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UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

- - - - - x

XENCOR, INC., : IPR2025-00604
Petitioner, : Patent No. 9,358,286
v. :
MERUS N.V., : IPR2025-00605
Patent Owner. : Patent No. 11,926,859

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Deposition of BRIAN J. SUTTON, PH.D.
New York, New York
Thursday, March 19, 2026
9:06 A.M.

Job No.: 621850
Pages: 1 - 246
Reported By: Anita M. Trombetta, RMR, CRR,
California CSR No. 14647

1 Deposition of BRIAN J. SUTTON, Ph.D., held
2 at the offices of Cahill Gordon & Reindel LLP, 32
3 Old Slip, New York, New York 10005, pursuant to
4 notice, before Anita M. Trombetta, a Certified
5 Shorthand Reporter in the State of California,
6 RMR, CRR, and Notary Public in and for the State
7 of New York.

1 A P P E A R A N C E S

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1 A P P E A R A N C E S C O N T I N U E D

2

3

4 ALSO PRESENT:

5 ROBIN SILVA, Esq., Xencor

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7 XIAOWEI SUN, Ph.D., Merus

8 ERIC CHANG, Xencor

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1	-----I N D E X-----	
2	WITNESS - BRIAN J. SUTTON, Ph.D.	
3	EXAMINATION BY	Page
4	ATTORNEY ASHKENAZI	6
5	-----E X H I B I T S-----	
6	(Previously Marked.)	
7	Exhibit	Page
8	Exhibit 2010	7
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1 P R O C E E D I N G S

2 B R I A N J. S U T T O N, P h. D., called as
3 a witness, having been duly sworn by a Notary
4 Public, was examined and testified as follows:

5 EXAMINATION BY

6 ATTORNEY ASHKENAZI:

7 Q Good morning. Can you please state your
8 full name for the record.

9 A Brian Jones Sutton.

10 Q Dr. Sutton, thank you for being with us
11 this morning.

12 And just so we're clear, in front of you,
13 you have a binder with your four declarations from
14 the two IPRs; is that correct?

15 A Yes, that's correct.

16 Q Okay. And just so the record is clear,
17 the IPRs are IPR 2025-00604 and IPR 2025-00605.

18 Is that correct?

19 A I would have to --

20 Q Yeah, it should be on the top of your
21 declaration.

22 A Is that what you call --

1 (Reporter clarification.)

2 Q I'll ask the question again.

3 If you go to your first declaration, it
4 was Exhibit 2010 and IPR 2025-00604; is that
5 correct?

6 A I'm seeing this --

7 Q I'm sorry, 605. I apologize.

8 Dr. Sutton, let me -- I'll make this a
9 little easier for you.

10 You submitted four --

11 A Four --

12 Q Four declarations, right?

13 A Four declarations.

14 Q Okay. And can you go to the top of one of
15 the documents. Tab 1.

16 Okay. Is there an IPR number listed
17 there?

18 A There is.

19 Q At the bottom right --

20 A Yes.

21 Q -- what's that IPR number?

22 A IPR 2025-00604.

1 Q Okay. Great.

2 Now if you go to your first declaration
3 from the other IPR, what is the IPR number there?

4 A IPR 2025-00605.

5 Q Okay. Great.

6 Doctor, have you been deposed before?

7 A No.

8 Q No?

9 Okay. Maybe if we can just go over a
10 little bit of ground rules, it will -- some of the
11 procedures, it will help with the court reporter.

12 We have a court reporter in the room.

13 You understand that, right?

14 A I do.

15 Q Okay. Which means we can't speak over one
16 another because she has to transcribe in words
17 what we're saying.

18 Is that fair?

19 A Yeah, that's understood.

20 Q Okay. So that means that I will do the
21 best I can to let you finish answering the
22 question before I ask my next question. And I'll

1 ask that do you the reverse; let me finish my
2 question before you begin your answer.

3 Is that fair?

4 A Understood.

5 Q Okay. If at all you don't understand my
6 question, can you please let me know?

7 A Yeah, yes.

8 Q Also, it's important -- and if you
9 don't -- if you don't ask me a -- ask me to
10 clarify, I'll assume you understood my question.

11 Is that fair?

12 A Yes.

13 Q Okay. It's also important that you give
14 verbal answers because the court reporter can't
15 really take down head nods or "mm-hmms."

16 Is that okay?

17 A Understood.

18 Q Okay. Great.

19 We'll try to go for about one-hour
20 sessions, but if you need breaks at any earlier,
21 just let me know. The only thing I'll ask is that
22 we -- you -- if there is a question pending, you

1 answer the question before we take the break.

2 Is that okay?

3 A That sounds all right.

4 Q And is about one hour okay for each
5 session? Would you like --

6 A Yes, yes, yes.

7 Q Okay. What did you do to prepare for your
8 deposition today?

9 A To -- my preparation for today was to
10 review the documents that I -- the declarations
11 that I made and to look over some notes that I
12 made along the way and to look at some of the
13 details in the patents and the -- other materials.

14 Q Did you meet with any attorneys to prepare
15 for the deposition today?

16 A No.

17 Q No.

18 Did you have any meetings over the past
19 couple of days to -- with any attorneys at all,
20 related to these IPRs?

21 A Yes.

22 Q Okay. And who did you meet with?

1 A My colleagues. The guys sitting here
2 (indicating).

3 Q Okay. So you met with the attorneys that
4 are in the room today on your side of the table
5 representing Merus and Merus; is that correct?

6 A Yes.

7 Q Okay.

8 ATTORNEY ASHKENAZI: And madam court
9 reporter, if you're having a problem with the
10 volume, we can --

11 (An off-the-record discussion was held at
12 this time.)

13 Q How long would you say you spent in total
14 preparing for today's deposition?

15 A I'm unsure exactly what you -- preparation
16 for today -- for today or preparation of the
17 document that we presented?

18 Q All right. Let's take this -- you did
19 read documents and meet with your attorneys to
20 prepare for this deposition, correct?

21 A Correct.

22 Q And how long did you review documents and

1 meet with your attorneys to prepare for this
2 deposition?

3 A Could you repeat the question?

4 Q Sure.

5 About how long did you review documents
6 and meet with your attorneys to prepare for this
7 deposition?

8 A Well, over several days.

9 Q Okay.

10 A And so since I arrived here, for two or
11 three days. And then for -- over Zoom calls over
12 a few days before --

13 Q Okay.

14 A -- before I came.

15 Q All right. Did you refamiliarize yourself
16 with your declarations that you submitted in the
17 two IPRs?

18 A Yes.

19 Q Okay. And if I -- what would be the best
20 way for me to refer to these two different IPRs
21 for you? Would you like me to refer to the IPR
22 numbers or to the patent numbers?

1 A To -- to the patent numbers.

2 Q Okay. Fair enough.

3 And given that you have all your
4 declarations in front of you, feel free at any
5 point during the deposition to look towards the
6 declaration if you think you need to. Okay?

7 A Yes.

8 Q But I will do my best to direct you to
9 specific portions to help move the conversation
10 along.

11 Is that fair?

12 A That's fair.

13 Q Okay. Great.

14 Is there any reason you cannot give
15 complete, accurate, and truthful answers today?

16 A No.

17 Q I'd just like to go over a little bit of
18 your background, if we can, for a moment.

19 Is it safe to characterize you as a
20 structural biologist?

21 A Yes.

22 Q Okay. And in fact, if we look at your

1 second declaration -- well, withdrawn.

2 Have you ever in your career designed
3 antibody analogs?

4 A I have -- I've been part of a
5 collaborative effort to produce an antibody analog
6 that -- but it wasn't my direct responsibility.

7 Q So you've never had any direct
8 responsibility to design an antibody analog,
9 correct?

10 A Well, I -- I have been involved in -- in
11 aspects of the project that -- that led to the
12 design of a -- of an antibody-like molecule, but I
13 think the short answer is no.

14 Q So I --

15 A Only -- only peripherally.

16 Q Yeah, and I apologize. Sometimes I may
17 restate the question, because it gets a little
18 confusing with negatives and positives
19 sometimes --

20 A Yeah, sure.

21 Q -- so I'm going to ask my question again.

22 You've never had any direct responsibility

1 to design an antibody analog, correct?

2 A Correct, I have never had direct
3 responsibility, yeah.

4 Q Now, you said you worked as part of
5 collaborative team that worked on an antibody
6 analog; is that correct?

7 A Yeah.

8 Q Okay. And what was your responsibility on
9 that team?

10 A Well, leading the crystallographic --
11 X-ray crystallographic studies of relevant parts
12 of the molecule.

13 Q Okay. So your responsibility on that one
14 team that you referenced to us that was working on
15 an antibody analog was to head up the X-ray
16 crystallographic studies; is that correct?

17 ATTORNEY WOLFE: I'm sorry, can we take
18 one second. The realtime isn't working on the
19 tablet.

20 (Discussion off the record.)

21 BY ATTORNEY ASHKENAZI:

22 Q I'll re-ask my question.

1 So your responsibility on the one team you
2 referenced that was working on an antibody analog
3 was to head up the X-ray crystallographic studies,
4 correct?

5 A Correct.

6 Q Okay. Have you ever worked on a --
7 bispecific antibody?

8 A No.

9 Q Have you ever -- I'll make my questions a
10 little broader.

11 Have you ever done any work on bispecific
12 antibodies?

13 A No.

14 Q Have you ever done any work on
15 heterodimeric antibodies?

16 A No.

17 Q Have you ever done any work on antibodies
18 with amino acid substitutions?

19 A Yes.

20 Q Okay. Have you ever designed an antibody
21 with an amino acid substitution?

22 A Again, I've been part of a team looking at

1 the structural effects of mutations.

2 Q Okay. I understand you have published a
3 number of publications over the years; is that
4 right?

5 A I've published a number of publications.

6 Q Have you ever published any publications
7 relating to the making of heterodimeric
8 antibodies?

9 ATTORNEY MARGOLIS: Objection. Vague.

10 A I haven't been directly involved in -- I
11 haven't been involved in projects concerning
12 bispecific antibodies.

13 Q Okay.

14 A Until very recently with some studies
15 of -- of the B-cell receptor, which are
16 unpublished and that's ongoing work.

17 Q Okay. Let's maybe take this into a couple
18 of pieces.

19 I think you've said that you have never
20 been involved in any projects concerning
21 bispecific antibodies, correct?

22 A By -- correct, if by bispecific

1 antibodies, you mean soluble -- soluble
2 antibodies.

3 Q And you've never been involved in any
4 projects concerning heterodimeric antibodies,
5 correct?

6 A Yes. With the same caveat, this is -- I
7 haven't been involved in projects involving --
8 involving hetero-antibodies, soluble antibodies.

9 Q Okay.

10 Apologies. At times, I may pause -- I
11 have a lot of different documents up, so it's --
12 I've got to move through things.

13 Is it safe to say you have not been
14 involved in any experiments with -- withdrawn.

15 Is it safe to say you have not been
16 involved in any projects relating to making
17 substitutions in the CH3 domain of antibodies?

18 ATTORNEY MARGOLIS: Objection. Vague.

19 A I have been -- to the extent that I'm
20 involved in -- current planned studies to employ
21 the bispecific antibody technology to generate
22 B-cell receptor molecules, I have -- in any event,

1 followed the field and reviewed the methods for
2 making bispecific antibodies.

3 Q Okay. When did you begin your work on the
4 project related to the B-cell receptors?

5 A Four or five years ago.

6 Q Okay. So sometime after 2020?

7 A Sometime after 2020.

8 Q Okay. So is it safe to say, then, before
9 the year 2020, you had not been involved in any
10 projects relating to the making substitutions in
11 the CH3 domain of antibodies?

12 ATTORNEY MARGOLIS: Objection. Vague.

13 A I -- I think that's correct, yes.

14 Q Okay. And then is it safe to say that
15 before 2020, you had not been involved in any
16 project using common light chains for
17 heterodimeric antibodies?

18 A Correct.

19 Q And is it safe to say before 2020 --
20 withdrawn.

21 Is it safe to say that you have not been
22 involved in any projects relating to charged swap

1 approaches for making heterodimeric antibodies?

2 ATTORNEY MARGOLIS: Objection. Vague.

3 A Correct.

4 Q Okay. And is it safe to say that you have
5 not been involved in any projects using
6 electro-steering for making heterodimeric
7 antibodies? Withdrawn.

8 Is it safe to say you have not been
9 involved in any projects or research relating to
10 electrostatic steering for making heterodimeric
11 antibodies?

12 ATTORNEY MARGOLIS: Objection. Vague.

13 A That -- that's correct.

14 Q Okay. And is it safe to say you have not
15 been involved in any projects or research relating
16 to making substitutions on the CH3 domain for
17 heterodimeric antibodies?

18 ATTORNEY MARGOLIS: Objection. Vague.

19 A Certainly with -- with the -- the rider
20 that any mutations in CH3 were -- CH3 were to --
21 were concerning bispecific antibody production,
22 that's true.

1 Q Okay. Have you been involved in any
2 research or projects relating to making or using
3 any of the antibody structures shown in the
4 Kontermann reference that you discussed in your
5 declarations?

6 ATTORNEY MARGOLIS: Objection. Vague.

7 A I mean, I'm familiar with the Kontermann
8 review, and it reviews many ways of making
9 bispecific antibodies.

10 And as I have said, I haven't been
11 involved directly in projects directed to that, so
12 I think it's fair to say that I haven't worked
13 with --

14 Q Okay.

15 A -- molecules on that list.

16 Q If at all you need a reference, please let
17 me know.

18 A Yeah, sure.

19 Q I'm not trying to test you.

20 A No, no, no, I was going to ask for it
21 until I saw it there. But I don't need to see it.

22 Q Okay. Have you been published any

1 literature on heterodimeric -- related to
2 heterodimeric antibodies?

3 ATTORNEY MARGOLIS: Objection. Vague.

4 A No.

5 Q Have you been published any literature
6 relating to bispecific antibodies?

7 ATTORNEY MARGOLIS: Objection. Vague.

8 A No.

9 Q Have you published any literature relating
10 to techniques for making heterodimeric or
11 bispecific antibodies?

12 ATTORNEY MARGOLIS: Objection. Vague.

13 A Let me just ask you to repeat the
14 question.

15 Q Absolutely.

16 Have you published any literature relating
17 to techniques for making heterodimeric or
18 bispecific antibodies?

19 ATTORNEY MARGOLIS: Objection. Vague.

20 A Published, no.

21 Q And do you hold any patents relating in
22 any way to heterodimeric or bispecific antibodies?

1 ATTORNEY MARGOLIS: Objection. Vague.

2 A No.

3 Q Okay. So I'd like to turn your attention
4 to your second declaration from -- for the '859
5 patent. That's IPR 2025-00605, okay?

6 And again, we'll be referencing all your
7 declarations. So if at any point today, given
8 that this is one deposition for both
9 proceedings -- let me -- let me clarify.

10 Given that this is one deposition for both
11 proceedings, the questions will go for both IPRs.
12 So if you need to refer to any other portion of
13 your declaration or other declarations, feel free
14 to do so, okay?

15 A Yes.

16 Q Thank you.

17 If you turn your attention to
18 paragraph 30, please, of your second declaration
19 in the '605 IPR, you'll see you reference claim 1
20 of the '859 patent?

21 A Okay. Do you -- repeat the part --

22 Q Sure.

1 I'm just trying to orient you.

2 A Yes. Is it paragraph or page?

3 Q So if you turn to paragraph 30, 3-0, of
4 your second declaration, Exhibit 2019 in the '605
5 IPR, you'll see it references the claim language
6 of claim 1 of the '859 patent.

7 Do you see that?

8 A I do, yes.

9 Q Okay. Now, you'll agree with me that
10 claim 1 of the '859 patent requires a positively
11 charged amino acid at position 364; is that
12 correct?

13 A Correct.

14 Q And claim 1 of the '859 patent also
15 requires a negatively charged amino acid residue
16 at position 368, correct?

17 A Correct. Could --

18 Q Thank you.

19 You said "correct," right?

20 A I'd like to withdraw that answer and just,
21 and ask for a copy of the '859 patent.

22 Q Sure.

1 Dr. Sutton, do you have a copy of
2 Exhibit 1001, the '859 patent in front of you?

3 A Yes, I have it.

4 Q Okay. So I'll re-ask my questions.

5 You will agree with me that the -- claim 1
6 of the '859 patent requires a positively charged
7 amino acid residue at position 364, correct?

8 A Correct.

9 Q And claim 1 of the '859 patent requires a
10 negatively charged amino acid residue at position
11 368, correct?

12 A Correct.

13 Q Okay. And looking at the '859 patent, do
14 you understand that the provisional application
15 was filed on April 20th, 2002, which you can find
16 on the first page of the patent?

17 ATTORNEY MARGOLIS: Objection.
18 Mischaracterizes the document.

19 Q Okay. Let me withdraw the question and
20 ask it again.

21 Dr. Sutton, can you turn to the front page
22 of the '859 patent?

1 A Yes.

2 Q And you'll see that the provisional
3 application for the '859 patent was 61/635935.

4 Do you see that on the right -- on the
5 left-hand side about line 60, where the number 60
6 is?

7 Do you see that?

8 A I do.

9 Q Okay. And you understand if I refer to
10 that provisional application as the '935
11 provisional, you'll understand that I'm referring
12 to the provisional application for the '859
13 patent?

14 A Yes, I do.

15 Q Okay. And the '935 provisional
16 application was filed on April 20th, 2012,
17 correct?

18 A Correct.

19 Q Okay. And you reviewed the '935
20 provisional application, correct?

21 A Correct.

22 Q Okay. Now, going back to your

1 declaration, paragraph 31, let me know when you
2 get there, please.

3 A Yes, I'm there.

4 Q Okay. In paragraph 31 of your second
5 declaration in the '605 IPR, you state that it is
6 your opinion that "The '935 provisional
7 application reasonably conveys to a POSA that the
8 inventors" had possessed -- "had possession of the
9 claimed subject matter, including a positively
10 charged amino acid residue at position 364 and a
11 negatively charged amino acid residue at position
12 368."

13 Is that fair?

14 ATTORNEY MARGOLIS: Objection.
15 Mischaracterizes the document.

16 A Correct.

17 Q Now, you will agree with me that the '935
18 provisional application does not explicitly
19 disclose an antibody having a positively charged
20 amino acid at position 364 and a negatively
21 charged amino acid at position 368, correct?

22 A No, that's not my -- I don't agree with

1 that.

2 Q Okay. It's your position that there is an
3 explicit reference in the '935 provisional
4 application to an antibody having a positively
5 charged amino acid residue at position 364 and a
6 negatively charged amino acid residue at position
7 368?

8 A I would like to see a copy, if I may, of
9 the '935 patent.

10 Q Doctor, you have in front of you
11 Exhibit 1030, which is a copy of the '935
12 provisional application; is that correct?

13 A That's right.

14 Q And do you need me to re-ask the question,
15 the original question? I'll ask it just so you
16 have it in the front of your mind.

17 Is it your position that there is an
18 explicit reference in the '935 provisional
19 application to an antibody having an positively
20 charged amino acid residue at position 364 and a
21 negatively charged amino acid residue at position
22 368?

1 A No, there is no reference to positively
2 charged.

3 Q Okay. So I will then ask the question --
4 because there is a couple of negatives there, I'm
5 going to make sure I just ask the question so it's
6 clean for the record.

7 So you will agree with me, then, that the
8 '935 provisional application does not explicitly
9 disclose an antibody having a positively charged
10 amino acid residue at position 364 and a
11 negatively charged amino acid residue at position
12 368, correct?

13 A Correct.

14 Q Now, your position for asserting that the
15 '935 provisional application conveyed to a POSA --
16 well, withdrawn.

17 When I use the word "POSA," do you
18 understand I mean person of ordinary skill in the
19 art?

20 A I do.

21 Q Okay. So with that, it's your position
22 that a POSA reading the '935 provisional

1 application would understand that the inventors
2 possessed an antibody having a positively charged
3 amino acid residue at 364 and negatively charged
4 amino acid residue at 368 because of the
5 information contained in table 7 of that
6 application, correct?

7 ATTORNEY MARGOLIS: Objection. Vague.

8 A I'm happy to answer the question in the
9 affirmative, understanding that you're not
10 implying that -- the only data in table 7.

11 Q Okay. You will agree with me that the
12 basis for your -- well, withdrawn.

13 You will agree that the premise of your
14 argument that the inventors possessed a
15 heterodimeric antibody with a positively charged
16 amino acid residue at 364 and negatively charged
17 amino acid residue at position 368 is a result of
18 the data contained in table 7 of the provisional
19 application, correct?

20 ATTORNEY MARGOLIS: Objection. Vague.

21 A Yeah, I can reply -- I can reply in the
22 affirmative with the caveat that the -- it's not

1 only data in table 7, which I think I think is
2 left open by your question.

3 Q Okay. Let me ask you a different
4 question.

5 Was there any data at all in the '935
6 provisional application relating to an amino
7 acid -- an antibody that contained a positively
8 charged amino acid residue at -- at position 364
9 and a negatively charged amino acid residue at
10 position 368?

11 A Could I have you repeat the question?

12 Q Sure.

13 Is there any data at all that shows --
14 withdrawn.

15 Is there any data within the '935
16 provisional application relating to a positively
17 charged amino acid residue at position 364 and
18 negatively charged amino acid residue at position
19 368?

20 A Yes.

21 Q Okay. And which date -- where is that
22 data?

1 A The data on table 7.

2 Q Okay. So is there any other data that you
3 would reference in the '935 provisional
4 application that you were relying on for your
5 assertion that the '935 provisional application
6 showed the inventors in possession of the
7 claims -- of the subject matter of the claims of
8 the '859 patent?

9 A Yes.

10 Q What data is that?

11 A Data presented in table A, page 17.

12 Q Sorry. Anything else?

13 A Yes, there is additional -- additional
14 statements in this -- in this specification here.
15 It related to the questions you asked.

16 Q Okay. So I just want to make sure we're
17 clear.

18 I want to know what data that's in the
19 '935 provisional application that you're relying
20 on for your assertion that the '935 provisional
21 application shows the inventors in possession of
22 the claims of the '859 patent. Okay?

1 A Yes.

2 Q You've identified for me table 7 and table
3 A; is that correct?

4 A Yeah.

5 Q Is there any other data in the '935
6 provisional application that you're relying on for
7 your assertion that the '935 provisional
8 application showed the inventors in possession of
9 the claims of the '859 patent?

10 ATTORNEY MARGOLIS: Objection. Asked and
11 answered.

12 A Interpreting data as a term, including
13 statements and -- and more detailed
14 descriptions -- specification of the patent, yes,
15 the -- there is more in the patent, provisional
16 patent than just figure A, table -- the table --
17 the data presented in table A and table 7.

18 Q Okay. Doctor, let's try this maybe in
19 another way.

20 You've referenced at least two tables for
21 us, table A and table 7 of the '935 provisional
22 application, correct?

1 A Correct.

2 Q Okay. You'll agree with me that table A
3 is a list of known CH3 domain interface residues,
4 correct?

5 A Correct.

6 Q And when I say "known," I mean table A
7 identifies CH3 domain interface residues as they
8 were identified in the prior art, correct?

9 A Correct.

10 Q Now, that's not data that was generated by
11 Merus, correct?

12 ATTORNEY MARGOLIS: Objection. Vague.
13 Calls for speculation.

14 A It's certainly not data exclusively.

15 Q Well, you've reviewed the prior art in
16 these two IPRs, correct?

17 A Yes, I have.

18 Q And you have seen reference to table --
19 the information contained in table A of the '935
20 provisional application in the prior art, correct?

21 A Yes, agreed.

22 Q And you'll agree with me that Merus is not

1 the author of the information contained in table A
2 as it was provided in the prior art to the '935
3 provisional application, correct?

4 A Correct.

5 Q Okay. So then you then will agree with me
6 that Merus was not the originator of the
7 information contained in table A of the '935
8 provisional application, correct?

9 A Table A represents -- presents the data
10 accumulated from a number of crystal structures
11 and others -- crystal structures known at the time
12 and...

13 Q I'll re-ask my question.

14 You will agree with me that Merus was not
15 the originator of the information contained in
16 table A of the '935 provisional application,
17 correct?

