UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,

Petitioner,

v.

Halozyme, Inc.,

Patent Owner.

Case PGR2025-00003
U.S. Patent No. 11,952,600

Case PGR2025-00004
U.S. Patent No. 12,018,298

Case PGR2025-00006
U.S. Patent No. 12,152,262

Case PGR2025-00009
U.S. Patent No. 12,123,035

VIDEO DEPOSITION OF GREGORY PETSKO, Ph.D.

Quinn Emanuel

111 Huntington Street, Boston, MA

Thursday, December 4, 2025 - 9:10 a.m.

Stenographically reported by:

Katherine A. Tevnan, MA-CSR/RPR/RMR

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1 I N D E X

2 Deposition of: Direct Cross Redirect Recross

3 GREGORY PETSKO, PhD

4 By Mr. Kushan

5

6 E X H I B I T S

7 Number Description Page

8

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14 *Original exhibits retained by USLegal
15 ** Documents quoted on the record are transcribed as read.
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1 P R O C E E D I N G S
2 THE VIDEOGRAPHER: We are now on the
3 record. Today's date is December 4, 2025, and
4 the time on the monitor is 9:10 a.m.
5 This is the video-recorded deposition of
6 Gregory Petsko. This is being taken in the
7 matter of Merck Sharp & Dohme LLC versus
8 Halozyme, Inc.
9 This proceeding is being held at Quinn
10 Emanuel Urquhart & Sullivan, LLP, 111 Huntington
11 Avenue, in Boston, Massachusetts.
12 My name is Alex Jandrow, and I am a legal
13 videographer on behalf of US Legal Support.
14 The court reporter is Kathy Tevnan.
15 Counsel will introduce themselves for the
16 record, and the witness will be sworn.
17 MR. KUSHAN: Jeff Kushan of Sidley
18 Austin, for the petitioner. With me is Amy
19 Mahan, Ryan Mulligan, Chelsea Himes, and Leif
20 Peterson, from Sidley; and Brian Goldberg from
21 Dechert.
22 MS. MARTIN: Lauren Martin from Quinn
23 Emanuel on behalf of Halozyme. With me I have
24 Elliot Choi, also from Quinn Emanuel; Eldora
25 Ellison from Sterne Kessler, and Josh Mack from

1 Halozyme.
2
3 GREGORY PETSKO, Ph.D.,
4
5 a witness called for examination by counsel for
6 the Petitioner, being first duly sworn, was
7 examined and testified as follows:
8
9 DIRECT EXAMINATION
10 BY MR. KUSHAN:
11 Q. Dr. Petsko, can you state your full name
12 for the record.
13 A. Gregory A. Petsko.
14 Q. And where do you reside?
15 A. Currently at 17 Commonwealth Avenue in
16 Boston.
17 Q. Do you have a work affiliation presently?
18 A. Yes. I am professor of neurology at
19 Harvard Medical School, and also professor of
20 neurology at Brigham and Women's Hospital, which
21 is an affiliated hospital to the medical school.
22 Q. Okay. You have been deposed before,
23 right?
24 A. Yes.
25 Q. Do you know how many times?

1 You can say a lot, that would be fine.
2 A. I -- it's certainly probably at least
3 ten.
4 Q. Okay. Okay.
5 So as you know, in the course of the
6 deposition, I will present questions to you. You
7 can answer my questions. Your counsel may object
8 to the questions. They will be short objections.
9 Unless she's instructed you not to answer for a
10 privilege basis, you have to answer my question.
11 You understand that?
12 A. I do.
13 Q. Okay. If I give you a question and it's
14 imprecise or you don't understand, you just let
15 me know. I will try to give you a better
16 question. Okay?
17 A. Thank you.
18 Q. You understand you are under oath and
19 your testimony today must be truthful, right?
20 A. I do.
21 Q. All right. Is there any reason you
22 cannot testify truthfully today?
23 A. No.
24 Q. Okay. Also, if I need to have a
25 conversation with your counsel I may ask that you

1 step out of the room, but I will try to limit
2 when I need to do that.
3 A. I will limp out of the room, but yes.
4 Q. I will -- and you can wheel out of the
5 room if you like. I am happy -- happy to
6 accommodate you as you need be.
7 When were you first contacted about
8 scheduling this deposition?
9 A. Scheduling of this deposition, probably a
10 few months before the deposition. The time kept
11 changing, but this particular scheduling,
12 probably a few months ago.
13 Q. Okay. And I understand that you just
14 had -- you said you had recent knee surgery?
15 A. Yeah, just a few weeks ago.
16 Q. Okay.
17 A. Total knee replacement. Right knee.
18 Q. All right. So we will make sure we do
19 take breaks every hour at least. If you need to
20 take a break more frequently than that, just let
21 me know.
22 A. Appreciate it.
23 Q. One thing we do want to make sure we do
24 is just the back and forth of questioning, it is
25 always great if you can wait until my question

1 ends before you answer it so that it gets
2 captured accurately in the transcript. Okay?
3 Do you understand that you have provided
4 four declarations in four different proceedings
5 in the patent office that are the subject of the
6 deposition today?
7 A. I do.
8 Q. Okay. And I see you -- are those your
9 four declarations you brought with you?
10 A. They are.
11 Q. Are there any markings or notes in those?
12 A. No.
13 Q. Great. So that will avoid us having to
14 move a lot of paper around. We will just go
15 ahead and use your copies of the depo- -- of the
16 declarations.
17 Because there are four proceedings, I am
18 going to ask that you use the -- what's called
19 Exhibit 2007, which is your declaration in the
20 PGR 2025-00003 proceeding.
21 A. That's the '600 patent.
22 Q. Correct.
23 A. Yes.
24 Q. We can use that for the references today.
25 If there is an answer you would give that's

1 different based on the other three proceedings,
2 please let me know. Otherwise, I will just treat
3 your answer as being applicable to the four
4 declarations. Is that all right?
5 A. Thank you.
6 Q. If you could turn to your declaration in
7 the 003 proceeding. Just go to page 226 and
8 verify that's your signature at the end of the
9 declaration.
10 A. It is.
11 Q. And do you see there's a block of text
12 above your signature?
13 A. Yes.
14 Q. And you understand that's the statement
15 you made about assuring that the testimony is
16 accurate and truthful?
17 A. Yes.
18 Q. And you -- did you carefully review your
19 declaration before you signed the declaration?
20 A. Oh, yes.
21 Q. Okay. Are you aware of any errors in
22 your declarations?
23 A. Not that I'm aware of.
24 Q. Okay. Did you personally draft the
25 declarations?

A. Yes.
Q. You typed it up?
A. No, not all of it.
Q. All right. If you can just describe generally how you went about preparing your declaration, what topics you took up, and how you decided to make decisions about which topics to address.
MS. MARTIN: Objection. It sounds like you're calling for privileged information.
MR. KUSHAN: No. No. I'm just asking for his understanding of what he did.
MS. MARTIN: So counsel -- just caution the witness to not divulge the content of communications with counsel. If you can answer that question without doing so, go ahead.
A. I responded to requests for opinions on various topics.
MR. KUSHAN: Okay. I'm going to introduce something which is a spreadsheet. This is Exhibit 2166.
One thing that happened when we tried to print 2166 is that this column turned dark green and the text was not legible, so we have turned the text white so it's visible.

1 MS. MARTIN: Okay.
2 MR. KUSHAN: This is just the first tab
3 of the spreadsheet. So we're going to introduce
4 this as a new exhibit, if that's all right, 1124.
5 It's the same exhibit as the spreadsheet that we
6 received from counsel.
7 (Exhibit 1124, Spreadsheet, marked for
8 identification.)
9 BY MR. KUSHAN:
10 Q. This was originally -- this is tab -- the
11 first tab of what is Exhibit 2166 in the
12 proceeding.
13 Do you recognize this spreadsheet?
14 A. Yes, I think so.
15 Q. Okay. Great.
16 Did you prepare this spreadsheet?
17 A. Myself directly? No. I don't work with
18 Excel.
19 Q. Okay. So you were given an Excel
20 worksheet, and then you reviewed it?
21 A. Yes.
22 Q. All right. We'll just put that away for
23 a minute, and you can leave it. I just wanted --
24 I just wanted to make sure that you saw this was
25 a new document. I just want to make sure you're

1 comfortable, and it's the exhibit that you are
2 familiar with.
3 A. Yeah. As you say, the print is small,
4 but we'll work with that.
5 Q. Perfect.
6 You understand there are four different
7 patents that are at issue in these four
8 proceedings; is that right?
9 A. I do.
10 Q. Okay. I'm going to introduce these.
11 They're already marked as Exhibit 1001 in each of
12 the four proceedings. I'm going to hand you the
13 '600 patent first.
14 And again, for the same reasons -- for
15 the same reasons about your declarations, we'll
16 use the '600 patent. I'm also going to use
17 another document.
18 This is the '298 patent.
19 This is the '262 patent.
20 A. Thank you.
21 Q. And I'm providing these in case you need
22 to look at any of the different patents. We
23 decided we'll use the '600 patent as the
24 reference point.
25 And this is the '035 patent.

1 Have you reviewed all these patents?
2 A. I've read all those -- all of them.
3 Q. And you understand that the body of
4 patents are the same roughly or mostly and at the
5 very end there are different sets of claims in
6 each patent?
7 A. That is my understanding.
8 Q. Okay. Great.
9 And you know that the four patents have
10 some -- the claims are directed to mutations at
11 particular locations in the PH20 protein. Each
12 patent has a different location that has been
13 focused on in the claims. You understand that?
14 A. Yes, I do.
15 Q. Okay. So for the '600 patent, it's
16 position 320; for the '298 patent, it's position
17 313; for the '262 patent, it's position 317; and
18 for the '035 patent, it's position 312.
19 And these are positions in the mature
20 polypeptide sequence of human PH20. You
21 understand that?
22 A. Yes.
23 Q. I used the word "mature polypeptide." Do
24 you know what that means?
25 A. Yes, I do. I understand the sequence

1 numbering issue.
2 Q. Perfect. It took me a while.
3 All right. Is it fair to say that the
4 declarations you prepared regarding these
5 four patents are expressing the same opinions
6 across the four patents except for any issues
7 specific to those positions that may be raised by
8 each of the four patents?
9 A. Yes, I believe so.
10 Q. Okay. Great.
11 MR. KUSHAN: Let me introduce the last
12 large pile of paper. This is Exhibit 1026. This
13 is U.S. Patent Application No. 13/68 -- 694,731.
14 We'll call that the '731 application.
15 BY MR. KUSHAN:
16 Q. And what I'd like you to do is put that
17 down and go back to the '600 patent.
18 And if you look at the '600 patent, on
19 the second page of the patent, you'll see a text
20 block over here titled "Related U.S. Application
21 Data" (indicating).
22 A. Yes.
23 Q. All right. And if you go to the very
24 bottom of that paragraph, you'll see a reference.
25 It says "which is a division of application

1 No. 13/694,731 filed on Dec. 28, 2012."
2 Do you see that line?
3 A. I do.
4 Q. That's referring to this new Exhibit 1026
5 that I've just handed to you.
6 The 1026 application is the application
7 that was filed with the patent office in December
8 of 2012. It eventually turned into all these
9 different patents.
10 What I'd like you to do today is use the
11 contents of the application, the
12 '731 application, for my questions because it has
13 the common disclosure with all the other patents,
14 and it's an easier thing for me to work with.
15 Okay?
16 All right. If I use the word "common
17 disclosure" today, I'm referring to the shared
18 contents of the '731 application and all these
19 four patents. Okay? Is that -- so when you hear
20 that word, it's just referring to the part of the
21 patents and the application that are in common,
22 which is the bulk of it.
23 A. You're referring to the specification?
24 Q. The specification, the drawings in those
25 documents, those are what I'm referring to as the

1 common disclosure. Okay?
2 I wanted to make sure we all had the same
3 foundation of what I'm referring to so the --
4 hopefully we'll have clearer questions.
5 If you could go to your declaration now,
6 and go to paragraph 24 of your declaration.
7 A. Yes.
8 Q. This is -- you've stated in paragraph 24
9 that you have reviewed documents, references that
10 are listed as exhibits in an exhibit list. And
11 that exhibit list is on page 224 of your
12 declaration. And you can take a look at the
13 exhibit list on page 20 -- 224.
14 A. Yes, I see it.
15 Q. So you reviewed all of those exhibits
16 that are listed?
17 A. Yes, I've looked at all of them.
18 Q. Okay. Were there any other documents or
19 information that you reviewed that are not listed
20 on that exhibit list?
21 A. To the best of my ability, there are not.
22 Q. Did you review the institution decisions
23 from the patent trial and appeal board in these
24 four proceedings?
25 A. Not -- not particularly, no.

1 Q. All right. Did you review a declaration
2 from Dr. Melanie Simpson that was filed in these
3 proceedings?
4 A. I do not believe I've ever seen that
5 declaration. I have seen declarations from
6 Dr. Hecht and Dr. Park.
7 Q. Okay. Have you spoken with Dr. Simpson?
8 A. No.
9 Q. Did you review a declaration from
10 Dr. Gary Cherr?
11 A. Again, I think the answer is no. There's
12 a paper I believe where Dr. Cherr was the first
13 author. That I certainly looked at.
14 Q. Okay. Did you speak with Dr. Cherr?
15 A. No.
16 Q. Have you reviewed a declaration from
17 Dr. James Moon -- Dr. James Moon?
18 A. No.
19 Q. Have you spoken with Dr. Moon?
20 A. No.
21 Q. Have you reviewed transcripts from
22 depositions of Dr. Moon or Dr. Cherr?
23 A. No.
24 Q. Okay. You did review deposition
25 transcripts from Dr. Hecht?

1 A. I reviewed the declaration and also there
2 were transcripts of the depositions.
3 Q. Okay.
4 A. Yes.
5 Q. You're not offering any opinions on any
6 of the statements of -- that have been made by
7 Dr. Simpson, Cherr, or Moon in these proceedings?
8 A. Not as far as I know.
9 Q. Okay. Have you spoken with any
10 scientists from Halozyme?
11 A. No.
12 Q. Have you reviewed any experimental
13 records generated by Halozyme scientists that are
14 not contained in the patents?
15 A. No.
16 Q. All right. So you mentioned you had
17 reviewed the declarations from Dr. Sheldon Park
18 and from Dr. Michael Hecht?
19 A. Yes.
20 Q. And you reviewed the entirety of their
21 declarations?
22 A. Yes.
23 Q. Did you review the appendices that were
24 in Dr. Park's declaration?
25 A. I looked at those. Some of them are

1 common to the appendices in my declaration.
2 That's -- the ones that were different, I did
3 look at them.
4 Q. All right. When you -- so you mentioned
5 you reviewed transcripts. Did you -- from
6 Dr. Hecht and Dr. Park. Did you review the
7 entire transcript, or did you just review
8 particular sections of it?
9 A. As far as I know, I was given the entire
10 transcript, and I read what I was given.
11 Q. Okay. Great.
12 Could you go to page -- page 10 and 11 of
13 your declaration?
14 A. Yes.
15 Q. And there are two paragraphs. Just look
16 at paragraphs 25 and 27.
17 A. Yes.
18 Q. These are paragraphs that are referring
19 to a person of ordinary skill in the art, or
20 something which is abbreviated POSA.
21 Did you use the definition of the POSA
22 that is in your declaration at paragraph 25 in
23 forming your opinions in this proceeding?
24 A. I applied that definition. I was asked
25 to do so.

1 Q. Okay. Great.
2 And do you see that in paragraph 27 there
3 are a few different dates referenced in that
4 paragraph?
5 A. Yes.
6 Q. And is your testimony as to the views of
7 the person of skill in the art the same across
8 that spectrum of time between December of 2011
9 and December of 2012?
10 A. Yes.
11 Q. If any of my questions today -- today
12 raise or cause you to give me a different answer
13 based on a different time point in that spectrum
14 of time just let me know.
15 A. I will ask you one in return.
16 Q. Sure.
17 A. Is the December 28, 2012, date
18 specifically referring to this large document you
19 just handed me?
20 Q. Yes. So that -- so that application was
21 the one that was filed on December 28th of 2012.
22 There were two earlier applications filed in --
23 starting in December of 2011. So I just want to
24 make sure that your -- your answers are
25 addressing that spectrum of time. If there is

1 any difference across that time just let me know.
2 A. I don't believe there will be.
3 Q. Okay. Great.
4 So I am going to go over some terms and
5 concepts we are going to discuss today and make
6 sure we are on the same page as to what they
7 mean. When I say the "wild-type sequence," do
8 you understand that to mean the sequence that
9 occurs naturally in an organism?
10 A. If you use that term generally, yes.
11 Are you also referring to something
12 specific here?
13 Q. Yeah. I will ask, for example, the
14 wild-type sequence of the human PH20 sequence,
15 that will be the sequence that occurs naturally
16 in humans, right?
17 A. Yes.
18 Q. And if it is a wild-type sequence from
19 another species, I would refer to that species.
20 All right? Okay?
21 A. That's fine.
22 Q. And do you understand the patents concern
23 making modifications to the human PH20 wild-type
24 sequence?
25 A. Yes.

1 Q. Okay. Human PH20 catalyzes the
2 hydrolysis of hyaluronic acid, right?
3 A. Also called hyaluronan, yes.
4 Q. It is also called -- sometimes referred
5 to as HA, right?
6 A. Yes.
7 Q. So if I say any of those words we are
8 referring to the same kind -- structure?
9 A. Perhaps we should clarify one thing.
10 Q. Sure.
11 A. HA could also refer to a subunit of the
12 larger polymer. That's used in the literature as
13 well.
14 Q. Okay.
15 A. Typically a disaccharide.
16 Q. So you -- so HA would be a disaccharide
17 or -- or an oligomer?
18 A. It could be the disaccharide, it could be
19 the whole polymer, depending on the context.
20 There's no agreed-upon notation as far as I know.
21 Q. What's the best word for you to refer
22 to --
23 A. I think if we just -- if the -- if it is
24 obvious from the context I'm not worried.
25 Q. Okay.

1 A. If it isn't, I will ask; or you can ask,
2 if it is relevant to you.
3 Q. Perfect.
4 So hyaluronic acid is also called a
5 substrate for the PH20 enzyme, right?
6 A. Yes.
7 Q. On the PH20 protein, there are positions
8 that will bind to the substrate; is that right?
9 A. Yes.
10 Q. And that substrate binding is part of the
11 requirements for the enzyme to catalyze the
12 PH20 -- I'm sorry -- to catalyze the hyaluronic
13 acid; is that right?
14 A. The hydrolysis of hyaluronic acid is what
15 I think you were trying to say.
16 Q. It was. Thank you.
17 A. Okay. Yes.
18 Q. Are you aware of any other functions
19 associated with human PH20?
20 A. Yes.
21 Q. What are they?
22 A. It can also catalyze the hydrolysis of
23 chondroitin, albeit less efficiently.
24 Q. Is there other -- any other functional
25 capability you identified as being associated

1 with human PH20?
2 A. I think I would like a clarification of
3 what you are implying by function. That's a
4 broad term.
5 Q. Yeah, that's always a complicated word,
6 "function."
7 If you look at page 109 of your
8 declaration in paragraph 213?
9 A. Okay.
10 Q. You mentioned that PH20 is possibly
11 involved in interactions with proteins on the
12 surface of an egg. So that would be a binding
13 capability of the protein that would interact
14 with the protein on the egg, right?
15 A. It is a speculative binding capability.
16 I don't know that it's been demonstrated
17 experimentally in vivo.
18 Q. Did you look for any literature that
19 documents the phenomenon of PH20 binding to
20 the -- to a protein on the surface of the egg?
21 A. No.
22 Q. If that was a functional property of the
23 PH20 protein, would you expect that to be
24 associated with a particular region of the
25 protein?

1 A. At least one, but it may be associated
2 with more than one region.
3 Q. All right. Would that require there to
4 be a particular structure on the surface of the
5 protein to cause that binding?
6 A. There would be a binding site, what's
7 called a binding site, which is formed by a
8 particular structure. And there would be one or
9 more than one.
10 Q. Okay. All right. Would a -- and are you
11 aware there are five human hyaluronidase
12 proteins?
13 A. I know that five have been discovered so
14 far.
15 Q. And I'm speaking specifically of the
16 human variants.
17 A. Yes.
18 Q. What's the word you use to refer to human
19 variants of a protein that are from the same
20 family?
21 A. You would -- you would call them paralogs
22 in the genome. You could call them that, but I
23 think if we talk -- talk about them as variant
24 proteins in the same family, that's okay. The
25 complication comes in the use of the word

1 "variant" in genetics also can mean a particular
2 point mutation in the wild-type sequence. But
3 since I think we are talking here about protein
4 mutations more than the gene itself, if we refer
5 to those as mutants then we can use variant the
6 way you've used it. And I -- I think without any
7 ambiguity.
8 Q. Okay. Are the five hyaluronidase
9 proteins homologous proteins?
10 A. So the definition of the word
11 "homologous," should we talk about that?
12 Q. Sure. Go ahead. What's your
13 understanding of the meaning of homologous?
14 A. Homologous means related by divergent
15 evolution from a common ancestor.
16 Q. And based on that terminology, would you
17 consider -- do you believe a POSA would consider
18 the five human hyaluronidase proteins --
19 (Reporter clarification requested.)
20 BY MR. KUSHAN:
21 Q. Based on that clarification, do you
22 believe a POSA would consider the five human
23 hyaluronidase proteins to be homologous proteins?
24 A. Yes.
25 Q. Did you investigate the differences

1 between the human hyaluronidase proteins?
2 A. I did. I looked at the alignment of
3 sequences.
4 Q. Do they have the same C-terminal
5 structures?
6 A. No. They -- they differ.
7 Q. Do they have functional differences?
8 A. Yes. Some do.
9 Q. Are some enzymes in that family not
10 capable of hydrolyzing hyaluronic acid?
11 A. Yes.
12 Q. Do you know the amount of sequence
13 identity between PH20 and the other four?
14 A. Off the top of my head, no; but I seem to
15 recall it is in the 30 to 40 percent range,
16 typically.
17 Q. When you investigated this family of
18 homologous human hyaluronidase proteins, was it
19 important to your decisions in this case that
20 they were homologous proteins but had different
21 structures and different activities?
22 A. I can't agree with the statement you
23 made.
24 Q. What -- what is wrong with my statement?
25 A. The statement "different structures" is

1 too general of a statement. I -- we would need
2 to get more specific.
3 Q. All right. So was it important to your
4 decisions in this case that the five human
5 hyaluronidase proteins have different C-terminal
6 structures?
7 A. Only in one or two occasions. In
8 general, that was not -- that was not -- only on
9 one or two occasions.
10 Q. What were -- what were those occasions
11 that prompted that --
12 A. When -- when we considered issues such
13 as, for example, the EGF domain.
14 Q. So was the EGF domain something that was
15 present in all of those five human hyaluronidase
16 proteins?
17 A. No.
18 Q. No?
19 A. No. Sorry. I'm sorry. You said the
20 correct thing. I misspoke.
21 Q. Okay.
22 A. The human proteins, yes. I was also
23 including bee venom, and I shouldn't have.
24 Q. Is the Hyal-EGF domain present in
25 mammalian proteins -- mammalian hyaluronidase

1 proteins?
2 A. Say that again, please.
3 Q. Sure.
4 Is the Hyal-EGF -- let's make sure we are
5 on the same page. I am referring to this term
6 "Hyal-EGF domain." Do you remember that was the
7 term that I think was referred to in the Chao
8 paper?
9 A. It was.
10 Q. Okay. So the Hyal-EGF domain, is that a
11 domain that's present in mammalian hyaluronidase
12 proteins?
13 A. Yes.
14 Q. Okay. It's in -- it's present in the
15 five human hyaluronidase proteins?
16 A. No. I think there's one that lacks it
17 because it's a truncated protein.
18 Q. Okay. Is the Hyal-EGF domain present in
19 the Hyal-1 and PH20 proteins?
20 A. I think so.
21 Q. All right. So let's go with some really
22 basic concepts. What is the primary structure of
23 a protein?
24 A. It is the amino acid sequence of a
25 protein.

1 Q. What's a polypeptide?
2 A. A polypeptide is a chain of amino acids
3 linked by amide bonds formed between the carboxyl
4 and one amino acid and the amino end of another
5 amino acid. This process is repeated
6 indefinitely to form a longer polymer called a
7 polypeptide.
8 Q. Is there a difference between a
9 polypeptide and a protein in the terminology you
10 use?
11 A. Sometimes. It's a sloppy terminology.
12 So you will sometimes find in the literature
13 people will refer to things of 50 or so amino
14 acids and less in length as a polypeptide rather
15 than a protein.
16 This gets complicated when you're dealing
17 with hormones like insulin, which are right
18 around that number, and which usually gets
19 referred to as a protein. So it is not a
20 hard-and-fast terminology.
21 Q. Do -- do the two terms -- are they used
22 interchangeably?
23 A. Frequently by people. Okay.
24 Q. Would you use the word "polypeptide" to
25 refer to something which has a three-dimensional

1 structure, or would you use a protein term to use
2 that -- to connect that reference to structure?
3 A. Unfortunately, that's also sloppy. You
4 could imagine using polypeptide to refer to
5 something that doesn't have a structure, that's
6 just a linear polymer. But it's not -- it's not
7 established as a term that way. It gets used
8 that way sometimes. Other times, it's simply a
9 synonym for protein.
10 Q. If some of my questions today use the
11 two words "polypeptide" or "protein" in a way
12 that you think has some significance as a
13 difference between the two, just let me know
14 because if -- you'll see there are -- those two
15 words very frequently in the documents.
16 A. Yes. You should do the same if I use
17 them in a way that's not clear. Because as I
18 said, this is sloppy on the part of scientists
19 unfortunately.
20 Q. Okay. What is a protein secondary
21 structure?
22 A. So there are elements of what are called
23 secondary structure that involve hydrogen bond
24 interactions between amino acids in the primary
25 structure.

1 Two of these elements of secondary
2 structure involve hydrogen bonds between residues
3 that are literally next to each other in the
4 sequence. Those are called alpha helices,
5 because of the shape that they make, or beta
6 turns, because of the shape they make.
7 The other kind of secondary structure
8 element is what's called a strand of a beta
9 sheet. And when you have more than one strand,
10 it's called a beta sheet. They can be parallel
11 or antiparallel, and they involve hydrogen bonds
12 between residues that are distant -- more distant
13 from one another in the sequence. They're not
14 consecutive. Okay?
15 Those three elements of structure
16 constitute the well-known secondary structure
17 features of proteins. And most proteins contain
18 a mixture of those, although some are purely
19 helical, for example.
20 Q. And in the protein structure, these
21 secondary structures are interspersed with other
22 sequences which are not as defined or rigid in
23 their structure; is that right?
24 A. Yes. That's exactly the right way to put
25 it. They are loops. We call them often loops.

1 They can of indeterminate length. You can have
2 very large loops. You can have small loops. And
3 those are not classified technically as secondary
4 structure.
5 Q. And then just the last one is: What's
6 the -- what is a protein's tertiary structure?
7 A. So these individual secondary structure
8 elements can be visualized as independent
9 entities. The tertiary structure involves how
10 the protein folds up to bring all of those
11 elements together to make a compact structure.
12 It isn't always globular, but it's more compact
13 than when it's a linear sequence.
14 And the interactions between those
15 elements are what hold the whole globular protein
16 together.
17 Q. So is it fair to say that the tertiary
18 structure is the structure that results from the
19 folding and arrangement and packing of all of
20 these different secondary structures and other
21 unstructured regions of the protein into a final
22 state of a structure?
23 A. To a relatively stable state. You can
24 have situations where there are more than one
25 tertiary structure, depending on conditions.

1 Q. So I'm going to try to say this
2 correctly, but if I said "for a polypeptide to
3 function as a protein," is that a phrase that
4 makes sense to you?
5 A. It does now that we've gone over the
6 terminology, yes.
7 Q. All right. For a polypeptide to function
8 as a protein, it must be able to form a stable
9 tertiary structure under physiological
10 conditions; is that right?
11 A. No. Unfortunately, it's not.
12 Q. Okay. What's wrong with that statement?
13 A. It doesn't apply to all
14 polypeptide/proteins. We now know that there are
15 a number of proteins in virtually all living
16 organisms that are intrinsically disordered.
17 Namely, on a time-average basis, they do
18 not seem to have either any secondary structure
19 or tertiary structure, and yet they exist in the
20 living organism and the organism pres- -- has
21 preserved this over evolution.
22 Q. Is the human PH20 protein a protein that
23 forms a stable tertiary structure under
24 physiological conditions?
25 A. Fortunately, yes.

