UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,

Petitioner,

v.

HALOZYME, INC.,

Patent Owner.

VIDEOCONFERENCE AND VIDEOTAPED 30(B)(6)

DEPOSITION OF

MELANIE ANN SIMPSON, PH.D

December 9, 2025

Reported By: SUSAN ASHE, CER

Job No.: 7005333

1 Tuesday, December 9, 2025
2 9:13 a.m. Eastern Standard Time
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7 Videoconference and videotaped deposition
8 of MELANIE ANN SIMPSON, PH.D. taken on behalf of the
9 Petitioner, beginning at 9:13 a.m., on Tuesday,
10 December 9, 2025, at the law offices of Sterne
11 Kessler Goldstein & Fox, 1101 K Street, Northwest,
12 Washington, D.C., before Susan Ashe, Certified
13 Electronic Reporter and a Notary Public of the
14 District of Columbia.
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PREVIOUSLY MARKED EXHIBITS

PETITIONER

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HALOZYME

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1 INSTRUCT THE WITNESS

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22 (REPORTER'S NOTE: All quotations from exhibits are

23 reflected in the manner in which they were read into

24 the record and do not necessarily denote an exact

25 quote from the document.)

1 TUESDAY, DECEMBER 9, 2025;
2 9:13 A.M. EASTERN STANDARD TIME
3 --o0o--
4 VIDEOGRAPHER: We are now on the
5 record. The time is 9:13 a.m. The date
6 is December 9, 2025.
7 This is the video deposition of
8 Melanie A. Simpson, Ph.D., taken in the
9 matter of Merck Sharp & Dohme LLC versus
10 Halozyme, Incorporated. Case filed with
11 the U.S. Patent and Trademark Office
12 before the Patent and -- Patent Trial and
13 Appeal Board. It'll be Case
14 No. PGR2025-00003 and related cases
15 PGR2025-00004, -00006, and -00009.
16 We are at the offices of Sterne
17 Kessler, located at 1101 K Street,
18 Northwest, in Washington, D.C.
19 The videographer is Jonathan
20 Perry, and the court reporter is Susan
21 Ashe, both here on behalf of U.S. Legal
22 Support, located at 16825 Northchase
23 Drive, Suite 900, in Houston, Texas 77060.
24 And would counsel present please
25 introduce themselves and state whom they

1 represent.
2 MR. KUSHAN: Jeff Kushan from
3 Sidley Austin for Petitioner.
4 With me is Amy Mahan and Kalen
5 Sullivan from Sidley, and Brian Goldberg
6 from Dechert.
7 MS. MARTIN: Lauren Martin from
8 Quinn Emanuel on behalf of Halozyme.
9 And with me, I have Eldora
10 Ellison, Ralph Powers, III, and Haley Ball
11 from Sterne Kessler; Zach Summers and
12 Elliot Choi from Quinn Emanuel.
13 Whereupon,
14 MELANIE ANN SIMPSON, PH.D.
15 having been first duly sworn, was examined
16 and testified as follows:
17 EXAMINATION
18 BY MR. KUSHAN:
19 Q. Good morning. Could you state your full
20 name for the record.
21 A. My full name is Melanie Ann Simpson.
22 Q. And what is your present employer?
23 A. My present employer is North Carolina
24 State University.
25 Q. And you're based in Raleigh?

A. I am based in Raleigh.
Q. Have you been deposed before?
A. I have not been deposed before.
Q. Okay. We'll go over some ground rules.
First, I'll ask you questions. If you don't understand my question, let me know. I'll try to give you a better question.
You should proceed to answer my question after you've heard it and understood it.
Your counsel may raise an objection. Once she's finished, you proceed to answer the question I've asked you.
If she instructs you to not answer the question on the basis of privilege, of course you can follow the guidance of your counsel. But I'll want to confirm that you're doing that.
I'll show you exhibits during the course of the day. I hope to not overwhelm the space you have there. So if we need to move some of them off of the table, we can do that. They'll be handed to you, and then you can review them.
You understand that today you're under oath, and you're obligated to tell the truth to the best of your knowledge?
A. I do understand that.

Q. Okay. Is there any reason you cannot testify truthfully today?

A. No.

Q. Okay. No medical issues?

A. No.

Q. Okay. If I need to, I may ask you to step out of the room, if I need to have a conversation with opposing counsel. But we'll try to minimize those.

Also, anytime you need a break, just let us know. We can take a break. We'll finish answering the question that is presented to you, and then, once you finish that, we can -- that's the normal time for a break. Okay?

Do you understand all of these procedural steps here we've got?

A. Yes.

Q. Okay. Now, do you understand that you have provided declarations in four different proceedings in front of the Patent Trial and Appeal Board?

A. Yes, I do.

MR. KUSHAN: Okay. I'm going to call that the "PTAB." That's the entity that's going to be evaluating the

1 different sides of this dispute.
2 This is Exhibit 2068 in
3 "PGR2025-0003" concerning the U.S. Patent
4 11,952,600.
5 It's already marked.
6 (Whereupon, Halozyme Exhibit 2068,
7 previously marked, was presented to the witness.)
8 MR. KUSHAN: I'm also going to
9 hand to you Exhibit 2068 in
10 "PGR2025-0004," Exhibit 2068 in
11 "PGR2025-0006," finally, Exhibit 2068 in
12 "PGR2025-0009."
13 (Whereupon, Halozyme Exhibits 2068,
14 previously marked, were presented to the witness.)
15 MS. MARTIN: So, Counsel, we
16 have bound versions of all four of these.
17 I don't know if you have a
18 preference for which one it is that she
19 uses, but those are the four documents
20 that we brought.
21 MR. KUSHAN: Are there any
22 markings in the four that you brought with
23 you?
24 WITNESS: There are no markings.
25 MR. KUSHAN: Then if you wish to

use the spiral-bound version -- whichever one is more comfortable for you.

WITNESS: Thank you. I would prefer to use the spiral version.

MR. KUSHAN: All right. Then why don't we put those on the ground --

WITNESS: Thank you.

MR. KUSHAN: -- Ms. Court Reporter.

BY MR. KUSHAN:

Q. So my question today, these four declarations, are the opinions you've expressed in them generally the same except for particular position numbers in the PH20 sequence that may be relevant to particular patents?

A. They are substantively the same, with that exception, and, in one case, with the exception of the percent identity of the sequence.

Q. Okay. What I would propose to do is we'll use your declaration in the -0003 proceeding. I'll make reference to that with -- for page numbers so we can direct you to the right paragraph and the right document. Okay?

A. I understand.

Q. Could you go to your declaration in the

1 -0003 proceeding and go to the last page that --
2 where you've signed the declaration, which is
3 Page 173.
4 Is that -- is that your signature?
5 A. That is my signature.
6 Q. And when you signed this declaration, did
7 you confirm that you believed the statement above
8 your signature was correct?
9 A. I did so confirm.
10 Q. Great. Great.
11 And you signed this on September 23rd of
12 2025?
13 A. Yes.
14 Q. Did you form opinions in your declaration
15 before September 22, 2025?
16 MS. MARTIN: Object to form.
17 A. So the declaration documents the summary
18 of my opinions. They were not all formed in one
19 day.
20 Q. Yeah. So I just want to confirm. You
21 formed the bulk of your opinions prior to
22 September 23rd of 2025. Right?
23 MS. MARTIN: Object to form.
24 Q. Let me give you a better question.
25 Were there any opinions that you had

1 formed only on the 23rd of September of 2025?
2 A. Ah. I understand your question.
3 There were no opinions that were changed
4 on September 23, 2025.
5 Q. Okay. Can you recall when you were
6 retained to work on this matter?
7 A. Yes. I was first contacted in
8 January 2025 and formally retained in February 2025.
9 Q. All right. If you had -- if you could,
10 just give me an estimate of how many hours you've
11 worked on the matters that resulted in these
12 declarations.
13 A. My estimate to date would be about
14 150 hours.
15 Q. And do you recall when you began to
16 prepare a declaration that ultimately became this
17 declaration in the -0003 proceeding?
18 A. I don't recall a specific date, but the
19 time frame would have been about in April or May of
20 2025.
21 Q. Are you aware of any errors in your
22 declarations?
23 A. I am not aware of any errors in my
24 declarations.
25 Q. Okay. And you understand that these four

1 declarations each cons- -- there are four patents at
2 issue in the four proceedings. Correct? You
3 understand that?
4 MS. MARTIN: Object to form.
5 Q. You understand that each of the four
6 proceedings has one patent involved in it. Right?
7 A. I understand that each of these
8 declarations pertains to one specific patent.
9 Q. All right. Great.
10 MR. KUSHAN: I'm going to just
11 introduce the patents so that we have them
12 accessible. These are all numbered
13 Exhibit 1001, so I'll have to refer to the
14 other proceedings they're in.
15 First, we're going to introduce
16 U.S. Patent No. 11,952,600, which is the
17 patent at issue in the -0003 proceeding.
18 (Whereupon, Petitioner Exhibit 1001,
19 previously marked, was presented to the witness.)
20 COURT REPORTER: Is it
21 previously marked?
22 MR. KUSHAN: Yes.
23 COURT REPORTER: Thank you.
24 MR. KUSHAN: Also, Exhibit 1001
25 in the -0004 proceeding is U.S. Patent

1 12,018,298.
2 (Whereupon, Petitioner Exhibit 1001,
3 previously marked, was presented to the witness.)
4 MR. KUSHAN: Exhibit 1001 in the
5 2025-00006 proceeding, U.S. Patent
6 12,152,262.
7 (Whereupon, Petitioner Exhibit 1001,
8 previously marked, was presented to the witness.)
9 WITNESS: Thank you.
10 MR. KUSHAN: And finally,
11 Exhibit 1001, U.S. Patent 12,123,035 in
12 the -00009 proceeding.
13 (Whereupon, Petitioner Exhibit 1001,
14 previously marked, was presented to the witness.)
15 WITNESS: Thank you.
16 BY MR. KUSHAN:
17 Q. Just to start with these, did you review
18 each of these patents in their entirety?
19 A. I did review each of these patents in
20 their entirety.
21 Q. They're long, aren't they?
22 A. They are.
23 Q. All right. But you understand that the
24 four patents have the same drawings and
25 specification, and then they each have a different

1 set of claims at the end.
2 You understand that?
3 A. Yes, I understand that.
4 Q. And so, that -- that drawing and
5 specifications that are the same across those four
6 patents, those you've reviewed, basically, once.
7 There may be different numbers and columns and
8 things for each of the patents, but across the four
9 of them, you're looking at that as the same
10 information. Is that right?
11 A. I did actually review each one --
12 Q. Yeah.
13 A. -- carefully, page by page. But I do
14 recognize that, yes.
15 Q. Okay. And each of the patents is -- has a
16 claim set where they have identified a particular
17 position within the PH20 polypeptide sequence.
18 Right?
19 For example, in the '600 patent, they
20 refer to a position at 320. Right?
21 A. Yes.
22 Q. Okay. So we're familiar with the claims
23 that differ in each patent relative to the common
24 specification that they share. Right?
25 A. Yes.

1 Q. Okay. If you could -- if you could, go to
2 the '600 patent.
3 Can you go to the second page of this --
4 you know, just on the front of the '600 patent, you
5 see the -- there's a bunch of information, like the
6 number of the patent and the inventors, and then
7 there's a section on the left column under the
8 Item 60 that says "Related U.S. Application Data."
9 Do you see that?
10 A. Yes.
11 Q. If you could turn the page, and....
12 Do you see that there is a continuation of
13 the related information -- application information?
14 A. Yes, in the left column.
15 Q. And if you go to the very bottom of that,
16 you see a patent application that has the number
17 13/694,731?
18 (No audible response.)
19 Q. I'm at the bottom of that paragraph.
20 A. "13/694,731."
21 Q. Correct.
22 A. Yes.
23 Q. And that was filed on December 28th of
24 2012. Right?
25 A. Yes.

1 Q. Okay. And then below that, you see there
2 is another paragraph that lists two provisional
3 applications. They were filed on November 1, 2012
4 and December 30, 2011?
5 A. Yes.
6 MR. KUSHAN: All right. I'm
7 going to introduce the application that
8 has the number 13/694,731. This is
9 Exhibit 1026.
10 (Whereupon, Petitioner Exhibit 1026,
11 previously marked, was presented to the witness.)
12 Q. This -- you understand that the '731
13 application was the very first thing that was filed
14 by Halozyme in the patent office? This was their
15 first patent application -- well, the patent
16 application they filed on December 28th of 2012.
17 Right?
18 MS. MARTIN: Object to form.
19 Q. Sorry. You understand that the thing I've
20 handed you is the application that was filed with
21 the Patent and Trademark Office by Halozyme as the
22 '731 application?
23 A. Yes.
24 Q. Have you seen that document before?
25 A. Yes, I have.

Q. Great. I'm going to use that document because it is the original filing, and the specification and drawings in that are the same as the four patents. Okay?

I'm going to refer to this, all the specification and drawings of that, along with the four patents, as the "common disclosure." Okay?

A. Okay.

Q. And I think you've used a term like that as well, right, in your declarations?

A. Yes.

Q. I just want to make sure we're speaking about the same thing when I ask you a question. So we'll just use that as a reference point. Okay?

A. Yes.

Q. All right.

A. I understand.

MS. MARTIN: Counsel, is it possible for you to speak up? I'm having a really hard time hearing you.

MR. KUSHAN: Sure.

MS. MARTIN: Thank you.

Q. Do you recall if you reviewed the two provisional applications that were referenced in the patents?

A. I did not specifically review the provisional applications.

Q. Would any of your opinions in your declarations change between the dates of December of 2011 and December of 2012?

A. I don't --

MS. MARTIN: Object to form.

A. Okay. Could you ask me again? I'm sorry.

Q. Yeah. So the original application -- the provisional applications were filed in December of 2011. Then there was another one. The '731 application was filed in December of 2012.

I just want to make sure if you have different opinions about the state of the art or what a person of skill might have believed between those two dates.

Do you have a recollection if you have a difference of opinion around those two dates?

MS. MARTIN: Object to form and scope.

A. The majority of my opinions would not be substantively different between 2011 and 2012 consideration times.

Q. If I ask you a question today and there is a difference of your opinion between those two

1 dates, will you please let me know?
2 A. Yes.
3 Q. All right. Are you familiar with the fact
4 that these patents have also been filed with
5 sequences of -- amino acid sequences and nucleotide
6 sequences?
7 A. Yes.
8 Q. Do you know how many sequences were filed
9 with each of these patents?
10 A. The sequence identification numbers are
11 given for each of the patents within the claims.
12 And so, I understand that each patent
13 covers some of the same sequence identification
14 numbers and some different sequence identification
15 numbers.
16 The sequences -- the reference sequences
17 are given -- sometimes they're the same, sometimes
18 they're different -- for modified PH20 polypeptides
19 in each of the patents.
20 Q. Do you know how many sequences are
21 actually included with the patent?
22 A. I know how many sequences are listed in
23 this patent. There's a summary of them in the -- on
24 the Appendix A page of my declaration.
25 And I haven't counted them line by line,

1 but I think it's somewhere around 30 sequences.
2 Q. Would it surprise you to know that there's
3 about 800 sequences listed with this patent?
4 A. Actually, it does not surprise me to know
5 that. I know that the sequences that are listed
6 here are reference sequences and that additional
7 sequences are also referred to within the patent
8 that have presumably also been filed alongside these
9 sequences.
10 What -- so my uncertainty actually is with
11 respect to what is considered filed with this patent
12 versus what is part of the sequence IDs that they
13 are referencing in their specifications.
14 Q. You didn't look at all the 800 sequences
15 and evaluate them as part of your opinions, did you?
16 MS. MARTIN: Object to form.
17 A. I was not asked to evaluate all
18 800 sequences.
19 Q. Okay. Did you review any documents
20 from -- issued by the Patent Trial and Appeal Board,
21 the PTAB, in connection with these four proceedings?
22 A. I reviewed the prosecution history of the
23 patent -- patents.
24 Q. You didn't review any decisions coming out
25 of the Patent Trial and Appeal Board concerning

1 these four proceedings, did you?
2 A. The materials I reviewed are in my table
3 of exhibits.
4 Q. That's at Page 174 of your declaration?
5 A. 174 and 175. Yes.
6 Q. Well, I can just make it easier. Are the
7 materials you used in connect- -- sorry.
8 Are the materials that you reviewed in
9 connection with preparing your opinions what you
10 have listed on Pages 174 and 175 of your
11 declaration?
12 A. In combination with my general knowledge
13 and expertise in the field, these specific documents
14 are what I reviewed to prepare my declaration and to
15 prepare for this discussion.
16 Q. You reviewed a declaration from
17 Dr. Petsko. Right?
18 A. Yes. I reviewed Dr. Petsko's declaration.
19 Q. Do you recall being given Dr. Petsko's
20 declaration from counsel?
21 MS. MARTIN: Oh, objection, to
22 the extent that that's calling for
23 privileged information.
24 That sounds like a yes-or-no
25 question.

A. Yes.
Q. Do you recall when you were given the declaration from Dr. Petsko?
A. I don't recall a specific date. It was certainly prior to my completion of my declaration.
Q. Do you recall if you were given more than one version of Dr. Petsko's declaration?
A. Yes.
Q. You were?
A. No, I was not.
Q. Oh, you were not.
A. I recall.
Q. I apologize. Thank you for that.
So you were given more than one version of Dr. Petsko's declaration, and you do not recall which dates you received them? Is that your testimony?
MS. MARTIN: Object to form.
A. I was given only the final signed declaration from Dr. Petsko, which I received and -- at a date I'm not certain of, and reviewed prior to finalizing my declaration.
Q. Do you recall how much time you spent reviewing Dr. Petsko's declaration?
A. I don't recall specifically.

Q. Can you give me a ballpark number?
A. I can. Each of the -- including Dr. Petsko's declaration, required several hours for me to review.
Q. Do you recall providing any feedback on the declaration to counsel about Dr. Petsko's declaration?
MS. MARTIN: Objection. That's calling for the contents of communications with counsel. I'm going to instruct the witness not to answer.
MR. KUSHAN: All right.
Q. Do you recall seeing a spreadsheet that Dr. Petsko created that compiled information from the patent in it?
A. Yes.
MR. KUSHAN: I'm going to introduce what is Exhibit 2166.
(Whereupon, Halozyme Exhibit 2166, previously marked, was presented to the witness.)
Q. Do you recall if you received this document in paper form or PDF or in an Excel sheet format?
A. I received a PDF. I have since received a paper copy. I have also seen the spreadsheet

1 document, which I received at the same time of the
2 signed declaration.
3 Q. And you reviewed the spreadsheet?
4 A. Yes.
5 Q. Did you review the version in the Excel
6 format?
7 A. Yes.
8 Q. Okay. Did you -- when you reviewed this
9 spreadsheet, did you inspect like the formula that
10 are embedded in the cells?
11 (Speakerphone voice.)
12 COURT REPORTER: Was there
13 someone speaking online?
14 (No response.)
15 COURT REPORTER: Thank you.
16 (Witness reading.)
17 Q. So I had asked you a question whether,
18 when you received the spreadsheet in Excel format,
19 did you inspect the formulas used in the cells of
20 the spreadsheet?
21 A. In some cases, yes.
22 Q. When you reviewed this document, did you
23 identify any errors in it?
24 A. I did not detect errors in the document.
25 Q. Did you compare the information in this

1 document to the information in the common disclosure
2 when you reviewed it?
3 A. I did do that comparison, yes.
4 Q. And what was the nature of that
5 comparison? What did you do when you were -- what
6 were you looking for when you were comparing them?
7 A. I was looking to make the comparison
8 between the arrangement of data by Dr. Petsko with
9 respect to the data that were reported and how the
10 data were collected, as reported within the patent
11 specification.
12 Q. Did you identify -- or -- identify any
13 classifications of the information that you saw in
14 the declaration as being inaccurate with what had
15 been described in the common disclosure?
16 A. I did not identify inaccuracies in
17 Dr. Petsko's spreadsheet.
18 Q. All right. Between the time you were
19 retained by counsel and the time you signed your
20 declaration in September of 2025, have you had any
21 conversations with Dr. Petsko?
22 A. No, I have not.
23 Q. Did you have any questions about
24 Dr. Petsko's spreadsheet when -- after you had
25 reviewed it?

1 A. No, I didn't.
2 Q. Did you have any questions about
3 Dr. Petsko's declaration that you reviewed?
4 A. No, I didn't.
5 Q. So you were able to use the spreadsheet
6 and his declaration as they were written, without
7 getting any clarifications from Dr. Petsko?
8 A. The declaration and the spreadsheet
9 presented information that was, to me, very clear.
10 Q. Do you understand that Dr. Petsko was
11 deposed last week, similar to what you're going
12 through now?
13 A. I didn't know the date of his deposition.
14 I knew that he was to be deposed.
15 Q. Are you -- have you been given a
16 deposition transcript from his deposition?
17 A. No, I have not.
18 Q. Are you aware in any way of what
19 Dr. Petsko said during his deposition?
20 A. No, not in any way. It would be pure
21 speculation.
22 Q. All right. So you have not been given any
23 information about what he said in his deposition?
24 A. No, I have not been given information
25 about Petsko's deposition.

