to a 21 more general discussion. 22 For example, at the end of the last paragraph 23 of column 15: 24 "It is evident from the above 25 results, that both DNA from a</p>

24 (Pages 90 to 93)

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1 eukaryotic source and RNA
 2 transcribed from the eukaryotic DNA
 3 can be formed in a bacterial cell
 4 and isolated," etc.
 5 **Q In conducting your anticipation analysis,**
 6 **with respect to Cohen & Boyer, did you take into**
 7 **account what sections the various phrases you've**
 8 **pulled out -- what sections those appear in?**
 9 A I paid attention to what --
 10 MR. McCORMICK: Object; characterization.
 11 But go ahead.
 12 THE WITNESS: I paid attention to whether
 13 they were in the specification or the claims.
 14 BY MS. DAVIS:
 15 **Q Did you take into account anything else**
 16 **regarding what sections they appeared in?**
 17 A I paid attention to what was trying to be
 18 said, so I know the difference between an abstract
 19 and background and summary. I took into account
 20 that, but -- but, you know, to me the section head
 21 is just part of the -- part of the explanation. It
 22 helps guide the reader to what's contained below,
 23 but there's a distinct difference between claims and
 24 specification, and that's the one I paid the most
 25 attention to.

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1 **Q In the three examples we have discussed so**
 2 **far that are in your -- your sort of first two lines**
 3 **regarding the Cohen & Boyer patent --**
 4 A Yes.
 5 **Q -- have -- have we seen any reference to**
 6 **heavy chains or light chains?**
 7 A In those three lines, it just says
 8 antibodies.
 9 **Q And Cohen -- please finish.**
 10 A Which -- which inherently have heavy chains
 11 or light chains, but they don't use the words
 12 "heavy" and "light."
 13 **Q And, in fact, at no point in Cohen & Boyer is**
 14 **there a reference to either a heavy chain or a light**
 15 **chain; is that correct?**
 16 A I'm not aware of a -- I would have to -- it
 17 would take too long to check, but I'm not aware of a
 18 specific use of heavy chain or light chain.
 19 **Q Did any of the three passages that we have**
 20 **discussed -- did those refer to the concept of a**
 21 **single host cell?**
 22 A Let's see. So 1:39: "Thus, it becomes
 23 practical to introduce into a particular
 24 microorganism," that would be a single host cell.
 25 Line 28 refers back to that first full

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1 paragraph of column 9: "By introducing one or more
 2 exogenous genes into a unicellular organism," that's
 3 a single cell.
 4 And then 16:63, let me take a look. I'm
 5 sorry to go through this so laboriously.
 6 "In addition, the products" -- I'm now
 7 reading from line 60 on column 16.
 8 "In addition, the products of the
 9 enzymic reactions may be more
 10 readily isolated and more
 11 efficiently produced by a
 12 transformant than by the original
 13 host."
 14 So a transformant, again, is singular. The
 15 antibody reference follows that. So, again, it
 16 would seem to be a single host cell.
 17 **Q Are you familiar with -- well, strike that.**
 18 **In your reports, you have referred to the**
 19 **early work producing insulin; correct?**
 20 A Yes.
 21 **Q And you are aware that, early on, insulin was**
 22 **produced by putting one of the insulin chains in one**
 23 **cell and the other insulin chain in another cell;**
 24 **correct?**
 25 A The City of Hope and Genentech group did

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1 that, yes. Mm-hmm.
 2 **Q In the passages we have just discussed in**
 3 **Cohen & Boyer, do you understand those passages to**
 4 **exclude the type of process that the Genentech and**
 5 **City of Hope individuals used in producing insulin**
 6 **with one chain in one cell and the other chain in**
 7 **another cell?**
 8 A Exclude that. I think Cohen & Boyer is
 9 completely compatible with expressing a single
 10 polypeptide.
 11 **Q So let's --**
 12 A Yeah.
 13 **Q -- let's start with column 1, the first**
 14 **section we looked at.**
 15 A Right.
 16 **Q And you had said that the language in**
 17 **column 1 you understood to refer to a single host**
 18 **cell.**
 19 A Yes.
 20 **Q Could the language in column 1 also refer to**
 21 **a method like the method used by Genentech and City**
 22 **of Hope to produce insulin with each of the chains**
 23 **in a separate cell?**
 24 A That could be. I could see that, yes.
 25 **Q And is the same true of the other passages of**

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

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1 "Thus, it becomes practical to
 2 introduce into a particular
 3 microorganism, genes specifying such
 4 metabolic or synthetic functions as
 5 nitrogen fixation, photosynthesis,
 6 antibiotic production, hormone
 7 synthesis, protein synthesis...
 8 enzymes or antibodies, or the
 9 like..."
 10 For -- some of those processes are -- are
 11 complex and require several -- several actors to
 12 work in -- in series, like the -- well, you know,
 13 photosynthesis, nitrogen fixation, antibiotic
 14 production -- that's a metabolic pathway -- you
 15 would need the machinery, multiple genes present
 16 within the same cell for that to work.
 17 BY MS. DAVIS:
 18 **Q So in the example of nitrogen fixation --**
 19 **A Yes.**
 20 **Q -- the goal in nitrogen fixation is not to**
 21 **produce a protein that is harvested, it's to**
 22 **transform the organism into one that fixes nitrogen?**
 23 A Can live off the air, yes.
 24 **Q And so in a case like that, it's not the --**
 25 **the project isn't a success unless the single**

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

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1 **Q When was the first time you used CDNA?**
 2 A That would have been 1977.
 3 **Q How difficult would it have been in 1974 to**
 4 **put both the heavy chain and light chain of an**
 5 **antibody into a single host cell?**
 6 A In 1974, the first antibody chains had not
 7 even been cloned, so that would have made it very
 8 hard in 1974.
 9 **Q If, in 1974, someone succeeded in cloning**
 10 **them, would there be other difficulties in getting**
 11 **both the antibody heavy chain gene and antibody**
 12 **light chain gene into a single cell?**
 13 MR. McCORMICK: Objection --
 14 THE WITNESS: If someone --
 15 MR. McCORMICK: -- incomplete hypothetical.
 16 THE WITNESS: -- had cloned them, I -- I see
 17 much less problem. The big problem was cloning them
 18 in the first place. I should add. That was true
 19 for a lot of proteins. There were not very many
 20 cloned proteins in 1974.
 21 MS. DAVIS: I had promised half an hour,
 22 so -- we can keep going?
 23 MR. McCORMICK: If -- you mean another
 24 15 minutes? Whatever the witness --
 25 MS. DAVIS: Okay.

<p style="text-align: right;">Page 102</p> <p>1 MR. McCORMICK: -- he --</p> <p>2 MS. DAVIS: Sure.</p> <p>3 MR. McCORMICK: -- he needs the breaks more</p> <p>4 than we do.</p> <p>5 MS. DAVIS: All right.</p> <p>6 THE WITNESS: No, we are fine.</p> <p>7 MS. DAVIS: We can keep going? All right.</p> <p>8 We will go a little further.</p> <p>9 Q So in the same box, there's the language --</p> <p>10 the Cohen & Boyer box, you had referred earlier to</p> <p>11 the passage on column 9, lines 12 through 14.</p> <p>12 Do you want to turn to that?</p> <p>13 A Oh, sorry. Where are we in the table?</p> <p>14 Q Still in the first Cohen & Boyer box --</p> <p>15 A Yeah.</p> <p>16 Q -- the sentence beginning: "See, e.g." --</p> <p>17 A Oh, "See, e.g., 9:12 to 14."</p> <p>18 Q And that language is the sentence beginning:</p> <p>19 "By introducing one or more exogenous genes";</p> <p>20 correct?</p> <p>21 A Let me -- I'm on the wrong column. Sorry.</p> <p>22 Where did it go. There. By introducing one or more</p> <p>23 exogenous genes, yes.</p> <p>24 Q The language that you have quoted in your</p> <p>25 chart at column 9, lines 12 through 14, does not say</p>	<p style="text-align: right;">Page 104</p> <p>1 Q Well, let me ask it this way: It's --</p> <p>2 A Yeah.</p> <p>3 Q -- your understanding that the language at</p> <p>4 the end of that paragraph -- that those are the</p> <p>5 genes that are being introduced?</p> <p>6 A Means for preparing these, so these are</p> <p>7 introduced, yes.</p> <p>8 Q And as we have discussed earlier, there's no</p> <p>9 mention anywhere in Cohen & Boyer that you are aware</p> <p>10 of of heavy chain or light chain; correct?</p> <p>11 A Not specific language for heavy chain and</p> <p>12 light chain.</p> <p>13 Q And this language in particular does not</p> <p>14 include a reference to either a heavy chain or a</p> <p>15 light chain, then?</p> <p>16 A It doesn't break antibodies down into heavy</p> <p>17 chain or light chain. And I might point out, an</p> <p>18 antibody is a globulin. It is a glycoprotein, so</p> <p>19 it's included multiple times, but not broken down</p> <p>20 into heavy chain or light chain.</p> <p>21 Q Is there any reference in the Cohen & Boyer</p> <p>22 patent to the variable domain of a heavy chain or a</p> <p>23 light chain?</p> <p>24 A It's not broken down that far either. Again,</p> <p>25 someone knowing the structure of antibodies in 1974</p>
<p style="text-align: right;">Page 103</p> <p>1 which specific genes are going into the unicellular</p> <p>2 organism; is that correct?</p> <p>3 A 12 to 14 --</p> <p>4 MR. McCORMICK: Objection.</p> <p>5 THE WITNESS: -- does not say which. That</p> <p>6 follows later. Mm-hmm.</p> <p>7 BY MS. DAVIS:</p> <p>8 Q Continuing in your chart, now you have the</p> <p>9 reference to column 16, lines beginning at line 53.</p> <p>10 Do you see that?</p> <p>11 A Yes.</p> <p>12 Q And that is -- strike that.</p> <p>13 That section begins: "In addition, the</p> <p>14 subject method provides means for preparing enzymes,</p> <p>15 enzymic products from bacteria," and then it goes</p> <p>16 on.</p> <p>17 Is that the language you were referring to?</p> <p>18 A Yes.</p> <p>19 Q That particular language does not say</p> <p>20 anything about which specific genes are being</p> <p>21 introduced into the cell, does it?</p> <p>22 A Doesn't it say other proteins can be</p> <p>23 produced; antibodies, antigens, albumins, globulins?</p> <p>24 Or am I looking in the wrong place or</p> <p>25 misunderstanding your question?</p>	<p style="text-align: right;">Page 105</p> <p>1 would know there are heavy chains and light chains</p> <p>2 and variable domains and constant domains. That was</p> <p>3 all known then from the protein-level analysis, even</p> <p>4 in advance of the study of antibody genes.</p> <p>5 Q You said a few minutes ago that, as of 1974,</p> <p>6 antibody genes had not been cloned; correct?</p> <p>7 A That's right.</p> <p>8 Q Do you believe that it is a predicate to be</p> <p>9 able to use the Cohen & Boyer method to produce an</p> <p>10 antibody that you have cloned the antibody genes?</p> <p>11 MR. McCORMICK: Hold on. Let me read this.</p> <p>12 I'll just object as ambiguous to time frame.</p> <p>13 But you can answer.</p> <p>14 THE WITNESS: Can I have that again?</p> <p>15 MS. DAVIS: Sure.</p> <p>16 THE WITNESS: Yeah.</p> <p>17 BY MS. DAVIS:</p> <p>18 Q Do you believe that it is a predicate to be</p> <p>19 able to use the Cohen & Boyer method to produce an</p> <p>20 antibody that you have cloned the antibody genes?</p> <p>21 A Well, part of Cohen & Boyer is about cloning</p> <p>22 genes, so many of these other things hadn't been</p> <p>23 cloned either. This was the start of cloning. This</p> <p>24 is what it would be good for. So you don't need to</p> <p>25 have them in hand right in 1974, if that's what you</p>

27 (Pages 102 to 105)

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1 were asking.

2 **Q When did it become possible, in your opinion,**

3 **to produce an antibody using the method of Cohen &**

4 **Boyer?**

5 A Possible. There's some complexity to that

6 question because it would have been possible in 1974

7 if you had the right pieces of DNA there. Those

8 pieces of DNA started emerging later in the 1970s,

9 so by 1977, we were making a serious effort in

10 Dressler's lab. Of course, Tamagawa, who got the

11 Nobel Prize, was making an even more serious effort.

12 Other people were working on that by late '70s, in

13 that region.

14 **Q You believe -- for purposes of your opinion**

15 **in this case, you believe that there is a point, a**

16 **time in which using the Cohen & Boyer method, a**

17 **person of ordinary skill in the art would be able to**

18 **produce an antibody; correct?**

19 A A point in time or region in time. I

20 couldn't name a day, an hour, minute, but.

21 **Q What is the region of time?**

22 A Region of time: 1978, '79, '80, '81, in

23 there, maybe '82, but in that region, it became

24 possible.

25 **Q What are you basing that opinion on?**

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1 A I'm basing that, I confess, on my own

2 experience, having tried to do that as a technician

3 in the lab. I thought it was possible then. But

4 other papers began to appear with parts of

5 antibodies cloned. The genes themselves appeared,

6 the -- the first constant region clones by Tamagawa.

7 The mechanisms of antibody rearrangement were

8 understood.

9 So basing it on those factors, a kind of wave

10 of understanding of antibody genes as they existed

11 in humans and animals, and the dynamics they would

12 go through and what their DNA sequences were; how

13 they were -- their expression was controlled; what

14 cells they would appear in. This was a body of

15 knowledge that was developing then.

16 **Q How much work was being done with the genes**

17 **for human antibodies in the range of time period you**

18 **have identified?**

19 A I would say --

20 MR. McCORMICK: Objection. Just outside the

21 scope of his report.

22 THE WITNESS: Right.

23 I did not study human antibodies for this

24 report, but my impression is that not much work was

25 being done on human antibodies at that time. The

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1 big focus was on hybridomas, which had appeared in

2 1975.

3 BY MS. DAVIS:

4 **Q Is there a point in time, in your mind, in**

5 **which the focus switched away from hybridomas?**

6 A The focus switched away from hybridomas. I

7 used the word "focus," but I might have better said

8 "foci." There were different groups. There were

9 some groups interested in how expression of these

10 genes are controlled; other groups were interested

11 in therapeutic use.

12 You asked about a period of time where it

13 shifted away from hybridomas. I think hybridomas

14 are still of interest, but the beginning of -- well,

15 I couldn't really identify a point in time where

16 interest shifted away from hybridomas.