1 Q. Okay. So that question I asked would be
2 true for human PH20?
3 A. Yes.
4 Q. All right. Is it true that -- and I'll
5 use this for human PH20, since we're speaking of
6 that. Does the naturally occurring -- the
7 naturally occurring human PH20 protein have only
8 a single compact biologically active fold in its
9 native state?
10 A. As far as has been determined, I believe
11 that's true.
12 Q. Okay. And do you agree that a
13 PH20 protein must form a stable tertiary
14 structure or physiological conditions to exhibit
15 enzymatic activity?
16 A. Yeah.
17 (Reporter requested clarification)
18 MR. KUSHAN: Exhibit enzymatic activity.
19 A. Yes. That's generally considered to be a
20 requirement.
21 BY MR. KUSHAN:
22 Q. Do you embrace the principle that
23 structure dictates function in a protein?
24 A. Yes. Again, with some qualifications
25 like those peculiar disordered proteins where you

1 would have to talk about it differently, yes.
2 Q. We've used the word "folding," and I've
3 also seen the word "fold" used as a noun. Is
4 the -- is a protein fold the protein's tertiary
5 structure?
6 A. Usually. Occasionally, it could refer to
7 the secondary structures, but usually that's
8 context obvious.
9 Q. All right. So "fold" could refer to the
10 fold of a discrete domain in a protein structure?
11 A. Yes.
12 Q. Okay. So if I say -- if a scientist uses
13 the word "fold" generally in connection with the
14 protein, that's when they would be referring to
15 the entire tertiary structure?
16 A. Normally, that would be the default
17 interpretation.
18 Q. Okay. So when a protein like PH20 folds,
19 does it proceed through intermediate states or
20 structures before it reaches its final folded
21 tertiary state?
22 A. It's thought to for all proteins that
23 fold, but it has not been determined
24 experimentally for PH20, as far as I know.
25 Q. When -- and just generally for those

1 proteins that do proceed through intermediate
2 states, those are transient states in the process
3 of folding before the protein adopts its final
4 tertiary structure; is that right?
5 A. Under normal physiological conditions,
6 yes.
7 Q. And the intermediate structures or
8 intermediate states have different
9 three-dimensional shapes compared to the final
10 structure?
11 A. It depends on what you mean by different.
12 I like to think of it in terms of altitude. All
13 right? For some of these intermediates, if you
14 looked at them from 1,000 feet, you wouldn't be
15 able to tell that they were different from the
16 final folded protein. But nevertheless, there
17 would be differences, which would be clear if you
18 got closer.
19 For others, even at 1,000 feet of
20 altitude, they don't look like a final folded
21 protein. So there are multiple intermediates,
22 and their difference from the final folded
23 protein is not the same.
24 Q. I'm going to use my hands because
25 sometimes, when we speak of structure, it's hard

1 to do it with words.
2 Is there -- is it -- is it possible that
3 the intermediate states are not as tightly packed
4 as the final protein structure?
5 A. So you're using your hands correctly.
6 Okay?
7 That's -- there is something called a
8 molten globule, which is an intermediate in the
9 folding of many proteins, some people believe
10 nearly all proteins. A molten globule may have
11 most of the same secondary structure elements
12 that the final folded protein has, but they have
13 not yet coalesced into a compact form. Instead,
14 they are like you did with your hands, they are
15 somewhat separated and very loosely interacted.
16 Yes, that is a possible structure of an
17 intermediate in the folding of many proteins.
18 Q. So when you introduced mutations into a
19 naturally occurring protein, does -- can that set
20 of -- or can those mutations cause the protein to
21 misfold relative to the naturally occurring
22 protein?
23 A. Occasionally. Okay. For some mutations.
24 It is usually not the case for most mutation.
25 Q. Do the number of changes that are made to

1 the amino acid sequence effect how frequently
2 those misfolding events occur in the protein?
3 A. It can. It's probably protein dependent.
4 Q. Is it fair to say that even a single
5 amino acid change can prevent a protein like PH20
6 from adopting its normal finally folded state?
7 MS. MARTIN: Object to form.
8 A. It's known for some proteins that there
9 are single amino acid mutations that appear to
10 result in the production of no stably folded
11 protein. Whether that happens by the process you
12 are -- you are trying to indicate is not -- not
13 always clear. It could simply involve the
14 failure of the protein to exit from the
15 endoplasmic reticulum. For example, the protein
16 might still be mostly folded.
17 So the number of mutations that have been
18 made in proteins across the spectrum of proteins
19 that have been mutated where a single point
20 mutation causes the inability of protein to fold
21 at all, that's a pretty small number.
22 Q. Is it possible that a mutation will cause
23 the protein, at least a portion of the protein,
24 to have a different structure relative --
25 different local structure relative to the native

1 protein structure?
2 A. That has happened in some cases. Nearly
3 all of the cases with which I am familiar involve
4 proteins that are flexible, that have multiple
5 domains whose relative arrangements are not
6 terribly tight. That would not be the case for
7 PH20.
8 Q. Can mutations cause proteins to
9 aggregate?
10 A. Yes. Sickle cell hemoglobin is one
11 example.
12 Q. And you study aggregation frequently in
13 your own research; is that right?
14 A. We encounter aggregation in our own
15 research. But yes, we have studied it as well.
16 Q. You are not trying to cause aggregation?
17 A. No. In the case of my work on
18 neurodegenerative diseases like Alzheimer's, we
19 are trying to prevent it.
20 Q. Can aggregation occur during the process
21 of protein folding if there has been a mutation
22 to the protein?
23 A. It can occur even if there hasn't been a
24 mutation in the protein depending on the external
25 conditions. Okay. But usually, that's

1 concentration dependent. And it typically
2 requires nonphysiological concentrations.
3 Q. Can aggregation occur within the cell
4 during transcription/translation?
5 A. Yes. It can. And often, that's the
6 result of overexpression that occurs because of,
7 say, a promoter mutation.
8 Q. Can it occur because a mutation causes a
9 different rate of folding or different pattern of
10 folding inside the cell?
11 A. That will take some -- some discussion if
12 you want a complete answer because the rate and
13 patterns of folding involve rather different
14 things.
15 Proteins have to fold within a defined
16 time period, otherwise a partially folded protein
17 might accidentally get degraded while it hasn't
18 got enough time to complete the folding. There
19 are proteins, for example, that if they -- if
20 they weren't protected from that in some fashion,
21 would literally take minutes to hours to fold --
22 to be synthesized, much less fold. So that's an
23 issue.
24 As far as the pattern of folding is
25 concerned, I think I need to understand what you

1 mean by that word.
2 Q. So when a protein is folding as it's
3 being translated -- maybe we should start with
4 that point. So transcription takes it from DNA
5 to the RNA, then RNA is the translation into the
6 protein sequence where it assembles the amino
7 acid sequence, right? So far so good?
8 A. So far so good.
9 Q. Okay. During the process of translation,
10 is folding beginning as the protein is being
11 translated inside the cell?
12 A. So nobody knows that for sure.
13 Experiments that were done suggest yes. But it
14 is complicated because antibodies were used to
15 detect the folded form of the protein, and the
16 antibody could be inducing the folding. All
17 right. But what evidence there is suggests that
18 the protein probably starts to fold during
19 synthesis.
20 Q. So you have a native protein which has
21 occurred in an organism because it's survived
22 this evolutionary pressure. So that's a stable
23 protein. It is a protein that has persisted over
24 many years and now is -- is something which
25 yields a stable structure in the final folded

1 state. Right?
2 A. Well, stable enough.
3 Q. Stable enough.
4 Well, are proteins inherently unstable?
5 A. They are to some extent because,
6 remember, proteins must turn over. There are
7 only one or two immortal proteins in the human
8 body. All the others must be constantly degraded
9 and resynthesized. And if a protein were as
10 stable as a rock, all right, that frequently
11 would be bad because it would accumulate. In
12 fact, there are mutations that would give you ALS
13 that do exactly that to a protein. They make it
14 far more stable than it should be.
15 Q. So in that process of translation, the
16 native sequence of the protein has survived
17 whatever has happened over eons of time, to
18 survive the process of folding to yield these
19 stable proteins that exist in the native state?
20 A. Yes.
21 Q. Okay. So if you introduce mutations --
22 different amino acids into that sequence, that
23 can alter the rate at which those proteins will
24 fold. Right?
25 A. It can, theoretically.

1 Q. And if that happens, that is something
2 that may cause the protein to either not fold in
3 the time span we referred to earlier that would
4 cause it to be degraded by the cell, right?
5 That's one possibility?
6 A. That's one possibility. It doesn't seem
7 to be the most common thing that can happen.
8 Q. Is there some -- another bad outcome?
9 A. It's hard to know whether you would
10 always call it bad. But the most common result
11 of a mutation that affects what you would call
12 folding affects the stability of the folded
13 protein not the ability of the protein to reach
14 that state. That is, by far, the most common.
15 Q. Okay. Just at a high level, what causes
16 proteins to aggregate?
17 A. So there are a number of factors. One is
18 concentration. All right? Some proteins you can
19 concentrate them until you are blue in the face
20 and they will not aggregate. But other proteins,
21 at certain threshold concentration, may
22 aggregate. And what keeps them from doing so in
23 the cell is that they are at a lower
24 concentration. That's one thing.
25 Another thing is -- I will use again

1 sickle cell hemoglobin as an example. A mutation
2 in the protein might create a patch that didn't
3 exist before that allows the protein to
4 self-associate. And that can form an
5 aggregation. In the case of sickle cell
6 hemoglobin, it forms filaments.
7 Q. So those -- those interactions, those are
8 hydrophobic patches that become exposed on the
9 surface of the protein?
10 A. Or that are created on the surface, yes.
11 Those are the most common ways that you would see
12 that kind of aggregation, would be hydrophobic.
13 Q. And when those interactions occur, those
14 are basically random interactions between the
15 locations on the proteins that are interacting
16 with each other, right?
17 A. No. It can be, but in the case of sickle
18 cell hemoglobin it is an extremely precise
19 interaction.
20 Q. So I was -- so if I -- I am trying to
21 make sure I understand.
22 The hydrophobic patches that may be
23 exposed by a mutation, they can interact with any
24 other hydrophobic patch of another molecule that
25 is in the environment of that protein, right?

1 A. No.
2 Q. No. Okay.
3 A. No. Not with any kind of reasonable
4 affinity. Because there -- you are thinking in
5 terms of the enthalpy of interaction due to a
6 hydrophobic patch. But remember, there is also
7 shape complementary that's important, because you
8 have to exclude water.
9 So only patches that are suitably
10 complementary are likely to form the kind of
11 interaction that would lead to the aggregation
12 you are thinking of.
13 MS. MARTIN: So -- sorry. But we have
14 been going for almost an hour. Greg, do you need
15 a break?
16 THE WITNESS: I am okay for another 20,
17 30 minutes, I think.
18 MR. KUSHAN: All right.
19 MS. MARTIN: All right.
20 THE WITNESS: But then, yes. Thank you.
21 MS. MARTIN: Okay.
22 BY MR. KUSHAN:
23 Q. Do you agree that some amino acid
24 mutations made to a protein can cause that
25 protein to become more prone to aggregation?

A. Yes. That can happen. It is not -- it's not a common consequence.

Q. When you say "common," give me some context for that.

A. If I make, typically, 100 mutations in a protein, okay, one or two might do that. None of them might do that. But it's -- I have never seen a case where 20 or 30 do that.

Q. So you have not seen a case where one or two, maybe just say three, mutations made to the amino acid sequence caused a protein to aggregate?

A. Maybe once.

Q. Is it fair to say that aggregated proteins tend to be degraded by those internal cellular mechanisms more frequently than regular proteins or native proteins?

A. No. That's not a statement that I think you would want to make.

Sometimes the aggregates can be degraded by a process called autophagy, where -- which is a Greek term for self-eating -- where the protein has ways of engulfing those aggregates and digesting them and milyses them.

But in many cases, they can be resistant

1 to digestion and they can accumulate.
2 Q. Is protein aggregation a concern for
3 pharmaceutical development?
4 A. It is, but more commonly for issues of
5 storage and immunogenicity than for efficacy.
6 Usually the proteins that are employed
7 pharmaceutically -- I am thinking of things like
8 antibodies. All right? -- have been carefully
9 developed so that they don't have that kind of
10 problem. But on long-term storage, if the
11 temperature changes or something goes wrong, you
12 can have some misfolding and aggregation. And
13 that can be an issue.
14 Q. And just the phenomenon of aggregation of
15 a protein in solution, you're aware of that,
16 that's the context we just were discussing. Can
17 aggregates form that eventually become
18 particulates?
19 A. Oh, yes. You can get -- you can get
20 turbidity as a way of determining that
21 aggregation has occurred. But you can also have
22 aggregates that are completely soluble.
23 Q. If an enzyme like PH20 started to form
24 aggregates because of mutations, just take that
25 hypothetical, would the -- if it forms

1 aggregates, is the enzyme able to be
2 enzymatically active when it's in the aggregate?
3 A. It could be.
4 Q. Is it possible it might not be?
5 A. That's also possible. It would depend on
6 the nature of the aggregation.
7 MR. KUSHAN: You know, you said you
8 wanted -- you had another 20 minutes in you, but
9 I would actually suggest we take a break now, if
10 that's okay with you.
11 THE WITNESS: It's okay with me.
12 MR. KUSHAN: All right.
13 THE VIDEOGRAPHER: All right. Going off
14 record at 10:04.
15 (Recess taken)
16 THE VIDEOGRAPHER: Back on record at
17 10:20.
18 BY MR. KUSHAN:
19 Q. Dr. Petsko, did you speak with counsel
20 during the break?
21 A. About the case, no.
22 Q. All right. If you can go to your
23 declaration, and go to page 123, paragraph 241.
24 A. Wait a moment. Page 123. What was the
25 paragraph number again?

1 Q. 241.
2 A. Okay.
3 Q. And do you see in paragraph 241 you
4 reproduced claim 1 of the '600 patent?
5 A. Yes.
6 Q. All right. In the first line of the
7 claim, there is -- you see there are the words
8 "modified PH20 polypeptide"?
9 A. Yes.
10 Q. So this claim is directed to modified
11 PH20 polypeptides, right?
12 A. Yes.
13 Q. Okay. And look at the first paragraph
14 under that. That's a paragraph that is requiring
15 the modified PH20 polypeptide to have 95 percent
16 sequence identity with one of a list of
17 referenced sequences, right?
18 A. No. It's at least 95 percent.
19 Q. At least 95. So 95 percent or higher
20 sequence identity?
21 A. Yes.
22 Q. Okay.
23 MS. MARTIN: I'm sorry. Can we go off
24 the record for one second?
25 MR. KUSHAN: Sure.

1 THE VIDEOGRAPHER: All right. Going off
2 record at 10:22.
3 (Recess taken)
4 THE VIDEOGRAPHER: Back on record at
5 10:23.
6 BY MR. KUSHAN:
7 Q. We were just starting to talk about
8 paragraph (a) of the claim, and you've clarified
9 that it specifies that the modified PH20
10 polypeptide has at least 95 percent sequence
11 identity.
12 A. Yes.
13 Q. And those are a sequence identity
14 relative to a number of referenced sequences,
15 right?
16 A. Yes.
17 Q. And do you understand that those
18 sequences are wild-type human PH20 polypeptide
19 sequences?
20 A. Yes.
21 Q. Do you understand that they have varying
22 truncations at the C-terminus?
23 A. Yes.
24 Q. Okay. So they are between 430 residues
25 to 465 residues in length?

A. Yes.
Q. All right. 95 percent sequence identity of a protein between 430 and 465 residues. Have you calculated how -- calculated how many changes that encompasses?
A. Yes. As I recall, it's between like 17 and 23 or 24.
Q. All right. I think for the 95 percent sequence identity to 430 --
A. Oh, sorry. Not for the short one.
Q. I think it's 20 -- I think it's 21 to 23 for 95 percent sequence identity. But that's roughly consistent with your recollection?
A. Yes.
Q. Okay. So the -- according to paragraph (a), that's -- would permit a modified PH20 polypeptide to have up to 21 to 23 changes to it?
A. Yes.
Q. And do you understand those changes can be -- one kind of change could be a substitution of the amino acid?
A. Yes.
Q. Another kind could be a deletion of an amino acid?

1 A. Yes, I think so.
2 Q. And a third kind would be an addition of
3 an amino acid. That would also count as a change
4 that gets calculated as part of the sequence
5 identity?
6 A. If it doesn't cross the threshold.
7 Q. Correct.
8 A. Yes.
9 Q. Okay. So then in paragraphs (b) and (c),
10 those two paragraphs specify that there's a
11 particular substitution at position 320 of the
12 sequence, and then the choices for that
13 substitution are enumerated as four options in
14 this claim in paragraph (c); is that right?
15 A. Yes.
16 Q. All right. So the claim language
17 specifies modified PH20 polypeptides that can
18 have up to 21 to 23 changes and where one of
19 those changes is a change at position 320 to one
20 of four alternative amino acids, right?
21 A. Yes.
22 Q. Is there any language in claim 1 which
23 restricts the positions at which changes can
24 occur, other than position 320?
25 A. Not as far as I know. Well, it does say

1 "to maximize identical residues, and wherein
2 terminal gaps are treated as non-identical," so
3 depending on how you line up the sequences. But
4 basically, yes.
5 Q. So anywhere across the let's say --
6 Sequence ID 3 is a 447 residue protein, right?
7 Do you remember that?
8 A. Yes.
9 Q. Okay. So let's go with Seq ID 3 for a
10 minute. So in Seq ID 3, that means this language
11 in the claim would allow the substitutions to
12 occur at anywhere from position 1 to 447 in the
13 sequence?
14 A. Excluding position 320, yes.
15 Q. Yes. All right. Does any language in
16 the claim restrict what amino acid could be put
17 into the sequence as a substitution of a
18 wild-type sequence -- of a wild-type residue?
19 A. Not as far as I know.
20 Q. And nothing in the claim language
21 prohibits deletions from occurring within the
22 polypeptide sequence?
23 A. Let me look again. I think that's right.
24 Q. Okay. So do you agree that these claims
25 are defining sets of different modified PH20

1 polypeptides?
2 MS. MARTIN: Object to form.
3 A. I wouldn't use the term "sets."
4 Q. What word -- what word would you use?
5 A. I would use -- I would say that this
6 claim defines a genus of proteins.
7 Q. Right. So you're familiar with the
8 terminology of genus and species in the context
9 of patents?
10 A. I've been given the information about
11 that over the years, yes.
12 Q. Okay. So claim 1 is defining a genus of
13 modified poly- -- PH20 polypeptides, right?
14 A. Yes.
15 Q. And one -- and one of those would be a
16 species of modified PH20 polypeptide?
17 A. That's one of the terms that's used.
18 Q. Okay. Great.
19 Do you know how many different species of
20 modified PH20 polypeptides are captured by the
21 language of claim 1?
22 A. I haven't calculated that myself.
23 Q. Are you aware that Dr. Park calculated
24 that number?
25 A. Yes.

1 Q. And you reviewed his declaration?
2 A. Yes.
3 Q. I'm going to hand you Exhibit 1004 from
4 the 0003 proceeding.
5 A. Um-hmm.
6 Q. If I could have you turn to
7 paragraphs 168 to 171, which are towards the back
8 end, about page 90 --
9 A. I'm already there.
10 Q. You're already there. Perfect. Okay.
11 So from 1 -- paragraphs 168 to 171,
12 Dr. Park has outlined how he calculated the
13 number of different polypeptides that are
14 captured by the language of claim 1. Did you
15 find any errors in Dr. Park's calculations?
16 A. No. I didn't attempt to reproduce them
17 though.
18 Q. So would you agree that approximately
19 1.35 times 1066 in different polypeptide sequences
20 would satisfy the parameters that are set forth
21 in claim 1 of the '600 patent?
22 A. I wouldn't disagree.
23 Q. Okay. And if you look at his table on
24 page 96, he has calculated numbers for some of
25 the different parameters where smaller numbers of

1 changes down to 17 were made. And that lower
2 number is 6.14 times 1049 different polypeptide
3 sequences?
4 A. Yes.
5 Q. All right. I may use that number,
6 6.14 times 1049, as an approximation of the scale
7 of this genus; is that fair?
8 A. Sure.
9 Q. So we're in agreement that at least
10 1049 or greater different amino acid sequences
11 would meet the requirements of, one, having
12 95 percent sequence identity to Sequence ID No. 3
13 and, two, including one of the four alternative
14 amino acids at position 320?
15 MS. MARTIN: Object to form.
16 A. Assuming there are no errors in the
17 calculation, that's the number that's given in
18 this table. But I need you to repeat the various
19 criteria that you mentioned, please.
20 BY MR. KUSHAN:
21 Q. Sure.
22 The criteria are that the modified PH20
23 polypeptide sequence has 95 percent sequence
24 identity to Seq ID No. 3, and that it includes
25 one of four alternative amino acids at

1 position 320.
2 And my question was: That's at least
3 1049, and likely greater, as a number?
4 MS. MARTIN: Same objection.
5 A. I can't accept the statement "likely
6 greater." I haven't done the calculation.
7 BY MR. KUSHAN:
8 Q. All right. So if we want to just go
9 back.
10 So if you look at the second row of the
11 table on page 96 from Dr. Park's declaration. So
12 that's assuming that the reference sequences has
13 447 amino acids, which is the length of the Seq
14 ID No. 3, right?
15 A. Yes.
16 Q. All right. And 22 changes reflects
17 95 percent sequence identity of the polypeptide
18 sequence with 447 amino acids?
19 A. Yes, I think that's right.
20 Q. And then you see in the third column,
21 position 320, there are four options as the
22 parameter there?
23 A. Yes.
24 Q. Okay. And so based on those parameters
25 of the 447 amino acid sequence, 95 percent

1 sequence identity, along with 22 changes and four
2 options at position 320, that translates into 1.5
3 times 1063 different polypeptide sequences, right?
4 A. Assuming there are no errors in the
5 calculation. I haven't verified it.
6 Q. Okay. And you don't have a basis for,
7 today, disputing that number as accurate?
8 A. As I said, I don't disagree.
9 Q. Could you go to your declaration again
10 and go to paragraph -- I'm sorry -- page 125,
11 paragraph 244.
12 A. Paragraph?
13 Q. 244?
14 A. Yes.
15 Q. You state in paragraph 244 your opinion
16 that neither claim 1 nor claim 21 expressly refer
17 to any hyaluronidase activity or any required
18 level of activity.
19 In the genus of polypeptides that are
20 defined by claim 1, would you agree that there
21 are enzymatically active, properly folded,
22 modified PH20 polypeptides?
23 A. Yes.
24 Q. Okay. And so some number of those 1049
25 -plus polypeptide sequences will be properly

1 folded PH20 proteins that are enzymatically
2 active?
3 A. Yes.
4 Q. Do you know how many?
5 A. No.
6 Q. Do you have an approximation that you can
7 come up with of how many might be?
8 A. Not an approximation, no.
9 Q. Do you think it's closer to the 1049
10 scale, or some smaller number?
11 A. I think it's a lot of them.
12 Q. What does that mean?
13 A. A large number.
14 Q. Is that, like, 100,000?
15 A. Well, on the scale of 1049, that would not
16 be a large number. I think it's a large number.
17 But I don't know how large.
18 Q. So you have -- you have a perception it's
19 a large number. Can you just put me on --
20 somewhere on that scale of 0 to 1049 --
21 A. No. I don't think that level of
22 speculation is appropriate.
23 Q. Do you agree that there are a large
24 number of polypeptide sequences that are not
25 properly folded within that set of protein

1 sequences?
2 A. Now I feel like asking you what you mean
3 by "a large number." But the answer is: I don't
4 know how large that number is.
5 Q. How would a person of ordinary skill in
6 the art determine what that number is in the
7 2011, 2012 timeframe; of -- of active, properly
8 folded PH20 polypeptides?
9 MS. MARTIN: Object to form.
10 A. A person of ordinary skill in the art
11 wouldn't do that.
12 BY MR. KUSHAN:
13 Q. That's a slightly different answer -- or
14 slightly different question. We will talk -- I
15 think that's a question you address in your
16 declaration about whether someone would go down
17 that path. I just want to have a starting point
18 here of understanding.
19 If someone were asked in 2011 or 2012 and
20 they were a person of ordinary skill in the art,
21 and they were asked to determine the number of
22 PH20 polypeptides in that genus of claim 1, that
23 were properly folded and enzymatically active,
24 how would they go about doing that?
25 MS. MARTIN: Object to form.

1 A. They wouldn't even go about doing that.
2 BY MR. KUSHAN:
3 Q. Can you -- again, my question is, I am
4 asking that person to do that. And I am asking
5 you to tell me how they would do that.
6 A. What I'm saying is that would be their
7 answer. They would say, I am not -- I won't do
8 that because there isn't a simple way to do that.
9 Q. Is it possible to calculate that number,
10 in 2011, 2012?
11 A. I don't believe so.
12 Q. Is it possible to experimentally
13 determine which ones are properly folded and
14 enzymatically active in 2011 or 2012?
15 MS. MARTIN: Object to form.
16 A. Not from experimenting on the entire
17 ensemble.
18 BY MR. KUSHAN:
19 Q. Could you go to page 188, paragraph 390,
20 of your declaration.
21 A. Page 188?
22 Q. Yes.
23 A. Yes. Which paragraph?
24 Q. 390.
25 A. Yes.

1 Q. So at paragraph 390, you state your
2 opinion that: "POSAs understand that the set of
3 claim modified PH20 polypeptides that satisfy the
4 claims share many common structural features."
5 A. Um-hmm.
6 Q. Then if I could have you, the next
7 paragraph, paragraph 391. You say there that the
8 claimed modified PH20 polypeptides that fold are
9 a limited set of structurally homogeneous
10 proteins.
11 A. Yes.
12 Q. So you're explaining in these two
13 paragraphs that within -- or that claim 1 is
14 directed to a set of modified PH20 polypeptides
15 that are -- have particular structural features,
16 right?
17 A. They have structural features in common.
18 Q. Structural features in common.
19 Can you list for me what the common
20 structural features are of that set?
21 A. So every protein in that set, every
22 protein in that set will contain an amino acid
23 sequence that is at least 95 percent identical to
24 the amino acid sequence of one of the reference
25 proteins referred to in the claims. All right?

1 That's a common structural feature. It limits
2 the space that those, that that sequence, that
3 the proteins can have.
4 Q. Is that the only common structural
5 feature?
6 A. That is the structural feature that is
7 most common to all of them. They have additional
8 ones that is common -- there's another one that's
9 common to all of them. They will all have a
10 particular amino acid substations at residue 320,
11 which is one of only three residues. That's
12 another common structural feature.
13 Q. Are there other common structural
14 features shared by this set?
15 A. Those are the two that are most common
16 to -- that are common to all the members of the
17 set.
18 Q. If you could go to paragraph 395 of your
19 declaration.
20 A. Um-hmm.
21 Q. That's on page 190.
22 A. Um-hmm.
23 Q. Is one of the common structural features
24 of the claimed modified polypeptides the set of
25 critical residues that enable them to fold and

1 function that are conserved?
2 A. Not all of the sequences in this genus
3 will have all of those residues. But most, many
4 of them, most of them will. And those will share
5 that common feature. Those that do.
6 Q. So these are, these are the conserve
7 residues in, that you might see in an alignment
8 of homologous PH20 polypeptides, right?
9 A. Yes.
10 Q. Sometimes those are called invariant
11 residues because they don't change in the
12 position as to the identity of the amino acid
13 among the homologous proteins, right?
14 A. Yes, that's how they are referred to
15 frequently.
16 Q. Would you also refer to them as essential
17 residues?
18 A. No. That would usually involve a bit
19 more discussion. You would refer to them as a
20 variant or sometimes conserved.
21 Q. Are those conserved or invariant residues
22 essential to form the structure of the fold of
23 the protein?
24 A. Many of them will be.
25 Q. Are some of those conserved residues

1 essential for the protein to exhibit its
2 enzymatic activity?
3 A. Some will be.
4 Q. If you can look at paragraph 396.
5 A. Yes.
6 Q. Once you've looked at that, is another
7 common structural feature of the claimed modified
8 polypeptides that they all have the same
9 alpha-beta barrel fold?
10 A. No. You don't know that for certain.
11 But you do know that a vast number of them will
12 have the alpha -- that alpha-beta barrel fold
13 because of the requirement of 95 percent sequence
14 identity with proteins that do have the -- that
15 alpha-beta barrel fold.
16 Q. Are you speaking of the alpha-beta fold
17 that is the one observed in the human PH20
18 protein?
19 A. I'm speaking of that specific alpha-beta
20 barrel fold. It's a subset of a common
21 alpha-beta barrel super family.
22 Q. All right. And just so I'm -- I make
23 sure I am clear about this in my own mind.
24 Is the alpha-beta barrel fold of the
25 human PH20 polypeptide, is that also called the

1 tertiary structure of the human PH20 polypeptide?
2 A. It's part of the tertiary structure
3 because there are other elements in the protein
4 besides that particular subdomain, if you will.
5 But yes, it is part of the tertiary structure.
6 Q. So is it fair to say that -- that a
7 portion of the amino acid sequence of the human
8 PH20 polypeptide is responsible for creating the
9 alpha-beta barrel fold in the PH20 protein?
10 A. I wouldn't use that terminology, no.
11 Q. How would you explain the relationship
12 between the part of the sequence in the part that
13 causes the folded protein?
14 A. You used the phrase "responsible for
15 creating." That's an active verb.
16 Q. Right.
17 A. Okay? I would say that there was a
18 particular sequence in the complete sequence of
19 the protein that is -- what's the exact word I
20 want to use? -- that is contained within the
21 alpha-beta barrel fold. Okay?
22 The way you phrased it, it implied a
23 mechanism, and I don't think we want to do that.
24 Q. The amino acid sequence, the primary
25 structure of a protein, will dictate the ultimate

1 tertiary structure of the protein, right?
2 A. Under most circumstance, yes.
3 Q. So when you're referring to the
4 relationship between the amino acid sequence and
5 the alpha-beta barrel fold of PH20, is it fair to
6 say that the amino acid sequence in its entirety
7 is going to be responsible for creating the
8 tertiary structure that represents that
9 alpha-beta barrel fold of PH20?
10 A. The amino acid sequence of the protein in
11 its entirety, okay, is responsible for the
12 entirety of the tertiary structure. Within that,
13 there is a set of residues that is compatible
14 with an alpha-beta barrel fold and adopts that
15 fold. Okay.
16 Q. All right. If you look at paragraph 400
17 of your declaration, and you can look at
18 paragraph -- pages 191 to 192.
19 A. Yup.
20 Q. So you have an observation that you've --
21 illustrating the alpha -- common alpha-beta
22 barrel fold as wild-type PH20.
23 Just a clarification, when you're saying
24 wild-type PH20 there, you're referring to
25 wild-type human PH20, right?