1 Q. In Dr. Petsko's declaration, there are
2 images of protein structures.
3 Do you recall that that is the case?
4 A. Yes, I do.
5 Q. Were you -- and are you familiar with the
6 file format used for those types of image
7 structures?
8 A. Yes, I am.
9 Q. What is it?
10 A. He used PyMOL to present the structures
11 that he presented.
12 Q. Were you given PDB files that have in them
13 information that reflects coloring and residues or
14 orientations of the protein structure?
15 A. No. The PDB file for the HYAL1 crystal
16 structure is available, obviously, in the PDB. It's
17 public domain information.
18 The models that were made by Dr. Petsko
19 were shared with me with specific images, not the
20 specific files that he generated.
21 The specific images he generated were part
22 of my consideration and analysis.
23 Q. So you received the PDB files of the
24 modeled PH20 protein. Correct?
25 MS. MARTIN: Object to form.

A. I did not receive Dr. Petsko's PDB files of his modeled PH20.

Q. Did you receive any PDB files having a model of PH20?

A. I did not.

Q. Did you inspect the -- so you didn't inspect the structure of the PD- -- sorry.

You did not inspect the model PH20 structure in PyMOL. Is that right?

A. As an expert in the study of the structure and function of hyaluronidases, I have myself modeled PH20 against the crystal structure of HYAL1 previously, quite a number of years ago.

I have done the exercise of considering the model in three dimensions. I did not use that information to influence my review in this -- my declaration.

I used, exclusively, the analysis in Dr. Petsko's declaration and the images he presented to form my opinions.

Q. I think that mostly answers my question, but I just want to make sure I understand -- I'm just kind of trying to understand how you went about your process of evaluating and forming your opinions.

1 I want to just understand whether, in the
2 course of forming your opinions, you used a tool
3 like PyMOL to inspect a PH20 model at all in
4 connection with your opinions that you've filed in
5 this case.
6 A. Not in connection with forming my opinions
7 for filing in this case.
8 Q. Did you look at a structure of HYAL1 in
9 PyMOL as part of your work in preparing your
10 opinions?
11 A. I did not. I did not look at any
12 structures in PyMOL in preparation for these
13 proceedings. I considered solely the analysis in
14 Dr. Petsko's declaration as I prepared my
15 declaration --
16 Q. And so --
17 A. -- coupled with my general knowledge and
18 preexisting knowledge in the field.
19 Q. And so, when you were addressing or
20 expressing opinions about the structure of PH20 that
21 were addressed by Dr. Petsko, you were using his
22 images of those structures that are in his
23 declaration?
24 A. Yes. I relied on his images.
25 Q. And you didn't rely on other images of the

structures in forming your opinions?
A. Other than the ones that are the published crystal structure and my own published work that are listed within the list of exhibits that I have declared.
Q. Okay. So when you were forming your opinions, you didn't, for example, have a session -- use a session with PyMOL where you were inspecting the different residues or the orientation of residues relative to the -- a particular area of the structure of the protein?
A. I did not personally do that, that analysis. I relied on Dr. Petsko's analysis, in which he did do that.
Q. Did you review a declaration from Dr. Gary Cherr?
A. I did.
Q. Did you speak to Dr. Cherr?
A. I did not.
Q. Did you review a declaration from Dr. James Moon?
A. Yes, I did.
Q. Did you speak to Dr. Moon at any point?
A. I did not.
Q. Are you aware in any way of what Dr. Cherr

said at his deposition?
A. Not in any way.
Q. You haven't been given a deposition transcript from Dr. Cherr?
A. I have not.
Q. And what about Dr. Moon; have you learned of anything that he said at his deposition in any way?
A. I have not.
Q. Have you reviewed a deposition transcript from Dr. Moon's deposition?
A. No, I have not.
Q. Have you spoken with any scientist from Halozyme?
MS. MARTIN: Object to form.
A. In connection with this matter?
Q. Yes.
A. No, I have not.
Q. Have you ever spoken with scientists from Halozyme?
A. Yes.
Q. Do you recall when?
A. I frequently attend a meeting of the International Society for Hyaluronan Sciences. The most recent time I would have spoken with a

1 scientist from Halozyme would have been at our most
2 recent meeting in June 2025.
3 Q. Do you recall speaking with scientists
4 from Halozyme in the 2011-2012 time frame?
5 A. I could not give you a specific date or
6 event, but this is a biannual meeting, and Halozyme
7 attends it, as do I and others in the field of
8 hyaluronan sciences. It is likely.
9 Q. Okay. Were you aware in the 2011-2012
10 time frame of any activities, any efforts by
11 companies such as Halozyme to engineer modified
12 forms of the PH20 protein?
13 A. Yes. I was aware of that type of an
14 activity, yes.
15 Q. Do you have recollections about what the
16 goal of those efforts were that you referred to?
17 MS. MARTIN: Object to form.
18 A. Could you be more specific?
19 Q. Sure. Were people developing those
20 molecules for a particular reason?
21 MS. MARTIN: Object to the form.
22 A. It's -- that's a very general question.
23 In general, the engineering of proteins
24 does have a reason associated with it.
25 And I could not necessarily name a

1 specific goal, but I can certainly say with
2 certainty that the scientists I know always have a
3 goal in that type of an experiment.
4 Q. I was wondering whether some of the
5 activities you were referring to were efforts to
6 make a more stable form of the PH20 protein, for
7 example.
8 Was that something you were aware of in
9 the 2011-2012 time frame?
10 A. I was not aware of it. If it was
11 occurring, if my colleagues were engaged in that
12 research, it was not something I discussed with
13 them.
14 Q. Have you reviewed any experimental records
15 obtained from or provided by Halozyme, other than
16 what might be reflected in the body of the common
17 disclosure?
18 A. No.
19 Q. On your list of exhibits, you've reviewed
20 declarations from two experts from Merck. One is --
21 who have provided testimony in this proceeding on
22 behalf of Merck -- one is Dr. Park and one is
23 Dr. Hecht. Right?
24 A. Yes.
25 Q. Did you review the entirety of their

1 declarations?
2 A. Yes.
3 Q. Did you review the annexes in their
4 declarations?
5 A. Meaning the appendices?
6 Q. Appendices, yes.
7 A. Yes.
8 Q. Okay. Do you have any reason to doubt the
9 scientific credentials of Dr. Hecht or Dr. Park?
10 A. No.
11 Q. Are you aware of Dr. Hecht from your --
12 working in this field?
13 A. I was not actually previously aware of
14 Dr. Hecht's work.
15 Q. You also reviewed deposition transcripts
16 from the depositions of Dr. Hecht and Dr. Park.
17 Right?
18 A. Yes.
19 Q. Did you review the entirety of each of
20 their deposition?
21 A. Yes.
22 Q. Did you review -- review the exhibits to
23 the declarations -- sorry, to the depositions?
24 Sorry.
25 For the deposition transcripts, there are

1 often a list of exhibits that were discussed in the
2 deposition. And I'm just wondering if you had
3 reviewed those deposition exhibits for any of these
4 proceedings.
5 A. I looked to see what the exhibits were.
6 And in some cases, they were documents I've
7 reviewed. In some cases, they were not.
8 Q. All right. Why don't we go to your
9 declaration in the -0003 proceeding. Let me know
10 when you have that in front of you.
11 Could you turn to Paragraph 50 of your
12 declaration, Page 17.
13 A. Yes.
14 Q. This is a section of your declaration --
15 you're discussing the person of ordinary skill in
16 the art, which is abbreviated "POSA." Right?
17 A. Yes.
18 Q. Okay. If I say "POSA," you'll know what
19 I'm referring to. Right?
20 A. Yes.
21 Q. Okay. And you quote what is Merck's
22 definition of a POSA in your declaration at
23 Paragraph 50. Right?
24 A. Yes.
25 Q. Would you consider yourself a person of

1 ordinary skill in the art in the 2011-2012 time
2 frame?
3 A. In Paragraph 53:
4 Considering my ample
5 practical experience with
6 hyaluronidases as described in
7 my background and
8 qualifications, I'm more
9 experienced than a POSA under
10 Merck's definition and was
11 before 2011.
12 Q. Are the opinions you're presenting in your
13 declaration being presented from the perspective of
14 a POSA in the 2011-2012 time frame?
15 A. Yes; throughout my declaration.
16 Q. You refer to a POSA working as part of a
17 multidisciplinary team. Right?
18 A. Yes.
19 Q. So if I'm looking at the team that I see
20 here, you have yourself, Dr. Hecht -- I'm sorry.
21 I'll try that one again.
22 The multidisciplinary team that you have
23 here would be yourself, Dr. Petsko, Dr. Moon, and
24 Dr. Cherr. Right?
25 A. Yes, I would look at it that way. That is

1 a multidisciplinary team.
2 Q. So in this multidisciplinary team, do the
3 individuals have particular roles?
4 MS. MARTIN: Object to form.
5 A. In this specific multidisciplinary team?
6 Q. Yes.
7 A. Each of us was asked to review a certain
8 aspect of each of these patents and a certain
9 experimental aspect of those patents that was within
10 our areas of expertise. In that sense, each of us
11 had a role.
12 In the sense that we did not discuss among
13 each other what our individual roles were, which is
14 what a multidisciplinary team often would do, it's
15 more or less assumed, based on our expertise, that
16 we had individual roles.
17 Q. What is your understanding of the role of
18 Dr. Moon in this team?
19 MS. MARTIN: Object to form.
20 A. Dr. Moon, in his declaration, states what
21 his role was and what he was asked to analyze and
22 what opinions he was asked to provide.
23 His -- a review of his CV shows me that
24 his expertise is in immunology. And so, I view his
25 role as an expert in immunology.

1 Q. What about Dr. Cherr; what do you see his
2 role to be, based on your understanding?
3 A. Similarly to Dr. Moon, Dr. Cherr was
4 engaged with a specific scope that he was asked to
5 form opinions around.
6 In reviewing his CV, I can also see that
7 his expertise is in reproductive biology, in
8 generation of polyclonal antibodies, and especially
9 in the role of PH20 in reproductive biology.
10 Q. And what is the role of Dr. Petsko in this
11 team?
12 A. Dr. Petsko is a leading expert in
13 structural entomology, and in analysis of
14 structure/function relationships, in protein
15 crystallography, and in the use of crystal
16 structures to provide models and predictive -- use
17 of predictive tools and statistical frameworks to
18 provide confidence intervals for the results of
19 those -- the application of those statistical tools,
20 to provide confidence in his modeling.
21 He's an expert in redox biology and the
22 study of Parkinson's disease and other neuro- --
23 neurological disorders.
24 Q. And then, finally, what's your role in
25 this multidisciplinary -- disciplinary team?

1 A. My role has been as a person who has been
2 studying the family of hyaluronidase enzymes,
3 specifically mammalian hyaluronidases, since
4 approximately 1998, so as an expert in extracellular
5 matrix biology, in biochemistry and molecular
6 biology, with a special attention to structure and
7 enzymology, and the use of those tools in the study
8 of the hyaluronidase family, as well as other
9 research areas.
10 Q. Do you believe that your role or your
11 skill set is overlapping in some sense with
12 Dr. Petsko's?
13 A. Every multidisciplinary team is most
14 effective if there is sufficient overlap in their
15 expertise that they can speak to each other and
16 understand each other, develop a common language, to
17 be able to use each other's opinions in an
18 intelligent and independent way.
19 It is certainly the case that I have
20 reviewed Dr. Petsko's textbook and used it in some
21 of my teaching, some of my courses in the past, and
22 that, with great humility, I would say Dr. Petsko
23 and I do have some overlapping expertise.
24 Q. And just to be clear, in this setting,
25 there was no what I would call ordinary interaction

that would occur between this multidisciplinary team in the course of the work that you prepared in this proceeding?

MS. MARTIN: Object to form.

Q. You haven't spoken to each other?

A. No. Thank you.

Q. Normally, the members of the team would speak to each other. Right?

A. At least email each other. Yes, there would be some communication among the members of the team.

Q. Okay. I forgot to mention this, but at the beginning, one thing we do want to make sure we do is take periodic breaks.

And we've been going for about -- almost an hour. If you'd like to take a break now, we can do that, before I move on to my next topic.

A. Sure. That sounds great. Thank you.

MR. KUSHAN: All right. Why don't we do that.

VIDEOGRAPHER: Off the record at 10:02.

(Whereupon, a recess was taken.)

VIDEOGRAPHER: On the record at 10:19.

1 BY MR. KUSHAN:
2 Q. Dr. Simpson, did you speak with counsel
3 during the break?
4 A. Not about any matters concerning the case.
5 Q. What did you speak about?
6 A. How cute the decorations were in the
7 corridor.
8 Q. Could I have you go to your declaration in
9 the -00003 proceeding. And if you could turn to
10 Page 109, Paragraph 260.
11 Do you see, in Paragraph 260, you have
12 reproduced the text of claim 1 of the '600 patent?
13 A. Yes, I see that.
14 Q. Okay. I just want to go through some of
15 the language in the claim with you. Okay?
16 A. Yes.
17 Q. So the first clause in the claim states:
18 A modified PH20
19 polypeptide comprising an amino
20 acid sequence....
21 Right?
22 A. Yes.
23 Q. Okay. And then, in the next three
24 paragraphs, you see parameters relating to that
25 amino acid sequence. Right?

A. Yes.
Q. Okay. So in the first paragraph, that requires the amino acid sequence to have 95% sequence identity to one of a number of reference sequences. Right?
MS. MARTIN: Object to form.
A. Could you please repeat your question?
Q. Sure. In Paragraph (a) of the claim, it specifies that the amino acid sequence must have 95% sequence identity to one of a list of reference sequences. Right?
MS. MARTIN: Object to form.
A. So Part (a) specifies that:
At least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66.
And then specifies that they should be aligned to maximize identical residues and treating terminal gaps as non-identical.
Q. So the amino acid sequence of the modified

1 PH20 polypeptide must have 95% sequence identity
2 relative to the -- one of those reference sequences.
3 Right?
4 MS. MARTIN: Object to form.
5 A. It's my understanding that the claim in
6 Part (a) states that the modified PH20 polypeptide
7 comprises an amino acid sequence that is 95%
8 identical to the sequence of SEQ ID NO: 3 and --
9 and/or one of the sequences from among 32-66.
10 Q. Okay. And you're familiar with this
11 concept of sequence identity between two amino acid
12 sequences?
13 A. Yes.
14 Q. Okay. So if I refer to 95% sequence
15 identity in the claim, you'll know what I'm
16 referring to. Right?
17 A. Yes.
18 Q. Okay. So the -- in Paragraph (b), there
19 is a requirement that the amino acid sequence have a
20 modification at position 320. Right?
21 A. Yes.
22 Q. And then the third paragraph adds the
23 requirement of that modification has to be a
24 replacement of the wild-type amino acid at
25 position 322, one of four alternative amino acids.

1 Right?
2 A. Yes.
3 Q. Okay. And then, the claims in the other
4 patents have similar style to this format. Right?
5 MS. MARTIN: Object to form.
6 Q. They have a sequence identity parameter,
7 they have a particular residue that's been
8 identified, and there are often choices for which
9 amino acids could be replaced at that position, in
10 those other claims. Right?
11 A. Yes. If that's what you're referring to
12 with the word -- the term "style," that's my
13 understanding, yes.
14 Q. Perfect. If you could go to Page 110,
15 which is the next page, and go to Paragraph 264 --
16 I'm sorry.
17 Go to Page 111, which is where 264 is
18 located.
19 In this paragraph, you're referring to a
20 passage in the common disclosure. Right?
21 MS. MARTIN: Object to form.
22 A. Yes. The passage is excerpted from the
23 '600 patent.
24 Q. And what you're saying is -- in
25 Paragraph 64 [sic], you're saying that in this

1 passage from the '600 patent, it is, like the
2 claims, referring to a modified PH20 polypeptide by
3 reference to an amino acid sequence, its primary
4 structure. Right?
5 A. Yes.
6 Q. And then it only describes the structural
7 features of the sequence of amino acids, the
8 existence in that amino acid sequence of an amino
9 acid modification relative -- relative to a
10 reference sequence. Right?
11 MS. MARTIN: Object to form.
12 A. The passage:
13 ...defines "modified PH20
14 polypeptide" by reference to
15 its primary structure, amino
16 acid sequence, not a particular
17 function. It describes
18 structural features:
19 (i) a sequence of amino
20 acids (ii) with at least one
21 modification (iii) relative to
22 a reference sequence.
23 Q. Okay. So the focus in your comment on
24 Paragraph 20 -- 264 is that this passage is
25 referring to the amino acid sequence of the modified

1 PH20 polypeptide and attributes of that amino acid
2 sequence. Is that fair?
3 A. Yes.
4 Q. Okay. Could I have you go to Page 11 at
5 the front of your declaration, Paragraph 28.
6 A. Yes.
7 Q. And you state that it's your:
8 ...opinion that a POSA
9 would have understood that
10 claims define the invention by
11 reference to its structure,
12 without regard to a particular
13 function....
14 And then, in the second sentence, you
15 identify those structural components as being:
16 (i) a sequence of amino
17 acids (ii) with at least one
18 amino acid modification (iii)
19 having 95% identity relative to
20 a reference sequence.
21 Right?
22 Those are the structural features of the
23 sequence that you've identified?
24 MS. MARTIN: Object to form.
25 A. As you've recited from this paragraph,

1 that is accurate.
2 Q. Okay. So you believe that any polypeptide
3 that has an amino acid sequence with 95% sequence
4 identity to SEQ ID 3, for example, plus a
5 replacement of aspartic acid at 320 to any of
6 histidine, lysine, arginine, or serine would meet
7 all the requirements of claim 1. Is that right?
8 A. Any polypeptide with 95% sequence identity
9 to the reference sequence, SEQ ID 3, for example,
10 with position 320 modified 95% identity, those are
11 the polypeptides covered in claim 1.
12 Q. Okay. So in the first line of the claim,
13 does the word "PH20" add any requirements to
14 claim 1?
15 MS. MARTIN: Object to form.
16 Objection; scope. Objection; relevance.
17 A. Can you repeat the question? I'm not
18 actually sure what you mean.
19 Q. Sure. In claim 1, it refers to "a
20 modified PH20 polypeptide comprising an amino acid
21 sequence." Right?
22 A. Yes.
23 Q. And I asked you if a polypeptide that met
24 the sequence requirements in the claim met the claim
25 requirements. Right?

1 You answered "yes."
2 A. I understand.
3 So the term "modified PH20 polypeptide" is
4 specifically defined by the patent.
5 Q. Right. I want to -- I'm focusing on just
6 the word "PH20."
7 Does PH20 add any requirements into the
8 amino acid sequence or the protein beyond what's
9 recited as to the requirements of the amino acid
10 sequence in the claim?
11 MS. MARTIN: Object to form.
12 A. I'm still not sure I understand your
13 question. Could -- maybe be specific about what....
14 Q. Sure. So you see the words "modified
15 PH20" and "polypeptide." Right?
16 Those are three different words.
17 A. Yeah.
18 Q. Okay. So if PH20 were not in the phrase,
19 would you identify a different set of amino acid
20 sequences compared to if it is present in the phrase
21 "modified PH20 polypeptide"?
22 MS. MARTIN: Object to --
23 Q. I'm trying to understand whether PH20 is
24 imposing any additional requirement beyond the
25 features of the amino acid sequences that are

1 recited in the claims.
2 MS. MARTIN: Object to form.
3 A. Because there is a specific sequence
4 given, the term "PH20" doesn't impose any greater
5 restraints. That is the sequence of PH20 in a
6 modified polypeptide, as defined by the claims and
7 by the patent.
8 Q. So if I'm visualizing claim 1 as defining
9 a set of amino acid sequences -- is that term
10 conceptually accessible to you, that the claim is
11 defining a set of amino acid sequences that share
12 these features? Is that -- you understand that?
13 A. Yes.
14 Q. Okay. So that set of amino acid sequences
15 defined by the parameters in claim 1 does not vary
16 based on the presence of the word "PH20" in the
17 first line of the claim. Right?
18 MS. MARTIN: Object to form.
19 A. The term "PH20" is embedded in the phrase
20 "modified PH20 polypeptide," which has a specific
21 definition as defined in the patent disclosure.
22 Q. So it's not -- "PH20" is not adding
23 anything as a requirement into the features of the
24 polypeptide or the amino acid sequence defined by
25 the claim. Is that right?

MS. MARTIN: Object to form.

A. I'm still not sure I understand what you're getting at.

Q. Why don't -- why don't you -- why don't you go back to Paragraph 260, where you see the language of the claim. And I'll try to make a better question for you.

A. Thank you.

Q. If I were to remove the word "PH20" from the first line of the claim, would you see a different set of amino acid sequences relative to what is there in the claim?

MS. MARTIN: Object to form.

Objection; scope.