17 **Q Are you equating hybridomas with murine**

18 **hybridomas?**

19 A Yes.

20 **Q Are you familiar at all with human-murine**

21 **hybridomas?**

22 A I'm dimly aware that people have tried hard

23 to make human hybridomas and did not have much

24 success.

25 **Q Are you aware of some reports of success**

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1 **with -- well, first, I want to start with**

2 **human-murine hybridomas.**

3 MR. McCORMICK: Objection; time frame, vague,

4 ambiguous.

5 THE WITNESS: Right.

6 I didn't study this. I don't recall specific

7 reports, so I can't answer that with any confidence.

8 BY MS. DAVIS:

9 **Q You mentioned hearing reports of individuals**

10 **having difficulties with human-human hybridomas; was**

11 **that correct?**

12 A I -- I did not follow that literature well at

13 the time, and I haven't followed it since. I can't

14 really give an informed answer there.

15 **Q Do you know if there's any difference**

16 **between -- strike that.**

17 **Do you know if the -- the difficulties you**

18 **are vaguely recalling related to human-human**

19 **hybridomas or humine (sic) -- human-murine**

20 **hybridomas?**

21 A I would barely be aware the difference. I

22 couldn't -- I couldn't say.

23 **Q If you could turn to page C-2.**

24 A C-2.

25 **Q And in the top of this is a carry-over box**

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1 from --
 2 A Right.
 3 Q -- your first Cohen & Boyer --
 4 A C-1.
 5 Q -- limitation.
 6 A Okay.
 7 Q The last sentence is:
 8 "The one or more genes include
 9 antibodies having at least the
 10 variable region of the heavy and
 11 light chains."
 12 Do you see that?
 13 A Yes.
 14 Q And you agree, as we've discussed a couple
 15 times, that heavy and light chains -- those don't
 16 appear anywhere in Cohen & Boyer; right?
 17 A Right. Those -- those words don't appear,
 18 but I did mention earlier that antibodies were
 19 understood to have separate heavy and light chains.
 20 That much was well known.
 21 Q The next limitation of the Cabilly II patent
 22 is the second box on the -- the left:
 23 "Independently expressing a first
 24 DNA sequence encoding at least the
 25 variable domain of the

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1 immunoglobulin heavy chain and a
 2 second DNA sequence encoding at
 3 least the variable domain of the
 4 immunoglobulin light chain so that
 5 said immunoglobulin heavy and light
 6 chains are produced as separate
 7 molecules in said single host cell
 8 transformed with said first and
 9 second DNA sequences."
 10 A Yes.
 11 Q Do you see that?
 12 A Yes.
 13 Q And in your box on Cohen & Boyer, you say:
 14 "The transformed microorganism is
 15 capable of independently expressing
 16 the DNA sequences encoding the heavy
 17 and light chains," and then you
 18 quote some language in the patents.
 19 A That's right.
 20 I was wondering: Are we going to start
 21 something pretty long or would now -- now be a good
 22 time for a break?
 23 MS. DAVIS: Let's go ahead and --
 24 THE WITNESS: Okay.
 25 MS. DAVIS: -- break for lunch.

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1 MR. McCORMICK: Was there a question pending?
 2 I just want to --
 3 MS. DAVIS: I --
 4 THE WITNESS: It seemed like we moved to a --
 5 I'm sorry to --
 6 MS. DAVIS: If there was a
 7 question pending --
 8 MR. McCORMICK: You'll withdraw it --
 9 MS. DAVIS: -- I will withdraw it.
 10 THE WITNESS: Thanks.
 11 MS. DAVIS: It might have been: Are those
 12 words on the page? So --
 13 THE VIDEOGRAPHER: Off the record at 12:40.
 14 (Lunch recess taken.)
 15 ---o0o---
 16
 17
 18
 19
 20
 21
 22
 23
 24
 25

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1 AFTERNOON SESSION 1:28 P.M.
 2
 3 THE VIDEOGRAPHER: Back on the record at
 4 1:28.
 5 BY MS. DAVIS:
 6 Q So, Dr. Foote, I want to start with C-2 of
 7 your report, which is still the chart.
 8 A Yes.
 9 Q And I want to talk about the portions of
 10 Cohen that you have listed as corresponding to the
 11 Cabilly II claim 33 limitation that begins
 12 "independently expressing."
 13 Are you there?
 14 A Yes.
 15 Q And you indicate in your report that the
 16 transformed microorganism of the Cohen & Boyer
 17 patent is capable of independently expressing the
 18 DNA sequences encoding the heavy and light chains.
 19 Do you see that?
 20 A Yes.
 21 Q And the portion that you -- the first portion
 22 you cite is column 5, line 64 to 65.
 23 A That's right.
 24 Q So can we go there.
 25 And the sentence in question, which you have

<p style="text-align: right;">Page 114</p> <p>1 also quoted in the chart, is: 2 "The DNA fragment may include one or 3 more genes or one or more operons"; 4 is that correct? 5 A Yes. 6 Q Does that language refer to independent 7 expression? 8 A Yes, more than one gene expressed. 9 Q Are you equating the expression of more than 10 one gene with independent expression? 11 A Yes. 12 Q And why is that? 13 A Because the alternate is a fusion protein, 14 and I think that's a very special case, so my -- I 15 think the default is that if you express two genes, 16 you get two polypeptides. 17 Q Continuing on in your chart -- 18 A Yes. 19 Q -- you have a reference to column 6, lines 1 20 through 3? 21 A Yes. 22 Q And you say that, in your chart: 23 "(the foreign DNA fragment should 24 have 'an intact promoter and base 25 sequences coding for the initiation</p>	<p style="text-align: right;">Page 116</p> <p>1 most -- those are exceptional cases. 2 Q In most cases, so long as you have an intact 3 promoter and initiation and termination sequences, 4 you would expect to get at least some expression? 5 A Yes. 6 Q What else would you need, if anything, in 7 order to get at least some expression? 8 A Those are all you would need, really. Those 9 are the minimum. 10 Q Is one promoter sufficient to get expression 11 of both heavy and light chain? 12 MR. McCORMICK: Objection; incomplete 13 hypothetical. 14 THE WITNESS: Yes. You need at least one. 15 What I'm thinking is that if you had one 16 promoter, you could have a construct, like in the 17 genes for ATCase where you have an intracistronic 18 region where one chain stops being translated, you 19 go along a bit, and then the new one starts. So you 20 wouldn't -- you don't need two promoters. You can 21 get by with one promoter. 22 BY MS. DAVIS: 23 Q Would you be concerned at all -- strike that. 24 As of 1983, if you were constructing a -- a 25 plasmid according to Cohen & Boyer, would you be</p>
<p style="text-align: right;">Page 115</p> <p>1 and termination sites... for gene 2 expression.'") 3 A Yes. 4 Q Is it your opinion that so long as you have 5 an intact promoter and initiation and termination 6 sequences, you will get at least some expression of 7 the gene you've inserted into the microorganism? 8 A Yes -- oh. 9 MR. McCORMICK: Objection; incomplete 10 hypothetical. 11 Go ahead. 12 THE WITNESS: You would need those, promoter 13 and terminator. 14 BY MS. DAVIS: 15 Q Is it your opinion that so long as you have 16 the promoter and terminator in -- that you have 17 inserted into the microorganism, that you will get 18 at least some expression of the gene of interest? 19 A I can think of ways that would go wrong, but, 20 in most cases, it would work. 21 Q In what ways could it go wrong? 22 A Well, if you had a -- like a nonsense code 23 on -- in your reading frame, that might mess you up, 24 or, you know, some other structure that would 25 interfere with transcription or translation. But in</p>	<p style="text-align: right;">Page 117</p> <p>1 concerned at all about the possibility that you 2 would get uneven expression of the heavy chain and 3 the light chain with your vector? 4 A Uneven expression. So more of one than the 5 other? 6 Q Yes. 7 A You could well get that. I'm not at all sure 8 that would be a problem though. 9 Q Why do you say you are not at all sure that 10 would be a problem? 11 A I don't know why it would be a problem if you 12 get an unequal expression, unless you had almost 13 none of one. 14 Q Would you be able to recover intact antibody 15 if you had a vector that resulted in uneven 16 expression of the heavy and light chain? 17 MR. McCORMICK: Objection; vague, ambiguous. 18 THE WITNESS: I think you would. You would 19 end up throwing part of it away because there wasn't 20 a partner for the chain that was in excess. 21 BY MS. DAVIS: 22 Q You would agree that Cohen & Boyer does not 23 say that heavy and light chains would be produced as 24 separate molecules? 25 A Could I have that again? I would agree</p>

30 (Pages 114 to 117)

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1 that --

2 **Q Cohen & Boyer does not say that heavy and**

3 **light chains would be produced as separate**

4 **molecules?**

5 A Cohen & Boyer doesn't mention the words

6 "heavy" and "light chains."

7 **Q And with respect to other multimeric**

8 **proteins, Cohen & Boyer also doesn't specify that**

9 **any of those multimeric proteins, their component**

10 **chains, would be produced independently?**

11 A Which multimeric proteins do you mean?

12 because there are several appearances of that

13 throughout.

14 **Q Are there any multimeric proteins discussed**

15 **in Cohen & Boyer in which you believe Cohen & Boyer**

16 **describes the constituent chains being expressed**

17 **independently?**

18 A I don't recall, no.

19 **Q Is it fair to say that you believe Cohen &**

20 **Boyer should be read to call for the production of**

21 **heavy and light chains as separate molecule because**

22 **you believe that's the better option as compared to**

23 **a fusion protein?**

24 A The better option. I don't know what's meant

25 by "better option," but I would like to learn more,

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1 and maybe I could help you then.

2 **Q You had said a little while ago that you**

3 **didn't believe that a fusion protein was what**

4 **coin -- Cohen & Boyer meant; is that fair?**

5 A Cohen & Boyer could accommodate a fusion

6 protein, but they don't insist on it, yes. I

7 remember the discussion, I think, and for a fusion

8 protein, you need a very precise joining. If you

9 are doing it with restriction enzyme sequences, that

10 has to match just perfectly for -- to make your

11 polypeptide sequence be translated in frame.

12 Okay. Let me stop there. I'm getting off

13 track.

14 **Q Let me just ask it this way: Can you explain**

15 **to me again why you are assuming that the proteins**

16 **produced, according to Cohen & Boyer, are produced**

17 **as separate molecules as opposed to, for example, a**

18 **fusion protein?**

19 A Oh, I'm saying that they would be produced as

20 separate molecules as the kind of default; that if

21 Cohen & Boyer wanted to talk about a fusion protein

22 or if someone wanted to describe making a fusion

23 protein, you need to have more precise language,

24 more precise instructions.

25 So if I were reading Cohen & Boyer and it

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1 says "express two genes," I wouldn't assume that

2 those two genes would be fused in frame unless there

3 had been a deliberate effort to fuse them in frame.

4 **Q Why, in that example, would you assume that**

5 **they would be produced as separate molecules?**

6 MR. McCORMICK: Objection; asked and

7 answered.

8 THE WITNESS: Because if their -- if two

9 genes are juxtaposed, having been cut on fragments

10 with restrict- -- restriction sequences, it would

11 be -- it would be a tremendous coincidence if they

12 lined up exactly in frame flush right together. One

13 goes out to its end and immediately the next one

14 starts. There would have -- there has to be a very

15 concerted effort to achieve that.

16 So if one talks about just two genes, there's

17 no way those would form a fusion protein unless

18 there was a deliberate effort to -- to fuse them.

19 BY MS. DAVIS:

20 **Q Is there any particular type of cellular**

21 **machinery that would be required such that two genes**

22 **would be produced as separate molecules?**

23 A Cellular machinery. Well, you are right;

24 someone has to stop translating the first one and

25 start translating the second one, or a new ribosome

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1 can start translating the second one, but you do

2 need the ribosome to stop adding polypeptide, and

3 the termination codon would usually do that.

4 **Q And to get the ribosome to start on the**

5 **second chain or a new ribosome to start on the**

6 **second chain, is machinery required for that?**

7 A There's a ribosomes start site usually, yeah.

8 **Q Were those types of machinery known in 1983?**

9 A Yes.

10 **Q Do you believe that there's any other type of**

11 **cellular machinery other than what we have just**

12 **discussed that would be required to get two genes**

13 **within the same cell produced as separate molecules?**

14 A That's the -- that's the chief requirement

15 that the -- there's an independent start site for

16 ribosome to start translating the second one. You

17 do need the thing to be transcribed, but that would

18 be for making -- transcribing one gene or two, you

19 need a promoter in there somewhere. You need a

20 promoter before the first thing you want

21 transcribed, not just somewhere. In a particular

22 place.