18 ATTORNEY MARGOLIS: Objection. Lacks
19 foundation.

20 A I can agree. I do agree that the data
21 presented in table A comes from a variety of
22 sources.

1 Q Okay.

2 A And my hesitation is -- is precisely who
3 in the world contributed to the -- contributed to
4 the 50-odd crystal structures that were probably
5 available at the time, the description of which --
6 the data from which in terms of context is
7 summarized in this table.

8 Q Okay. The information that's contained in
9 table A -- well, withdrawn.

10 Just so we're clear, the information
11 that's contained in table A of the '935
12 provisional application, that was in the prior art
13 for both the '286 and the '859 patents, correct?

14 A Correct.

15 Q Great.

16 Now, you rely on table A -- how does table
17 A inform a POSA that the inventors were in
18 possession of an antibody containing a positively
19 charged residue at position 364 and a negatively
20 charged residue at position 368?

21 A As I have described here, a POSA in my
22 statement -- a POSA would look at the data in

1 table 7 and -- and would -- a POSA would look at
2 these data and would understand that a number of
3 mutations here were tested in an assay that
4 recorded the inhibition of homodimer formation.
5 The background of that is the extent of homodimer
6 formation in the production of a bispecific
7 antibody is -- is -- is one way of looking at the
8 propensity for that mutation to be valuable in
9 production of a heterodimeric antibody.

10 Q Okay. So -- I didn't mean to cut you off.

11 Is there anything else you'd like to add?

12 A No, I think that's it.

13 ATTORNEY ASHKENAZI: Okay. Why don't we
14 go off the record.

15 (Recess.)

16 BY ATTORNEY ASHKENAZI:

17 Q Now, Doctor, before the break, we were
18 referencing table A of the '935 provisional
19 application, correct?

20 A Correct.

21 Q Okay. And my question to you is, how does
22 table A inform your assertion that the inventors

1 were in possession of a positively charged amino
2 acid residue at position 364 and negatively
3 charged amino acid residue at position 368?

4 A Table 7 indicates that the mutation Serine
5 364 Lysine S64K was tested in this -- inhibition
6 of homodimerization assays that we referred to
7 earlier, and -- and to a POSA looking at these
8 data, that would -- for reasons that we may
9 explore, is a -- is a promising amino acid residue
10 in a partnership. It would generate a pair, a
11 promising pair of residues.

12 And having identified position 364, the
13 role of data in table A is to identify a partner
14 for residue 364, and that partner is -- is residue
15 368.

16 And in the context of generating residue
17 pairs of oppositely charged residues that will
18 stabilize formation of heterodimerization, in the
19 experimental data from figure 7, together with the
20 data presented in table A, would lead a POSA to
21 conclude that a pair with positively charged
22 residue at 364 and negatively charged residue at

1 368 would form a promising pair of residues.

2 Q Okay. I'm going to want to follow up on
3 that, but I want to maybe try to make it a little
4 easier on the court reporter.

5 If I say "364 plus," do you understand me
6 to be saying that there is a positively charged
7 amino acid residue at position 364?

8 A After mutation, yes.

9 Q Yes.

10 And if I say "368 minus" or "negative,"
11 you'll understand I'm referring to a negatively
12 charged amino acid residue at position 368 after
13 mutation; is that correct?

14 A I'll use your shorthand, yes.

15 Q And that's what I want to do is I want to
16 say 364 plus, 368 minus would be positively
17 charged amino acid residue at position 364 and
18 negatively charged amino acid residue at position
19 368.

20 Is that fair?

21 A That's fair.

22 Q Okay. Great. Hopefully it will make it

1 easier for the court reporter and for everyone
2 else reading the transcript.

3 Okay. So let's look at table A for a
4 second. And I'm looking at table A of the '935
5 provisional application specifically.

6 This table shows the amino acid residues
7 at the CH3 domain interface that interact with one
8 another?

9 A Yes, yes.

10 Q Okay. So if I'm looking at the left-hand
11 column of table A of the '935 provisional
12 application, it identifies a residue, and then the
13 right-hand column is showing me the amino acid
14 residues that the left-hand column interacts with;
15 is that correct?

16 A Yes.

17 Q Okay. Now, if I understood correctly,
18 it's your assertion that table 7 of the '935
19 provisional application identifies 364 plus as a
20 promising residue, correct?

21 A Correct.

22 Q Okay. And then it's your assertion that a

1 POSA would infer from that, that you want to look
2 for the -- a corresponding amino acid that would
3 pair with 364 plus; is that correct?

4 A Correct.

5 Q Okay. And then the POSA would then need
6 to consider what amino acid residues could
7 interact with 364 plus, correct?

8 A Correct.

9 Q And then the POSA would consider a number
10 of different options that the POSA could use to
11 identify an amino acid residue that would pair
12 with 364 plus, correct?

13 ATTORNEY MARGOLIS: Objection. Lacks
14 foundation. Vague.

15 A I'll ask you to repeat the question.

16 Q Sure.

17 After the POSA inferred that they want to
18 look for an amino acid residue that could pair
19 with 364 plus, it's your assertion that they would
20 then look into elsewhere within the patent and the
21 prior art to identify which amino acid residues
22 can be paired with 364 plus, correct?

1 A Correct.

2 Q Okay. And then it's your assertion that
3 they would identify two amino acid residues --
4 well, withdrawn. I'll ask the question again.

5 It's your assertion that a POSA, after
6 identifying 364 plus, would -- withdrawn.

7 And then it's your assertion that the POSA
8 would identify residues 368 and 370 as potential
9 pairing with 364 plus; is that accurate?

10 A Yes, that's correct.

11 Q Okay. And then a POSA could infer that
12 the inventors were potentially contemplating --
13 well, withdrawn.

14 And with all of that information, it's
15 your assertion that a POSA would infer that the
16 inventors contemplated all potential pairs with
17 364 plus, correct?

18 ATTORNEY MARGOLIS: Objection. Vague.

19 A I would happily state that a POSA would --
20 would look at this table, would look at Serine 364
21 and would realize that there were two potential
22 contact residues and would consider both of them

1 in the first instance.

2 Q Okay. Now, the POSA would consider both
3 of them and there is nothing in the patent that
4 would say to avoid -- withdrawn.

5 There is nothing within the '935
6 provisional application that says to avoid pairing
7 364 plus with 370, correct?

8 A I would need to check the text, but I
9 would -- a POSA would shortcut that because the
10 POSA would understand that K370 is not going to
11 be -- it's not going to be promising as a -- as a
12 partner because as it stands, it's positively
13 charged. If it's going to be a partner to a
14 positive charge, it would have to be -- and we're
15 talking about thing --

16 (Reporter clarification.)

17 A We have to have its charge changed from
18 plus to minus. But the POSA would also understand
19 that K370 -- K370 is part of -- of a -- of a salt
20 bridge within the CH3-CH3 interface, one that's
21 highly conserved, one of four very well-identified
22 and understood salt bridges around the periphery

1 of the interface.

2 And in fact, the -- looking at the crystal
3 structures, a POSA would -- would realize that the
4 interactions with 370 are very slight and more
5 extensive with Leucine 368.

6 Q So Doctor, let me ask you a couple of
7 follow-up questions if I can.

8 When we think about the '935 patent and
9 the pairs, we're trying to make a positively
10 charged amino acid residue and a negatively
11 charged amino acid residue that interact with one
12 another; is that correct?

13 A Yes.

14 Q Okay. And the point is electrostatic
15 interactions, a positive and a negative attract,
16 right?

17 A Correct.

18 Q The old adage, opposites attract?

19 A Okay.

20 Q That's fine. Withdrawn.

21 So the point is, I'm looking for -- if I
22 look at table A, I want to have a positive on one

1 side.

2 And then table A is telling me if I have a
3 positive on one side, take a negative on the
4 other?

5 A Yes.

6 Q Correct?

7 A Yes, correct.

8 Q And I'll make sure I'm clear.

9 If there is a positively charged amino
10 acid residue in chain A, then a POSA knows to look
11 for a negatively charged amino acid residue in
12 chain B, correct, of table A of the '935
13 provisional application, correct?

14 A Yes.

15 Q Now, I want to make sure we're clear.

16 The concept of electrostatic steering,
17 that was known in the prior art before the '935
18 provisional application, correct?

19 A Correct.

20 Q And at table A, the information that's
21 contained in table A was known in the prior art as
22 well, correct?

1 A Correct.

2 Q All right. And it was known that there
3 will be interactions between the amino acid
4 residues in chain A and the amino acid residues
5 identified in chain B of table A of the '935
6 provisional application, correct?

7 A So I figure -- it's a long sentence.

8 Q Sure. Absolutely.

9 It was known -- well, withdrawn.

10 And you'll agree with me that if you have
11 a positive in chain A of table A of the '935
12 provisional application and a negative -- and a
13 positive in chain B, so two positives, those would
14 actually repel one another, correct?

15 A Yes.

16 Q Okay. So what we don't want to have is a
17 positively charged residue, according to you, in
18 chain A and a positively charged amino acid
19 residue in chain B, according to you, correct?

20 A That's -- I can't agree with that
21 statement as -- as it stands. It has to be
22 qualified.

1 Q All right. Okay. Let me take it
2 differently.

3 There would be a concern that you would
4 not get heterodimeric -- or increase the rate of
5 heterodimerization if you had a positively charged
6 residue in chain A and a positively charged
7 residue in chain B, correct?

8 ATTORNEY MARGOLIS: Objection. Vague.
9 Compound.

10 A Your question implies that you're talking
11 about amino acid residues -- amino acid residues
12 chain A and amino acid residue in chain B which
13 carry in the example you've just given a positive
14 charge, a positive charge plus-plus, but -- and
15 you're implying that we discuss this in relation
16 to that amino acid having a free positive charge.
17 But 370, K370, although carrying a positive charge
18 in this example, is already part of a salt bridge.
19 So it's already neutralized within the structure.

20 So although we're looking at K370, we
21 can't look at that in the context of the crystal
22 structure of the complex and say that is -- that

1 it's positively charged because you must first
2 consider whether it's going to be -- it's going to
3 carry a free positive charge or whether that
4 charge has already been neutralized within the
5 structure.

6 Q Okay. What are the four salt bridges that
7 were known to exist, looking at table A, for the
8 CH3 domain?

9 A I'm happy to recite them to you. I would
10 like to see -- the numbers are all -- they're not
11 all in my head, so I would need to see them. I
12 would like to see, for goodness sake, the paper or
13 the -- Gunasekaran paper.

14 Q Doctor, you now have in front of you
15 Exhibit 1012, which is a copy of the Gunasekaran
16 reference titled, "Enhancing antibody Fc
17 heterodimer formation through electrostatic
18 steering effects."

19 Do you have that in front of you?

20 A I do.

21 Q Is this the reference you were asking
22 about?

1 A It is. Thank you.

2 Q Okay. Now, you'll agree with me that the
3 salt bridges you were referring to -- withdrawn.

4 Can you tell me what were the four known
5 salt bridges that were present in the CH3 domain
6 of antibodies?

7 A Yes, I can.

8 Q And what were they?

9 A Well, let me say they're mentioned
10 variously in the paper. But in table 1 on
11 page 19641, the four salt bridges are delineated
12 and are described -- are listed and -- and so we
13 have the first --

14 Q Okay. Thank you.

15 Doctor, I just want to make sure we're
16 clear. The four salt bridges were --

17 A Sure.

18 Q -- the first one was position 356 to 439;
19 is that correct?

20 A Correct.

21 Q The second salt bridge that you say was
22 known in the prior art was 357 to 370; is that

1 correct?

2 A Correct.

3 Q The third one is 392 to 399; is that
4 correct?

5 A Correct.

6 Q And the last salt bridge that you say was
7 known in the prior art was 409 to 399; is that
8 correct?

9 A Correct.

10 Q And it's your assertion that once you have
11 a charged amino acid residue that is part of the
12 salt bridge, it no longer raises a concern about
13 it interacting with other charged residues within
14 the antibody?

15 A Correct.

16 Q Okay. So if I'm taking a look at table A
17 of the '935 provisional application, which you
18 have in front of you, when I look at position 405,
19 I see that position 405 has -- interacts from
20 chain A with three amino acid residues in chain B,
21 correct?

22 A Correct.

1 Q Now, two of those amino acid residues, 392
2 and 409, those are from known salt bridges,
3 correct?

4 A Yes.

5 Q Therefore, they would not raise a concern
6 when trying to make an electrostatic pair with
7 position 405, correct?

8 ATTORNEY MARGOLIS: Objection. Vague.

9 A No, I couldn't agree with that. I don't
10 agree with that statement.

11 Q And why don't you agree with that
12 statement?

13 A I have to go back and check what you said
14 in your previous question. But let me just say
15 first that if -- if -- if F405 is going to be
16 mutated --

17 Q Yes.

18 A -- to a positively charged residue --

19 Q Yes.

20 A -- then -- then you will run into
21 difficulties because there are -- well, that
22 could -- that could carry a positive -- that could

1 carry a positive charge because the -- the -- the
2 392 and the 409, which are identified already as
3 having positive charges on the salt bridges. So
4 in the same way that K409 is not an issue for
5 pairing with three -- three -- forgive me, let me
6 go back.

7 Just as K37 -- K370 is not an issue for --
8 for generating a pair with 364, neither would --
9 and you were mentioning K409 and K392, the
10 formation of pairs with F405.

11 Q Okay. So let's see if I can make sure
12 that we're clear.

13 It's your position that changing or
14 putting a positively charged amino acid residue at
15 position 405 would not be a concern -- a POSA
16 would not be concerned with that because there
17 was -- even though they were already known to have
18 positively charged residues, the interacting amino
19 acids to be 392 and 409, correct?

20 A Yes.

21 Q Okay. In other words, even though
22 position 405 is known to interact with three

1 different amino acids, it is not a concern to put
2 a positive charge there because positions 392 and
3 409 are already part of salt -- the known salt
4 bridges; is that correct? Is that your position?

5 A Yes.

6 Q Okay. And similarly, putting a positively
7 charged amino acid at position 407 would not be a
8 concern for a POSA because -- even though there
9 are already four amino acid residues that it
10 interacts with because there is only one positive
11 charge at position 409, which is part of an
12 existing salt bridge; is that correct?

13 A Would you repeat the question?

14 Q Sure.

15 Similarly, if a POSA had a positively
16 charged amino acid residue at position 407, that
17 POSA would not have a concern with that, even
18 though they were -- there are four known amino
19 acid residues it interacts with because the only
20 positive charged amino acid residue it interacts
21 with is at position 409, which is a known,
22 existing salt bridge, correct?

1 A I -- I won't -- I can't agree with that
2 statement because you've broadened it from just
3 considering the interaction of the charge residue
4 that it generates in chain A and the residues in
5 chain B on a -- am I concerned about their
6 charges, existing charge -- on the basis -- am I
7 concerned about their existing charges to -- to
8 broaden it to, am I concerned about the -- the
9 environment of the pair that I'm considering to
10 make.

11 Q Okay.

12 A So -- I'll stop there.

13 Q Let's make sure we're clear.

14 A Yes.

15 Q You are not concerned with the fact that
16 there are other amino acid residues that pair with
17 40 -- that interact with amino acid 407 that are
18 charged when considering a potential electrostatic
19 steering strategies for forming heterodimeric
20 antibodies, correct?

21 A I'm not especially concerned about
22 the charge -- the charge -- the apparent charge,

1 charge being negative. But I am concerned about
2 the fact that the -- in the examples that you've
3 moved on to, compared with 364. These are more
4 complicated environments with more complicated
5 contacts.

6 And so a POSA would be looking for the
7 simplest possible arrangement of -- of a -- where
8 the crystal structure shows contacts predominantly
9 between two amino acid residues.

10 So just to make myself clear, I -- so I'm
11 sorry I'm being a bit convoluted here. S364 makes
12 extensive interactions with 368. So going back to
13 364, a POSA would look at the data at 364 --

14 (Reporter clarification.)

15 A A POSA would look at the data in table 7,
16 as we were discussing a little earlier, and would
17 realize that Leucine 368 was a good partner
18 because there are many contacts with that residue
19 and would be less worried about, as I indicated,
20 about the -- the Lysine 370, because Lysine 370 is
21 already neutralized as part of salt bridges.

22 You've drawn my attention to other

1 examples where the same sorts of logic can be
2 applied, but the interaction -- what the data in
3 table A correctly indicates is the interaction
4 between the two examples you gave, F405 and Y407.
5 The interaction is more complicated because it --
6 it involves more immediate residues in the
7 vicinity -- more residues in the immediate
8 vicinity.

9 Q Okay.

10 A And I'll finish by just saying that we --
11 we'll be looking there if you were going to follow
12 F405 or Y407. You would make -- you're going to
13 have to make a mutation in that region of -- on
14 the other -- across the interface. And that's
15 going to be more difficult to -- to handle, to
16 deal with, likely to be more effective --

17 Q So Doctor --

18 A -- if it's a complicated interaction.

19 I'm sorry, I'm --

20 Q Okay. So let me break this down into a
21 couple of parts. I just want to make sure I
22 understand your position.

1 So a POSA looking at the information
2 contained in table A would understand that you're
3 going to look at the amino acid residues that had
4 the simplest interactions or the least
5 interactions when looking to perform electrostatic
6 steering.

7 Is that your position?

8 A Not the least -- not least number of
9 interactions, but the interactions were focused on
10 a single residue. So most of the interactions, as
11 is the case between Serine 364 and Leucine 368,
12 that interacting pair represents most of the
13 interactions between Serine 364 in chain A and the
14 interactions with chain B.

15 Q Okay. So let's make -- see if I
16 understand what you're saying correctly.

17 A POSA looking at the information
18 contained in table A would know that when
19 considering an electrostatic steering approach,
20 one of the simplest things to look for is a
21 mutation or a pairing between 364 and 368, a
22 positive to a negative; is that correct?

1 ATTORNEY MARGOLIS: Objection. Vague.

2 A You've introduced into your description
3 "electrostatic steering," which is a term used
4 in -- in the Gunasekaran paper. In the title of
5 the paper, it refers to electrostatic steering,
6 the effects. And that's -- that's a general term
7 for formation of salt bridges, stabilized
8 structures.

9 Q I'll ask --

10 A But we haven't actually used that phrase
11 yet in -- in relation to what we're trying to do
12 here.

13 Q So I'll withdraw the question and ask
14 it -- well, I'll ask the question a little
15 differently.

16 It's your position -- again, I'm just
17 trying to make sure I understand your opinion in
18 this -- in these matters.

19 It's your position that the information
20 that's contained in table A would tell a POSA that
21 when considering positive and negative pairs of
22 amino acid residues, one of the simplest positions

1 to focus on would be the pairs 364 and 368.

2 Is that your -- is that your opinion?

3 ATTORNEY MARGOLIS: Objection. Vague.

4 A I agree that a POSA would look at table A
5 and would see a -- a relatively
6 straightforward-looking situation for -- for 364,
7 because there is 368 as a stand-out partner,
8 potential partner for 364.

9 Q Okay.

10 A There is only one other residue involved.
11 And in fact, the POSA might appreciate the crystal
12 structure that -- the contact between 364 and 370.
13 It's actually only one or two Van der Waals
14 interaction. So it's a very slight interaction.
15 But nonetheless, the -- whether or not that was
16 appreciated, K370 is involved in a salt bridge, as
17 we've described, and is therefore in the -- within
18 the context of the structure, neutralized. And so
19 it's not going to be sitting there as a positive
20 charge.

21 (Reporter clarification.)

22 A Positive charge, it's not going to be in

1 the structure with a full positive charge because
2 it's neutralized by the salt bridge partner.

3 Q Okay.

4 A We still -- we have a plus-minus
5 interaction still. So although it's not going to
6 act as a free positive charge, it's still there,
7 but it is only a single residue. And the --
8 whereas the other examples that you showed me
9 involve a similar argument to say, well, we -- we
10 shouldn't perhaps worry about the positive charges
11 that we see there because they're part of salt
12 bridges.

13 But there are two or more. There are
14 three of them. So the environment -- we want to
15 be in a situation where we've got two residues
16 that are clearly responsible for the majority of
17 the interaction at that point.

18 And we don't want to have a situation
19 where any other residues have to be involved,
20 because the engineering of a mutation is going to
21 cause some structural reorganization.

22 Q So Doctor, I just -- I'm going to take

1 this in pieces --

2 A Yes.

3 Q -- because when it goes on very long, it
4 becomes complicated. So I want to take this in
5 parts.

6 A Sure.

7 Q It's your position that a POSA looking at
8 table A --

9 A Yes.

10 Q Withdrawn.

11 It's your position that a POSA looking at
12 the information contained in table A is -- what
13 shows the known CH3 domain interface residues,
14 will look at this table and see that one of the
15 simplest or easiest amino acid residues to form a
16 positive-negative pair is positions 364 and 368;
17 is that correct?

18 ATTORNEY MARGOLIS: Objection. Vague.

19 A It's -- it -- it looks from table A
20 as a -- as a very promising example because of the
21 simplicity you've just described. There may be
22 others.

1 Q Okay. So a POSA looking at table A,
2 according to you, would say that making
3 modification -- positive modification at 364,
4 should then make a negative mutation at position
5 368, according to you, correct?

6 A Correct.

7 ATTORNEY MARGOLIS: Objection. Vague.

8 Q Now, I just want to make sure we're clear.
9 It's your position that somebody looking
10 at position 351, on the other hand -- well,
11 withdrawn. Withdrawn.

12 I want to turn our attention to table 7,
13 if we can. And I'm referring to table 7 of the
14 '935 provisional application, which is
15 Exhibit 1030 to the '605 IPR, and it's about
16 page 52, I believe, Doctor.

17 A Yes.

18 Q Okay. Now, when I look at table 7 -- I
19 want to make sure I understand the information
20 that's contained there.

21 The title is, "List of amino acid
22 substitutions and the various constructs that were

1 made (EU numbers)."

2 Is that right?

3 A That's correct.

4 Q Okay. And table 7 is showing us the
5 effect on homodimer formation for specific amino
6 acid substitutions in the CH3 domain; is that
7 correct?

8 A Yes, that's correct.

9 Q Table 7 does not provide any information
10 whatsoever on heterodimer formation, correct?

11 ATTORNEY MARGOLIS: Objection. Vague.

12 A By implication, it does, because if -- if
13 there is -- effective inhibition of
14 homodimerization, then the heterodimerization will
15 be promoted.

16 Q Isn't it true that you can have an effect
17 promoting or inhibiting homodimer but also have
18 a -- an effect inhibiting heterodimer formation?

19 A There may be instances where -- well, no,
20 I -- let me say -- let me start again and say that
21 the -- if you -- if you can inhibit
22 homodimerization, then it's a good indication that

1 that is going to promote heterodimerization.

2 I -- I -- wouldn't rule out that there
3 might be some instances where the inhibition of
4 homodimerization might not -- might not yield
5 to -- to automatically lead to high
6 heterodimerization, but a POSA looking at the data
7 would take the straightforward view that
8 inhibition of homodimerization is a good way --
9 good place to start.

10 Q Okay. So I want to make sure we're clear.

11 It's your position that the data contained
12 in table 7 gives a POSA an -- an idea of a good
13 place to start --

14 A Yeah.

15 Q -- when considering to make heterodimers,
16 correct?

17 A Correct.

18 Q Okay. You will agree with me, however,
19 that the data contained in table 7 of the '935
20 provisional application does not actually provide
21 any data on the rate of heterodimerization,
22 correct?

1 A Correct.

2 Q You'll agree with me that the information
3 contained in table 7 does not actually show me any
4 corresponding positive and negative pairs forming
5 heterodimers, correct?

6 A Correct.

7 Q You'll agree with me that the data
8 contained in table 7 does not in any way tell a
9 POSA explicitly to pair a positive 364 and
10 negative 368 amino acid for a heterodimeric
11 antibody, correct?

12 A No, it does. I disagree. It does provide
13 direct information that --

14 Q Where within table 7 was there a test
15 pairing 364 plus and 368 minus?

16 A That wasn't explicitly tested.

17 Q Okay.

18 A But that's not -- I don't rely on that for
19 the statement that I made earlier.

20 Q Okay. So my question -- I'll ask the
21 question again.

22 You'll agree with me that the data

1 contained in table 7 does not in any way tell a
2 POSA explicitly to pair positive 364 and negative
3 368 for a heterodimeric antibody, correct?

4 A No, I -- I wouldn't agree with that
5 statement, because table 7 presents a number of
6 possibilities --

7 Q Table 7 --

8 A -- one of which we've been considering.
9 But it doesn't...

10 Q Okay. But let's -- there is no data in
11 table 7 showing a 364 plus, 368 minus,
12 heterodimeric antibody pair, correct?