A. The claim is on the basis of sequences that are identified and given. The sequences are absolute.

The nomenclature of "modified PH20 polypeptide" helps a POSA understand what the context is for those sequences and where they're found biologically, but the sequence structure itself doesn't necessarily require the term "PH20" to define it.

And the patent claim would not change if the word "PH20" wasn't there, but it is defined

1 within the disclosure of the patent. So it's part
2 of the specific phrase used to define this
3 polypeptide sequence and refer to it throughout the
4 patent disclosure.
5 Q. Okay. Could I have you go to
6 Paragraph 263 of your declaration. And that's what
7 we mentioned a minute ago.
8 You say that the '600 patent explicitly
9 defines, quote, modified PH [sic] polypeptide, and
10 then you reproduce your -- the definition in the
11 patent of that phrase. Right?
12 A. Yes.
13 Q. And you read -- the first sentence of the
14 paragraph that you've quoted is the portion that is
15 defining the meaning of the phrase "modified PH20
16 polypeptide." Is that right?
17 A. I'm sorry. Could you repeat that, please?
18 Q. The section that you've quoted --
19 A. Yes.
20 Q. -- is a paragraph. It has more than one
21 sentence. Right?
22 A. Yes.
23 Q. Do you see that?
24 A. Yes.
25 Q. Okay. I'm asking you: Is your

1 understanding that the phrase "modified PH20
2 polypeptide" is defined by the first sentence of
3 that paragraph?
4 (Witness reading.)
5 A. Yes, the phrase "modified PH20
6 polypeptide" is defined by the first sentence.
7 Q. Do you view the additional sentences in
8 this paragraph to not alter the definition of that
9 term, "modified PH20 polypeptide"?
10 A. I do view that, yes.
11 Q. Could you go to Exhibit 1026, which is the
12 very big '731 application.
13 A. Yes.
14 Q. If you could go to Page 54 of
15 Exhibit 1026.
16 A. Yes.
17 Q. If you want to take the binder clip off,
18 it might be easier, but it's up to you.
19 Okay. And do you see, at Lines 5 to 14,
20 that's the paragraph you had reproduced in
21 Paragraph 263 of your declaration?
22 (Witness reading.)
23 A. Yes.
24 Q. Okay.
25 A. The two appear identical.

1 Q. So you're using a portion of the common
2 disclosure that defines this term, "modified PH20
3 polypeptide," in a particular paragraph in the
4 disclosure. Right?
5 MS. MARTIN: Object to the form.
6 A. So this is -- the paragraph from Lines 5
7 to 14 of the '731 application is the paragraph
8 reproduced in my declaration.
9 Q. And you're treating the first sentence of
10 that paragraph as being the definition of the term
11 "modified PH20 polypeptide." Right?
12 A. The first sentence of this paragraph is
13 the definition, yes, of "modified PH20 polypeptide."
14 Q. Could you go to Page 50 of the common
15 disclosure. It's 1026.
16 And at the bottom of the page, do you see
17 a definition of the word "PH20" around Line 31?
18 A. Yes.
19 Q. And what is the definition of PH20 that
20 the common disclosure provides?
21 A. (Reading:)
22 As used herein, PH20
23 refers to a type of
24 hyaluronidase that occurs in
25 sperm and is neutral-active.

1 Q. So as the term "PH20" is defined in the
2 common disclosure, it's PH20 on sperm cells. Right?
3 MS. MARTIN: Object to form.
4 A. As PH20 is defined?
5 Q. Yes.
6 A. That was the --
7 Q. Yes.
8 A. -- question. As PH20 is defined here in
9 this sentence, it refers to a type of hyaluronidase
10 that occurs in sperm and is neutral-active.
11 It does state that it occurs on the sperm
12 surface as well.
13 Q. So when the PH20 is on the sperm surface,
14 is it a folded protein?
15 A. Yes.
16 Q. And it's enzymatically active. Correct?
17 A. In normal biology, surface-associated PH20
18 would be enzymatically active.
19 Q. And it's -- because it is properly folded,
20 it is enzymatically active. Right?
21 MS. MARTIN: Object to form.
22 A. Properly folded PH20 should have enzymatic
23 activity, yes.
24 Q. Okay. And this is how the common
25 disclosure defines the term "PH20." Right?

1 MS. MARTIN: Object to form.
2 A. PH20 is defined as a type of hyaluronidase
3 that occurs in sperm and is neutral-active.
4 It explains further that it occurs on the
5 sperm surface. In this particular paragraph, the
6 folded structure is not specified.
7 Q. But it would just be the folded structure
8 that occurs naturally with the PH20?
9 A. If PH20 is active on the sperm surface, it
10 is assumed to be folded.
11 Q. Okay. Could you go to Page 110 of your
12 declaration.
13 And just take a look at Paragraphs 262 and
14 263. We talked about 263, but look at 262 as well.
15 And when you finish reading that, let me
16 know.
17 (Witness reading.)
18 A. Yes.
19 Q. Is it your opinion that Dr. Hecht's
20 opinion is that the phrase "modified PH20
21 polypeptide" by itself imposes a requirement for
22 enzymatically active proteins, as you state in
23 Paragraph 262?
24 MS. MARTIN: Object to form.
25 A. I understand that Dr. Hecht's position is

1 that the term "modified PH20 polypeptide" in the
2 claim requires greater than equal to 40%
3 hyaluronidase activity compared to wild type.
4 Q. And I'm just asking: Do you understand
5 Dr. Hecht to be saying that the phrase "modified
6 PH20 polypeptide" by itself is what requires it to
7 have enzymatic activity?
8 MS. MARTIN: Object to form.
9 A. I think I see what you're saying. Could
10 you repeat the question once more, please?
11 Q. Sure. Is it your opinion that Dr. Hecht
12 is relying on the words "modified PH20 polypeptide"
13 by themselves to be imposing the requirement in the
14 claims that the enzyme be enzymatically active?
15 MS. MARTIN: Object to form.
16 A. My opinion is that Dr. Hecht formed his
17 opinion by making an interpretation for himself of
18 what modified PH20 polypeptide referred to.
19 Q. And so, your understanding is that he
20 formed his opinion about the words "modified PH20
21 polypeptide," and when they occur in the claim,
22 those words by themselves imposed a requirement that
23 the PH20 polypeptide was enzymatically active.
24 MS. MARTIN: Object to --
25 Q. Is that right?

1 MS. MARTIN: Object to form.
2 A. Without looking directly, at the moment,
3 at Dr. Hecht's declaration, I don't recall whether
4 he specifically said that he was defining modified
5 PH20 polypeptide differently than I have defined
6 modified PH20 polypeptide according to the first
7 sentence of the claim.
8 The way in which he has rendered his
9 opinions certainly reflects that he is interpreting
10 modified PH20 polypeptide to mean an active PH20
11 polypeptide.
12 Q. Do you believe he relied on anything else
13 in the claim to reach his conclusion that the claim
14 required the PH20 polypeptide to be enzymatically
15 active?
16 MS. MARTIN: Object to form.
17 A. I didn't try to understand what motivated
18 Dr. Hecht to form his opinions.
19 Q. Could you go to Paragraph 257 of your
20 declaration. It's back a few pages.
21 You make a similar observation in
22 Paragraph 257 [sic] to what you referred to in 262,
23 where you say you:
24 Do not see any reason why
25 a POSA would understand the

1 claims to require a particular
2 type of function, let alone 40%
3 or more activity.
4 And that's what you're stating in
5 Paragraph 257. Right?
6 MS. MARTIN: Object to form.
7 A. In Paragraph 257, I am stating my
8 understanding of Dr. Hecht's tested -- testimony at
9 deposition that the claims require greater than or
10 equal to 40% hyaluronidase activity compared to wild
11 type, such that if it had less than 40% activity, it
12 would not be covered by the claims.
13 I did not, in that paragraph, disagree
14 with his opinion --
15 Q. Look at --
16 A. -- but I did in the following.
17 Q. -- Paragraph 258.
18 A. And could you please repeat your question?
19 Q. Sure. You stated in 258 that you don't
20 agree with Dr. Hecht. Right?
21 A. Yes.
22 Q. And you say, based on your review of the
23 claims and the specification, it's your conclusion
24 that the claims are defined by the recited
25 structure: The amino acid sequences, the mutation

at 3 -- D320, in reference to SEQ ID 3, and the 95% sequence identification.

Right?

A. Yes.

Q. Okay. And then you state:

I don't -- I do not see any reason why a POSA would understand the claims to require a particular type of function, let alone 40% or more activity. There's no language in the claim suggesting it.

Right?

A. Yes, that was my stated opinion.

Q. So it was your understanding that Dr. Hecht based his opinion that the claim required enzymatic activity solely on his use -- or the claim's use of the phrase "modified PH20 polypeptide"?

MS. MARTIN: Object to the form.

A. Again, difficult for me to offer an opinion about how Dr. Hecht formed his opinions.

Q. Well, you're offering opinions -- opinions about his opinion in your declaration. Right?

A. I offered an opinion about what he stated

1 as his opinion. I did not speculate on how he
2 formed it.
3 Q. Do you believe, when -- well, when you
4 reviewed Dr. Hecht's declaration, did you identify
5 any explanation in his declaration as to why he
6 concluded that the claim required enzymatic
7 activity?
8 A. I would prefer to have his declaration in
9 front of me before commenting.
10 Q. Sure. We'll do that in a second.
11 As you state your opinion in
12 Paragraph 257, you're referring to the thing he said
13 in his deposition. Right?
14 MS. MARTIN: Object to form.
15 (Witness reading.)
16 A. The opinion that I stated does reflect a
17 statement that Dr. Hecht made in his deposition.
18 Q. You also state you:
19 ...don't see any reason
20 why a POSA would understand the
21 claims to require a particular
22 type of function, let alone 40%
23 or more activity.
24 Is there any reason, from your review of
25 the patent -- of the common disclosure to -- for a

1 person of ordinary skill to conclude that 40%
2 activity has significance for PH20 polypeptides?
3 A. In my review of the common disclosure,
4 there is not a reason to consider a specific
5 activity level in interpreting the statement in
6 claim 1.
7 Q. Do you recall if the common disclosure
8 uses that 40% activity number in any context to
9 characterize the polypeptides, the PH20 polypeptides
10 that it's describing?
11 A. I do.
12 Q. And what was that role? What is it using
13 that 40% number for?
14 MS. MARTIN: Object to form.
15 (Witness reading.)
16 A. As an example, on Page 93 of the common
17 disclosure in the '731 application, Table 3 lists
18 active mutants of PH20 polypeptides, wherein they
19 are listing mutants and characterizing activity as
20 40% of the hyaluronidase activity of the PH20
21 polypeptide set forth in SEQ ID 3.
22 Q. And that SEQ ID 3 is the wild-type
23 sequence truncated at position 447 of PH20, human
24 PH20?
25 Make it easier: Wild-type -- it's the

1 wild-type sequence except for the truncation.
2 Right?
3 A. Yes, that's correct.
4 Q. Okay. So it's measuring the mutant
5 activity relative to the activity of the wild-type
6 human PH20, truncated PH20. Right?
7 A. Yes.
8 Q. Okay. So does the common disclosure
9 differentiate those modified PH20 polypeptides from
10 other kinds of PH20 polypeptides?
11 MS. MARTIN: Object to form.
12 A. In what way?
13 Q. Is there another class of modified PH20
14 polypeptides identified in the common disclosure,
15 besides active mutants?
16 A. Yes.
17 Q. And what are they?
18 A. They also list, for example, in Table 5 of
19 '731 application in the common disclosure, on
20 Page 132, inactive mutants of PH20.
21 Q. And are inactive mutants of PH20 defined
22 by some enzymatic characteristic?
23 A. The disclosure states, for this specific
24 table, that the term "inactive" refers to exhibiting
25 less than 20%, and generally less than 10%, of the

1 hyaluronidase activity of the PH20 polypeptide in
2 SEQ ID 3.
3 Q. So inactive mutants -- inactive mutants
4 are the modified PH20 polypeptides that have less
5 than 20% activity relative to the wild-type PH20?
6 MS. MARTIN: Object to form.
7 A. As defined in Table 5.
8 Q. Is that -- it's limited to Table 5?
9 A. There are additional tables in the
10 disclosure in which there may be other definitions
11 of inactive or criteria for inactive.
12 Here in this table, inactive is defined as
13 less than 20%, generally less than 10%,
14 hyaluronidase activity.
15 Q. Do you recall if there's another table
16 compiling inactive mutants in the patent?
17 A. Yes.
18 Q. Table 10? Is that the one you're thinking
19 of?
20 A. Yes. Thank you.
21 Q. If you want -- and does Table 10 define
22 inactive mutants differently than Table 5 defines
23 inactive mutants?
24 A. Within this table are listed other --
25 other mutants of PH20 that also exhibit less than

1 20% hyaluronidase activity. So it's a similar
2 definition.
3 Q. So the patent is classifying modified PH20
4 polypeptides as active mutants if they have activity
5 above 40% relative to the wild-type sequence.
6 Right?
7 MS. MARTIN: Object to form.
8 A. The patent lists the mutants in a table as
9 active mutants if they have 40% or more activity.
10 The patent also discloses polypeptides
11 with activity that is not 40%.
12 Q. Do you, as you sit here now -- I want to
13 probe this a little bit later today -- but are you
14 aware that -- of the classification procedure they
15 use for putting modified PH20 polypeptides into
16 Table 9?
17 (Witness reading.)
18 A. Yes.
19 Q. So there are two samples measured in the
20 example they describe here for the experimentation
21 that was done. Right?
22 MS. MARTIN: Object to form.
23 Q. For each mutant, there were two samples
24 measured. Right?
25 A. Each mutant was tested in duplicate, yes.

1 Q. And if one of the two samples -- one of
2 the two duplicates recorded activity above 40% of
3 the wild type, it was classified, at that position
4 in that mutant, as an active mutant. Right?
5 A. Following normalization and within the
6 overall experimental context, which we haven't
7 discussed -- but, yes.
8 Q. All right. So the patent is classifying
9 as one kind of PH20 polypeptide those that had
10 activity measured above 40% relative to the wild
11 type. Right?
12 MS. MARTIN: Object to form.
13 A. The patent provides a table that lists all
14 of the mutants that were tested that exhibited
15 greater than or equal to 40% activity.
16 Q. Could you go to -- go to your declaration,
17 please. And if you could, go to Page 127 and
18 Paragraph 303.
19 This is a fairly long paragraph, so if you
20 want to just take a minute and review it. It
21 extends on to the next page.
22 (Witness reading.)
23 A. Yes.
24 Q. Okay. So in this Paragraph 303, you're
25 discussing inactive mutants. Right?

A. As you said, it's a lengthy paragraph. It does touch on inactive mutants. That's not the exclusive topic of the paragraph.

Q. You're addressing some attributes of inactive mutants. Let me just do a terminology check.

You use the word "inactive variants."

Are you using inactive variants to mean something different than inactive mutants in the patent?

A. No.

Q. Okay.

A. No, it's --

Q. Okay.

A. -- the same term.

Q. And then, in your Paragraph 303, you're identifying a number of positions in PH20 that are essential to the enzymatic -- enzymatic activity of PH20. Right?

A. Yes. There are a number of known -- known substitutions that are known to inactivate the enzyme, yes.

Q. And these are positions that, if you change them from their wild-type amino acid, it will cause problems for the protein. Right?

A. I just want to be clear what you mean by "cause problems."

Q. So there are a couple things you mentioned here. One is that you could disrupt the folding of the protein. Right?

A. Yes.

Q. Another thing, you may cause a loss of enzymatic activity of the native protein by making a mutation at one of these essential positions. Right?

A. Yes.

Q. Those are perhaps not exclusive scenarios. Right? Fold --

A. Correct.

Q. -- to -- okay. Go ahead.

A. Yes. That's correct.

They could occur together.

Q. All right. They could destabilize disulfide bond formation as well. That would be another impact that would be adverse for the protein structure. Right?

A. Yes.

Q. And you say that the common disclosure identifies several of these positions that have this essential characteristic for the either folding or

1 activity of the PH20 protein. Right?
2 A. Yes.
3 Q. And your view is that a POSA would not
4 consider any of those essential positions to be
5 tolerant to change. Is that fair?
6 MS. MARTIN: Object to form.
7 A. My view is that where there are published
8 data available, in particular, a POSA would already
9 be aware of those published data. And that included
10 where there were invariant residues in the sequence
11 that had been functionally demonstrated to be
12 required for enzymatic activity and/or for disulfide
13 bond formation and proper folding of the protein. A
14 POSA would be aware of that.
15 Q. Which -- so those were residues that have
16 been identified before this patent was filed in
17 2011 -- first filed in 2011?
18 A. Yes.
19 Q. How would the person of skill in the art
20 identify those positions from the literature?
21 (No audible response.)
22 Q. Well, I'll make it simpler: How would
23 they identify those positions?
24 A. So a literature search. Is that what
25 you're asking?

1 Q. Let me make you -- let me give you a
2 better question.
3 How would a person of skill in the art
4 identify the essential residues we've been
5 discussing from available information as it existed
6 in 2011?
7 A. A number of publications were available
8 that either had identified experimentally, within
9 the context of PH20 polypeptide, what the specific
10 catalytic residues were, together with the available
11 crystal structure for HYAL1, in addition to critical
12 residues demonstrated in the context of HYAL1, and
13 then being able to superimpose a model of PH20 and
14 its active site residues onto the active site
15 residues of the HYAL1 structure.
16 We would have a full picture, as POSAs, of
17 what residues were responsible for catalytic
18 activity.
19 Q. What about folding; how would you identify
20 which positions were important or necessary for
21 folding of the protein?
22 A. One of the ways that can be used,
23 especially in the hyaluronidase family, in which the
24 structures are relatively invariant, is to align the
25 sequences, as has been done by not only the authors

1 of the Chao paper, the HYAL1 crystal structure
2 paper, but also by probably everyone involved in
3 writing a declaration in this case.
4 The alignments are also super --
5 reproduced within this declaration. By looking at
6 the alignments, there are a number of invariant
7 residues. A knowledge of which invariant residues
8 are the active site residues allows us to exclude
9 those from consideration as active site residues.
10 There are a number of other invariant
11 residues using the structure that can be deduced to
12 be responsible for substrate docking.
13 Those may or may not be folding
14 determinants, but additional residues that don't
15 appear to be directly in contact with the substrate
16 and are not directly defined as active site residues
17 within 5 angstroms of a docked substrate are likely
18 candidates for structural determinants.
19 Q. When you're using structural determinants
20 here, those are the residues that are essentially
21 necessary for the protein to fold and adopt its
22 three-dimensional structure. Right?
23 MS. MARTIN: Object to form.
24 A. When I say "structural determinants," I do
25 generally mean amino acids and/or elements of

1 secondary structure or tertiary structure that are
2 involved in the fold that's adopted by the family of
3 hyaluronidases.
4 Structural determinants can be atomic,
5 molecular, or elements of folded structure within
6 the polypeptide. I'll try to be more precise.
7 Q. So they can be -- the determinants can be
8 due to the chemical character of the residue and the
9 atoms in it. Right? That's one variable?
10 MS. MARTIN: Object to form.
11 A. The structural determinants, if I'm
12 talking about just the amino acid sequence -- so we
13 were talking about sequence alignment and how I
14 would identify structural determinants.
15 If I'm looking just at the amino acid
16 residue as the structural determinant I'm
17 considering, then, yes, its -- its physicochemical
18 properties and its position within the folded
19 structure are informing my decision about whether I
20 consider it a structural determinant.
21 Q. All right. If you could go to the '731
22 application again and go to Page 93.
23 By the way, there are two numbers on every
24 one of these pages. I'm referring to the number on
25 the bottom right corner, 93.

1 And if there's ever any confusion, just
2 let me know. I'll try to make sure we don't have
3 any confusion in the record.
4 So this is Page 80 in the printed
5 document, and it's Page 93 on the exhibit.
6 A. Thank you.
7 Q. So at this -- on this page, you'll see a
8 sentence -- or a paragraph that begins, "The results
9 herein confirm the requirement of PH20 amino acids
10 corresponding to positions," and then it gives a
11 list of them.
12 You've reviewed that paragraph before?
13 A. Yes.
14 Q. Okay. And this is reporting that the
15 testing in the patent has confirmed that all of
16 these positions in the PH20 sequence are required
17 for hyaluronidase activity. Right?
18 (Witness reading.)
19 A. Sorry. Could you please repeat your
20 question?
21 Q. Sure. This paragraph is stating that the
22 experimental results in the patent are confirming
23 these positions that are listed as being required
24 for hyaluronidase activity in the PH20 protein.
25 Right?