23 **Q Were promoters known in 1983?**

24 A Oh, yes.

25 **Q How many promoters were known in 1983?**

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

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

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1 **Is that a reference to the section of --**
 2 A I'm lost. Eight --
 3 **Q Column 8, beginning at line 6.**
 4 A Column 8, line 6. Okay.
 5 **Q That is a reference to the section
 6 "Replication and Transcription of the Plasmid"?**
 7 A Yes.
 8 **Q And then you also refer to column 16, lines 8
 9 through 12?**
 10 A Yes.
 11 **Q And in that section, the language you are
 12 referring to, as quoted in your report, is:**
 13 **"... and entire operon can be
 14 introduced into a bacterial cell and
 15 the cell becomes capable of
 16 transcription, translation, and
 17 production of a functional gene
 18 product."
 19 Do you see that?**
 20 A 12. Yes, I do.
 21 **Q You would agree that an operon -- in an
 22 operon, the genes are contiguous?**
 23 A The genes are contiguous, separated by small
 24 bits of DNA, yes.
 25 **Q And you would also agree that this portion of**

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

<p style="text-align: right;">Page 126</p> <p>1 Q Could you turn to page C-3 of your report.</p> <p>2 A Okay.</p> <p>3 Q This corresponds to claim 15 of Cabilly II,</p> <p>4 this page?</p> <p>5 A Okay.</p> <p>6 Q And you see that, on the left, claim 15 is</p> <p>7 set forth?</p> <p>8 A Yes.</p> <p>9 Q And then you have a box setting forth the</p> <p>10 portions of Cohen & Boyer that you believe</p> <p>11 correspond?</p> <p>12 A Yes.</p> <p>13 Q The middle paragraph of your Cohen & Boyer</p> <p>14 column states:</p> <p>15 "Cohen does not explicitly disclose</p> <p>16 whether the one or more genes are</p> <p>17 located at different insertion sites</p> <p>18 (non-contiguous). However, Example</p> <p>19 III teaches transcription of 18S and</p> <p>20 28S" RNA -- "rRNA in E. coli."</p> <p>21 Do you see that?</p> <p>22 A Yes, I do.</p> <p>23 Q You agree that, as you have stated, Cohen &</p> <p>24 Boyer does not explicitly disclose whether the one</p> <p>25 or more genes are located at different insertion</p>	<p style="text-align: right;">Page 128</p> <p>1 that correct?</p> <p>2 A Yes.</p> <p>3 Q Does Cohen & Boyer have an example of both</p> <p>4 the transcription and translation of two</p> <p>5 non-contiguous genes?</p> <p>6 A Oh, well, in the tryptophan operon, any two</p> <p>7 genes in a room might be next to each other, but,</p> <p>8 you know, the first gene is not contiguous with the</p> <p>9 third gene, let's say.</p> <p>10 Q In the tryptophan operon, the thing</p> <p>11 separating the third gene from the first gene in</p> <p>12 your description is the second gene --</p> <p>13 A That's correct --</p> <p>14 Q -- correct?</p> <p>15 A -- yes.</p> <p>16 Q Other than in that context, does Cohen &</p> <p>17 Boyer describe both a description and translation of</p> <p>18 non-contiguous genes?</p> <p>19 MR. McCORMICK: Objection.</p> <p>20 THE WITNESS: Sorry. In -- in that context?</p> <p>21 BY MS. DAVIS:</p> <p>22 Q Other than --</p> <p>23 A Other than --</p> <p>24 Q -- strike that.</p> <p>25 You have explained that in the -- the --</p>
<p style="text-align: right;">Page 127</p> <p>1 sites?</p> <p>2 A Yes.</p> <p>3 Q Does Cohen & Boyer describe 18S and 28S as</p> <p>4 being non-contiguous?</p> <p>5 A Well, these were known to be non-contiguous</p> <p>6 in the -- at the time the application was written.</p> <p>7 I don't know whether they used that word. I can</p> <p>8 look for it if you like.</p> <p>9 Q Well, I don't want to limit you specifically</p> <p>10 to the word "non-contiguous."</p> <p>11 Do you know whether Cohen & Boyer describes</p> <p>12 18S and 28S, in words or substance, as</p> <p>13 non-contiguous?</p> <p>14 A I would have to look to be sure.</p> <p>15 Would you like me to read it and look for</p> <p>16 "non-contiguous" or?</p> <p>17 Q Let me ask it this way: Are you aware,</p> <p>18 sitting here now, of a place in Cohen & Boyer in</p> <p>19 which they describe those two genes as being</p> <p>20 non-contiguous, in words or substance?</p> <p>21 A I can't remember a passage with that in it.</p> <p>22 I haven't memorized it. I'm sorry.</p> <p>23 Q You then say -- strike that.</p> <p>24 Your reference to "18S" and "28S" is a</p> <p>25 reference to transcription of those two genes; is</p>	<p style="text-align: right;">Page 129</p> <p>1 A Tryptophan.</p> <p>2 Q -- tryptophan context, because there are more</p> <p>3 than two genes, the, for example, first and third</p> <p>4 are not contiguous to each other. They are</p> <p>5 separated by the second gene; correct?</p> <p>6 A That's right.</p> <p>7 Q And so my question is: Other than in that</p> <p>8 context, does Cohen & Boyer disclose one or more</p> <p>9 genes that are not contiguous being both transcribed</p> <p>10 and translated?</p> <p>11 MR. McCORMICK: Objection.</p> <p>12 THE WITNESS: I don't think he does. I could</p> <p>13 look at the examples, but I don't think there's one.</p> <p>14 The others are -- the other examples are one product</p> <p>15 at a time, I think. But then he does have this --</p> <p>16 those are the specific examples.</p> <p>17 BY MS. DAVIS:</p> <p>18 Q In the third paragraph of your Cohen box on</p> <p>19 page C-3 --</p> <p>20 A Yes.</p> <p>21 Q -- you say:</p> <p>22 "Furthermore, in order to express</p> <p>23 separate heavy chain and light chain</p> <p>24 subunits that could assemble into an</p> <p>25 immunoglobulin, the genes would</p>

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1 necessarily have to be
 2 non-contiguous, i.e., separated in
 3 the vector by sufficient non-coding
 4 DNA sequence to ensure that they are
 5 produced as separate molecules and
 6 not as a "sig- -- "single heavy
 7 chain/light chain fusion."
 8 Do you see that?
 9 A Yes.
 10 Q A minute ago you had said it would be
 11 difficult to get expression as a fusion protein; is
 12 that correct?
 13 A You would have to take specific steps to do
 14 it; although, not always. To have the end of one
 15 protein exactly coincide with the beginning of the
 16 next is very hard. Sometimes you can clone into a
 17 preexisting gene, so I think in cloning insulin, by
 18 Gilbert's group, not by Genentech group, they cloned
 19 into the middle of a beta-lactamase gene, and their
 20 insulin was fused to that, so that wasn't so hard.
 21 It was just -- but it wasn't the same kind of thing
 22 as having two independent genes. The beta-lactamase
 23 gene was destroyed.
 24 Q In the language in -- in your report,
 25 you're -- you indicate that you would need the genes

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1 to be non-contiguous to ensure that they are not
 2 produced as a fusion chain; is that correct?
 3 A Let's see. Sorry. My head's pounding. Can
 4 you repeat, please.
 5 Q Sure.
 6 A Yeah.
 7 Q In the language in your report --
 8 A Yes.
 9 Q -- you indicate that you would need the genes
 10 to be non-contiguous to ensure that they are not
 11 produced as a fuse -- fusion chain; is that correct?
 12 A The genes would be non-contiguous. They
 13 would not -- that is, the genes would be separated
 14 by some piece of DNA that wasn't translated.
 15 Q And you believe that's necessary because,
 16 otherwise, they would be produced as a fusion
 17 protein?
 18 A They -- I'm using this to rule out a fusion
 19 protein in this case. If they are separated by a
 20 little piece of DNA, they are not a fusion protein.
 21 Q In your report, you have said that the reason
 22 you assume that they are separated by at least some
 23 DNA --
 24 A All right.
 25 Q -- is to ensure that they are produced as

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1 separate molecules and not as a single heavy
 2 chain/light chain fusion.
 3 Do you see that?
 4 A Please point it out to me. I believe you,
 5 but --
 6 Q In the box corresponding to claim 15.
 7 A Oh.
 8 Q The carry-over paragraph.
 9 A Okay. Oh, so there's more to it.
 10 "... in order to express separate
 11 heavy chain and light chain" subu-
 12 -- "subunits that could assemble
 13 into an immunoglobulin, the genes
 14 would... have to be
 15 non-contiguous..."
 16 And that relies on knowledge that was -- been
 17 known for many years by then; that the end terminal
 18 of the light chain and the end terminal of the heavy
 19 chain are relatively close to each other. That is,
 20 the variable domains of the heavy chain and light
 21 chain in three-dimensional space line up next to
 22 each other, but if you did one of these fusions,
 23 let's say a light chain followed by heavy chain,
 24 that would physically move the heavy chain very far
 25 from the light chain and could never get back in

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1 three-dimensional space to form a -- an association
 2 that would be capable of binding antigen. That's
 3 why they would have to be separate.
 4 Q Do you have a particular reference in mind
 5 that you were referring to in the answer you just
 6 gave?
 7 A A particular reference that shows what?
 8 Q In the answer you just gave, you described
 9 the -- the reasons why you wouldn't want a fusion
 10 protein if you wanted the heavy and light chain to
 11 assemble correctly; is that correct?
 12 A Why you wouldn't want them as a fusion
 13 protein, yeah.
 14 Q Do -- is there a particular article or patent
 15 or other reference that you have in mind?
 16 A That deal specifically with the fusion
 17 problem and the impossibility of having a fusion
 18 between heavy and light chains?
 19 Q Yes.
 20 A I don't have one in mind that was present in
 21 1983. I'm relying kind of on -- not kind of. I'm
 22 relying on common sense and also what was known
 23 about antibody structure.
 24 Q Was it known, prior to April 1983, that
 25 the -- that a fusion protein of an antibody heavy

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1 **chain and light chain would be -- would present**
 2 **difficulties in terms of getting a functional**
 3 **antibody?**
 4 MR. McCORMICK: Objection; asked and
 5 answered.
 6 THE WITNESS: Was it known in the sense of
 7 had it been proven or -- I don't think that had been
 8 addressed. But the structure of antibodies was
 9 known, even the three-dimensional structure. And
 10 just knowing about what the parts of the antibody
 11 do, it -- it wouldn't make sense. It would be like
 12 having a cat with two, you know, feet going down and
 13 two more feet going up. You just wouldn't make a
 14 construct like that.
 15 BY MS. DAVIS:
 16 **Q Are you familiar with instances in the prior**
 17 **art, prior to April of 1983, in which proteins,**
 18 **other than antibodies, were expressed as fusion**
 19 **proteins and then later recombined?**
 20 A Well, the insulin chains were expressed as
 21 fusion proteins and recombined.
 22 **Q Would it be possible, in your view, prior to**
 23 **April of 1983, to express the antibody heavy and**
 24 **light chains as a fuse- -- fusion protein and then**
 25 **later recombine them?**

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1 A Could they be expressed --
 2 MR. McCORMICK: Objection; vague, ambiguous,
 3 confusing.
 4 THE WITNESS: So they would be expressed as a
 5 fusion protein and then perhaps cut away from the
 6 thing they were fused to and then recombined.
 7 I forgot your original question, but if I --
 8 I'm not aware of that having been done by 1983, but
 9 it sounds to me like it could be done or -- in 1983,
 10 you could have done it that way.
 11 BY MS. DAVIS:
 12 **Q Were fusion proteins always -- strike that.**
 13 **Prior to April of 1983, are you aware of**
 14 **proteins, other than insulin, that were expressed as**
 15 **fusion proteins intentionally?**
 16 A I didn't study the list of fusion proteins,
 17 but insulin is the main example that comes to mind
 18 by several labs. The somatostatin in the Cohen &
 19 Boyer paper was another one. I think the same group
 20 made human growth hormone. But I don't -- I didn't
 21 read the human growth hormone papers. I can't be
 22 sure of that.
 23 **Q Did you read the somatostatin papers?**
 24 A No. My knowledge on somatostatin comes from
 25 Cohen & Boyer, their example.

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1 **Q Was somatostatin expressed as a fusion**
 2 **protein?**
 3 A I believe it was. Let me -- so we are
 4 looking at "Example V: Cloning of Synthetic
 5 Somatostatin Gene."
 6 "Because of the failure to detect
 7 somatostatin activity from cultures
 8 carrying plasmid" -- I'm reading
 9 column 15, line about -- starting
 10 about 17.
 11 "Because of the failure to detect
 12 somatostatin activity from cultures
 13 carrying plasmid pSOM1, a plasmid
 14 was constructed in which the
 15 somatostatin gene could be located
 16 at the COOH-terminus of the
 17 beta-galactosidase gene, keeping the
 18 translation in phase."
 19 So that's a fusion protein, yes.
 20 **Q Would the method described in Cohen & Boyer**
 21 **for producing somatostatin as a fusion protein --**
 22 **would that have worked to produce an antibody heavy**
 23 **and light chain as a fusion protein?**
 24 MR. McCORMICK: Objection.
 25 THE WITNESS: So do you mean that if we took

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1 a light chain gene and used that the way they used
 2 somatostatin, fused that, and then separately made a
 3 heavy chain fused with beta-galactosidase and fused
 4 that, would that -- would that have produced these
 5 separate chains.
 6 It would have produced fusion polypeptides,
 7 but part of the trick here with somatostatin was
 8 that -- I don't recall the somatostatin sequence
 9 offhand, but with insulin, there was a reliance on
 10 particular chemical reaction to cleave the fused
 11 polypeptide chain right at a specific place that
 12 would free up the insulin part, independent of the
 13 thing it had fused to. And I don't think the same
 14 technique could be applied to an antibody, which is
 15 much longer than these short peptide hormones.
 16 BY MS. DAVIS:
 17 **Q With respect to insulin, you are referring to**
 18 **cleavage at the methionine?**
 19 A That's right.
 20 **Q Do you know whether somatostatin -- whether**
 21 **it was cleaved at methionine?**
 22 MR. McCORMICK: Objection; foundation.
 23 THE WITNESS: Cleaved at a methionine in this
 24 paper?
 25 MS. DAVIS: Correct.

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1 THE WITNESS: I don't recall offhand, but I
 2 can look and tell you.
 3 Looks like they didn't do that chemical
 4 workup.
 5 BY MS. DAVIS:
 6 **Q Can you tell from Cohen & Boyer how the**
 7 **somatostatin protein was cleaved?**
 8 MR. McCORMICK: Objection; foundation.
 9 THE WITNESS: I don't see a cleavage reaction
 10 here.
 11 BY MS. DAVIS:
 12 **Q Are you able to tell whether the fusion**
 13 **protein method used for somatostatin in Cohen &**
 14 **Boyer would have worked to produce antibody and --**
 15 **antibody heavy and light chains?**
 16 MR. McCORMICK: Objection.
 17 THE WITNESS: Well, it wouldn't have given
 18 antibody heavy chain and light chains, it would have
 19 given a fusion to something else. I'm sorry I
 20 hadn't read this more carefully before, but it's
 21 detailed biochemistry here I'm trying to understand
 22 on the fly.
 23 BY MS. DAVIS:
 24 **Q Are you still reviewing?**
 25 A It's okay.