13 A Correct.

14 Q All right. Table 7 does not include
15 specific information -- withdrawn.

16 I think you mentioned this earlier.

17 You will agree with me that just because
18 you have a decrease in homodimer formation does
19 not necessarily mean you will have an increase in
20 heterodimer formation, correct?

21 A In general, an increase in homo -- an
22 increased inhibition of homodimerization is going

1 to be coupled with a better production of the -- a
2 better yield of the heterodimer. But I -- I
3 qualified my answer by saying that there may well
4 be -- there may be some instances where a change
5 in the -- an inhibition of homodimerization is not
6 accompanied by the expected increase in
7 heterodimer formation, but -- but the expectation
8 would be that it would.

9 Let me summarize what I'm trying to say.

10 The inhibition of homodimerization would
11 be expected to be associated with an increased
12 formation of heterodimerization.

13 Q Okay. So --

14 A I'm just qualifying it by saying that I
15 haven't considered every -- there may be data
16 outside of this --

17 (Inaudible. Reporter clarification.)

18 A I beg your pardon.

19 There may be other examples of data
20 outside this table where -- where you see
21 inhibition of homodimerization, but actually you
22 also see inhibition of heterodimerization.

1 Q So let's take this in -- let's take a
2 couple of parts here.

3 Is it your position that if I see an
4 increase in -- withdrawn.

5 Is it your position that if I see a
6 decrease in homodimer formation, that would tell a
7 POSA there should be an increase in heterodimer
8 formation?

9 A Yes.

10 Q Okay. So a POSA looking at table 7 would
11 say that if I see a decrease -- withdrawn.

12 A POSA looking at table 7 of the '935
13 patent, according to you, if they see a decrease
14 in homodimer formation, they would believe there
15 would necessarily be an increase in -- well,
16 withdrawn. I put the word "necessarily" in. I'll
17 take that out.

18 It's your position that a POSA looking at
19 table 7 of the '935 provisional application if
20 they see a decrease in homodimer formation, they
21 would believe there would be an increase in
22 heterodimer formation, correct?

1 A Correct.

2 Q Okay. Now, I just want to make sure I'm
3 clear.

4 It's your -- you do need to pair the
5 homodimer -- the constructs that we're seeing on
6 table 7 with a corresponding monomer, right?
7 Withdrawn.

8 When I look at table 7 and I see a
9 decrease in homodimer formation, you still need to
10 pair the amino acid substitutions that are
11 identified here with the corresponding amino acid
12 substitution on the other chain, correct?

13 A Yes.

14 Q And is it your position that it doesn't
15 matter what amino acid residues I have on the
16 second chain; you're still going to have an -- an
17 increase in heterodimer formation?

18 A Yes, that's the general expectation, yes.

19 Q Okay.

20 A The caveat is that there may be some
21 examples where this doesn't always work. But,
22 yes, that's the expectation.

1 Q It doesn't matter what mutations I have on
2 the second chain. As long as I see a decrease in
3 homodimer formation on the first chain, that will
4 mean I will have an increase in heterodimer
5 formation according to you, correct?

6 ATTORNEY MARGOLIS: Objection. Vague.

7 A Yes, I generally agree with that.

8 Q Okay. Now, when I look at table 7 of the
9 '935 provisional application, the right-hand
10 column goes from negative, which is no effect, to
11 plus-plus-plus, which is max inhibition, correct?

12 A Correct.

13 Q And that means that -- plus-plus-plus
14 means it has a max -- the lowest amount of
15 homodimer formation?

16 A It means that the -- it means that the
17 inhibition of homodimerization is -- is higher for
18 those with three pluses than those with two
19 pluses, et cetera.

20 Q Okay.

21 A Which is virtually what you said, but...

22 Q Yeah, I just want to make sure --

1 A Yes, yes.

2 Q -- we're on the same page.

3 In other words, when I look at table 7,
4 anything that has a plus-plus and a
5 plus-plus-plus, in your mind, would be mutations
6 that show a decrease in homodimer formation and a
7 necessarily increase in heterodimer formation,
8 correct?

9 ATTORNEY MARGOLIS: Objection. Vague.

10 A When you made a similar statement earlier,
11 you withdrew the term "necessarily," but -- and I
12 don't agree with you that -- it's extremely likely
13 that if you -- if you find a mutation that has a
14 positive effect on homodimerization that would
15 result in a reduction of homodimerization, the
16 expectation -- the likelihood is that this will be
17 accompanied by an increase in heterodimer
18 formation.

19 Q Let's make sure we're clear on this.

20 It's your position that looking at
21 table 7, any constructs that had a plus-plus or a
22 plus-plus-plus, so two pluses and three pluses,

1 will have a high likelihood of -- or an
2 expectation that there would be an increase in
3 heterodimerization?

4 Is that your position?

5 ATTORNEY MARGOLIS: Objection. Vague.

6 A Table 7 indicates that those with three
7 pluses or two pluses would be -- would be
8 associated with -- actual heterodimer formation,
9 but would be particularly good candidates for
10 enhancements of such an effect by making mutations
11 that generated a plus-minus interaction across the
12 interface.

13 Q Okay. Doctor, will you agree with me it's
14 your position that the inventors of the '935
15 provisional application had a good understanding
16 of the homodimer and heterodimer formation?

17 ATTORNEY MARGOLIS: Objection. Lacks
18 foundation. Calls for speculation.

19 A Could you repeat your question?

20 Q Sure. And I'll try to address the
21 objection.

22 You've read the '935 provisional

1 application, right?

2 A Yes.

3 Q Based on your review of the '935
4 provisional application, would it be your
5 understanding that the inventors had a good
6 understanding of homodimer and heterodimer
7 formation?

8 A Yes, for sure.

9 Q Okay. And it's -- is it your position,
10 based on your review of the '935 provisional
11 application, that the inventors would have a good
12 understanding of what would and would not be
13 promising constructs to move forward with for
14 identifying good mutations that promote
15 heterodimerization?

16 A Yes.

17 Q Okay. Now, it's your position that
18 starting from table 7, the reason why you would
19 find position 364 promising -- I'll be clear,
20 position 364K promising was because it showed a
21 plus-plus, two positives, in the column of effect
22 on homodimer formation, correct?

1 A Correct.

2 Q So anything with a plus-plus and a
3 plus-plus-plus, in your mind, would be considered
4 promising for consideration of forming
5 heterodimers, correct?

6 ATTORNEY MARGOLIS: Objection. Vague.

7 Q Withdrawn.

8 ATTORNEY ASHKENAZI: Why don't we take a
9 break.

10 (Recess.)

11 BY ATTORNEY ASHKENAZI:

12 Q Welcome back.

13 So we're still on table 7 --

14 A Yes.

15 Q -- of the '935 provisional application.

16 And you have that in front of you, Doctor?

17 A I do.

18 Q Okay. Table 7, just so we're clear,
19 starts on page 52, and it goes through page 54; is
20 that correct?

21 A Correct.

22 Q Now, table 7 lists one example of a single

1 substitution at L368; is that right?

2 A Sorry, L --

3 Q 368.

4 A -- 368.

5 Q And you'll see that's on the first page?

6 A Yes.

7 Q Page 52.

8 A Yes.

9 Q Okay. So Doctor, you'll agree with me
10 that L368K was not actually tested, correct?

11 A Yes, apparently not.

12 Q Okay. Okay. So it doesn't have a rating
13 on homodimer formation, correct?

14 A Correct.

15 Q Now, just so we're clear, this table
16 relates to identical heavy chains to prevent
17 homodimerization, correct?

18 A Correct.

19 Q It does not relate to testing of heavy
20 chains with different modifications for
21 heterodimerization, correct?

22 ATTORNEY MARGOLIS: Objection. Vague.

1 A It relates to the issue of heterodimer --
2 heterodimerization.

3 Q Okay.

4 A Potential -- as we've earlier discussed,
5 but it is -- but these mutations are only tested
6 in --

7 Q Let me ask you this.

8 This table, table 7 of the '935
9 provisional application does not provide any data
10 relating to heterodimerization of two different
11 heavy chains, correct?

12 ATTORNEY MARGOLIS: Objection. Vague.

13 A I would answer by saying not directly but
14 by implication.

15 Q Not directly. By that, meaning there was
16 no actual data results from experiments that
17 show -- that test two heavy chains having
18 different modifications, correct?

19 A Correct, yes.

20 Q Now, it's your position that a POSA would
21 be discouraged from modifying positions 405 and
22 407 based on the information contained in table A

1 of the '935 provisional application, correct?

2 A Yes.

3 Q Okay. Now, if we could stay on table 7
4 now, you'll agree with me that the inventors
5 actually did -- withdrawn.

6 You'll agree with me that the '935
7 provisional application actually did test F405K
8 and Y407K in table 7 for homodimerization effects,
9 correct?

10 A Correct. The inhibition of --

11 (Reporter clarification.)

12 A Correct.

13 Q And in fact, the inventors found that when
14 you had modified F405K, that there was a triple
15 plus on effect of homodimer formation, correct?

16 A Correct.

17 Q And that triple-plus score would have
18 indicated that the inventors actually thought F405
19 could be a promising modification, correct?

20 ATTORNEY MARGOLIS: Objection. Calls for
21 speculation. Vague.

22 A Well, I -- they would see three pluses and

1 would -- would think that one was -- considering
2 further.

3 Q So according to you, reading the data
4 contained in table 7, a POSA would believe that
5 the inventors thought that F405K was promising and
6 worth pursuing further, correct?

7 A Correct on the -- to the extent that the
8 three positives in the column, but the POSA is
9 also aware that other considerations have to be
10 taken into account, such as those that we
11 discussed earlier, the complexity of the
12 interaction when we come to designing a pair,
13 so...

14 Q Now --

15 A Well, I'll --

16 Q Okay. I just want to make sure we're
17 clear.

18 It's your position that three pluses in
19 table 7 shows that there was a decrease in
20 homodimer formation, a max effect, correct?

21 A A maximum inhibition, yes, of homo.

22 Q And accordingly, according to you, F405K

1 would show an increase in heterodimer formation?

2 A Very likely.

3 Q Okay. And therefore, a POSA would
4 consider that promising when -- well, withdrawn.

5 Therefore, a POSA reading the '935
6 provisional application would consider the F405 --
7 405K modification to be promising for heterodimer
8 formation, correct?

9 ATTORNEY MARGOLIS: Objection. Vague.

10 A Promising for further consideration.

11 Q Okay. Now, let's look at Y407K.

12 Y407K has a plus-plus in table 7 of the
13 '935 provisional application, correct?

14 A Correct.

15 Q And you'll consider a plus-plus to be a
16 good score with respect to inhibition of homodimer
17 formation, correct?

18 A Correct.

19 Q And you would agree with me that the --
20 that a POSA, reviewing the '935 provisional
21 application, including table 7, would consider
22 Y407K, as promising for further pursuit, correct?

1 ATTORNEY MARGOLIS: Objection. Vague.

2 A Yes, it would be worth further
3 consideration.

4 Q Right.

5 And you'll go with me even further, which
6 is that a POSA reading table 7 of the '935
7 provisional application would see the double-plus
8 score for Y407K and believe that there would be an
9 increase in heterodimer formation, correct?

10 A Very likely.

11 Q Okay. Now, you'll agree with me that the
12 inventors didn't -- with respect to F407 and Y4 --
13 withdrawn.

14 Table 7 isn't the only place that the
15 inventors show modifications at F405 and Y407, is
16 it?

17 Why don't I help guide you, Doctor.

18 A Well, are you asking --

19 Q I'll point you to where I'm focused on.

20 A Okay.

21 Q You'll agree with me that -- well, you've
22 reviewed the '935 provisional application,

1 correct?

2 A Correct.

3 Q Okay. I'd like to turn your attention to
4 table B on page 31.

5 Now, you start on page 30, right before
6 table B, if you can. You'll see at the bottom of
7 page 30 of the '935 provisional around lines 29 --
8 28.

9 A At the bottom of page --

10 Q At the bottom of the page, yes.

11 Are you there, Doctor?

12 A I am.

13 Q Okay. And it describes what information
14 is contained in table B, correct?

15 A Yes.

16 Q And here, the '935 provisional application
17 says table B provides "an overview of mutations
18 that can be introduced in the CH3 domain as
19 preferred means for preferentially pairing to
20 create either heterodimers or homodimers," right?

21 Do you see that, Doctor?

22 A Those are words that you just read.

1 Q I'm sorry?

2 A This is -- table B is those constructs,
3 and you just described it as a list of constructs
4 that were -- and those words, where did those
5 words come from?

6 Q They're on page 30. The last two lines on
7 page 30, right before table B.

8 A Oh, I -- I beg your pardon.

9 Yes, you read it, yes.

10 Q Let's start again, okay?

11 A Yeah.

12 Q You'll agree with me that the '935
13 provisional application identifies table B on
14 page 30, last two lines on the page, as "an
15 overview of mutations that can be introduced in
16 CH3 domains as preferred means for preferentially
17 pairing to create either heterodimers or
18 homodimers."

19 Do you see that?

20 A I do.

21 Q Okay. And you will agree with me that,
22 for example, construct 7 -- sorry, construct

1 number 7 does identify mutations to -- a mutation
2 to 407, correct?

3 A Yes.

4 Q Okay. And if we look at table 1 on
5 page 38 --

6 A Yes.

7 Q -- you'll see that the mutation of CH3 at
8 construct 7 that has a modification on the amino
9 acid 407 actually had an 86.7 percent bispecific
10 product reported, correct?

11 A Can you just repeat the numbers that I'm
12 looking for?

13 Q We're looking at construct number 7 --

14 A Yes, yes.

15 Q -- that pairs with construct number 6.

16 A Yes.

17 Q And that shows an 86.7 percent bispecific
18 product, correct?

19 A Correct.

20 Q Okay. In other words, the '935 -- in
21 other words, the '935 provisional application
22 shows that the inventors were making modifications

1 to position 407 to increase heterodimerization,
2 correct?

3 A Yes.

4 Q Okay. And in fact, if we look on page 38,
5 around line 18 of the '935 provisional
6 application, it says, "Constructs 1, 2, and 3, or
7 alternatives thereof, have previously been
8 described to drive heterodimerization," there is a
9 parentheses. And it goes on to say, "as have
10 constructs 6 and 7."

11 Do you see that?

12 A Yes.

13 Q In other words, the inventors of the '935
14 provisional application -- withdrawn.

15 In other words, the '935 provisional
16 application explicitly states that modifications
17 to the 407 amino acid, among other things,
18 increase heterodimerization, correct?

19 ATTORNEY MARGOLIS: Objection. Vague.

20 A I agree that mutation at 407Y to V in
21 construct 7, when made together with two other
22 mutations promotes heterodimerization.

1 Q Now, I want to make sure we're clear.

2 You've reviewed the '286 and the '859
3 patent claims, correct?

4 A I just want to be sure, the '286 --

5 Q I want to make sure, you've reviewed the
6 '286 and the '859 patent and the claims for both
7 of those patents, correct?

8 A Yes. Correct.

9 Q All right. You'll agree with me that
10 those claims allow for additional mutations, not
11 just the ones identified in the claims, correct?

12 ATTORNEY MARGOLIS: Objection. Compound.
13 Vague.

14 A I would like to see --

15 Q Sure.

16 You have the --

17 A -- where these statements are.

18 Q Well, sure.

19 You have the '859 patent in front of you?

20 A I have that one ready.

21 Q Okay. And I'm going to hand you the '286
22 patent as well.

1 Now, why don't we turn to the claims of
2 the '286 patent.

3 Now, looking at claim 1 of the '286
4 patent -- Doctor, let me know when you're there.

5 A I'm there.

6 Q Okay. Claim 1 of the '286 patent in
7 general talks about having a positively charged
8 amino acid residue in one CH3 domain and a
9 negatively charged amino acid residue in the
10 corresponding CH3 domain on the second heavy
11 chain, correct?

12 A That's -- that's correct.

13 Q Okay. Now, these claims do allow for
14 additional modifications to be made to the amino
15 acid residues on the heavy chains, correct?

16 A I prefer to see that in black and white.

17 Q Well, I'm asking what you understand from
18 the claims. So let's -- let's restart so we make
19 sure we're on the same page.

20 As part of your analysis in this case, you
21 did review claim 1 of the '286 patent, correct?

22 A Yes.

1 Q Okay. And you have an understanding
2 that -- of what that claim covers, correct?

3 A Yes.

4 Q And you will agree with me that claim 1 of
5 the '286 patent does allow for additional
6 modifications to be made to the heterodimeric
7 antibody, correct, other than those listed
8 specifically in the claim itself?

9 A (Document review.)

10 Q Doctor?

11 A Claim 1 of the '286 patent claims a method
12 for producing heterodimeric antibodies by having
13 at least one substitution of a neutral amino acid
14 by a positive in one chain and at least one
15 substitution.

16 So yes, the wording admits the possibility
17 that other mutations can be made.

18 Q In other words, a POSA could combine and
19 have numerous different modifications on the CH3
20 domains for both heavy chains and fall --

21 (Reporter clarification.)

22 Q In other words, a POSA can make multiple

1 modifications to both CH3 domains on the heavy
2 chains and still fall within the scope of claim 1
3 according to you, correct?

4 A Correct, yes, because it's -- yes,
5 correct.

6 Q Okay. And in fact, you will agree with me
7 that it was known in the prior art that having
8 multiple modifications can increase -- withdrawn.

9 And you'll agree with me that it was known
10 in the prior art that having multiple
11 modifications in the CH3 domains on both sides of
12 the heavy chain can increase the rate of
13 heterodimerization, correct?

14 ATTORNEY MARGOLIS: Objection. Vague.

15 A I would like to be definitive if that's
16 stated in the literature.

17 Q Okay. Well, you've reviewed the
18 literature with respect to bispecific antibodies,
19 correct?

20 A I've reviewed literature, but relevant
21 to bispecific -- I haven't reviewed the entirety
22 of the literature.

1 Q Okay. You have reviewed the literature
2 that you've cited in your -- in your declarations,
3 correct?

4 A Yes, that's correct.

5 Q Okay. You are familiar with the
6 knob-in-hole concept for increasing
7 heterodimerization that was known in the prior
8 art?

9 A Yes.

10 Q Okay. And you are familiar with disulfide
11 bonds that were used to increase heterodimeric
12 formation in the prior art as well, correct?

13 A Yes.

14 Q Now, you'll agree with me that
15 knob-in-hole and disulfide bonds, those are
16 different techniques for increasing
17 heterodimerization, correct?

18 A Correct.

19 Q And you'll agree with me that it was known
20 in the art that you can use orthogonal methods to
21 increase the rate of heterodimerization, correct?

22 A Correct.

1 Q And in fact, one example of using
2 orthogonal methods for increasing the rate of
3 heterodimerization is combining knob-in-hole and
4 disulfide --

5 (Reporter clarification.)

6 Q And in fact, you'll agree with me that one
7 example of using orthogonal methods for increasing
8 the rate of heterodimerization was combining
9 knob-in-hole and disulfide bonds strategies,
10 correct?

11 A Correct.

12 Q Okay. Therefore, it was known that you
13 could combine different strategies that were known
14 to improve the rate of heterodimerization to
15 increase that rate even further, correct?

16 A Yes, correct.

17 Q Okay. Now, going back to table 7 if we
18 can.

19 So Doctor, looking at your second
20 declaration, I want to turn to paragraph 56. And
21 please let me know when you're there.

22 A Referring to my second declaration --

1 Q In the '605 IPR for the '859 patent.

2 A '859 yes, yes.

3 Q Thank you very much for that. And I
4 appreciate the -- the need for being specific.
5 It's very important for the court reporter. So
6 thank you for that.

7 Okay. So let's start.

8 Are you at paragraph 56?

9 A Page -- pardon. Page -- oh, paragraph.

10 Q Paragraph 56. I think it's page 25.

11 A Yes.

12 Q You believe that -- based on your review
13 of table 7 of the '935 provisional application,
14 T366 and S364K substitutions occur most
15 frequently, right?

16 A Yes.

17 Q Okay. But in order to do that, you have
18 to remove the 405 and the 407 mutations, correct?

19 A Correct.

20 Q Okay. Now, you'll agree with me that the
21 366 mutation in table 7 appears more than the 364
22 mutation?

1 Apologies, Doctor. Let me take a step
2 back.

3 You will agree with me that the L351K
4 mutation appears in four variants, right?

5 And I'm looking at table -- if you go back
6 to the '935 provision, so I think it's --

7 A Yeah, I need table 7.

8 Yeah. Okay.

9 Q I'm going to draw your attention to
10 specifically construct 14.

11 A Yes.

12 Q You'll see that has an L351K mutation,
13 right?

14 A Yes.

15 Q The same thing with construct 16, 21, and
16 40, right?

17 A Yes. Yes.

18 Q Okay. And you'll agree with me that those
19 four constructs, 14, 16, 21, and 40, each have two
20 pluses or three pluses, correct, with respect to
21 effect on homodimer formation, correct?

22 A Yes.

1 Q Okay. And that's more times than the T366
2 or S364 have two pluses or three pluses with
3 respect to homodimer formation, correct?

4 A Yes -- yes, yes.

5 Q Okay. So you'll agree with me, then, that
6 if a POSA was looking at the frequency of the
7 variants that appear in table 7 to determine which
8 variants the inventors thought were most
9 promising, the POSA would be guided to L351K,
10 correct?

11 ATTORNEY MARGOLIS: Objection. Lacks
12 foundation.

13 A Well, I agree. They would -- they would
14 look at L351K and see that as a -- promising.

15 Q And you've offered no opinion in your
16 declaration for why a POSA would not have
17 considered L351K at least as promising as T366 or
18 S364, correct?

19 A Well, I haven't in my analysis of this
20 weighed up all the relative advantages,
21 disadvantages of the different mutations that
22 might promise -- a number that would look

1 promising.

2 Q Okay. Just so we're clear, in your
3 report -- sorry, in your declarations that you
4 submitted in the IPR here, specifically the '605
5 IPR, you have offered no opinions why for a POSA
6 would not have considered L351K at least as
7 promising as T366 or S364, correct? And mutations
8 to those --

9 A Well --

10 Q -- correct?

11 ATTORNEY MARGOLIS: Objection. Vague.

12 A I have in my declaration noted that these
13 residues, in particular T366K that you referred
14 to, looked promising.

15 I mean, I -- I don't think the POSA would
16 look at this table and say: I'm going to take one
17 conclusion from this.

18 I would look at this -- these data and --
19 and apply a number of criteria as we've discussed
20 earlier and come up with a list.

21 And --

22 Q So --

1 A -- so I'm saying here, I -- T366K occurs
2 frequently, and they sometimes get high ratings.

3 Yes, 364K also appears.

4 Q Doctor, that wasn't my question. I want
5 to make sure it's clear.

6 A Okay.

7 Q In your declarations -- in your
8 declaration, you have or ever offered no opinion
9 for why a POSA would not have considered L351K at
10 least as promising as mutations to T366 or S364,
11 correct?

12 ATTORNEY MARGOLIS: Objection. Vague.

13 A I haven't made a comment about L351K,
14 that's correct.

15 Q All right. Now, I think you mentioned
16 earlier that there are a number of different
17 mutations that a POSA would consider as promising
18 from table 7 of the '935 provisional application,
19 correct?

20 A Correct.

21 Q Okay. So -- and we discussed some of
22 those would include S364K, T366K, L351K, F405K,

1 and Y407K, correct?

2 A We have discussed those, yes.

3 Q And we've discussed that a POSA reading
4 table 7, from your perspective, would consider
5 those as promising for further pursuit, correct?

6 ATTORNEY MARGOLIS: Objection. Vague.

7 A They -- yes, yes, yes.

8 Q Okay. And the point here is that a POSA
9 looking at this would look at the data and say:
10 Well, this is something that I can consider to
11 look into further.

12 Correct?

13 Withdrawn. Let me make the question a
14 little clearer.

15 It's your opinion that a POSA looking at
16 table 7 would say: There is some interesting data
17 in here that I think identifies some amino acid
18 modifications that could potentially promote
19 heterodimerization, so I'll consider those
20 further.

21 Is that your position in this case?

22 ATTORNEY MARGOLIS: Objection. Vague.

1 A Yes.

2 Q Okay. Now, when I look at -- the
3 inventors didn't only conduct experiments in
4 table 7.

5 Withdrawn. I'll ask the question a little
6 clearer.

7 There were a number of different
8 experiments that were reported by the inventors in
9 the '935 provisional application, correct?