1 MS. MARTIN: Object to form.
2 A. This paragraph asserts that the results
3 herein -- meaning, within the application, at those
4 positions -- I think you said "PH20," but it
5 specifically says that the residues refer to the
6 mature PH20 lacking signal sequence, such as set
7 forth in those specific references required for
8 hyaluronidase activity.
9 Q. So these are the positions -- the amino
10 acid residues at these positions are required for
11 hyaluronidase activity, according to this paragraph.
12 Right?
13 MS. MARTIN: Object to form.
14 A. So the paragraph refers to results within
15 the disclosure that show amino acids that are
16 required for hyaluronidase activity, which is
17 dependent on hyaluronidase correct expression as a
18 soluble polypeptide.
19 And this particular paragraph doesn't
20 distinguish from among these residues with respect
21 to which of them is required for activity in the
22 successfully secreted soluble protein versus the
23 expressed but not successfully secreted polypeptide.
24 Q. And it's confirming that these residues
25 had been previously identified -- it's confirming

1 the -- the connection between these particular
2 positions and their necessity for hyaluronidase
3 activity that had been published before or known
4 before 2011. Right?
5 (Witness reading.)
6 A. I want to use precise language in
7 answering your question.
8 I can't recall the exact content of the
9 references cited with respect to the residues
10 involved in disulfide bond formation.
11 It's possible to implicate those residues
12 in disulfide bond formation by nature of their being
13 cysteines, which are capable of disulfide bonds, and
14 being conserved and with reduction of the bonds and
15 testing of activity without specifically
16 mutagenizing each residue.
17 In this paragraph, it doesn't state
18 whether those cysteines were mutagenized in those
19 prior publications.
20 So the listing of these residues is
21 confirming their requirement for activity as
22 previously published, without specifically
23 implicating them in solubilized activity versus
24 expression.
25 Q. Okay. So -- and this paragraph is kind of

at the end of a section that's kind of doing a survey of what had been known before the patent was filed. Right?

MS. MARTIN: Object to form.

A. The purpose of this section overall is to explain the state of the art with respect to what's known about PH20 and specifically about its structure.

Q. Okay.

MS. MARTIN: So, Counsel, we've been going for almost exactly an hour. Is it time for a break?

MR. KUSHAN: Yeah. Why don't we -- if it's okay, let's just -- I have a couple quick questions to finish this. Maybe a couple minutes, if that's all right.

MS. MARTIN: Would you like a break? Or....

MR. KUSHAN: Can you just go for another minute or two?

WITNESS: I've been advised to --

MS. MARTIN: Let's take a break.

WITNESS: -- stick with what my

1 counsel advises.
2 MS. MARTIN: Let's take a break.
3 WITNESS: We'll take a break.
4 MR. KUSHAN: All right.
5 VIDEOGRAPHER: Off the record at
6 11:16.
7 (Whereupon, a recess was taken.)
8 VIDEOGRAPHER: On the record at
9 11:37.
10 BY MR. KUSHAN:
11 Q. Dr. Simpson, did you speak with counsel
12 during the break?
13 A. Not on matters relevant to the case.
14 Q. What did you speak about?
15 A. Still on the decor of the building. Those
16 interesting tube lights and the living moss.
17 Q. Are you still on Page 93/80 of the common
18 disclosure? That paragraph we were looking at,
19 at -- starting at Line 19, can you go there? Okay.
20 A. Yes.
21 Q. Are any of the positions listed in that
22 section we were discussing before the break
23 position 320?
24 A. No.
25 Q. What about position 313?

A. Specifically in this paragraph? No.
Q. And is position 317 in that set?
A. No; 317 is not there.
Q. What about position 312; is that in that set?
A. No; 312 is not.
Q. What about position 324?
A. Position 324 also is not in this set.
Q. What about position 307?
A. Position 307 is not in this set.
Q. And then, what about position 309?
A. Position 309 is not in this set.
Q. All right. Earlier today we had a discussion about Dr. Petsko's declaration.
Do you remember that?
A. Yes.
MR. KUSHAN: Okay. I'm going to introduce Exhibit 2070.
(Whereupon, Halozyme Exhibit 2070, previously marked, was presented to the witness.)
Q. And I had asked you previously if you had reviewed Dr. Petsko's declaration. I believe you said you had reviewed what was the final version of the declaration?
A. Yes.

1 Q. Could you turn to Page 226 of
2 Exhibit 2070.
3 Do you see that Dr. Petsko executed the --
4 his declaration on September 22nd?
5 A. Yes.
6 Q. And that was a day before you executed
7 your declaration. Right?
8 A. Yes.
9 Q. Did you conduct your review of
10 Dr. Petsko's declaration for the purposes of forming
11 your opinions in your declaration between the 22nd
12 of September and the 23rd of September of 2025?
13 A. I reviewed Dr. Petsko's declaration
14 between September 22nd and 23rd.
15 However, the section that addresses the
16 opinions on structure and function within my
17 declaration were formed prior to September 22nd.
18 Q. Did you review only the section of
19 Dr. Petsko's declaration that corresponds to the
20 region you just mentioned that you used for your
21 opinions?
22 A. I reviewed the full declaration from
23 Dr. Petsko.
24 Q. Do you know if the full version of
25 Dr. Petsko's declaration that you reviewed is

1 identical to the one that he executed on the 23rd --
2 sorry, the 22nd of September 2025?
3 A. Yes. I confirmed that.
4 Q. Did you have a red line or something of
5 the two documents?
6 A. I reviewed the full declaration as he had
7 signed it. I reviewed a red-lined copy of a draft
8 that he -- that was completed prior to his signature
9 being appended.
10 Q. And they were identical?
11 A. They were not substantively different.
12 Q. Do you have any recollections of what was
13 different?
14 MS. MARTIN: Object to....
15 Q. I'm just asking about what you just
16 mentioned.
17 A. I do not have a recollection. Given that
18 they were not substantive, it didn't impact my final
19 declaration.
20 Q. So the version that you reviewed before he
21 attached his signature to it, do you remember when
22 you reviewed that version?
23 A. Not precisely.
24 Q. Like a week or two ahead of the 22nd, or
25 was it further away from -- earlier -- I'm sorry.

1 Was it within a week or two of him signing
2 the declaration on the 22nd of September?
3 MS. MARTIN: Object to form.
4 A. It was -- I don't recall the date
5 precisely. I can estimate that it was within a
6 couple of weeks of the declaration's signature.
7 I can say that it was a near-final draft,
8 and I can recall that the differences that I state
9 as nonsubstantive were typographical.
10 Q. Do you recall if you saw a version of his
11 spreadsheet at that time, when you were reviewing
12 this draft you just mentioned?
13 MS. MARTIN: Object to form.
14 A. Yes.
15 Q. And did you check the version of the
16 spreadsheet that you used at that time, relative to
17 the version that was -- the final version, which we
18 showed you earlier today?
19 MS. MARTIN: Object to form.
20 A. I carefully reviewed all documents,
21 particularly those that I cited in my list of
22 exhibits, in the final 24 hours before signing my
23 declaration, and particularly attended to details
24 such as whether representative tables were identical
25 to the tables that were being cited in the list of

1 exhibits, yes.
2 Q. And they were identical?
3 A. They were identical.
4 Q. Okay. Could I have you go to Page 13 of
5 your declaration and look at Paragraph 33.
6 A. Yes.
7 Q. Just some terminology. What do you mean
8 by "claimed genus" in the first sentence?
9 MS. MARTIN: Object to form.
10 A. I'm referring to the claimed genus as the
11 set of modified PH20 polypeptides that are defined
12 within claim 1.
13 Q. So that's the set of polypeptides that
14 meet the claim parameters in claim 1. Right?
15 A. Yes.
16 Q. Okay. You -- in this Paragraph 33, you
17 indicate that the claimed genus --
18 (Reading:)
19 A POSA would have
20 understood that the claimed
21 genus is a narrow set of PH20
22 variants and sub-variants that
23 are structurally homogeneous.
24 Are you referring to the primary structure
25 being the basis of structural homogeneity?

A. In the first sentence, I'm referring to the primary structure.

Q. And you understand that the 95% sequence identity permits up to 21 or 22 or 23 changes, depending on which reference sequence it is -- is used as the reference point for that 95% identity requirement. Right?

A. I understand what 95% identity means numerically.

Q. And that translates into up to 20, 21, 22 changes in the primary sequence relative to the wild type of PH20. Right?

A. In the case of the modified PH20 polypeptide claimed here with respect to the sequence, the reference sequence, yes.

Q. You portray this as a narrow set of PH20 variants.

Do you mean that the number of different polypeptide sequences that are in that set is a narrow set of sequences?

MS. MARTIN: Object to form.

A. I maintain that -- or have expressed that POSAs would have understood the claimed genus to be a narrow set of PH20 variants and subvariants, structurally homogeneous.

1 Q. Is the set of distinct polypeptides in
2 that set a small number?
3 MS. MARTIN: Object to form.
4 A. The theoretical maximum number of
5 sequences that can potentially be defined within
6 that claimed set is potentially not a small number.
7 The theoretical maximum is a large number.
8 Q. Do you have an understanding of what that
9 number is?
10 A. I understand Dr. Hecht and Dr. Park
11 calculated it.
12 Q. Did you find any errors in their
13 calculations?
14 A. I don't disagree with the method they used
15 to calculate the theoretical maximum in the number
16 of variants.
17 Q. And you agree that in the modified PH20
18 polypeptides, the changes that might exist between
19 the wild type and the claimed modified PH20 can be
20 either a substitution of an amino acid or more than
21 one substitution of amino acid. Is that -- that's
22 one possibility?
23 MS. MARTIN: Object to form.
24 A. Could you repeat it?
25 Q. Sure. The changes that constitute the

1 difference that translates into the 5% difference
2 from the amino acid sequences of the wild-type PH20,
3 there could be substitutions, deletions, or
4 additions of amino acids. Right?
5 A. Yes. Those are possibilities.
6 Q. So in the set of those modified PH20
7 polypeptides, you may have polypeptides that have a
8 deletion of three or five amino acids from the
9 wild-type residue. That's within the set of PH20
10 polypeptides being claimed. Right?
11 A. That is a potential scenario for one of
12 the claimed polypeptides.
13 MS. MARTIN: Counsel, I'm going
14 to ask you again to speak up. I'm sorry.
15 I'm having a really difficult time hearing
16 the whole question.
17 MR. KUSHAN: All right.
18 Q. And just so we're on the same page, that
19 theoretical maximum you referred to a minute ago,
20 that's a number bigger than 1049 different
21 polypeptide sequences. Right?
22 A. I don't have Dr. Park's declaration in
23 front of me, but the number is something in that
24 ballpark.
25 Q. It's of that scale. Right?

A. Yes.
Q. Would you agree that in the claimed genus of modified polypeptides, there are some number of modified PH20 polypeptides that are enzymatically active?
A. Yes. I agree.
Q. Do you know how many of the 1049 or so different polypeptide sequences are enzymatically active?
MS. MARTIN: Object to form.
A. Neither Drs. Park nor Hecht were asked to offer an opinion on that.
I also haven't considered an opinion on that.
Q. How would you go about determining which of those 1049 sequences are enzymatically active PH20 polypeptides?
MS. MARTIN: Object to form.
A. As a POSA taking a first step, I would consider the amino acid sequence in the context of the crystal structure and the likely folded structure.
So in doing that comparison, superimposing the model of PH20, its sequence, onto the model for HYAL1, and comparing the sequence, I would be able

1 to identify residues that would likely maintain the
2 activity of the enzyme.
3 And that would significantly narrow the
4 scope down from 10 to the 49th to a very small
5 number of reasonable polypeptides that would fit
6 that criterion.
7 That would be my first step as a POSA.
8 Q. Did you do that in preparing your
9 opinions?
10 MS. MARTIN: Object to the form.
11 A. I'm sorry. I actually missed part of that
12 question.
13 Q. Did you perform that analysis you just
14 described of comparing the possible sequences to
15 some smaller number of them that match the structure
16 of the model of PH20?
17 MS. MARTIN: Object to the form.
18 A. I did not go sequence by sequence and do
19 that.
20 I guess maybe I need to say that no POSA
21 would start with the theoretical maximum number of
22 potential sequence variants as a starting point for
23 making a comparative analysis of what amino acids
24 would retain activity in a PH20 polypeptide.
25 Q. Can you give me an approximation of the

1 number of different PH20 polypeptides that would be
2 in that smaller set that you believe the POSA would
3 focus upon?
4 MS. MARTIN: Object to form.
5 A. I could not possibly give you an absolute
6 number without doing a calculation to determine how
7 many exactly there would be relative to the 10 to
8 the 49th. I can tell you it's orders of magnitude.
9 Q. So it would be 10 to the 40th or 10 to the
10 35th? Where -- give me just a sense of scale, where
11 we are relative to the theoretical maximum.
12 MS. MARTIN: Object to form.
13 A. Without doing a calculation, I'm unwilling
14 to give a number.
15 Q. But you believe it's a number that could
16 be determined?
17 MS. MARTIN: Object to form.
18 A. I believe that a POSA could determine,
19 using the information in the claim, using the
20 information in the disclosure, what would be
21 reasonable locations to narrow down -- to make
22 mutations such that the POSA would be able to narrow
23 down the set of variant PH20 polypeptides to a
24 manageable set that was fully accessible to them
25 experimentally.

Q. So they could select a set of sequences that match these criteria that you're referring to.

Is that what you're saying?

MS. MARTIN: Object to form.

A. I'm saying that a POSA would have had the information to choose to make a set of PH20 polypeptides that fit the criteria of the claim, and to be able to use them in the manner they intended.

They would be able to visualize the species within the claim.

Q. They'd be able to visualize discrete sequences that have, let's say, 10 or 15 changes in them as being within the claim.

Is that what you're saying?

MS. MARTIN: Object to form.

A. A POSA could use the information in the patent, as well as the structural knowledge of HYAL1 with PH20's model superimposable on the HYAL1 crystal structure, to determine how they could make a 95% identical PH20 polypeptide that would have the parameters or the criteria that they set in their experimental objectives.

They would be able to use the claim, the scope of the claim.

Q. So the parameters they're using in

1 their -- in that experimental -- have -- let me make
2 sure I get this correct.
3 So the person would have in their mind
4 parameters of the experiment they were doing. Are
5 those parameters the particular modification
6 locations and the nature of the modifications they
7 are contemplating making?
8 I'm just trying to understand the
9 parameter reference you made.
10 A. A POSA attempting to make and use the
11 polypeptides that are claimed would have an
12 objective for making those polypeptides.
13 They would have internal experimental
14 criteria that they would be seeking to meet in
15 generating a polypeptide that met the claims.
16 Q. Just to be clear, are you saying these
17 criteria they're seeking to try to meet are the --
18 are they the -- that the modified PH20 polypeptide
19 has activity?
20 Or are you speaking of it's a PH20
21 polypeptide with a particular sequence that they
22 were trying to make?
23 A. I would hesitate to constrain the
24 imagination of the POSA by attempting to articulate
25 on their behalf what their experimental objective

1 would be.
2 I could actually see a POSA seeking any
3 and all of those possible experimental goals.
4 Q. I'm just trying to track the process
5 you're describing the POSA would go through.
6 Is the POSA approaching the task of
7 evaluating a particular amino acid sequence by
8 asking if that sequence will exhibit a property,
9 such as enzymatic activity, or will fold, or is
10 inactive?
11 Or are you saying that the task is simply
12 devising a sequence and comparing it to see if it
13 matches the criteria of the claims?
14 A. My view of the goal of the POSA is that
15 they have an experimental design plan in mind, and
16 that this patent discloses an enormous amount of
17 data that help them beyond what was published in the
18 literature at the time, which was the sequence, the
19 sequence alignment to other hyaluronidases for PH20,
20 as well as the knowledge of where it can be
21 truncated to make it a soluble polypeptide, the fact
22 that it retained activity as a soluble PH20
23 polypeptide.
24 And now, in addition, mutagenesis at every
25 single residue of the polypeptide that gives data on

1 whether or not that single substitution remained
2 active.
3 The POSA could then use that information
4 to choose, depending on whether their goal was to
5 have the protein remain active or whether they did
6 not care about having activity retained and had a
7 different experimental goal. They would have
8 information that would allow them to make the 95%
9 identical polypeptide that would meet those criteria
10 for them.
11 Q. So they could pick, out of the 1049
12 theoretical maximum sequences, which of those will
13 have the characteristics necessary for those
14 selected sequences to be enzymatically active
15 modified PH20 polypeptides? That's what you're
16 saying?
17 A. I'm saying that a POSA would not start
18 with that calculation of 10 to the 46th or 10 to the
19 49th or 10 to the 63rd. A POSA would not start by
20 calculating the theoretical maximum number of
21 sequences.
22 A POSA would start with the knowledge of
23 the PH20 polypeptide sequence, the knowledge of its
24 truncated sequence, the knowledge of its mature
25 sequence, and the ability to superimpose the PH20

1 sequence onto the model for the HYAL1 crystal
2 structure.
3 And the POSA would know exactly what every
4 one of those modified PH20 polypeptides looked like.
5 And they would have all the information they needed
6 with respect to its activity to create a sequence
7 that was 95% identical, that would either adopt the
8 fold and be enzymatically active, or adopt the fold
9 and not be enzymatically active, or not adopt the
10 fold.
11 Q. And so, you're saying a person of ordinary
12 skill in the art, looking at the sequence and
13 comparing it to homology models in 2012, could
14 differentiate sequences that will not fold from
15 those that will?
16 A. That is actually not a yes-or-no question.
17 I think it depends.
18 But, yes, a POSA could potentially
19 identify sequences that would be certain to fold and
20 could identify sequences that would certainly not
21 fold.
22 Q. And there will also be a third category of
23 sequences where they wouldn't be able to tell one
24 way or the other. Is that fair?
25 MS. MARTIN: Object to form.

A. In every polypeptide, there are places where you could make a mutation and predict -- the vast majority of places, you can make a mutation and predict what's going to happen to the protein.

Given the amount of activity data and the amount of structural homology and the sequence information, you would be able to predict the vast majority of activity structure, function relationships, for that family of modified PH20s.

There's always going to be a mutant that -- very few, but always -- I could come up with one in every data set -- that is going to be something that I didn't expect.

For the most part, a POSA is going to look at the data set that they have in hand and choose conservatively, strategically, where they will place mutations.

Given all of the information they have at hand, which is considerable, they will strategically choose positions that will meet the criteria of their experiment.

Q. And they'll do that based on -- like, what drives their selection of the place of mutations?

Is it just the information in the patent?

I'm just trying to understand: What's

1 guiding the design of the sequences in your
2 description there?
3 A. What would guide the POSA is the POSA's
4 experimental design goal.
5 Again, I don't want to limit the
6 imagination of the POSA by articulating specific
7 goals on behalf of the POSA.
8 Q. So if I'm trying -- if I'm a POSA trying
9 to make an enzymatically active modified PH20
10 polypeptide that is going to meet the requirements
11 of the claims -- let's stick with that as their --
12 that would be a design objective that you've been
13 describing. Right?
14 A. That is one possibility, yes.
15 Q. All right. So you're saying the POSA
16 could take the information in the patent and then
17 devise sequences of the modified PH20 polypeptides
18 with an expectation that they would become
19 enzymatically active modified PH20 polypeptides?
20 A. Yes.
21 Q. So the information in the patent is kind
22 of like a starting point for them to then devise the
23 sequences that will be enzymatically active PH20
24 polypeptides?
25 A. The information in the patent, yes, is a

1 starting point.
2 However, the POSA would also need their
3 ability to look at the structure of HYAL1, develop a
4 model of PH20 structurally overlaid on HYAL1.
5 I'd look at the bee venom hyaluronidase
6 structure, in which the tetrasaccharide substrate is
7 docked, compare where the substrate binding domain
8 is.
9 And they would have the information from
10 alignments, sequence alignments among the
11 hyaluronidases; their knowledge of the structural
12 features conserved within the family of
13 hyaluronidase proteins, possibly by doing an --
14 homology modeling of all five human hyaluronidases
15 to increase their confidence in their model.
16 Then, coupled with the data from the
17 patent on activity, the POSA would have strong
18 certainty about their likelihood of success in
19 creating a 95% identical mutant polypeptide -- PH20
20 polypeptide soluble that would be enzymatically
21 active.
22 Q. You've mentioned a few times the homology
23 models of PH20.
24 And these are models that are created
25 using the human HYAL1 structure published in Chao?

1 A. The structural model of PH20 is based --
2 would have been, at the time, based on the crystal
3 structure of HYAL1 by Chao, published by Chao, yes.
4 The alignments are also present in Chao.
5 But the POSA would have been independently able to
6 do those alignments.
7 And those types of sequence alignments had
8 also been published earlier by Stern and Jedrzejas,
9 in particular, in a 2006 review article.
10 Q. Thank you for pronouncing that man's name.
11 I've not been able to figure out how to do that.
12 I imagine you know him. Right?
13 A. I do know Dr. Jedrzejas.
14 Q. Okay. In the homology models that are
15 developed based on or used -- I'm sorry.
16 In the homology models that use the Chao
17 HYAL1 as the template, is that terminology accurate?
18 A. A HYAL -- so --
19 Q. So a PH20 --
20 A. -- a homology --
21 Q. Let me make sure I get my question clean.
22 A. Okay.
23 Q. The PH20 homology model is a model devised
24 by software that uses the structure published in
25 Chao of the HYAL1 protein. Right?