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1 **Q It's fine if you are. I just want to make**
 2 **sure --**
 3 A Let's try the next question.
 4 **Q Are you aware of any reason why, following**
 5 **Cohen & Boyer, a person of ordinary skill in the art**
 6 **could not express antibody heavy and light chain in**
 7 **a manner similar to the somatostatin experiments and**
 8 **then reconstitute those chains into a functional**
 9 **antibody?**
 10 A I -- I don't see an impediment.
 11 **Q The chains in that hypothetical would be**
 12 **expressed attached to another protein?**
 13 A Well, if you make a fusion, you have to get
 14 rid of the thing it's fused to.
 15 **Q And you see no impediment to producing**
 16 **antibody heavy and light chains, according to Cohen**
 17 **& Boyer, where each heavy and light chain -- each of**
 18 **the heavy and light chain is fused to another**
 19 **protein?**
 20 A I -- I see potential problems in getting rid
 21 of the thing it's fused to.
 22 **Q You would need to identify a method to cleave**
 23 **away the fusion partner?**
 24 A That's right.
 25 **Q You don't know what method was used to cleave**

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1 **away the fusion partner in the somatostatin example?**
 2 A No, I don't.
 3 MR. McCORMICK: Objection.
 4 THE WITNESS: I haven't been able to figure
 5 it out just here.
 6 MS. DAVIS: Okay. I want to move on to a new
 7 topic.
 8 THE WITNESS: Okay.
 9 MS. DAVIS: Do we -- is -- does anyone need a
 10 break?
 11 THE WITNESS: Time flies. I don't need a
 12 break.
 13 MS. DAVIS: Okay. Then let's mark the next
 14 exhibit. This is Exhibit 7, the Bujard patent.
 15 U.S. Patent 4,495,280.
 16 (Exhibit 7 was marked for
 17 identification by the Reporter.)
 18 BY MS. DAVIS:
 19 **Q Do you have that in front of you?**
 20 A I do.
 21 **Q So if you could turn in your report back to**
 22 **page 15, you see that you have a section labeled**
 23 **"Bujard."**
 24 A Yes.
 25 **Q My first question is about paragraph 48,**

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1 **which carries over onto page 16. In that paragraph,**
 2 **you state:**
 3 **"The invention is an elaboration of**
 4 **the recombinant expression method of**
 5 **the Cohen & Boyer patent."**
 6 **Do you see that?**
 7 A Yes.
 8 **Q Is it a fair statement that Bujard is an**
 9 **elaboration of Cohen & Boyer as opposed to being an**
 10 **entirely separate invention?**
 11 A An elaboration --
 12 MR. McCORMICK: Objection.
 13 THE WITNESS: Scientifically speaking, it's
 14 an elaboration. I don't know about a legal term,
 15 but, yes.
 16 BY MS. DAVIS:
 17 **Q For purposes of your anticipation analysis,**
 18 **did you view that Bujard and Cohen & Boy- -- Boyer**
 19 **references as similar?**
 20 MR. McCORMICK: Objection.
 21 THE WITNESS: Yes, they were similar.
 22 BY MS. DAVIS:
 23 **Q In your opinion, they anticipate the asserted**
 24 **claims of the Cabilly II patent for similar reasons;**
 25 **fair?**

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1 A Yes.

2 **Q In paragraph 49, you say that:**

3 **"The Bujard patent generally relates**

4 **to methods and compositions for**

5 **preparing and cloning strong**

6 **promoters and terminator regulatory**

7 **signals, and utilizing the strong**

8 **regulatory sequences in the**

9 **transcription and expression of a**

10 **gene or genes of interest."**

11 **Do you see that?**

12 A Yes.

13 **Q You agree that the thrust of the Bujard**

14 **patent is the strong promoter and terminator**

15 **combination?**

16 MR. McCORMICK: Objection.

17 THE WITNESS: That's why Bujard made a

18 plasmid with these properties, yes. The thrust,

19 yes.

20 BY MS. DAVIS:

21 **Q At a very high-level, what does a promoter**

22 **do?**

23 A A promoter causes an enzyme called RNA

24 polymerase to begin transcription of a strand of DNA

25 near the promoter.

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1 **Q We discussed earlier that you had done some**

2 **work with the SV40 promoter; correct?**

3 A That's right.

4 **Q Had you, personally, done work with other**

5 **promoters prior to April of 1983?**

6 A "Other promoters," you mean eukaryotic

7 promoters or any promoters?

8 **Q Any promoters.**

9 A No, I hadn't.

10 **Q Approximately how much had you worked with**

11 **the SV40 promoter?**

12 A I worked for at least two quarters while

13 taking classes, but that was maybe six months.

14 **Q And this is prior to 1983?**

15 A That's right. This is 1981.

16 **Q Could you turn to page 17 of your report.**

17 A Yes.

18 **Q In paragraph 51, you state, in part:**

19 **"The overall goal of the invention**

20 **is to optimize production of**

21 **recombinant proteins encoded by the**

22 **DNA sequence of interest."**

23 **Do you see that?**

24 A Yes.

25 **Q What did -- what did you mean by "optimize"?**

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1 A Optimize. That -- that term basically means

2 getting the most of what you want for the least

3 expenditure of resources. So if you are growing up

4 a cell, having the cell make more protein.

5 **Q Is it fair to say that, prior to 1983,**

6 **expression levels could vary in terms of the gene of**

7 **interest being expressed?**

8 A It could vary depending on what other factor,

9 depended on promoter or cell type, other factors

10 could -- yes.

11 **Q One of the goals of Bujard was a particular**

12 **way in which to optimize levels of expression.**

13 A That's right.

14 **Q Could you turn to paragraph 54.**

15 A Yes. Ah, yes.

16 **Q This paragraph you refer to Bujard's use of**

17 **the term "multimer"?**

18 A Yes.

19 **Q You have a number of references in here that**

20 **are references to "multimeric proteins"; is that**

21 **fair?**

22 A That is.

23 **Q You would agree that Bujard was not using**

24 **"multimer" to refer to a protein. It was, instead,**

25 **using "multimer" to refer to a gene?**

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1 A I think he was using -- he was referring to

2 gene or genes coding a multimeric protein.

3 **Q Does Bujard use "multimeric protein," the**

4 **term?**

5 A Does he use it in the patent at all? I know

6 we are talking about this one line. He uses the

7 term "multimer." What's the quote? "Plurality of

8 genes, including multimers and operons."

9 **Q In that quote, the multimer is genes;**

10 **correct, not proteins?**

11 A His usage is a little awkward, and I

12 interpreted it as genes encoding for multimers, but

13 it's genes, plurality of genes, yes.

14 **Q What led you -- what are you relying on to**

15 **conclude that his reference to "multimer" was**

16 **referring to genes encoding multimeric proteins?**

17 A Because an alternative of just repeated genes

18 in a row wouldn't make sense. I -- I know he says

19 "a plurality of genes, including multimers and

20 operons." Well, you know, an operon is not a gene

21 either. It's more complex, so I think his language

22 was a little sloppy here.

23 **Q In your report at paragraph 54, you have a**

24 **number of uses of "multimer" and "multimeric";**

25 **correct?**

Page 146

1 A That's right.

2 **Q Those are in the context of the use of the**

3 **term "multimer" referring to a protein; correct?**

4 A That's correct.

5 **Q Do you have any similar examples of the use**

6 **of the word "multimer" in which it is referring to a**

7 **gene?**

8 A Do I have any. You mean, did I put any in my

9 report or can I think of any?

10 **Q Both.**

11 A I didn't put that into my report.

12 Back to Dressler's lab. After working with

13 this antibody project, the other one ongoing in the

14 lab that I joined was looking at recombination

15 between plasmids. This is not in vitro

16 recombination the way Cohen & Boyer is, but natural

17 recombination.

18 And if you think about it, if a plasmid is

19 two circles and two circles recombine -- for the

20 audio record, I'm making two circles with my

21 fingers. If they recombine, you get one big circle,

22 and we would call those "multimers." They could be

23 the size of two little circles or three little

24 circles or four little circles. So that was a

25 usage, but, again, that's not repeated genes.

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1 "Multimer" is an English word, and in

2 biochemistry it has the specific meaning about

3 proteins with multiple subunits, or I may have

4 quoted the Oxford English dictionary. There was a

5 specific technical meaning. Usually refers to that.

6 **Q Is it your understanding that "multimer"**

7 **usually refers to multiples of the same gene?**

8 A Multi- -- sorry. Multi- -- "multimer"

9 refers to multiples of?

10 **Q The same gene.**

11 A In this case, it would be the same protein

12 or -- I'm confused by the question. Maybe we should

13 try it again.

14 **Q My question is whether it is your**

15 **understanding that "multimer" usually refers to**

16 **multiples of the same gene.**

17 A No. "Multimer" refers to multiples of the

18 same protein subunit.

19 **Q Could you turn to page 19?**

20 A Yes.

21 **Q Paragraph 57?**

22 A Yes.

23 **Q You note in here that the Bujard patent**

24 **inventors themselves -- well, strike that, because**

25 **there's a -- the reference will not be clear.**

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1 **Beginning a little higher up:**

2 "A person of ordinary skill in the

3 art would have known in 1983 that

4 antibodies are assembled from

5 multiple, discrete polypeptides

6 (four - two heavy chains and two

7 light chains) encoded for by two

8 different genes. The Bujard patent

9 inventors themselves recognized this

10 when they identified the structure

11 of each type of immunoglobulin that

12 can be produced according to their

13 method. For instance, they

14 recognized that IgG has the

15 molecular formula of gamma 2 kappa 2

16 and gamma 2 lambda 2 (two heavy

17 chains and two light chains)."

18 **Do you see that?**

19 A Yes.

20 **Q Turning to Bujard, you were referring to**

21 **column 5?**

22 A Yes.

23 **Q If you could turn back to column 4, do you**

24 **see, at column 4, line 35, in the same list of**

25 **proteins, "immunoglobulins, e.g., IgA, IgD, IgE, IgG**

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1 **and IgM and fragments thereof"?**

2 A Yes.

3 **Q You would agree that Bujard lists the**

4 **different types of antibodies twice?**

5 A He lists them here, and then he lists them in

6 column 5, yes.

7 **Q In column 5, he lists them with their**

8 **molecular formula?**

9 A Yes.

10 **Q In column 4, he does not list them with their**

11 **molecular formula?**

12 A Gives just their name, yes.

13 **Q What do you make of the fact that Bujard**

14 **lists the different types of antibodies twice?**

15 MR. McCORMICK: Objection; foundation.

16 THE WITNESS: Well, he's giving a kind of --

17 he's just being redundant. He's giving a kind of

18 paragraph list, and then he's taking more care and

19 listing things one by one, one protein per line --

20 or per several lines, but he's saying the same thing

21 for antibodies.

22 BY MS. DAVIS:

23 **Q Do you --**

24 A And also -- I'm sor- -- sorry to interrupt --

25 I notice, at the top, he says "and fragments

<p style="text-align: right;">Page 150</p> <p>1 thereof." So this is a more -- sorry.</p> <p>2 In column 4, after IgA, 'D, 'E, 'G, and</p> <p>3 fragments thereof, so this is a kind of summary in</p> <p>4 one line. And then he spells it out in two lines:</p> <p>5 immunoglobulin G, IgG, or gamma G-globulin,</p> <p>6 molecular formula, like that. So summary -- summary</p> <p>7 statement and then a verbose statement.</p> <p>8 Q You mentioned the antibody fragments are</p> <p>9 mentioned.</p> <p>10 A Yes.</p> <p>11 Q Does Bujard describe what is meant by</p> <p>12 "fragments of immunoglobulins"?</p> <p>13 A I don't recall if he has a description</p> <p>14 outside that statement. I don't know that he has a</p> <p>15 specific description.</p> <p>16 Q In 1983, would it -- strike that.</p> <p>17 An IgG antibody can be conceived of as having</p> <p>18 three fragments; is that fair?</p> <p>19 A Three fragments?</p> <p>20 Q Yes.</p> <p>21 A I'm just trying to count them. You are</p> <p>22 thinking Fv fragments, FAB fragments. There's an</p> <p>23 Fd fragment. Several fragments, yes.</p> <p>24 Q An IgG antibody can be broken into two fab</p> <p>25 fragments and one Fc fragment; is that correct?</p>	<p style="text-align: right;">Page 152</p> <p>1 Peak B were the same thing, and he couldn't figure</p> <p>2 out what the difference was, so he started calling</p> <p>3 them FAB, and I thought this was just some weird</p> <p>4 story until I did it myself, and I got three peaks</p> <p>5 off a column, and I ran one and it split into two</p> <p>6 more peaks.</p> <p>7 But Fc, I know what you mean.</p> <p>8 Q That was in Dr. Milstein's lab?</p> <p>9 A I -- that was after I left his lab, and I was</p> <p>10 at Fred Hutchinson when I did that experiment, with</p> <p>11 a very modern HPLC column, and it still split into</p> <p>12 three peaks.</p> <p>13 Q The Fc fragment of an IgG antibody is</p> <p>14 composed entirely of heavy chain; is that correct?</p> <p>15 A That's correct.</p> <p>16 Q It's the second and third constant domains of</p> <p>17 the heavy chain joined to each other?</p> <p>18 A That's correct.</p> <p>19 Q There's no light chain in the Fc fragment;</p> <p>20 correct?</p> <p>21 A That's correct.</p> <p>22 Q Do you have an opinion as to whether an Fc</p> <p>23 fragment would be included in the fragments thereof</p> <p>24 that Bujard describes as being a protein that could</p> <p>25 be produced by this method?</p>
<p style="text-align: right;">Page 151</p> <p>1 A That's right, yes.</p> <p>2 Q Would it have been known, in 1983, that an</p> <p>3 IgG antibody could be broken into two fab fragments</p> <p>4 and one Fc fragment?</p> <p>5 A Yes.</p> <p>6 Q The Fc fragment, that's the fraction</p> <p>7 crystallizable fragment?</p> <p>8 A That's the common knowledge, but I don't</p> <p>9 think that's what it stands for.</p> <p>10 Q What -- what do you think it stands for?</p> <p>11 A Milstein told me this story. His very close</p> <p>12 friend -- his closest friend, Rodney Porter, is the</p> <p>13 one who did this fractionation, and in undergraduate</p> <p>14 courses, you hear FAB stands for fragment antigen</p> <p>15 binding, and Fc stands for fraction crystallizable,</p> <p>16 or fragment crystallizable.</p> <p>17 But this wasn't true; that Porter did these</p> <p>18 digestions of IgG with proteolytic enzymes, and he</p> <p>19 would run them on chromatography columns, and he</p> <p>20 would elude peaks off these columns, and he got one</p> <p>21 peak, two peaks, three peaks, and he called them</p> <p>22 Peak A, Peak B, and Peak C.</p> <p>23 And then, later, he took Peak A, thinking it</p> <p>24 was different from Peak B, and he ran it again, and</p> <p>25 he got two peaks again, and he found that Peak A and</p>	<p style="text-align: right;">Page 153</p> <p>1 A Right. In his verbose list, he doesn't -- he</p> <p>2 doesn't mention Fc, so it's ambiguous. In the short</p> <p>3 summary list, he says "fragments," and Fc was</p> <p>4 certainly a -- a well-known fragment. For that</p> <p>5 reason, I would be inclined to believe that an Fc</p> <p>6 would be produced by his method.</p> <p>7 Q Do you believe that Bujard anticipates the</p> <p>8 production of an IgA or an IgM antibody?</p> <p>9 MR. McCORMICK: Objection.</p> <p>10 THE WITNESS: Yes. He says this can be used</p> <p>11 to make IgA or IgM.</p> <p>12 BY MS. DAVIS:</p> <p>13 Q To your mind, is there any difference in how</p> <p>14 a person of ordinary skill in the art, in 1983,</p> <p>15 would go about producing an IgA or an IgM as opposed</p> <p>16 to an IgG antibody, according to the method of</p> <p>17 Bujard?</p> <p>18 A Well, these have an extra chain that ties the</p> <p>19 end of the heavy chains together, the J chain, most</p> <p>20 well known for IgM. But you can still make IgAs</p> <p>21 lacking a J chain, and they assemble.</p> <p>22 Q How about -- oh, please finish your answer.</p> <p>23 A Yeah. And they are considered IgAs.</p> <p>24 Q How about IgM; do you believe a person of</p> <p>25 ordinary skill in the art would have been able to</p>