A. Yes.

Q. Okay. So these are four structures that share the alpha-beta barrel fold that you're illustrating on page 192, right?

A. Yes.

Q. And is there a portion of those structures that you've illustrated which is not the entire protein that is -- that is the alpha-beta barrel fold, or is the entire protein structure the alpha-beta barrel fold?

A. No. A large portion of the protein is the -- is the alpha-beta barrel fold, but there are other parts that are not part of that, strictly speaking.

So if you look at the first figure, you're looking down the mouth of the barrel in that hole in the center that looks a bit like the hole in a donut. All right? You're looking into the mouth of the barrel. In fact, you're looking from the end terminal side -- from the C-terminal side of the barrel. Okay.

The helices that are immediately around those beta strands are part of the alpha-beta barrel fold. But some of the longer ones, like, for example, to the far left, there's a very long

1 helix that's going at a slant, that would be an
2 additional tertiary structure component that
3 isn't necessarily part of the alpha-beta barrel
4 per se. The alpha-beta barrel fold can
5 accommodate a lot of things around it, and
6 inserted into it, in some cases.
7 Q. So when you refer to the common
8 structural features of the claimed modified PH20
9 polypeptides -- and you can go back to --
10 A. Um-hmm.
11 Q. -- paragraph 396, if you wish.
12 A. Yes.
13 Q. -- you say one of the common structural
14 features is this alpha-beta barrel fold, right?
15 A. Yes.
16 Q. And is that shared by all of the mem- --
17 species in the genus?
18 A. It's shared by all of the species in the
19 genus that give a stable protein fold.
20 Q. Is it possible to know which portion of
21 the genus will produce that stable fold that
22 gives rise to that structure?
23 MS. MARTIN: Object to form.
24 A. If you look at the sequences, you can
25 tell whether or not you have significant changes

1 in the residues that make up the alpha-beta
2 barrel fold, and that will give you a way of
3 predicting whether or not that fold is likely to
4 be preserved in that particular variant.
5 BY MR. KUSHAN:
6 Q. Are those residues you just referred to
7 the set of the variant residues that are shared
8 by PH20 proteins that are homologous to each
9 other?
10 A. Oh, those are some, but there are many
11 others that will accommodate -- can be
12 accommodated in this fold. It is a very tolerant
13 fold.
14 Q. Did you -- okay. I'm just trying to
15 understand.
16 How would a person of skill in the art
17 looking at the information in the '600 patent or
18 the common disclosure know which positions are
19 necessary for creating the alpha-beta barrel
20 fold?
21 A. Well, again, I'm not comfortable with
22 some of the words you're using. I wouldn't say
23 "creating," for example.
24 If you want to -- if you want to know
25 whether a particular sequence is compatible with

1 the alpha-beta barrel fold, you could do that
2 relatively easily, both in terms of a multiple
3 sequence alignment, to show you what might be
4 still possible, but you can also, and it's the
5 first thing I would do, is look at the data in
6 the patent to see if those particular sequence
7 changes have been explored for those residues and
8 if those residues retained -- if those sequences
9 retained activity. All right? So that's --
10 that's one of the first things you would do.
11 But you also know that very few protein
12 folds have been studied as extensively as this
13 one. All right? And so there is a wide amount
14 of information available about the tolerance of a
15 fold like this for sub- -- amino acid
16 substitutions. You can also draw on that
17 previous information.
18 Q. So if I'm looking to identify a set of
19 positions in the PH20 polypeptide sequence
20 that -- I'm going to use the word "enable the
21 sequence to adopt."
22 A. That will do.
23 Q. Okay. So if I'm looking for the
24 positions that will enable the modified PH20
25 polypeptide sequence to adopt the alpha-beta

1 barrel fold, has the patent identified which
2 positions will cause the sequence to do that?
3 A. The pat- -- the patent has identified a
4 large number of those positions, yes.
5 Q. And how does it -- what part of the
6 patent is doing that?
7 A. The part where you look at whether or not
8 a substi- -- a set of substitutions where it
9 retains activity. All right? "Activity" in this
10 case is a proxy for forming a proper fold. All
11 right? You can't have activity without the
12 proper fold.
13 So if you look at that, you can say this
14 position, for example, is completely tolerant.
15 All 15 substitutions that were tried still
16 retained activity. That will tell you that that
17 particular position can be substituted more or
18 less whenever you want. Another position might
19 be completely intolerant. That will tell you
20 something as well.
21 You know how those positions map onto the
22 alpha-beta barrel fold because you have the
23 homology model of the PH20 structure.
24 Q. So let me parse those points a bit.
25 So one thing you mentioned was that the

1 proteins that have retained activity, those are
2 the proteins that you can say have adopted the
3 alpha-beta barrel fold?
4 A. You would be comfortable saying that,
5 right.
6 Q. For a protein that is not active, can you
7 assume that the protein has adopted an alpha-beta
8 barrel fold?
9 A. In some cases, you can assume it probably
10 has if those are, for example, substitutions
11 directly at the catalytic site. In other cases,
12 you may not be able to be as sure.
13 Q. So unless it's a mutation that has been
14 identified at a position that's responsible for
15 the catalysis of hyaluronic acid, there's a
16 question mark that would exist in your mind as to
17 whether that mutation -- that mutated protein has
18 properly folded?
19 MS. MARTIN: Object to form.
20 A. I wouldn't phrase it in terms of a
21 question mark.
22 Q. Right.
23 A. I would say your prediction might have a
24 different degree of confidence, but you would
25 still in most cases, given the data in the

1 patent, be able to make the prediction with some
2 level of confidence.
3 Q. So let me give you a better question
4 because I think the last one I asked was not a
5 good question, not well formed.
6 So what I'm asking is, in the previous
7 question and your previous answer, you had
8 indicated that there is a set of positions in the
9 protein that you would be able to have a higher
10 confidence that that mutant with that change at
11 that position would be folded because it was a
12 position involved in catalysis, right?
13 A. No, not exactly.
14 Q. All right.
15 A. What I've tried to say was, there are a
16 set of positions of -- that occur within the
17 alpha-beta barrel fold itself, and those
18 positions, if they retained activity, immediately
19 tell you that the fold must still be essentially
20 intact. All right? But that doesn't necessarily
21 mean those residues are directly involved in
22 catalysis. They're reporting on the structure in
23 that case. Okay? Some may be directly involved
24 in catalysis. Most will not be.
25 The structure function relationship is --

1 enables you to go beyond just the question of
2 chemical capability.
3 Q. Can I have you go to page 17 and
4 paragraph 51 of your declaration.
5 A. Yup.
6 Q. So you say in paragraph 51, "The POSA
7 would have understood that properly folded PH20s
8 adopt the same tertiary structure-an alpha-beta
9 barrel fold."
10 And then you say, "The claimed modified
11 PH20s," the -- "that fold" in parenthesis, "thus
12 share this fundamental common structure," and
13 then in paren, "the PH20 alpha-beta barrel fold."
14 So in one of your previous answers, you
15 confirmed that when you use a phrase like "the
16 PH20 alpha-beta barrel fold," that's the one in
17 the tertiary structure of the human PH20 protein,
18 right?
19 A. Yes.
20 Q. And then you are saying that there is a
21 subset of proteins within the genus that will
22 fold to have that structure, right?
23 A. I'm saying that many of the pro- -- the
24 sequences in the genus will fold, and when they
25 fold, they will have that structure. Okay.

1 Q. Do you believe that most of the
2 PH20 mutants that were tested and classified as
3 inactive mutants in the patent have properly
4 folded to possess the alpha-beta barrel fold?
5 A. I can't give you a relative estimate.
6 What I can say is, from years of experience in
7 mutating enzymes and looking at them, just
8 because a mutation has no activity or low
9 activity doesn't mean it has disrupted the fold.
10 Q. It may have a mutation that induces
11 aggregation, for example?
12 A. Yes. Although, that you can probably --
13 you know, you may be able to make a guess about
14 that.
15 But the most common things are more
16 complicated and more subtle. They involve, for
17 example, action at a distance. You could have a
18 mutation that changes the electrostatic potential
19 of the protein at the active site even though
20 it's not in the active site, for example. But it
21 would still have exactly the same fold. We see
22 that sort of thing often.
23 Q. Are there sets of changes that might be
24 made that could induce a change in the structure
25 of the protein to prevent it from having the same

1 alpha-beta barrel fold as in the PH20 native
2 protein?
3 A. I think that would be very difficult for
4 this family of proteins. Okay.
5 Q. So if I put a -- took a stretch of
6 50 amino acids within a region that has one of
7 the alpha helices and I changed 15 amino acids --
8 A. Change how much?
9 Q. Changed 15 amino acids with --
10 A. 1-5 or 5-O?
11 Q. -- 1-5 within the 5 --
12 A. Um-hmm.
13 Q. -- within the 5-0 length of the alpha
14 helical structure, is that a scenario that could
15 disrupt the alpha helix structure?
16 A. It could, but you would probably be able
17 to assess that from the nature of the changes.
18 Q. If it did disrupt the alpha helical
19 structure, could that disrupt the alpha-beta
20 barrel fold?
21 A. Maybe, maybe not. So remember when we
22 looked at the picture of the structure, one of
23 the things we noted was that there were other
24 helices that were not directly part of the
25 alpha-beta barrel fold.

1 Could you have a scenario where you might
2 partially disrupt one of those helices while
3 retaining the alpha-beta barrel fold, which is
4 where the activity is primarily localized? Yes,
5 you can absolutely imagine that.
6 Q. Is the -- is it possible to know, without
7 actually making that mutation that I just
8 described, whether it will properly fold or not
9 properly fold?
10 MS. MARTIN: Object to form.
11 A. It's possible to predict with a very high
12 degree of confidence for many mutations whether
13 they will do that.
14 BY MR. KUSHAN:
15 Q. In the one that I was just describing
16 that had the consequence of disrupting one of the
17 alpha helices involved in the alpha-beta barrel
18 fold, could you predict for that example whether
19 that disruption would prevent folding of that
20 mutant?
21 MS. MARTIN: Object to form.
22 A. Quite possibly. Depending on where in
23 the structure the -- that helix was and how it
24 was likely to be disrupted, yes, you would have a
25 chance to do that.

1 BY MR. KUSHAN:
2 Q. And you would know what percentage
3 confidence that you have about that prediction?
4 A. I wouldn't quantify it in terms of an
5 absolute percentage. I think you could say
6 whether it was more likely than not or more
7 highly likely than not. I think you could make
8 statements like that in many cases.
9 Q. Is it your view that --
10 A. Sorry. I wanted to add one thing.
11 Q. Sure.
12 A. Which is, what part of the reason for
13 that confluence in the data in the patent which
14 allows you to understand the structure function
15 relationship for this protein at a level that's
16 much higher than that for most proteins.
17 Q. Is the dataset that you refer to in the
18 patent, does that dataset include mutants that
19 incorporated more than one amino acid change in
20 them?
21 A. There were a few of those.
22 Q. Were those the ones that related to the
23 glucosylation sites of the protein?
24 A. Those, certainly.
25 Q. Were there other changes -- any other

1 examples of modified PH20 polypeptide that had
2 more than one substitution?
3 A. Modified in terms of the experiments in
4 the patent, or modified in terms of looking at
5 sequences of other P- -- other PH20-related
6 enzymes?
7 Q. For the former.
8 A. I don't think so.
9 Q. So that dataset, that was the basis of
10 your -- call it a tolerance assessment, that
11 dataset consists of modified PH20 polypeptides
12 that have one amino acid change?
13 A. That's one of the datasets in the patent.
14 But remember, there are also sequences of related
15 PH20s from other organisms. That's additional
16 information.
17 Q. And the other sequences from other
18 organisms, those are all naturally occurring PH20
19 polypeptides?
20 A. As far as I know.
21 Q. Okay. Is there experimental
22 characterization of the enzymatic activity of
23 those proteins in the -- or the common
24 disclosure?
25 A. Not as far as I know.

1 Q. So those -- those proteins, those other
2 nonhuman PH20 proteins that were referenced, that
3 you are -- you are using those as examples of
4 polypeptide sequences that are different than the
5 human polypeptide sequence that folded to
6 proteins that exhibit PH20 activity?
7 A. Yes. My shorthand would be nature's
8 experiments.
9 Q. Got it.
10 Do you know how many of those nonhuman,
11 naturally occurring proteins fall within the
12 scope of the claims?
13 A. In the total ensemble of known sequences,
14 no. For the ones that are mentioned in the
15 patent, like the gibbon and so forth, those all
16 fall within the scope of the claims except for
17 the residue 320.
18 Q. Is it correct that there is three of
19 those sequences that fall within the scope of the
20 claim?
21 A. I think there were at least three, yeah.
22 Q. You have the chimp, gibbon, and --
23 A. Orangutan.
24 Q. -- orangutan? Yes.
25 A. Yeah, those are the ones I remember, but

1 I'm trying to remember if there was another one,
2 but those are the ones I remember. You asked me,
3 I think, if they were active.
4 Q. Let's -- let's take it in two steps. So
5 one question was just whether the -- the genus of
6 modified PH20 polypeptides, that very large
7 genus, most of those you believe will fold into a
8 protein that will adopt the alpha-beta barrel
9 fold of the human PH20 protein?
10 A. That is my prediction.
11 Q. That prediction is based on the naturally
12 occurring PH20 proteins from other species in
13 combination with the -- the data from the
14 mutagenesis library of single mutants in the
15 common disclosure?
16 A. Plus my understanding of the properties
17 of the alpha-beta barrel fold. Which, as you
18 know, go back a long way.
19 Q. And we use these words like "most," but
20 we still don't know what that number mean -- what
21 that means as a number or percentage of the genus
22 size, right?
23 A. I am not trying to calculate an exact
24 number.
25 Q. And you can't give the proportion of the

genus either, right?

MS. MARTIN: Object to form.

A. I don't know what you mean by "proportion" anyway. I mean...

BY MR. KUSHAN:

Q. I am just struggling with you -- you are comfortable saying "most will." And that most is referring to the set of species within the genus of the claim. I am just trying to understand what proportion of the genus size you are saying means most will fold to adopt the PH20 structure.

A. More than one.

Q. More than 50 percent?

A. Yes. But I'm not -- 51? 90? I don't know. But I think it's -- I think it is a big number. That's my prediction.

Q. So if you could go to page 54, and look at -- there is actually a footnote on page 54. Footnote 12.

A. There is actually a what -- a footnote, yes.

Q. Yes.

This is where you say: "When I say 'enzymatically active' in this context, I am not referring to a specific level of enzymatic

1 activity. Rather, I am using enzymatic activity
2 as a proxy for a properly folded protein."
3 So that first point sounds like something
4 you mentioned earlier where if you saw that a
5 mutant was active, you had -- you would infer
6 that it has properly folded?
7 A. Yes.
8 Q. Okay. And the other point you make in
9 Footnote 12 is that: "Secretion is another proxy
10 that could be used for a properly folded protein;
11 proteins that do not fold will not generally" --
12 "generally will not be secreted."
13 Right?
14 A. Yes.
15 Q. So if a protein fails to secrete, you
16 would infer that protein was not properly folded?
17 A. No. There are other reasons why it might
18 not secrete.
19 Q. So --
20 A. But if it does secrete, I would infer
21 that it was probably properly folded.
22 Q. If it secreted and showed no activity,
23 would you assume it is properly folded?
24 A. Yes, it still could be.
25 Q. What would cause it to not exhibit

1 activity after it had been secreted?
2 A. Mutation at the active site residue would
3 do it every time.
4 Q. Would a -- is it also possible that the
5 protein had a mutation that caused it to not
6 remain stable and unfold once it's in -- outside
7 of the cell?
8 A. So -- okay. The extracellular
9 environment is harsh. That's one reason this
10 protein has disulfide bridges. So mutations in
11 the disulfide bridges could, in fact, have the
12 effect that you are talking about. And you could
13 still retain a large part of the fold but it
14 would not be as precise as you would want -- as
15 it would need to be to have activity outside the
16 cell. You could imagine things like that.
17 There is a vast difference in the --
18 what's the word I want to use? -- insults that a
19 protein must suffer on the outside of the cell
20 versus the more protective environment inside the
21 cell. So when you are dealing with a secreted
22 protein, one of the things you usually find is
23 that that protein is stable, has evolved to be
24 stable; and therefore, has evolved to be fairly
25 tolerant of things that can happen to it and

1 retain its stabi- -- it's fold because it needs
2 to be.
3 Q. So if I -- if I understand you, there is
4 one kind of mutation that you can rationalize as
5 explaining the lack of activity of a secreted,
6 mutated PH20 polypeptide, and that is one which
7 affects the -- one of those residues involved in
8 catalysis or hydrolysis?
9 A. That's one of the mutations I can
10 envision. There are others.
11 Q. And the -- the other, I think, we talked
12 about it earlier, mutations that were made to the
13 invariant residues of the protein that are found
14 across the homologous protein set?
15 A. That's another.
16 Q. Okay. The other category, I think, were
17 residues that you indicated a person wouldn't
18 understand or associated with the alpha-beta
19 barrel fold structure?
20 A. That's third. But there are others.
21 Q. What are -- what are other ones?
22 A. For example, I mentioned earlier
23 long-range interactions. Usually of the
24 electrostatic type. Those are often -- it is
25 often possible to determine that that's likely

1 what happened by the nature of a substitution in
2 its location.
3 Q. And the disruption of that long-range
4 electrostatic interaction would cause the protein
5 to no longer adopt the PH20 alpha-beta barrel
6 fold?
7 A. Quite the opposite.
8 Q. Quite the opposite.
9 A. We'd still have the alpha-beta barrel
10 fold, but it would have an effect at the active
11 site that would perturb it's catalytic activity
12 without directly modifying the amino acids in the
13 active site.
14 Q. So that scenario is one where the spatial
15 positioning of the atoms that are involved in
16 hydrolysis in the catalysis activity of the
17 protein have shifted somehow so --
18 A. No. That's yet another category, which
19 we can talk about. No, it's actually more a
20 question of the chemical nature of the residue.
21 So for example, there is a glutamic acid residue
22 in the active site as of hyaluronic base. It
23 must be able to donate a proton to the substrate
24 in the catalytic mechanism.
25 That requires that it's pKa be

1 appropriate with respect to the environment.
2 Let's say, the extracellular environment of pH
3 7.4. All right? That glutamic acid must have a
4 pKa that would allow it to function as a proton
5 donor at pH 7.4. You could have a change distant
6 from that site that perturbs the electrostatic
7 environment of the glutamic acid such that its
8 position would be the same. Okay? The residues
9 around it would be the same. But the local --
10 there would be a kind of local pH effect, all
11 right, that would alter the ability of that
12 glutamic acid to donate a proton. There are many
13 examples of things like this in enzymology. All
14 right.
15 And the other you mentioned was changing
16 the position of the substrate in the active site.
17 For an enzyme like this that has a polymeric
18 substrate, yes, that's easily possible. All
19 right. If you have the polymers bound in more
20 than one place on the enzyme you could have
21 mutations at one of those other sites that shifts
22 the position of the polymer in the active site
23 slightly, and it wouldn't take much. And yet,
24 the alpha-beta barrel fold is perfectly
25 preserved.

1 Q. So is -- just so I am clear, the -- the
2 alpha-beta barrel fold structure does not
3 include, in your mind, these variations in the
4 structure of the protein that may affect the
5 enzymatic activity of the protein or ligand
6 binding or substrate binding?
7 A. It certainly includes them in the sense
8 that the alpha-beta barrel is still there.
9 Q. That was a bad question.
10 I am trying to --
11 A. Is that because it was a good answer?
12 Q. No, it was --
13 A. Okay.
14 Q. -- because it was a bad question. It was
15 an imprecise question.
16 A. All right.
17 Q. The -- the point I am trying to
18 understand is these changes that cause a loss of
19 activity, they have -- if you positioned that
20 changed protein, that mutated protein, and
21 overlaid it on the structure of the human PH20
22 protein, is it likely that individual residues
23 have shifted in the spatial positioning of them
24 relative to the native protein?
25 A. Maybe a few, but not many. And the

alpha-beta barrel might be completely superimposed.

Q. All right. And there's other possibilities where it has shifted, right?

A. Yes. Although, again, given the stability of this fold and its tolerance, big shifts are not likely.

Q. Is there a magnitude of a spatial position in shift that would be accommodated as being the same alpha-beta -- beta fold structure, in your mind?

A. Probably for different people it would look different. Again, I -- I'm going to go back to my altitude thing.

Q. Right.

A. It depends on what altitude you're going to look at the alpha-beta barrel fold then. If you're looking at it from a couple hundred miles up, the likelihood is you're not going to be able to tell any differences.

If you get down within a few feet, maybe you'd see that this residue has moved a little bit and that that residue was moved a little bit. What you -- what -- or you may not, you may not see anything at all.

1 Q. So is it your view that the set of
2 proteins within this genus that constitute the
3 alpha-beta-barrel-fold-possessing species, they
4 can accommodate variations in the structure
5 relative to the native PH20 tertiary structure
6 but would still retain something you would
7 describe as an alpha-beta barrel fold structure?
8 A. The way I would phrase it is that the
9 common structural feature is one of the things
10 that is most likely to be preserved throughout
11 this genus and that the common -- specifically,
12 the common structural feature of the alpha-beta
13 barrel part of the fold.
14 Q. When you reviewed the common disclosure,
15 did you see a description of the PH20 polypeptides
16 that used alpha-beta barrel fold to describe it?
17 A. Not in the -- I looked at this actually.
18 Not in the text of the specification, but the
19 structure of the bee venom hyaluronidase was
20 referenced in the patent application.
21 Q. Do -- do you recall if you saw the words
22 "alpha-beta barrel fold" in the comment section?
23 A. I don't recall whether they were or not.
24 MS. MARTIN: So we've been going for
25 about another hour. Greg, do you want another

1 break?
2 THE WITNESS: Let's do 10 to 15 more
3 minutes, then we'll break.
4 MS. MARTIN: Okay.
5 THE WITNESS: Unless other people need it.
6 MR. KUSHAN: Let me ask maybe just one or
7 two questions, then we'll take a break. Maybe
8 five minutes.
9 THE WITNESS: Fine with me.
10 MS. MARTIN: Okay.
11 BY MR. KUSHAN:
12 Q. So we talked before about protein --
13 cells can degrade proteins that have misfolded,
14 right?
15 A. Sometimes.
16 Q. All right. But there's like -- there's
17 a -- I've heard the word "garbage collection
18 pathways" or "protein degradation pathways" in
19 this --
20 (Simultaneous crosstalk)
21 A. "Trash compactor" has been used as well.
22 Yeah. So it -- but it depends on the --
23 on what's happened to the protein. Right? And
24 what protein it is.
25 So there are proteins that misfold that

1 you can't get rid of, and there are other
2 proteins that misfold that you can get rid of
3 like that (indicating). And it depends on the
4 molecule, and it -- sometimes it can even depend
5 on the organism.
6 Q. Is one of the reasons they get degraded
7 that they're misfolded, the proteins?
8 A. Yes, that's one of the reasons.
9 Q. Is it a common reason they get degraded?
10 A. I -- yeah, probably.
11 Q. Have you heard the term "intrinsic
12 stability" be used in connection with protein
13 structure?
14 A. Yes.
15 Q. What does that mean?
16 A. Well, it -- it's another one of these
17 somewhat sloppy terms in that it can be context
18 dependent.
19 For some people, it means the ability of
20 a protein that you've made and purified to
21 withstand some denaturing conditions in a test
22 tube. For other people, it means the property of
23 the protein in the cell to withstand stress
24 conditions and so forth. And for yet other
25 people, it may mean the protein being in an

1 organism that is itself able to withstand say
2 extreme temperatures.
3 So it's -- it's -- you've got to be
4 precise if you use it.
5 Q. So that term kind of across all three of
6 these meanings is referring to the -- kind of the
7 energy state of the protein confirmation and it
8 being in an energy state that permits it to stay
9 folded as opposed to pushing it over to become
10 unfolded; is that what --
11 A. I hope you mean free energy.
12 Q. Free energy, yes, that's exactly what I
13 mean.
14 A. Okay. Because if you meant other, it's
15 not true.
16 Q. Correct. So let's recast that question
17 to be in the context of free energy.
18 Is the protein's intrinsic stability in
19 the context of it having -- sorry. I'm not
20 sure -- I can do a better job asking this
21 question. Let me try.
22 Does a protein's ability to resist
23 thermal unfolding reflect its intrinsic
24 stability?
25 A. Okay. That's a -- that's a better

1 question. I'll give you a better answer than I
2 would have maybe had to give in the other case.
3 Sometimes yes. Often yes. Not always.
4 All right? The intrinsic -- if you want to
5 define the term correctly, as I said, it gets
6 used sloppy, intrinsic stability of a protein is
7 the difference in free energy between the folded
8 form of the protein and the unfolded form of the
9 protein. All right?
10 So that can change not only because you
11 can lose stability of the folded form, but you
12 can -- that can change because you can gain
13 stability of the unfolded form. And it matters
14 which that is sometimes, and a careful scientist
15 who studies protein folding and stability always
16 has to keep that in mind, that you're dealing
17 with a difference between a state that you can
18 not only measure but in many cases visualize with
19 crystallography and a state that isn't one state
20 but that it's a distribution of unfolded forms.
21 And yet the stability -- the ability of
22 that particular state to exist and how much of it
23 exists in that form is critical to the stability
24 of the protein, even though it's not -- I'm
25 sorry. I'm -- I'm not going to ramble anymore.

1 Do you see what I mean?
2 Q. Yes.
3 A. Okay.
4 Q. So is it fair to say that the protein's
5 free -- net free energy of stabilization is the
6 composite of all of the different influences that
7 contribute positive or negative to that stability
8 of the protein?
9 A. Yes. Compared with the stability of the
10 unfolded form.
11 Q. And is it possible for mutations made to
12 the protein to shift the net-free-energy level to
13 cause a protein to go from -- that had a tendency
14 to be stable at one temperature to be unstable at
15 that temperature with the mutations in it?
16 A. Yes. In case of some mutations, it is.
17 That will depend to some extent on how
18 intrinsically stable a fold is.
19 Q. Are you aware of instances where two or
20 three mutations to a protein can shift that
21 thermal stability of a protein that intrinsic?
22 A. Yes.
23 Q. Would introducing 15 or 20 changes into a
24 protein structure as mutations be more likely to
25 shift the thermal stability of the protein?

1 A. It depends on the protein.
2 Q. Is the -- is the net free energy of --
3 sorry. Let me try -- use the right word.
4 Is the net free energy of stabilization
5 of most proteins large or small?
6 A. Most physiological proteins. We're not
7 talking about the data of the design proteins.
8 Of a relatively small net free energy of
9 stabilization.
10 Q. So if you introduced ten destabilizing
11 mutations into a protein structure, that would be
12 more likely to cause that to move it toward
13 the -- toward a tendency to unfold as to remain
14 folded?
15 A. You can't answer the question that way.
16 It's too general. It would depend on the
17 mutations, what they are and where they are.
18 Q. So you'd have to assess each one in -- or
19 each combination of changes and try to predict
20 the effect of --
21 (Simultaneous crosstalk)
22 A. You would want to look at them.
23 Q. When you are doing that, you -- can you
24 look at them and calculate the free energy
25 change?

A. People have tried to do that, and there are programs that will allow you to do that, but the numbers are very imprecise, so I would normally not do that. I would rely on my years of experience.

Q. Wait. You would -- you would rely on your instincts, or would you rely on use of experimental techniques to --

A. I would rely on, if you will, an instinct developed by years of experimentation, reading the literature, and so forth.

Q. Do you think a person of ordinary skill would have those same instincts that you do?

A. If they had gone -- if they had studied proteins the way we were talking about in the definition of a person of ordinary skill in the art, yes, I think they would have some of that.

They -- they might not have as much as if you'd lived as long as I have, but if you've lived as long as I have, you also wouldn't have your right knee.

Q. Do you -- so those comments you've been providing, those opinions, are they from a perspective of 2011/2012, or they are current?