1 A. Yes. It's -- it uses the coordinates from
2 the Protein Data Bank, which are the published
3 coordinates that were used by Chao to provide models
4 of HYAL1 in the 2007 paper.
5 Q. Got it. In the 2011-2012 time frame, how
6 accurate were the PH20 models as an indicator of the
7 actual protein structure?
8 MS. MARTIN: Object to form.
9 A. I haven't experimentally examined the
10 accuracy of the PH20 versus HYAL1 model, because
11 that would entail a look at an actual PH20
12 structure.
13 What we can say from the model, the
14 superimposed model of PH20, on the basis of HYAL's
15 structure, is to what extent there is a root mean
16 square deviation in elements of secondary structure,
17 alpha helices, beta sheets, loops, as well as the
18 RMS deviation in locations of specific atoms within
19 side chains that are exposed or not exposed, that
20 are part of the hydrophobic core that's folded, that
21 are part of the substrate binding domain, where the
22 substrate docks, and that are part of surface
23 aspects of the polypeptide.
24 We can look at RMSD as a measure of
25 variability in different aspects of the protein

1 structures. And with that RMSD value, we can
2 estimate to what extent the quality of the model is
3 reproduced -- is highly reliable on the basis of the
4 HYAL1 structure.
5 Q. In preparing your opinions, did you
6 perform that kind of assessment?
7 A. I relied on Dr. Petsko's declaration, in
8 which Dr. Petsko evaluated the reliability of the
9 PH20 model on the basis of the HYAL1 crystal
10 structure.
11 Q. Is the reliability of the PH20 homology
12 model consistent throughout the entire sequence of
13 the PH20 sequence?
14 Let me ask you a better question.
15 So the PH20 homology model that is built
16 from the HYAL1 template structure, is it giving you
17 an accurate depiction of the structure of the PH20
18 throughout its entire sequence?
19 A. PH20 and HYAL1 have identity over only a
20 portion of their sequence, which is up to the 4- --
21 447 position of the soluble PH20 -- modified PH20
22 polypeptide.
23 The region beyond amino acid 447 in that
24 sequence is not modeled onto the HYAL1 crystal
25 structure because HYAL1 lacks that portion of

1 sequence.
2 In fact, a portion of HYAL1 sequence, a
3 short region in the C-terminus, is also not visible
4 in the electron density. And so, that region also
5 cannot be fully modeled because it's not even
6 modeled for HYAL1.
7 But the region that can be modeled between
8 PH20 and HYAL1 is virtually superimposable.
9 Q. When you do your modeling, do you rely on
10 the portions of a sequence that can't be modeled?
11 MS. MARTIN: Object to the form.
12 A. With respect to hyaluronidases, we use
13 SWISS-MODEL to do modeling on HYAL1 crystal
14 structure.
15 So in modeling the other hyaluronidases,
16 there's no other way, then, to consider the
17 reference template.
18 And the regions that are not part of the
19 reference template can't be modeled on the reference
20 template.
21 Q. So you can't derive conclusions for those
22 portions of the protein that don't have the
23 structure from -- the HYAL1 structure that
24 correspond to that portion of the sequence?
25 MS. MARTIN: Object to the form.

1 A. Let me clarify.
2 The structural model, the modeling
3 software only allows you to model the portion that's
4 reproduced by the template.
5 That doesn't mean you can't derive any
6 information about the portion that is not modeled
7 according to the template. But it isn't necessarily
8 part of the model.
9 So the additional information would be
10 derived from your knowledge of that sequence,
11 possibly the knowledge of function.
12 Q. But you don't have a reliable basis for
13 knowing what the structure of that portion of the
14 protein is beyond the boundary of the template
15 structure being used to create the model?
16 A. So again, in the context of PH20, what we
17 know about PH20 is that the portion -- from 447. So
18 we know the first 35 amino acids are cleaved as a
19 signal peptide.
20 So not being able to model that is
21 irrelevant because it's not part of the mature
22 protein.
23 Similarly, we know, in the mature,
24 full-length protein, if we're talking about modeling
25 the full-length PH20 polypeptide, we know that that

1 polypeptide has the -- an attachment site for a GPI
2 anchor, a glycosylphosphatidylinositol.
3 That GPI anchor has a predictable -- a
4 known biology for its -- for its attachment and a
5 known biology for what happens to the signal peptide
6 for GPI attachment following its attachment.
7 And so, it's known that that portion of
8 PH20 is relatively unstructured because it's a
9 signal peptide for the GPI attachment machinery
10 before the protein is secreted to the cell surface.
11 So we can say we do know what happens to
12 that portion of the protein. It's cleaved off
13 before it gets secreted as a mature polypeptide.
14 In the case of the modified PH20
15 polypeptide defined in claim 1, this is a
16 polypeptide that doesn't contain the GPI attachment
17 site.
18 And so, the -- essentially, the full
19 spectrum of the amino acids that are contained
20 within that polypeptide are fully able to be modeled
21 against the HYAL1 structure.
22 Q. So the -- in that region near the GPI
23 anchoring sequence, that is how far away from the
24 447 termination? Do you know?
25 A. Yes.

(Witness reading.)

A. Yes. The position at which the GPI is attached is position 490 in the precursor sequence, which is approximately eight residues away from 447 --

Q. Okay.

A. -- in the mature sequence.

MR. KUSHAN: All right. I'm going to introduce Exhibit 1006, which is the Chao paper we've been mentioning.

Sorry.

(Whereupon, Petitioner Exhibit 1006, previously marked, was presented to the witness.)

Q. This is the -- just to confirm, this is the Chao paper that we've been discussing this morning. Right?

A. Yes.

Q. And you're familiar with this paper. Right?

A. Yes.

Q. This was published in 2007, when you were doing work -- I believe you said in your declaration you were doing work that was modeling the PH20 protein based on the bee venom structure?

A. Yes.

1 Q. So this came out while that work was
2 underway?
3 A. Yes.
4 Q. Had you produced a PH20 homology model
5 based on the bee venom structure?
6 A. At the time this was published?
7 Q. Yes.
8 A. I don't recall exactly when I first
9 produced models of the different hyaluronidases
10 relative to HYAL1.
11 It may have been later than 2007.
12 Q. Do you recall if the work that was
13 eventually published in the Zhang paper had
14 progressed to the point where you were identifying
15 specific positions you were investigating for
16 possible mutation, before Chao became available?
17 A. Yes.
18 Q. Okay. So you had identified potential
19 sites of mutation as part of your investigation of
20 HYAL1 before the Chao paper was published. Is that
21 right?
22 A. Yes.
23 Q. And you identified those positions using a
24 homology model of PH20 or another protein?
25 A. Our specific interest was in HYAL1, so we

1 used alignments that I said Stern and Jedrzejas had
2 already published.
3 They had also published models of PH20 and
4 the other hyaluronidases on the basis of the bee
5 venom structure in that same review article.
6 We used that information, as well as the
7 model of HYAL1 on the basis of the bee venom
8 structure, to determine residues that we test
9 functionally.
10 Q. Okay. So you used those existing models
11 of the different human hyaluronidases to -- well,
12 you focused on HYAL1. Right? Okay.
13 A. Yes, correct.
14 Q. So you were selecting positions in HYAL1
15 that you were interested in mutating to see the
16 effect of those mutations. Is that right?
17 A. Yes.
18 Q. Okay. Chao published, in its paper, a
19 characteristic sequence that's associated what --
20 with what it calls the "HYAL EGF domain." Is that
21 right?
22 A. Yes.
23 Q. Is that the first time that a group had
24 published this characteristic sequence as kind of
25 correlating to that region of the human

1 hyaluronidase family?
2 MS. MARTIN: Object to form.
3 A. The EGF-like domain had been previously
4 identified as a domain.
5 Is that what you're asking?
6 Q. No. I'm just -- if you look at Page 6912,
7 on the bottom -- sorry -- left column, toward the
8 second-to-bottom paragraph, there's a discussion
9 there of a cysteine-rich pattern.
10 This was the first publication that
11 identified that pattern as correlating to that EGF
12 domain. Right?
13 MS. MARTIN: Object to form.
14 A. I'm not totally sure I'm understanding
15 your question. I think you're asking me about
16 sequence.
17 The sequence was already identified and
18 noted as an EGF-like domain.
19 Q. Right. Let's just look at what Chao is
20 saying here.
21 It says -- about halfway down into that
22 second-to-last paragraph, it says:
23 No sequence homology has
24 been reported in the scientific
25 literature for the C-terminal

1 domains of the mammalian
2 hyaluronidases.
3 Right? That's what they're stating
4 there -- is that accurate, in 2007?
5 MS. MARTIN: Objection; scope.
6 A. Is it accurate? The cysteine-rich domain
7 was noted. The presence of cysteines was noted.
8 When Chao uses that specific verbiage,
9 that no sequence homology had been reported for the
10 C-terminal domains, it's looking at the homology
11 irrespective of the cysteines.
12 And so, it appears that there's no other
13 homology, other than the cysteines.
14 Q. And then they -- so Chao deduced that
15 there's actually this characteristic pattern of
16 amino acid and cysteine residues that is depicted in
17 the next sentence, where it states, "This region
18 contains a cysteine-rich pattern," and then has a --
19 the pattern described, with a bit of a formula for
20 what the different residues can be and how they're
21 spaced apart. Right?
22 MS. MARTIN: Object to form.
23 A. I guess I'm still not exactly sure what
24 you're asking me.
25 Q. So Chao is the first group that published

1 a description of the pattern of residues in the
2 C-terminal region of mammalian hyaluronidases that
3 was associated with that HYAL EGF domain. Right?
4 MS. MARTIN: Object to form.
5 (Witness reading.)
6 A. The Stern and Jedrzejas -- Jedrzejas
7 review article in 2006 did homology modeling of each
8 mammalian hyaluronidase on the basis of the bee
9 venom crystal structure.
10 When they did those homology models, they
11 modeled the domain that had identity to bee venom
12 hyaluronidase structurally. Bee venom hyaluronidase
13 lacks the EGF-like domain.
14 So that domain was modeled separately,
15 without context for what it would look like, other
16 than the disulfide bonds potentially being present.
17 That review article also referred to that
18 domain separately. So it had been observed.
19 I believe what Chao is doing is defining
20 that according to the ability to use algorithms such
21 as SMART and PROSITE to identify that motif in a
22 database.
23 Q. It's the first paper that correlated this
24 pattern of residues to the HYAL EGF domain in
25 mammalian hyaluronidases, Chao. Right?

MS. MARTIN: Object to form.

A. This is a minor detail that I would have to specifically check in the Jedrzejas paper. They were published around the same time.

So my recollection is that the EGF-like domain had been discussed, whether or not it had been reported by Chao.

The structure had never been visualized, however.

Q. In fact, if you go over to Page 6913 of Chao and look at the paragraph -- a small paragraph in the middle of the right column, do you see that Chao is observing that:

> The HYAL EGF-like fold does not remem- -- does not resemble the Hyal-1 C-terminal fold predicted by ab initio approaches.

And then, if you want to look at Reference No. 33, that's the Jedrzejas and Stern paper that you've been referring to. Right?

It says -- 6913, paragraph in the right column, first sentence of that middle paragraph.

A. Gotcha. Right there.

(Witness reading.)

A. Yes, that is what it says. Yes.
Q. Okay. So they had -- this paper had pointed out that the ab initio modeling in the Jedrzejas and Stern paper wasn't resembling what they actually observed in the HYAL1 structure. Right?
A. That is among the things that this paper showed for us. Yes, it was a huge breakthrough in the field.
Q. Got it. Is the information about this pattern of position -- of residues that Chao identified reported in the common disclosure?
MS. MARTIN: Object to form.
A. Yeah, could you reask that? I'm not sure what you're specifically asking me.
Q. Is the information associating this cysteine-rich pattern of residues in the Chao paper also reported in the common disclosure?
MS. MARTIN: Object to form.
A. It's -- the information in the Chao paper is summarized in the disclosure. The patent authors are different authors than those who made this discovery about HYAL1.
Q. Do you believe that the inventors -- or the -- let me be sure it's precise.

1 Do you believe that the common disclosure
2 refers to the work that was published in Chao?
3 A. Yes.
4 Q. If you could go to Figure 3 of Chao. This
5 is a sequence alignment.
6 I think you mentioned the sequence
7 alignment a minute ago. Right?
8 A. Yes.
9 Q. All right. So in Figure 3, these are the
10 five human hyaluronidases that are aligned. Right?
11 A. Yes.
12 Q. Chao's alignment identifies the invariant
13 residues in this protein family. Right?
14 A. Yes.
15 Q. And let's just go through the color
16 coding.
17 Most of them are blue. Right?
18 A. Most of the invariant -- yes, are blue.
19 Q. So the red coloring denotes the ones --
20 the positions or residues that are involved in the
21 catalytic function of the proteins. Right?
22 A. Three key catalytic residues are
23 identified in red.
24 Q. And then the disulfide bond-implicated
25 cysteine residues are in gold. Right?

A. Cysteine residues are go- -- yellow, gold.
Q. Yeah. And then the N-glycosylated asparagine residues are in turquoise?
A. Yes.
Q. These are all of the essential residues we've been talking about from earlier this morning that are shared by these five human hyaluronidases. Right?
MS. MARTIN: Object to form.
A. They're showing invariant residues, without making a judgment on essential residues.
Q. They're showing the invariant -- and some of the invariant residues do have a functional connection to them. Those are the catalytic residues, for example?
A. Yes, the catalytic residues do have a function associated with them as invariant residues. Yes.
Q. And the gold residues also are ones that are implicated for folding, in some sense, because they form disulfide bonds. Right?
A. So all of the cysteines are shown in gold.
The ones that are implicated as participants in disulfide bonds are separately indicated by stars underneath those gold cysteines.

Q. Got it. How would a person -- how would a POSA view these positions marked in blue, gold, red, and turquoise in Chao's figure --

MS. MARTIN: Object --

Q. -- in terms of positions to modify for making enzymatically active forms of the protein?

MS. MARTIN: Object to form.

A. I'm not sure what you mean by "how would they view them."

Q. If a person -- if a POSA was attempting to make a modified PH20 that had enzymatic activity, would they choose to modify the protein at the positions marked in blue, red, and gold?

MS. MARTIN: Object to form.

Objection; scope.

A. Could you please reask your question?

Q. Of course.

If you were a person of skill in the art and you were attempting to make a modified PH20 that was enzymatically active, would you select positions that are marked in blue, red, or gold as positions to modify the protein?

MS. MARTIN: Object to form.

Objection; scope.

A. If my objective was to make a modified

1 PH20 polypeptide, I would need more information than
2 is given in the alignment.
3 The alignment also is supported by actual
4 previously published functional data that
5 demonstrated which residues of PH20 are inactive
6 residues or are key catalytic residues. So that's
7 why they're colored separately.
8 To retain enzymatic activity, certainly
9 you would not mutagenize those, because it's
10 previously been confirmed that mutagenesis at those
11 sites eliminates hyaluronidase activity.
12 Similarly, with respect to the cysteines,
13 because of the prior implication, whether or not it
14 was by mutagenesis or by general reduction of
15 disulfides and loss of activity in PH20, it's been
16 shown that cysteine disulfides are important for
17 enzymatic activity of PH20.
18 Again, a POSA would not choose one of the
19 cysteines involved in a disulfide as a site to
20 mutagenize to retain enzymatic activity of PH20.
21 When I say that you would need more
22 information than what this has, this structure, this
23 alignment, does not indicate the position of the GPI
24 anchor attachment site, which is important to a
25 POSA's knowledge of how to make a modified PH20 as

1 defined in the patent, which is soluble.
2 Q. So do you think a POSA would choose to
3 make modifications at the blue positions -- the blue
4 marked residues in the PH20 if they're trying to
5 make an enzymatically active form of the PH20
6 protein?
7 MS. MARTIN: Object to form.
8 A. It is my opinion that a POSA would use the
9 information about this structure, use the sequence
10 alignment, and model PH20 according to this new
11 structural information, and evaluate whether the
12 blue invariant residues were located in a position
13 of critical -- of a critical nature to the folded
14 structure of PH20, and evaluate them individually,
15 potentially, for their location in the structure, if
16 they wanted absolute certainty about their role in
17 maintaining the structure.
18 It's also my opinion, though, that if I
19 have this information about invariant residues in an
20 alignment and about functional data that implicates
21 certain of those invariant residues in maintaining
22 enzymatic activity of the enzyme, that a POSA would
23 avoid residues that are invariant if they wish to
24 maintain activity of the polypeptide.
25 MR. KUSHAN: Okay.

MS. MARTIN: So, Counsel, we've been going for about another hour.

MR. KUSHAN: Yeah. You need to give me some credit, Lauren. I was about to propose we take a break for lunch. So....

MS. MARTIN: All right.

MR. KUSHAN: Why don't we take a break for lunch, if that makes sense.

VIDEOGRAPHER: Off the record at 12:38.

(Whereupon, a recess was taken for lunch at 12:38 p.m.)

- - -

A F T E R N O O N S E S S I O N

(Time noted: 1:37 p.m.)

VIDEOGRAPHER: On the record at 1:37.

BY MR. KUSHAN:

Q. Dr. Simpson, did you have lunch with counsel?

A. Yes.

Q. Can you just give me a brief summary of what you discussed during lunch.

A. A variety of topics, including the physical accuracy of some of the decor and several theological topics.

Q. Did you discuss anything relating to the deposition so far?

A. Absolutely nothing.

MR. KUSHAN: Okay. I'm going to introduce your Zhang paper. This is Exhibit 1010.

(Whereupon, Petitioner Exhibit 1010, previously marked, was presented to the witness.)

WITNESS: Thank you.

Q. You're an author on this paper?

A. Yes.

Q. Are you the principal author? Or, no.

1 What -- how do you describe yourself, as being the
2 last author?
3 A. The corresponding author.
4 Q. "Corresponding author."
5 Did Mr. Zhang -- or Dr. Zhang, is he the
6 person who did a lot of this work? Was he the -- as
7 a principal author?
8 A. He was a graduate student, yes.
9 Q. Then he was -- why was he designated lead
10 author?
11 A. It's typical in -- particularly in the
12 discipline of biochemistry and experimental
13 research, for the primary author to be the person
14 that is most significantly involved in generating
15 the data that comprised the manuscript.
16 So as the leading author, he generated a
17 majority of the data that are published in the
18 paper.
19 Q. Okay. So in the Zhang paper, you're
20 describing work you did where you use the -- a model
21 of the HYAL1 structure to identify specific
22 positions that you're interested in investigating as
23 far as the effect they have on activity or structure
24 of the protein. Right?
25 A. That was the goal of the paper, yes.

1 Q. And you -- so you selected positions'
2 residues in the HYAL1 sequence based on use of a
3 model at the structure. Right?
4 A. We used a combination of information from
5 sequence alignments, as well as then, subsequent to
6 the alignment, other functional data implicating
7 specific residues in maintaining key elements of the
8 catalytic activity, in addition to this examination
9 of where that -- those sequences place those
10 residues in the context of the HYAL1 crystal
11 structure.
12 Q. Okay. Thank you. That was helpful.
13 So you used the alignment data -- sorry.
14 You used information about -- from
15 alignments, you used published information from
16 prior mutagenesis studies, and you used the homology
17 model.
18 Those are the three main sources that you
19 used to identify the positions that you wanted to
20 investigate. Is that fair?
21 MS. MARTIN: Object to the form.
22 A. So we used the PH20 HYAL1 through 4
23 alignment to -- particularly PH20, because that was
24 the sequence in which specific active site residues
25 with specific roles in catalysis had been

1 functionally identified.
2 And then we used the HYAL1 crystal
3 structure, ultimately, for the interpretations that
4 are documented in the paper as our structural
5 visualization tool to interpret the results of our
6 studies.
7 Q. But the process you went through was you
8 did the analysis of the alignments, you had the
9 model of the structure, along with the work prior to
10 your work, and you used all that information to
11 select specific mutations to make into the HYAL1
12 sequence. Right?
13 A. One additional piece of information was
14 the bee venom crystal structure, in which the
15 tetrasaccharide substrate had been docked, because
16 that information was not available in the HYAL1
17 structure and provided support to our choice of
18 residues and our interpretation of what we would
19 expect to happen by mutagenizing those residues.
20 Q. Got it. So you selected these positions
21 to mutate, and then you actually made the HYAL1
22 mutants, each of which has one amino acid change in
23 the HYAL1 sequence. Right?
24 A. That's true. Yes --
25 Q. Yeah.