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1 **make an IgM antibody, according to the method of**
 2 **Bujard, prior to 1983?**
 3 A IgM could have been made. Again, he -- you
 4 know, he gives the subunit substructure and doesn't
 5 mention the J chain, but could be made.
 6 **Q Could you make an IgM without a J chain?**
 7 A Well, you could certainly make the
 8 polypeptides inside a cell, and you could probably
 9 assemble them either in the cell or by in vitro
 10 methods.
 11 **Q In the answer you just gave, were you**
 12 **contemplating that the J chain would be made in a**
 13 **different cell?**
 14 A No. I mean, you could make it without having
 15 the gene for the J chain there.
 16 **Q Would that still be considered -- strike**
 17 **that.**
 18 **Would the end product of that still be**
 19 **considered an IgM?**
 20 A I think it would.
 21 **Q In 1983?**
 22 A Yes.
 23 MR. McCORMICK: We have been going about --
 24 MS. DAVIS: Yeah.
 25 MR. McCORMICK: -- an hour, more than one

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

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1 **Q Have you considered whether there are reasons**
 2 **a researcher might have wanted free light chain in**
 3 **1983?**
 4 A I didn't consider -- I'm considering now, but
 5 can't come up with much. They are a bit simpler
 6 than heavy chains.
 7 **Q Are you aware of any uses of free light chain**
 8 **as reagents?**
 9 A Light chains. Something called Bence Jones
 10 proteins are light-chain dimers, and those were
 11 studied for a time because they were easily obtained
 12 from cancer patients.
 13 **Q Are you familiar with any other instances in**
 14 **which -- well, strike that.**
 15 **A light-chain dimer is two light chains;**
 16 **correct?**
 17 A That's correct.
 18 **Q Are you familiar with any other instances of**
 19 **light-chain dimers being intentionally produced?**
 20 A I can't think of any.
 21 **Q In paragraph 59, you say:**
 22 **"In short, the inclusion of**
 23 **immunoglobulins (as well as the**
 24 **other multi-subunit proteins**
 25 **mentioned above) as an exemplar**

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1 **protein that could be produced by**
 2 **the Bujard method would have**
 3 **indicated to one ordinarily skilled**
 4 **in the art that the plasmid vehicle**
 5 **could, and necessarily must in the**
 6 **case of immunoglobulins, contain**
 7 **more than one foreign gene -- one**
 8 **each for the heavy and light**
 9 **chains."**
 10 **Do you see that?**
 11 A Yes.
 12 **Q You say must contain the genes for the heavy**
 13 **and light chains in the case of an antibody; is that**
 14 **correct?**
 15 A "Necessarily must," yes.
 16 **Q What is the basis for saying that if you were**
 17 **producing an antibody by the Bujard method, you must**
 18 **include both the heavy and light chain gene in the**
 19 **same plasmid?**
 20 A Well, that comes from the previous paragraph;
 21 that just reading through Bujard for -- reading that
 22 list, I would see, oh, free light chains, but -- but
 23 here he doesn't say free heavy chains. I can't find
 24 it anywhere. So that, to me, as someone skilled in
 25 the art reading that in 1983 would think, oh, well,

<p style="text-align: right;">Page 158</p> <p>1 there must be something wrong with making free heavy 2 chains, so I'll make them together; I won't try to 3 make them separately and later recombine them. 4 Q Is free light chain considered a contaminant? 5 A A contaminant of? 6 Q In an antibody production. If you were 7 producing antibodies, do you sometimes end up with 8 free light chain? 9 MR. McCORMICK: Objection; incomplete 10 hypothetical. 11 THE WITNESS: Not usually. I haven't had 12 that problem. 13 BY MS. DAVIS: 14 Q A minute ago you had said that the reason -- 15 your basis for saying necessarily must include both 16 a heavy and light chain is the absence of an entry 17 for free heavy chain -- 18 A That's right. 19 Q -- correct? 20 Do you have any other basis for saying that 21 when producing an antibody by the method of Bujard, 22 one of skill in the art necessarily must include the 23 heavy and light chain in the same cell? 24 A No. I'm referring to that argument right 25 there.</p>	<p style="text-align: right;">Page 160</p> <p>1 Q If Bujard had said free heavy chain but did 2 not list light chain, would your opinion be the 3 same? 4 A If he listed free heavy chain but not free 5 light chain, that would suggest to me, just from 6 this patent alone, that it might be hard to make 7 light chains by his method, and that would make me 8 more inclined to try and express them together, the 9 two chains. 10 Q Do you interpret the Bujard patent to be 11 suggesting that it is difficult to make heavy chains 12 alone? 13 A There's a suggestion there by its absence in 14 that list, yes. 15 Q How, if at all, do you reconcile that with 16 the fact that Bujard contemplates producing 17 fragments of antibodies which could include the 18 all-heavy-chain Fc fragment? 19 A Well, he doesn't list the Fc would make me 20 think again about whether he meant to include that, 21 but also, the Fc is not a heavy chain, it's a 22 smaller part. Maybe it's okay to make Fc. 23 Q Is it, in fact, true that it is harder to 24 make a heavy chain than it is to make a light chain? 25 A There's some lore that it's harder, and there</p>
<p style="text-align: right;">Page 159</p> <p>1 Q You agree that an antibody could be produced 2 by the method of Bujard by way of having the heavy 3 chain in one cell, the light chain in another cell, 4 followed by in vitro reconstitution? 5 A I think it could; although, Bujard seems to 6 be warning me not to try to produce heavy chains. 7 Q You said -- oh, please finish. 8 A He didn't -- that's right. I might try 9 anyway, but that would be a disincentive for me to 10 try producing heavy chains separately. A 11 disincentive doesn't mean it absolutely won't work. 12 Q You said you might try it anyway. 13 A Yes. 14 Q Why might you try that? 15 A Well, if I needed to make an antibody, I 16 would probably try making the two chains together, 17 but as I said before, it's a disincentive but not an 18 absolute prohibition, so I have to make the heavy 19 chain some way, and this would direct me to make it 20 together with the light chain in the same cell. 21 Q Do you have any opinion as to why, in your 22 view, the -- Bujard chose to express this concept by 23 listing light chain but not listing heavy chain as 24 opposed to vice versa? 25 A I don't know what was in his mind.</p>	<p style="text-align: right;">Page 161</p> <p>1 was this precedent of finding a lot of these Bence 2 Jones proteins in cancer patients, because it would 3 come out in the urine. That's how it would be 4 isolated. 5 My old professor talked about being in 6 Wisconsin where it was so cold all the time. You 7 could just take the stuff and -- the urine and leave 8 it on the roof, and the next day you would have your 9 Bence Jones protein. 10 So there was more experience with light-chain 11 dimers. 12 Q The potential difficulty with producing heavy 13 chain, how, if at all, in your opinion, is that 14 overcome by producing it in the same cell with a 15 light chain? 16 A In -- I don't think that gets you much of 17 advantage, unless -- if they are made as separate 18 polypeptides -- let's say in E. coli -- and they're 19 not assembled, I don't think that buys you much 20 advantage. If you could get to the stage of an 21 assembled immunoglobulin, an IgG in assembled 22 immunoglobulin tends to be very stable. It's not 23 necessarily true of a isolated heavy chain. 24 Q Is it your opinion that in vivo -- well, 25 strike that.</p>

41 (Pages 158 to 161)

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

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

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1 **1983; correct?**
 2 MR. McCORMICK: Objection; incomplete
 3 hypothetical.
 4 THE WITNESS: I believe a person skilled in
 5 the art could.
 6 BY MS. DAVIS:
 7 **Q If that person proceeded to make the heavy**
 8 **chain in one cell and the light chain in another**
 9 **cell and then combined those two chains to make an**
 10 **antibody, would you expect to refer to the**
 11 **constituent heavy and light chains as "free light**
 12 **chains" and "free heavy chains"?**
 13 A Free light chains and free heavy chains.
 14 That would be -- you could call them that.
 15 **Q In your experience, does "free light chain"**
 16 **more commonly refer to light chain that will not go**
 17 **on to be combined with heavy chain to form an**
 18 **antibody?**
 19 A In my experience, free light chain can --
 20 well, this is outside of the Bujard patent, but free
 21 light chain, by itself, when it associates with
 22 itself, can associate with itself as a dimer, and
 23 that structure is fairly stable.
 24 **Q Are you familiar with any uses of the term**
 25 **"free light chain" other than in the Bujard patent?**

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1 A I don't have specific instances, but it --
 2 it's a commonly understood term. It's a -- I
 3 wouldn't call it straight English, but it's common
 4 parlance in biochemistry.
 5 **Q Is it your understanding that, in common**
 6 **parlance, it is acceptable to refer to a light chain**
 7 **that is then joined with a heavy chain to form an**
 8 **antibody as a free light chain?**
 9 A A free light chain that's joined with a heavy
 10 chain is not -- no longer a free light chain.
 11 **Q Could you turn to page -- strike that.**
 12 **Could you turn to page 22.**
 13 A Yes.
 14 **Q There is a section on Riggs & Itakura?**
 15 A Yes.
 16 **Q So my question is about the carry-over**
 17 **sentence, and you say that Dr. Riggs and Dr. Itakura**
 18 **were among the first scientists to use recombinant**
 19 **DNA technology and synthetic DNA to express**
 20 **mammalian polypeptides in bacteria.**
 21 **Do you see that?**
 22 A Yes.
 23 **Q Is that correct?**
 24 A Yes. They were leaders, yes.
 25 **Q What is the significance of being among the**

<p style="text-align: right;">Page 166</p> <p>1 first scientists to express a mammalian polypeptide 2 in bacteria?</p> <p>3 A The significance? Oh, just, in general, it's 4 a good thing to be first, to be first than to be 5 second.</p> <p>6 Q Why is it significant that they were among 7 the first to express a mammalian polypeptide in 8 bacteria?</p> <p>9 MR. McCORMICK: Objection; foundation. 10 THE WITNESS: Is it significant. This is 11 just a kind of benign compliment. There's no deeper 12 meaning to that. I'm showing that these are leaders 13 in the field who have written this article that I'm 14 going to quote from.</p> <p>15 BY MS. DAVIS:</p> <p>16 Q Prior to the work of Dr. Riggs and 17 Dr. Itakura, scientists had expressed bacterial 18 proteins in bacteria; fair?</p> <p>19 A Yes.</p> <p>20 Q And Dr. Riggs and Dr. Itakura are among the 21 first to express a mammalian protein in bacteria; 22 correct?</p> <p>23 A That's right.</p> <p>24 Q What significance, if any, do you ascribe to 25 the mammalian aspect of their work?</p>	<p style="text-align: right;">Page 168</p> <p>1 For example, when my group in Berkeley cloned 2 that ATCase gene, they didn't even take it from a 3 bacterium, they took it from a bacteria-phage. So 4 it represented much of -- a fair amount of -- a 5 significant amount of that bacteria-phage was the 6 gene of interest, so they had to separate it from a 7 much smaller mass than if they had to take that from 8 a huge eukaryotic genome. So there was a technical 9 triumph to expressing mammalian genes in bacteria, 10 having to do with isolation of the gene itself, not 11 really that the proteins were too different.</p> <p>12 Q In this paragraph, you describe the -- the 13 insulin production process at a high-level; is that 14 correct?</p> <p>15 A Yes.</p> <p>16 Q You agree that Dr. Riggs and Dr. Itakura used 17 separate cells for each of the two insulin chains?</p> <p>18 A Separate transformation of E. coli cells, 19 yes.</p> <p>20 Q Was that a significant result?</p> <p>21 MR. McCORMICK: Objection. 22 THE WITNESS: Significant. Not really. That 23 seems like the easiest way to do it.</p> <p>24 BY MS. DAVIS:</p> <p>25 Q Do you remember hearing about Dr. Riggs and</p>
<p style="text-align: right;">Page 167</p> <p>1 A The fact that it was mammalian -- nothing 2 really special. They weren't even the first. I 3 mean, Gilbert expressed insulin in bacteria before 4 them. It just happened to be red insulin.</p> <p>5 Q Not specific to Dr. Riggs and Itakura, but 6 with respect to the scientists who first expressed a 7 mammalian protein in bacteria, what significance, if 8 any, do you ascribe to their success in expressing a 9 mammalian protein in bacteria as opposed to a 10 bacterial protein in bacteria?</p> <p>11 A I think, at the time, it showed that -- well, 12 there really was a universal genetic code that -- 13 you know, here you could take something from a human 14 or a mouse or a monkey or a rabbit and put it in 15 bacteria, and it would make the same protein, 16 essentially, in bacteria as was being made in the 17 higher organism.</p> <p>18 Q You believe that --</p> <p>19 A That, and there was also a -- it was, in a 20 way, kind of technical triumph in that mammalian 21 DNA, the DNA in one mammalian genome, the DNA within 22 one cell, is many, many times larger -- or longer, 23 containing more nucleotides, than in a bacterium. 24 So, in this case, they are taking a much smaller 25 part of a big mass and cloning that.</p>	<p style="text-align: right;">Page 169</p> <p>1 Dr. Itakura's work --</p> <p>2 A I do.</p> <p>3 Q -- at around the time?</p> <p>4 A I do. Very much.</p> <p>5 Q Do you remember what you thought when you 6 heard about their production of insulin?</p> <p>7 A I remember what I thought about it, because 8 it was, at that time, that I was working in the 9 Gilbert group, which was the rival, and I thought, 10 oh, Gilbert lost, and I wasn't feeling kindly to 11 him -- toward Gilbert, at that time, so it was, ah, 12 Gilbert lost, but I -- I liked the audacity of using 13 synthetic DNA.</p> <p>14 Gilbert's group had not really invested in 15 organic chemistry. They took the purely biological 16 approach of making cDNA clones, and they had gone on 17 a kind of pretentious expedition to this biohazard 18 facility in Britain to try and clone a human gene, 19 and I was -- I found that a pleasing result; that 20 Itakura is the one who gave the talk that I heard 21 that he had done it by this way. I thought, you 22 know, good for chemistry.</p> <p>23 Q Do you recall having any reaction to the -- 24 the fact that Dr. Riggs and Dr. Itakura put each of 25 the two insulin chains in separate cells?</p>