A. No. They're perspective as of 2011/2012.

1 Q. So your testimony is that a person of
2 ordinary skill in the art in the 2011-2012
3 timeframe would be able to predict the change to
4 a protein's net free energy of stabilization
5 associated with a set of 10 or 15 or 20 mutations?
6 A. No. They would not be able to predict
7 the number. They would be able to get a sense of
8 whether those were likely to be destabilizing or
9 not.
10 Q. Likely to be destabilizing to the point
11 that they would cause a protein to tend toward
12 unfolding?
13 A. Depending on the nature of the mutations
14 and their locations, possibly.
15 Q. So you'd have to assess each one and
16 reach this conclusion from inspection of it
17 within a structure of the protein?
18 MS. MARTIN: Object to form.
19 A. Each protein family in particular, and
20 maybe some of the proteins within the family, is
21 going to be a case that you need to think about.
22 But in the case of PH20, you have the
23 patent data. Okay? That's a tremendous amount
24 of information that allows you to become more
25 confident in the kind of predictions you're

1 talking about.
2 Q. Does the common disclosure report
3 experimental testing of the thermal stability of
4 any mutants?
5 A. It talks about the stability of some of
6 the mutants, yes.
7 Q. Two of them, right?
8 A. Yes.
9 MS. MARTIN: So then we can --
10 MR. KUSHAN: Yeah, I was going to -- I
11 was going to say we can take a break. Why don't
12 we -- why don't we take the break now and then we
13 can resume this conversation, if that makes
14 sense.
15 MS. MARTIN: Yeah.
16 THE WITNESS: Fine with me.
17 THE VIDEOGRAPHER: All right. Going off
18 record at 11:26.
19 (Recess taken)
20 THE VIDEOGRAPHER: Back on record at
21 11:50.
22 BY MR. KUSHAN:
23 Q. Dr. Petsko, did you speak with counsel
24 during the last break?
25 A. Not about the case, no.

1 Q. What did you speak about?
2 A. Pardon?
3 Q. What did you speak about?
4 A. Actually, I think I was mentioning my
5 knee.
6 Q. Understandable.
7 A. As you see, I'm wearing this device on
8 both legs that compresses and releases my calf
9 muscle. That's to prevent blood clotting. I was
10 explaining that.
11 Q. Well, if you at any point feel like you
12 need another break or need a longer break just
13 let me know. I can --
14 A. No. This is routine. I have to do this
15 a couple times a day. But the Velcro, when I
16 have to take this off, is going to make a
17 terrible noise. You might -- I will let you
18 know.
19 Q. Perfect.
20 Okay. So Dr. Petsko, when POSAs think of
21 PH20, do they think of it as a folded protein?
22 A. Usually.
23 Q. Can I have you go to page 169 of your
24 declaration and go to paragraph 346.
25 A. Page 159, did you say?

1 Q. Sorry. Sorry -- 1- -- 169.
2 A. Sorry.
3 Q. That was my bad.
4 A. And paragraph was 346?
5 Q. Correct.
6 A. Okay. I'm there.
7 Q. Okay. You say that: "POSAs modify
8 existing proteins for a purpose."
9 Could you just explain what purposes that
10 a POSA would modify a PH20 for?
11 A. There are a number of them. They might
12 want to increase activity. Okay. They might
13 want to abolish activity, in some cases, to
14 retain a protein that binds hyaluronic acid but
15 doesn't hydrolyze it. They might want to abolish
16 binding as well as activity. They might want to
17 actually, deliberately, misfold the protein for
18 purposes of creating antibodies at a higher rate
19 of efficiency than you can through the folding
20 protein. Those would be some of the reasons.
21 You might want to improve stability to
22 temperature. You might want to improve stability
23 to certain denaturing preservatives.
24 Q. So for those various purposes, would
25 those have motivated a POSA to introduce one or

more amino acid substitutions into the human PH20 protein?

MS. MARTIN: Object to form.

A. Usually.

BY MR. KUSHAN:

Q. And that would have been true in 2011, right?

A. Yes.

Q. Could you go to pages 169 and 170, and there are a few paragraphs, just 347 to 349, and just skim those and let me know when you're ready.

A. Okay. Okay.

Q. If you could look at paragraph 347 -- 347.

Are you saying that, after reading the '600 patent, a POSA would not have tried to make PH20 polypeptides by generating combinatorial libraries of mutants having random combinations of substitutions and screening them for activity.

A. I am saying that under most of the circumstances I can envision, the POSA would not start that way at all. They would start with a much more focused program making use of the data in the patent.

Q. Did you find anything in the common disclosure suggesting that they should do the path -- should take the path of making combinatorial libraries and screening them to produce PH20 proteins with multiple mutations?

A. Didn't suggest that to me. Again, I think as long as you are dealing with a -- with a situation like this where you have a wealth of information at every position in the sequence, you would first start to do it by -- if you -- I'm not -- I don't want to use the word "design" in its broadest sense.

But if you understand what I mean by that. You would try to -- you would predict -- you would be able to write down sequences where you could predict what you were likely to see and you would test those first.

Q. So you'd use the data in the patent as kind of a starting point for then a person to pick combinations, design them, and then evaluate them?

MS. MARTIN: Object to form.

A. I would say the data in the patent provide a framework, if you will, or a -- a -- it provides a wealth of information that can be used

1 to identify from the genus proteins that contain
2 the properties you are interested in.
3 BY MR. KUSHAN:
4 Q. Do they also contain -- do they give you,
5 as a POSA -- sorry. Let me start over.
6 The properties you are interested in, are
7 you referring to the increase stability-type
8 property?
9 A. The sort of things we talked about.
10 Q. So basically a feature or an attribute of
11 the resulting mutated protein, that's what you
12 are referring to by "properties you are
13 interested in"?
14 A. Yes.
15 Q. Okay.
16 A. Usually.
17 Q. And then what you are saying is that the
18 data in the patent allows somebody who is a
19 person of ordinary skill to select combinations
20 of mutations that will deliver those desired
21 properties in a particular mutant?
22 A. That's correct.
23 Q. So the patent, in your view, and data in
24 the patent in particular, is giving the ability
25 of a skilled person to select combinations that

1 they could then put together and test to see if
2 they have the properties that they are looking
3 for?
4 MS. MARTIN: Object to form.
5 A. Remember, you are not only talking about
6 combinations, for one thing. Might be a single
7 substitution is all you require. In fact, in a
8 number of cases it probably will be.
9 As far as testing is concerned, it
10 depends -- right? -- again, on what you want to
11 do. What you can do, however, is predict, with a
12 high degree of likelihood, that the changes that
13 you make are going to have properties of the kind
14 you are interested in.
15 Q. And that's true from the individual
16 single mutants -- sorry.
17 So you can reach that conclusion by
18 looking at single mutants and you extrapolate
19 that data for the single mutant to combinations
20 of mutations?
21 A. In some cases, many cases, maybe most
22 cases, yes, because you also, remember, have the
23 structure. So you know where those mutations are
24 as well as what they are.
25 Q. So do you -- is there -- was there a

1 published structure, experimentally determined
2 structure, of PH20 in 2011 or 2012?
3 A. PH20, no, but there was the bee venom
4 structure in 2012. It was -- Hyal-1 was
5 available, I think, in 2012. I don't know the --
6 I can't remember the year of publication but I
7 think I'm right that that structure was available
8 in 2012.
9 Q. That was published in the Chao paper?
10 A. Yeah, that's right. I can't -- I just
11 can't remember the date of publication.
12 Q. Did you use the bee venom structure or
13 the Hyal-1 structure to produce the PH20 model
14 you used?
15 A. Hyal-1 was the -- was the structure that
16 was used. The bee venom structure was used to
17 compare with Hyal-1 and the PH20 structure. And
18 also, to look at the interactions of hyaluronic
19 acid with those models because the bee venom
20 structure, if you will recall, has hyaluronic
21 acid dimer present in the protein.
22 Q. Does the patent provide examples of
23 particular combinations of mutations that are
24 correlated to PH20 proteins with desired
25 properties such as increased activity or

1 increased stability?
2 A. The main combinations referred to have to
3 do with the glycosylation. I don't remember that
4 any of those increased the activity. I don't
5 know if the stability was measured. Solubility
6 of those can effect -- I think that might have
7 been looked at but I don't remember that either.
8 So no, I don't think so.
9 Q. So your opinion is that a POSA could use
10 the data from testing single mutants in the
11 patent to select 15 or 20 substitutions in the
12 PH20 sequence, and you would be able to predict
13 whether that mutated 15 or 20 residue-mutated
14 PH20 will exhibit the activity that you are
15 hoping to get?
16 A. My opinion is that you could do so. My
17 opinion is also that you would almost never do
18 so. You would probably rarely, if ever, make
19 that many substitutions. You wouldn't need to.
20 Q. Have you used the word "protein space" to
21 describe kind of the universe of protein variants
22 that might be the subject of an investigation?
23 A. I don't know that I've used the word
24 "protein space." If I have, confirmational space
25 might have been a better choice. But I think we

1 mean the same thing when we are talking about
2 that.
3 Q. Yeah. So I am trying to see if there is
4 a word that correlates to the genus -- although
5 you used the genus definition, which may be fine.
6 What I'm trying to get to is, in that genus of
7 claim 1 of the '600 patent, and you said this
8 earlier, it's -- you don't have an ability to
9 kind of draw these lines about how much of it is
10 active mutant, inactive mutant, etc.
11 What I'm trying to understand is, within
12 that genus, how much of it is made up of multiply
13 modified PH20s as compared to singly modified
14 single mutant?
15 A. I haven't done that calculation. The
16 genus is defined in the claims.
17 Q. Right.
18 A. So claim 1 will tell you what you have to
19 do.
20 Q. So if you just look at the universe of
21 modified PH20 polypeptides that have one amino
22 acid substitution in the 447 residue sequence, I
23 think there are probably around 9,000 species in
24 that genus, right?
25 A. I don't know. Thousands sounds right,

1 but I don't know.
2 Q. So if you look at the entire genus that
3 it has a set of changes that can include up to 21
4 or 22 mutations, the portion of the genus that is
5 reflected in the dataset is a tiny, tiny fraction
6 of that genus, right?
7 MS. MARTIN: Object to form.
8 A. So the -- what is reflected in the patent
9 is a subset. Okay. Which has a particular
10 number of mutations. A few thousand. Sounds
11 about right.
12 The real question is: What about the
13 information content? The information content of
14 that particular set of substitutions is enormous.
15 And when combined with the structural information
16 from modeling the PH20 structure, it allows you
17 to visualize and make predictions about much more
18 of the dataset than just what you see here.
19 BY MR. KUSHAN:
20 Q. So using that dataset, the person could
21 predict which combinations might yield an active
22 form of a mutated PH20 polypeptide let's say with
23 15 changes to it?
24 A. You could, but as I said, you would not
25 tend to do that. A person of skill in the art

1 would tend to only be interested in a much
2 smaller number of mutations, because you can
3 almost certainly get where you want to go that
4 way.
5 Q. So a POSA is not interested in trying to
6 practice the entire scope of this genus, they
7 would focus on a portion of it, right?
8 MS. MARTIN: Object to form.
9 A. A POSA would have the capability of both
10 visualizing and practicing the full scope of the
11 claims if they needed to. They could -- that is
12 to say, they could look at any particular type of
13 variant that fit the claim and they could make
14 that variant and they would be able to predict
15 beforehand what that variant might do with a --
16 in many cases, on a high degree of confidence.
17 Q. And they could do that for 1049 -- a
18 number that -- I'm sorry. They can do that for a
19 number of modified PH20 polypeptides that
20 approaches 1049 different sequences?
21 A. They can do that for any member of the
22 1049 sequences that they wish to examine. Okay?
23 A person of skill in the art would do it that
24 way.
25 Q. If you had to estimate the portion of the

genus of the claim 1 that we've been discussing, that you are focusing on with what the POSA would be interested in, how much of a portion of the whole is that portion that the POSA would focus on, do you think?

MS. MARTIN: Object. Object to form.

A. I don't know.

Okay. Heads up. I'm unwrapping the --

MR. KUSHAN: You know, I'm actually wondering, maybe we should just take a lunch break now because I have -- I think it would make sense to do that.

THE WITNESS: It's up to you.

MS. MARTIN: All right.

THE VIDEOGRAPHER: All right. Going off record at 12:06.

(Lunch recess taken)

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

THE VIDEOGRAPHER: Going back on record at 12:56.

BY MR. KUSHAN:

Q. Dr. Petsko, can you go to page 141 of your declaration and look at paragraph 290.

A. Okay.

Q. In the last sentence of paragraph 290, you say that "POSAs, like Dr. Park, use multiple sequence alignments to identify conserved residues precisely because tolerance to mutation is not random," right?

A. Yes.

Q. Okay. So you had reviewed Dr. Park's analysis in his declaration, right?

A. I knew that he used multiple sequence alignment from the declaration, yes.

Q. You use the word "tolerance" in that sentence in paragraph 290. Are you using tolerance to mean the ability of the PH20 protein to properly fold despite incorporating mutations or modifications into its amino acid sequence?

A. In some cases. In other cases, it might be the ability to retain activity by substitution of a residue in or near the active site, that

1 sort of thing.
2 Q. In that second scenario, that's kind of a
3 derivative of the protein preserving its
4 structure, right?
5 A. Usually. Although it might be a very
6 local change.
7 Q. Right. So you're using this concept of
8 tolerance in a way that is similar to the way
9 that Dr. Park is using it?
10 A. I'm hope -- I hope I have, yes.
11 Q. Why don't we do this, why don't you go to
12 paragraph -- why don't we go to the Park
13 declaration.
14 A. I don't have a copy.
15 Q. Exhibit 1004.
16 MS. MARTIN: Yeah. It should be
17 somewhere in here.
18 A. Oh, here it is. Yeah. I see it.
19 Q. All right. I'm going to -- go to
20 page 126. First, I just want to make sure we --
21 126 is Appendix D-1.
22 A. Yup.
23 Q. And in this appendix, this is a
24 position-by-position readout of the frequency of
25 amino acids that occur at that position in PH20

in the homologous set of PH20s, right?
A. Yes.
Q. Is this something you would be familiar with?
A. Pardon?
Q. Is this something that you would be familiar with, this --
A. Yes.
Q. Okay. So it's basically showing how frequently different amino acids occur at a position corresponding to the PH20 --
A. Yes. In naturally occurring organisms.
Q. Perfect.
Why don't you go to page 6 of Dr. Park's declaration, paragraph 20. And what I'd like you to do is read paragraph 20, and once you've done that, let me know.
A. Not lately.
Q. That's okay. Take your time.
A. Page 6 did you say? I've got paragraph 19.
Q. I'm sorry. I'm sorry. Page 7 --
A. All right.
Q. -- paragraph 20.
A. Okay.

(Pause)

A. Um-hmm.

BY MR. KUSHAN:

Q. So is his usage of "tolerate" consistent with your usage of tolerating in your opinion?

A. It's a subset of my usage of tolerate, yes.

Q. What part is broader in your description -- in your usage?

A. So I may be interested in things that are slightly more non-local than he is sometimes. But since I'm not quite clear on what he means by local, how big that is, it might not be different at all.

Q. So if he, for example, is saying that -- or if a POSA was saying, "This amino acid substitution at this position was tolerated," so that you were kind of using the word "tolerated" in connection with a particular position in the sequence, then your interp- -- your usages would align with Dr. Park's?

A. In that particular situation.

Q. Okay. All right.

MR. KUSHAN: Let me do this. Let's go over to the Chao paper and introduce this as an

exhibit, 1006.

THE WITNESS: Where can I find a copy of that?

MR. KUSHAN: You're going to be getting one in a second.

THE WITNESS: Thank you.

(Discussion off the record)

(Exhibit 1006, Biochemistry 2007 paper- Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis- Kinlin L. Chao, pre-marked for identification.)

BY MR. KUSHAN:

Q. Just confirm you -- this is the Chao paper we've been discussing that discusses the Hyal-1 structure and the --

A. Yes. The one from Biochemistry, yes.

Q. And you can see this is published in 2007, right?

A. Yes.

Q. Okay. You rely on information in Chao at several parts of your declaration, and I just wanted to walk through some of those. So if you can just put Chao down for a second -- Chao down for a second, and let's go back to your

1 declaration. Go to para- -- page 53 --
2 A. Um-hmm.
3 Q. -- paragraph 127.
4 A. Um-hmm.
5 Q. And in paragraph 127, you're referencing
6 Chao to support your views about similarities
7 shared by human Hyal-1 and then PH20 and bee
8 venom hyaluronidase, right?
9 A. Um-hmm.
10 Q. Right?
11 A. Yes.
12 Q. So go to pages 61 and 63 and take a look
13 at paragraphs 141 and 143. So just skim --
14 A. Um-hmm.
15 Q. -- skim 141 and 143, and then tell me
16 when you're done.
17 A. Yes.
18 Q. So here you were relying on Chao to
19 support similarities about the active site clefts
20 in three hyaluronidases.
21 A. I think I need to know what you mean by
22 relied on.
23 Q. You're -- you're using the Hyal-1
24 structure and -- to help understand what the --
25 what that cleft looks like as a structure, right?

A. That's correct.
Q. And that comes from -- part of that information comes from Chao, right?
A. Yes. Chao is -- if you will, providing the initial frame -- the initial use of that particular comparison.
Q. Okay. All right. Go to page 66, paragraph 146.
A. Okay.
Q. And I think in this paragraph, you're relying on Chao to support your opinions about how the three hyaluronidases share a common structure/function relationship, right?
A. In this case, I'm quoting Chao and Stern and Park, all of them --
Q. So that's all --
A. -- as basically making the same statement.
Q. Okay. Let's go to a couple more. Look at 60 -- pages 67 to 68 and paragraphs 148 to 149.
A. Yes.
Q. And here you're relying on Chao to support your views about four critical active site residues, right?

A. Yes.
Q. All right. Go to page 97 and paragraph 191.
A. Yes.
Q. So in paragraph 191, you're citing to Chao in -- as part of a discussion of a mutation to the glutamate residue at position 249, right?
A. Yes, I am quoting his paper's description of the experiment that he did on that residue.
Q. And that's the residue in Hyal-1, right?
A. Yes. That would be the residue in Hyal-1.
Q. And that's relevant to PH20 because of the homology between Hyal-1 and PH20?
A. Yes. And also, because you -- the structures can be directly compared. The model of the PH1 -- of the PH20 structure shows that the residues are in the same position.
Q. Okay. Look at page 108 of your declaration, paragraph 211.
A. 108, yup, I got it.
Q. So you put a picture from Chao in your declaration that shows the positioning of Hyal-EGF domain --
(Reporter clarification requested.)

BY MR. KUSHAN:

Q. From Chao in your declaration that shows the positioning of the Hyal-EGF domain within the Hyal-1 structure, right?

A. Yes.

Q. Okay. And it shows the kind of spatial positioning of the Hyal-EGF domain relative to the active site; is that right?

A. Yes, although it is not particularly clearly visible in this orientation.

Q. And you are using this to illustrate this positioning of the Hyal-EGF domain relative to the rest of the protein?

A. Specifically relative to the positioning of the active site cleft.

Q. Okay. So we have been talking about the Hyal-EGF domain, and why don't we go over to Chao, and I want to just go through a few points in the Chao paper with you.

A. Okay.

Q. First, if you could go to page 691 -- 6916 in Chao.

A. Yes.

Q. Do you see in the left column under the italicized where it is: "Role of the

1 HyalEGF-like Domain"?
2 A. Yes.
3 Q. And is Chao confirming in this paragraph
4 that the Hyal-EGF domain is present in all
5 mammalian hyaluronidases?
6 A. Let me read this.
7 Q. Sure.
8 (Pause)
9 A. Yes, although he does mention the
10 additional cysteine residues in Hyal-3 and PH20.
11 BY MR. KUSHAN:
12 Q. Do you recall if Chao identified a
13 particular pattern of amino acids that is present
14 in mammalian hyaluronidases that is necessary to
15 form the Hyal-EGF domain?
16 A. I thought he did but let me take a look.
17 Q. Go back, I think -- go back to page 6912
18 in the left column. It is the second full
19 paragraph.
20 A. Yup.
21 Q. So did Chao indicate that there is a
22 particular pattern of amino acids that occurs
23 that is --
24 A. You are not talking about alternative
25 splice transcripts. I am not looking at the

1 right place.
2 Q. No. Look at 6912 in the paragraph that
3 starts "Human Hyal-1."
4 A. Ah, okay.
5 Q. And then go down --
6 A. So the second full paragraph. I have got
7 it.
8 Q. Yeah, yeah.
9 A. All right.
10 Q. Just let me know when you finish reading
11 that.
12 A. Give me a second.
13 Q. Of course.
14 (Pause)
15 A. Yes. He is referring only to the pattern
16 of cysteine residues. Okay. He is not -- in
17 this paragraph, he is not looking at any of the
18 other amino acids in the domain.
19 BY MR. KUSHAN:
20 Q. He is also referring to the spacing of
21 the residues, right?
22 A. Yes, that's what I mean by the pattern.
23 Q. He also says that there are particular
24 amino acids that have character, like the
25 hydrophobic residue is an "a" in the pattern,

1 right?
2 A. Yes.
3 Q. And that there is -- "x" is denoting any
4 residues that's showing a tolerance to the
5 position next to the hydrophobic one after that
6 cysteine, right?
7 A. That's right.
8 Q. But overall, he is making it fairly clear
9 that there is a characteristic pattern that is
10 found in the sequence that is associated with the
11 Hyal-EGF domain?
12 A. Yes, and that pattern is primarily
13 established by the disulfide bridges.
14 (Reporter clarification requested.)
15 A. That pattern is primarily established by
16 the disulfide bridges.
17 BY MR. KUSHAN:
18 Q. And the gaps can vary in length?
19 A. It would seem so.
20 Q. All right. Chao was the first to report
21 this characteristic pattern, do you --
22 A. I don't know that.
23 Q. Well, at least he thinks he does, I
24 think.
25 A. I don't think so. Because he refers to

the Smart and Prosite databases as establishing that as -- as referring to that as an EGF-like motif. That suggests that the observation was made earlier, probably from other proteins that have this motif.

Q. There was no association of this motif with hyaluronidase before Chao made it, right?

A. I think that's probably right.

Q. And that's why he says -- before the comment about the pattern, he says in the preceding sentence: "No sequence homology has been reported in the scientific literature for the C-terminal domains of the mammalian hyaluronidases."

A. That's right. But I wanted to be sure we weren't trying to say that he discovered this domain --

Q. No, no, no --

A. -- or the pattern of residues that produce the domain.

Q. Yeah, I am focused more on the association of this domain within the hyaluronidase family.

A. Fine.

Q. So he is the first to publish on that?

A. As far as I know --
MS. MARTIN: Object to form.
A. -- that's right.
BY MR. KUSHAN:
Q. So do you believe a -- would a POSA believe that if one modified the amino acids that make up the positions in a PH20 protein that are correlated to this motif, this sequence -- sorry. Let me try that one again.
If someone were to modify the amino acids that make up the stretch of residues that are identified as being associated with the Hyal-EGF domain, would a person of skill in the art expect that to disrupt the Hyal-EGF domain structure?
MS. MARTIN: Object to form.
A. So are you referring to all of the residues of the domain or the cysteine residues or what?
BY MR. KUSHAN:
Q. Do you think it is possible to make mutations to that region of the protein and disrupt the Hyal-EGF domain?
A. It's known that the cysteine residues are required for the formation of the EGF domain. And if you have an odd number -- say if you would

1 disrupt one, you'd have an odd number of
2 cysteines that can produce disulfide scrambling.
3 As far as the other residues are
4 concerned, the implication here is that there is
5 variability. But that variability is derived
6 from comparing sequences of different EGF
7 domains. It's almost certain that those will not
8 encompass every possible substitution at each of
9 those locations.
10 However, we have the patent. The patent
11 does explore those locations in more detail. So
12 the answer is, we can turn to the data in the
13 patent for a better answer to the question.
14 Q. In your declaration, did you -- well, did
15 you compare the mutation data in the patent to
16 this region of the PH20 sequence and offer any
17 opinions on how the data influences
18 decision-making on changing this region of the
19 protein?
20 A. Not explicitly.
21 Q. If a person of ordinary skill made a
22 deletion within this region -- that is, the
23 characteristic region associated with the
24 Hyal-EGF -- could that disrupt the Hyal-EGF
25 domain found in PH20?

A. Depends on the size of the deletion. Probably.

Q. It looks like a five-residue deletion, would that --

A. That might be bad. A one-residue delete might not be. It would depend on the location, certainly. But also, as I said, the length of the deletion matters.

Q. Could the deletion disrupt the ability of the disulfide bonds to form?

A. Yes, that can happen.

Q. That's true even if the cysteines were preserved in the sequence after the deletion?

A. Yes, because they have to find each other.

Q. Based on what you reviewed in Chao, could mutations affect the stability of the whole PH20 protein if changes were made within the Hyal-EGF region?

A. It's hard to know. Because it's a C-terminal domain. You could often do things within a domain at one end of the protein structure that you couldn't do if the domain was more internal. You might -- the structure might be more tolerant. I suspect it would be more

1 tolerant.
2 And I have a little bit of support for
3 that statement because of the bee venom protein,
4 which lacks the domain completely but the rest of
5 the fold is the same. So that suggests that it
6 is certainly possible to remove vast chunks of
7 that domain and not necessarily prevent the
8 folding of the rest of the protein.
9 Q. In the human PH20 protein, the Hyal-EGF
10 domain is part of its tertiary structure, right?
11 A. Yes.
12 Q. And is it also part of the -- it is
13 necessary for the activity of the human PH20
14 protein, right?
15 A. Yes.
16 Q. Okay. Could you go to your declaration
17 and look at page 107, paragraph 207.
18 A. Um-hmm.
19 Q. Here, you are indicating that another
20 common structural feature shared by Hyal-1 and
21 PH20 is the EGF -- Hyal-EGF domain, right?
22 A. Yes.
23 Q. So a POSA would recognize that the
24 Hyal-EGF domain is one of the common structural
25 features shared by the claimed modified

PH20 polypeptide?

(Reporter clarification requested.)

BY MR. KUSHAN:

Q. A POSA would recognize that the Hyal-EGF domain is one of the common structural features shared by the claimed modified PH20 polypeptides, right?

A. A person of ordinary skill in the art would recognize that the EGF domain is a common structural feature shared between PH20 and the Hyal-1 structure, and shared by all of the proteins in the genus that contain the EGF domain sequence.

Q. Wait. So that's -- isn't that tautological? I mean, you are saying that the -- the set shares the set that has it, right? Let me -- let me make it a better question for you.

A. Go ahead.

Q. So is the Hyal-EGF domain a common structural feature of the modified PH20 polypeptides in this genus of claim 1?

Let me stop there and ask you that.

A. Nearly all of them, yes. I don't know about all of them because of possible deletions of that part of it.

Q. Do you know how long -- how many residues are -- that constitute the Hyal-EGF domain?

A. No. It is not many, but I don't know the exact number. I think -- wait a minute. Isn't it about 70 or so? Something like that.

Q. So if you deleted the Hyal-EGF domain, it would no longer be within the scope of --

A. If you delete the whole domain certainly, yes.

Q. Okay. So it is fair to say that it is part of the tertiary structure of Hyal-1 and PH20, right?

A. Yes.

Q. And it is part of -- do you have an approximation of how much of the genus requires the common -- sorry.

Would you have an ability to predict how much of the genus of claim -- of proteins claimed in claim 1 will have this Hyal-EGF as a common structural feature?

A. It should be a vast part of it. I don't know how -- exactly how many, but most of it I should think.

Q. Okay. In the work you did to prepare your opinions, you didn't attempt to figure out

1 where in the human PH20 sequence the Hyal EGF
2 region is, did you?
3 A. I didn't have to figure it out. I could
4 see it. Remember, I -- you displayed what
5 displays the structure.
6 Q. Let me -- so let's focus on the amino
7 acid sequence that creates -- or sorry, the amino
8 acid sequence associated with that structure.
9 You didn't identify the boundaries of the amino
10 acid sequence?
11 A. I didn't have to because it's been done
12 elsewhere in the literature (indicating).
13 Q. And so, for example, you could see that
14 from the alignment in the Chao --
15 A. That's one place.
16 Q. Do you recall if Dr. Park also identified
17 it?
18 A. I thought he did.
19 Q. Okay.
20 A. I can't point you to the paragraph.
21 Q. So, but you didn't look at the individual
22 amino acid makeup or compare that to the
23 mutational data of the sequence that correlates
24 to the human PH20 Hyal-EGF domain as part of your
25 work in this case?

A. Not focusing on that domain. I looked at the entire set of mutations.

Q. But you didn't consider individual sets of changes in the Hyal EGF -- localized just to the Hyal EGF in forming your opinions?

MS. MARTIN: Object to form.

A. Not in -- not in that particular domain. As I said, it was part of the whole set of mutations that I did consider.

Q. So you considered the mutations in the Hyal EGF region as part of the whole set of mutations that you considered?

A. Yes.

Q. And you didn't consider the effect of mutations on the Hyal-EGF domain?

A. Per se --

Q. Per se.

A. -- no.

Q. All right. Let's go to page 109 and go to paragraph 212.

A. Yes.

Q. And here you're connecting work that was done by Arming to work that was done in a paper by Zhang?

A. Yes.

1 Q. And you're saying that "the Arming
2 results are consistent with Zahn ... that the
3 EGF motif appears to be required for enzymatic
4 activity for both Hyal-1 and PH20," right?
5 A. Yes.
6 MR. KUSHAN: Okay. So let me introduce
7 Zhang. This is Exhibit 1010.
8 A. Um-hmm.
9 BY MR. KUSHAN:
10 Q. Please confirm this is the Zhang paper
11 that -- that you addressed in your declaration.
12 A. Yes.
13 Q. So Zhang reported experimental results
14 from mutations of the Hyal-1 protein, right?
15 A. Yes.
16 Q. And --
17 A. This -- this is subsequent to the
18 structure of the Hyal-1 protein.
19 Q. Yeah. So Zhang actually uses the Chao
20 Hyal-1 structure to study and then performed
21 mutations to the structure to compare the effect
22 of predicted changes to actual changes?
23 A. Yes. It's more specific than that.
24 They're probing the mechanism of catalysis.
25 Q. Got it. Could you go to page 9439 of

1 Zhang?
2 A. Um-hmm.
3 Q. And in the right column there's
4 a paragraph --
5 A. Um-hmm. The deletion?
6 Q. Yeah. There's a paragraph in -- what is
7 that section? What does it say there -- I'm
8 sorry. Was is the title there?
9 A. "Deletion of EGF-like domain," is that
10 what you're referring to?
11 Q. Yeah. And it says "Abolishes Hyal-1
12 Activity Independently" --
13 A. Yes.
14 Q. -- "of Asparagine 350."
15 A. Yes.
16 Q. Okay.
17 A. That's the paragraph I assume you want.
18 Q. Okay. So Zhang attempted to produce a
19 Hyal-1 mutant that deleted the entire Hyal-EGF
20 domain?
21 A. Yes.
22 Q. And Zhang said that the transfected cells
23 did not secrete the Hyal EGF truncation mutant,
24 right?
25 A. That's right.