1 A. It was --
2 Q. You also did a truncation mutant, which
3 removed the HYAL EGF region of HYAL1. Right?
4 A. Yes.
5 Q. Okay. So for this -- these questions, I'm
6 focusing on the mutations you did that were the
7 single mutations into specific locations of HYAL1.
8 You made the mutants with the single amino
9 acid changes, and then you characterized the mutants
10 by their activity?
11 A. Yes --
12 Q. Okay.
13 A. -- among other things. That was one of
14 the things we characterized, was their activity.
15 Q. So if you look at your paper, 9433. And
16 this is in the section where you're describing, at
17 the bottom, your focus on Glu131 and aspartic acid
18 at 129. Right?
19 These are two residues within --
20 implicated in catalysis. Right?
21 A. Yes. So the -- you're talking about the
22 second paragraph of the introduction, describing --
23 discussing the roles of aspartate and glutamate --
24 129, 131, respectively -- yes.
25 Q. Can you say -- there's a depiction of the

1 Scheme 1, which is on the next page.
2 That's the catalytic reaction that's being
3 mediated by HYAL1?
4 A. Yes.
5 Q. Okay. In this paragraph we were at on
6 9433, you say:
7 Briefly --
8 There's a description kind of in the
9 middle of the paragraph.
10 You say:
11 Briefly, in the resting
12 state at its optimal pH of 4.0,
13 aspartate 129 and glutamate 131
14 essentially share a proton.
15 Catalysis is thought to require
16 initiation of intramolecular
17 resonance of the amide bond of
18 N-acetylglucosamine in the
19 bound HA polymer.
20 So this is kind of the hypothesis you had
21 about how the reaction was going to proceed that was
22 being mediated at the active site.
23 MS. MARTIN: Object to form.
24 A. So in formulating a hypothesis for what we
25 would expect from our mutagenesis results, we looked

1 at the information that was available in the
2 structure, and any additional mechanistic
3 information from prior studies, to formulate our
4 hypothesis.
5 We also looked at the structure, in which
6 you can actually determine that two acidic residues
7 are oriented such that they must share a proton
8 in -- at a particular pH, as defined in the crystal
9 solution, the solution from which the protein
10 crystallized.
11 And so, the distance between the two
12 carboxylates -- you can't see the proton in a
13 crystal structure --
14 Q. Right.
15 A. -- in an X-ray crystal structure, so you
16 have to deduce by the distance of those two
17 carboxylate moieties that they're sharing a proton.
18 Q. Okay.
19 A. If that makes sense.
20 Q. Yeah. Yeah, I understand.
21 So when you tested the glutamate -- the
22 glutamate at 131, that mutant lost all activity.
23 And if you want to look at Table 1 of your
24 paper, which is on 9438.
25 A. Yes.

1 Q. So that -- that mutation abolished the
2 activity of HYAL1. Right?
3 A. The mutation almost completely abolished
4 the activity we could detect in HYAL1.
5 It retained a small percentage of activity
6 that we considered insignificant in the context of
7 the work, to the extent that we could implicate that
8 residue as a key catalytic component.
9 Q. The mutation at position 129 did not
10 abolish the activity of the HYAL1 enzyme. Right?
11 A. So it's difficult to put -- you put it on
12 a spectrum.
13 It's difficult to say it did not abolish
14 activity. But because it retains 5% activity, we
15 described it in the manuscript as not having fully
16 abolished activity.
17 Q. So based on your hypothesis, the mutation
18 at E1- -- E131 was consistent with your hypothesis.
19 Right?
20 A. In that our hypothesis was that both
21 aspartate and glutamate would be critical residues
22 for catalytic activity, yes, that was consistent.
23 Q. And is the result for the D129N
24 mutation -- that's not consistent with your
25 hypothesis because it retained 5% of the activity.

1 Right?
2 A. It isn't that it's inconsistent with our
3 hypothesis.
4 When we looked at the active site docked
5 with the tetrasaccharide, we could see that it was
6 very likely that one of the residues, likely
7 glutamate, would be a -- the key proton donor during
8 the catalytic reaction, and that the residues
9 aspartate and the proximal tyrosine 247 were going
10 to be key residues that would function to polarize
11 the N-acetyl group of the substrate, which is a
12 critical step in substrate-assisted cleavage, which
13 is the mechanism by which this family of enzymes
14 hydrolyzes hyaluronan.
15 In that sense, we expected that activity
16 would be significantly diminished by mutagenizing
17 that residue because it wouldn't be able to perform
18 its role as we expected in the mechanism.
19 But we did not actually expect,
20 necessarily, that it would fully abolish activity.
21 And so, in that sense, it was consistent with our
22 hypothesis.
23 Q. And is it fair to say, from what you
24 published, that the D- -- the -- sorry.
25 So is it fair to say, from what you

1 published, that the aspartic at position 129 was not
2 essential to the HYAL1 activity?
3 A. We expressed the interpretation --
4 articulated the interpretation that it was important
5 for activity, but not essential, because the enzyme
6 retained activity if -- in the D129N mutant, if we
7 had mutagenized D to a different amino acid, it's
8 possible that it would not have retained any
9 activity.
10 So in the context of the D20- -- D129N
11 mutant, we interpreted that as implicating that as a
12 key residue, though it did not appear to be
13 essential if you replaced it with another polar
14 group like asparagine.
15 Q. Okay.
16 A. I'm trying to be very precise. Sorry.
17 Q. Thank you.
18 You also -- you had a hypothesis that
19 there was a disulfide bond that was near the
20 substrate -- potentially substrate binding groove.
21 And in this experiment, you didn't change
22 the residues. You just reduced the disulfide bonds
23 and then measured the effect of that. Right?
24 A. In this paper, we used a reducing agent to
25 reduce all the disulfide bonds and measured activity

1 in the presence and absence of the reducing agent,
2 and saw no loss of activity.
3 So for that reason, we did not
4 specifically mutagenize the cysteines; not because
5 they aren't important or the disulfides aren't
6 important, but in the context of our experiment,
7 those residues could be reduced, implying that the
8 folded structure, once folded in that secreted
9 soluble protein, was relatively stable.
10 Q. And the finding you had was that that
11 disulfide bond which you -- and just to be clear,
12 you identified that disulfide bond in the structure
13 that you were visualizing. Right?
14 A. So we were guided by Chao's paper, in
15 which Chao pointed out where cysteines were likely
16 or were certainly, depending on the electron -- the
17 resolution at that region and whether they could see
18 electron density between the cysteines that -- that
19 supported direct visualization of the disulfide.
20 It isn't always possible to see it. But
21 you can -- you can quantify the distance, measure
22 the distance, between the two sulfurs.
23 And again, same way as for sharing a
24 proton. You can see that the sulfurs must be in a
25 disulfide because there isn't sufficient distance

1 for them to each have their own proton as well.
2 Q. All right.
3 A. So based on where Chao said disulfides
4 were and where we visualized a cysteine association
5 as a disulfide, that was how we identified the
6 residues that were involved.
7 Q. In -- what you have in your paper on
8 Page 9438, in this left column, you have a summary
9 of that experiment. Right?
10 The di- -- this disul- -- disulfide
11 stabilization is not critical for activity.
12 A. Yes. Gotcha.
13 Q. Okay.
14 A. Yes.
15 Q. And what you concluded, in the very last
16 sentence, is that the disulfide bonds probably
17 affect the folding of the enzyme and long-term
18 stability of the hyaluronidases. Right?
19 And then you also observed that it did not
20 intrinsically appear to require the disulfide bonds
21 for optimal conformation of the protein. Right?
22 A. That was our conclusion -- our
23 interpretation on the basis of the data, that the
24 secreted polypeptide would not have been secreted if
25 the disulfide bonds could not form during maturation

1 of the protein intracellularly.
2 Q. Okay.
3 A. And that because we could secrete and
4 purify abundant soluble protein that had a certain
5 amount of wild-type activity, and we could add a
6 reducing agent following the secretion of the
7 protein, following the purification of the protein,
8 and not affect its activity over whatever period of
9 time we tested it in this particular assay....
10 It's in the experimental....
11 You may or may not care about that detail,
12 how long we tested activity after disulfide
13 reduction.
14 (Witness reading.)
15 So for one hour at 37 degrees, we treated
16 with DTT and then did our activity analysis. So it
17 was stable to a reducing agent for up to an hour
18 without having any loss of activity.
19 And so from that, we concluded that once
20 the protein was in its folded structure, the
21 disulfides were not essential for a period of an
22 hour at least to keeping it in that fold such that
23 it still had activity.
24 MR. KUSHAN: Okay. Let's go --
25 I'm going to introduce two documents which

you've addressed in your declaration.

First is Exhibit 1005, which is U.S. Patent 7,767,429, sometimes called the '429 patent.

(Whereupon, Petitioner Exhibit 1005, previously marked, was presented to the witness.)

MR. KUSHAN: And also introducing Exhibit 2165, which is a published U.S. patent application ending with '457.

(Whereupon, Halozyme Exhibit 2165, previously marked, was presented to the witness.)

MR. KUSHAN: We call that the '457 publication.

'429 patent, '457 publication.

Q. And you've reviewed both of these documents?

A. Yes, I have.

Q. Okay. If you look at the front -- if you look at the front of the patent, you see this is a patent owned by Halozyme. Right?

Under "Assignee" in the left column?

A. Yes.

Q. Now, are you aware that Halozyme also owns the '457 publication?

(No audible response.)
Q. I can represent to you that Halozyme owns that application too.
A. Okay. Yes.
Q. All right. Both of these applications -- both the application and the publi- -- and the patent were referenced in the common disclosure. Right?
I'm just asking if you recall that.
A. Yes, they're incorporated by reference in the common disclosure.
Q. Got it.
A. Yes.
Q. So if a POSA was interested in making modified PH20 proteins, they would consider both of these, the '429 patent and the '457 application. Right?
MS. MARTIN: Object to form.
A. Depending on the objective of the POSA, they would have access to the data and the disclosures of this patent and this publication.
Q. And they would consider both of them. Right?
MS. MARTIN: Object to the form.
A. Again, depending on the objective,

depending on the data desired for their experimental objective, they would consider these references, particularly if they're considering the -- implementing the invention in the '600 patent.

Q. If they -- if a person wanted to make soluble active forms of PH20, would they consider the '429 patent?

MS. MARTIN: Object to form.

A. What do you mean by "consider"?

Q. When you do an experiment, do you kind of go into a place where you ignore everything that published before you, or do you look in the literature to become aware of what work has preceded the time of your experiment?

MS. MARTIN: Object to form, and scope.

A. So you asked me about a POSA --

Q. Yes.

A. -- what a POSA would do. With that experimental objective, the POSA would seek all available information about how to construct a modified soluble PH20.

Q. And some of that information is reported in the '429 patent. Right?

A. Yes.

1 Q. So this would be something they would
2 consult as part of that body of knowledge about
3 soluble human PH20 proteins. Right?
4 MS. MARTIN: Object to form.
5 A. If it's -- so if the objective, again, is
6 to make a soluble hyaluronidase, PH20 hyaluronidase,
7 there are data in this patent that would be relevant
8 to consult.
9 Q. Okay. Could you go to column 153 of this
10 patent.
11 It's toward the very end.
12 A. At the very end.
13 I'm sorry. Could you tell me again?
14 Q. Go to column 153.
15 And if you could look at claim 1 of the
16 patent, it's on -- under column 153, toward the
17 bottom of the page.
18 When you reviewed the '429 patent, did you
19 review the claims of the '429 patent?
20 A. Yes.
21 Q. Okay. Do you see, in claim 1, that it
22 defines a substantially purified hyaluronidase
23 protein?
24 That's the first line of claim 1.
25 MS. MARTIN: Object to form.

1 And objection; scope.
2 A. Can you repeat your question, please?
3 Q. Yeah. If you look at Line 1 of claim 1,
4 it's -- it says "a substantially purified
5 hyaluronidase glycoprotein."
6 So this is a claim directed to
7 substantially purified hyaluronidase glycoproteins.
8 Right?
9 MR. KUSHAN: Object -- object to
10 form. Objection; scope.
11 (Witness reading.)
12 A. Okay. Can you please repeat your question
13 one more time?
14 Q. I'm just -- this is very basic.
15 This claim is directed to substantially
16 purified hyaluronidase glycoproteins. Right?
17 MS. MARTIN: Object to form.
18 Objection; scope.
19 A. Claim 1 is directed to a substantially
20 purified hyaluronidase glycoprotein that consists of
21 a sequence of amino acids set forth as a specific
22 set of amino acids that refer to a reference
23 sequence, SEQ ID NO: 1.
24 Q. Right. And I'll represent -- you can
25 consider this -- SEQ ID 1 is the precursor sequence

1 of the human wild-type protein.
2 And if you want to look, look at -- you
3 see these strings of residues. There's one there
4 that's 36 to 42. That would be 1-447 if you have a
5 35 amino acid leader sequence. Right?
6 If you want to go to SEQ ID 1 -- the
7 description of it, obviously -- it's column 99.
8 And I -- you know, if your counsel wants
9 to object to you -- me representing to you that this
10 is the same sequence of human precursor PH20, we can
11 have a conversation about that, but I'm pretty sure
12 it's correct.
13 So if we --
14 A. 509, mature full length -- sorry --
15 precursor full length....
16 In PH20, yes.
17 Q. Okay. Great.
18 So if you look at Lines 36 to 40, that's
19 referring to a form of the purified hyaluronidase
20 glycoprotein that has the wild-type sequence with
21 the start and termination positions in those
22 different sets of numbers. Right?
23 MS. MARTIN: Objection; scope.
24 Object to form.
25 Q. Do you understand that?

A. No. Could you please repeat it and show me --

Q. Sure.

A. -- again what you're --

Q. So in that very first clause, it says -- up until Line 41 -- you see the SEQ ID 1, and then there's a comma?

A. That's -- so that I can confirm what page you're on, this is --

Q. 153.

A. 153.

Q. Claim 1.

A. Thank you.

Q. Are we in the same place?

A. In the same place. Thank you.

Q. Okay. Great.

I'm looking at the first few lines of the claim, and that is referring to sequences that are of the wild-type sequence in human PH20, which is the portion of the claim that goes from about 36 to about 40, the line numbers. Right?

MS. MARTIN: Object to form.

Objection; scope.

Q. It's -- it just says, has -- "consists of the sequence of amino acids set forth" in the

1 sequence, which is SEQ ID 1, at those specified
2 positions.
3 So that's referring to the wild type, the
4 sequence that's unmodified. Right?
5 MS. MARTIN: Object to form.
6 Objection; scope.
7 A. The reference sequence, SEQ ID NO: 1, is
8 referring to the precursor full-length human PH20
9 sequence.
10 Q. Correct.
11 So these sequence ranges that are in that
12 first portion of the claim are the wild-type
13 sequences. Right?
14 MS. MARTIN: Object to form.
15 Objection; scope.
16 A. So the full claim --
17 Q. I'm not asking about the full claim. I'm
18 just asking about this portion of --
19 A. It's a full sentence. You -- you are
20 asking me -- I'm sorry to interrupt.
21 You are asking me if this sentence refers
22 only to wild type. And I was going to --
23 Q. No, no.
24 A. Okay.
25 Q. Then you may have misunderstood my

1 question.
2 I'm asking you about this portion of the
3 claim before the comma, before some -- it says:
4 A substantially purified
5 hyaluronidase glycoprotein that
6 consists of the sequence of
7 amino acids in these ranges of
8 SEQ ID 1....
9 Do you see that clause?
10 A. I do see that, yes.
11 Q. All right. So that's referring to where
12 the amino acid sequence is the same as the one in
13 SEQ ID 1 bounded by the numbers of each range.
14 Right?
15 MS. MARTIN: Object to form.
16 Objection; scope.
17 (Witness reading.)
18 A. You're asking me if the numbers refer to
19 SEQ ID 1, the location of amino acids in SEQ ID 1?
20 Q. Okay. Let me ask you -- just so we're
21 understanding how you read patent claims -- because
22 you have 200-and-some pages devoted to that in your
23 declaration for the common disclosure, so I want to
24 just go back to maybe how we work through this.
25 I'm just asking you if, in this region of

the claim, where it's listing the range of amino acids within a SEQ ID number, you can decipher what that's referring to.

MS. MARTIN: Object to form. Objection; scope.

Q. So if I said -- for example, if we're in the common disclosure and it said positions 1-447 of SEQ ID 3, do you know what that is referring to?

Not in this patent, but in the common disclosure.

MS. MARTIN: Object to form.

A. If I -- I'm sorry. If we can --

Q. Let's just walk -- I want to understand how you understand some of these terms. Okay?

A. Okay.

Q. Because we've spent five minutes trying to confirm that we're just looking at a range in SEQ ID 1, I want to make sure we are speaking the same language here.

So when you reviewed the claims in the disclosure of the '600 patent -- you don't have to look at it right now; it's just a very basic question -- there was a SEQ ID 3 that you referenced, which is disclosed in that common disclosure.

1 That's the 1-447 length human PH20
2 wild-type sequence. Right?
3 SEQ ID 3 in the common disclosure?
4 A. SEQ ID 3 in the common disclosure refers
5 to the PH20 sequence, with very specific definitions
6 about what it constitutes.
7 Q. Great. So when I say "SEQ ID 3" and
8 "positions 1-447 of SEQ ID 3," you know what I'm
9 referring to. Right?
10 A. When I look at SEQ ID 3, it has numerical
11 designation of what the amino acids are in the
12 sequence ID.
13 So I know which numbers those are. I know
14 how to find them in the SEQ ID.
15 Q. Right. And if you see a reference, for
16 example, in claim 1 of the '429 patent that says
17 "positions 1-44- -- 1-477 of SEQ ID 1," are you able
18 to understand what that's referring to?
19 (Witness reading.)
20 A. Yes.
21 Q. Okay. So in the first five lines of
22 claim 1, it's referring to a substantially purified
23 hyaluronidase glycoprotein that consists of the
24 sequence of amino acids set forth at -- as amino
25 acids 1-477, for example, of SEQ ID 1. Right?

A. Yes.
Q. Okay.
A. As an example, that -- that is one. Yes.
Q. So then -- and you look at Line 41, as an alternative, it says -- this is basically taking the first line of the claim, "a substantially purified hyaluronidase glycoprotein that...contains amino acid substitutions in the sequence of amino acids set forth as amino acids 1-477," etc., of SEQ ID NO: 1. Right?
MS. MARTIN: Object to form. Objection; scope.
A. So:
A substantially purified hyaluronidase glycoprotein that consists of the amino acid -- the sequence of amino acids set forth as amino acids with given numbers of ranges, SEQ ID 1, or contains amino acid substitutions in the sequence of amino acids set forth as amino acids --
-- again, in these ranges of SEQ ID NO: 1.
Q. Okay. So this is a substantially purified

1 hyaluronidase glycoprotein that has at least one
2 amino acid substitution in it relative to the
3 wild-type sequence. Right?
4 MS. MARTIN: Object to form.
5 Objection; scope.
6 A. You said "this" is.
7 Specifically, what do you mean by "this"?
8 Q. The claim is to a substantially purified
9 hyaluronidase glycoprotein, and one of them is
10 covered by the middle section, where it allows for
11 an amino acid substitution in the sequence. Right?
12 MS. MARTIN: Object to form.
13 Objection; scope.
14 A. So the claim allows for one of these
15 ranges of sequences, one or more of all of these
16 ranges of sequences of SEQ ID NO: 1, in the
17 wild-type context or containing amino acid
18 substitutions in the same sequence, where the
19 sequence is at least 95% identical with the --
20 Q. Right.
21 A. -- with the sequence in the range --
22 ranges in SEQ ID 1.
23 Q. So this claim covers both proteins that
24 have the wild-type sequence, as well as proteins
25 with substitutions in them, as long as the overall

1 sequence identity is below -- or above 95%. Right?
2 A. Above 95 --
3 MS. MARTIN: Object to form.
4 Objection; scope.
5 COURT REPORTER: Did you say an
6 answer?
7 WITNESS: I was repeating the
8 "above 95%," yes.
9 Q. All right.
10 A. (Reading:)
11 ...wherein -- there's also
12 another clause -- the
13 glycoprotein contains at least
14 one sugar moiety...attached to
15 an asparagine.
16 Q. When you produce human PH20 in a CHO cell,
17 does that glycosylate that position?
18 A. There isn't a specific position given for
19 the glycosylation in this -- in this location.
20 Q. Are there residues in the PH20, if not
21 mutated, will become glycosylated when you produce
22 it in a CHO cell?
23 MS. MARTIN: Object to form.
24 Objection; scope.
25 A. In which form of PH20?

1 Q. A form in which a mutation does not remove
2 the residues that are ordinarily glycosylated in
3 human PH20.
4 A. So it depends.
5 Q. All right. Well, I'll withdraw that
6 question, because we're -- what I'm interested in is
7 just confirming that this claim language is not only
8 claiming the wild-type version of the PH20, but also
9 mutations -- those that have mutations, as long as
10 they're 95% or higher sequence identity to the
11 reference sequence. Right?
12 MS. MARTIN: Object to form.
13 Objection; scope.
14 A. So the claim -- claims sequences with
15 reference to SEQ ID 1 that are either identical to
16 the wild type or contain a mutation, where the
17 sequence is 95% or more sequence identity, with
18 specific ranges of sequences in SEQ ID 1, and the
19 glycoprotein contains at least one sugar moiety
20 attached to an asparagine that is not specified.
21 Q. Okay. So some of the proteins that are in
22 the scope of this claim would be modified PH20
23 polypeptides that are addressed in the '600 patent.
24 Right?
25 MS. MARTIN: Object to form.