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

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

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1 **When two or more genes of interest**
 2 **are present in this region, the**
 3 **insertion of one or more regulatory**
 4 **signals before each gene will result**
 5 **in expression of both gene and**
 6 **separate production of the**
 7 **encoded-for polypeptide."**
 8 **Do you see that?**
 9 A Yes.
 10 **Q Is it always true that when you have two or**
 11 **more genes of interest in the coding region with one**
 12 **or more regulatory signals before each gene, you**
 13 **will achieve expression of both genes and separate**
 14 **production of the encoded-for polypeptide?**
 15 A If they are appropriate signals and
 16 regulatory sequences, yes.
 17 **Q What would you need to know in order to**
 18 **figure out what would be the appropriate signals and**
 19 **regulatory sequences?**
 20 A Well, let's say I was making one of these
 21 intercistronic constructs. I would like to know
 22 that the region between the two polypeptide genes
 23 would include this ribosome restart site.
 24 At the upstream end, I would want to know
 25 that the promoter is going to be functional in that

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1 particular cell type.
 2 **Q In 1983, do you believe a person of ordinary**
 3 **skill in the art would have been able to select**
 4 **appropriate promoters for use in expressing the**
 5 **antibody heavy and light chain gene?**
 6 A Yes.
 7 MR. McCORMICK: Objection.
 8 BY MS. DAVIS:
 9 **Q What types of promoters do you believe a**
 10 **person of ordinary skill in the art could have**
 11 **selected in 1983 to express antibody heavy and light**
 12 **chain genes?**
 13 A Are these --
 14 MR. McCORMICK: Same objection.
 15 Go ahead.
 16 THE WITNESS: Are these using Bujard's
 17 method?
 18 MS. DAVIS: Yes, using Bujard's method.
 19 THE WITNESS: Well, could use some of the
 20 genes that Bujard himself found from the T5 page.
 21 One could use lack promoters. There have been quite
 22 a few promoters active in E. coli identified by
 23 then.
 24 BY MS. DAVIS:
 25 **Q Would a lack promoter work to express an**

<p style="text-align: right;">Page 174</p> <p>1 antibody heavy or light chain gene? 2 A I think it could be used to do that. 3 Q Could you turn to page 29. 4 A 29, yes. 5 Q And so on page 29, you have a section 6 entitled "Obviousness of Asserted Claim 33 in the 7 Cabilly II Patent." 8 A Yes. 9 Q This section addresses obviousness. 10 A Yes. 11 Q Paragraph 84 on the next page, are you there? 12 A Yes. 13 Q You state: "Cohen & Boyer and Riggs & 14 Itakura" -- strike that. 15 You say: 16 "Cohen & Boyer and Riggs & Itakura 17 are all publications in the same 18 general field of research: the 19 production of eukaryotic proteins in 20 heterologous host cell systems, 21 specifically microorganisms." 22 Do you see that? 23 A Yes. 24 Q What is the significance to your analysis 25 that Cohen & Boyer and Riggs & Itakura are in the</p>	<p style="text-align: right;">Page 176</p> <p>1 arguments that certain claims of Cabilly II were 2 invalid for obviousness-type double patenting? 3 A I believe I did see that. 4 Q Do you know what the resolution of that issue 5 was? 6 A The patent was issued, so they must have 7 decided against it. 8 Q Did you consider the arguments made in 9 connection with the -- in the file history regarding 10 the obviousness-type double-patenting argument 11 raised with respect to Cabilly II? 12 A I'm sorry. Was -- 13 Q Let me rephrase. 14 A Yeah. 15 Q In conducting your analysis of whether 16 Cabilly III is invalid for obviousness-type double 17 patenting, did you examine the arguments that were 18 rejected by the Patent Office with respect to 19 Cabilly II? 20 A I -- I did have a look, but I don't really 21 remember what they are as we sit here, and mostly my 22 analysis was -- rested on looking at this Cabilly 23 claim -- or this claim 2 from Cabilly I and the 24 Cabilly II and III in light of Cohen & Boyer and 25 Bujard, and Mr. McCormick explained the concept of</p>
<p style="text-align: right;">Page 175</p> <p>1 field of the production of eukaryotic proteins in 2 heterologous host cell systems? 3 A The significance of that? Common goals. 4 Q Is that the field in which you believe a 5 person of ordinary skill in the art in 1983 faced 6 with the problem of producing a recombinant 7 antibody, the field in which that person would be 8 looking to? 9 A Yes. 10 Q Could you turn to page 32. 11 Page 32 you have a heading "Invalidity of the 12 Asserted Claims of the Cabilly III Patent under 13 ODP"; correct? 14 A Yes. Uh-huh. 15 Q As discussed earlier, that's obviousness-type 16 double patenting? 17 A Yes. 18 Q For purposes of your opinion that certain 19 claims of Cabilly III are invalid for 20 obviousness-type double patenting, did you consider 21 the Cabilly II file history? 22 A I looked at the file history here and there. 23 I didn't master it, so it didn't enter tremendously 24 into my analysis. 25 Q Are you aware that the PTO considered</p>	<p style="text-align: right;">Page 177</p> <p>1 obvious-type double patenting. That's mostly 2 where -- that's where most of my information came 3 from to reach this conclusion, this opinion. 4 Q Did you compare the arguments that you are 5 making with respect to double patenting of 6 Cabilly III to the arguments made before the PTO 7 about the alleged obviousness-type double patenting 8 of Cabilly II? 9 A I didn't compare. I didn't write my piece 10 and then go back and compare. I did -- again, 11 vaguely looked at the old file history, but I 12 wouldn't say that it was influential. 13 Q Do you know whether the PTO considered, in 14 connection with Cabilly II, combinations of a claim 15 of Cabilly I with particular art references? 16 A I don't recall what they put together. My 17 recollection of the action between your client and 18 the PTO is very vague. 19 Q Do you know what art references had been 20 combined with Cabilly I claims in the context of the 21 Cabilly II ODP arguments? 22 A I don't recall, no. 23 Q Do you know whether any of the arguments that 24 you are making with respect to the alleged double 25 patenting of Cabilly III are similar to the</p>

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1 arguments that have been raised with respect to
 2 alleged double patenting of Cabilly II?
 3 A As we sit here, I don't, offhand, know the
 4 relation of my arguments to what happened before the
 5 PTO.
 6 Q Could you turn to page 34.
 7 A Mm-hmm.
 8 Q You have a footnote on page 34.
 9 Do you see that?
 10 A Yes.
 11 Q You say in the footnote:
 12 "... once it was known that
 13 non-chimeric heavy and light chains
 14 could be successfully co-expressed
 15 (i.e., transcribed and translated)
 16 in a single host cell and that a
 17 chimeric heavy or light chain could
 18 also be successfully expressed
 19 (i.e., transcribed and translated)
 20 in a single host cell, a person of
 21 ordinary skill in the art would have
 22 been confident that chimeric heavy
 23 and light chains could be
 24 successfully co-expressed (i.e.,
 25 transcribed and translated) in a

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1 single host cell."
 2 Do you see that?
 3 A Yes.
 4 Q That statement is true?
 5 A Let me read that.
 6 Yes, and this -- this jogs my memory; that
 7 one result of the action between your client and the
 8 PTO was the emphasis that, in Cabilly I, a chimeric
 9 light chain or a chimeric heavy chain could be
 10 expressed, but not both. It was "or" not "and/or."
 11 Q Do you -- strike that.
 12 A Right.
 13 Q I -- I appreciate the clarification.
 14 A Yeah. Mm-hmm.
 15 Q I want to ask you about the statement just in
 16 isolation.
 17 A Right.
 18 Q Not necessarily --
 19 A Okay.
 20 Q -- with respect to Cabilly I.
 21 A Right.
 22 Q Do you agree with the statement you made in
 23 Footnote 10?
 24 A Right. So let me read it again.
 25 Yes, I agree with that.

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1 Q In this footnote, do you distinguish -- well,
 2 strike that.
 3 I don't see in this footnote any particular
 4 type of DNA that you are describing as being
 5 expressed, whether it be murine or rabbit or
 6 something else; is that fair?
 7 A It just says "chimeric" or "non-chimeric,"
 8 mm-hmm.
 9 Q One option for -- for chimeric DNA would be
 10 part murine, part human; is that fair?
 11 A That's -- that's chimeric.
 12 Q Did you -- do you believe the -- well, strike
 13 that.
 14 A murine-human chimeric antibody is within
 15 what you are discussing in Footnote 10?
 16 A Yes.
 17 Q What significance, if any, do you ascribe to
 18 the fact that in a murine-human chimeric antibody, a
 19 portion of the DNA is human?
 20 A What effect do I describe -- ascribe to that?
 21 MR. McCORMICK: Objection; foundation.
 22 THE WITNESS: Effect from the point of view
 23 of a molecular biologist expressing, because they
 24 will have different functions in vivo, but just in
 25 terms of expression, what effect does that have. No

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1 particular effect comes to mind.
 2 BY MS. DAVIS:
 3 Q Are human antibody heavy and light chain
 4 genes expressed in a fashion similar to murine
 5 antibody heavy and light chain genes?
 6 MR. McCORMICK: Objection; incomplete
 7 hypothetical.
 8 THE WITNESS: Do you mean in humans and in
 9 mice?
 10 MS. DAVIS: Recombinantly.
 11 THE WITNESS: Recombinantly.
 12 MR. McCORMICK: Same objection.
 13 THE WITNESS: They are expressed the same
 14 way.
 15 BY MS. DAVIS:
 16 Q Would you -- well, strike that.
 17 A Yeah.
 18 Q You say in this that once it was known that
 19 non-chimeric heavy and light chains could be
 20 successfully co-expressed and then a chimeric heavy
 21 or light chain could also be expressed, a person of
 22 ordinary skill in the art would be confident that
 23 chimeric heavy and light chains could be
 24 successfully co-expressed.
 25 And my question is: In that statement, did

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1 you have in mind a particular type of non-chimeric
 2 heavy or light chain, whether it be murine or some
 3 other type of chain?
 4 A I didn't have a particular one in mind, but
 5 most were murine at that point.
 6 Q Would a person of ordinary skill in the art,
 7 having seen a non-chimeric murine and a heavy light
 8 chain being successfully co-expressed, be confident
 9 that a human-murine chimeric heavy and light chain
 10 could be successfully co-expressed?
 11 A That is --
 12 MR. McCORMICK: Hold on.
 13 Objection; incomplete hypothetical and to the
 14 extent it's outside the scope of his expert report.
 15 THE WITNESS: So you mean a murine variable
 16 region attached to a human constant region?
 17 MS. DAVIS: Yes.
 18 THE WITNESS: Yes. There would be
 19 confident -- confidence that that could be
 20 expressed.
 21 BY MS. DAVIS:
 22 Q What would be the basis of the confidence
 23 with respect to expression of the human constant
 24 region?
 25 A The confidence is not so much positive as a

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

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

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1 expression vectors, without undue
 2 experimentation."
 3 Correct?
 4 A Correct.
 5 Q Is it your opinion that, in 1974, following
 6 the methods of Cohen & Boyer, a vector could have
 7 been created without undue experimentation that
 8 contained the antibody heavy and light chain genes?
 9 A There would have been undue experimentation
 10 to isolate those genes.
 11 Q In 1974?
 12 A In 1974.
 13 Q At what point between 1974 and 1983 do you
 14 believe that the vector containing the heavy and
 15 light chain genes could be created without undue
 16 experimentation?
 17 A Oh, I think by around 1980. What was missing
 18 in 1974 were the genes themselves. The antibody
 19 genes had never been cloned by anyone, and introns
 20 hadn't been discovered. The genomic gene structure
 21 of the antibodies was unknown at that time.
 22 That's what would have made it very hard for,
 23 you know, a second-year post-doc to do it in 1974.
 24 It would have been more possible in '80, '81, '82,
 25 '83.

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

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1 **according to Cohen & Boyer?**
 2 A Yes.
 3 **Q Would it have been possible at all to make a**
 4 **heavy chain gene and a light chain -- strike that.**
 5 **Would it have been possible at all in 1974 to**
 6 **create a single vector containing the heavy chain**
 7 **gene and the light chain gene?**
 8 A In 1974, possible at all. And leaving out
 9 the idea of undue experimentation.
 10 **Q Correct.**
 11 A I think it would have been.
 12 **Q Could you have made, in 1974, a vector**
 13 **containing the heavy chain gene and the light chain**
 14 **gene both in the form of genomic DNA?**
 15 A Genomic DNA. It would have been split into
 16 exons, and that wasn't known in 1974, and it would
 17 have -- it would have taken a genomic gene and put
 18 it into a bacterium. You wouldn't have gotten a
 19 polypeptide, so that would have prevented it. So,
 20 no, it would not have been possible with genomic.
 21 **Q Was there another option in 1974 other than**
 22 **the use of genomic DNA that would have let you put**
 23 **both a heavy chain gene and a light chain gene in a**
 24 **single vector?**
 25 A I'm thinking more of fragments thereof. That

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

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1 There may have been an expectation that genes were
 2 contiguous then, but we found out that was wrong.
 3 We found out that was wrong the first time someone
 4 sequenced an antibody gene.
 5 **Q That happened after 1974?**
 6 A That did.
 7 **Q You mentioned variable domains and constant**
 8 **domains were known in 1974.**
 9 A Yes.
 10 **Q Was the boundary between the constant domain**
 11 **and the variable domain of an antibody known in**
 12 **1974?**
 13 A Yes.
 14 **Q When did that become known, do you know?**
 15 A Oh, that was defined by protein sequencing
 16 and was known, I would say, by 1971. In 1971, Cabot
 17 published a compilation of amino acid sequences, and
 18 he got the boundaries about right.
 19 **Q You did some early work attempting to clone**
 20 **an antibody gene; correct?**
 21 A That's right.
 22 **Q That was in the late 1970s?**
 23 A 1977.
 24 **Q Did you know, at that time, the boundary**
 25 **between the variable domain and the constant domain?**