10 A Yes, we -- yes, we've --

11 Q And table 7 is just one experiment that
12 they ran to identify potential modifications that
13 could be made to the CH3 domain for promoting
14 heterodimerization, correct?

15 A It is one experiment that they ran.

16 Q Now, I want to be clear. The goal for the
17 inventors and a POSA is to get -- promote
18 heterodimerization, correct?

19 A Correct.

20 Q The goal is not -- the goal for the
21 inventors and a POSA would not be with respect to
22 bispecific antibodies promoting homodimerization,

1 correct?

2 A Correct.

3 Q Okay. But at the end of the day, with
4 the -- what a POSA wants and what the inventor
5 want is not just a decrease in homodimer rate, but
6 rather an increase in heterodimerization, correct?

7 A Yes, correct.

8 Q Now, if we can turn to -- in your
9 declaration, you have not provided a reason why a
10 POSA would choose S364K over T366K, correct?

11 ATTORNEY MARGOLIS: Objection.
12 Mischaracterizes.

13 Q I'll withdraw the question and ask it a
14 little differently.

15 A POSA reading the '935 provisional
16 application -- withdrawn.

17 You'll agree with me that the '935
18 provisional application actually did a number of
19 additional tests on T366K, correct?

20 A I believe we looked at one just now.

21 Q And I'm talking about outside of table 7,
22 right?

1 A Yeah.

2 Q I'll draw your --

3 A Yeah, yeah, yes.

4 Q I'll draw your attention to table 11,
5 table 12, example 15. So with that, I'll ask my
6 question again, Doctor.

7 You'll agree with me that the '935
8 provisional application actually contained a
9 number of additional experiments on the T366K
10 mutation for promoting heterodimerization,
11 correct?

12 A While I look through these examples of
13 further experiments that were carried out, just to
14 save time, you're asking me to respond with
15 respect to --

16 Q I just gave you some examples, tables 11
17 and 12, example 15. I just want to make sure
18 we're on the same page that the '935
19 provisional --

20 A Yes.

21 Q -- application actually contained a number
22 of additional experiments on the T366K mutation --

1 A Just the T3 --

2 Q -- for promoting heterodimerization,
3 correct?

4 A I just wanted to check which particular
5 mutation you were -- you were looking at and...

6 (Document review.)

7 Q Would you like me to ask the question
8 again, Doctor?

9 A No.

10 I -- you'll appreciate that if I'm looking
11 for additional experiments carried out that relate
12 to mutations of that particular residue, I'm going
13 to need to first of all look up the -- know which
14 constructs that we're talking about to be sure
15 that -- that I can agree with you that certain
16 tables show further experimental data that relate
17 to a particular mutation, because the mutations
18 are not listed.

19 Q Yes, they are.

20 A Well, they are through the construct
21 numbers.

22 Q That's -- okay.

1 A Yeah.

2 Q Doctor, why don't we move on. And if I
3 have time a little later, I'll get back to it,
4 okay?

5 Let's make sure we're clear on one thing,
6 though. The only data, and I'm talking about
7 experimental data, that you referred to for S364K
8 is in table 7 of the '935 provisional application;
9 is that accurate?

10 ATTORNEY MARGOLIS: Objection. Vague.

11 A (Document review.)

12 I agree that the -- the principal basis
13 that -- that put Serine 364K on the promising list
14 for the POSA is the data in table 7. Whether I --
15 whether I have ruled -- made reference to other
16 experimental data might need to be taken -- might
17 be there to consider. I honestly just don't
18 remember at the moment because it's been a while
19 since I read the particular wording.

20 Q Okay.

21 A But I'm certainly aware that there are
22 other experiments -- experimental data relating to

1 these mutations and this list of potential
2 mutations that a POSA has. There are additional
3 experiments reported in -- in the provisional
4 application.

5 Q Okay.

6 A Is that -- does that answer your question?
7 Forgive me for asking you a question, I should
8 say.

9 ATTORNEY ASHKENAZI: Why don't we go off
10 the record.

11 (Luncheon recess.)

12 BY ATTORNEY ASHKENAZI:

13 Q Dr. Sutton, just so we're clear, did you
14 speak about the substance of the deposition during
15 any of the breaks today?

16 A No, not at all.

17 Q Thank you.

18 I want to shift our attention to, for the
19 time being, to the '604 IPR, which relates to the
20 '286 patent. And I'm going to focus on your
21 declaration, which was -- the second declaration,
22 which was Exhibit 2016.

1 Actually, let's start with your first
2 declaration, if we can. So we're looking at the
3 first declaration from the '286 IPR?

4 A Sure.

5 Q So that's probably your first tab.

6 A So this is -- that's the second one.

7 Q I think it's going to be probably the
8 first one.

9 A Yeah.

10 Q Okay.

11 A Good.

12 Q So let's start, if we can -- so in your
13 first declaration in the '286 patent IPR, the '604
14 IPR, you provided a definition for heavy chain,
15 correct?

16 A Excuse me, yes, I did.

17 Q Okay. And it was your assertion that you
18 were providing a definition of the term "heavy
19 chain" as it would have been understood to the
20 person of ordinary skill in the art at the time of
21 the filing of the patent in 2012, correct?

22 A Yes.

1 Q And it was your assertion that that -- in
2 your first declaration, the definition that you
3 provided for heavy chain was what a POSA would
4 understand was the ordinary and customary meaning
5 for that term, correct?

6 A Correct.

7 Q Now, it is your position that there was no
8 explicit definition in the '286 patent defining
9 what the term "heavy chain" is, right?

10 A Yes, that's correct.

11 Q But you'll agree with me that the board
12 did not adopt your definition of the term "heavy
13 chain" that you put forth in your first
14 declaration in the '604 IPR?

15 ATTORNEY MARGOLIS: Objection. Calls for
16 a legal conclusion and lacks foundation.

17 A Do you want me to go ahead and answer the
18 question?

19 Can we look at the --

20 Q Well, let me -- let me --

21 A Is it a general question or --

22 Q Why don't I withdraw the question --

1 A Yeah.

2 Q -- because the record is what it is. So
3 let me withdraw the question and try to start
4 somewhere different.

5 If we could turn to paragraph 46 of your
6 first declaration, Exhibit 2008 in the '604 IPR.

7 A Paragraph?

8 Q 46.

9 Are you there, Doctor?

10 A Yes.

11 Q Okay. And at the end of paragraph 46, you
12 say, "A POSA would understand that the '286 patent
13 is directed to producing bispecific antibodies
14 with two heavy chains, each having VH1, CH1, CH2,
15 and CH3 domains and two Fab arms, each with a
16 different binding-site specificity."

17 Do you see that?

18 A I do.

19 Q And is that what you believe the -- the
20 understanding of the term "heavy chain" should be
21 as a POSA would understand it in the context of
22 the '286 patent?

1 A It's a description of the definition of a
2 heavy chain in relation to an IgG molecule. And
3 two classes of human antibody have -- have more
4 than one -- have an additional constant region
5 domain. And so to have a definition of heavy
6 chain that encompasses all five human subclasses
7 of antibody, we need to -- to speak about defining
8 antibody -- defining heavy chain as running from
9 the N-terminus -- the N-terminus of the V region,
10 VH domain, to the C-terminal residue of the most
11 C-terminal C domain. And so there might be IgM
12 and IgE --

13 Q In the case of IgM and IgE?

14 A I beg your pardon.

15 IgM and IgE, there might be -- there may
16 be one -- there will be one extra domain.

17 So in reading the sentence that you point
18 out to me, that refers to an IgG antibody.

19 Q Okay. So let's see if I can break this
20 down into a couple of parts.

21 A Okay.

22 Q You had originally proposed a definition

1 for the term "heavy chain" that had a VH, CH1,
2 CH2, CH3 and two Fab arms, each with different
3 binding-site specificity; is that correct?

4 A Yes, that's right.

5 Q And you have since said that that is the
6 only the way that the term "heavy chain" would be
7 understood within the context of an IgG antibody,
8 correct?

9 A I want to be clear about this. The -- the
10 sentence that we're referring to here, "A POSA
11 would understand the '286 patent is producing
12 bispecific antibodies" --

13 (Reporter clarification.)

14 A I'm sorry. I'm reading from this
15 paragraph 46, which -- to which we are drawing our
16 attention.

17 "A POSA would understand that the '286
18 patent is producing bispecific antibodies with two
19 heavy chains, each having VH, CH1, CH2 and CH3
20 domains and two Fab arms each with different
21 specificities."

22 And that would be -- that is a description

1 of a bispecific IgG antibody. And we were --
2 those antibodies that have been engineered and the
3 discussions we've been having about IgG antibodies
4 and the illustration that we use -- there
5 isn't one just here, but the illustration I used
6 in my second declaration of an IgG antibody,
7 but -- heavy chain should -- should be defined --
8 is common in -- is -- heavy chain can relate
9 to -- to any one of the five human subclasses, and
10 the definition should be more carefully written to
11 encompass those because they have more than three
12 constant region domains, for example.

13 And -- but the concept is the same. It's
14 still with -- heavy chain is the complete amino
15 acid sequence of the polypeptide chain starting
16 from the N-terminus of the VH domain, variable
17 heavy domain, through to the C-terminal domain --
18 residue of the C-terminal domain. And that's the
19 common -- that's the current usage -- that's the
20 only way in which the heavy chain should be used.

21 Going back to the original discovery of
22 it -- of heavy and light chains by Rodney Porter,

1 heavy chain is as I just described.

2 In the case of IgG, which he was working
3 on it, was in the VH. It was 1, 2, 3, 4 domains.
4 But we now know there are classes of antibody, and
5 so we broaden it -- the definition. So it is more
6 explicitly wrote later, but the concept is the
7 same. It's the whole --

8 Q Again, I want to take that in pieces. I
9 think you've had the opportunity to say what you
10 want to say.

11 A Yeah.

12 Q So try to listen, if you can, to the
13 questions, because it's going to be pieces of what
14 you were discussing.

15 With that, I'm going to start fresh.

16 You had originally put forth in your
17 opening -- in your first declaration,
18 Exhibit 2008, in the '604 IPR, a definition of
19 heavy chain that was a VH -- that each -- that
20 includes a VH, CH1, CH2, CH3 domains and two Fab
21 arms and a -- withdrawn.

22 You had originally put forth the

1 definition of a heavy chain in your first
2 declaration that included a VH, CH1, CH2, CH3 and
3 a Fab region, correct?

4 A That's -- that's pretty much what I wrote.
5 It's -- it is poorly written in the sense that the
6 two Fab arms are in addition to that. But I
7 think anyone look -- certainly a POSA looking at a
8 schematic diagram of an IgG antibody would --
9 would be -- would accept this, what has been
10 written here.

11 Q So --

12 A But in the absence of --

13 Q Doctor --

14 A I'll stop at that point. You ask me the
15 questions and I'll answer.

16 Q So let's just go to the question again.

17 A Yeah.

18 Q In your first declaration that you
19 submitted in the '604 IPR for the '286 patent, you
20 asserted that the heavy chain has a VH, a CH1,
21 CH2, CH3 domains and a Fab region, correct?

22 A Yeah. Yes, yes.

1 Q Okay. Now, the concept or what you were
2 looking for -- okay, withdrawn.

3 In your second declaration, you have now
4 changed that definition, correct?

5 ATTORNEY MARGOLIS: Objection.
6 Mischaracterizes.

7 Q Of heavy chain.

8 A No, I haven't changed the definition. I
9 have just been more explicit about the wording in
10 order to render it applicable to all five human
11 subclasses.

12 Q So in your original declaration, you
13 assume that the term "heavy chain" would be only
14 applicable to IgG antibodies, correct?

15 A No, no, I -- sorry, not correct. No, I
16 was -- I had in my mind an IgG molecule as my --
17 when I wrote that sentence. And --

18 Q So let me make sure that --

19 A -- I'm not --

20 Q Let me make sure that I'm clear.

21 A Okay.

22 Q In your first declaration, the

1 understanding that you put forth for a heavy chain
2 was based on the IgG naturally occurring antibody;
3 is that fair?

4 ATTORNEY MARGOLIS: Objection. Vague.

5 A The -- the heavy chain -- the heavy chain
6 and IgG antibody might be the wild-type antibody,
7 in which case it's the wild-type sequence. It
8 might also be an IgG antibody that has
9 incorporated mutations. But the heavy chain
10 definition, like the heavy chain is the -- it must
11 be defined as the -- as commonly understood as the
12 whole of the chain from the C-terminus to the --
13 the N-terminus of the VH domain to the C-terminus
14 of the most -- in the case of IgG CH3 domain --

15 (Reporter clarification.)

16 A IgG, for the IgG molecule, whether
17 wild-type or mutant, if it's -- if -- if it's an
18 IgG molecule, the heavy chain is always understood
19 to be the complete polypeptide chain from the
20 N-terminal residue of the VH domain through to
21 the --

22 (Reporter clarification.)

1 A I didn't finish. I apologize. I'm not
2 being very lucid. I'll warm up in a minute.

3 To the -- to the N-terminal domain --
4 N-terminal residue of the VH domain to the
5 C-terminal of the CH domain, CH3 domain. And that
6 would be a wild-type heavy chain. Or if there is
7 an mutation in the IgG molecule, that heavy chain
8 would carry a mutation, and we would refer to it
9 as a mutative heavy chain. But heavy chain refers
10 to the complete chain --

11 Q Okay.

12 A -- as I --

13 Q Doctor, I just, again -- and my questions
14 are a little narrower.

15 A Yeah, yeah.

16 Q I'm trying to take it in pieces, and I
17 think --

18 A Yeah.

19 Q -- we're doing a lot here, so I'm going to
20 try to take this in pieces.

21 A Okay.

22 Q In your original -- your first

1 declaration, Exhibit 2008 for the '604 IPR, the
2 words and the focus that you put on for heavy
3 chain was having in mind an IgG molecule; is that
4 correct?

5 A That's correct.

6 Q Okay. And you later said in your second
7 declaration that heavy chain should be expanded to
8 make sure that it includes any of the domains that
9 would be included in the naturally occurring Ig
10 molecules, including IgM and IgE, correct?

11 A Correct.

12 Q When you were doing your analysis for
13 claim construction, you began with what you
14 understood the understanding of the term "heavy
15 chain" should be to a POSA when considering the
16 naturally occurring Ig molecules; is that fair?

17 A Yes. Yes.

18 Q Okay. And you have said that's why you
19 need to expand or make sure that the definition of
20 heavy chain includes additional constant regions
21 to make sure that the IgM would be included in the
22 definition of heavy chain, correct?

1 A IgM and IgE, yes.

2 Q Okay. Now, you will agree with me that
3 the '286 patent isn't discussing exclusively
4 naturally occurring antibodies, correct?

5 A (Document review.)

6 Q I'll withdraw the question and I'll ask it
7 a little differently.

8 When you refer to Ig antibodies, the five
9 naturally occurring -- withdrawn.

10 When you refer to the Ig molecules, you
11 are referring to the naturally occurring
12 antibodies that we know of, including the IgG,
13 IgM, and IgE, correct?

14 A Could you repeat the question?

15 Q Sure.

16 When you were referencing the Ig
17 molecules, those are the Ig antibodies that we
18 know exist in nature, correct?

19 A When you say I was addressing --

20 Q Okay. I'll withdraw the question.

21 Let's do this a little different, Doctor.

22 A Yeah.

1 Q I want to make sure that we're getting
2 this right.

3 A All right.

4 Q Let's go to your second declaration.

5 A Yeah.

6 Q So that's Exhibit 2016 from the '604 IPR.
7 And I want to go to paragraph 25.

8 A My second declaration relating to the
9 '286?

10 Q Yes.

11 A Yes.

12 And to page --

13 Q Paragraph 25.

14 A Yes.

15 Q And this is where you provide your current
16 understanding of the term "heavy chain" with
17 respect to the -- as a POSA would understand it in
18 2012 in the context of the '286 patent, correct?

19 A I disagree with your implication that this
20 is my current -- this is my current definition.
21 It is a more complete definition of what is meant
22 and what is commonly understood by "heavy chain."

1 Q Okay. So --

2 A The -- heavy chain only means one thing
3 and --

4 Q Okay.

5 A -- this is what it is. And this is
6 written in such a way so it can encompass the
7 possibility that we might be talking about IgM
8 rather than IgG.

9 Q Okay. Let's make sure we're clear.

10 A Yeah.

11 Q You provide a definition in paragraph 25
12 of Exhibit 2016 in the '604 IPR for the term
13 "heavy chain," correct?

14 A Correct.

15 Q Okay. And you assert in this paragraph
16 that the term "heavy chain" has to mean "a
17 polypeptide chain starting at the N-terminal
18 residue in the variable region, VH, and ending at
19 the C-terminal residue in the final constant
20 region, CH, including all intervening constant
21 regions, CH, and the hinge region."

22 Is that correct?

1 A That's correct.

2 Q Okay. And you took this term, the way
3 you're applying it here is what you say a POSA
4 would understand the term "heavy chain" to be in
5 the art when referring to antibodies, correct?

6 A Yes.

7 Q And that's a complete, intact antibody
8 that you are referring to, correct?

9 A Yes, it's an intact antibody.

10 Q Okay. Now, you do recognize that the '286
11 patent does cover antibody fragments, right?

12 ATTORNEY MARGOLIS: Objection. Vague.

13 A I'm sorry, the -- the 28- -- which patent?

14 Q '286.

15 A '286, yes.

16 Well, the title of the patent is "Methods
17 and means for the production of Ig-like
18 molecules." So it's focusing on antibody
19 molecules and -- it refers to fragments of
20 antibodies, I'm sure, but...

21 Q The definition that you've applied for the
22 term "heavy chain," you did so in the context of

1 complete intact antibodies, correct?

2 A Correct.

3 Q Now, you will agree with me that your
4 definition of the term "heavy chain" requires
5 there to be a hinge region, right?

6 A Yes.

7 Q Okay. And it requires at least three CH
8 domains, correct?

9 A Yes, correct.

10 Q And your proposed construction of the term
11 "heavy chain" requires one VH domain, correct?

12 A Correct.

13 Q You will agree with me, at least, that the
14 patent allows for additional -- let's make sure
15 I'm clear. Withdraw the question.

16 You'll agree with me that the claims of
17 the '286 patent allow for additional regions to be
18 added on to the heavy chain -- heavy chains of the
19 antibodies that are being referenced in the
20 claims, correct?

21 ATTORNEY MARGOLIS: Objection. Vague.

22 A I can -- if additional domains are added

1 in the way you suggest, then the -- one would
2 describe it as -- well, it's described as such,
3 that they -- these would be additional domains
4 added to the wild-type antibody and the -- and
5 added to the polypeptide chain which was defined
6 as the heavy chain. Though, I'm -- that was not
7 very well expressed.

8 Q Why --

9 A The heavy chain means -- heavy chain is
10 understood to be that the polypeptide chain that
11 is present in the wild-type antibody, and if one
12 is discussing, describing molecules that are more
13 or less than that, then you would describe them in
14 terms of domains added to the heavy chain.

15 Q Okay. I'm handing you the Lazar
16 reference, which was Exhibit 1004.

17 And maybe just for ease of conversation --

18 A Yeah.

19 Q -- I just want to make sure I understand
20 your position.

21 So if you could, turn to figure 8 in
22 Lazar, which is on page 13 of 137 of Exhibit 1004.

1 A Yes.

2 Q And are you there, Doctor?

3 A I am.

4 Q Okay. So figure 8 describes a number of
5 different types of antibodies, correct?

6 A I wouldn't accept that --

7 Q Okay.

8 A -- the way you described it.

9 Q Okay.

10 A So no, it doesn't. It -- be more explicit
11 of what it does describe.

12 Q Sure.

13 So if you can keep figure 8 open from the
14 Lazar patent, and I want to just quickly go the
15 '286 patent as well, column 11, line 16. It's
16 going to be on page 47 of 79.

17 A I'm nearly there.

18 Can you repeat?

19 Q Column 11, line 16. And I'll start my
20 question.

21 Doctor, looking at the '286 patent,
22 column 11, line 16, it provides an understanding

1 of antibodies that are covered by the inventions
2 of the '286 patent, correct?

3 ATTORNEY MARGOLIS: Objection. Vague.

4 Q Doctor, is that correct?

5 A May I read it and just go through?

6 Antibodies are --

7 Q Why don't we break it down.

8 A Yes, yes.

9 Q Let me start -- let me withdraw the
10 question and restart.

11 Column 11 of the '286 patent, line 16
12 states, "An antibody, according to the invention,
13 may be any of these isotypes or a functional
14 derivative and/or fragment of these."

15 Do you see that?

16 A Yes, I see that.

17 Q Okay. And you will agree with me that the
18 understanding that you applied to the patents in
19 this case, the '286 and the '859, for the term
20 "antibody" was included at least functional
21 derivatives or fragments of the Ig isotype
22 antibodies, correct?

1 A We're talking about here wild-type
2 antibodies and antibody-like molecules based upon
3 the wild-type structures. And I think that's what
4 I -- if you're happy with that, I'm happy with
5 that.

6 Q In other words, the term "antibody" as
7 used in the '286 patent is referring to what you
8 said is wild-type antibodies but also
9 antibody-like molecules, correct?

10 A No, not -- no. I'm saying that the
11 wild -- an antibody is -- a wild-type antibody, as
12 we've been discussing, or we're talking about an
13 antibody-like molecule may be different in some --

14 Q Doctor, let me take a step back.

15 A Yeah.

16 Q And what I'm trying to get at is I just
17 want to know what term -- what you understood the
18 term "antibody" in the context of the inventions
19 of the '286 and the claims of the '286 patent to
20 mean.

21 Okay. Do you have that in your mind,
22 Doctor?

1 I'll ask my question. I just want to make
2 sure you understand the context.

3 Doctor, do you have that context in mind?

4 A Yes, I do, but --

5 Q Okay. So now I'll ask you, the word
6 "antibody" as used in the '286 patent can be any
7 of the Ig isotypes or a functional derivative
8 and/or fragment of them, correct?

9 A No. I -- I distinguish between a fragment
10 of a -- a fragment of an antibody or a wild-type
11 antibody will be just that. It's -- it would be
12 a -- an antibody-like molecule, a derivative
13 antibody. And certain fragments -- what I had in
14 mind as I answer this question is that if the
15 fragment that you're considering is -- for
16 example, an Fc fragment, without variable domains
17 that combine antigen, such a fragment could never
18 be referred to as an antibody. So --

19 Q So --

20 A -- the --

21 Q Okay. So I just want to make sure we're
22 clear.

1 A Yeah.

2 Q From the term "antibody," the way you had
3 applied the term "antibody" in the context of the
4 '286 patent would not include fragments; is that
5 correct?

6 ATTORNEY MARGOLIS: Objection.
7 Mischaracterizes his testimony.

8 A I believe that we should define
9 antibody -- antibody means a molecule conforming
10 to the architect of -- complete architecture of
11 the -- one of the known human subclasses. And any
12 deviation from that that, for example, retained
13 vitamins would -- and still had the capability of
14 binding antigen would be -- could be described as
15 an antibody-like molecule because it had the
16 properties of binding to an antigen. But equally,
17 it might -- the fragment might be a molecule that
18 was incapable of binding to antigen, and
19 therefore, one would not consider that as
20 antibody-like. It would be a -- an antibody
21 fragment.

22 So --

1 Q So let's see if we can --

2 A So I --

3 Q So let's see if we can -- I want to make
4 sure I get this straight.

5 With respect to the term "antibody" and
6 its understanding for the context of the claims of
7 the '286 patent and the context of the entire
8 patent, you understood the term "antibody" to mean
9 conforming -- it has the complete structure
10 conforming to one of the known human subclasses of
11 antibodies, correct?

12 A Correct.

13 Q All right. Now, you do recognize,
14 though -- and that is the definition of the term
15 "antibody" in the context in which you applied the
16 definition of the term "heavy chain," correct?

17 A Yes. Yes.

18 Q Okay. Now, just so we're clear, though --
19 well, withdrawn.

20 And that is how you undertook the claim
21 construction analysis in this IPR, which is you
22 looked at what the term "antibody" would be

1 understood to be to mean and what the term "heavy
2 chain" would mean in the context of an antibody
3 and applied that in this IPR, correct?