1 Q. Assuming that there -- one of those
2 substitutions was D320K?
3 MS. MARTIN: Object to form.
4 Objection; scope.
5 A. So I'm going to need you to reask your
6 question, please.
7 Q. Of course. If one of the substitutions
8 specified or allowed in this claim were made at
9 position 320 and went from D at 320 in the wild type
10 to lysine, K, at that position, then one of the --
11 that -- that particular substitution addressed in
12 this claim is also covered by the claims of this
13 '600 patent. Right?
14 MS. MARTIN: Object to form.
15 Objection; scope.
16 A. The '600 patent -- the scope of the '600
17 patent claims....
18 (Witness reading.)
19 Q. I can try to make it easier for you.
20 Do you believe that the '600 patent covers
21 a single substitution mutation in the 1-447 human
22 PH20 sequence where the -- that substitution is D to
23 lysine, K, D320K?
24 MS. MARTIN: Object to form.
25 A. I'm sorry. Which patent are we talking

about now?

Q. In the '600 patent --

A. Yes.

Q. That's the patent that specifies that the position where a mutation could occur is -- is required to occur is at position 320. Right?

A. Yes.

Q. Okay. And one of the permitted or required changes is from the wild-type aspartic acid to lysine. Right?

A. That's correct.

Q. Okay. So if I have a PH20, 447 residues in length, with a D320K mutation in it, is that protein in the scope of claim 1 of the '600 patent?

A. So claim 1 of the '600 patent refers to a different reference sequence than claim 1 of the '429 patent.

Q. Right. I'm asking: The human PH20 sequence is the same -- it was the same in 2000 and -- it is same today. Right?

A. The human PH20 sequence is the same.

Q. Okay.

A. The SEQ ID sequences are not the same.

Q. Correct. So I asked if the 1-447 in the mature protein sequencing of the human PH20 with the

1 D320K substitution in it -- if that protein with
2 that mutation is within the scope of the claims of
3 the '600 patent.
4 Are you with me?
5 A. So you're asking me about 1-447 in the
6 '600 patent, which refers to SEQ ID 3, in which the
7 numbering sequence is relative to the start of the
8 mature polypeptide.
9 Q. Correct.
10 A. And asking me, if it has a D320K mutation,
11 is that covered by the claims of the '600 patent?
12 Q. Exactly. Yes.
13 A. If it's 1-447, relative to SEQ ID 3, with
14 a D320K?
15 Q. Yes.
16 A. Yes, I think I follow you.
17 Q. And is it in the scope of the claims of
18 the '600 patent?
19 A. That would be in the scope of the claims.
20 Q. And it would also be in the scope of the
21 claims of the '429 patent. Right?
22 MS. MARTIN: Object to form.
23 Objection; scope.
24 A. So the numbering system you used is --
25 refers to a different thing in the context of the

1 '600 patent than it does in the context of the '429
2 patent.
3 Q. Yes. So in the SEQ ID 1, it includes the
4 leader sequence. So that's 35 amino acids in the
5 human precursor sequence. Right?
6 A. The leader sequence is 35 amino acids,
7 yes.
8 Q. Right. So if you look at the range in the
9 middle clause here, 41 -- in the 41 to 45 range of
10 the claim, one of the ranges is 36-482 -- right? --
11 and that translates to 1-447 in the mature sequence
12 numbering. Right?
13 A. Yes.
14 Q. All right.
15 A. Yes. And with the D320K. Yes.
16 Q. Okay. So that -- so this clause would
17 include -- because it doesn't restrict what
18 substitutions are made in this claim, it would
19 include the D320K substitution in the 1-447 form of
20 the PH20 protein and its mature sequence numbering?
21 MS. MARTIN: Object to form.
22 Objection; scope.
23 A. So D320 also is a numeric position that is
24 relative to the start of the -- actually, the
25 precursor polypeptide, the D320 position -- sorry,

1 the mature polypeptide D320 position.
2 So it would be a different residue in the
3 context of SEQ ID 1.
4 Q. So it would be 320 plus 35: 355.
5 MS. MARTIN: Object to form.
6 Objection; scope.
7 Q. Is that right?
8 MS. MARTIN: Object to form.
9 Objection; scope.
10 A. Can we go back to the original question,
11 because I --
12 Q. Yeah.
13 A. -- think it's changed with the numbering
14 system.
15 Q. Yeah. My question is: If you look at
16 36-478 in the SEQ ID 1, which has the leader
17 sequence, that translates to 1-447 in SEQ ID 3
18 without the leader sequence. Right?
19 A. Okay. I think you just said 36-477.
20 Q. No, no.
21 A. I'm getting --
22 Q. Sorry. I apologize.
23 A. The numbers are messed up.
24 Q. I'm just trying to -- I mean, this is the
25 challenge whenever you have two different numbering

1 schemes. So I don't want to have any confusion.
2 So I'm just trying to confirm that the
3 sequence 36-482 in the full-length precursor
4 sequence, with the leader sequence, is the same
5 sequence as the 1-447 in the mature sequence of
6 human PH20. Right?
7 MS. MARTIN: Object to form.
8 Objection; scope.
9 A. Human PH20 sequence SEQ ID 1 is the full
10 length, from start to finish, signal peptide intact,
11 GPI anchor site intact. SEQ ID 3 is a modified PH20
12 polypeptide.
13 So SEQ ID 3 has a different numbering
14 system than SEQ ID 1.
15 320, in the -- is designated -- is so
16 designated in the context of SEQ ID 3.
17 You're asking if it could be designated as
18 355 in the context of the full-length protein, PH20
19 sequence in SEQ ID 1, and if 36-482 in SEQ ID 1
20 corresponds to 1-1- -- 1-447 in SEQ ID 3.
21 D320K in SEQ ID 3, D355K in SEQ ID 1,
22 36-482, would that be the same?
23 Q. Yes.
24 A. It is my interpretation that those are the
25 same.

1 Q. Okay. So these two different patents have
2 claims that encompass the same D320K 1-447 mature
3 sequence human PH20 protein?
4 MS. MARTIN: Object to form.
5 Objection; scope.
6 A. So in the '429 patent, there's no
7 stipulation on what amino acid should be modified to
8 be compliant with the claim -- to meet this, the
9 requirements of the claim -- to produce and use the
10 invention.
11 In the '600 patent, there is a specific
12 requirement for a specific amino acid to be modified
13 to one of four potential other amino acids in order
14 to meet the claims of the invention.
15 So, no, they're not the same thing.
16 Q. They're not the same claims, but they --
17 both claims cover the same single D320K mutant.
18 Right?
19 MS. MARTIN: Object to form.
20 Objection; scope.
21 A. If a D320 -- if a D355K, not even a D320,
22 were selected and made under this claim, it would be
23 covered under this claim in reference to SEQ ID 1.
24 Q. Yeah.
25 A. Is that what you're asking?

Q. Yeah, I was just confirming that.
Let's -- if you could, put that aside for a moment, the '429, and go to the '457 publication.
And if you look at -- if you have your -- do you have the '457 publication?
A. Yes.
Q. Why don't we clean up a little bit.
So you have the '457 available?
A. Yes.
Q. Okay. And do you have your declaration available?
A. Yes.
Q. Go to your declaration and look at Paragraph 180.
A. Yes.
Q. And now take a -- you've -- so 180 refers to:

> The '429 patent Example 4 as describing using ELISA assays to measure hyaluronidase activity for C-terminal truncation mutants.

You say that. Right?
A. Yes.
Q. Okay. And then in 185, take a look at

1 that paragraph.
2 (Witness reading.)
3 A. Okay.
4 Q. Okay. And that paragraph, 185, is
5 indicating that:
6 The '457 patent examples
7 also used an ELISA assay to
8 measure HA activity.
9 Right?
10 A. Yes.
11 Q. Do you know what they were referring to as
12 the ELISA assays to measure hyaluronidase activity?
13 MS. MARTIN: Object to form.
14 A. Yes.
15 Q. Can you just describe that assay?
16 (Witness reading.)
17 A. So in this assay, hyaluronan, the
18 substrate for PH20 and other hyaluronidases, is
19 biotinylated, labeled. The substrate is adsorbed to
20 a microwell plate and transfected supernatants from
21 cells transfected with human PH20 hyaluronidase is
22 added at a specified -- in specified buffer
23 conditions, particularly specifying pH.
24 But all the other compositions are also
25 given in the disclosure.

1 Following an incubation period of
2 90 minutes at 37, the reaction is terminated by the
3 addition of a strong denaturant.
4 The wells are washed, and then the
5 remaining biotin is detected by the addition of
6 streptavidin-horseradish peroxidase conjugate,
7 followed by the addition of tetramethylbenzidine,
8 which is a substrate for horseradish peroxidase that
9 is colorimetric, produces a color that can be read
10 at an absorbance value of 450 nanometers in a
11 microwell plate reader.
12 The absorbance values are compared to a
13 standard curve that's generated by the inclusion of
14 specific amounts -- known amounts of hyaluronidase
15 and the amount of activity -- known amount of
16 wild-type PH20 hyaluronidase.
17 The activity is then calculated as a
18 percentage, or fraction, or in units per mil. In
19 this case, it's in units per mil relative to the
20 standard and the -- the amount -- the units per mil
21 that were in the standard that it equated to on the
22 standard curve.
23 Q. Okay. So the biotinylated HA assay is
24 used in both the '429 patent and in the '457
25 publication to measure the activity of the

1 hyaluronidase PH20 enzymes?
2 A. Both the '429 and the '457?
3 Q. Yeah. And you cite to -- in the '429, you
4 can go to column 86, Line 4, to column 88, 24. You
5 can just confirm that is what you said in your
6 declaration.
7 (Witness reading.)
8 A. The assay is -- it is a similar assay
9 that's used in both -- both patents, yes.
10 Q. Is it similar to the assay that's used in
11 the common disclosure, as well, for the primary
12 screen of the mutants?
13 And you can look at Example 3.
14 (Witness reading.)
15 That's....
16 (Witness reading.)
17 Q. It starts at Page 248. Are you there?
18 A. Yes.
19 Q. Okay.
20 A. Yes. The assays are similar.
21 Q. Okay. In your own work where you're
22 characterizing hyaluronidase enzyme, do you use this
23 type of biotinylated HA assay?
24 A. We use several assays. Among them is this
25 one, or one that is similar to it.

1 Q. So you're familiar with this -- use of
2 this assay. Right?
3 A. Yes.
4 Q. Okay.
5 MS. MARTIN: Counsel, we've been
6 going for, I think, exactly an hour.
7 MR. KUSHAN: Can -- I'm in --
8 no, just give me about five minutes, if
9 that's okay.
10 MS. MARTIN: Would you like a
11 break?
12 MR. KUSHAN: Counsel, I just
13 would prefer to finish this line of
14 questioning. It'll be five minutes, if
15 that's all right.
16 MS. MARTIN: Well, the
17 witness --
18 MR. KUSHAN: Can you --
19 MS. MARTIN: -- can take a break
20 if she would like a break, Counsel, so....
21 MR. KUSHAN: Would a --
22 MS. MARTIN: It's not an
23 interrogation.
24 MR. KUSHAN: I'm in the middle
25 of a question. Could I just --

MS. MARTIN: Actually, you weren't --

MR. KUSHAN: -- finish --

MS. MARTIN: -- in the middle of a question.

MR. KUSHAN: Okay.

MS. MARTIN: If you were in the middle of a question, I would -- I wouldn't say anything.

MR. KUSHAN: Dr. Simpson, are you okay if I ask you one or two more questions while we're on this point?

WITNESS: I would like to take the advice of my counsel.

MR. KUSHAN: All right. I'm not asking -- your counsel suggests you can take a break. That's not the type of legal advice we should be dealing -- I'm just asking you if you can -- we've gotten to this point. I just want -- I have one or two more questions.

If you really need a break, we'll take a break. It's just up to you.

WITNESS: I would like to take a break. Thank you.

MR. KUSHAN: Great. We'll take a break.

Counsel, if you do this again, I'm going to raise an issue with the Board, okay --

MS. MARTIN: Fine.

MR. KUSHAN: -- because you're disrupting the --

MS. MARTIN: No, I'm not.

MR. KUSHAN: -- examination of the witness.

Yes, you are. Absolutely.

MS. MARTIN: No, I'm not. Absolutely not. So --

MR. KUSHAN: Hundred percent.

MS. MARTIN: -- go for it. You can --

MR. KUSHAN: We can go off the record.

MS. MARTIN: -- complain to the Board all you want --

MR. KUSHAN: Thank you.

MS. MARTIN: -- but....

VIDEOGRAPHER: Going off the record at 2:38.

(Whereupon, a recess was taken.)

VIDEOGRAPHER: On the record at 3:01.

BY MR. KUSHAN:

Q. Dr. Simpson, did you speak with counsel during the break?

A. Yes, briefly.

Q. And did you discuss anything relating to this proceeding?

A. Nothing related.

Q. All right. Could you go to your declaration and go to Paragraph 182.

It's at Page 67.

A. Yes.

Q. Are you with me?

A. Yes.

Q. Okay.

A. I want to make a correction to earlier testimony.

Q. Right. What about?

A. Earlier, I had testified that position 320 was relative to the signal peptide cleaved sequence numbering system.

I want to correct that it's not. It's relative to the full-length numbering system. And

1 it's the same -- 320 is the same in both SEQ ID 1
2 and SEQ ID 3 in terms of its position relative to
3 the start site of the full-length polypeptide PH20.
4 This was in the context of asking me to
5 construe claims from the '429 patent, which was not
6 part of the scope of my assignment.
7 Q. Did you discuss any aspect of this point
8 you just raised with me with counsel during the
9 break? And I'll just remind you, you're under oath.
10 A. I am under oath, and I did not.
11 Q. Okay. And what are you trying to tell me,
12 that you have reached a different conclusion that
13 the -- there's a D320K mutation that's in a
14 different location, depending on the numbering
15 scheme?
16 A. I'm not trying to tell you that.
17 Q. Okay. It's the same position in the
18 same -- it's the same position in context of whether
19 there's a leader sequence or not leader sequence
20 present in the protein?
21 Sorry. That's a bad question.
22 What are you trying to tell me? Why don't
23 you just explain it.
24 A. That -- so we were talking about whether a
25 mutation at position 320 meant the same thing in the

1 '600 patent as it did in the '429 patent.
2 It does.
3 Q. Okay. Great.
4 A. But I did not construe the claims of the
5 '429 patent as part of the scope of what I was asked
6 to provide for the declaration in this matter.
7 Q. Okay. So you didn't prepare to do that
8 prior to your deposition today, and during the
9 course of the deposition day, you just provided that
10 answer as you were reviewing the information that I
11 was giving you in the documents. Right?
12 A. As you asked about the claim, I responded
13 to your questions.
14 Q. Perfect. Could you go -- let's go to
15 Paragraph 182 of your declaration, if that's okay,
16 on Page 67.
17 A. Yes.
18 Q. Do you see that -- you're discussing some
19 testimony from Dr. Hecht. In the second sentence of
20 the paragraph, you say:
21 The degree -- or -- but
22 that degree of variability is
23 expected in hyaluronidase
24 activity ELISA assays like this
25 and is in line with what a POSA

1 would expect.
2 Do you see that?
3 A. I do see that.
4 Q. And do you understand you're referring to
5 a degree of variability in the biotinylated HA
6 assays we've been discussing -- we were discussing
7 just before the break. Right?
8 A. These results were generated in -- using a
9 microtiter assay, which was the one we were
10 discussing before the break, yes.
11 Q. Okay. What is -- what do you mean -- what
12 would the POSA believe to be the degree of
13 variability in the hyaluronidase assay that's
14 referenced in Paragraph 82 -- 182?
15 A. There would not be a precise value, per
16 se, that a POSA would have in mind.
17 Because of the nature of the assay as an
18 ELISA, and because of the nature of the enzyme and
19 its mechanism, there is inherent variability
20 possible within the assay. There are ways to
21 control for the impact of the variability within the
22 assay.
23 So there are ways to evaluate, as a POSA,
24 whether the variability is significant in the
25 context of the results in the assay.

1 Q. In your experience using these types of
2 assays, what kind of range in activity have you
3 typically seen with the assay as to the measurement
4 of the hyaluronidase activity?
5 MS. MARTIN: Object to the form.
6 A. The range in activity is very much
7 dependent on which enzyme you're assaying.
8 So my experience has been largely in the
9 context of the other members of the hyaluronidase
10 family, and not specifically with respect to PH20.
11 Q. When you said in your declaration that the
12 degree of variability is expected in hyaluronidase
13 activity ELISA assays, was that tied to the enzyme
14 being tested in the assay or to the assays
15 generally, regardless of which enzyme was being
16 tested?
17 A. When I'm speaking of that degree of
18 variability in that specific paragraph, I'm
19 referring generally to the microtiter plate assay
20 for hyaluronidase activity.
21 Q. Are you able to give me kind of a
22 percentage range of variability that a POSA would
23 expect to exist, based on that type of biotinylated
24 HA assay?
25 A. It's not so much that we would look for a

1 percentage variability in the range.
2 It is more so that as you look at -- so,
3 for example, in the context of this series of data,
4 the experiment is looking at successive C-terminal
5 truncations and the impact of that on the residual
6 activity of the enzyme.
7 Because it's a series of successive
8 mutations that have comparable activity on either
9 side of a single value, it's likely that a minor
10 variation such as is present in this column of data
11 in the table that's also presented above this
12 paragraph -- because it's in a different order of
13 magnitude of conditions in which the enzyme is
14 relatively -- has relatively low activity, and it's
15 within a trend of successive truncations that have
16 similar values, it's more likely that it's a
17 variability in the assay.
18 Q. Do you -- if I was just testing the
19 activity of the -- of a wild-type positive control
20 PH20 in multiple tests, what would be the
21 variability you would expect to see in the
22 hyaluronidase assay in that setting?
23 A. So in a microwell assay, using multiple
24 conditions of the exact same enzyme, with the exact
25 same substrate, depending on the quality of the

1 substrate, the quality of the enzyme purification,
2 preparation, the skill of the person performing the
3 assays, a number of conditions such as those, there
4 can be variability that is in the same order of
5 magnitude as the value, the average value.
6 So you would look for changes in -- in
7 activity that were greater than one or two standard
8 deviations of the mean of a number of replicates
9 within the assay.
10 So the degree of variability can change --
11 can be different from day to day.
12 Q. So you're going to take the set of
13 samples -- in this case, the set of positive
14 samples, you calculate the mean, and then you
15 calculate standard deviations around the mean?
16 You're looking for the values to stay
17 within one or two standard deviations of the mean?
18 A. That is one way to estimate the
19 variability on a given day within a microtiter plate
20 assay.
21 Q. All right. Could you go to Paragraph 225
22 and 226 of your declaration, which is on Page 87 and
23 it goes over to 88.
24 A. 225?
25 Q. Correct, 225.

A. Yes.
Q. And 226.
And just a simple question: In these paragraphs, you make an observation about an assay being run in the presence of a denaturing agent like m-cresol.
Do you see that?
A. Yes.
Q. And was the basis of your comment, responding to Dr. Hecht's statements, your belief that Dr. Hecht was just addressing the variability of the assay when the m-cresol was present in the samples being tested?
(Witness reading.)
A. So the previous example that you called my attention to in Paragraph 182 was an assay performed in the absence of m-cresol, in which Dr. Hecht was criticizing the variability of the assay.
Q. Right. I'm asking now about what you're saying with respect to his comments about Example 5.
And I'm just trying to understand: Is your -- is your criticism -- is your statement in Paragraph 225 assuming that his comments about the variability observed in the assay was only for the samples that had m-cresol in the sample being

1 measured?
2 MS. MARTIN: Object to form.
3 A. Dr. Hecht criticized results in both of
4 these experiments, specifically as it -- commenting
5 on the significance and variability in his opinion.
6 Q. Correct.
7 A. One of the examples contained m-cresol;
8 the other one did not.
9 Q. So I'm just trying to understand: Is
10 your -- your comment -- in 225, you say:
11 But I -- as I have
12 explained repeatedly, POSAs
13 expect variability for these
14 types of assays. And for this
15 assay in particular, which
16 involves incubating PH20 for
17 four hours with a reagent known
18 to denature PH20 (i.e.,
19 m-cresol), a POSA would expect
20 even greater levels of
21 variability.
22 I'm just trying to understand: Is your
23 underst- -- is your criticism focused on his
24 comments about the samples that were tested in the
25 presence of m-cresol or all the samples that were

1 tested in that assay?
2 A. Dr. Hecht was evaluating all of the data
3 for variability, all of the data within the tables,
4 the example, Example 5, and criticizing the
5 variability in all of the conditions, particularly
6 because, within -- within the experiment, there
7 appeared to him to be significant variability.
8 He specifies it in his declaration, and
9 I'm not comfortable paraphrasing Dr. Hecht without
10 looking at his declaration.
11 Q. Yeah. I'm just trying -- so I think
12 you've answered.
13 So your comments in this paragraph are not
14 limited just to his comments about the
15 m-cresol-containing samples. Right?
16 A. Which specific comments?
17 Q. The ones I read in a minute ago:
18 And for this assay in
19 particular, which involves
20 incubating PH20 for four hours
21 with a reagent known to
22 denature PH20, a POSA would
23 expect even greater levels of
24 variability.
25 You're not focusing only on his comments

1 for the samples that have the m-cresol in them.
2 Right?
3 A. Within the assay that contains the data
4 for samples containing m-cresol, there are also data
5 for samples that do not contain it. And he's
6 concerned about variability across all the
7 conditions.
8 Q. And you're addressing all of the comments
9 he made about both the samples with m-cresol and
10 without m-cresol. Right?
11 A. He was criticizing the variability of the
12 assay.
13 I'm addressing the variability of the
14 assay.
15 Q. Okay.
16 A. I put in a superlative, "even greater," to
17 address that this assay was done in a different set
18 of conditions than the assay in consideration in the
19 previous example, where I defended the -- or
20 explained the variability in the assay and what a
21 POSA would expect.
22 Q. When you run the biotinylated HA
23 microtiter assay, do you typically run it at
24 37 degrees C?
25 A. Are you speaking of me personally?