<p style="text-align: right;">Page 190</p> <p>1 A Yes.</p> <p>2 Q Do you think, essentially, everyone in the</p> <p>3 field working with antibodies knew where the</p> <p>4 boundary between the variable domain and the</p> <p>5 constant domain was?</p> <p>6 MR. McCORMICK: Objection.</p> <p>7 THE WITNESS: Yes.</p> <p>8 BY MS. DAVIS:</p> <p>9 Q Do you believe that Drs. Cohen & Boyer</p> <p>10 believed an antibody could be produced using their</p> <p>11 methods in 1974?</p> <p>12 A Yes.</p> <p>13 Q Why do you think they believed an antibody</p> <p>14 could be produced using their methods in 1974?</p> <p>15 A Even though those genes weren't -- oh,</p> <p>16 produced using their method in 1974. That's the</p> <p>17 question.</p> <p>18 I don't know what they, personally, believed.</p> <p>19 The impression I get from reading the patent is that</p> <p>20 all these problems of expressing proteins would fall</p> <p>21 into place, and they would fall into place using</p> <p>22 this method, and there will be difficulties on the</p> <p>23 way, but those will be overcome, and so I think that</p> <p>24 they believed the problem could be overcome using</p> <p>25 their method, even if there were difficulties along</p>	<p style="text-align: right;">Page 192</p> <p>1 specifications, combined with a</p> <p>2 scientific literature of the day,</p> <p>3 and the 'ordinary' experimenter's</p> <p>4 years of training, and common</p> <p>5 sense."</p> <p>6 Do you see that?</p> <p>7 A Yes.</p> <p>8 Q What scientific literature of the day did you</p> <p>9 have in mind when you wrote this sentence?</p> <p>10 A Let me read this again. One sec.</p> <p>11 And you asked about what's the relative</p> <p>12 scientific literature of the day?</p> <p>13 Q Yes.</p> <p>14 A Oh, well, that's -- literature of the day is</p> <p>15 all about the knowledge of the different antibody</p> <p>16 genes and where the pieces were.</p> <p>17 The -- the problem that Boyer & Cohen faced</p> <p>18 was that the antibody genes were kind of a black</p> <p>19 box. We didn't really know what they looked like,</p> <p>20 but, in a way, solving that was a research problem</p> <p>21 that was outside of the Cohen & Boyer method. If</p> <p>22 someone had handed Cohen & Boyer, you know,</p> <p>23 restriction fragments with heavy chain and the light</p> <p>24 chain, they could have put them in their plasmid and</p> <p>25 made antibody protein.</p>
<p style="text-align: right;">Page 191</p> <p>1 the way.</p> <p>2 Again, there hadn't -- it was at the dawn of</p> <p>3 cloning. This was the key cloning patent, but they</p> <p>4 had envisioned that these problems would be solved;</p> <p>5 you know, antibodies, nitrogen fixation,</p> <p>6 photosynthesis. Complicated things could be slotted</p> <p>7 into the -- into a restriction plasmid and would</p> <p>8 function in vivo.</p> <p>9 Q Could you turn to pages 4 and 5.</p> <p>10 A Yes.</p> <p>11 Q The paragraph 12 at the bottom of page 4?</p> <p>12 A Yes.</p> <p>13 Q You state:</p> <p>14 "... a person of ordinary skill in</p> <p>15 the art in April 1983 was able to</p> <p>16 create a vector capable of</p> <p>17 expressing both the heavy and light</p> <p>18 chain genes, including the necessary</p> <p>19 regulatory elements, without undue</p> <p>20 experimentation. Although a</p> <p>21 step-by-step methodology for</p> <p>22 creating this vector is not</p> <p>23 explicitly recited in the prior art</p> <p>24 patents, a workable route could be</p> <p>25 devised from a reading of the patent</p>	<p style="text-align: right;">Page 193</p> <p>1 By 1983, all those problems had been cleared</p> <p>2 up. We had ways of making antibodies with</p> <p>3 predetermined specificity. Milstein had done that.</p> <p>4 Human and mouse constant region genes had been</p> <p>5 cloned. We knew about the gene rearrangements.</p> <p>6 So all that scientific knowledge that had</p> <p>7 accumulated made the problem much easier.</p> <p>8 Q Are there any specific pieces of literature</p> <p>9 that you have in mind by name that you were</p> <p>10 referring to in this sentence regarding the</p> <p>11 scientific literature of the day?</p> <p>12 A Oh, well, the -- we can start with the genes,</p> <p>13 per se, from the -- from the -- for the constant</p> <p>14 regions. Those were known in '83.</p> <p>15 Q Is there a particular reference you have in</p> <p>16 mind that you would look to for the constant region</p> <p>17 genes of an antibody?</p> <p>18 A Well, I think Phil Leder may have been the</p> <p>19 first one to clone a human kappa gene. That might</p> <p>20 have -- I think that was published by 1983. That's</p> <p>21 where I got mine from.</p> <p>22 Leroy Hood had papers on constant region</p> <p>23 genes. Hanjo, Japanese group, had papers on</p> <p>24 constant region genes. Those are some.</p> <p>25 Q Is there any other literature that you have</p>

49 (Pages 190 to 193)

<p style="text-align: right;">Page 194</p> <p>1 in mind by name that you were referring to in the 2 sentence regarding the scientific literature of the 3 day? 4 A Papers by Tamagawa showing the rearrangement 5 of variable and constant region genes during 6 formation of a lymphocyte. 7 Q Anything else? 8 A Those are what spring to mind. 9 Q Continuing on in that paragraph, you have a 10 list of -- of techniques that you opine would have 11 been within the skill set of the ordinarily skilled 12 genetic engineer. 13 Do you see that? 14 A Oh, yes. Uh-huh. 15 Q In addition to the techniques that you have 16 listed here, would you have needed to incorporate 17 into the vector features to control the proper ratio 18 of the amounts of each immunoglobulin chain? 19 MR. McCORMICK: Objection. 20 THE WITNESS: That's more like fine-tuning. 21 That's more optimization rather than creating an 22 antibody in the first place. 23 BY MS. DAVIS: 24 Q Was controlling the ratio the amount of each 25 immunoglobulin chain critical to being able to</p>	<p style="text-align: right;">Page 196</p> <p>1 certain papers on the subject of the ATCase protein. 2 A That's right. 3 Q You are not arguing that these references 4 anticipate the claims of the Cabilly II or 5 Cabilly III patents; correct? 6 A That's right. I'm not using them as prior 7 art. 8 Q You are not using them for either 9 anticipation -- 10 A Right, for anticipation, yes. 11 Q Are -- you are also not using these 12 references in combination with other references to 13 argue that any claim in Cabilly II or Cabilly III is 14 obvious; correct? 15 A That's right. 16 Q When did you become aware of the ATCase 17 papers that are listed in paragraph 20? 18 A Papers. So the thesis, when it was written, 19 that was someone in the lab. The paper Pauza, 20 et al., before it was published, it's very similar 21 to the thesis. 22 The other papers, Wild, et al., Roof, 23 Turnbough, I became aware of when they were 24 published, or sometime slightly before. Let's just 25 say when they were published. I don't -- yeah.</p>
<p style="text-align: right;">Page 195</p> <p>1 create a functional antibody in 1983? 2 A I don't think it was critical. I wouldn't 3 say so, no. 4 Q You would expect to get some antibody 5 regardless of whether you controlled the ratio of 6 the amounts of each immunoglobulin chain? 7 A Yes. 8 MR. McCORMICK: Objection. 9 BY MS. DAVIS: 10 Q Could you turn to page 6. 11 MR. McCORMICK: Are we at a good breaking 12 point? 13 MS. DAVIS: Sure. 14 MR. McCORMICK: We have been going about an 15 hour and ten. 16 THE WITNESS: Yeah. 17 THE VIDEOGRAPHER: Off the record at 3:52. 18 (Recess taken.) 19 THE VIDEOGRAPHER: Back on the record at 20 4:07. 21 BY MS. DAVIS: 22 Q Dr. Foote, could you turn to page 9 of your 23 rebuttal report, which is Exhibit 2. 24 A Yes. 25 Q In paragraph 20 on page 9, you refer to</p>	<p style="text-align: right;">Page 197</p> <p>1 MS. DAVIS: Let me mark, as the next exhibit, 2 the PNAS Pauza paper. 3 (Exhibit 8 was marked for 4 identification by the Reporter.) 5 MS. DAVIS: For the record, Exhibit 8 6 is -- strike that. 7 Exhibit 8 I'm handing to you. 8 THE WITNESS: Thank you. 9 MS. DAVIS: And for the record, Exhibit 8 is 10 a PNAS paper, cites 79, 4020 through 4024. 11 Q Do you have that? 12 A Yes. 13 Q This is the PNAS Pauza paper referred to in 14 your paragraph 20? 15 A Yes. 16 Q The title of the paper, "Genes encoding 17 E. coli aspartate transcarbamoylase: The pyrB-pyrI 18 operon." 19 A "pyrB-pyrI operon." 20 Q The genes encoding the ATCase, these are 21 bacterial genes? 22 A They are. 23 Q In this particular work, there are references 24 to E. coli genes and Salmonella genes; is that 25 correct?</p>

50 (Pages 194 to 197)

<p style="text-align: right;">Page 198</p> <p>1 A In this work, yes. Are there? And 2 Salmonella?</p> <p>3 Q My first question to you is -- 4 A Yes.</p> <p>5 Q -- are the gene -- the ATCase gene that 6 the -- that Pauza was working with, are those -- 7 A E. coli.</p> <p>8 Q E. coli? 9 A Yes.</p> <p>10 Q What host cell are they being expressed in? 11 A Let's see. 12 I think mostly they were expressed in 13 E. coli. At some point they were -- people in the 14 lab also expressed them in Salmonella. Was it this 15 paper or a later paper? I -- I think I mention that 16 in my report, but let's see. 17 No, it should be in here. Oh, you wanted me 18 to find that; is that right, or --</p> <p>19 Q We don't have to find the specific reference. 20 A Yeah.</p> <p>21 Q It's your recollection that the ATCase genes 22 were expressed in Salmonella? 23 A Yes.</p> <p>24 Q Salmonella is a bacteria? 25 A That's right.</p>	<p style="text-align: right;">Page 200</p> <p>1 regulation. Others in the lab were interested in 2 protein expression.</p> <p>3 Q Is the focus of the Pauza paper gene 4 regulation? 5 A It is, yes.</p> <p>6 Q You would agree that the Pauza paper that is 7 Exhibit 8 is not in the field of the expression of 8 eukaryotic genes? 9 A It's -- doesn't concern eukaryotic genes; 10 that's right.</p> <p>11 Q As we discussed earlier, the ATCase gene is 12 an operon? 13 A pyrB-pyrI operon, yes.</p> <p>14 Q The genes are contiguous to one another? 15 A They are.</p> <p>16 Q They are, therefore, necessarily on the same 17 chromosome? 18 A They are.</p> <p>19 Q The heavy chain gene of an antibody and the 20 light chain gene of an antibody are on different 21 chromosomes; correct? 22 A That's correct.</p> <p>23 Q You said that -- that E. coli ATCase or -- 24 was expressed in Salmonella; correct? 25 A Yes.</p>
<p style="text-align: right;">Page 199</p> <p>1 Q So this work is the expression of a bacterial 2 gene in a bacteria? 3 A That's right.</p> <p>4 Q Do you know the percentage of homology 5 between E. coli and Salmonella? 6 A Not offhand, no.</p> <p>7 Q Do you have any guess as to the degree of 8 homology? 9 A The homology, no. The number that sticks in 10 mind is that there are about -- they diverged in 11 evolution a hundred million years ago.</p> <p>12 Q How closely related are E. coli and 13 Salmonella for purposes of using the two as host 14 cells? 15 MR. McCORMICK: Objection; foundation. 16 THE WITNESS: Well, let's see. I'm trying to 17 remember the hierarchy. They might be the same 18 class or order, not the same genus, obviously. But 19 the E. coli genes were expressed in Salmonella, 20 though. They -- so the control sequences, which 21 were also from E. coli, worked in Salmonella. 22 BY MS. DAVIS: 23 Q Would you agree that the goal of the Pauza 24 work was not protein synthesis? 25 A Pauza himself was interested in gene</p>	<p style="text-align: right;">Page 201</p> <p>1 Q Salmonella itself expresses ATCase; correct? 2 A Its own, yes.</p> <p>3 Q ATCase is a protein that is naturally 4 expressed in Salmonella? 5 A That's right.</p> <p>6 Q Do you consider the expression of E. coli 7 ATCase in Salmonella to be the expression of a 8 heterologous protein? 9 A Yes.</p> <p>10 Q Why is that? 11 A It's a different species.</p> <p>12 Q Do you consider there to be any significance 13 to the fact that Salmonella expresses ATCase on its 14 own? 15 A We all -- you and I express ATCase.</p> <p>16 Q Does it make it easier to have Salmonella 17 express E. coli ATCase that Salmonella itself 18 expresses ATCase? 19 MR. McCORMICK: Objection. 20 THE WITNESS: It's not so much that 21 Salmonella expresses ATCase, it's that the control 22 signals from the E. coli gene are active in 23 Salmonella. 24 BY MS. DAVIS: 25 Q Why are the control signals from the E. coli</p>

51 (Pages 198 to 201)

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1 **gene active in Salmonella?**
 2 A Why are they. I would have to speculate on
 3 that. I would guess they are -- they have some
 4 similarity to signals in Salmonella.
 5 **Q Could you turn to page 10 of your rebuttal**
 6 **report.**
 7 A Yes.
 8 **Q You discuss, in paragraph 22, the size of the**
 9 **ATCase protein; correct?**
 10 A Correct.
 11 **Q It is -- strike that.**
 12 **In the first sentence, you take issue with**
 13 **Dr. Fiddes' statement that the size and complexity**
 14 **of an intact antibody was a significant advance in**
 15 **the art?**
 16 A Sorry. Please repeat the --
 17 **Q Sure.**
 18 A Yeah. In the size --
 19 **Q In paragraph 52 --**
 20 A Yes.
 21 **Q -- you are taking issue with Dr. Fiddes'**
 22 **statement regarding the size and complexity of an**
 23 **antibody --**
 24 A Yes.
 25 **Q -- reflecting a significant advance in**

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

Page 204

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

Page 205

1 **translation."**
 2 **Do you see that?**
 3 A Yes.
 4 **Q Do you agree with Dr. Skerra that, by April**
 5 **of 1983, many heterologous proteins were being**
 6 **expressed as fusion proteins?**
 7 A I don't know enough about expression of
 8 fusion proteins. I haven't studied that issue.
 9 **Q Dr. Skerra states:**
 10 **"... fusion proteins are often more**
 11 **stable in bacteria than the native**
 12 **eukaryotic protein."**
 13 **Do you see that?**
 14 A I see that.
 15 **Q Do you agree with that statement?**
 16 A Again, my -- I haven't studied that. I don't
 17 know enough to agree or disagree.
 18 **Q Could you turn to page 14, paragraph 49.**
 19 **Are you there?**
 20 A Yes.
 21 **Q Dr. Skerra states:**
 22 **"None of the proteins expressed in**
 23 **1983 compare in size and complexity**
 24 **to an immunoglobulin molecule."**
 25 **Do you see that?**

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1 A I do.