Q. So would a POSA -- would a POSA conclude that, without the Hyal-EGF domain, the human hyaluronidases do not properly fold?

MS. MARTIN: Object to form.

A. Not necessarily. They would -- they would conclude exactly what's stated here, that they don't secrete properly.

Q. So I think you said earlier that one indication that a protein has folded properly is that it secretes?

A. Correct.

Q. So if a protein here doesn't secrete, would that suggest that it doesn't have the proper folding of the protein?

A. No. The statement cannot be inverted that way. Proteins that do not fold properly usually do not secrete, but proteins that do not secrete do not always do so because they're completely not folded properly.

Q. Something happened that was not good for secretion, right?

A. That's correct. But it doesn't have to be a complete change in folding.

Q. So we don't -- we don't know what happened that caused the cells to not secrete the

1 Hyal-EGF domain, right?
2 A. Well, evidently they didn't at this time.
3 I don't know if it's been determined since.
4 Q. Right. And Zhang measured activity in --
5 from the lysed cells, and they recovered protein
6 from the lysed cells, right?
7 A. Yes, I believe so.
8 Q. And they reported the activity being
9 6 percent from that recovered lysed cell?
10 A. I think that's right.
11 Q. All right.
12 A. And that's not zero, by the way.
13 Q. Right. So they -- the Zhang authors
14 portray that level of activity as being -- as
15 indicating the activity has been abolished,
16 right?
17 A. Yeah. I don't know that a person of
18 skill in the art would always accept that
19 statement without some additional data.
20 Q. The Zhang author did?
21 A. Yes. And -- that's correct.
22 Q. If you can go to the paragraph we were
23 referring to a minute ago at page 9439.
24 A. Excuse me. Can we go back to the
25 previous question for one second?

1 Q. Sure.
2 A. If we look at the last two sentences of
3 that paragraph, it may be germane to what I just
4 said. "The lysates showed ... 2.5 and ... 6.3%
5 of wild-type activity for N350tr and L356tr,
6 respectively, at the 125 µm amount of HA [sic].
7 Thus, loss of this domain is deleterious to both
8 secretion and activity of Hyal-1, although the
9 residual activity suggests the effect is
10 indirect."
11 So that sort of gets at what I was trying
12 to say.
13 Q. So --
14 (Simultaneous crosstalk)
15 A. Because there was residual activity that
16 suggests that the effect of truncating the domain
17 is not necessarily to abolish the folding of the
18 rest of the protein.
19 Q. Why don't you look at page 9441.
20 A. Okay.
21 Q. And if you look up in the top right
22 paragraph of 9441.
23 A. "It has been proposed"?
24 Q. Yes. Take a look -- just read that, and
25 let me know when you're done.

A. Um-hmm.
Q. And so Zhang is reporting that based on their analysis in -- of their experimental work, that because the inactivity of the truncated mutants and their inability to be secreted, that implies that this region do not function as an independently folded domain, right?
A. That's their conclusion.
Q. Right. And so they're saying that this protein motif is part of the structure of the -- the tertiary structure of the protein, it's not an independently functioning domain?
A. It's not the -- they're concluding it means it doesn't hang out in space by itself, disconnected from the bulk of the protein. That's basically what they mean.
Q. All right. So if you can go back to 9439, which is where this came from.
A. Um-hmm.
Q. If you look at the sentence in that paragraph starting, "Deletion of the EGF-like Domain" --
A. Um-hmm.
Q. -- the sentence that starts with "Inspection of the human Hyal-1 model."

A. Yes.
Q. So Zhang is reporting that "Inspection of the human Hyal-1 model reveals a single overall folded domain, with extensive contacts between the EGF-like region, the sugar moieties," at asparagine 350, "glycosyl adduct housed within that region ... the remainder of the protein."
A. Yes.
Q. So they're viewing it as a single folded domain, right?
A. They are.
Q. So it's not an independent domain, right?
A. They don't consider it that way. And in fact, if you look at my declaration on page 109, you can sort of see that interaction surface, where the one is colored in yellow and the rest of the protein is colored in gray. It's a fairly extensive surface.
Q. Got it.
So a POSA would conclude from Zhang and from Chao that the Hyal-EGF domain is required for the catalytic mechanism of hyaluronidases?
A. I don't think you'd say that.
Q. Why not?
A. I think you'd say it's required for

1 forming an active protein. You're implying that
2 that has to do with an alteration of mechanism.
3 That suggests the chemical process of catalysis
4 to me. I think that's a more specific conclusion
5 that you're able to draw from these data.
6 Q. What if the mechanism contemplated it
7 from the perspective of binding to the substrate
8 and causing catalysis, so a broader perspective?
9 A. That's -- that's a -- that's a better
10 conclusion to draw because it encompasses more
11 possibilities that I think are consistent with
12 the data.
13 Q. And in that setting, from that
14 perspective, a person of skill in the art would
15 believe that a Hyal EGF was necessary for that
16 mechanistic capability?
17 A. Or something like that.
18 Q. Okay.
19 A. Yeah.
20 Q. All right. So going back to that one
21 paragraph on 9439.
22 A. Wait. Where -- which document are we in?
23 Q. Sorry. We're back -- still with -- still
24 with Zhang.
25 A. Okay. Which page?

1 Q. 9439.
2 A. Yes.
3 Q. So in -- in this experiment, Zhang
4 produced the mutant that truncated the protein
5 just before the Hyal EGF region, right?
6 A. Yes. That was one of the deletions. I
7 think he did two.
8 Q. Right. And so when they tried to see --
9 detect enzymatic activity in the supernatant,
10 they didn't see anything?
11 A. No. They saw 6 percent or 2 1/2 percent,
12 depending on what they were looking at.
13 Q. I think they actually saw 0 percent in
14 the supernatant, right?
15 A. I don't remember that.
16 Q. Well, it wasn't secreted.
17 A. That's true, yes.
18 Q. So they recovered this -- they recovered
19 the protein from the lysate, and then in that
20 lysate they then found 6 percent activity, right?
21 A. Yes, so they found activity where they
22 found the protein.
23 Q. Right.
24 A. Okay.
25 Q. So if I did a screen for activity in the

1 supernatant in the hyaluronidase and I got zero,
2 it might indicate the protein had not secreted,
3 right?
4 A. That would be the first conclusion you
5 would check.
6 Q. All right. Let's go to page 132 of your
7 declaration, paragraph 262.
8 A. Page 132?
9 Q. Yup.
10 A. Paragraph 262?
11 Q. Correct.
12 A. Okay.
13 Q. So -- bear with me for one second.
14 This is the part of your declaration
15 where you are introducing the analysis you did of
16 mutagenesis data in the patent, right?
17 A. Yes.
18 Q. Okay. And you relied on the data from
19 that mutagenesis experiment which is reported in
20 Tables 9 and 10 of the patent, right?
21 A. Yes.
22 Q. You said that the data are extremely
23 useful because they show the tolerability of each
24 position in PH20 to substitution, right?
25 A. Yes.

Q. And you said the data shows which amino acids and which types of amino acids were tolerated at each position of PH20, right?
A. Yes.
Q. All right. And you also say that the data provides a POSA seeking to make PH20 variants with certain insights about making modifications to the PH20 protein, right?
A. I specifically said "are likely to abrogate activity," on one hand, and which do not.
Q. Okay. So your opinion is that with the data in the patent, the POSA knows which positions, if changed, are likely to abrogate activity and which ones are not?
A. For the single mutation.
Q. For the single mutations.
A. And that's -- yes.
Q. Okay. In your opinion, the data in the patent enables a POSA to generate single and mutual -- sorry.
In your opinion, the data in the patent enables a POSA to generate single and multiple mutants with desired properties?
A. Yes.

1 Q. So is it fair to say that you could not
2 have formed those opinions about the tolerability
3 of individual positions in PH20 to modification
4 without the mutagenesis data in the common
5 disclosure?
6 A. I could not have formed that opinion for
7 most of the residues in the protein without the
8 mutagenesis data.
9 Q. Could you have formed opinions about some
10 of those positions based on the multiple sequence
11 alignment and homologous sequence information
12 available before 2012?
13 A. You could have tried to do that. And in
14 some cases, you would have a high probability of
15 being right but it would be for a small number of
16 residues.
17 So for example, the catalytic residues
18 you probably pick up that way. The cysteines in
19 the EGF domain you probably pick up that way.
20 For most of the rest of the protein, no.
21 Q. All right. So you also relied on the
22 classification of each mutant in the common
23 disclosure as an active or inactive mutant to
24 form your opinions on tolerability, right?
25 A. Yes.

Q. So --
A. But also the list of what the mutants were.
Q. Right. In terms of the -- if you can go to the table that you've compiled at pages 135 to 136.
A. Yup.
Q. It is very colorful.
A. Yup.
Q. All right. For that table, you are using counts of active and inactive mutants to form the percentages that are the basis of your color --
A. Of the color coding, yes, that's correct. But it is not all the data that are available.
Q. Right. For the -- for this table, this is more of a mathematical extrapolation of the dataset?
A. I would call it more a summary of the dataset.
Q. All right. So let's make sure I understand what the colors mean. The colors are indicating how tolerant each position is to change, right?
A. So it is explicitly stated what the coloring is on page 134 of the declaration.

1 Q. All right.
2 A. For each of the colors that are used.
3 Q. Sure. So dark green indicates positions
4 where all substitutions are tolerated, right?
5 A. That's correct.
6 Q. And that means 100 percent of the tested
7 mutants were active mutants?
8 A. That's correct. And those -- that could
9 be a variable -- that's a variable number for
10 different amino acids, how many were tested.
11 Q. So that -- so that color is going to be
12 true -- that dark green color is going to be true
13 if you had seven mutants tested and all seven
14 were active, as well as if you had 15 mutants
15 tested and all 15 were active?
16 A. Correct.
17 Q. Light green means they are generally
18 tolerant to change?
19 A. Specifically. Okay. Positions where
20 60 percent or more of the substitutions were
21 tolerant are colored light green.
22 Q. Okay. And then no color means that
23 between 30 and 60 percent of the tested mutants
24 were active mutants, right?
25 A. Correct.

1 Q. And you didn't offer opinions on the
2 tolerability of those positions?
3 MS. MARTIN: Object to form.
4 A. No. I mean, that's not true. I
5 considered those positions sometimes when I
6 thought about what substitutions one might make
7 or not make. The coloring is simply to give you
8 an indication of where in the spectrum of
9 tolerability to the mutations those particular
10 residues fall.
11 Q. Let's look at the last couple of colors
12 and see if we can make some sense. So orange,
13 you said means generally intolerant of
14 substitution, right?
15 A. Yes. That's less than 30 percent.
16 Q. And then, finally, red are positions that
17 tolerate no changes, right?
18 A. Correct. So you can --
19 Q. And that's again -- sorry.
20 A. Sorry.
21 Q. So that's 100 percent of the tested
22 mutants were inactive, regardless of the number
23 of them?
24 A. Correct.
25 Q. So what I'm wondering is, in your

1 description of these different colors, there is
2 no characterization of tolerance for the 30 to
3 60 percent range that you had for all the other
4 ranges, right?
5 A. It is an intermediate set of activity
6 that was determined. Okay.
7 Q. So if you -- if you looked at one of
8 those positions that is uncolored, can you
9 characterize it as a position that is or isn't
10 tolerant to change?
11 A. Then you would go back to the original
12 data and look at the values for each of the
13 individual mutants. That's what I implied
14 earlier.
15 Q. So there's no --
16 A. But you wouldn't use this alone
17 (indicating).
18 Q. So from -- from this table, from the
19 coloring, you wouldn't associate kind of a degree
20 of tolerability, generally, to that position that
21 is at 30 to 60 percent range?
22 A. You would know that it was in the range
23 but you would want to know what it is
24 specifically.
25 Q. So some changes were tolerated and some

1 changes weren't?
2 A. Some changes were more tolerated, if you
3 will, than others. Produced a different level of
4 activity than others. You would want to look at
5 that carefully.
6 Q. So in -- in the table you have presented,
7 in those classifications that are used in the
8 coloring of them, they don't reflect some metric
9 of how many mutants were tested at a position,
10 right?
11 A. No, they don't reflect the absolute
12 number of mutations at each position.
13 Q. There is also no indicator or factor
14 that's built into your coloring scheme that
15 reflects the character of the change of the amino
16 acids at these positions that were -- that were
17 substituted. So going from a wild type to --
18 like, take an example, if the wild type is a
19 hydrophobic residue, you don't have a metric
20 that's evaluating in your table how big of a
21 change could be tolerated as to other kinds of
22 amino acids?
23 A. In this table, no. But the data exists
24 in the patent to get that information very
25 easily.

Q. So someone could look at individual positions and determine that some residues might be tolerated and others might not?

A. And one could determine what type of residues those are.

Q. If I am just using your coloring scheme, none of that context is in this coloring scheme, right?

A. Correct. But as I said, this is meant to be a quick summary.

Q. If you can -- I want you to go and look at the -- so you made -- you illustrated structures of the PH20 model -- sorry. Let me make that a better question.

You have a number of pictures in your declaration that are depicting a three-dimensional structure of PH20 and it has been colored to reflect the coloring scheme that you employed here, right?

A. Largely, although sometimes we use the colors for a somewhat different purpose.

Q. Right. So let's go through and just -- I want you to just look at the sets of images and talk and just confirm what's going on with each. So page 144 to 146.

A. 127?
Q. Sorry. 144 to 146.
A. It is not your fault. I don't hear well. I apologize.
Q. It is partly my fault because I didn't speak up. So I will take half the blame there. So 144 to 146.
A. I have it.
Q. So those images, those are using the same coloring scheme that you have in your table, right?
A. Let's see.
Q. Well, it doesn't have a dark green, to my eye, right?
A. Right. It has green for 60 percent or more.
Q. So basically, in the coloring scheme here you absorbed the light green and dark green and they are just green?
A. Yes, and that's largely because the perspective of the view will sometimes darken the colors of some colors like green. So it would have been -- could give false impressions.
Q. Right. So if I see green, it just means more than 60 percent were active mutants?

A. Correct.
Q. Okay. And then cyan is basically not colored. That was the default color of the structure, right?
A. I'm sorry?
Q. The cyan residues, are those just the default color of the model?
A. Yes.
Q. Okay. So those are basically putting no color into the model?
A. That's correct.
Q. All right. The red ones are the 100 percent not tolerated ones, right?
A. Yes.
Q. And then the orange are the less than 30 percent?
A. That's correct.
Q. But more than zero?
A. More than zero.
Q. Right. Okay. Go to 152 to 155.
A. Yes.
Q. So you changed the representation of the residues in this set of images, right?
A. Yes.
Q. But you were using the same coloring

scheme?

A. The's green is once again those residues that tolerate 60 percent or more of the substitutions that were made.

Q. Is there something you're trying to convey about the size of the residues that are displayed here?

A. The spheres are roughly the same size within -- you know, within a certain small range because that has to do with the size of the atoms involved.

The reason for choosing that here is specifically to do two things. One, to show the extent to which these might lie on the surface of the protein. And you get that impression from how much they cover of the rest of the protein in a given projection.

But the other reason, which is even more important, is to show their physical proximity to one another. In other words, these are not isolated sets of spheres scattered around the proteins. These are clusters. And they're -- that's much easier to see in this kind of representation, at least for me and I think for most people of skill in the art.

Q. Did you perform any calculations to determine which residues were surface residues?

A. You can, and in some cases I did. All right? So, for example, you can replace this particular representation with a solvent-accessible surface representation. And in some cases, I did that, but I don't believe I illustrated that in the declaration ever.

Q. Did you do the actual calculations to measure the solvent accessibility of individual residues?

A. No. Although in PyMOL you can.

Q. Right. So the opinions that you're presenting don't explicitly identify a connection between positions that you're discussing and the solvent-accessible character of them?

A. Not quantitatively, no.

Q. All right. Let's go back to your table -- sorry. One -- sorry. Two more pictures, 162 to 163.

A. Yes.

Q. So these are -- these are surface ones?

A. Those are the solvent-accessible surface ones. That's correct.

Q. All right. And again, the coloring

1 scheme is the same coloring scheme you used in
2 your table.
3 A. Let me make sure that that's true. I
4 believe it is.
5 (Pause)
6 A. Yes, I believe that's correct.
7 BY MR. KUSHAN:
8 Q. All right, let's go back to 135 and 6,
9 which is your table.
10 A. Okay.
11 Q. So I want to understand the designation
12 of these positions as dark green. That's
13 100 percent tolerated, right?
14 A. It's 100 percent tolerant for the mut- --
15 substitutions that were made.
16 Q. Okay. If I had an instance where I had
17 only seven substitutions that were tested --
18 A. Um-hmm.
19 Q. -- and all of them are active, is it --
20 is it fair to infer that all 19 choices that
21 could be put in that position also would be
22 tolerated?
23 A. You -- it might. It would depend on what
24 those seven were.
25 Q. Did you --

A. Okay?

Q. Did you make determinations that the seven that were tested in one position were diverse enough to support that conclusion?

A. In some cases, I noted that, and -- but that's not the purpose of this table. It's not reflected in this table.

The table is where all the substitutions that were made, whatever they were, that were tolerated is dark green.

Q. Are you using the color designations in the table to indicate how a person of skill would view the ability to mutate the PH20 protein and expect it to retain activity?

A. Not in -- not by itself, no. You would start -- the person of skill in the art might start with this table because it's a convenient summary, but they would then go to the original data to find out what the substitutions were made at each position, the character of the amino acids, and so forth.

Q. And is -- is your opinion that the POSA would believe that any amino acid substitution tolerated at a particular position, for example, in the dark green ones, would be tolerated in any

1 PH20 mutant regardless of how many changes or
2 where those changes were in the protein?
3 A. Most of the time, yes. If the other
4 changes were in adjacent residues, residues in
5 contact with that one, then you would want to
6 look at the structure.
7 Q. Okay. So that's something you'd have to
8 kind of do on a case-by-case basis?
9 A. You would do that on a case-by-case basis
10 when you were trying to make the mutants that had
11 the purposes that you intended.
12 Q. All right. If I picked 15 of the dark
13 green spots to mutate --
14 A. Okay.
15 Q. -- is it your view that a protein that
16 had those 15 mutations in them would fold,
17 regardless of which amino acids were put in each
18 position?
19 A. That would depend on which mutations you
20 picked. If you picked a mutation that only
21 had -- a residue that was only mutated to one or
22 two others, you might be hesitant to make that
23 prediction without first checking with the
24 structure.
25 Say that residue was on the surface of

1 the protein, sticking out into the solvent, and
2 making no contact with any other residue in the
3 protein. Then even though you only had two
4 mutations at that position, you might well be
5 justified in assuming that you could make many,
6 if not all, substitutions at that position and
7 they would tend to be tolerated.
8 But it depends -- as I said, it's context
9 dependent, context in this case being structure.
10 MS. MARTIN: So we -- sorry. We've been
11 going for almost an hour exactly. So, Greg, do
12 you need a break?
13 THE WITNESS: I'm okay for another few
14 minutes.
15 MR. KUSHAN: Yeah. Why don't we just --
16 I think just a couple more questions and we can
17 take a break.
18 MS. MARTIN: All right.
19 BY MR. KUSHAN:
20 Q. So is there -- just kind of a surrogate
21 of evaluating tolerability, is there some number
22 of substitutions above which you would feel that
23 the position had been interrogated enough to
24 support the position being, for example, highly
25 tolerant or likely tolerant to change?

A. Not -- not on the basis of that question by itself, no. You would look -- as I said, you would look at what those substitutions were, and you'd look at where they were.

Q. All right. So I want to just drill down a little bit into that question and your answer.

So if I'm looking at a position let's say that had 18 or 17 alternatives tested and they all were active, would I -- would I be able to infer that basically any position in this protein that had 17 residues tested that retained activity, would that be enough to say I am comfortable that any position -- any amino acid will be tolerated at that position?

A. Most of the time, yes. I could conceive of a scenario where that might not be true.

Q. Well, if you put a proline in a place that it shouldn't be.

A. That would be one, but a more -- a more sensible one perhaps, if you say 17, would be -- let's pose the one you left out, phenylalanine, tyrosine, and tryptophan. So you've left out all the larger aromatic residues.

Q. Right.

A. Well, you might not know completely

1 whether or not those would give you the same
2 result until you looked at the structure. Okay?
3 If those residues, the other 17
4 mutations, are in a site that's not in contact
5 with the rest of the protein much, but not in a
6 buried region of the protein, then you might be
7 justified in saying phenylalanine, tyrosine, and
8 tryptophan will almost certainly be tolerated as
9 well. But if the packing around it is somewhat
10 different from that, then you might need to think
11 about it some more.
12 The -- you see, you don't want to just
13 use this. You want to use all the data in the
14 patent. The patent has a lot of data. You want
15 to use all of it in making sensible decisions.
16 That's what a person of skill in the art would
17 do.
18 Q. And again, so that the -- what you're
19 saying is that a person of skill in the art would
20 need to take this table, look at the character of
21 changes in individual mutations, study it in the
22 context of the position you're contemplating
23 changing, and then make judgments with all that
24 data to say, yes, this one is a substitution I
25 believe would be tolerated?

A. A person of skill in the art would use their skill in the art, and those are the different skills you're talking about.

Q. And so they would basically have to use all this information and translate it basically into sets of changes that they would conclude should be combined into a single protein?

MS. MARTIN: Objection. Object to form.

A. No. We haven't talked about combination. Okay? So I want to -- I want to keep my answer to what it was. Okay?

At a particular site, you asked me about whether, if you had a certain number of mutations, you would be justified in thinking that the rest that were not made might have the same property. I've tried to go through the reasoning process you would do to do that.

MS. MARTIN: Do you want to take a break now, since we've gone a few more minutes?

Greg, do you --

MR. KUSHAN: I'm happy to take a break if you want to. Do you need a break?

THE WITNESS: Not at the moment.

MR. KUSHAN: All right. So why don't we just --

BY MR. KUSHAN:

Q. So when you're doing this assessment of the types of residues at a position being tolerated, that's based on an assessment of interactions of that residue's atoms with essentially the neighbors of the -- of that residue?

A. Based -- let's just say based on the structural context of the residue. That's a simpler way to put it.

Q. What I'm trying to understand is, to reach a conclusion one way or another of an impact of a change at a position, you're -- you're trying to assess what would happen if an amino acid with a different character or size, what would happen if I put that in that place where the other one wasn't necessarily the same?

A. That's correct.

Q. All right. And that is dictated by the interactions of the new amino acid in the place of the old amino acid with the surrounding structure and -- and I guess solvent?

A. Yes.

Q. So it's the collective effect of solvent and neighboring residues that have the potential

1 to interact with the one that you've substituted?
2 A. Solvent, neighboring residues, but in
3 some cases, also the secondary structure that
4 you're in, that can make a difference, for
5 example.
6 Q. So a residue that might be tolerated in
7 an unstructured loop might not be tolerated if it
8 is part of an alpha helical sequence?
9 A. Perhaps. Or if it is at the end of an
10 alpha helix its charge may matter because of what
11 is called helix cAMPing effect. A person of
12 skill in the art knows all these things. And a
13 person of skill in the art will make use of that
14 knowledge together with the data in the patent.
15 Q. So using that kind of understanding of
16 assessment of interactions and environment, a
17 person of skill could conclude that a particular
18 amino acid substitution would be tolerated at a
19 particular position?
20 A. I think you would be able to make that
21 prediction with a high degree of confidence for
22 most of the mutations, yes.
23 MR. KUSHAN: All right. If you want to
24 take a break, we can take a break now.
25 THE WITNESS: That's fine.

1 MR. KUSHAN: All right.
2 THE VIDEOGRAPHER: Going off record at
3 1:58.
4 (Recess taken)
5 THE VIDEOGRAPHER: Going back on record
6 at 2:19.
7 BY MR. KUSHAN:
8 Q. So before the break, we were discussing
9 some of the information that led to your table
10 there. And we briefly touched on multiple
11 sequence alignments.
12 Can you just give me a better sense of
13 how a POSA would identify homologous proteins to
14 PH20 in the 2011 to 2012 timeframe and use that
15 with the multiple sequence alignment?
16 A. So a person of ordinary skill in the art
17 in 2011 would take the sequence of PH20, which
18 they have, and would put it through a program
19 like BLAST. I think both Dr. Hecht, Dr. Park,
20 and myself would all have stated that we would
21 tend to use BLAST. That was most commonly used.
22 BLAST would then go through -- you
23 would -- you could restrict that to all mammals,
24 you could restrict it to mammals and insects, or
25 you could -- you could look at every organism

1 under the sun. BLAST would then give you
2 sequences that had various levels of identity,
3 all right, not similarity, but identity to your
4 sequence. It would attempt to do so by
5 minimizing the number of insertions and gaps in
6 the alignment.
7 You would then tend to use cutoffs. All
8 right? 40 percent identity, or whatever. And
9 look at those alignments. And in most cases,
10 unless there were a lot of gaps of things, you
11 could be comfortable in saying that this sequence
12 with 40 percent identity or more to PH20 is part
13 of a family of PH20-related enzymes. And so you
14 would then begin to use that in multiple sequence
15 alignments. And you would pull other sequences
16 out in the same way.
17 Q. Okay. That's helpful.
18 Just to confirm, when -- when the BLAST
19 algorithms are selecting sequences for homology
20 they are not just doing kind of a 40 percent
21 overall identity, they are doing -- kind of
22 checking segments or regions and looking for
23 those segments to have a sufficient level of
24 identity?
25 A. Yes. They start by doing local

1 alignments and then extend it over the -- the
2 whole protein. And that was what was done in
3 2011. There have now been some refinements to
4 the algorithm. If you did it today, you might
5 get a few more additional proteins showing up.
6 But in general, the -- that technology was well
7 developed.
8 Q. I want you to look at pages 36 to 37 of
9 your declaration in paragraph 91.
10 A. Yes.
11 Q. So you see on -- there is an image of a
12 multiple sequence alignment, I think, on page 92,
13 right?
14 A. I am looking at page 36. Is that what
15 you are talking about?
16 Q. I'm sorry. It's 37.
17 A. Right. Paragraph 92?
18 Q. Yeah.
19 A. Okay.
20 Q. So that's -- that's the picture out of
21 your textbook, right?
22 A. Yes.
23 Q. And this is a multiple sequence alignment
24 of homologous proteins?
25 A. Yes, and that would have been done around

about 2000, 2001.

Q. Okay. The positions where the amino acid is identical in every sequence is in red, right?

A. Yes.

Q. And then there are -- there is an orange column with -- which is nearly all of them are identical --

A. Or a significant number anyway, yeah.

Q. And we call those conserved residues, right?

A. Relatively conserved, yes.

Q. Relatively conserved.

A. The word "conserved" gets misused sometimes. I tend to think of it as meaning it is always the same residue, but people -- people use it frequently to mean most of the time it is the same residue; and when it isn't, it is a residue that's similar.

Q. So it has kind of like a -- a similar character to the one that was there if it is not identical?

A. Precisely.

Q. Okay. And the presence of these conserved residues is indicating positions that are going to be important to the fold shared by

1 these homologous proteins, right?
2 A. Usually, yes.
3 Q. Could a POSA know whether one of the
4 conserved positions was going to be necessary for
5 those structure and activity without experimental
6 testing?
7 A. Say that again, please.
8 Q. Could a POSA have known from the position
9 of a conserved residue whether it was important
10 for both structure and activity without testing?
11 A. Conserve -- position where? In the
12 sequence or position in the structure?
13 Q. So having just the sequence, the
14 conserved sequence position, a person looking at
15 that conserved residue at that position in the
16 sequence, could they know whether that one was
17 going to be important for both structure and
18 activity without testing?
19 A. Unless one of the proteins in question
20 were a protein for which there was
21 three-dimensional structural information; or, or
22 for which experiments had been done that
23 identified one or more residues as being
24 essential for activity, for example. And that
25 was often done before structures.

If you didn't have those pieces of information, you would -- you would be hard pressed to know why something was conserved. You could make guesses, but...

Q. Is the -- is your kind of first instinct that the -- as a POSA, that it is important for structure?

MS. MARTIN: Object to form.

A. No.

BY MR. KUSHAN:

Q. No. Is it no because you can't reach a conclusion that conserved has any consequence?

A. No. That's because you would reach a conclusion that a conserved residue can have any consequence.

Q. Right.

So basically, the conserved residues are telling the person of skill in the art that this is likely to be a residue you shouldn't change?