4 ATTORNEY MARGOLIS: Objection.

5 Mischaracterizes his testimony.

6 A I wouldn't agree with the way -- with that
7 statement because the term "heavy chain"
8 clearly -- is understood has always been
9 understood to be as we've explicit -- explicitly
10 described it. And --

11 Q Okay. Let me -- let me take a step back
12 then, Doctor.

13 A So --

14 Q I want to draw your attention to
15 column 11, line 9, please. So I think you're on
16 column 11.

17 A Yes.

18 Q We're in that same paragraph. And it
19 says, "The term 'antibody' as used herein."

20 Do you see that? And I want you to take a
21 moment to read from column 11 of the '286 patent,
22 line 9 -- line 9 through -- through line 21. And

1 read that to yourself and then I'm going to ask
2 you a question.

3 A (Document review.)

4 Q Doctor, do you have that in mind?

5 A I do.

6 Q You'll agree with me that the term
7 "antibody" in the context of the '286 patent,
8 after reading column 11, line 9 through line 21
9 is -- does include things other than the structure
10 of the known human subclasses of antibodies,
11 correct?

12 A I think this -- this phraseology described
13 in these lines that I've read indicates that this
14 patent relates to molecules that are wild-type
15 structure antibodies and derivatives that may
16 have -- may retain the properties of the
17 antibodies, and therefore behaving in an
18 antibody-like manner in a live antigen. Strictly,
19 you would call the antibody-like molecules, but,
20 yes, they're antibody molecules.

21 Q Doctor --

22 A In contrast to other fragments of --

1 (Reporter clarification.)

2 A In contrast to other fragments of
3 antibodies that you couldn't call antibodies
4 because they don't bind antigens.

5 Q Doctor, you will agree with me that the
6 '286 patent explicitly states that the term
7 "antibody" as used in the patent does include what
8 are known to be fragments of the known human
9 isotypes, correct?

10 Doctor, do you agree with that statement?
11 If you disagree -- it's a yes-or-no question.

12 I'll repeat it.

13 Doctor, you agree with me that the '286
14 patent explicitly states that the term "antibody"
15 as used in the patent does include what are known
16 to be fragments of the known human isotypes,
17 correct?

18 A That is literally what it's saying and I
19 think that's acceptable. And I would say yes,
20 with the caveat that certain fragments could not
21 be -- fragments could not be so described as -- as
22 antibodies.

1 Q Okay. Now, you'll agree with me that the
2 definition of "antibody" does include things that
3 could have more on the structure than just the
4 components contained in the known human isotypes,
5 correct, as applied in the '286 patent?

6 Withdrawn. I'll ask the question a little
7 clearer.

8 You'll agree with me that the
9 understanding of the term antibody as used in the
10 '286 patent does include structures that contain
11 more than just the components of the known human
12 isotypes, correct?

13 A No, I -- no.

14 Q Okay. So if there is anything added, if
15 you have a -- an antibody that has anything -- any
16 regions that are not contained in the naturally
17 occurring human isotypes, that would not fall
18 under the definition of -- well, withdrawn.

19 If you have a structure that has any
20 regions that were not contained in the naturally
21 occurring human antibody isotypes, that would not
22 fall under the definition of an antibody according

1 to you as used in the '286 patent?

2 ATTORNEY MARGOLIS: Objection. Vague.

3 A I can't quite answer to that wording of
4 the question. I -- because you -- the -- because
5 you refer specifically there to adding additional
6 fragments -- additional fragments of a -- I think
7 of an antibody.

8 In other words, if you took it -- let me
9 try to be more -- if -- because I think there is
10 an issue here.

11 An antibody -- if we're looking at a
12 molecule that has an architecture based on that --
13 of a wild-type antibody but contains more because
14 it's been engineered to contain additional
15 domains, which in your wording have come from --
16 come from the wild-type antibody, that would be an
17 Ig-like molecule. It -- it would be Ig-like
18 because it would have a basic structure that was
19 that of shared -- that of an antibody, but it had
20 more.

21 Q Okay. And we agree that the term
22 "antibody" as used in the '286 patent -- and we

1 can look at column 11, lines 18 -- it says that
2 "Ig-like molecules are covered by the term
3 'antibody.'"

4 Do you see that?

5 A I see "An antibody, according to the
6 invention, may be any of" --

7 (Reporter clarification.)

8 A Antibodies are known in -- "An antibody,
9 according to the invention, may be any of these
10 isotypes or functional derivative and/or fragments
11 of these."

12 So to my mind, that would be slightly
13 ambiguous because it's suggesting that it can be
14 an antibody or it --

15 Q Doctor --

16 A It's not -- it's not insisting that --

17 Q Okay.

18 A -- that anything comes of being called an
19 antibody.

20 Q Let's take a step back.

21 A Yeah.

22 Q You'll agree with me that there is a

1 definition of the term "antibody" contained in
2 column 11 of the '286 patent, correct?

3 It's a yes-or-no question, Doctor.

4 A Yes.

5 Q Okay. And then we agree that on line 16,
6 it says "An antibody, according to the invention,
7 may be any of these isotypes," referring to the
8 IgGs in line 15, "or a functional derivative
9 and/or fragment of these."

10 Do you see that?

11 A I see that.

12 Q And you agree with that as used, the term
13 "antibody" is used in the '286 patent, correct?

14 A Yes, I see that.

15 Q And the next sentence says, "In a
16 preferred embodiment, Ig-like molecules are
17 produced," right?

18 Do you see that?

19 A Yes.

20 Q So you will agree with me that the term
21 "antibody" is including Ig-like molecules as used
22 in the '286 patent, correct?

1 A Let me just focus on -- let me just be
2 sure.

3 Could you just repeat the question?

4 Q And you'll agree with me that the term
5 "antibody" as used in the '286 patent includes
6 Ig-like molecules, correct?

7 A Well, I agree with what --

8 Q Okay.

9 A The way this is worded. I think it covers
10 an adequate description of what -- of -- of what
11 follows.

12 Q Okay. So you'll agree with me that the
13 '286 patent -- withdrawn.

14 You'll agree with me that the term
15 "antibody" as used in the '286 patent includes
16 Ig-like molecules, right?

17 It's a yes-or-no question, Doctor.

18 A Yes.

19 Q And you'll agree with me that you've
20 referred to structures that have or the components
21 of naturally occurring Ig molecules but that have
22 additional regions added on to them would be

1 considered Ig-like molecules, correct?

2 A Yes.

3 Q With that in mind, Doctor, I just want to
4 turn to figure 8 of Lazar, okay?

5 A Yeah.

6 Q And you have it in front of you. It's on
7 page 13.

8 A I do.

9 Q And Lazar is Exhibit 1004.

10 A Yes.

11 Q Now, you will agree with me that the first
12 figure is an IgG antibody, correct?

13 A Right.

14 Q You'll agree with me that the second
15 figure that's identified as mAb-Fv is and Ig-like
16 antibody as used -- as the definition of the '286
17 patent identifies, correct?

18 A Yes.

19 Q You will also agree with me that the
20 mAb-Fab structure is an Ig-like antibody?

21 A Yes.

22 Q And you'll agree with me, therefore, that

1 both the mAb-Fv and mAb-Fabs would be considered
2 antibodies according to the '286 patent, correct?

3 A It would be more correct to describe them
4 as -- as antibody-like molecules because both
5 examples that you quote are actually trimeric.
6 They have the trivalent structures. They have
7 three binding sites.

8 Q Doctor, we've gone over -- we've spent
9 some time to go over the definition of the term
10 "antibody" in the '286 patent. And I'm saying
11 applying that definition of the term "antibody,"
12 you will agree with that both the mAb-Fv and the
13 mAb-Fab structures identified in figure 8 of Lazar
14 fall under the term "antibody" as used in the '286
15 patent, correct?

16 A As you said, yes.

17 Q Okay. Now you will also agree with me
18 that the mAb-Fv and the mAb-Fab have heavy chains
19 on both sides of the antibody, correct?

20 A This is where we have to be more precise
21 about the wording. They contain heavy chains.

22 Q Okay. So let me make sure we're more

1 precise.

2 You'll agree with me that the mAb-Fv and
3 the mAb-Fab structures shown in figure 8 of Lazar
4 contain heavy chains on both sides of the
5 antibody, correct?

6 A They -- yes, they contain poly -- a
7 polypeptide chain that are -- in the context of
8 a -- of a wild-type antibody would be the -- the
9 complete -- would be the heavy chain, yes, but
10 they have more than that. So you couldn't look,
11 for example, at mAb-Fv and say that the heavy
12 chain, the polypeptide chain running from the
13 N-terminus of the VH domain through the whole of
14 maybe -- I'm not implying through the whole of the
15 molecule, the heavy chain. The heavy chain -- I
16 would use the term -- the heavy chain -- heavy
17 chain means, as we've already said it, so mAb-Fv
18 structure contains a heavy chain and an
19 additional -- additional domains.

20 Q Let me make sure we're clear on this.

21 You would agree with me that both the
22 mAb-Fab and the mAb-Fv antibodies identified in

1 figure 8 of Lazar --

2 (Reporter clarification.)

3 Q You will agree with me that the mAb-Fv and
4 the mAb-Fab structures shown in figure 8 of Lazar
5 contain heavy chains on both sides of the
6 antibody, correct? It's a "yes" or "no."

7 A Yes.

8 ATTORNEY ASHKENAZI: Why don't we go off
9 the record.

10 (Recess.)

11 BY ATTORNEY ASHKENAZI:

12 Q Doctor, do you have the Gunasekaran
13 reference, which is Exhibit 1012, in front of you?

14 A Yes.

15 Q And you've referenced this reference --

16 A I have.

17 Q -- correct?

18 A I have.

19 Q Yes. Thank you.

20 I want to talk about some of the
21 structures that are included within this patent,
22 if we can -- I'm sorry, within this publication,

1 the Gunasekaran reference, Exhibit 1012.

2 Now, just so we're clear, this is a 2010
3 article, right?

4 A Yes.

5 Q Now, the title of Gunasekaran is
6 "Enhancing antibody Fc heterodimer formation
7 through electrostatic steering effects," right?

8 A Correct.

9 Q And the purpose of this article is to say
10 techniques that can be used for making
11 heterodimeric antibodies, correct?

12 A Correct.

13 Q And the focus of the Gunasekaran
14 reference, Exhibit 1012, is modifications that can
15 be made to the Fc domain so increase heterodimer
16 formation, correct?

17 A Correct.

18 Q Okay. Now, I want to make sure -- I want
19 to take a look at the figures of the things that
20 were being tested and evaluated in Gunasekaran.
21 In particular, why don't we turn to figure 2 on
22 page 6 of the PDF -- I mean of the document.

1 Are you at figure 2 of Gunasekaran?

2 A Yes.

3 Q And I see on the top left-hand side, there
4 is a figure A.

5 Is that one of the constructs that were
6 being evaluated in the Gunasekaran reference?

7 A Yes. Yes.

8 Q Okay. And from your perspective, would
9 figure A have a heavy chain as used within the
10 '286 patent?

11 A No.

12 Q Okay. And just so we're clear, figure A
13 has an Fc region. And it has on one side an --
14 scFv-Fc region on the left-hand side, correct?

15 A Yes.

16 Q Okay. Let's take a look at figure 3.

17 That's another bispecific that was
18 evaluated in Gunasekaran, correct?

19 Actually, I'll withdraw that.

20 Actually, if you take a look at figure 3,
21 figure 3A, that shows a bispecific that was
22 evaluated in Gunasekaran, correct?

1 A Correct.

2 Q And in fact, it's the only bispecific that
3 was evaluated in Gunasekaran, correct?

4 A Yes, I think that's true.

5 Q And in fact, we see in the legend here, it
6 says, "figure 3A, schematic drawing of bispecific
7 scFv-Fc generated by using the Fc heterodimer with
8 charged pair mutations left panel."

9 Is that right?

10 A Sorry, can you just --

11 Q Orient you?

12 A Yeah, yeah.

13 Q Yes. It's going to be underneath --
14 underneath the figures, there is a caption or
15 legend, whatever it may be, right?

16 A Yeah.

17 Q So I'm going to point to you figure 3A.

18 A Yeah.

19 Q It states -- Gunasekaran states, "A
20 schematic" -- "is a schematic drawing of
21 bispecific scFv-Fc generated by using the Fc
22 heterodimer with charged pair mutations."

1 Right?

2 Do you see that?

3 A Yes, I do.

4 Q And do you agree with that statement?

5 A Yes, yes.

6 Q Okay. Just so we're clear, it's your
7 position that figure 3A does not have -- or does
8 not illustrate a heavy chain as that term is used
9 within the '286 patent, correct?

10 A Correct.

11 Q Okay. Now, if we go to figure 4, which is
12 on page 8 of Gunasekaran, that's Exhibit 1012, we
13 have another drawing of a monovalent IgG, right?

14 A Yes. Yeah, it's a monovalent molecule.

15 Q It's a monovalent molecule, you would
16 agree with me?

17 A Yeah.

18 Q Is it your position -- withdrawn.

19 Does figure 4A have a heavy chain as
20 defined -- as used within the '286 patent?

21 A Yes.

22 Q Okay. Does it have two heavy chains as

1 used within the patent?

2 A No.

3 Q Okay. In other words, the construct of 4A
4 does not have heavy chains, plural, correct, as
5 used within the '286 patent, correct?

6 A That's correct.

7 Q Are there any other constructs that were
8 evaluated by the Gunasekaran reference?

9 Withdrawn.

10 Are there any constructs other than 2A,
11 3A, and 4A that were evaluated by the Gunasekaran
12 reference?

13 A That might take me a lot longer to
14 establish.

15 Q I mean, I know you've read it, but if you
16 want to take a few minutes to take a quick look at
17 it, please go ahead and do so.

18 A It's been a while since I've read it from
19 end to end.

20 Q Yeah.

21 Well, let me ask you -- let me maybe ask
22 you this.

1 Can you recall any other constructs that
2 were evaluated by Gunasekaran, other than 3A --
3 2A, 3A, and 4A?

4 A (Document review.)

5 I'm just aware there is supplemental data
6 to this paper, and they may -- I've speed-read
7 through this, and -- perhaps I should say that --
8 there might be related molecules that -- for which
9 data represented in the supplementary data.

10 Q Okay.

11 A So you've highlighted --

12 (Reporter clarification.)

13 A You've clearly highlighted three.

14 Q You've clearly highlighted --

15 A You've clearly highlighted three principal
16 molecules that have been studied, and I think I
17 would just reserve the -- do you want me to go
18 through -- no, I imagine, reserve the --

19 Q Doctor --

20 A -- my answer to -- includes the fact that
21 there might be a -- another molecule, related
22 molecule with data presented -- with data

1 presented in the in the supplement sections of
2 this page, but...

3 Q So Doctor, let me just see if I can
4 clarify here.

5 Sitting here right now, based on your
6 limited review --

7 A Yeah.

8 Q -- withdrawn.

9 Sitting here right now, based on your
10 previous review of the Gunasekaran reference and
11 the limited time you've had to review it now, you
12 will agree with me that the best of your
13 knowledge, there were three constructs, only three
14 constructs that were evaluated in the Gunasekaran
15 reference, and those were presented by figures 2A,
16 3A, and 4A; is that correct?

17 A I agree with everything you say except the
18 word "only."

19 I'll say, yes, the -- my review of this
20 paper -- basically my review of this paper, I
21 would agree with you that the three principal --
22 three principal constructs were evaluated.

1 Q I'll ask -- I'll ask it differently.

2 Sitting here right now, can you point me
3 to any other construct identified in Gunasekaran
4 other than those in figures 2A, 3A, and 4A?

5 A I can't at this moment, but I simply
6 reserve the right to look at the -- supplementary
7 data which might refer to it as a slightly
8 different molecule, another molecule.

9 Q Okay.

10 A But I don't think --

11 Q Let me --

12 A -- that's an issue.

13 Q Okay. Let me ask you another question.

14 Will you agree with me that
15 figures that -- let's look at figure 4A for a
16 minute.

17 Looking at figure 4A of Gunasekaran --

18 A Yeah.

19 Q -- would you say that that is illustrating
20 heavy chains that show amino acid residues on --
21 of opposite charges being used -- withdrawn.

22 Is it your assertion -- withdrawn.

1 Do you believe that figure 4A of
2 Gunasekaran shows mutations in CH3 domains of
3 heavy chains that are employing a charge-reversal
4 strategy?

5 A You just have to give me a minute to --

6 Q Yes. Take your time. And if you need,
7 let me know and I'll repeat the question once
8 you're done reviewing, okay?

9 A You are referring to -- to save time --

10 Q I'm focusing on figure 4A.

11 A 4A.

12 Q And with that in mind, I'll ask you the
13 question again.

14 Do you believe that figure 4A of
15 Gunasekaran shows mutations in the CH3 domains of
16 heavy chains that are employing a charge-reversal
17 strategy?

18 A (Document review.)

19 Q Doctor, I'm going to repeat my question
20 since I know you've been reviewing it.

21 Well, let's start with the first thing.

22 Do you believe that figure 4A of

1 Gunasekaran shows mutations of the CH3 domains of
2 heavy chains?

3 As the term is used within the -- as the
4 term "heavy chain" is used within the '286 patent?

5 A Yes.

6 Q You do?

7 Do you believe that Gunasekaran figure 4A
8 shows mutations of the CH3 domains of heavy chains
9 that are employing a charge-reversal strategy?

10 A Yes.

11 Q Okay. I just want to make sure we're
12 clear.

13 When we look at figure 4A, what does VH
14 stand for?

15 A Variable domain of the heavy chain.

16 Q And what does the VL stand for?

17 A Variable domain of a light chain.

18 Q Okay. So -- and then if we see CH1, what
19 does that stand for?

20 A First constant heavy chain region.

21 Q And what do we see on the right-hand side,
22 what does CH stand for?

1 A Constant region of the light chain.

2 Q Okay. So it's your opinion that there are
3 two heavy chains within figure 4A that we -- in
4 Gunasekaran?

5 A No, there is one heavy chain.

6 Q Okay. So then I'll ask my question that I
7 referenced a little earlier again.

8 Do you believe that Gunasekaran figure 4A
9 shows mutations of the CH3 domain of heavy chains?

10 A It shows -- no, it doesn't.

11 Q No, it does not?

12 A No. So I -- I would have to -- I wish to
13 change the answer to the earlier question.

14 It shows mutations in -- in a heavy chain
15 and in the second chain, which doesn't fall under
16 the definition of heavy chain.

17 Q Okay. So then I'll ask another question
18 then.

19 Do you believe that Gunasekaran figure 4A
20 shows mutations of the CH3 domains of heavy chains
21 that are employing a charge-reversal strategy?

22 A Could you repeat?

1 Q Sure.

2 Do you believe that Gunasekaran figure 4A
3 shows mutations of CH3 domains of heavy chains
4 that are employing a charge-reversal strategy?

5 A No, that's not -- that is not a correct
6 statement.

7 Q In other words, to the best of your
8 knowledge, we do not see in any of the figures
9 identified by Gunasekaran any structures that have
10 two heavy chains, correct?

11 A 4A doesn't, 3A doesn't, and 2A doesn't.

12 Q And to the best of your knowledge, sitting
13 here right now, understanding that you want to
14 reserve your rights, you are not aware of any
15 other constructs that were evaluated in
16 Gunasekaran -- well, withdrawn.

17 To the best of your knowledge, sitting
18 here right now, understanding you want to reserve
19 your rights, you are not aware of any constructs
20 within Gunasekaran that evaluated CH3 domain --
21 mutations in the CH3 domain of heavy chains?

22 ATTORNEY MARGOLIS: Objection. Vague.

1 A To me that's not -- would you like to
2 just --

3 Q Yeah, let me restate the question so
4 you -- well, withdrawn. I think we're fine.

5 (An off-the-record discussion was held at
6 this time.)

7 Q Okay. I want to shift our attention, if I
8 can, to the '286 patent, claim 1, if you can. So
9 if you can pull that up.

10 I want to go through the components of
11 claim 1. So when you get there, let me know. If
12 you want to take a quick review of it, you can,
13 and then I'll ask you some questions.

14 A (Document review.)

15 Okay.

16 Q So -- so when we look at '286 patent,
17 claim 1, the first component, it
18 says, "Provided" -- after the comprising,
19 says, "Providing a host cell with certain
20 characteristics."

21 Would you agree with me?

22 A Yes.

1 Q And then when we look at B, it
2 says, "Culturing that same host cell to produce a
3 heterodimeric antibody," correct?

4 A That's what it -- yes, yes.

5 Q Okay. And then part C is harvesting that
6 heterodimeric antibody, correct?

7 A Correct.

8 Q Okay. Now, when we look at part B, there
9 is a discussion of the -- there is the use of the
10 word "interacts," right?

11 A Yes.

12 Q And part B of the claim 1 of the '286
13 patent, the interacts limitation recites the --
14 "at least one positively charged amino acid
15 residue substituted in the CH3 domain of set first
16 antibody, heavy chain interacts with the at least
17 one negatively charged residue" -- "negatively
18 charged amino acid residue."

19 Is that accurate?

20 A Yes.

21 Q Okay.

22 A That's correct.

1 Q Now, claim 1 of the '286 patent does not
2 say what type of interaction takes place, correct?

3 ATTORNEY MARGOLIS: Objection. Vague.

4 A No, it doesn't -- I mean, it says -- there
5 is an interaction between two residues.

6 Claim 1 states that there is an
7 interaction between the two substituted residues,
8 but no, it doesn't describe in any greater details
9 the nature of that interaction.

10 Q Okay. In other words, there is no
11 specificity provided by the patent on what that
12 interaction needs to be between the two residues
13 that are being modified in the CH3 domains,
14 correct?

15 ATTORNEY MARGOLIS: Objection. Vague.

16 A I wouldn't agree with that statement.

17 Q All right. Let's break it down into some
18 parts.

19 A Okay.

20 Q Claim 1 of the '286 patent does not say
21 that the interaction between the two modified
22 amino acids on the heavy -- in the CH3 domains

1 needs to form a salt bridge, correct?

2 A It doesn't state that it has to be a salt
3 bridge. It doesn't mention the words "salt
4 bridge."

5 Q And you'll agree with me that a POSA
6 reading the '286 patent would not believe that
7 claim 1 of the '286 patent requires that the two
8 modified amino acids in the CH3 domains are
9 required to form a salt bridge in order to satisfy
10 that limitation of the claim, correct?

11 A No, I wouldn't agree with what you just
12 stated. The -- it clearly says it here that the
13 substitutions are to generate a positively charged
14 residue in one chain and a second negatively
15 charged mutation in -- negatively charged mutation
16 in the other chain, and that there is an
17 interaction between the two.

18 Q So Doctor --

19 A And the POSA would understand that this
20 was -- this was -- an interaction can be described
21 as a salt bridge.

22 Q Okay. So I want to take this into some

1 parts here.

2 First, well, I'm going to hand you the
3 Kannan reference, the Kannan patent publication.
4 It's Exhibit 1007.

5 Do you have that in front of you?

6 A Yes.

7 Q And have you reviewed this before?

8 A Yes, I have.

9 Q Okay. And if you turn to page 13 of
10 Kannan, you will see a table 5. I apologize, it's
11 table 4 -- page 4 -- 14 of 47. So let me start
12 again.

13 Please turn your attention to page 14 of
14 47 of Kannan, and let me know when you're there,
15 Doctor.

16 A Yes.

17 Q And you'll see there is a table 5 there.

18 Do you have that?

19 A I do.

20 Q And table 5 is showing a list of amino
21 acid residues that interface with one another in
22 the heavy chains, correct?

1 I'll withdraw the question. I'll make it
2 a little easier for you, Doctor.

3 Table 5 is titled, "List of CAPA
4 light-chain interface residues and their
5 contacting residues in the heavy chain."

6 Do you see that?

7 A I do.

8 Q I'm sorry. I went to the wrong figure.
9 That's why I was getting confused.

10 Please turn to table 1 of Kannan, page 8
11 of 47.

12 Are you there, Doctor?

13 A Yeah.

14 Q Apologies for that. I'm sure we were all
15 asking why we were talking about light chains.

16 Okay. So now we're on the same page.

17 Looking at Kannan, page 8 of 47, table 1,
18 it's titled "List of CH3 domain interface residues
19 in the first chain A and the contacting residues
20 in the second chain B."