2 **Q Do you agree with that statement?**

3 A Well, he seems to have overlooked ATCase, and

4 I wonder, again, if he's qualifying this with some

5 subset like eukaryotic or -- I don't know what, but

6 because of the ATCase exception, which I think was a

7 large complex molecule, I would disagree. My

8 testimony is opposite of his, yes.

9 **Q If Dr. Skerra had stated: None of the**

10 **proteins expressed in 1983 -- strike that.**

11 **If this said: None of the eukaryotic**

12 **proteins expressed in 1983 compare in size and**

13 **complexity to immunoglobulin molecule, would you**

14 **agree with that statement?**

15 A I don't know enough to say whether I would

16 agree with that or not, but that would -- that would

17 exempt ATCase. That might explain our disagreement

18 there.

19 **Q Could you turn to page 15?**

20 A Yes.

21 **Q Paragraph 51?**

22 A Yes.

23 **Q In the middle, there is a sentence that**

24 **begins: "Moreover, as of April."**

25 A Yes.

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1 **Q Dr. Skerra states:**

2 **"Moreover, as of April 1983, neither**

3 **I, nor Genentech's previous experts**

4 **Drs. Harris and McKnight, were aware**

5 **of any reported example of**

6 **expression of a recombinant**

7 **multimeric protein, let alone an**

8 **immunoglobulin tetramer, in a single**

9 **bacterial host cell."**

10 **Do you see that?**

11 A Yes.

12 **Q Do you agree that there was no reported**

13 **example of an -- of expression of a recombinant in a**

14 **single bacterial host cell as of April 1983?**

15 A No, I don't. There's the ATCase example, as

16 we have discussed.

17 **Q Are there any other examples that you are**

18 **aware of?**

19 A I think the nitrogenase may have been

20 expressed before April 1983, and that's a multimeric

21 protein.

22 **Q What was the protein again?**

23 A Nitrogenase.

24 **Q What type of protein is nitrogenase?**

25 A In the particular case, it was a bacterial

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1 protein I'm thinking of. That's in my rebuttal

2 report.

3 **Q Is that one of the nitrogen-fixing proteins?**

4 A That's right, yes.

5 **Q You can set aside Exhibit 9.**

6 A Wow, this exhibit's long. He's very

7 thorough.

8 **Q Back to your rebuttal report, Exhibit 2.**

9 **Could you turn to page 11?**

10 A Yes.

11 **Q In paragraph 23, you are discussing nitrogen**

12 **fixation?**

13 A Yes. Yes.

14 **Q The goal of nitrogen fixation is to take an**

15 **organism that does not fix nitrogen and get it to**

16 **fix nitrogen; correct?**

17 A That's correct.

18 **Q The goal of nitrogen fixation is not protein**

19 **synthesis; is that correct?**

20 A Well, that depends how you break the project

21 down. What's key to success is expression of -- or

22 other -- well, expression of these nitrogen-fixation

23 gene proteins, and the overall goal is to extract

24 nitrogen from the air and put it into organic form,

25 such as proteins.

Page 209

1 **Q Is the goal of the nitrogen-fixation work the**

2 **recovery of the protein expressed by the**

3 **nitrogen-fixation genes?**

4 A The -- that's an intermediate goal. The

5 long-term goal is to take nitrogen out of the

6 atmosphere. Expression of the nitrogen-fixation

7 genes -- in one project, you would just be content

8 to have the nit- -- nitrogenase expressed in the

9 cell, not isolated, and I think that's the one I was

10 writing about here.

11 **Q You were writing about the project in which**

12 **it was expressed but not isolated?**

13 A It may have been isolated, but it was not

14 going to be isolated and used medically, if

15 that's -- yeah.

16 **Q What field of work would you say the nitrogen**

17 **fixation papers fall into?**

18 A I would say gene expression. And although

19 the initial work was with prokaryotic genes, would

20 not necessarily be -- well, let me just say -- let

21 me go back to my first statement.

22 It was -- the field is protein expression.

23 **Q Is the field protein expression or gene**

24 **expression?**

25 A Sorry. Gene expression, expression of

Page 210

1 recombinant proteins.
 2 **Q The -- strike that.**
 3 **You refer to a number of papers in these**
 4 **pages in your report on nitrogen fixation; correct?**
 5 A Yes. Yes.
 6 **Q You are not relying on those papers to argue**
 7 **that the claims of the Cabilly II or III patents are**
 8 **anticipated; correct?**
 9 A That's correct.
 10 **Q You are not relying on those papers to argue**
 11 **that the claims of the Cabilly II and III patents**
 12 **are obvious; correct?**
 13 A That's correct.
 14 **Q The nitrogen-fixation genes that you describe**
 15 **in these paragraphs in your report are all bacterial**
 16 **in origin; correct?**
 17 A That's right.
 18 **Q If you look at paragraph 24?**
 19 A Yes.
 20 **Q You refer to the mapping of the "(nif) genes**
 21 **of Klebsiella pneumoniae"?**
 22 A Yes. That's probably what I have right now,
 23 yeah.
 24 **Q That's a type of bacteria?**
 25 A That is.

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

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1 **Q This paper reports on the recombinant**
 2 **expression of E. coli nitrogen-fixing genes; is that**
 3 **correct?**
 4 A Rhizobium nitrogen-fixing genes, and they are
 5 expressed in E. coli.
 6 **Q Rhizobium is a type of bacteria?**
 7 A Yes.
 8 **Q Do you know how closely related Rhizobium is**
 9 **to E. coli?**
 10 A I know that it's not very closely related.
 11 **Q Is Rhizobium more or less closely related to**
 12 **E. coli than E. coli is to Salmonella?**
 13 A Less closely related than Salmonella and
 14 E. coli.
 15 **Q You are not relying on the -- this work for**
 16 **purposes of arguing that the Cabilly II or III**
 17 **patents are anticipated or obvious; correct?**
 18 A That's correct.
 19 **Q When did you become aware of the Fuhrmann &**
 20 **Hennecke paper?**
 21 A Fuhrmann & Hennecke. After Dr. Fiddes'
 22 report appeared, I made an investigation of
 23 nitrogen-fixation chains. I had been aware of that
 24 work going on. One of the people in my lab went to
 25 do that as a post-doc, and some of the early work

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

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1 A I don't recall offhand.

2 **Q Is the ultimate goal of the work described in**

3 **the Fuhrmann paper the creation of E. coli that**

4 **fixes nitrogen?**

5 A I think that's a stage that the -- the

6 project passes through. I think this is more

7 investigational still, cloning the genes, learning

8 about their expression, and E. coli might be the

9 host of choice to work with in the short-term.

10 In the longer term, these genes might, in

11 turn, be put into transgenic plants, let's say, so

12 that the plants wouldn't have to rely on

13 nitrogen-fixing microbes in the soil, though. You

14 could have plants that essentially would fertilize

15 themselves.

16 **Q Could you turn to page 14 of your report?**

17 A Yes.

18 **Q Beginning at page 14 and continuing on**

19 **through the next several pages, you make reference**

20 **to a number of different U.S. patents; is that**

21 **correct?**

22 A Yes.

23 **Q Are you relying on any of those U.S. patents**

24 **to argue that the claim of the Cabilly II or III**

25 **patent are anticipated?**

Page 215

1 A No.

2 **Q Are you relying on any of those patents to**

3 **argue that the claims of the Cabilly II or III**

4 **patent are obvious?**

5 A No. These are arguing against Dr. Fiddes'

6 claim about the prevailing mindset.

7 **Q Could you turn to page 18.**

8 A 18.

9 **Q And this is referring to a reference called**

10 **"George"?**

11 A Yes.

12 **Q In the middle of the paragraph, there's a**

13 **sentence that begins: "For example"?**

14 A Yes.

15 **Q And you say that the inventors approach**

16 **recombinant protein production by**

17 **co-expressing (sic) -- co-expressing a fusion**

18 **protocol, i.e., the gene for the protein of interest**

19 **fused to a carrier protein, and the unfused protein**

20 **of interest.**

21 **Do you see that?**

22 A Yes, I do.

23 **Q Do you agree that fusion proteins would**

24 **sometimes be desired end product of work in the late**

25 **'70s and early 1980s?**

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1 A Sometimes the end product. That's --

2 would -- would I agree. Usually you don't want the

3 fusion protein; you want to get rid of the things

4 it's fused to. But I can't say categorically that

5 you never want the fusion protein, and they seem to

6 be making use of it here as a -- as a way of getting

7 the protein of interest.

8 **Q Let me rephrase my question.**

9 A Yes.

10 **Q I -- I phrased it poorly.**

11 **Would you agree that, in the late 1970s and**

12 **early 1980s, fusion proteins were sometimes an**

13 **intended product of the recombinant expression**

14 **process to then be later reconstituted?**

15 A Fusion protein was the -- sorry. Was it

16 the --

17 **Q An intended -- an intended product in the**

18 **process.**

19 A Yes, it was made intentionally.

20 **Q You agree that, in the late 1970s and early**

21 **1980s, persons of ordinary skill in the art**

22 **sometimes set out to intentionally make a fusion**

23 **protein?**

24 A Yes, but I haven't studied that issue. I

25 don't know specific examples. I know that usually

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1 it's not the fusion partner you want but the unfused

2 protein.

3 **Q Could you turn to page 20.**

4 A Yes.

5 **Q You refer, in paragraph 40, to a patent**

6 **relating to the production of cholera toxins?**

7 A Yes.

8 MS. DAVIS: If you will bear with me one

9 moment --

10 THE WITNESS: Sure.

11 MS. DAVIS: We will attempt to find my copy.

12 (Exhibit 11 was marked for

13 identification by the Reporter.)

14 MS. DAVIS: I'm marking, as Exhibit 11,

15 U.S. Patent 4,666,837.

16 THE WITNESS: Okay.

17 BY MS. DAVIS:

18 **Q Exhibit 11 is the patent you are discussing**

19 **in paragraph 40?**

20 A Paragraph 40, '837, yes.

21 **Q When did you become aware of this patent?**

22 A During my work on the rebuttal report in

23 November and early December.

24 **Q Do you see that the assignee on this patent**

25 **is a SmithKline entity?**

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1 A Yes.

2 **Q Do you have an understanding as to how that**

3 **entity is related to GlaxoSmithKline?**

4 A I don't have specific knowledge. I vaguely

5 recall that Glaxo used to be separate from

6 SmithKline and other ent- -- entities.

7 **Q Were you aware of this patent when you**

8 **prepared a report in connection with the prior**

9 **Cabilly litigation in which you were hired by Glaxo?**

10 A I don't recall seeing this then.

11 **Q In what field is the '837 patent?**

12 A This is in expression of recombinant

13 proteins.

14 **Q The cholera toxin proteins, what type of**

15 **proteins are there -- are those?**

16 A What type of proteins. You mean their

17 bacterial proteins?

18 **Q Let's start there.**

19 **They are bacterial proteins, yes?**

20 A Bacterial proteins. They encode a medically

21 significant molecule, and even the cholera toxin is

22 toxic. I believe they were going to use this as

23 a -- as part of a vaccine.

24 **Q The specific bacteria that these -- the**

25 **cholera strain in question is vibrio cholera?**

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1 A That's right.

2 **Q Do you know the degree of hemology between**

3 **that and E. coli?**

4 A Not offhand.

5 **Q Do you know, generally, how closely related**

6 **those two species are?**

7 A I don't know.

8 **Q It is fair to say, at least, that they are**

9 **both bacteria?**

10 A They are both bacteria. They grow in the

11 gut.

12 **Q You are not relying on the '837 patent to**

13 **argue that the claims of the Cabilly II and III**

14 **patents are anticipated; correct?**

15 A That's right.

16 **Q You are not relying on the '837 patent to**

17 **argue that the claims of the Cabilly II or III**

18 **patents are obvious; correct?**

19 A That's correct.

20 MS. DAVIS: Can we take a break --

21 MR. McCORMICK: Sure.

22 MS. DAVIS: -- just to hopefully wrap up

23 shortly thereafter?

24 MR. McCORMICK: Oh, okay. Great. Thanks.

25 THE VIDEOGRAPHER: Off the record at 4:44.

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1 (Recess taken.)

2 THE VIDEOGRAPHER: Back on the record at

3 4:56.

4 MS. DAVIS: No further questions.

5 MR. McCORMICK: Thank you.

6 THE WITNESS: Thank you.

7 THE VIDEOGRAPHER: Here marks the end of

8 Volume 1, Video No. 3 in the deposition of

9 Dr. Foote.

10 Going off the record, the time is 4:56.

11 (Whereupon, the deposition was

12 concluded at 4:56 p.m.)

13 ---o0o---

14 I declare under penalty of perjury that the

15 foregoing is true and correct. Subscribed at

16 _____, California, this ____ day of

17 _____, 2015.

18

19 _____

20 Signature of the witness

21

22

23

24

25

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1 CERTIFICATE OF REPORTER

2 I, RACHEL FERRIER, a Certified Shorthand

3 Reporter, hereby certify that the witness in the

4 foregoing deposition was by me duly sworn to tell

5 the truth, the whole truth, and nothing but the

6 truth in the within-entitled cause;

7 That said deposition was taken down in

8 shorthand by me, a disinterested person, at the time

9 and place therein stated, and that the testimony was

10 thereafter reduced to typewriting by computer under

11 my direction and supervision and is a true record of

12 the testimony given by the witness;

13 That before completion of the deposition,

14 review of the transcript [X] was [] was not

15 requested. If requested, any changes made by the

16 deponent (and provided to the reporter) during the

17 period allowed are appended hereto.

18 I further certify that I am not of counsel or

19 attorney for either or any of the parties to the

20 said deposition, nor in any way interested in the

21 event of this cause, and that I am not related to

22 any of the parties thereto.

23 DATED:

24

25 _____

RACHEL FERRIER, CSR No. 6948

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