A. It tells a person of skill in the art this is important to be what it is. It often won't tell you why.

Q. Would a person of skill in the art looking to modify, for example, PH20 avoid these conserved residues as positions they would

1 change?
2 A. Not given the information in the patent.
3 They would look at the information in the patent.
4 Q. Let's just go back --
5 A. Because this is a restricted range of
6 residues.
7 Q. Sorry. My question was not great because
8 I was focusing mostly -- I wanted it in the
9 context of an MSA.
10 If all they had was an MSA of the
11 homologous proteins, would a person of skill in
12 the art avoid the positions that were conserved?
13 MS. MARTIN: Objection. Scope.
14 BY MR. KUSHAN:
15 Q. When making modifications.
16 MS. MARTIN: Objection. Scope.
17 A. When you're making modifications, it
18 depends on the purpose. So if your purpose was
19 to identify catalytically important residues you
20 might focus on the residues that were conserved,
21 not avoid them. So it will depend on the
22 purpose.
23 BY MR. KUSHAN:
24 Q. If I am trying to make enzymatically
25 active mutants that have a change to them --

1 (Reporter clarification requested.)
2 BY MR. KUSHAN:
3 Q. If I am a POSA attempting to make
4 enzymatically active mutants of PH20, would I
5 avoid the conserved residues as positions to
6 change?
7 MS. MARTIN: Objection. Scope.
8 A. If you are trying to make enzymatically
9 active mutants, those wouldn't be the residues
10 you change first, probably.
11 BY MR. KUSHAN:
12 Q. You'd prioritize other residues?
13 A. You would probably prioritize other
14 residues, depending on what the sequence
15 alignment looks like. It's not something that
16 you want to be too general about without looking
17 at a specific case.
18 Q. Would a person of ordinary skill in the
19 art have believed, in 2011, that making a single
20 amino acid substitution at a position that is not
21 a conserved residue would be tolerated by a
22 protein?
23 MS. MARTIN: Object to form.
24 A. I am -- I am sorry. I've got to hear
25 that one again.

1 BY MR. KUSHAN:
2 Q. Would a person of ordinary skill in the
3 art who is trying to make an enzymatically active
4 PH20 have believed that they could modify a
5 position that is not a conserved residue and
6 expect that PH20 to retain its activity?
7 MS. MARTIN: Object to form.
8 A. It is probably too general a question to
9 give you a good answer to. All right?
10 BY MR. KUSHAN:
11 Q. So if I have mutational data combined
12 with an MSA, so I have mutated a bunch of
13 different positions, I am equipped as a person of
14 skill in the art with a number of positions, have
15 lost activity because of a mutation, and then I
16 have my MSA in this, which is identifying
17 conserved residues.
18 Does the combination of those two things
19 give the person, collectively, more information
20 than just the MSA?
21 MS. MARTIN: Objection. Scope.
22 A. So the multiple sequence alignment is
23 limited in its nature because there are lots of
24 reasons why residues get selected in evolution,
25 including the frequency with which codons can

1 change, for example.
2 You would -- the mutational data when it
3 is on the scale of what's in this patent, all
4 right, is where you would tend to start
5 (indicating).
6 Q. The -- in -- before 2012 and before 2011,
7 there were studies that had identified through
8 single point mutations effects on PH20 structure
9 and activity, right?
10 A. Yes.
11 Q. So that set of information would be
12 useful to a skilled person trying to make
13 modified PH20s, right?
14 A. Yes. Those you have maybe a half dozen
15 or so residues, something like that.
16 Q. Could you go to Dr. Park's declaration
17 again, which is 1004.
18 A. Thank you. Where?
19 Q. Go to pages 10 and 11.
20 A. Yes.
21 Q. And Dr. Park is describing kind of his
22 methodology of what he did at pages 10 and 11 --
23 A. Um-hmm.
24 Q. -- paragraphs 27 to 29.
25 A. Um-hmm.

1 Q. So he identified homologous PH20 --
2 proteins homologous to PH20 using a BLAST search,
3 right?
4 A. Yes.
5 Q. And he aligned it into -- from a -- from
6 multiple sequence alignment with Clustal Omega,
7 and that was a conventional tool back then,
8 right?
9 A. That's right. And I think he had about
10 90 sequences when all was said and done.
11 Q. Right. So those are steps that a person
12 of skill in the art would have taken in the 2011
13 to 2012 timeframe if they were undertaking a
14 study of protein for modifications?
15 A. Prior to the patent.
16 Q. Yes.
17 A. That's one of the things you could do.
18 Q. Okay. Go to paragraph 30. And do you
19 see --
20 A. Yes.
21 Q. He's also referring to an Appendix D-3.
22 Don't go there yet.
23 He's put a table on page 14 of what he's
24 identified as the "largely invariant residues" in
25 human PH20 from his MSA, right?

A. That's right.
Q. And do you understand what -- how he arrived at the selection of those residues?
A. He states in the paragraph, I take him at his word, that he did this based on positions where the amino acid was conserved 90 percent of the time or more, and non-identical amino acids appear in less than 5 percent of the proteins in the dataset.
Q. So he's taking these conserved residues because, out of the dataset, each amino acid is in -- that's on this list is there in the set of proteins at least 95 percent of the time?
A. That's one of the criteria that he's using.
Q. And that was a reasonable thing for him to do, right?
A. It's -- it's -- it's okay.
Q. Okay. So he's identified 68 of these largely invariant residues, right?
A. That's correct.
Q. Could you go to your declaration?
A. Yes.
Q. Page 148, paragraph 308.
A. Yes.

1 Q. So you point out that the Y184 mutant had
2 activity, and that is not one of the -- and
3 that's at a position -- there was a mutant made
4 from the wild type that went from tyrosine to
5 tryptophan, right?
6 A. Yes.
7 Q. And that's at one of the positions
8 Dr. Park had identified as one of these conserved
9 residues, right?
10 A. That's a position that he's identified as
11 a residue that cannot change.
12 Q. Right. And so did you -- that's one
13 mutant out of the set that was tested in the
14 patent, right?
15 A. One of those mutants had activity.
16 Q. Do you know how many mutants were tested
17 at that position?
18 A. I don't remember. We could look it up.
19 Q. Why don't we do that. Why don't you look
20 at this big sheet (indicating).
21 A. Um-hmm.
22 Q. And go to page 4. Are there page numbers
23 on this?
24 A. 184.
25 Q. Yeah. 184, which --

A. All right. And --
Q. So just tell me how many mutants were tested.
A. 3, 6, 9, 12 -- it looks like 15 or 16.
Q. All right. And how many mutants were inactive?
A. All of the others except tryptophan.
Q. Right. So 14 out of 15 amino acids test -- that occur in that position that were tested were inactive?
A. Correct.
Q. And you designated this a yellow on your rating, right?
A. Um-hmm.
Q. Because it wasn't 100 percent?
A. A, because it wasn't 100 percent, and B, it's interesting to me that it's tryptophan, a big bulky residue.
Q. So the big bulky residue was tolerated?
A. Yeah. At least that big bulky residue is. Phenylalanine is not. That's starting to teach you something.
Q. Okay. So would a POSA have viewed position 184 as being tolerant to amino acid substitutions?

A. A person of skill in the art looking at the mutagenesis data would have viewed that position as being tolerant to at least one substitution and possibly more because not all the 20 have been tested.

Whereas, if the person had relied only on a multiple sequence alignment, they would have assumed that residue could not be mutated at all.

Q. Got it. So there are three other possible amino acids that hadn't been tested?

A. Correct.

Q. Okay. And that leads you to conclude that you couldn't draw the conclusion that that had been tested enough in nature?

A. That's correct.

Q. All right. If it's not tested in nature, is it -- does that conclusion also apply to positions which hadn't been tested in a mutagenesis study?

MS. MARTIN: Object to form.

A. I'm not sure I understand the question.

Q. So nature tested -- let's say nature tested 15 out of the 20 amino acids.

A. At that position?

Q. At that position.

A. That's unlikely, but okay.
Q. But let's say if it's -- so if I had 15 tested in nature through the homologous proteins and you had 15 tested in the mutagenesis study, would they be equivalent in sites at that position?
A. No. Because they wouldn't necessarily be the same list of mutations.
Q. Sorry. I may have stated my question wrong.
One position -- the same position. You're looking at it through the lens of the MSA. You've got 15 changes in nature that are tolerated -- or not -- well, sorry. Let me frame the question differently.
There's 90 -- so we're at: 95 percent of all proteins have the same amino acid at that position.
A. Um-hmm.
Q. And there's one protein out there maybe that has a different amino acid.
A. One different amino acid.
Q. Right.
A. That's correct.
Q. So at that position, you have a lot of

1 proteins with invariant activity, invariant
2 occurrence. In your mutation -- in your
3 mutagenesis study, you have one that is not
4 inactive.
5 A. Yes.
6 Q. Four unknowns --
7 A. Yes.
8 Q. -- or three -- there unknowns.
9 A. Yes.
10 Q. Okay. So that conserved residue readout
11 is different, in your view, than the mutagenesis
12 study at that position?
13 A. You're comparing apples to golf balls.
14 Q. Right.
15 A. Okay? They're very different. Because
16 the one is in the context of a protein whose
17 entire structure is subject to variation by
18 evolution, but which, for most sequences, are
19 going to be very similar to each other because
20 they're going to be not so far apart on the
21 evolutionary tree. Since you've a lot of
22 sequences, then you're covering more of the
23 evolutionary tree.
24 In this -- in a case of the mutagenesis
25 data, you're doing something very precise.

1 You're taking the same protein, mutating one
2 residue, seeing what it does in the context of
3 the wild-type sequence.
4 Q. What about the converse, where you look
5 in the -- in the MSA data and you see
6 15 different amino acids occurring at that
7 position.
8 A. Correct.
9 Q. Does that give a more comparable
10 assessment of tolerability to the mutagenesis
11 study that has also tested 15 amino acids at that
12 same position?
13 A. So I got half the question, but it
14 sounded like the two halves were the same, which
15 means I must have misunderstood it. I apologize,
16 but please try again.
17 Q. So one position -- there's one position
18 that is looked at through the lens of MSA data.
19 A. Okay.
20 Q. Looking at the same --
21 A. And what do we see when we look at it?
22 Q. We see 15 different amino acids of
23 various kinds being tolerated at that position in
24 nature.
25 A. Okay.

1 Q. And now I have a mutagenesis study that
2 has studied the same position and has tested
3 15 alternative amino acids.
4 A. Same 15?
5 Q. Same 15.
6 Would you draw the same kind of
7 conclusion about tolerability from the MSA data
8 as you would from the mutagenesis data?
9 A. You would say that -- you could say that
10 the two sets of data were consistent. All right?
11 That's what you would say.
12 Q. If you concluded that the mutagenesis
13 from the mutagenesis study, that it would be
14 tolerated at that position, would you reach the
15 same conclusion of being tolerated from the MSA
16 data?
17 A. If you had the MSA data alone, you might
18 not -- you might be a little more careful about
19 drawing that conclusion, for the reasons I
20 indicated. It's a very limited set of proteins
21 you're looking at.
22 I think the MSA -- the mutational data,
23 you're more comfortable in drawing a specific
24 conclusion like that at that position under the
25 conditions of the -- the way this study was done.

1 Q. So you identify I believe three positions
2 where there was variation in the set of positions
3 that Dr. Park had identified as essential.
4 A. Um-hmm.
5 Q. Did you identify any other positions
6 where --
7 A. Yeah, there was -- there were others. I
8 just listed these.
9 Q. Where -- what other ones were they?
10 A. I don't remember. I'm sorry.
11 Q. So based on what you have in your
12 declaration, 65 out of the 68 positions were
13 consistent with what Dr. Park had reported in
14 his --
15 A. I don't -- I can't say that.
16 Q. So is -- did you -- did you reach a
17 conclusion before you completed your declarations
18 that there were additional positions that were
19 different in the conclusion of being conserved
20 relative to Dr. Park's MSA analysis?
21 A. Yes. I believe there were more than
22 three.
23 Q. Did you write it down anyplace?
24 A. Sorry. I did not.
25 Q. So as far as we know, from what you put

in your declaration, you found three?
A. We know there are at least three.
Q. But we can't know what the rest might be?
A. Not -- not without repeating what I did.
Q. All right. So before we were asking about views you had. Why don't we go back to the -- one second.
MR. KUSHAN: 135?
MS. MARTIN: Yes.
BY MR. KUSHAN:
Q. Go back to your table that's on page 135.
A. Sorry. Which document are we looking at? I kind of have a mountain of documents here.
Q. Yes. Your declaration.
A. Thank you.
Q. Just go to 135. It is the color coded one.
A. Yup.
Q. So we had a discussion before about the dark green positions?
A. Um-hmm.
Q. And you -- I began asking you a question about the light green positions, and I think you indicated that those were more of a -- have to assess each change individually?

MS. MARTIN: Object to form.
A. You always want to look at what was done in the patent. You always want to look at the data you have. You don't want to ignore it. You want to take a look at the total body of data. Not just for those positions, for anything you look at. A person of skill in the art would not ignore the data.
BY MR. KUSHAN:
Q. Right.
Can you go to page 174 of your declaration.
A. Yes.
Q. And look at paragraph 358.
A. Yes.
Q. You say: "A person of skill in the art could also select positions that tolerate 60% or more of the tested substitutions and still have a reasonable expectation of success in maintaining activity."
A. Yes.
Q. You are not referring to other factors, you are just saying 60 percent of the tested mutants is the basis of this reasonable expectation of success, right?

A. In this particular context, yes.
Q. And this is in the context of the frequency of tested out of the set that was tested?
A. Yes.
Q. As it is stated, just 60 percent of however many were tested?
A. Yes.
Q. And that's your opinion?
A. Yes.
Q. And that -- so if I was a person of skill in the art and I looked at the mutagenesis data and it had seven mutants tested and five of them were active, that would give the person a reasonable expectation of success that a mutation of any -- to any amino acid at that position would have a reasonable expectation of success in maintaining activity?
A. No, I didn't say that.
Q. Okay.
A. All right. You would want to look at those residues that had activity. The 60 percent that did. And you would want -- if you were trying to make a different mutation that was likely to fall into the same category, you would

1 want it to have somewhat similar properties to
2 the residues that were changed. Okay?
3 So if it were a large hydrophobic
4 residue, you would want to know if the large
5 hydrophobic residues tended to do that, for
6 example.
7 Q. Are those types of changes you are
8 speaking of called conservative changes?
9 A. They could be. But conservative can have
10 different meanings in context. So it could mean
11 a charge conservation only. It could mean a
12 conservation of shape. It could mean a
13 conservation of polarizability, or position in
14 the structure could be important for what
15 property you think is -- is a conservative
16 property. But often, it will mean what you say.
17 Q. So if I understood the last answer you
18 gave, kind of a chemical or size attribute of the
19 residue in the context of the position is what
20 you would look to to assess?
21 A. That's the first thing you would look at.
22 Q. All right. And is that -- the use of
23 that perspective something that gives a
24 predictable indicator of whether a substitution
25 to a similar residue is going to be tolerated at

1 the position?
2 A. Most of the time, it should.
3 Q. Sometimes it won't?
4 A. If you don't have enough substitutions at
5 that position, you might -- it might -- you might
6 have to not -- not be able to just use the
7 mutational data. You might have to really look
8 carefully at the structure if you are putting in
9 an amino acid that's very different. But you do,
10 at least, still have the structure. And so that
11 will help you to some extent.
12 Q. Now, before you -- when I asked a
13 question about substitutions, you had emphasized
14 that your comments were made with respect to a
15 single substitution, right?
16 A. That's right.
17 Q. Why?
18 A. Because I was referring -- I was asked to
19 comment within the context of the data in the
20 patent.
21 Q. All right. So you would not be able to
22 extrapolate the data in the patent to mutations
23 that have multiple changes to them?
24 MS. MARTIN: Object to form.
25 BY MR. KUSHAN:

1 Q. Sorry. Modified PH20 polypeptides that
2 are incorporating multiple changes?
3 MS. MARTIN: Object to form.
4 A. I didn't say I wasn't able to do that.
5 BY MR. KUSHAN:
6 Q. So let me -- I am just trying to
7 understand the restraint you are expressing about
8 that last opinion.
9 Is the -- are you able to rely on the
10 tolerance criteria that you laid out in your
11 table to predict the effect of making multiple
12 changes to PH20?
13 A. A person of skill in the art could use
14 the information in that colored table together
15 with the other information in the patent -- let's
16 keep remembering we want to look at all of the
17 data -- and could make predictions about multiple
18 substitutions, yes.
19 Q. And these predictions, those are based on
20 your comments about each individual mutation?
21 A. The individual -- the data for the
22 individual mutations is one of the most important
23 things you would take into consideration, yes.
24 Can we turn off the sound for a second?
25 MR. KUSHAN: Do you just want to take a

1 break?
2 MS. MARTIN: Do you want to go off the
3 record?
4 Yeah, let's take a break.
5 THE WITNESS: No, I am just getting rid
6 of my leg wrappings.
7 THE VIDEOGRAPHER: You are fine.
8 (Discussion off the record)
9 THE WITNESS: Okay. I am good.
10 THE VIDEOGRAPHER: All set.
11 BY MR. KUSHAN:
12 Q. So if I could have you go to page 156,
13 paragraph 323.
14 A. Yes.
15 Q. So in this paragraph, you are discussing
16 substitutions at individual -- individual --
17 where the substitution --
18 In this paragraph, you are discussing
19 substitutions that are in different parts of the
20 protein?
21 A. I am discussing what criteria you might
22 use in thinking about those, yes.
23 Q. All right. And what you say is, a person
24 of ordinary skill, POSA, would expect that if
25 substitutions were made at these -- at the light

1 green residues in different parts of the protein,
2 they would be independent of each other, and that
3 that person would generally expect multiple
4 independent changes to be tolerated.
5 A. I am talking about the distribution of
6 the mutations in space. The structural space.
7 If those are different -- if those are separated
8 from each other in the structure there is a high
9 degree of likelihood that they will operate
10 independently.
11 Q. Can multiple changes to the protein in
12 these -- I call them spatially distinct; is that
13 fair?
14 A. Yes.
15 Q. So a POSA makes changes at spatially
16 distinct regions of the protein. Is it possible
17 that even as separate spatial, distinct
18 regions --
19 (Reporter clarification requested)
20 (Discussion off the record)
21 A. Want me to do it for you?
22 BY MR. KUSHAN:
23 Q. I have a feeling you will.
24 So I am wondering if it's possible for a
25 substitution made in spatially distinct parts of

1 the protein can still unpredictably cause the
2 protein to not tolerate both of those changes?
3 A. It can happen. It is less likely that it
4 does happen.
5 Q. Do you have any sense of frequency with
6 which it happens?
7 A. Not in any absolute terms. But as a
8 general rule based on years of experience, they
9 are more -- they are certainly more likely to be
10 independent than not.
11 Q. So when you are inserting changes at
12 different spatially distinct parts of the
13 protein, can the mutations cause formation of
14 intermediate states of the protein during the
15 folding process relative to the native sequence?
16 A. Theoretically, yes. Practically, those
17 are -- there are very few residues that do that
18 in any given protein. And in some cases, none
19 have been found.
20 Q. What -- what are the circumstances where
21 it does happen?
22 A. There is not a rule of thumb. Because
23 the folding pathways of different proteins are
24 quite different.
25 Q. They are not really things that can be

1 easily characterized, right?
2 A. It's hard to -- it's hard to do the
3 experiments. Okay. And it was thought,
4 originally, that there might be a common pathway.
5 Doesn't seem to be true.
6 Q. Can a -- can a set of mutations that are
7 spatially -- in spatially distinct parts of the
8 protein cause a particular combination of changes
9 in the sequence to cause a --
10 If changes are made in spatially distinct
11 regions of the protein substitutions, can the set
12 of substitutions cause the protein to not fold?
13 A. It's been, it can happen but it is rare.
14 For changes that are spatially distinct like
15 that, it is rare.
16 Q. Do you -- can you predict when they will
17 impact folding?
18 A. If you have a protein whose folded
19 pathway has been characterized, yes. If you
20 don't, it will depend to some extent on the
21 protein. There are proteins that belong to
22 families where one member of the family is
23 folding pathway characterized. You might assume
24 that that pathway is common. The short answer
25 is, not easily.

Q. Okay. All right. So go to page 156 and look at paragraph 324.

A. Yup.

Q. So in this paragraph, you are addressing multiple changes that are made where the changes are more proximate to each other, right?

A. Yes.

Q. And what you say is: "A POSA would be able to make informed decisions about making several changes close together on the protein using the data in the '600 patent regarding which substitutions were tested and the results for each, combined with an assessment of the local environment of the residues in question in the protein."

That sounds, generally, what you've been saying in the last few answers you have given me, right?

A. Yes. Except there's even more of a structural consideration here.

Q. Right. And what is that?

A. Because the residues, for example, might be interacting, in which case, you'd want to know what parts of the residues interact and how they interact.

Q. Is that -- sorry. The person of ordinary skill would have to use a PH20 homology model to do the assessment of those types of set of changes?

A. Yes. But a person of ordinary skill in the art would have already made that model.

Q. So would the person make a variance sequence and then model the variance sequence in a tool like SWISS-MODEL to do that?

A. You can. I did in some cases. You could also -- depending on the nature of the substitution and where it is, you could simply use one of the tools in PyMOL or other programs like Coot to replace the amino acid in the structure without doing anything to the surrounding environment. You would -- that would be most commonly done for residues on the surface.

Q. Do you -- are you familiar with how SWISS-MODEL creates models?

A. Yes.

Q. Does SWISS-MODEL, in the development of a model, take into account whether the modeled sequence is a naturally occurring protein?

A. SWISS-MODEL first tries to find a

1 naturally occurring protein sequence that is
2 highly homologous to the sequence it is trying to
3 model. That's the first thing it does. Okay?
4 It doesn't -- if it can't find one that
5 covers the whole protein, it may look at various
6 segments of it.
7 Q. So I -- there's two -- kind of two
8 variables in the -- in my question here. So
9 certainly there's a template that's going to be
10 selected for a sequence that's submitted to
11 SWISS-MODEL, right?
12 A. If it can find one, yes.
13 Q. All right. And then the sequence itself,
14 does SWISS-MODEL factor into any of its
15 assessment of the model whether that is a
16 naturally occurring protein sequence as opposed
17 to an artificial sequence?
18 A. I have no idea. But as of 2010, I think
19 the only thing in the database SWISS-MODEL was
20 using were naturally occurring sequences. I
21 don't think there's an artificial sequence in it.
22 Q. Right. I'm still doing a poor job of
23 explaining my question.
24 So I have two things that I'm matching.
25 I have an amino acid sequence, and I have a

1 solved structure that is a template structure
2 that could be used by SWISS-MODEL.
3 A. Right.
4 Q. Right? So I have a sequence that has not
5 yet been experimentally determined as to its
6 structure.
7 A. Yes.
8 Q. And what I'm wondering is, when I put
9 that sequence into the Swiss model algorithm,
10 does SWISS-MODEL account for the fact that the
11 sequence is a naturally occurring protein or if
12 it's an artificial sequence?
13 A. No. SWISS-MODEL only looks for
14 homologies. It doesn't look at the organism or a
15 source of the protein, as far as I know.
16 Q. And if it were a naturally occurring
17 protein, you'd know that protein folds, right?
18 A. Most of them. Not all of them.
19 Q. Sure. For the -- for the assumption I'm
20 making here, this is a protein that you can, for
21 example, isolate.
22 A. If it's an -- let's say it's an enzyme.
23 Q. So it's an enzyme that occurs naturally.
24 A. Then you'll -- then it faults.
25 Q. Okay. So you -- you have a sequence

1 associated with a folded protein going into
2 SWISS-MODEL to create a PH20 homology model,
3 right?
4 A. Yes.
5 Q. Okay. So what I'm wondering is, if I
6 send a sequence in for modeling to SWISS-MODEL
7 that is an artificial sequence, that isn't one
8 than has been demonstrated to fold and be
9 functional, does SWISS-MODEL account for that in
10 any way in the output of the model results?
11 A. Only in -- to the extent that it might
12 not have very -- any significant sequence
13 identity to the existing sequences in its
14 database. But if it does, then SWISS-MODEL
15 doesn't care where it comes from.
16 Q. So SWISS-MODEL -- when you run a job with
17 SWISS-MODEL, you get a report back that gives you
18 quality metrics of the model, right?
19 A. Um-hmm.
20 Q. And one of them is an overall quality
21 score, right?
22 A. Yes.
23 Q. And the other perspective is a
24 residue-by-residue quality metric?
25 A. A local quality.

Q. A local quality.
MR. KUSHAN: Let me introduce Exhibit 1070.
BY MR. KUSHAN:
Q. While we're waiting for 1070, another basic question about SWISS-MODEL.
When I have two proteins, a template protein and a sequence that's being modeled, the SWISS-MODEL can only reliably give you a model for the overlapping portion of the two sequences if the -- like, for example, if the -- if the sequence you're sending in is longer than the structure, the sequence associated with the structure can't model the part that extends past the boundary of the other protein, right?
A. In 2010, it could not do that.
Q. Okay. So when you're looking at the models coming back from SWISS-MODEL in 2010, you're going to restrict your analyses to the overlapping part that's based on a template?
A. Those are the reliable parts.
Q. Okay. This is Dr. Park's -- this is Exhibit 1070.
A. Um-hmm.
Q. And this is the SWISS-MODEL report that

1 came back when the -- I think this is the
2 D320K PH20 model.
3 And in the middle of the page, you see
4 this histogram with red and blue. That's the
5 local quality score?
6 A. Yup.
7 Q. Okay. And when you're doing your
8 assessments of modeling with the SWISS -- with
9 the PH20 homology model, are you relying on
10 essentially the portions of the local quality
11 region that are kind of consistently either
12 blue -- or, well, consistently blue?
13 A. You take the -- you trust those more.
14 Okay?
15 The red ones are red for a variety of
16 reasons. All right? If you just have an
17 occasional red one here, it may simply mean that
18 the sequence identity at that point was so
19 different that it's not quite sure what might
20 happen. But if you're looking at blocks of red
21 residues, those tend to be loops, and loops in
22 2010 were not as well modeled by SWISS-MODEL as
23 other parts of the structure.
24 Q. So it's fair to say that where you see
25 those stretches of red, you're going to be a

1 little bit more cautious about predicting the
2 effective changes in that region?
3 A. On structure -- affect on structure, yes,
4 yes. Um-hmm.
5 Q. Okay. When you formed your opinions in
6 this case, did you consider the local quality or
7 overall quality metrics of the model you created?
8 A. Yes. When I used the model, I did.
9 Q. All right. This is --
10 MR. KUSHAN: I'm going to introduce
11 Exhibit 2183.
12 THE WITNESS: Thank you.
13 BY MR. KUSHAN:
14 Q. And this is the exhibit that was provided
15 in this case. Did you create this printout?
16 A. Looks like it.
17 Q. I don't see any local quality scores on
18 this.
19 A. We certainly calculated them.
20 Q. Were --
21 A. Okay?
22 Q. Did you --
23 A. You can't not calculate them. The
24 program does it.
25 Q. Right. What I'm wondering is, did you

1 create this and kind of view this on a computer?
2 A. I did, but I -- I didn't massage it in
3 any way. I just downloaded the files and printed
4 them out.
5 Q. Got it.
6 A. So I may have missed the file that had
7 the quality control, but I remember -- I believe
8 I even stated in my declaration, I think I can
9 find it for you if I had to, that the quality --
10 the local quality control in the model I
11 generated was very similar to that in the model
12 that Dr. Park generated, and that's true.
13 Q. Okay. So there's basically the same
14 regions at -- the same reliable regions in them?
15 A. Yes.
16 Q. Okay.
17 A. And in fact, you can sort of see that
18 from the color scheme, you know? And the
19 appearance of the model, you can see how similar
20 the models are if you look at the two pictures.
21 Q. So the red is deviation from the
22 template?
23 A. Yeah. I think so. Yeah.
24 Q. Okay. And then orange and yellow are not
25 as deviant, but -- and then this green --

A. But, yeah, in any case, it gives you a sense of the extent to which these model structures are -- resemble one another.

Q. Do those -- so these are factors that go into the assessment of, you know, confidence and the prediction of the change, right?

A. Yes. And -- that and the overall sequence identity, of course, which is around 40, 41 percent in this case, as I recall.

Q. Okay.

A. I might add, in 2024, SWISS-MODEL does a better job of modeling loops than it used to. We have more loops.

Q. Right.

So do you think that in 2011 or 2012, a POSA using only a homology model could have predicted the effect of making five changes that are close together in a -- in the PH20 protein?

MS. MARTIN: Object to form.