21 Do you see that?

22 A I do.

1 Q Okay. Now, you'll agree with me that
2 table 1 in Kannan, from your understanding, is the
3 same as the -- table A of the '935 provisional
4 application?

5 A (Document review.)

6 ATTORNEY MARGOLIS: Objection. Vague.

7 Q I'll withdraw the question. I'll ask it a
8 little differently, Doctor.

9 You've reviewed table 1 of Kannan and
10 table A of the '935 provisional application,
11 correct?

12 A Yes, I have.

13 Q And to the best of your knowledge, do they
14 contain pretty much the same information?

15 ATTORNEY MARGOLIS: Objection. Vague.

16 A Well, I expect them to --

17 Q I'm sorry?

18 A I expect them to present basically the
19 same information because they're -- they're both
20 addressing the same issue. I mean, there might be
21 some detailed differences depending on how you
22 define content, but essentially --

1 Q Okay. They're essentially the same,
2 correct?

3 A Yes.

4 Q Okay. Now, looking at Kannan, table 1,
5 there are identification of residues in chain A
6 that you believe will interact with residues in
7 chain B, correct?

8 A That's the -- yes.

9 Q Okay. And it's your assertion that if I
10 have a positively charged residue in chain A and I
11 look at the corresponding interface residue in
12 chain B and that's negative, a salt bridge would
13 be formed?

14 ATTORNEY MARGOLIS: Objection. Vague.
15 Compound.

16 A I'd like to be -- could you repeat your
17 question so I --

18 Q Sure.

19 A -- the statement, so I could be sure
20 I'm --

21 Q Sure.

22 It's your assertion that if I have a

1 positively charged residue for a specific amino
2 acid in chain A and I look to the corresponding
3 side for chain B and I put a negatively charged
4 residue in chain B, then a salt bridge would be
5 formed?

6 ATTORNEY MARGOLIS: Objection. Vague.
7 Compound.

8 A You would expect a salt bridge to be
9 formed. The only --

10 Q Is that --

11 A The nature of the interaction might -- the
12 description of the interaction that you get might
13 be modified slightly from just being called a salt
14 bridge by hydrogen bond interactions or water
15 molecules, secondary water molecules. But to --
16 I'll agree that salt bridge -- essentially a salt
17 bridge.

18 Q So I want to make sure we're clear,
19 because I -- when we went to claim 1 of the '286
20 patent, you asserted that if I have a positively
21 charged residue on --

22 A Yeah.

1 Q -- one heavy chain in the CH3 domain and a
2 negatively charged residue at the corresponding
3 interface of the second CH3 domain, that a salt
4 bridge would be formed.

5 That's your opinion, right?

6 A Yes.

7 Q Okay. So if I look at, for example,
8 position 364, and if I put a positive charge at --
9 and I'm looking at table 1 -- withdrawn. Let's
10 start again.

11 I'm looking at table 1 of Kannan. And if
12 I put a positive charge at position 364 and a
13 negative charge at 368, it's your opinion that a
14 salt bridge would be formed, correct?

15 A Yes, the interaction would -- yes, yes.

16 Q Okay. Now let's do this the other way.

17 If I put a negative charge at position 364
18 and a positive charge at 368, it's still your
19 position that a salt bridge would be formed and
20 that these two amino acids would be interacting
21 with one another, correct?

22 A The interaction would be principally

1 described as a salt bridge, but as I said, a salt
2 bridge might be -- might -- a salt bridge might
3 be -- might involve heavy chain hydrogen bonding
4 or secondary water molecules or -- but -- and in a
5 straight -- so any -- any opportunity to -- to
6 point out the salt bridge is not a -- doesn't
7 always look the same.

8 "Salt bridge" is the general term for a --
9 an interaction from a positively charged residue
10 and a negatively charged residue, but the details
11 of the interaction might -- might differ slightly.

12 Q Okay.

13 A But --

14 Q So let's take this in some pieces here.
15 I'm going to take that last part first.

16 It's your assertion that a salt bridge is
17 a general term for the interaction between a
18 positively charged residue and a negatively
19 charged residue?

20 A Yes, yes.

21 Q Okay. And it's your assertion that the
22 general term "salt bridge" can be used to

1 characterize the interactions between a negatively
2 charged residue at 364 and a positively charged
3 residue at 368, correct?

4 A Yes.

5 Q Okay. And it's your assertion -- and
6 you'll agree with me that if you have a heavy
7 chain that has a negative charge at position 364
8 and a positive charge at position 368, that those
9 two amino acids would interact with one another,
10 correct?

11 I'll ask the question again, because I
12 think I messed that up.

13 Is it correct to say that if you have one
14 heavy chain that has a negative position at 364 --
15 withdrawn. I stumbled on myself.

16 Is it true that if you have a heavy chain
17 that has a negative at 364 and another heavy chain
18 that has a positive at 368, that those two amino
19 acids, 364 and 368, would interact with one
20 another?

21 A They might.

22 Q They might or they will?

1 A There is a likelihood that they will and
2 that that interaction will be a -- an
3 electrostatic interaction. But what I'm trying to
4 encompass in my answer is the fact that I alluded
5 to in an earlier answer that not all salt bridges
6 are the same. And although salt bridge is, in
7 essence, an electrostatic interaction between two
8 residues --

9 Q So Doctor --

10 A -- you -- some salt bridges are -- are
11 mediated by hydrogen bonding and some are not.
12 Some are stronger than others. Some might involve
13 hydrogen bonding via intermediate water molecules.

14 So I'm anxious to put on record, I feel
15 like at this stage, the salt bridge is not just a
16 straightforward that not all salt bridges are the
17 same. Positive residue and negative residue.

18 Q So let's take this in some parts.

19 Let's start off with -- let's stay on the
20 same page of 364 minus and 368 plus, okay?

21 We have two heavy chains: one 364 minus
22 and one 368 plus.

1 Is it your position that it would be
2 highly likely that those two amino acids would
3 interact with one another based on the information
4 in Kannan?

5 A It's certainly possible. In the absence
6 of experimental evidence for an interaction the
7 possibility remains that they wouldn't form a --
8 an interaction, but let me just make sure -- could
9 you -- it seems like it might be easier for you to
10 repeat the question --

11 Q Yes. Thank you.

12 A -- and I can agree or disagree with the
13 statement.

14 Q Sure.

15 You have two heavy chains. One has a 364
16 minus, one has 368 plus.

17 Is it highly likely that those two amino
18 acids would interact with one another based on the
19 information in Kannan?

20 A It's likely that they would -- highly
21 likely -- it's likely.

22 Q Just likely or highly likely?

1 A I would say it's possible. It's possible
2 there is an interaction.

3 Q So you would disagree with the assertion
4 that it's highly likely that a heavy chain that
5 had a 364 minus and another heavy chain that had a
6 368 plus, those two amino acids would interact
7 with one another; is that correct?

8 A It's possible that they will because these
9 are --

10 Q Doctor, I'm going to --

11 A Because these are -- these are wild-type
12 residues being substituted, and you can't be sure
13 of that experimental data that -- there is an
14 interaction, but it's possible that --

15 Q Okay. So let me --

16 A What I would like to state -- the reason
17 I'm hesitating here is that the charge reversal
18 concept that's underlying what we're talking about
19 here is -- is more complex -- complicated than --
20 it seems to be saying that if an interaction works
21 one way around, if we put it that way, a
22 positive-negative, and you reverse it, you're

1 necessarily going to get the -- the same
2 interaction.

3 And the reason for that is -- is not
4 described adequately in -- in the Kannan paper.
5 The second paper and the Kannan. Just to -- the
6 Gunasekaran paper and the Kannan patent that --
7 because when you look at the structures of these
8 salt bridges -- take, as an example, one of the
9 naturally occurring salt bridges of four famous
10 ones that we talked about earlier that have
11 evolved to occur on the periphery of the
12 interaction -- the interaction seems -- reversing
13 the charges implies -- well, is it -- it's a
14 very -- is a more complex process than -- than
15 just saying, plus-minus is the same as
16 minus-minus.

17 Q Let me break this down, please, if I can,
18 because I'm not talking about charger. I'm asking
19 you -- I'm looking at Kannan table 1, okay?

20 I have Kannan table 1 in front of me. I'm
21 a POSA, okay? And I see that there is two
22 residues, two contact residues, 368 and 364, okay?

1 Are you there, Doctor?

2 A Sure.

3 Q So table 1 of Kannan shows two
4 contact residues, 364 and 368.

5 Do you have that in your mind?

6 A Yes.

7 Q Okay. If I put a positive charge on one
8 of those residues and a negative charge on the
9 other, would they necessarily interact with one
10 another?

11 A They're very likely -- they likely -- it's
12 possible -- it's possible that they --

13 Q But it's not guaranteed, according to you?

14 A No.

15 Q Okay. So then if I have data that just
16 shows me a positive charge at position 364, I
17 don't know whether or not putting a negative at
18 position 368 would be a good thing, correct?

19 ATTORNEY MARGOLIS: Objection. Vague.

20 A That would be going too far to put in
21 those words. It's highly likely --

22 (Reporter clarification.)

1 A It's certainly possible there would be an
2 interaction between the two and --

3 Q But you would not know, correct?

4 A You couldn't be absolutely sure that that
5 would be the result.

6 Q So let me make sure that we're abundantly
7 clear here.

8 If I have a positive charged residue at
9 position 364, I do not know whether putting a
10 negative residue at position 368 would be a good
11 thing that would promote heterodimerization.

12 I would need to make it and test it,
13 correct, according to you?

14 Correct, Doctor?

15 A It would be good to test it. But I would,
16 I would say that in this case where you have a
17 positive at 364, a negative at 368, we discussed
18 this earlier, is -- is very likely to -- to
19 produce it -- a salt bridge --

20 Q Okay.

21 A -- interaction.

22 Q Let me ask it to you in the reverse.

1 If I have a negative at position 364 and a
2 positive at position 368, is it your belief that
3 it would be very likely for those two to interact
4 and to form a salt bridge and promote
5 heterodimerization?

6 A Yeah, I make the same statement for that
7 with the same caveats that the interaction might
8 differ in detail in terms of strength and hydrogen
9 bonding and -- and water molecules -- and
10 intermediate water molecules.

11 Q Are you drawing a distinction between what
12 a POSA would expect from knowing that the
13 information contained in table 1 from having 364
14 minus and 368 plus as opposed to 364 plus and 368
15 minus?

16 A No, I'm saying a POSA would have the same
17 concerns and caveats.

18 Q Okay. In other words, just so we're
19 clear, it's your position that whether you're 364
20 minus and 368 plus --

21 (Reporter clarification.)

22 Q So it's your position that whether you're

1 looking at a heterodimeric antibody that has 364
2 minus and 368 plus or a different one that had 364
3 plus or 368 minus, both would be likely to form
4 salt bridges and promote heterodimerization, the
5 extent of which, though, is what would be left
6 open for you; is that correct?

7 A Agreed, yes.

8 Q Okay.

9 ATTORNEY ASHKENAZI: Why don't we go take
10 it off the record.

11 (Recess.)

12 ATTORNEY ASHKENAZI: Back on the record.

13 BY ATTORNEY ASHKENAZI:

14 Q Dr. Sutton, just so I understand, you're
15 familiar with the structure of an IgM antibody?

16 A Yes.

17 Q IgM antibodies do not have hinges, right?

18 A That's -- that's correct, they don't have
19 a hinge --

20 Q Okay.

21 A -- like IgG. And I would agree with
22 describing it that way, they don't have a hinge,

1 but there is flexibility, which is something that
2 we particularly investigated and published on.
3 And the same is true in Ig -- IgE.

4 So just to be clear, the hinge region is
5 recognizable in IgG as a regional polypeptide
6 chain between the CH1 domain and CH2 domain.
7 That's referred to as the hinge. It mediates
8 flexibility.

9 The IgE and IgM don't have that structure.

10 Q So just --

11 A That's -- by the way, I mean the sort
12 of -- I think it's amino acids that would -- that
13 would look similar in length and composition to --
14 to IgG, but they do -- but hinge implies
15 flexibility, and there is flexibility in that.

16 So IgM can flex between open and bent
17 structures, and IgE does the same. It just does
18 it in a different way.

19 So maybe this is not what you want to talk
20 about, but it's intriguing that an evolution of
21 antibodies structure, the -- the hinge region of
22 IgG is equivalent in location and function to the

1 additional -- to the extra domain of IgM and IgE.

2 So that when you look at -- I don't need
3 to give you a lecture on antibody structure,
4 unless you want me to do that.

5 Q No, I'd like to just ask some specific
6 questions --

7 A Okay. Sure.

8 Q -- so I'm very clear.

9 The IgE and IgM antibodies do not have
10 hinges, correct?

11 A They don't have hinge -- they don't have
12 structures that are homologous to the -- they
13 don't have structures that are -- look similar in
14 terms of length and sequence to the hinge regions
15 of IgG.

16 Q Okay. And your definition of antibody --
17 I mean of heavy chain, you identified, should
18 include a hinge region, correct?

19 A Yes.

20 Q Okay. Now, so to be clear --

21 A The --

22 Q -- I just want to make sure we're clear.

1 Are you saying that -- is it your opinion
2 that the hinge region that you identify, your
3 definition of the term "heavy chain" is a flexible
4 term?

5 ATTORNEY MARGOLIS: Objection. Vague.

6 A No. My definition -- my definition of
7 heavy chain that is the commonly accepted --
8 meaning for the term "heavy chain," we've been
9 through that in its entirety many times and
10 some -- and -- and the --

11 (Reporter clarification.)

12 A The heavy chain is -- is the entire
13 polypeptide chain from the N-terminal residue for
14 the V domain through -- the V domain through the
15 constant region heavy chain to the C-terminal
16 residue of the most C-terminal constant domain.

17 And if this is an IgG molecule or an IgA
18 molecule or an IgG molecule, then with a hinge
19 structure, it's going to include that hinge
20 structure.

21 And if it's an IgM or an IgE, it's going
22 to include an additional constant domain, which

1 will mediate flexibility and might be called by
2 some a hinge region, but --

3 Q So Doctor --

4 A I'm sorry I'm complicating this. Because
5 what we said already covers everything that is
6 important. The -- the additional piece of
7 information that I'm adding is that the extra
8 domain that we cover ourselves -- that we refer to
9 in IgM and IgE is -- is a region that mediates
10 flexibility in the same way that IgG does, but it
11 is in fact a -- a complete domain.

12 Q Doctor --

13 A But defining heavy chain as -- as -- as we
14 do, we are -- we cover all these possibilities.
15 Whichever human -- human class we look at, our
16 definition, commonly understood meaning of heavy
17 chain is -- is -- is sufficient.

18 Q I want to take this in pieces.

19 Is it your assertion that the definition
20 of heavy chain includes a hinge region, yes or no?

21 ATTORNEY MARGOLIS: Objection. Form.

22 Q Withdrawn. I'll be very clear.

1 Is it your assertion that the
2 understanding of the term heavy chain as used in
3 the '286 patent includes a hinge region, yes or
4 no?

5 ATTORNEY MARGOLIS: Objection. Vague.

6 A One would have to be -- the answer to that
7 question implies -- begs the question of what we
8 mean by "hinge region." That's really all I'm
9 saying.

10 And if it's an IgG molecule, it will
11 include a hinge region. If it's an IgM molecule,
12 it will include an extra domain. And
13 evolutionarily, they are mediators of flexibility
14 and -- if you define mediators of flexibility
15 then.

16 Q Okay. You didn't provide any discussion
17 in your declarations that the hinge region is
18 really a flexible term that means either a
19 traditional hinge region found in the IgG
20 antibodies or some extra domain that's found in
21 the IgMs, correct?

22 A No, I didn't, that's correct. No.

1 Q Okay. And is it your assertion here
2 today, yes or no, that the term "hinge region"
3 means something different for IgG anti -- like
4 antibodies as opposed to IgM-like antibodies?

5 A Can you just repeat what --

6 Q Sure.

7 Is it your assertion here today that the
8 term "hinge region," as it would be understood by
9 a POSA, means something different for IgG-like
10 antibodies as opposed to IgM-like antibodies?

11 A Yes.

12 Q Okay. Now --

13 A Just beyond the understanding of a POSA,
14 but -- but a POSA would -- would know -- would
15 know that the term "heavy chain" refers to the
16 whole of the polypeptide chain, and if there is a
17 clearly defined hinge region and we -- going with
18 the definition of a hinge --

19 (Reporter clarification.)

20 A Let me say that again.

21 The -- the heavy chain refers to the whole
22 of the polypeptide chain, the N-terminus of the

1 domains of the C-terminus, the C-terminal -- most
2 C-terminal domain. And if it's an IgG, there will
3 be a segment that is understood by -- by all -- to
4 be a mediated flexibility. And it's referred to
5 as the hinge region.

6 If we're talking about IgM or an IgE,
7 there will be an extra domain included. And --
8 and if one has this understanding that the IgE and
9 IgM are also flexible, then -- and the additional
10 domain that we're including is the mediator of
11 that flexibility then that's included too.

12 So whichever way you look at it, however
13 much -- whatever -- whatever degree of
14 understanding you have of flexibility and how it's
15 mediated, whether by hinge, IgG by hinge or by an
16 extra domain, the definition of -- of heavy chain
17 is -- is satisfactory because it covers all these
18 possibilities.

19 Q In other words -- withdrawn.

20 It's your position that IgE and IgM
21 antibodies have heavy chains even though they
22 don't have a hinge region, correct?

1 A No, I'm not saying -- I'm not saying that
2 at all. I'm saying that IgM and IgE do not have
3 hinge -- do not have hinge regions as understood
4 and observed in IgG.

5 Nonetheless, they -- they have flexibility
6 in the same sort of region mediated by an
7 additional domain.

8 Q So it's your position that IgE and IgM
9 antibodies do not have heavy chains as a POSA
10 would understand them for the '286 patent?

11 A No, that's absolutely not what I'm saying.
12 I'm saying the Ig -- the definition of a heavy
13 chain has to encompass -- does encompass all
14 subclasses. And if you ask me particularly about
15 whether a -- a hinge region is included, then I
16 will say that the definition that we have for a
17 heavy chain includes that hinge region. Because
18 IgM, it doesn't have an IgG-like hinge region, but
19 it does functionally have a hinge region that
20 mediates flexibility that will essentially be --
21 that additional domain.

22 So I'm not quite sure what -- I don't --

1 nothing that I'm saying now changes what I -- I'm
2 just trying to make a statement that clarifies
3 what we've been discussing here. I'm not
4 modifying my definition of heavy chain. Heavy
5 chain is -- is clear -- it's the whole polypeptide
6 chain, et cetera.

7 But if it's -- if you ask me a specific
8 question about is there a sequence in there that
9 is -- we describe as the hinge as seen in the
10 IgG -- IgG structure, and in fact there are four
11 subclasses of human IgG, and they have hinges that
12 look different, some longer, some shorter, all
13 mediating flexibility.

14 So in the middle after the two domains
15 that define the Fab region and the terminal two
16 residues that define the Fc region, there is an
17 IgG sequence that's referred to as the hinge
18 region and an IgM and IgE there is an additional
19 domain which mediates flexibility, and our
20 definition of heavy chain covers all of these.

21 Q Doctor, you reviewed the prosecution
22 history of the -- of the '604 -- of the '289 --

1 '289 patent, correct -- '286?

2 A Yes, I did.

3 Q Okay. I'm handing you Exhibit 1008 from
4 the '604. It's a nice lengthy document.

5 A Yeah.

6 Q Now, we'll get into it in a second. I
7 just want to turn your attention to your second
8 declaration for the '286 patent, which is
9 Exhibit 2006 in the '604 IPR. So it's probably
10 tab 2 in your binder, Doctor.

11 A It's -- this is my second declaration?

12 Q For the '286 patent.

13 A Yeah.

14 Q And I'm going to ask you to turn to
15 page 25 -- paragraph 25. I'm sorry, paragraph 55.

16 Are you there, Doctor?

17 A I am.

18 Q So looking at paragraph 55 of your second
19 declaration, Exhibit 2016 from the '604 IPR, you
20 cite a portion of the prosecution history that you
21 argue supports your interpretation of the term
22 "interacts" in the claims of the '286 patent,

1 correct?

2 A Yes.

3 Q Okay. And you referred to an
4 October 13th, 2015, amendment that added the term
5 "interacts," that claim language, correct?

6 A Yes.

7 Q And you cite to the '286 prosecution
8 history at pages 240 and 245 -- 245 to 246; is
9 that right? Paragraph 55 at the end.

10 A Yes, I see that.

11 Q Okay. So now, if you can turn to
12 Exhibit 1008 from the '604 IPR. And I want to ask
13 you to turn to pages -- to page 240.

14 Now, if you go to that, I think you
15 probably meant page 239 in your -- in this; is
16 that accurate?

17 Withdrawn. I'll make the question
18 clearer.

19 You wrote -- you cited to page 240 of the
20 286 prosecution history, Exhibit 1008, but I
21 really think you meant to refer to page 239, which
22 is where it shows the amendment to claim 1.

1 Is that accurate, Doctor?

2 A I'm checking that out.

3 Q Doctor, it may help if you take the binder
4 clip off so you can put them side by side.

5 A I think it might.

6 Q Let me ask the question.

7 A Yeah.

8 Q At the end of paragraph 55 of your second
9 declaration, Exhibit 2018, you are pointing us to
10 the amendment to claim 1 that existed at the time
11 in the '286 patent, correct?

12 A Correct.

13 Q And that we can find specifically on
14 page 239 of the prosecution history, Exhibit 1008;
15 is that right?

16 A (Document review.)

17 Q Doctor, is that right? Or if you're not
18 sure, we can move on.

19 A No, I just want to be clear. I agree with
20 you, based on the changes.

21 Q Okay. So now I want to move to the next
22 part that you cite at pages 245 and 246.

1 Do you understand that those pages are
2 part of the responses to the examiner that are
3 being provided by Merus during the prosecution,
4 correct?

5 A Yes.

6 Q Okay. And have you reviewed this
7 prosecution history in detail, Doctor?

8 A I have.

9 Q Okay. So I want to ask you some questions
10 about this.

11 If we take a look starting at page 245 --
12 I'm sorry, starting at page -- yeah, 245, and
13 going to page 246, you'll see there is a -- middle
14 of page 245, a Roman numeral two.

15 A Yes.

16 Q Are you there?

17 A Yeah.

18 Q And you'll agree with me that the examiner
19 had rejected the claims that existed at the time
20 for the '286 patent based -- as being anticipated
21 by the Kannan reference, correct?

22 A Yes, I remember that.

1 Q Okay. And the applicant, Merus, in
2 response to the examiner, stated that -- and this
3 is in the middle of the second paragraph or
4 second -- third line of the second paragraph, that
5 "The Kannan reference does not teach replacement
6 of a neutral amino acid with a positively charged
7 amino acid in the CH3 domain of one antibody heavy
8 chain and the replacement of a neutral amino acid
9 with a negatively charged amino acid in the second
10 antibody heavy chain."

11 Do you see that?

12 A I was listening to you and not reading.
13 I'd like for you to show me where that's written.

14 Q Okay. I'll start again.

15 Why don't you take a moment and read the
16 paragraph that bridges pages 245 to 246 in
17 Exhibit 1008 from the '604 IPR, which is the
18 prosecution history for the '286 patent.

19 A Yes, yes.

20 Q Have you done that, Doctor?

21 When you do that, let me know.

22 A (Document review.)

1 Yes, okay.

2 Q So I want to make sure we understand a few
3 things about the prosecution history.

4 In order to overcome the rejections, the
5 applicant amended the claims to make clear that
6 they are providing a neutral-to-negative charge on
7 one amino acid heavy chain and a
8 neutral-to-positive charge on another amino acid
9 heavy chain; is that correct?

10 ATTORNEY MARGOLIS: Objection.
11 Mischaracterizes the document.

12 A The beginning of your question, could you
13 repeat?

14 Q Sure. Let's take this in parts.

15 You recognize that the examiner during the
16 '286 prosecution history prior to the pages -- to
17 the portion we're looking at now, to page 245 to
18 246, rejected the then-existing claims as being
19 anticipated by Kannan, correct?

20 A Yes, that's -- that's the issue that's
21 being discussed, yes.

22 Q And to overcome that rejection, the

1 applicants amended the claims and provided some
2 argument to the patent office, correct?

3 A Yes.

4 Q Okay. And the applicants argued that
5 Kannan does not teach a neutral-to-charge amino
6 acid on one residue and a neutral-to-charge --
7 withdrawn.