1 Q. You personally, or would a POSA use that,
2 that temperature?
3 A. My research team, which I think is
4 representative of what a POSA would do, runs the
5 assay at 37 degrees.
6 Q. Okay. Earlier, you referred to a
7 standard -- use of a standard curve.
8 And I believe you were explaining this is
9 how you translate the measured density, optical
10 density, the reading that you get, and turns -- turn
11 a sample of that measured -- optical measurement
12 into an activity measurement. Right?
13 A. Yes.
14 Q. So if I -- feel free to correct my
15 description of it.
16 I just want to understand: When you
17 perform that conversion using a standard curve, how
18 do you set up the standard curve?
19 A. So it depends on the assay.
20 Q. Let's just go with this assay we've been
21 discussing, the biotinylated microtiter assay.
22 A. So the biotinylated microtiter assay also
23 is set up in a very context-dependent way.
24 How you set up the standard curve needs to
25 be representative of the conditions in which you're

1 measuring the actual activity, so that the activity
2 relates to the amount of activity in the standard
3 curve.
4 MR. KUSHAN: All right. I'm
5 going to -- I'm going to introduce an
6 exhibit.
7 This is Frost and Stern,
8 Analytical Biochemistry, Volume 251,
9 Pages 263 to 269, from 1997.
10 This will be Exhibit 1128.
11 Can you put a sticker on that?
12 (Whereupon, Petitioner Exhibit 1128 was
13 marked for identification.)
14 MR. KUSHAN: Sorry.
15 I believe this is also Exhibit
16 No. 2096.
17 Q. I just -- have you ever seen this paper
18 before?
19 A. Yes.
20 Q. Okay. I had a feeling you might have.
21 So do you see a standard curve on
22 Page 266?
23 (Witness reading.)
24 A. Yes. The authors state that Figure 2 is a
25 standard curve.

1 Q. And so, as you said before, you would
2 use -- you would take a measurement, the optical
3 reading of the well, and you'd get a -- the density,
4 I guess, of the optical -- the density of the
5 material in the well dictates the reading you get
6 out of it. Right?
7 (No audible response.)
8 Q. Correct my description. You know what I'm
9 trying to ask. Right?
10 A. The absorbance value.
11 Q. Right.
12 A. It's slightly different from the density.
13 But, yes, the absorbance value.
14 Q. Okay. So you get an absorbance value for
15 a well.
16 And then you take that absorbance value,
17 and you use it to then figure out what the activity
18 is by matching it onto the standard curve. Right?
19 A. Correct.
20 Q. Is there a particular part of this curve
21 that you have to use for that process?
22 A. So the standard curve has a curve fit
23 associated with it that depends on all points in the
24 curve. In that sense, it's dependent on all points
25 in the curve.

1 Ideally, the region of the curve that
2 maintains the greatest contiguous linearity is the
3 region that would be where you would use on a
4 standard if you were comparing the values for
5 unknowns.
6 Q. In Figure 2, can you tell what that range
7 would be using the hyaluronidase TRU/well range
8 numbers?
9 A. I can tell approximately.
10 Q. That's fine.
11 A. I would probably use a -- the actual data
12 from the graph to dial it in more specifically, but
13 I can tell approximately.
14 Q. Okay. What, approximately, would it be?
15 A. I would use a -- an a range -- a range
16 approximately from slightly below .001 to slightly
17 above .01.
18 Q. Okay. And that's like the -- that's the
19 linear part of the curve?
20 A. Approximately.
21 Q. Approximately linear part of the curve.
22 Okay.
23 Can you go to Page 175 of your
24 declaration.
25 Hold on. Just one -- bear with me for one

1 second.
2 (Pause.)
3 Q. I had the wrong page number.
4 Could you go to Page 169 of your
5 declaration.
6 Paragraph 412, do you see that?
7 A. Yes.
8 Q. You also see there's a reference to
9 Exhibit 2077 and 2078. Those are transcripts from
10 Dr. Park -- Dr. Park's declaration -- sorry.
11 Those are transcripts from Dr. Park's
12 depositions. Right?
13 A. Yes.
14 MR. KUSHAN: Okay. I'm going to
15 give you Exhibit 2176.
16 (Whereupon, Halozyme Exhibit 2176,
17 previously marked, was presented to the witness.)
18 Q. Do you recognize Exhibit 2176?
19 A. Yes.
20 Q. This is the worksheet that Dr. Park
21 created when he was preparing his analysis of single
22 substitution mutations of the PH20 protein. Right?
23 (Witness reading.)
24 Q. If you want to look at Paragraphs 413 and
25 414, you discuss this there.

1 (Witness reading.)
2 A. Yes. Yes. Thank you.
3 Q. Great. If you could go back to
4 Paragraph 412 on Page 169 of your declaration,
5 you're discussing your opinion that Dr. Park did --
6 had a motiva- -- certain motivation about picking
7 positions to assess changes into the PH20 protein
8 sequence as a single substitution in his project.
9 Right?
10 MS. MARTIN: Object to form.
11 A. So Dr. Park did a full analysis -- excuse
12 me -- of essential and nonessential positions.
13 This paragraph is specifically referring
14 to his analysis in the context of establishing
15 motivation.
16 Q. Look at the footnote 19. You say:
17 I further note Dr. Park
18 admitted that his focus on
19 position 320 was not based on
20 an independent scientific
21 analysis, but that he was
22 "asked by counsel to report
23 [his] conclusions with respect
24 to position 320.
25 Considering this Exhibit 2176 as his

1 output, are you aware that Dr. Park looked at a
2 number of positions in the PH20 sequence, analyzed
3 it with a PH20 homology model, and assessed the
4 impact of particular amino acid substitutions at
5 those positions?
6 MS. MARTIN: Object to form.
7 A. The spreadsheet provided by Dr. Park
8 offers comments that he provided about specific
9 residues within the PH20 sequence, as modeled on the
10 HYAL1 sequence, with PH20 residues given relative to
11 HYAL1 residues.
12 Q. Let's go into this. Go to Page 4 of the
13 spreadsheet.
14 Do you see that in the column headers
15 there's a column H, which is "Rating." And then you
16 see, at certain rows, there are numbers in that
17 column associated with particular substitutions at
18 particular positions. Right?
19 So, for example, at row 29, you see
20 there's an entry there corresponding to position 8
21 of PH20. And it's going from the wild-type valine
22 to isoleucine. Right?
23 MS. MARTIN: Object to form.
24 Objection; scope.
25 A. So point me again to which one -- which

1 valine you're talking about.
2 Q. Yeah. And I apologize for the small
3 print.
4 But if you look at, in the spreadsheet
5 column -- sorry -- spreadsheet row number 29, from
6 the far left column, you kind of go across the row,
7 you see "8" in bold.
8 That's the position number in PH20 under
9 column D. Right?
10 A. Yes.
11 Q. Okay. And you see two [sic] rows ahead --
12 above that, you see the PH20 is valine. That's the
13 wild type amino acid at that position in PH20.
14 Right?
15 MS. MARTIN: Object to form.
16 A. So in Line 28, PH20 residue 8, PH20
17 residue valine?
18 Q. Yes.
19 A. That's the line you're talking about?
20 Q. And then in row 29, you see "Alternative
21 Residue" in column F is I, or isoleucine. Right?
22 A. Yes, I see that.
23 Q. Okay. And then a few columns over, you
24 see a rating of "2" for that substitution of valine
25 at position 8 to isoleucine at that same position.

1 Right?
2 A. Yes, I see that.
3 Q. And then you see his comments "gain:
4 increased hydrophobic contacts" in column I. Right?
5 A. Yes, I see that.
6 Q. And do you understand this spreadsheet
7 basically to be compiling his conclusions on
8 particular single amino acid substitutions at
9 positions throughout the PH20 sequence?
10 MS. MARTIN: Object to form.
11 (Witness reading.)
12 A. Dr. Park was compiling his conclusions
13 about substitution at certain residues with respect
14 to their -- the frequency with which an alternative
15 residue appeared in his alignment models, his
16 homology alignments, and with respect to its
17 position within the PH20 structure modeled -- the
18 PH20 model modeled on the structure of HYAL1.
19 Q. Do you know if Dr. Park did his analysis
20 and compiled all of his results in this spreadsheet
21 prior to the point in time that you reference in
22 footnote 19, where he was asked about his views
23 about position 320?
24 MS. MARTIN: Object to form.
25 A. So please ask your question again --

Q. Sure.
A. -- because I want to be sure I understand you.
Q. Do you know -- so just that we're on the same foundation, you're expressing your views in footnote 19 based on a certain understanding you have of how Dr. Park came to express a view about changes at position 320. Right?
MS. MARTIN: Object to form.
A. I am noting a comment from Dr. Park about his focus on PH20 --
Q. Sure. And I'm just trying --
A. -- with respect to position 320.
Q. Correct. So I just want to understand whether you appreciate that Dr. Park created this spreadsheet and captured his views from his assessments before he was asked about these positions, and including the one at position 320.
MS. MARTIN: Object to form, scope.
A. I don't know that.
Q. You don't know that.
MR. KUSHAN: Okay. Why don't we take a short break; maybe five minutes.
WITNESS: Okay.

VIDEOGRAPHER: Going off the record at 3:37.

(Whereupon, a recess was taken.)

VIDEOGRAPHER: On the record at 3:48.

BY MR. KUSHAN:

Q. Dr. Simpson, you had conversations with counsel on the break?

A. Nothing pertaining to the case.

Q. All right. Could you go to Page 100 of your declaration.

And in Paragraph 243, you explain that you've reviewed the declaration of Dr. Petsko, including the spreadsheet containing data from Patent Tables 3, 5, 9, and 10.

This section of your declaration, Section F, is addressing some of your views about his analysis of positions for tolerance to substitutions. Right?

(No audible response.)

Q. Is that right?

A. Yes.

Q. Okay. You have 2166, which is the spreadsheet, if you need it.

Can you -- why don't you see if you can

1 find the spread- -- I'm sorry -- Dr. Petsko's
2 spreadsheet.
3 A. Dr. Petsko's. 2166.
4 Yes.
5 Q. Why don't you -- okay. Do you have that?
6 A. I have it.
7 Q. Great. Do you have Paragraph 244 up from
8 your declaration as well?
9 A. Yes.
10 Q. Okay. So following on Page 101 and 1- --
11 102, you see a chart with coloring of positions of
12 the PH20 sequence. Right?
13 A. Yes.
14 Q. And in 244, you're describing what the
15 colors mean. Right?
16 A. Yes.
17 Q. Okay. So the colors that are assigned in
18 the table at Pages 102 and 103 reflect percentages
19 of substitutions as active and inactive mutants as
20 they were classified in the common disclosure.
21 Right?
22 A. Yes.
23 Q. Okay. Tables 3 and 9 provided the list of
24 active mutants. Right?
25 (Pause.)

A. Table 3, active mutants. Table 9, active mutants.

Q. Okay. So those are the two tables devoted to compiling the active mutants as they were classified in the common disclosure. Right?

A. Correct.

Q. Okay. And then Tables 5 and 10 are compiling the inactive mutants in the patent -- or in the common disclosure?

A. Table 5....

(Pause.)

A. Tables 5 and 10 compiling inactive mutants. Yes.

Q. Okay. And these are the sources for the inactive and active mutant counts that are used to create the coloring scheme for the table at Pages 102 and 103, right, of your dec?

A. From Dr. Petsko's declaration, spreadsheet containing data from 3, 5, 9, 10.

This is excerpted from Dr. Petsko's declaration.

Q. And the coloring is based on the counts of the active and inactive mutants at each position. Right?

A. The coloring scheme is explained in

1 Paragraph 244.
2 Q. And is -- and those colors are based on
3 counts at each position of the active and inactive
4 mutants, right; a percentage?
5 For example, the dark green; what does the
6 dark green indicate on your chart?
7 A. Yes. So -- yes.
8 So positions that are color green are the
9 positions at which each of the substitutions that
10 were made were -- resulted in active protein, active
11 PH20 polypeptide.
12 Q. Okay. If you could go down to
13 Paragraph 246, you say -- and this is Page 104,
14 after your table.
15 You say:
16 The '600 patent provides a
17 detailed functional map of PH20
18 through its comprehensive and
19 systematic analysis of PH20,
20 achieved through large-scale
21 mutagenesis and enzymatic
22 activity testing of thousands
23 of variants, with up to 18
24 mutations per position.
25 And then you say:

1 The results show positions
2 that a POSA would understand
3 are critical and tolerate
4 minimal modification or no
5 modification, as well as
6 residues that do tolerate
7 substitution, and particular
8 substitutions that
9 substantially increase
10 activity.
11 Right? Okay.
12 A. Yes.
13 Q. And the table with the coloring at the
14 individual positions is conveying the nature of this
15 guidance in the patent. Right?
16 MS. MARTIN: Object to form.
17 A. The table indicates the percentage of
18 amino acids that were tolerated at that position on
19 the basis of the color assigned to it, which is the
20 same color scheme that was applied to the structural
21 analysis.
22 Q. So the residues in the table and on the
23 structure that are shown in green -- or dark --
24 well, just say green -- are the positions at which
25 many different amino acids are tolerated. Right?

A. Yes. The positions in green on the structure, as well as on the spreadsheet, are the ones at which almost all the positions were tolerated to re- -- to retain activity.

Q. Okay. Why don't you go to your -- go to the table, and go to Page 103.

What -- if you look at -- look up position 431.

What color is used at position 431?

A. Light green is used at 431.

Q. So if a POSA was trying to make a modified PH20 polypeptide that retained hyaluronidase activity, would Dr. Petsko's table at position 431 tell her she could make substitutions at position 431?

A. Potentially, yes.

Q. Look at position 282 in the chart.

And what color is used in position 282?

A. That position is not colored.

Q. What does that signify?

A. The uncolored boxes signify that there were more than 30%, but fewer than 60%, of the mutations -- the substitutions tested that were tolerated to retain activity.

Q. So if a POSA was trying to make an

1 enzymatically active modified PH20 polypeptide that
2 retained -- is going to retain hyaluronidase
3 activity, would Dr. Petsko's table tell her she
4 might be able to introduce substitutions at
5 position 282?
6 A. With disclaimers and qualifications, it
7 could tell her that.
8 Q. Okay. Let's go to position 303 in the
9 table.
10 What color is used at position 303?
11 A. 303 is colored orange.
12 Q. If a POSA was trying to make a modified
13 PH20 polypeptide that retained hyaluronidase
14 activity, Dr. Petsko's table would tell her to
15 proceed with caution because substitutions are
16 likely to not be tolerated at position 303. Right?
17 MS. MARTIN: Object to form.
18 A. So it depends on the POSA's motivation for
19 creating a substitution.
20 If the objective was to retain PH20
21 hyaluronidase activity, the POSA would want to look
22 at the structural environment surrounding that amino
23 acid change and look at the specific amino acids
24 that were tolerated at that position.
25 If there were some tolerated, then it's

not the case, necessarily, that they would need to proceed with caution, were they to choose one of the tolerated ones.

Q. So the POSA, at position 303, might change position 303, based on what they see in the data set?

A. A POSA would use all of the data, both in the table and in the structural analysis of where those particular residues were located within the structure.

Q. So the POSA wouldn't rule out changing an amino acid at position 303, right, based on the analysis you provided?

A. Particularly if their objective did not require retaining activity --

Q. Well --

A. -- a POSA would not have to rule out position 303.

Q. Yeah. Well, in my question, I was assuming they wanted to retain activity.

A. And even if they want to retain activity, there is sufficient guidance within the information available through a structural model, combined with the mutagenesis data that have been provided, as well as alignment data, that could inform the POSA

about what their strategy might need to be to retain activity by changing that location.

Q. Okay. So that's -- that conclusion based on your analysis of all of the data in the patent?

A. All of the data in the patent are definitely informative.

Q. Okay. One last one: Look at position 299. What color is used at position 299?

A. That one is pink.

Q. And if a POSA was trying to make a modified PH20 polypeptide that retained hyaluronidase activity, Dr. Petsko's table would tell her not to introduce a substitution at position 299. Is that right?

MS. MARTIN: Object to form.

(Witness reading.)

A. To retain activity of the enzyme at position 299.

Q. Correct.

A. Caution. Dr. Petsko would advise caution --

Q. So they still might --

A. -- in making a substitution.

Q. So a POSA -- so you believe the -- based on Dr. Petsko's analysis, a POSA might change

1 position 299. It wouldn't rule it out completely?
2 A. Based on Dr. Petsko's analysis, which also
3 included looking at each residue in the context of
4 its environment, offered scenarios in which a
5 mutation, even in an invariant residue, could be
6 made if a compensatory mutation was also made in the
7 local environment to neutralize the effect of the
8 first mutation.
9 This is why Dr. Petsko would advise
10 greater scrutiny before considering undertaking that
11 mutation.
12 Q. So if I understand your answer, you're
13 saying that a POSA might change the residue of
14 position 299, despite it being marked in red in the
15 table?
16 A. I'm saying that a POSA might change that
17 residue if their objective to -- is to retain
18 hyaluronidase activity in careful examination with
19 what additional residues might need to be also
20 concurrently mutagenized to compensate for that, the
21 effects of that mutation.
22 I'm saying a POSA could predict that by
23 examining the area around that residue and
24 considering what they were seeking to substitute it
25 with.

MR. KUSHAN: Okay. We have no further questions.

MS. MARTIN: All right. We'll take a quick break.

VIDEOGRAPHER: Off the record at 4:04.

(Whereupon, a recess was taken.)

VIDEOGRAPHER: On the record at 4:08.

MS. MARTIN: We don't have any questions.

VIDEOGRAPHER: All right. Going off the record at 4:08. And this ends today's testimony.

(Whereupon the deposition concluded at 4:08 p.m.)

1 DEPONENT'S SIGNATURE
2
3 Please be advised I have read the
4 foregoing deposition, pages 1 through 196,
5 inclusive. I hereby state there are:
6 (Check one)
7 _____ No corrections
8
9 _____ Corrections per attached
10
11
12 _____
13 MELANIE ANN SIMPSON, PH.D.
14
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16 ( ) Reading and signing was waived.
17 (X) Reading and signing was not requested.
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20 Should the signature of the witness not
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22 have availed herself of the opportunity to sign or
23 the signature has been waived.
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25 --oOo--

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2 NAME OF CASE: Merck Sharp & Dohme LLC v.
3 Halozyme, Inc.
4 DATE OF DEPOSITION: December 9, 2025
5 NAME OF WITNESS: MELANIE ANN SIMPSON, PH.D.
6 Reason Codes:
7 1: To clarify the record.
8 2: To conform to the facts.
9 3: To correct transcription error.
10 Page _____ Line _____ Reason _____
11 From _____ to _____
12 Page _____ Line _____ Reason _____
13 From _____ to _____
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24 _____ _____
25 MELANIE ANN SIMPSON, PH.D. DATE

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8 knowledge.
9 I hereby declare under penalty of perjury
10 that the foregoing is true and correct.
11 In witness whereof, I hereby subscribe my
12 name this _____ day of _____, 2025.
13
14 _____
15 MELANIE ANN SIMPSON, PH.D.
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CERTIFICATE

I, SUSAN ASHE, a Certified Electronic Reporter and Notary Public, hereby certify that the foregoing is a true and accurate transcript of the deposition of said witness, who was first duly sworn by me on the date and place hereinbefore set forth.

I FURTHER CERTIFY that I am neither attorney nor counsel, nor related to or employed by any of the parties to the action in which this deposition was taken, and further that I am not a relative or employee of any attorney or counsel employed in this action, nor am I financially interested in this case.

Dated this 11th day of December 2025.

Susan Ashe, Notary Public
of the District of Columbia

My commission expires: May 14, 2028.

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