A. I cannot answer that without knowing which five changes and where they are.

Q. So it depends on the placement in the --

A. It will be context dependent to a large extent.

Q. And the same would be true if I asked you

1 the question with 15 changes?
2 MS. MARTIN: Object to form.
3 A. A person of ordinary skill in the art
4 probably wouldn't be doing that.
5 Q. And why not?
6 A. Because you wouldn't need to.
7 Q. You wouldn't need to?
8 A. Yeah. You'd be able to make -- you'd
9 almost certainly be able to make the kinds of
10 things you'd want to make with fewer changes than
11 that.
12 Q. So you're saying that no one would make a
13 PH20 protein with more than five changes?
14 A. No. I'm saying that you would rarely,
15 rarely, make PH20 with 15 changes.
16 Q. Is that -- is that because it's
17 unnecessary to achieve the purpose you're aiming
18 for?
19 A. Yes.
20 Q. So is it also true that the more that you
21 introduce as changes, the greater the likelihood
22 is that it may have a problem such as folding or
23 loss of activity?
24 MS. MARTIN: Object to form.
25 A. No. It will depend on where they are and

1 what they are. The primary -- primary reason is
2 a person of ordinary skill in the art would be
3 more efficient than that.
4 BY MR. KUSHAN:
5 Q. But isn't it correct that each -- each
6 position introduces some amount of
7 unpredictability as to the effect of the folding
8 on the protein, right?
9 A. No.
10 Q. No?
11 A. Because for some of these positions we
12 have virtually every amino acid in the database,
13 and so we know what they do.
14 Q. So in the database positions where you
15 have, let's say, three or five mutants tested,
16 for those positions are they different? Would
17 that be a different answer?
18 A. They could be more unpredictable, it
19 depends on what change you would make. A person
20 of ordinary skill in the art would probably look
21 at the changes that were made, and if they needed
22 to change that residue at all -- and they might
23 not choose to change that residue at all, but if
24 they needed to change that residue at all, they
25 would probably select an amino acid with

1 properties similar to the ones that did whatever
2 it is they wanted it to do.
3 MR. KUSHAN: Would you like to take a
4 break? It has been a little bit more than an
5 hour.
6 THE WITNESS: No. I am okay. The
7 massage of the calfs helped.
8 MR. KUSHAN: Why don't -- why don't we
9 take a break.
10 MS. MARTIN: Let's take a break.
11 THE WITNESS: Okay.
12 MR. KUSHAN: It won't be a long one.
13 THE VIDEOGRAPHER: Going off the record
14 at 3:08.
15 (Recess taken)
16 THE VIDEOGRAPHER: Back on record at
17 3:30.
18 BY MR. KUSHAN:
19 Q. Dr. Petsko, did you discuss anything
20 relating to the --
21 A. One second because I am now having
22 trouble hearing.
23 THE WITNESS: Check to see -- let's see
24 if that thing is turned on (indicating). That's
25 on all right. It has got battery. Okay. Let

me --

MR. KUSHAN: Do you want to go off the record and --

THE WITNESS: Yeah, sorry. I am going to boost --

MR. KUSHAN: That's okay.

THE WITNESS: I'm going to boost the volume.

THE VIDEOGRAPHER: Going off the record at 3:31.

(Recess taken)

THE VIDEOGRAPHER: Back on record at 3:31.

BY MR. KUSHAN:

Q. Dr. Petsko, can you go to page 130 to 131 and look at paragraphs 258 to 260.

A. 250?

Q. Sorry. Paragraph 258, page 130.

A. Yup. Got it.

Q. So between 258 and 260, you are describing how you --

A. Let me read them for a second.

Q. Sure.

(Pause)

A. Okay.

1 BY MR. KUSHAN:
2 Q. So this is describing kind of how the
3 patent classified the mutants into the different
4 categories of active mutants or inactive mutants?
5 A. Yes.
6 Q. Okay. And an active mutant was -- well,
7 first, each mutant was tested with two assays,
8 right?
9 A. Yes.
10 Q. And if one of the assays had a score of
11 40 percent relative activity to the control, then
12 it was classified as an active mutant, right?
13 A. 40 percent or greater.
14 Q. 40 percent or greater of the control.
15 And then what was reported in the table, Table 9,
16 was an average of the two activities?
17 A. Yes.
18 Q. Okay. So some of the instances are below
19 40 percent and they are still classified as
20 active mutants?
21 A. That's correct. That's because one of
22 the measurements was less.
23 Q. All right. There is two tables, a
24 Table 3 and Table 9 that are devoted to active
25 mutants and --

A. Yes.
Q. -- there is a Table 5 and a Table 10 for the inactive mutants, right?
A. I think that's right.
Q. Okay. Just look at footnote 18.
A. 18?
Q. 18. Which is on page 133.
A. That's page 133?
Q. Yeah.
A. Yes.
Q. And you were saying in footnote 18 that if you discovered this -- a discrepancy between 3 and 9, you went with Table 9's data conclusion, right?
A. Yes.
Q. And the same thing for 5 and 10, you went with Table 10?
A. Yes.
Q. So basically, if you had an inconsistency in the active mutant pair, you went with the Table 9 classification. And then with the inactive 5 and 10, you went with the Table 10 classification?
A. Yes.
Q. Did you identify any discrepancies

1 between Tables 9 and 10?
2 A. I don't recall.
3 Q. Did you look for any inconsistencies
4 where perhaps a mutant was double counted,
5 basically?
6 A. Yeah. I looked for that a little bit,
7 but I don't know that I was completely
8 systematic.
9 Q. If you had encountered any of those which
10 were classifying as the same mutant as both
11 active and inactive mutant, you couldn't really
12 rely on that for your tolerance score card,
13 right?
14 A. You might be cautious about that.
15 Q. Because that -- the classification based
16 on the percentages are based on just how their --
17 how a mutant is classified, as an active or
18 inactive, right?
19 A. Yes.
20 Q. So probably more cautious to take that
21 off the table as --
22 (Simultaneous crosstalk)
23 A. You could take it off the table or you
24 might look at some of those individually a little
25 bit more carefully.

1 Q. But for the -- just for your table, you
2 would probably take it off that because --
3 A. You mean the summary table?
4 Q. Yes.
5 A. Yes, you might.
6 Q. Okay. I want you to go to the '731
7 application, which is the -- this one
8 (indicating).
9 A. The big one.
10 Q. Yeah.
11 A. Yup.
12 Q. And you might want to take the binder
13 clip off because it is hard to --
14 A. I -- I had that thought.
15 Q. Could you go to page 250.
16 A. Yes. You mean Example 4?
17 Q. Yes. And I just want to walk through
18 this. In the active -- this is part of the
19 patent that is describing the active mutants
20 classification, right?
21 A. Yes.
22 Q. And it indicates that measured activity
23 values for samples of positive controls were used
24 to calculate the -- the percent activity values
25 for all of the mutants, right?

A. I am not -- let me see. You are talking about page 251?

Q. On page -- sorry. Page 251. Thank you.

A. Just a second.

Q. So the values that are reported in Table 9 are a percentage of a positive control value, right?

A. Yes, that's the normalization.

Q. That's the normalization. So they normalized relative to the wild-type PH20 that was being produced essentially on the same plate, right?

A. That's my understanding.

Q. Okay. And so there are a lot of samples of positive controls in this primary screen they did, right?

A. Yes.

Q. Did you find any values of positive control samples in the part of the patent relating to this Example 4, classification?

A. I don't recall.

Q. Do you recall seeing any data outside the patent that showed information about the positive control variability in activity?

A. Outside of the patent?

Q. Yes.
A. No, I don't think so.
Q. If the -- if the activity of the positive control varies by sample, the relative activity is also going to vary of the tested mutants, right?
A. Yes.
Q. Did you take that into account when you were evaluating the dataset?
A. A person of ordinary skill in the art would expect that there will be variability in measurements -- okay? -- that are repeated like that. It depends on how big a variability, how big the difference is. I tried to look at that in some cases.
Q. What would -- how big does a variability in the positive control have to be for you to have a concern of the values that you are evaluating at the --
A. So it depends on the nature of the assay and so forth. For the data I looked at, okay, I was happy if the variability was less than 10. 10, 15 -- 10 to 12 percent, something like that. That didn't surprise me too much.
Q. Did you -- did you attempt to learn of

1 the variability of the positive controls in the
2 primary screen?
3 A. How was I to do that?
4 Q. For example, did you ask counsel, or --
5 A. No.
6 Q. All right. Just to be clear, the
7 classifications in your table of the mutants
8 rests on the data of each mutant as its
9 activity readout?
10 A. You mean the color --
11 Q. Yes.
12 A. -- chart?
13 Q. Yes.
14 A. Yes, although we were also careful to
15 look for trends. Okay? On the data. That's
16 important.
17 Q. Trends in what sense?
18 A. In the sense that if you have -- you
19 know, if the measurements don't agree they
20 might -- they might be not agreeing but within
21 the same general direction. All right?
22 Increased activity, decreased activity. Those
23 are the things you pay attention to.
24 Q. Sorry. I'm not quite understanding. Are
25 you talking about in a positional stretch of

1 mutations?
2 A. Yes.
3 Q. So if you are looking at, like, 300 to
4 310, you are seeing a consistent increase in
5 activity, that's what you --
6 A. If you do, that might be useful
7 information.
8 Q. Is that what you actually did?
9 A. In some cases, we noted this. I noted
10 this. Okay.
11 Q. As far as the kind of measurement of
12 the -- or assessment of the data itself, you just
13 took at face value the activity readouts?
14 A. To a large extent.
15 Q. All right. And before, you had pointed
16 out that when the PH20 mutant is showing activity
17 such as ones that are in Table 9, those also
18 convey to you that those proteins are properly
19 folded, right?
20 A. Yes.
21 Q. Okay. Would some level of activity --
22 you're looking for activity of the mutant as a
23 basis for that conclusion of the protein being
24 properly folded, right?
25 A. Yes. I mean, remember that enzymatic

activity's hard to achieve. All right? So -- and enzymes are very efficient catalysts. So 5 percent enzyme activity doesn't sound like much, but it could actually represent a considerable amount of chemical turnover. So -- and you wouldn't normally expect to get that from a misfolded protein.

Q. Okay. Could you go to page 293 of Exhibit 1026.

A. Are we still in the same document?

Q. Yup.

A. That's Table 12?

Q. Table 11.

A. Um-hmm.

Q. Table 11.

A. Got it.

Q. Do you see Table 11?

A. I do.

Q. Okay. And do you know what the data is relating to in Table 11?

A. I'm not sure what the question --

Q. Why don't you -- why don't you back up a couple pages? This --

A. Yeah. I'm not sure what the question means.

Q. You -- do you -- so my question -- I want to first make sure you understand what you're looking at, a much simpler thing to do.

A. Actually, I'm backing up quite a few pages.

Okay.

Q. Sorry. Now --

A. Yeah. This is the primary screen data, as I recall.

Q. I'm sorry.

A. If you're talking about Table 11.

Q. No. Keep going back. This is --

A. Back or forward?

Q. Backward. You see this is Example 5?

A. See if what?

Q. This is Example 5, right?

A. Example 5. I'm sorry.

Q. Go back -- go backwards one more page.

A. Oh, got it. Yeah. Okay.

Q. So do you remember that some mutants were tested for -- under different temperatures and in the presence of m-Cresol?

A. Yes.

Q. Okay.

A. I do.

1 Q. And that's in -- that's what's being
2 described in Example 5, right?
3 A. Yes.
4 Q. Okay. So go back to page 293. 2-9-3.
5 A. Okay.
6 Q. And you see in the bottom of the Table 11
7 there's a bunch of samples that were portrayed as
8 being positive controls?
9 A. Yes.
10 Q. And that's showing, in the first four
11 columns, testing of the positive control at
12 4 degrees and 37 degrees, right?
13 A. Yes. In the pres- -- in the absence of
14 any phenol.
15 Q. Correct. So the -- basically, these
16 are -- these -- this is one glimpse into the
17 variability of the wild-type PH20 activity,
18 right?
19 MS. MARTIN: Object to form.
20 Q. This is -- this --
21 A. I missed the last two words.
22 Q. So I'll restate the question. This is
23 giving you some insights into the variability of
24 the positive control that was used in these
25 hyaluronidase assays, right?

1 MS. MARTIN: Object to form.
2 A. No. There's more -- it's more than that.
3 Q. There are 17 samples tested --
4 A. Yes.
5 Q. -- as the positive control. And they
6 have both values of two assays of each positive
7 control, right?
8 A. Yes.
9 MS. MARTIN: Object. Sorry.
10 BY MR. KUSHAN:
11 Q. So this is data you could have analyzed
12 to draw conclusions about the variability of the
13 wild-type PH20 activity in the assay for
14 hyaluronidase activity, right?
15 MS. MARTIN: Object to form.
16 A. At a given temperature, okay, it tells
17 you something about the assay results. All
18 right? You're looking at different batches of
19 protein and so forth, so the number of sources of
20 variability here.
21 It's also, remember, an assay that's
22 normalized, all right, to a soluble alkaline
23 phosphatase. That in turn has variability. All
24 right?
25 Q. So there's -- there's two sets of

1 variables that influence the readout of
2 each mutant --
3 (Simultaneous crosstalk)
4 A. Two at least.
5 Q. Okay. Is the --
6 A. Yes.
7 Q. So you didn't attempt to calculate the
8 range of activity that was observed in the
9 positive control at either of the two
10 temperatures?
11 A. No. I did not think that was
12 appropriate.
13 Q. Did you review Dr. Hecht's analysis of
14 the positive control data?
15 A. I -- I recall it, but I don't recall it
16 in detail.
17 Q. Do you recall his conclusion about the
18 variability in the positive control?
19 A. I know he concluded that it was variable,
20 but I don't remember his -- his numerical answer.
21 Q. Okay. And you're not offering any
22 different opinions relative to Dr. Hecht on that
23 point, are you?
24 MS. MARTIN: Objection. Scope.
25 A. I'm not offering an opinion on that,

1 period.
2 Q. Okay. All right. Could you go back to
3 page 251?
4 A. 251. Yes.
5 Q. And look at the paragraph that goes from
6 line 14 to 20.
7 A. Line?
8 Q. 14 to 20.
9 A. Okay. Um-hmm. Um-hmm.
10 Q. So this is reporting that over 600 tested
11 mutants exhibit activity that's increased
12 relative to wild type, right?
13 A. Yes.
14 Q. And then it starts walking through some
15 more specific observations?
16 A. Um-hmm.
17 Q. It says 536 mutants exhibited 120 percent
18 or greater activity, right? And then 75
19 exhibited 300 percent or greater activity?
20 A. Um-hmm.
21 Q. There weren't any other percentage
22 thresholds that the patent called out, right?
23 A. No. I think that's right.
24 Q. Okay. And then it goes through and
25 identifies one, two, three, four, five --

1 six specific mutants, right?
2 A. I'm sorry?
3 Q. It identifies six specific mutants as
4 active mutants in this section, right?
5 A. They say "in particular," yes.
6 Q. So there's two at position 69?
7 A. Yes.
8 Q. And three at position 170 -- or sorry,
9 position 70.
10 A. 70.
11 Q. Yeah. And then one at 127 -- or sorry.
12 I'm doing bad math here.
13 A. Um-hmm.
14 Q. Position 271, right?
15 A. Yes.
16 Q. Okay. So these are the six that the
17 patents calls out as examples of active mutants,
18 right?
19 A. Yes.
20 Q. Okay. It didn't call out any mutants
21 that had an activity of 500 percent, right?
22 A. If it's 22-fold, it's bigger than
23 500 percent.
24 Q. Right.
25 Does this part of the common disclosure

1 highlight any substitutions at positions between
2 300 and 325 of the --
3 (Simultaneous crosstalk)
4 A. I don't remember if it does. I'd have to
5 look.
6 Q. All right.
7 A. Between which residues again?
8 Q. It -- there's no -- in this section,
9 where they're discussing the results of the
10 activity classifications, they're not calling out
11 anything in the 300 to 325 range?
12 A. You mean residue range?
13 Q. Right.
14 A. 300 through --
15 Q. In the narrative. Not in the table, in
16 the narrative.
17 A. Oh, yes, that's right.
18 Q. Okay.
19 A. But it -- there -- there -- there --
20 there are some in the table, yes.
21 Q. Can I ask you to go back to Example 2,
22 which is -- starts at page 219?
23 A. Yes.
24 Q. All right. So -- and you're familiar
25 with this experimental description, right?

A. Yes. I've read it.
Q. Okay. So if you need to look at anything to check the things I'm going to ask you, please go ahead and do that.
So first I want to just describe the construction of the plasmid used to make the mutagen --
A. Yes.
Q. -- in the mutagenocide.
Plasmid used to make the mutants. So the plasmid has a single CMV promoter that drove expression of both the PH20 mutant and the SEAP protein.
A. Yes.
Q. In all of the cells in these plasmids, the SEAP is the same. It's -- it's unmodified.
A. It's soluble alkaline phosphatase.
Q. Right. And then the mutants are all the different single mutants of PH20 1-447, right?
A. Yes. Driven by the same promoter.
Q. Okay. So driven by the same promoter. Can the two proteins be expressed at different levels in the cell?
A. Yes.
Q. Okay. The -- there's also a possibility

1 of codon bias influencing the volume of the
2 expression of the different proteins?
3 A. Yes. Although, I thought they used codon
4 optimization.
5 Q. For both? For --
6 A. I don't know that.
7 Q. Okay. If the ratio of expression of the
8 SEAP in the particular mutant varied in that
9 cell, that would affect kind of the rating of
10 activity of the mutant, right?
11 A. It could unless you normalized, but they
12 do normalize.
13 Q. And they normalize against a standard
14 curve, right?
15 A. Yes.
16 Q. Okay. Could I ask you to turn to
17 page 130? Sorry.
18 A. 130?
19 Q. Hold on -- hold on one second.
20 Could you go to your declaration for a
21 minute?
22 A. Yup.
23 Q. Go to page --
24 A. Wait a moment.
25 Q. Sure.

A. I want to put the binder back. That would be a bad thing.

Q. Document handling is very important today.

A. Okay. Yes.

Q. All right. So go to page 130 of your declaration.

A. I am there.

Q. And you have a description of the assay in -- at paragraphs 255 to 258?

A. Yes.

Q. So do you explain how the mutants were tested for activity here?

A. Not in detail. I cite the example and the description therein.

Q. Do you know if the different mutants that were produced in the primary screen were isolated and tested?

A. Eventually the mutants were tested. Are you talking about were they tested as part of the primary screen?

Q. So the -- the primary screen tested the supernatant of each well with the cell in it, right?

A. Yes.

1 Q. What I'm asking is: Do you know if the
2 mutant proteins in each well were characterized
3 or tested in any manner as part of the primary
4 screen?
5 A. I have to double-check. I think I do.
6 Q. Yeah, go ahead and look at -- this is at
7 248.
8 A. Pardon?
9 Q. You can go to 248.
10 A. I am going to, to make sure I'm right. I
11 mean the primary screen.
12 Q. The primary screen was the source of the
13 values of activity, right?
14 A. No, I know. They then carried out a
15 activity assay.
16 Q. Right.
17 A. Is that what you asked?
18 Q. Yeah, I am just confirming they didn't
19 try to detect the presence of the mutant protein
20 in individual wells that were assayed, the
21 supernatants that were assayed, right? There
22 wasn't a step in the assay process that confirmed
23 an amount or presence of the mutant PH20, right?
24 A. I don't know that. It is not reported,
25 but I don't know if there was or not.

Q. As far as you can tell, the assay was conducted by taking supernatant samples, two of them, and then testing the supernatant samples for activity, right?

A. I think so.

Q. Okay. If you look at the top of page 248.

A. Yes.

Q. It says: "After transfection, supernatant from the transfected cells was collected at various time points after transfection, and generally 96 hours after transfection."

Right?

A. Yes.

Q. So then they took the samples and they stored them at minus 20 degrees?

A. Yes.

Q. So the assay was then performed on these samples around 96 hours after transfection, right?

A. Four days.

Q. Four days. Okay.

Go to Example 3 on page 248, which is a little bit down the page. It says -- you will

1 see there, there is a paragraph that starts "The
2 transfected variant or wildtype PH20
3 supernatants."
4 A. I haven't found it yet. This is on
5 page 248?
6 Q. Yup.
7 A. This is on 248?
8 Q. Yes.
9 A. Which paragraph?
10 Q. Hold on for a second. Do you see
11 paragraph that starts "Transfected variant or
12 wildtype PH20 supernatant" on page 249 --
13 A. There is -- that's not in any paragraphs
14 on -- are we in the patent or my declaration?
15 Q. We are in the patent.
16 A. I don't see that.
17 Q. Turn the page.
18 A. It is page 249 in the copy I have.
19 Q. Got it. Perfect.
20 A. Okay.
21 Q. Do you see the paragraph starting --
22 A. I do.
23 Q. -- "Transfected variant or wildtype PH20
24 supernatants"?
25 A. Yes.

1 Q. So they prepared them with the diluent
2 buffer, right, was the first step. They took a
3 sample of the supernatant and they put it in
4 diluent buffer, right?
5 A. Yes.
6 Q. And then at the bottom last sentence,
7 they said: "One hundred microliters of each
8 standard and sample were transferred to the assay
9 plates and incubated for approximately
10 1.5 hours."
11 This is where they are testing the mutant
12 for activity against the substrate, right?
13 A. Yes.
14 Q. Okay.
15 A. Which is in a -- which is bound to the
16 microplate.
17 Q. Correct. If you go to the next page.
18 A. Um-hmm.
19 Q. After this incubation step, they wash the
20 plates, right?
21 A. Yes.
22 Q. And then they put in an agent to realize
23 the color, basically, of each assay which is the
24 measurement -- the basis of the measurement of
25 the activity, right, it is a colorimetric assay?

A. Yes, I think it uses horseradish peroxidase.
Q. Something called TMB.
A. Pardon?
Q. It says TMB, 100 microliters of TMB solution?
A. Yeah, okay.
Q. Basically, this is kind of taking the -- stopping the enzymatic activity and then measuring the amount of digested hyaluronic acid in each assay well?
A. Yes.
Q. Okay. And it is measuring it with a colorimetric value, which is then put against the standard curve --
A. Yes, I think that's because you have -- you're forming a reactive group when the chain is cleaved to hyaluronic acid.
Q. All right. In this process, there isn't any step that's taken to quantify or confirm the existence of PH20 mutant protein in the supernatant, right?
A. I don't see a specific step.
Q. For the SEAP activity, go to page 250. That was also detected with a colorimetric assay,

1 right?
2 A. Yes.
3 Q. And do you know if the SEAP activity was
4 detected from the same sample, the supernatant as
5 the PH20 activity, or did they test different
6 samples of supernatant?
7 A. I don't know that they say.
8 Q. Would that have an effect on this
9 normalization process?
10 A. Depends on how robust the data are.
11 Q. The patent doesn't give any information
12 on -- on that parameter, right?
13 A. I don't recall any.
14 Q. Could you go to page 250, then go to
15 line 26 of page 250?
16 A. Yes. Starting with "the criteria for".
17 Q. Exactly. Did you -- did you review this
18 part of the experimental protocol?
19 A. I read it, yes.
20 Q. What -- what are they -- so they are
21 using one criteria for the high throughput assay
22 as a -- using the SEAP signal, right?
23 A. Yes.
24 Q. And then the other signal that they are
25 using is for the control PH20, right?

A. Yes.
Q. What they are looking for is values above a certain threshold?
A. Yes.
Q. The PH20 threshold is one unit per milliliter, right?
A. Yes.
Q. Is this being done with each sample on each plate, or is it being done with kind of a stock recombinant human PH20 protein solution?
A. I don't know that they specify that.
Q. All right.
A. I thought -- I had the impression that there was a control sample per plate. But I don't remember that that's said explicitly. It might have been. I simply don't remember.
Q. Are you familiar with these types of high throughput assays?
A. Not at this kind of throughput but at a lower throughput, yes. I have done similar assays in the lab.
Q. Do you typically use a positive control for each set of tested mutants?
A. For each plate, we would usually use -- I would use, actually, two positive controls per

1 plate.
2 Q. So you used two samples of positive
3 control or two different positive controls?
4 A. Yes. Well, it depends on the assay and
5 the protein. Sometimes you can't. Sometimes you
6 can. If you can do two different positive
7 controls, we would do it.
8 Q. If -- at a minimum, you would do two
9 samples of a positive control?
10 A. Yes.
11 Q. Okay. Do you do any negative controls?
12 A. Always, when we can. All right?
13 Q. Do you know if they used a negative
14 control in this assay?
15 A. I don't. I would hope that they did but
16 I don't.
17 Q. All right. So based on the protocol that
18 was followed, is it correct that no steps in the
19 screening process for the primary assay confirmed
20 there was mutant PH20 in the tested supernatants?
21 A. If you are getting activity, I think
22 that's...
23 Q. So activity would be a readout that's a
24 positive signal that there is a mutant there,
25 right?

A. That's certainly one such readout, yes.
Q. And if you don't have a readout for activity, that would suggest several possible outcomes, right?
A. Yes, it could.
Q. So it could be the protein wasn't secreted from the cell?
A. Yes.
Q. It could be that the protein was degraded before it could be secreted from the cell?
A. Yes.
Q. It could be that the protein was secreted but then aggregated to the point where it had no activity?
A. Less likely. You'd probably pick that up as turbidity.
Q. Right. There is no measurement of turbidity in these --
A. You just notice it, if you were careful.
Q. Just from what we have in the patent, we don't know if it is one possible outcome is -- it is an aggregated outcome, right?
A. Um-hmm.
Q. And then another outcome is the enzyme is there but it is not exhibiting enough activity to

1 clear the threshold?
2 A. Yes.
3 Q. All right. Can you -- could you go to
4 page 272 of Exhibit 1026.
5 A. Yes.
6 Q. This is a description of the inactive
7 mutant assay, right?
8 A. Um-hmm.
9 Q. So the inactive mutants were tested not
10 only at 96 hours after transfection, they were
11 then tested again the next day?
12 A. Yes.
13 Q. We don't know how many exact hours, we
14 presume when you just say 12 hours later?
15 A. Yes.
16 Q. Okay. So all of the inactive mutants had
17 two measurements for activity?
18 A. Yes.
19 Q. The Table 10, does that show the values
20 that were measured for the inactive mutants at
21 either of those measurements?
22 A. It lists the mutants.
23 Q. It just lists the mutants. So it doesn't
24 give you any activity values for any of the
25 active --

(Simultaneous crosstalk).
A. Not in Table 10.
Q. If you had activity values for the inactive mutants that were above zero, that might give you some indication that the protein had folded?
A. It would depend on how much above zero they were.
Q. If you had, let's say, 18 percent activity?
A. Oh, I would think that was a folded protein.
Q. If you had 18 percent activity for an inactive mutant, you also would be confident that it had been secreted, right?
A. Yes. Some of it anyway.
Q. So if -- if you look at the patent description of the assay, they ran the second assay to confirm -- what did they say? "Were rescreened to confirm ... the dead mutants are inactive," right? So they did this second screen to ensure that it was below 20 percent activity.
So is it possible that some of the mutants -- let's say they had a mutant that had an activity of 18 percent at the 96-hour time

1 point and then 18 percent activity at the
2 whatever -- 12 hours later. You'd have two data
3 points showing that this protein is exhibiting
4 activity?
5 A. The same activity.
6 Q. Would you conclude that protein, that
7 inactive mutant, had folded properly?
8 A. It's not an inactive protein necessarily
9 if it has 18 percent activity. If you -- if you
10 make a cutoff of 20 percent, then you call it
11 inactive. If your cutoff is 15 percent, you
12 might call it active. But you -- what you would
13 say is that it was a reproducible result.
14 Q. You would -- you would also -- because
15 you could see there was activity being exhibited
16 by the mutant, it's in a state that would be
17 likely folded and has some -- I don't know how
18 to -- how you would characterize it, but it's
19 meaningful information to you that there is
20 activity associated with that inactive mutant?
21 A. Usually. But again, be careful about
22 what we mean by inactive. All right? We may not
23 be talking about the same thing.
24 Q. Sure. In -- in the table, you wouldn't
25 be able to differentiate that inactive mutant

that had secreted and folded from an inactive mutant that never got out of the cell?

A. In the table --

Q. Yes.

A. -- that would probably be true.

Q. Okay. So do you -- the mutants in -- listed in Table 10 give you information about the folded state of each of those mutants?

A. Not from just the list of the mutants per se.

Q. Is there other sources of information in the patent that tell you the folded state of any of these inactive mutants?

MS. MARTIN: Object to form.

A. I'd have to look more -- in more detail to answer your question.

Q. What would you -- what would you be looking for?

A. I'd look at the various examples and tables and see if there's data that can be used to answer your question.

Q. Table 10 can't, right?

A. Table 10 cannot answer your question quantitatively, no.

Q. Why don't you turn to Table 11.

A. Yup.
Q. As you -- as you look at the beginning of Table 11, there's a narrative describing the experiment that is labeled Example 5. It starts on page 282.
A. Yeah, I have it.
Q. All right. So it said that "Supernatants from PH20 activity variants set forth in Table 9," were tested in Example 4 --
A. Um-hmm.
Q. -- sorry, from Example 4. So the samples that were tested in Example 5 were all active mutants from Table 9, right?
A. I think that's right.
Q. Okay. Do you know if there were any other assay tests done in the patent?
A. I don't recall them, but I would have to look at the patent before I would be sure.
Q. Why don't you -- this is the experimental section. If you want to take a minute and just read through the end of this --
A. Yup.
Q. -- and see if you -- if you find any more assays -- mutants.
A. So are we talking about only activity in

1 the absence of additives?
2 Q. I'm actually focused on, are -- were
3 there any experiments done besides the one we've
4 looked at which tested the activity of the
5 inactive mutants?
6 A. I don't see any.
7 Q. So the only description of the inactive
8 mutants that describes their kind of status, you
9 know, classification was the example -- sorry,
10 Example 4 in Table 10?
11 A. I believe that's correct.
12 Q. Okay. All right.
13 So based on the information in the patent
14 that experimentally characterized the inactive
15 mutants, from what you can tell, if an
16 inactive -- sorry, if a mutant PH20 polypeptide
17 was not secreted by the transfected cell, that
18 would give a rating of activity below 20 percent?
19 A. Yes.
20 Q. And so that -- that mutant would be
21 classified as an inactive mutant?
22 A. That would be -- would be classified as
23 inactive.
24 Q. And then if a mutant was secreted by the
25 cell, but within 96 hours after it was

1 transected, that mutant, 100 percent aggregated,
2 and that also would give you a result which would
3 result in that mutant being classified as an
4 inactive mutant?
5 A. Yes. Although that's rare -- that's a
6 rare phenomenon, relatively speaking.
7 Q. Okay. And then I have the two examples
8 of the mutant that had an 18 percent activity
9 that -- it's an 18 percent activity at 96 hours,
10 and then an 18 percent activity at -- 12 hours
11 later. That's also being classified as an
12 inactive mutant?
13 A. If the cutoff was 20 percent, yes.
14 Q. Correct. If I had an inactive mutant
15 that had 18 percent activity at that first
16 reading and then 0 percent activity at the
17 12-hour point, that also would be classified as
18 an inactive mutant, right?
19 A. Yes, that would be classified --
20 Q. Would you differentiate the two
21 18 percent mutants I just mentioned?
22 A. No, not necessarily. Again, it would
23 depend on your cutoff.
24 Q. Sorry. Let me make you a better
25 question.