8 A Yes.

9 Q Let me start again. Apologies. It was
10 not clear.

11 And the applicants argued that Kannan does
12 not teach a neutral-to-positive on one side of the
13 CH3 domain and a neutral-to-negative on the other
14 side of the CH3 domain, correct?

15 A Yes.

16 Q And in fact, that was the focus of the
17 claim amendment, was to make clear that there was
18 going to be a neutral-to-charge modification on
19 the CH3 domain of the two antibodies -- two heavy
20 chains of the antibody, correct?

21 ATTORNEY MARGOLIS: Objection. Vague.

22 A So could you just repeat?

1 Q Sure. Well --

2 A Just the --

3 Q Yeah, let's -- let's maybe try a different
4 piece of this.

5 A Or we can just --

6 Q You'll agree with me that the -- you argue
7 that the patent owner restricted a structural
8 interaction when they made the amendment to the
9 term "interact" in the claim language, right?

10 A You'll have to repeat that. I'd love to
11 hear that again, and then I'll --

12 Q Yeah. Okay.

13 A I understand what we're talking about. I
14 just want to make sure that I'm --

15 Q I understand.

16 In addition to arguing that Kannan does
17 not teach neutral-to-charge modifications --

18 A Yes.

19 Q -- the applicant discussed -- is it your
20 position the applicants discuss the interaction
21 that those two amino acid residues need to have?

22 A Yes, the -- it's important that there is

1 an interaction.

2 Q Okay. So to be clear, during the
3 prosecution of the '286 patent and the portions
4 that you cite in your declaration, the focus of
5 the -- by the applicant was that the two amino
6 acid residues that are being modified from neutral
7 to charge at the interface will interact with one
8 another, correct?

9 A Correct.

10 Q And that interaction is described as a
11 electrostatically favorable interaction, correct?

12 A Correct.

13 Q It does not say that a salt bridge needs
14 to form, correct?

15 A Correct.

16 Q The applicant did not put any restriction
17 on the level of interaction that needs to occur
18 between the modified CH3 domains that are covered
19 by claim 1 of the '286 patent, correct?

20 A Yes, correct.

21 ATTORNEY MARGOLIS: Objection. Vague.

22 Q The applicant did not state how much

1 interaction needs to occur in order for an
2 antibody that had the modified CH3 domains as
3 covered by claim 1 -- withdrawn.

4 The applicants did not state how much
5 interaction needs to occur between the two
6 modified CH3 domains in order for that antibody to
7 be covered by claim 1 of the '286 patent, correct?

8 A You use the phrase "extent of
9 interaction," and I want to be clear about that.

10 Could you repeat what you said?

11 Q Sure.

12 During the prosecution of the '286 patent,
13 the applicant did not state how much interaction
14 needs to occur between the two modified CH3
15 domains in order for an antibody to be covered by
16 claim 1 of the '286 patent, correct?

17 A Yes.

18 Q And in fact, the only thing that the
19 applicant stated that needs to occur when you
20 modify the two portions of the CH3 domain in order
21 for it to satisfy claim 1 of the '286 patent is
22 that there be an electrostatically favorable

1 interaction, correct?

2 A Yes.

3 Q And you'll agree with me that a positive
4 on one side of the interface and a negative on the
5 other side of the interface for amino acids that
6 are known to correspond to one another at the
7 interface is an electrostatically favorable
8 interaction, correct?

9 ATTORNEY MARGOLIS: Objection. Vague.

10 A It's very likely to be an
11 electrostatically favorable interaction. But as
12 we were discussing earlier -- that -- there might
13 be variants of this interaction involving hydrogen
14 bonding and/or water molecules.

15 So -- so, yes, there will be an
16 interaction, which will be electrostatic and
17 favorable, but the degree to which -- the precise
18 nature and degree might vary.

19 ATTORNEY ASHKENAZI: I apologize. Let's
20 go off the record for a moment.

21 (Recess.)

22 BY ATTORNEY ASHKENAZI:

1 Q So Doctor, do you have -- I'd like if you
2 can -- I'm going to want to reference Gunasekaran
3 and Kannan for a few minutes, okay?

4 Now, with the Gunasekaran reference, which
5 is Exhibit 1012 that you have in front of you,
6 that was looking at ways of modifying the Fc
7 domain to promote heterodimerization, correct?

8 A Correct.

9 Q And the point that we saw when looking
10 through the -- the figures is that they believe
11 that they could test the ability to make
12 modifications on the Fc domain -- I mean in the Fc
13 region, but apply that broadly to antibody
14 heterodimerization, correct?

15 A Yes. Yes.

16 Q Okay. In other words, if there were
17 modifications made to the CH3 domain in a
18 construct that didn't have a full heavy chain,
19 that would still be able to be translated over to
20 an antibody that you're trying to make as a
21 heterodimeric, correct?

22 ATTORNEY MARGOLIS: Objection. Vague.

1 A Well, that -- that's the big question,
2 whether -- whether what works in Fc will work in a
3 whole antibody.

4 Q Well, that's what they were purporting to
5 present, correct, in Gunasekaran, is that
6 modifications made to the Fc, even though they're
7 not in a full antibody, can be translated to
8 making bispecific heterodimeric antibodies,
9 correct?

10 A Yeah, that's the -- that's the hope.

11 Q And that's what they were -- that's what
12 they were putting forth, correct?

13 A Yes.

14 Q Okay. Now, going back to your second
15 declaration for the '604 IPR, that's the '286
16 patent, and I'd like you to turn to page 27,
17 paragraph 62.

18 A Yes.

19 Q Okay. Now, paragraph 62, the second
20 sentence you have states, "The only disclosure of
21 neutral-to-charged substitutions in Lazar is in
22 example 2."

1 Is that right?

2 A So I think I might be looking at the
3 wrong -- in the wrong place.

4 Q Go to your tab 2, the second tab.

5 A Yeah. No, I mean, I'm in the wrong --

6 Q Yes.

7 A So we're talking about '286?

8 Q Yeah. You know what, let's pause for a
9 second. Stay there for a second. Let me ask you
10 some questions outside and then we'll get into it,
11 okay?

12 A Okay.

13 Q The authors of Gunasekaran, at least the
14 first-named author, is the same inventor on the
15 Kannan patent, correct?

16 A Yes, that's correct.

17 Q Okay. And when we say the "Kannan
18 patent," we're really referring to WO2009/089004,
19 correct?

20 A Give me the numbers. That's really --
21 the -- the patent -- and here --

22 Q Okay.

1 A Yeah, sure.

2 Q Okay.

3 A Yes.

4 Q Now, with that, I'd like you now to please
5 turn to your second declaration in the '604 IPR,
6 Exhibit 2016, page 27, paragraph 62.

7 A Paragraph -- page --

8 Q 27, paragraph 62.

9 A Yes.

10 Q Okay. And the second sentence, you state,
11 "The only disclosure of neutral-to-charged
12 substitutions in Lazar is in example 2."

13 Do you see that?

14 A I do.

15 Q And you have Lazar in front of you in case
16 you need to refer to it, correct? That's
17 Exhibit 1004.

18 A Yes.

19 Q Okay. And you will agree with me that in
20 Exhibit 1004, Lazar, example 2, it explicitly
21 discusses neutral-to-charge substitutions,
22 correct?

1 ATTORNEY MARGOLIS: Objection. Vague.

2 A I'm looking for example 2.

3 Q You can find it on page 29 -- page 66 of
4 137 in the Lazar patent --

5 A Yeah.

6 Q -- application publication.

7 A Thank you.

8 Q So with that, Doctor, I'll re-ask my
9 question.

10 Will that help you?

11 A Yes.

12 Q You will agree with me that Lazar,
13 Exhibit 1004, explicitly discusses
14 neutral-to-charge substitutions?

15 ATTORNEY MARGOLIS: Objection. Vague.

16 A Lazar certainly presents data on
17 neutral-to-charge substitutions.

18 Q And you'll agree with me that Lazar in
19 table 1 on page 67 of 137 --

20 A Yeah.

21 Q -- includes a number of different
22 heterodimeric -- heterodimers that include

1 neutral-to-charge substitution on one side and
2 neutral-to-charge substitution on the other side
3 of the constructs, correct?

4 A No, I disagree with that statement.

5 Q Okay.

6 A It shows -- table 1 shows a number of
7 variants on the two chains, which -- some of which
8 are neutral-to-charged. But these are in Fc --

9 (Reporter clarification.)

10 A Fc -- Fc molecules.

11 Q Okay. So let's make sure we have this
12 clear, Doctor.

13 You will agree with me that table 1 of
14 Lazar on page 67 of 137 shows a number of
15 different variants where there is
16 neutral-to-charged substitutions on both sides of
17 the Fc domains that are being evaluated; is that
18 correct?

19 A Yes, that's correct.

20 Q Okay. And you'll agree with me that one
21 of the variants includes 364 and 368 on both
22 sides, on the corresponding sides of the Fc

1 heterodimer, correct?

2 A Yes, that's -- that's true.

3 Q And let's be more specific.

4 You will agree with me that when we look
5 at the -- the different preferred CH3 domain
6 variants that are identified in table 1 of Lazar,
7 it identifies one variant having a 300 -- a
8 neutral-to-charged substitution at 364 and a
9 neutral-to-charged substitution at 360 -- on the
10 corresponding 368 position, correct?

11 A Yes.

12 Q Okay. Let's go one step further.

13 You've asserted that the empty-Fc and the
14 scFv-Fc constructs of Lazar are not heavy chains,
15 correct?

16 A Correct.

17 Q And it's your assertion that table 1 of
18 Lazar is discussing empty-Fc/scFv-Fc constructs?

19 A Yes, these have come from that.

20 Q If the empty-Fc/scFv-Fc constructs are
21 considered heavy chains, you would agree with me,
22 then, that they would show a POSA that Lazar

1 possessed a neutral-to-charged substitution at
2 interface residues for an antibody, a
3 heterodimeric antibody, correct?

4 ATTORNEY MARGOLIS: Objection. Vague.

5 A I don't agree with what you said because
6 you -- you started your statement with the
7 suggestion that these were mutations made in --
8 you said antibody --

9 (Reporter clarification.)

10 A Could I rehear what --

11 Q I'll withdraw the question and try to take
12 this in pieces, okay?

13 You'll agree with me that Lazar said --
14 and we're looking at example 2, which is found on
15 page 67 of 137 --

16 A Yes.

17 Q -- that they were -- in order screen for
18 Fc variants that favor heterodimerization, an
19 empty-Fc/scFv-Fc system was developed as a test
20 system.

21 Do you see that?

22 A Yes.

1 Q And do you agree that that was what was
2 being presented in Lazar for their Fc
3 heterodimerization techniques?

4 A Fc heterodimerization, yes.

5 Q Okay. Now, Lazar actually represents that
6 the empty-Fc/scFv-Fc system is a test system for
7 them, correct?

8 A Yes, yes, that's true.

9 Q So the test system they were using used an
10 empty-Fc construct, correct?

11 A Yes.

12 Q And that's what we saw in figure one of
13 Lazar, right?

14 A Yes, well, yeah.

15 Q The test system also used an scFv-Fc
16 construct, right?

17 A Yes, figure 1 shows the three.

18 Q And the test system that was being used by
19 Lazar did use an scFv-Fc construct, correct?

20 A Yes.

21 Q Okay.

22 A As is shown in figure 1.

1 Q Now, you will agree with me that Lazar's
2 empty-Fc construct does have a CH3 domain,
3 correct?

4 A Yes.

5 Q And you'll agree with me that Lazar's
6 scFv-Fc construct also has a CH3 domain, correct?

7 A Yes, yes.

8 Q Okay. Going back to table 1 of Lazar,
9 which is found on page 67 of 137.

10 A Yes.

11 Q Table 1 lists out variants tested in the
12 empty-Fc/scFv-Fc system, correct?

13 A Yes.

14 Q Okay. Table 1 specifically lists
15 preferred CH3 domain variants that favor Fc
16 heterodimerization, correct?

17 A That's what it the table is headed, yes.

18 Q And you're not disputing that the
19 inventors on the Lazar patent referred to the
20 constructs table 1 as preferred CH3 domain
21 variants for that favor Fc heterodimerization,
22 correct?

1 A They -- they list it in a table with that
2 heading, yes.

3 Q Is it your assertion that those -- that a
4 POSA reading this -- the Lazar patent would not
5 believe that the inventors identified table 1 as
6 preferred CH3 domain variants that favor Fc
7 heterodimerization?

8 A I -- I've always considered that a POSA
9 would -- would not make that -- because I fail to
10 see the link between the data presented in that --
11 I need a shorthand for it, but the test system,
12 single-chain Fv-Fc null variants, test systems for
13 how that -- how that data translates into what is
14 presented in table 1 and table 2. And I don't
15 believe a POSA would -- would be able to -- to
16 make that link.

17 Q So I want to make sure I understand
18 where -- where a POSA would look at the words that
19 the inventor on one patent says but ignore those
20 for another.

21 A Well --

22 Q So let me -- let me get into specifics

1 here.

2 You're not disputing that Lazar explicitly
3 stated that the preferred CH3 domain variants that
4 favor Fc heterodimerization were included in
5 table 1, correct?

6 A I look at table 1 and I see these -- these
7 pairs and I -- I can't make the link between -- I
8 can't see how this table is generally -- why these
9 particular mutations appear listed.

10 I spend a lot of time looking at these
11 data and looking to see the behavior percentage
12 heterodimer for these different combinations
13 and...

14 Q Doctor, I'm going to take you -- I'm going
15 to ask you a question. I want to go piece by
16 piece, if you can with me, for a few minutes.

17 You're not disputing that Lazar identified
18 preferred and most preferred CH3 domain variants
19 in tables 1 and 2 respectively, correct?

20 A Yes, I am disputing that -- they generate
21 these -- they list these mutations. And I look
22 back at the data for these particular combinations

1 and I generally fail to understand why these
2 are -- on what basis these are selected as
3 preferred variants.

4 Q Okay. Let's -- Lazar, the inventors of
5 Lazar stated that the variants that are included
6 in table 1 and 2 are the preferred CH3 domain
7 variants and most preferred CH3 domain variants
8 that favor Fc heterodimerization, correct?

9 A They appear in a table with that title,
10 but I fail to see why -- how these tables are
11 generated. It's not -- it's not explained --

12 Q Now --

13 A -- why -- why some of these entries are
14 here and if -- many of these entries are here.
15 And the -- if I were to look at these data and a
16 POSA were to look at these data, they would --
17 with a view to producing molecules with high
18 percentages of heterodimer, the aim of the
19 exercise, you would -- you would look through
20 these and realize that there was one in particular
21 involving charge-to-charge substitutions that
22 generates 100 percent heterodimer.

1 Q Okay. Let me ask you --

2 A If -- if you approach these data, you
3 wouldn't conclude that mutual charge -- well,
4 there are many examples, but charge-to-charge or
5 charge-to-neutral is not clear from these data how
6 to proceed, what would be a good choice to make
7 except that I would be struck by the fact that --
8 some of these -- the -- claim to be preferred
9 variants. I really don't have very high
10 percentages of heterodimer information.

11 Q Doctor, let me break this down into a
12 couple of parts.

13 Will you agree with me that there is data
14 provided in figure 5 for a number of different
15 constructs that are identified in tables 1 and 2
16 of Lazar?

17 A Yes.

18 Q Okay. Will you agree with me that there
19 were a number of constructs -- and I'm using the
20 word "construct."

21 How would you like to refer to the
22 different CH3 variants? I just want to make sure

1 we're on the same page.

2 A Yeah. I'd refer to these as "variants."

3 Q Okay.

4 A I -- I identify in the Fc --
5 single-chain -- single-chain Fv-Fc construct.

6 Q Let me see if I get this right.

7 You'll agree with me that there are a
8 number of different variants identified in tables
9 1 and 2 that had neutral-to-charge --
10 neutral-to-positive substitutions on one variant
11 and neutral-to-negative substitutions on the other
12 variant, correct?

13 Withdrawn. There's too many variants in
14 there. I need to clean that up.

15 You'll agree with me that there are
16 specific heterodimers that are identified that
17 have a neutral-to-positive on one variant amino
18 acid and a neutral-to-negative variant on the
19 other -- I'm twisting myself here. Apologies.

20 Okay. Let's take this one thing at a
21 time.

22 I'm looking at table 1.

1 A Yeah.

2 Q You'll agree with me that on any given
3 line, there is an identification of one variant
4 and a second variant, correct?

5 A That's correct.

6 Q And looking at table 1, we see that for
7 specific heterodimers, you can have
8 neutral-to-charge on one variant and a neutral to
9 opposite charge on the other variant, correct?

10 A Yes, there are such examples.

11 Q And -- there are those examples, correct?

12 A Yes, there are -- amongst -- amongst
13 others charge-to-charge and neutral-to-charge,
14 yes. All possibilities were explored, and they're
15 examples of these different types, including, as
16 you point out, neutral-to-charge and
17 neutral-to-charge.

18 Q Doctor, let me just -- I just want to work
19 through this because I think these are very, you
20 know, simple questions that I'm hoping you're
21 going to be able to answer "yes" or "no."

22 So I'm looking at table 1, and I'm looking

1 at the different heterodimers that are identified
2 in table 1.

3 Are you with me, Doctor?

4 A Heterodimers of Fc -- Fc heterodimers,
5 yeah.

6 Q Okay. Great.

7 So let's be clear, table 1 and table 2
8 identify a number of different Fc heterodimers,
9 correct?

10 A Yes.

11 Q Okay. And you'll agree with me that in
12 these tables 1 and 2, a number of those different
13 Fc heterodimers have a neutral-to-positive charge
14 in one variant and a neutral-to-negative charge in
15 the other variant of the CH3?

16 A Yes, you can find examples of that.

17 Q And you'll agree with me that table 1 is
18 identified as, "Preferred CH3 domain variants that
19 favor Fc heterodimerization," correct?

20 A That's what the -- what the title -- the
21 title -- title of that table.

22 Q And you'll agree with me that table 2 is

1 titled as, "Most preferred CH3 domain variants
2 that favor Fc heterodimerization," correct?

3 A It's correct that that's what the title of
4 the table says, but I'll come back --

5 Q I'm going to get to the data now. I want
6 to go to the data.

7 Now, looking at the data in figure 5, you
8 will agree with me that for a number of these
9 preferred and most preferred CH3 domain variants
10 that favor Fc heterodimerization, there was an
11 increase above 50 percent in heterodimeric
12 percentage, correct?

13 ATTORNEY MARGOLIS: Objection. Compound.
14 Vague.

15 A Well, I looked at all of these pairs and
16 went back to see what the data looked like and
17 couldn't understand why these particular variants
18 were -- were listed.

19 I mean, I'm not quite sure what -- "most
20 preferred" should be better than "preferred,"
21 these pairs of residues identified in the Fc --
22 single chain of the Fc construct.

1 Q Doctor, let me ask you this question.

2 You point out that there was a construct,
3 an Fc heterodimer that had 100 percent
4 heterodimeric rate.

5 Do you recall that?

6 A Yes.

7 Q And is it your belief that a POSA would
8 focus on that Fc heterodimer that had the
9 100 percent heterodimeric rate to the exclusion of
10 all the other Fc heterodimers referenced in tables
11 1 and 2?

12 ATTORNEY MARGOLIS: Objection. Vague.

13 A Well, I would conclude that if my aim is
14 to produce maximum heterodimerization, I would be
15 struck by that example.

16 Q That wasn't my question. So I want to
17 make sure I understand -- you understand my
18 question.

19 Is it your assertion that a POSA would
20 focus on the Fc heterodimer that had 100 percent
21 heterodimeric rate to the exclusion of all other
22 Fc heterodimers that are referenced in tables 1

1 and 2 of Lazar?

2 ATTORNEY MARGOLIS: Objection. Vague.

3 A I would say that a POSA looking at these
4 data would conclude that if the -- if the purpose
5 of the exercise is to generate a high percentage
6 of heterodimer, these data suggests that pursuing
7 a charge-to-charge mutation, such as in the
8 example is 100 percent, would be the way forward.

9 Q What is the heterodimerization rate for --
10 withdrawn.

11 Looking at the '935 provisional
12 application, what is the heterodimerization rate
13 of 364K/368D construct?

14 A Could you repeat that?

15 Q Sure.

16 Yeah, let me ask you the question. I'll
17 make it easier for you.

18 You will agree with me that the '935
19 provisional application does not contain any data
20 on the percent of heterodimer form when there is a
21 modification of 364K on one CH3 domain and 368D on
22 the other CH3 domain, correct?

1 A Let me take that more slowly.

2 Can you repeat that?

3 Q Sure.

4 We went through the '935 provisional
5 application earlier today.

6 Do you recall that?

7 A Yeah.

8 Q And you recall that you focused on table 7
9 of the '935 provisional application that included
10 homodimerization ratings, correct?

11 A Inhibition.

12 Q Inhibition of homodimerization, correct?

13 A Correct.

14 Q You will also agree with me that we
15 discussed how the '935 patent does not provide any
16 information explicitly stating the rate of
17 heterodimerization for a heterodimeric antibody
18 that has 364K on one side and 368D on the other
19 side, correct?

20 A Yes.

21 Q Accordingly, there is no information at
22 all within the '935 provisional application

1 regarding the heterodimerization rate of the --
2 that construct, 364D, so 364K/368D, correct?

3 ATTORNEY MARGOLIS: Objection. Vague.

4 A Yes, the data presented as we discussed
5 was on inhibition of homodimerization, which was
6 an indication of -- of the direction to take
7 for --

8 Q So my question to you, Doctor, is what is
9 the rate of heterodimerization or the percent of
10 heterodimer formed when you have a bispecific
11 antibody that has 364K/368D on the two
12 corresponding CH3 domains?

13 A We don't -- we don't know.

14 Q We don't know. So there is no way to
15 know -- now I'll ask you the next question.

16 You'll agree with me that knob-in-hole and
17 disulfide bonds were used to show -- to make
18 heterodimeric antibodies, correct?

19 A Yes, they were.

20 Q Okay.

21 A They were established techniques.

22 Q And it was established that you can get to

1 95 percent heterodimeric -- heterodimers when
2 using knob-in-hole in conjunction with disulfide
3 bonds, correct?

4 A Yes.

5 Q And you'll agree with me that if you added
6 neutral-to-charge substitutions on both CH3
7 domains, that could increase the heterodimeric
8 rates for those types of antibodies, correct?

9 A Yes, that's true.

10 Q You'll also agree with me that the claim 1
11 of the '286 patent does not require a specific
12 amount of heterodimer, correct?

13 Withdrawn. Withdrawn.

14 At a minimum, you will agree with me that
15 if we look at table 5 -- withdrawn.

16 You'll agree with me that if we look at
17 the data in the Lazar reference for the Fc
18 heterodimers, if there is a percent of hetero
19 that's greater than 50 percent, it shows that the
20 variants are favoring heterodimerization, correct?

21 A Yes.

22 Q Okay. In other words, if we see a

1 variant -- if we see constructs that have variants
2 that have neutral-to-charge on both sides of the
3 interface, opposite charges, and the percent
4 hetero is greater than 50 percent, it shows that
5 those amino acids are interacting with one another
6 to produce a heterodimeric antibody, correct?

7 A No.

8 Q So if there is only a single modification
9 on one variant, neutral-to-positive, and a single
10 modification on the other variant,
11 neutral-to-negative, and the hetero percent is
12 greater than 50 percent, you would agree with me
13 that that -- those modifications are inter --
14 those amino acids are interacting with one another
15 to increase -- to produce an antibody, correct?

16 ATTORNEY MARGOLIS: Objection. Vague.

17 A No.

18 Q No.

19 A No.

20 Q Okay.

21 A You can't make any statement about
22 interaction.

1 These data, given the 50 percent is a low
2 heterodimerization rate in relation to what we
3 know is achievable by all means --

4 Q I didn't ask about whether it was ideal or
5 optimized. My question was simply, if you have
6 two Fc domains, as we see in tables 1 and 2,
7 without any mutations at all, what would you
8 expect the heterodimerization rate to be?

9 A Could you --

10 Q Sure.

11 I'm trying to figure out -- you're using
12 the percentages that we see in figures 5 and 6,
13 and you've been trying to focus on those, correct?

14 A Yes.

15 Q Okay. If there was no modification at all
16 to any of the variants, what would the hetero
17 percent be listed as?

18 A It would just be a third of --

19 Q We don't have to guess, do we? Because
20 it's actually listed on page 7 of 137, figure 5,
21 lane 1, correct?

22 A Yeah, the lane --

1 Q I'm sorry?

2 A Yes, I was just looking at that now.

3 Q Okay. And the percent hetero --

4 A I think it's 42 percent.

5 Q -- is 42 percent; is that correct, Doctor?

6 A That is correct.

7 Q Okay. So let's make sure that the record
8 is clear.

9 When we look at figure 5 and we look at
10 lane 1, we see what would happen if there were no
11 modifications made to either side of the CH3
12 domains of these Fc heterodimers, correct?

13 A Yes, that's correct.

14 Q And the hetero percent listed would be
15 42 percent, correct?

16 A Yes.

17 Q Now, we do see within the data in figures
18 5 and 6 that some of these neutral-to-positive,
19 neutral-to-negative variants have greater than
20 42 percent hetero, right?

21 A Yes.

22 Q And is it your position that by having the

1 neutral-to-positive, neutral-to-negative variants
2 that have a hetero percent greater than
3 42 percent, that it's clear that there is an
4 interaction between those modifications to produce
5 the heterodimers?

6 A You can't deduce that there is an
7 interaction between -- you have to take the data
8 as they --

9 Q And I'm talking about variants that had
10 greater -- I'm talking about lanes that had
11 greater than 42 percent hetero, okay, Doctor?

12 A Sure.

13 Q And are you telling me that where there is
14 a greater than 42 percent hetero for a lane from
15 figure 5 or figure 6, that --

16 A Which is for many.

17 Q Okay. Let's -- let me list it another
18 way.

19 If you have -- there are modifications
20 that are identified in each lane, correct?

21 A Yeah.

22 Q And those modifications are for what

1 happens on both sides of the CH3 domains, correct?

2 A Yes.

3 Q Okay. And if we see a percent that's
4 higher than 42 percent, we can conclude -- a
5 hetero percent that's greater than 42 percent, we
6 can conclude that those modifications interact
7 with one another to promote heterodimerization,
8 correct?

9 A No. They may have -- that pair leads to a
10 greater than 42 percent, if we take it as a
11 baseline heterodimerization rate. But you can't
12 conclude that these are residues that interact
13 with -- with one another.

14 Q If those residues are identified in -- as
15 interface residues, then you be able to conclude
16 they interact with one another?

17 A Yes, if you -- if you could find examples
18 of it.

19 Q Okay. Let's take one example.

20 If you're looking at -- if you could go to
21 figure 5 of Lazar, lane 11, it shows that one CH3
22 has an S364E; is that correct?

1 A Yes.

2 Q And the other variant -- the other side
3 has L368K; is that correct?

4 A Yes.

5 Q Okay. Now, S364E goes from neutral to
6 negative, correct?

7 A That's correct.

8 Q And L368K goes from neutral to positive,
9 correct?

10 A That's correct.

11 Q It was known in the art that 364 and 368
12 are interface residues that interact with one
13 another, correct?

14 A Yes, in the wild-type, yes.

15 Q And we see here that the hetero percent is
16 64 percent, correct?

17 A Correct.

18 Q And that's greater than the 42 percent
19 that would be expected for the wild-type, correct?

20 A Correct.

21 Q So you'll agree with me that for
22 construct -- for lane 11 of figure 5 of Lazar, we

1 are seeing a neutral-to-positive --
2 neutral-to-negative, neutral-to-positive Fc CH3
3 modifications that increase -- that interact with
4 one another to produce a heterodimer, correct?

5 A They are producing a -- an improvement in
6 heterodimer formation.

7 Q Okay.

8 ATTORNEY ASHKENAZI: Why don't we go off
9 the record.

10 (Recess.)

11 ATTORNEY ASHKENAZI: Back on the record.

12 BY ATTORNEY ASHKENAZI:

13 Q Dr. Sutton, it's your position that the
14 Gunasekaran reference taught a way for making
15 substitutions on the hydrophobic core of the CH3
16 domain, correct?

17 A Yes.

18 Q Is there any other reference that you've
19 identified in all the prior art that you've
20 reviewed that you argue teaches away from making
21 substitutions on the hydrophobic core of the CH3
22 domain?

1 I'll ask the question a little
2 differently. Let me withdraw it.

3 I have not identified any other reference
4 in all the prior art that you reviewed that you
5 assert taught away from making substitutions on
6 the hydrophobic core of the CH3 domain, correct?

7 A It's generally understood that you
8 wouldn't interfere with a region that offers the
9 principal source of energy for protein folding and
10 protein interaction.

11 So the -- you generally would -- would
12 leave the hydrophobic and uncharged residues
13 regions --

14 (Reporter clarification.)

15 A You're asking --

16 Q Okay. So Doctor, let me make my question
17 very clear.

18 A I don't understand.

19 Q Yeah, let me make my question very clear.

20 The only reference you've identified out
21 of all the prior art that you've reviewed that
22 you've asserted in your declarations teach away

1 from making substitutions on the hydrophobic core
2 of the CH3 domain is the Gunasekaran reference; is
3 that correct?

4 A I'd have to remind myself. That's
5 probably true for the -- that particular protein
6 interaction, but --

7 Q It wasn't my --

8 A The Gunasekaran is an example of a -- of a
9 protein-protein interaction and a typical
10 protein-to-protein interaction. And
11 protein-to-protein interactions are commonly
12 driven by such hydrophobic -- such combinations
13 are driven by the hydrophobic effect. So forgive
14 me for being a bit --

15 Q Doctor, I want to be abundantly clear with
16 my question.

17 A Yes, yes.

18 Q It's a yes-or-no question.

19 Gunasekaran is the only reference that
20 you've identified out of all the prior art in the
21 '604 and '605 IPR that you assert taught away from
22 making substitution on the hydrophobic core of the

1 CH3 domain, correct?

2 A I want to just take a moment, if I may
3 to -- to collect my thoughts.

4 Gunasekaran's intention that you should
5 avoid making substitutions in the hydrophobic
6 region is entirely consistent with the general
7 understanding for many years before this that
8 protein-to-protein interactions are driven by
9 interactions between the driving force for
10 protein-to-protein interaction comes from the
11 hydrophobic effect, and therefore you wouldn't
12 interfere with that region.

13 And so --

14 Q Doctor, I'm going to ask my question
15 again.

16 You've provided two declarations -- four
17 declarations in these two IPRs, correct?

18 A I have.

19 Q And you assert there was a teaching away
20 from making modifications on the hydrophobic core
21 on the CH3 domain, correct?

22 A Yes.

1 Q You identified the Gunasekaran reference
2 as the only reference -- withdrawn.

3 The only reference you've identified for
4 us to assert there was a teaching away of making
5 substitutions on the hydrophobic core of the CH3
6 domain is the Gunasekaran reference, correct?
7 It's a yes-or-no question.

8 A I -- yes, that's -- I think that's true.

9 Q Now, my next question to you is, you will
10 agree with me that dating back into the 1990s,
11 there were scientists that were making
12 modifications on the hydrophobic core of the CH3
13 domain in order to promote heterodimerization,
14 correct?

15 A Yes.

16 Q And you'll agree with me that the
17 knob-in-hole strategy makes modifications on the
18 hydrophobic core of the CH3 domain in order to
19 promote heterodimerization, correct?

20 A Yes.

21 Q Okay. And you'll agree with me that the
22 Kannan patent talks about making charge-charge

1 substitutions on the hydrophobic core of the CH3
2 domain, correct?

3 A Could you repeat that?

4 Q The Kannan patent references --
5 Exhibit 1007 that we discussed, discusses making
6 changes -- charge-charge substitutions on the
7 hydrophobic core of the CH3 domain, correct?

8 A Well, charge-charge substitutions at the
9 periphery of the hydrophobic region.

10 Q Are you saying that none of the
11 substitutions that Kannan identified in the patent
12 made modifications on the CH3 domain -- on the
13 hydrophobic core of the CH3 domain?

14 A It makes the charge-charge
15 substitutions on, as I said, the periphery of
16 the interface that --

17 Q You will agree with me that Kannan also
18 states that you can make neutral-to-charge
19 substitutions in the CH3 domain, correct?

20 ATTORNEY MARGOLIS: Objection. Vague.

21 A There is a statement in the Kannan patent
22 that such -- as you might make mutations in the --

1 a neutral-to-charge mutation, but there is no --
2 no examples are given. And --

3 Q Let's be clear. Kannan does make an
4 affirmative statement -- and Kannan, let's be
5 clear, is Exhibit 1007. That makes an affirmative
6 statement that you can make neutral-to-charge
7 substitutions in the CH3 domain, correct? It's a
8 yes-or-no question, Doctor.

9 A I don't think it's a yes-or-no question.
10 I think it's -- you could make mutations anywhere,
11 but it would be -- it would be unexpected for that
12 to have any beneficial.

13 Q Okay. Let's turn to Kannan. And I'd like
14 to turn to Kannan, page 10. So this is -- sorry,
15 page 11 out of 47. And this is going to be,
16 again, Exhibit 1007.

17 A Yep.

18 Q Now, I just want to make sure we're clear.
19 Again, the -- well, withdrawn.

20 You'll agree with me that Kannan, who is,
21 again, the same first-named author as the
22 Gunasekaran reference --

1 A Yes.

2 Q -- states on page 11 of 47, it's page 10
3 of the document, in the middle of the page at
4 lines 10 to 15 that a strategy for -- "can also be
5 extended to modifying uncharged residues to
6 charged residues at the CH3 domain interface,"
7 correct?

8 A I remember that, that statement.

9 Q Is that correct, Doctor?

10 A Can you just tell me --

11 Q Again, turn to page 11 of 47.

12 A Yes, I'm there.

13 Q It's page 10 of the document, line --

14 A Oh, sorry. Yeah.

15 Q On line -- the sentence starts on line 16,
16 okay? So I will start again.

17 A Okay.

18 Q Kannan, again, same author as Gunasekaran,
19 states that this strategy "can also be extended to
20 modifying uncharged residues to charged residues
21 at the CH3 domain interface."

22 Do you see that?

1 A I -- I remember it well. And I'm seeing
2 it now.

3 Q So you will agree with me --

4 A Yeah.

5 Q -- that Kannan explicitly states that
6 modifications can be made --

7 A Well, I've always been intrigued by this
8 statement. It's -- it's out of character with the
9 rest of the surrounding text.

10 Q So let's be clear what you mean by that.

11 It's your assertion that the statement
12 that we see in the Kannan patent publication
13 100 -- Exhibit 1007 at page 11 of 47, line --
14 lines 15 to 20 is not consistent with your view of
15 how you're --

16 A Well --

17 Q -- reading the Gunasekaran reference; is
18 that true?

19 A Yes. Yes.

20 Q Okay. Now I want to make sure we're
21 abundantly clear.

22 You do agree that Kannan 1007 is teaching

1 that electrostatic steering modifications can be
2 made at the CH3 domain interface, correct?

3 A At the periphery of the --

4 Q It doesn't say the word "periphery,"
5 right?

6 It says "CH3 domain interface," correct?

7 A Yes, that's right.

8 Q And in fact, Kannan also provides in
9 table 1 a list of CH3 domain interface residues,
10 correct?

11 Turn to page 8 of 47. I'll ask my
12 question again.

13 In fact, Kannan on page 8 of 47 includes
14 table 1, which is a list of CH3 domain interface
15 residues, correct?

16 A Yes.

17 Q And in -- therefore, you agree with me
18 that the proper reading of the sentence in Kannan
19 says that you can make neutral or uncharged
20 residues to charge residues at the CH3 domain
21 interface residues identified in table 1 of
22 Kannan, correct?

1 A Yes, he says that, but --

2 Q Okay. Now, I want to make sure we're
3 abundantly clear, Gunasekaran, when we go to that
4 -- now, if you have that in front of you I want to
5 turn to Gunasekaran. The sentence that you focus
6 on in Gunasekaran is from page 4 of 22 of
7 Exhibit 1012, correct?

8 On the top right-hand side, it starts, "In
9 addition"; is that correct, Doctor?

10 A Yes, I remember that.

11 Q Okay. And it says, "In addition,
12 exploiting charge residues as opposed to
13 hydrophobic residues at the CH3 domain interface
14 may have benefits in terms of retaining the
15 generally favorable biophysical properties of the
16 Fc."

17 Is that correct? Did I read that
18 correctly, Doctor?

19 A I just want to read this one.

20 Q Yes. Take your time and let me know
21 when -- when you've read it. All I did was ask
22 you I read that correctly. So when you're ready,

1 I'll restart it, okay?

2 A Yeah.

3 Q Thank you.

4 A Can you just point out --

5 Q Top right-hand side, second line says, "In
6 addition." It's the last three -- three words of
7 the line, okay?

8 When you're ready, I'll re-ask my
9 question, okay?

10 A (Document review.)

11 Q Doctor, are you ready?

12 A You read it correctly.

13 Q Okay. So now let me make sure -- I want
14 to ask some questions about this.

15 You'll agree with me that the sentence
16 that I read says that there may be benefits to
17 exploiting charge residues as opposed to
18 hydrophobic residues at the CH3 domain interface,
19 correct?

20 A Yes, but --

21 Q It is not saying in that sentence that a
22 POSA should not make modifications at the -- at

1 the hydrophobic core of the CH3 domain interface,
2 correct?

3 ATTORNEY MARGOLIS: Objection. Vague.

4 Q Withdrawn. Let me make sure I'm
5 abundantly clear.

6 We're looking at Gunasekaran, page 4 of
7 22, Exhibit 1012, and we just read the portion of
8 the Gunasekaran reference that you believe teaches
9 away from making modifications of the hydrophobic
10 core of the CH3 domain, correct, Doctor?

11 A I think --

12 Q Did we just read that section, that
13 portion, yes or no?

14 A Yes, we just read that portion.

15 Q Okay. Now you will agree with me that
16 when we focus on the sentence, the sentence "In
17 addition" only states that making modifications --
18 exploiting charge residues as opposed to
19 hydrophobic residues at the CH3 domain may have
20 benefits, right? Correct?

21 A Yes, but I don't know -- when one reads
22 that, one wonders what would motivate that

1 statement to be made.

2 The teaching away from making
3 modifications in neutral regions, neutral
4 hydrophobic residues interface is stated
5 explicitly in other --

6 (Reporter clarification.)

7 A In other places in this document, in the
8 Gunasekaran paper.

9 Q Can you show me where, Doctor? Because
10 I've looked at your declaration, and this is the
11 only paragraph that you've identified for me in
12 your declarations that I'm aware of.

13 A I will -- you have to give me a moment to
14 do this, but there are --

15 Q Doctor, maybe I'll ask it differently.

16 Did you identify in your declarations any
17 other portion of Gunasekaran that you assert
18 taught away from making modifications on the
19 hydrophobic core of the CH3 domain other than the
20 paragraph at the top right-hand side of page 4 of
21 22?

22 A (Document review.)

1 My reading of the Gunasekaran paper, which
2 I hope I reflected correctly in my declaration,
3 was that this paper remarkably reports -- reports
4 a remarkably effective strategy for electrostatic
5 steering through taking these conserved, naturally
6 occurring salt bridges and -- and doing the -- the
7 charge reversal.

8 Q I want to ask my question again, Doctor.

9 A I realize --

10 Q That wasn't the question, so I want to ask
11 my question again.

12 A So the interesting feature of those
13 mutations is that they are, as I said, at the
14 periphery of the hydrophobic interaction, region,
15 and --

16 Q Doctor, maybe is it better for me to
17 characterize your view of the Gunasekaran
18 reference is that it provides a way to modify CH3
19 domains that are not at the hydrophobic core, but
20 it's not necessitating or teaching that a POSA
21 should not make modifications on the hydrophobic
22 core of the CH3 domain?

1 ATTORNEY MARGOLIS: Objection. Compound.

2 A The -- the paper has -- the paper points
3 out that the principles we understand for protein
4 folding and protein-on-protein interactions, and
5 them being driven by the hydrophobic effect would
6 teach away from modifying that region -- the
7 hydrophobic interface.

8 Q Doctor, I want to ask you -- I just want
9 to be clear. You have -- let's -- you sitting
10 here right now, you have not been able to
11 identify -- and we don't have the time for you to
12 sit down and review the whole thing, so --
13 withdrawn. Let me start again.

14 Sitting here right now, after your review
15 of the Gunasekaran reference, you have not been
16 able to identify any portion of this reference
17 other than the top right-hand portion of page 4 of
18 22 of Exhibit 1012 that you believe teaches away
19 from making modifications on the hydrophobic core
20 of the CH3 domain, correct?

21 A I admit that the answer to your -- I can't
22 up with the quotation, but the -- there are --

1 there are sentences in here that explain that the
2 hydrophobic region is -- should be -- should not
3 be modified --

4 Q Now --

5 A -- because --

6 Q -- Doctor, I want to shift our attention
7 to Lazar for a moment.

8 You do recognize that Lazar does make
9 modifications on the hydrophobic core of the CH3
10 domain, neutral-to-positive and
11 neutral-to-negative, correct?

12 A Yes, yes, amongst many other mutations.

13 Q And you will agree with me that Lazar
14 identified those mutations as "preferred" and
15 "most preferred," correct?

16 A Yes. But as I explained, I couldn't see
17 the logic --

18 Q Okay.

19 A -- of that -- of the resubstitutions that
20 were quoted in the -- quoted in those tables.

21 Q Those tables?

22 A Lazar reported a number of mutations and a

1 very large number of mutations and --

2 Q Now, Doctor, I want to make sure we're
3 clear. Take Lazar in front of you, that's
4 Exhibit 1004 and paragraph 123 on column 12, which
5 is page 409 of 137.

6 A Lazar.

7 Q Paragraph 123, page 49 of 137.

8 A Paragraph 123?

9 Q Yes.

10 A Yeah.

11 Q You will agree with me that when talking
12 about hetero Fc variants that are preferred, it
13 identifies CH3 domains including 364 and 368,
14 correct?

15 A Yes.

16 Q And making substitutions on those domains,
17 correct?

18 A Substitutions at those positions.

19 Q Yes. Okay. Let's make sure we're clear.

20 Looking at paragraph123 of Lazar, you'll
21 agree with me that it talks about hetero Fc
22 variants that have substitutions at positions 364

1 and 368 of the CH3 domain, correct?

2 A Yes, there are.

3 Q And it identifies those as preferable,
4 correct?

5 A That isn't -- it doesn't imply those
6 particular substitutions are preferable.

7 Q Let's be clear. It says, "Hetero Fc
8 variants herein preferably comprise at least one
9 substitution at a position in the CH3 domain
10 selected from the group consisting of," and that
11 includes 364 and 368, correct?

12 A Yes, that's true. But it -- it's -- it's
13 one of the -- one of the enormous list of
14 substitutions that have been -- could be made.

15 Q Okay. So the enormous list of
16 substitutions are the numbers 349, 351, 354, 356,
17 357, 364, 366, 368, 370, 392, 394, 395, 396, 397,
18 399, 401, 405, 407, 409, 411, and 439.

19 Did I get that right?

20 A That sounds right.

21 Q Do you consider that to be an enormous
22 list?

1 A It's a lot that given that each can be
2 substituted for one of the number of different
3 amino acid residues.

4 Q And in fact, the next sentence in
5 paragraph 123, Lazar gives specific embodiments
6 that they identified as, quote/unquote, "preferred
7 embodiments," correct?

8 A The --

9 Q It's a yes-or-no question, Doctor.

10 A Are you referring to the tables or the --

11 Q The next sentence after the one that I
12 just read in paragraph 123. So the second
13 sentence of paragraph 123, Lazar states, "In a
14 preferred embodiment," and then it goes on to
15 identify a list of specific amino acid
16 substitutions, correct?

17 A Yes.

18 Q In other words, in paragraph 123 of Lazar,
19 it identifies specific amino acid substitutions
20 that the inventors of Lazar identified as
21 preferred embodiments, correct?

22 A (Document review.)

1 Q Correct, Doctor?

2 A (Document review.)

3 Q Correct?

4 A It says in a preferred embodiment, but
5 then it goes on to say that "each of these
6 variants can be used... or in any combination."

7 And so it's not clear.

8 Q Doctor, let me ask you this question --

9 A As you tested all -- it's a large number
10 here, and, and --

11 Q Okay.

12 A -- you have to choose one from each chain.
13 So there is -- the number of possible mutations to
14 test would be --

15 Q My question --

16 A -- is -- is an -- is a very large number.

17 Q My question to you, Doctor, is you'll
18 agree with me that Lazar identified CH3 domains --
19 I'm sorry, withdrawn.

20 You'll agree with me that Lazar identified
21 residues on the hydrophobic core of the CH3 domain
22 that can be modified from neutral to charge as

1 preferred embodiments, correct?

2 It's a yes-or-no question.

3 A Neutral-to-charge residues, substitutions
4 are included in a list.

5 Q And those residues include residues that
6 are at the -- as part of the hydrophobic core of
7 the CH3 domain, correct?

8 A Some are. Some are not.

9 Q Now, let's go back to Gunasekaran.

10 I want to turn your attention to page 9 of
11 22. That's Exhibit 1012.

12 Are you there, Doctor?

13 A Yes.

14 Q Okay. Now, starts off, there is a
15 paragraph that says, "In a pioneering study,"
16 left-hand side, last paragraph.

17 Do you see that?

18 A Yes.

19 Q And it begins, "In a pioneering study,
20 Carter and co-workers engineered the antibody
21 heavy chain for Fc heterodimerization using a
22 knob-into-hole strategy."

1 Do you agree with that?

2 A Yes.

3 Q And you'll agree with me that that
4 knob-into-hole strategy made modifications that
5 are part of the hydrophobic core of the CH3
6 domain?

7 A Yes.

8 Q Okay. In fact, it says as much later on
9 in the paragraph, going towards the bottom of the
10 page, correct?

11 A Yes.

12 Q Okay. Now, you will agree with me that
13 when looking for a teaching away, you need to
14 consider the art as a whole, correct?

15 A What do you mean by --

16 Q Okay. You've said that the Gunasekaran
17 reference teaches away from making modifications
18 on the hydrophobic core of the CH3 domain,
19 correct? Yes or no?

20 A Making modifications that would
21 destabilize the --

22 Q Doctor, Doctor --

1 A -- interface.

2 Knob-into-hole approach maintains
3 hydrophobic residue.

4 Q -- so you will agree with me.

5 Well, withdrawn.

6 Now, Doctor, I want to turn our attention
7 to Cabrera for a moment.

8 Actually, why don't we go off the record.

9 (Recess.)

10 ATTORNEY ASHKENAZI: Back on the record.

11 Pass the witness.

12 ATTORNEY MARGOLIS: We have no questions.

13 Thank you very much.

14 ATTORNEY ASHKENAZI: Going off the record.

15 (Time Noted: 6:41 P.M.)

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ACKNOWLEDGMENT OF DEPONENT

I, BRIAN J. SUTTON, Ph.D., do hereby
acknowledge that I have read and examined the
foregoing testimony and the same is a true,
correct, and complete transcription of the
testimony given by me and any corrections appear
on the attached errata sheet signed by me.

(SIGNATURE)

(DATE)

1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

2
3 I, Anita M. Trombetta, Certified Reporter
4 and Notary Public within and for the State of
5 New York do hereby certify: That BRIAN J. SUTTON,
6 Ph.D., the witness whose deposition is
7 hereinbefore set forth, was duly sworn by me
8 before the commencement of such deposition and
9 that such deposition was taken before me and is a
10 true record of the testimony given by such
11 Witness.

12
13 I further certify that the adverse party,
14 MERUS N.V., was represented by counsel at the
15 Deposition.

16
17 I further certify that the deposition of
18 BRIAN J. SUTTON, Ph.D., occurred at the offices
19 of Cahill Gordon & Reindel LLP, 32 Old Slip, New
20 York, New York 10005, on March 19th, 2026,
21 commencing at 9:06 A.M. to 6:41 P.M.
22

1 I further certify that I am not related to
2 any of the parties to this action by blood or
3 marriage, I am not employed by or an attorney to
4 any of the parties to this action, and that I am
5 in no way interested, financially or otherwise, in
6 the outcome of this matter.

7 IN WITNESS WHEREOF, I have hereunto set my

8 Hand this 19th day of March, 2026.

9 My commission expires: 3.21.2027

10

11



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13 NOTARY PUBLIC IN AND FOR THE STATE OF NEW YORK

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