So if I -- you said earlier that the fact that the first mutant with 18 percent activity at the first reading and the second reading, that protein has folded and has stayed folded at least for another 12 hours.

A. If your assay permits you to assign a value of 18 percent as a measurement of activity above error -- the error level, yes. But if it doesn't, then no.

Q. Okay. Assuming that it is above the error level, then that --

A. If the error levels say 10 percent, then you have 8 percent above that, you might be satisfied at calling that active.

Q. Okay. And -- and that means it's also folded?

A. It would -- mean that it's folded, yes.

Q. For the other mutant which drops to 0 percent at 12 hours, that is an unstable protein because it's got no residual activity at --

A. Could be, or you could have -- the two measurements could just have that much variation.

Q. All right.

A. You would have to know that.

1 Q. So the variation of the assay in terms of
2 the activity variation is something that would
3 influence these classifications that are made in
4 the patent?
5 A. It would -- it would certainly -- it
6 would certainly need to be considered in the way
7 you looked at the data. Okay?
8 Q. And that's not possible for the dataset
9 of the inactive mutants, which are classified
10 only by falling below the threshold?
11 A. Yes, that's correct.
12 Q. Did you -- so there were -- not all of
13 the mutants that were produced were classified as
14 an inactive or active mutant, right? If you want
15 to go to Example 2, I believe. Look at page --
16 it starts at 219, but goes to --
17 A. I have it.
18 Q. -- page 220.
19 A. Yes.
20 Q. So all -- all the mutants that were made
21 and tested are listed in Table 8, right?
22 A. As far as I know.
23 Q. And the number of those mutants is larger
24 than the number of total mutants that are active
25 and inactive mutants in Tables 9 and 10, right?

A. I think they made 6,000 mutants. Okay? I don't -- I don't how -- what the numbers are in the other tables.

Q. I'll represent to you that there are some mutants that were made and tested -- well, some mutants that the patent says were made and tested that are not in either Table 9 or Table 10.

A. Okay.

Q. What conclusions can you draw, if any, about those unclassified mutants?

A. I wouldn't speculate.

Q. You can't really draw any conclusions on tolerability?

A. Right.

Q. You can't draw any conclusions from that set of mutants?

A. I wouldn't speculate without thinking much longer about the question and going through a lot more data.

Q. All right. Do you have any idea why the mutants that were made but not classified weren't included in either of those two tables?

A. I think it's the same answer to the previous question.

MR. KUSHAN: All right. Just in view of

time, why don't we take a short break now. We've been going about 45 minutes, and then -- maybe a five-minute break, and then we'll come back.

THE VIDEOGRAPHER: All right. Going off record at 4:17.

(Recess taken)

THE VIDEOGRAPHER: Back on record at 4:26.

BY MR. KUSHAN:

Q. Well, put away the Exhibit 1026, the '731 application. I'm going to go back to your declaration. You can put that away for a minute.

A. By the way, I -- since I've not seen this document per se, I've been assuming that the tables and so forth are the same in the '600 patent.

Q. Yeah. We -- we actually used this because the -- some of the information in the tables was misprinted in the patent, and that lets you see better and more accurately. It's the same content.

A. The same content but not necessarily precisely the same information.

Q. Same information presented accurately may be the best way to say it.

A. All right.
Q. If you -- I mean, to be precise, in the patent -- when I showed you the samples of the positive controls in the patent, they don't have an explanation of what the label is relative to the number --
A. I see --
Q. -- and you can see that clearly in the table presented in '731?
A. Okay.
Q. All right. Could you go to page -- hold on one second.
Go to page 161 of your declaration.
A. Yup.
Q. And just very briefly, this is introducing surface residues intolerant to change, right?
A. Yes.
Q. So if you go to the next page, you have two images of the protein. And it appears there's -- is that -- are those molecules -- the HA molecule overlaid on the protein, or is that the protein structure just showing the residues?
A. No, those are -- those are HA.
Q. Okay. So then let's go to --

1 A. They are in the top of the active site
2 cleft.
3 Q. Okay. So go to page -- paragraph 335.
4 A. Yes.
5 Q. And this is the section of your report
6 where you're explaining that you used a tool
7 called AutoDock Vina to explore locations on the
8 surface of the protein where hyaluronic acid
9 might interact, right?
10 A. Yes, that's Vina, but yes.
11 Q. Okay. AutoDock Vina. Okay.
12 And the motivation for this was your
13 belief that it might be possible that residues in
14 hyaluronic acid bind to PH20 outside the active
15 site. This is a quote in paragraph 335, just
16 want to check if that was a typo. The sentence
17 you say: "Residues in HA bind to PH20 outside of
18 the active site groove."
19 Did you mean to say HA interacts with
20 residues in PH20 outside the active site groove?
21 A. Yes.
22 Q. Okay. Good. I just -- I thought that's
23 what you meant. I just wanted to make sure.
24 A. Yes.
25 Q. All right. And this thought you had

1 prompted you to do an investigation to determine
2 if the red-colored surface exposed regions are
3 predicted to be HA binding sites?
4 A. Yes. There were -- that was the
5 motivation for the calculation.
6 Q. Okay. So this is an analysis that you
7 did which is not in the patent. This is an
8 analysis you did?
9 A. No.
10 Q. Okay.
11 A. This is a demonstration of what the data
12 in the patent might be useful for. One of the
13 things it might be useful for.
14 Q. So what are you using from the patent to
15 do the AutoDock Vina experiment?
16 A. So I'm not using anything in the patent
17 to do the AutoDock calculation. All right? I'm
18 using the data in the patent to interpret what
19 the AutoDock calculation is telling me.
20 Q. And is the AutoDock calculation telling
21 you things like the -- which residues are
22 interacting with hyaluronic acid?
23 A. Not that specifically. The docking is
24 not accurate enough to find a single position for
25 something as small as hyaluronic acid in a

1 particular pocket. It will tend to find what it
2 calls "poses," but which I call "states," for the
3 hyaluronic acid.
4 So it may be sometimes here, sometimes
5 here, sometimes here. But always in the same
6 pocket. And so you wouldn't want to use it to
7 state exactly that residues X, Y, or Z are going
8 to specifically interact with hyaluronic acid.
9 In this case, it was a more general question.
10 The patches of residues on the surface that are
11 intolerant of mutations are interesting because
12 they are patches. And because they are on the
13 surface. And the question is, is it possible
14 that hyaluronic acid might like to sit there, at
15 least if you give it a chance to computationally.
16 Q. How does the AutoDock Vina tool tell you
17 if it does or doesn't interact with one of those
18 residues?
19 A. So you have to view it in a particular
20 way. You want to give the hyaluronic acid the
21 opportunity to explore the entire protein. You
22 also want to do so excluding the active site
23 because unless you run a very, very long docking
24 simulation you will tend to get mostly results in
25 the active site. That's what, obviously, it is

1 supposed to be.
2 So I did that. I gave it the whole
3 protein to look at, but to exclude the active
4 site, and to ask the simple question: Do I get
5 any positions on the rest of the protein where
6 the hyaluronic acid dimer, disaccharide, does
7 that particular molecule like to sit there more
8 often than -- more often than it does other
9 places?
10 I mean, it'll -- you are bombarding the
11 whole surface of the protein with hyaluronic
12 acid, but you are asking does it find a potential
13 stability in certain areas more than in others.
14 All right?
15 And you generally will run more than one
16 simulation because there is a certain randomness
17 to the parameters and you want to give it a
18 chance to look at several sets of parameters. I
19 did that. And then you take the results, you
20 aggregate them. You say for all of the different
21 simulations of docking that I run, where do I see
22 the hyaluronic acid on the surface of the
23 protein? And then I attempted to illustrate that
24 further along.
25 Q. So that illustration above paragraph 338

is --

A. Yes. That's correct.

Q. So how did -- how did you decide to place those hyaluronic acid molecules at the locations they are depicted on the image?

A. I didn't decide it.

Q. How did --

A. The AutoDock Vina decided it. Remember, it is exploring the entire surface of the protein. And the striking thing is, for nearly all the simulations, you didn't see HA sticking randomly at places in the protein. You saw it overwhelmingly choosing to bind to three or four different places on the surface of the protein in different -- slightly different orientations in those places, but nevertheless, always in the same general place. And it turned out those were the invariant regions.

Q. To reach that conclusion you had to -- you had to have some kind of experimental result from the AutoDock Vina tool that said these positions on PH20 are the positions at which the hyaluronic acid is interacting, right?

A. Is able to make favorable interactions. So AutoDock uses a number of criteria to

1 determine whether a ligand is possibly binding at
2 a site. One is shape complementary. It has to
3 fit. Right? If it doesn't fit, it is not going
4 to do that.
5 Does that fit perfectly? If the site is
6 larger, then it might -- and the site could
7 accommodate, say, a tetrasaccharide, but if I
8 gave it a disaccharide, you are going to see it
9 in multiple positions.
10 It also attempts to calculate an
11 interaction energy. That calculation is crude,
12 and the interaction energy is virtually useless
13 except to indicate that the interactions are more
14 favorable than unfavorable. So the interaction
15 energy would be calculated to be bad if, for
16 example, the only docked position put a
17 positively charged residue on the ligand next to
18 a positively charged residue on the protein.
19 But you would get a negative interaction
20 energy if it was positive with negative. The
21 energy function is not accurate enough to allow
22 you to discriminate between positions, to say
23 that this pose is more accurate -- is more likely
24 than this pose, or to say that this site is more
25 likely than that site. It only tells you that

1 something is, in general, favorable relative to
2 the rest of the protein.
3 Q. So what I'm trying to understand is --
4 and this is -- at a first level -- there is two
5 levels of comprehension I'm seeking. One is
6 simple and one is more complicated.
7 A. Okay.
8 Q. So my simple comprehension I'm aiming to
9 achieve is why -- what are the places on this
10 image that the molecules are sitting on? You
11 reached a conclusion somehow to place them --
12 A. No, AutoDock Vine has placed them.
13 Q. So are -- what are you -- are you getting
14 back from AutoDock Vina a pdb model with the
15 molecule sitting on them?
16 A. That's exactly right. I am getting back
17 the pdb model with almost no modifications. In
18 some cases, it may allow the residues in the
19 pocket to move just a tiny bit. And I'm getting
20 the -- all the positions that the ligand finds on
21 the protein where it can make a favorable energy
22 of interaction. Okay?
23 So you can see -- if you look at the
24 first figure, the one at the top. There are
25 three sites shown there pretty clearly. In each

1 case there is a whole bunch of little stick
2 figures. Those are the different orientations of
3 the HA dimer that you can see in that pocket, but
4 they are all favorable orientations.
5 And what you can see is that the rest of
6 the protein doesn't have any HA dimers in it at
7 all. This is where it wants to go. Again,
8 computationally, with really crude functions.
9 Q. So if I had the pdb model with the --
10 kind of the array of HA molecules complexed on
11 it, I could then look and see which of the
12 particular residues on PH20 that are the location
13 of these spots?
14 A. But those -- but given how much disorder
15 there is in the HA positions, right, you would
16 not -- you could see there are many different --
17 Q. Sure.
18 A. You would never say, oh, this position is
19 making a hydrogen bond to that part of HA. You
20 would never say that.
21 Q. Yeah, I -- just to be clear, I am just
22 trying to understand what -- kind of what region
23 of residues --
24 A. That you could do.
25 Q. -- so the -- okay. Great. So I could

1 have used the pdb model with the -- that I got
2 back from AutoDock Vina to identify the regions
3 in the PH20 protein where the HA molecules
4 interacted?
5 A. PyMOL will even do that for you if you
6 ask it to.
7 Q. Okay.
8 A. By the way, the lower one is informative
9 on that page, because you can see at the very low
10 left there is one spot where it looks like there
11 is maybe only one or two molecules of HA have
12 bound there.
13 Do you see that?
14 Q. Um-hmm.
15 A. So that's not an obviously good binding
16 site. It just happens to be something that came
17 up with a slightly negative energy.
18 Q. Okay.
19 A. The others are striking because so many
20 positions are possible for the HA there.
21 Suggesting that a significantly sized HA chain
22 could bind in that position.
23 Q. As far as I can tell, I'm looking at your
24 declaration, it looks like you are using this
25 kind of analytical output of the tool to form

1 opinions in paragraphs 338, 339, 340, 341, and
2 342; is that -- can you confirm that's right?
3 MS. MARTIN: Object to -- object to form.
4 A. I wouldn't call them opinions. I am
5 testing a hypothesis, and wondering whether the
6 computation gives me any evidence that the
7 hypothesis may have some valid -- value.
8 BY MR. KUSHAN:
9 Q. Sure. But I am just looking at your
10 declaration, and the part of your declaration
11 that is related to the work you have performed
12 with AutoDock Vina. It looks like it runs up to
13 paragraph 342, and it starts around
14 paragraph 3- -- 335.
15 A. Um-hmm.
16 MS. MARTIN: Object to form. Object to
17 form.
18 BY MR. KUSHAN:
19 Q. So 335 to 342 represent the statements
20 you made in your declaration relating to your
21 AutoDock Vina work?
22 A. This is --
23 MS. MARTIN: Object to form.
24 A. I think I need you to say that again
25 because --

Q. This is -- again, this is a simple question --

A. Yeah.

Q. -- I'm trying to articulate.

As I read your declaration, you're discussing the work you did with the AutoDock Vina tool in paragraphs 335 through 342, right?

MS. MARTIN: Object to form.

Q. Is that right?

A. That -- those paragraphs describe what was done with the calculation of HA and the PH20 structure.

Q. Okay. And just to confirm. When you use the AutoDock Vina tool, you get back, among other things, a pdb model with the complexed multi- --

(Simultaneous crosstalk)

A. Correct. But remember that that model knows nothing about invariant residues or anything like that.

MR. KUSHAN: All right. I'm going to introduce a new exhibit, which is -- do you have the number?

THE COURT REPORTER: 1125.

(Exhibit 1125, E-mail chain regarding AutoDock Vina, marked for identification.)

1 MR. KUSHAN: It's a revision exhibit,
2 which is an e-mail chain correspondence between
3 me and counsel for Halozyme in the first three
4 pages.
5 THE WITNESS: Thank you.
6 BY MR. KUSHAN:
7 Q. So, Dr. Petsko, in the first three pages
8 of this document are images and text that was
9 provided to us by counsel for Halozyme which
10 represent the -- a response to the request we
11 made for the information that was produced by the
12 AutoDock Vina tool and the work you did related
13 to it.
14 A. Are you sure you couldn't have made the
15 text smaller?
16 Q. I -- I am not sure that having -- making
17 it bigger may it -- may have given you any
18 further insight. But what I'm trying to
19 understand is, this information that we received
20 back from counsel for Halozyme, this is not
21 providing the information that was in the -- the
22 pdb files, right?
23 A. It illustrates what was in the pdb files.
24 Q. It illustrates it. It doesn't give us
25 the positional numbers of the residues that are

1 being interacted with with the molecules?
2 A. Nope.
3 Q. And the tables that are on these
4 three pages, what are those tables?
5 A. So for the various calculations done, as
6 I said, with various changes in the random
7 parameters, those represent the calculated
8 energies of the best confirmation out of the set.
9 Okay?
10 Q. Are there -- are each of these model
11 numbers a different pdb model with an energy
12 calculation associated with it?
13 A. Yes. Each of these would be the
14 PH20 structure with one set of hyaluronic acid
15 positions. Remember, you're scanning the whole
16 protein.
17 Q. Got it.
18 So if I could have you look at your
19 images. Just look at your image again on
20 page 165.
21 A. Um-hmm.
22 Q. So did you color those residues in the
23 pdb files after they came back from AutoDock
24 Vina?
25 A. Yes. Just to see which ones were

1 invariant residues, which ones -- which ones were
2 always active, which ones were always inactive,
3 and so forth. The red color here indicates that
4 those residues were, when mutated, inactive.
5 Q. Is -- I'm looking at these images. I see
6 a lot of different hyaluronic acid molecules
7 sitting in different spots. Did you superimpose
8 all of the pdb structures together to create
9 that?
10 A. Yes. But it -- but each pdb structure
11 will have more than one hyaluronic acid
12 orientation.
13 Q. And so this is -- this is a composite of
14 all the pdbs?
15 A. Yes. But they'll be -- they're
16 essentially identical.
17 Q. All right.
18 A. You would not be able to tell a
19 significant difference except an occasional
20 residue position here or there.
21 Q. All right. And did you save this like a
22 PyMOL session file that captured all of this
23 illustrated information?
24 A. I don't remember whether I saved it as a
25 session file or not, but you can, sure.

Q. Do you recall saving the doc- -- the electronic files used to create these images?
A. I don't remember, but I probably did.
Q. Okay. Did you provide them to counsel, the files?
A. I'm trying to remember. No, I don't think so.
Q. Did you create the images that are in your paper PD -- PDF document?
A. Yes.
Q. Okay. I mean, did you put them in the document?
A. Yes.
Q. Okay. And it's not possible to know which particular residues are vis- -- are interacting with the HA molecules just by looking at the pictures in your declaration, right?
A. Not without comparing it to another picture, but you can do it trivially. So if you have any other coordinates set for PH20, all right, all you have to do is render it in space, in surface form like this, and turn it to the same orientation, and then you will have those residues clearly delineated.
Q. So --

A. Or you can take the coordinates for this and simply ask what the residues are.

Q. So the -- the simple thing would be to look at the pdb files --

MS. MARTIN: Object to form.

Q. -- that came back from AutoDock Vina?

MS. MARTIN: Object to form.

A. No, I wouldn't do that. That's not simple. The simple thing would be to display the pdb files.

Q. That's a better answer. And can you inspect the pdb files and --

A. Well, you -- that's what PyMOL is for.

Q. Perfect.

Before you did this AutoDock Vina analysis, did you review the patent to see what it had said about hyaluronic acid binding sites on PD -- PH20?

A. No.

Q. Do you know if the patent has any discussion about the hyaluronic acid binding sites on PH20?

A. Indirectly, yes.

Q. How?

A. So the patent is aware of the fact, that

1 was first established experimentally by others,
2 that this enzyme is not processive. What I mean
3 by that is it doesn't sit on hyaluronic acid and,
4 like Pac-Man, chew one residue at a time all the
5 way along the chain. It doesn't do that.
6 It finds a particular site, binds
7 anywhere on the polymer, cuts there, and then the
8 moment it is cut, it dissociates and randomly
9 binds somewhere else and cuts. Okay? So that's
10 a hit-and-run, if you will, binding.
11 Oddly enough, for most enzymes that
12 operate on polymers, that's most often what
13 happens. The processive -- there are processive
14 enzymes, but they're not the most common. So it
15 turns out that's what hyaluronidase does, it hits
16 and runs.
17 But if you think about that from an
18 enzymologist's point of view, it's not very
19 efficient to make a cut and then wander off
20 somewhere and sometime later find the same or
21 another hyaluronic -- hyaluronic acid molecule,
22 bind and cut, defuse off, wander around some
23 more, and so forth.
24 So my hypothesis that I wanted to test
25 was the hypothesis that the enzyme might be

1 smarter than that, might actually bind hyaluronic
2 acid in more than one place, not just the active
3 site. But so that when it cut and the product
4 dissociated from the active site, it remained
5 tethered to the polymer and therefore could do a
6 one- or two-dimensional search for another
7 cleavage site rather than search
8 three-dimensional space after it wandered
9 somewhere. That could, in principle, give you a
10 considerable increase in the efficiency of
11 catalysis. All right?
12 So I simply asked the question, are there
13 sites on this protein that would accommodate a
14 model like that? And if they were, are they
15 sites that, when mutated, affect the activity of
16 the enzyme? And to my delight, both seemed to be
17 true. That doesn't mean the hypothesis was
18 right, but it's evidence in favor of it possibly
19 being correct.
20 Q. Okay. Could I have you look at
21 paragraph 251 in your declaration, which is on
22 page 128?
23 A. Yup.
24 Q. And you're quoting part of the patent
25 disclosure, the common disclosure.

1 A. Yes.
2 Q. And in the middle of it, you see:
3 [A]mino acid residues R176, 246, and 252 of the
4 sequence of amino acids in SEQ ID 3 or 7 are also
5 conserved between and among species and
6 contribute to substrate binding and/or
7 hyaluronidase activity. [As read]
8 A. Yes.
9 Q. So are you suggesting those are some of
10 the residues that interact with hyaluronic acid?
11 A. They might be. But the patent doesn't
12 form that conclusion. They say they could be.
13 All right? They could contribute in other ways.
14 These are charged residues. All right? And
15 charged residues can exert long-range
16 electrostatic effects, for example, that have
17 nothing to do with direct binding.
18 Q. Could you go back to the common
19 disclosure, which is the big document over there?
20 A. Okay. Where?
21 Q. Go to page 81.
22 A. Okay.
23 Q. Look at lines 7 to 14.
24 A. Yes.
25 Q. Could you read that paragraph?

A. Yes.
Q. Let me know when you're done.
A. I have.
Q. Okay. So the common disclosure is explaining that PH20 contains a hyaluronan-binding site, right?
A. Yes.
Q. And it indicates that the "site is located in the Peptide 2 region, which corresponds to amino acid," so I'm going to skip down, "170-200 of the mature polypeptide ...."
A. Yes.
Q. So the patent has identified positions 170 to 200 of the mature sequence as the location of the binding site for hyaluronan, right?
A. Yes.
Q. Are the residues that interact with the hyaluronic acid that you determined in your AutoDock Vina work, are they in this same region?
A. Yes, one of the sites is. But there are other sites that are not specified here.
Q. And where did you explain that in your declaration?
A. I didn't.

1 Q. That's something that you could have
2 determined by looking at the results of your
3 AutoDock Vina experiment and comparing it to this
4 information in the patent?
5 A. I could have.
6 Q. But you didn't?
7 A. I didn't. I treated it as an independent
8 calculation.
9 Q. All right. So your opinions relating to
10 the hyaluron and binding interactions with PH20
11 are not based on this observation --
12 A. That's correct.
13 Q. Are you aware of any publications prior
14 to December of 2012 that provide the same
15 information that you obtained by the work you did
16 with the AutoDock Vina tool?
17 A. No, I am not.
18 MR. KUSHAN: All right. So we are going
19 to have to have a conversation after we excuse
20 the witness. I have a couple of other topics I
21 want to get through. I am going to make -- I am
22 going to reiterate our objections to the use of
23 this information, and there definitely has been
24 prejudice caused by the failure to produce the
25 information prior to his deposition. We will be

1 addressing that with the board.
2 MS. MARTIN: Well, we can have a
3 discussion about it on the record.
4 Do you want to do it now, or would you
5 like to wait until after we're done?
6 MR. KUSHAN: We can do it after we are
7 done.
8 MS. MARTIN: All right. On the record
9 after we -- but on the record, correct? Because
10 you just grossly mischaracterized what he said.
11 MR. KUSHAN: Well, we will have that
12 conversation.
13 MS. MARTIN: Fine.
14 BY MR. KUSHAN:
15 Q. All right. Could you go to paragraph 120
16 of your declaration, which is on page 50.
17 A. Yes.
18 Q. The -- this is a paragraph where you
19 mention a tool called Modeller?
20 A. Yes.
21 Q. Did you use Modeller to do any of the
22 work that you performed in the course of
23 preparing your declarations?
24 A. No.
25 Q. Did you use the Rosetta tool for any --

A. No.
Q. No use of Rosetta?
A. No.
Q. Did you model the PH20 sequence in AlphaFold?
A. I did.
Q. You did?
A. But not for this -- not for my declaration.
Q. Did you derive any insights from that model that you created?
A. No. I was just curious as to whether it could do it.
Q. Did you -- why did -- so why did you do that?
A. Well, if you -- so it is a complicated story. All right? When AlphaFold came out, it was tremendously exciting to people. As you know, some of it is people who worked on it got a Nobel prize. But what was not appreciated, except by those of us who actually started to use it in our own research, was that not all the AlphaFold structures were accurate. Some of them had small inaccuracies, and that was to be expected, but some were grossly inaccurate. All

1 right? For sequences that were on the order of
2 30, 40 percent identical for certain proteins.
3 And so at one point, I went through a
4 systematic test of -- we -- we coded the Alpha
5 algorithm monitor on our machine and went through
6 a systematic test of the proteins of interest in
7 my lab, and a variety of other proteins that I
8 had access to the coordinates of, to see how bad
9 some of the errors were.
10 This was one of the proteins I used.
11 Q. And what was your conclusion?
12 A. Actually, AlphaFold did just fine with
13 PH20, if you compared it with the much later
14 determined cryo-EM structure of PH20. And it
15 also matched the PH20 model from SWISS-MODEL
16 pretty well.
17 Q. Did you also look at the cryo-EM model
18 that had been published in 2025?
19 A. For the purpose of the comparison with
20 AlphaFold, yes.
21 Q. In the process of comparing those two
22 structures, did you look at particular regions of
23 the protein?
24 A. No. No, it was an overall assessment.
25 Q. What was the takeaway you had from that

1 kind of analysis?
2 A. That, at least for this kind of protein
3 with an alpha-beta barrel fold and a bunch of
4 helical domains attached to it, looked like it
5 could do a good job.
6 Q. Do you think the analysis you did with
7 those two -- the AlphaFold model and the cryo-EM
8 model essentially confirmed your beliefs that you
9 are expressing in your declaration?
10 A. No, I never used it for any comparison
11 with the work in the declaration.
12 Q. No, but you were making a number of
13 observations about the stability or aspects of
14 the PH20 protein. I was wondering whether that
15 work you did provided any insights or validation
16 of your opinions?
17 A. Never -- never came up.
18 Q. I am going to introduce as Exhibit 1126,
19 a paper.
20 (Exhibit 1126, Im, et al article, marked
21 for identification.)
22 BY MR. KUSHAN:
23 Q. I am just going to explain what it is.
24 A. Yes.
25 Q. This is paper by Im, I-M, et al. in

1 Proteins: Structure, Function, and
2 Bioinformatics. It's dated 16 -- well, it's a
3 June 2025 publication.
4 A. It appeared in -- it was accepted in
5 December of 2024.
6 Q. So the citation is Volume 93, pages 1067
7 to 1073, dated 2025.
8 A. Yes, it appeared earlier in 2025.
9 Q. Is this the paper that has -- made
10 reference to the structures that you looked at?
11 A. This is a paper that describes the
12 cryo-EM structure of that protein, yes.
13 Q. All right. Could you go to the first
14 pages of the document.
15 A. The first page?
16 Q. Yes.
17 A. Yes.
18 Q. Do you see who the authors are?
19 A. Yes.
20 Q. Do you see what the affiliation is of the
21 authors?
22 A. Yes, they are from Korea.
23 Q. And what's the company they are
24 affiliated with?
25 A. Alteogen, maybe. If that's a company, I

1 don't know. They are certainly in some of the
2 university-type labs. Is that the one you are
3 talking about?
4 Q. Yes. Have you ever heard of Alteogen?
5 A. Nope. Never heard of them. That's --
6 which authors? Is it just -- that's three of the
7 authors are from there. I don't know -- I don't
8 know them and I don't know the company.
9 Q. So these are the individuals who actually
10 determined the structure experimentally of PH20?
11 A. I don't know that. If you were to just
12 go by the author list, you would say it would be
13 probably the first author and the last author who
14 are all at Daejeon.
15 Q. Right. I am just -- this is the first
16 publication of the experimentally determined
17 structure of PH20?
18 A. Correct. But what you -- the trouble
19 with this kind of thing for a scientist trying to
20 figure out who did what --
21 Q. I don't need that granularity. It came
22 from this group of scientists, right?
23 A. Yes.
24 Q. So the Alteogen scientists are the ones
25 who determined this experimentally determined

structure of PH20?
MS. MARTIN: Object to form.
A. No, you can't say that.
BY MR. KUSHAN:
Q. You think they just found it and published it?
A. No. We don't know what they -- what role they played in the whole project.
Q. Four out of -- four out of five of them are from Alteogen, right?
A. I'm sorry?
Q. Look at the footnote.
A. Which footnote?
Q. So you see there is -- 2 is affiliation with Alteogen, right?
A. Correct. And there are two central authors.
Q. Right.
A. Three central authors. Sorry.
Q. So they were involved with the work that published the structure of --
A. Correct, but we don't know specifically what contributions they made.
Q. Right.
Do you know if any scientists at Halozyme

1 determined experimentally the structure of PH20?
2 A. I don't know.
3 MR. KUSHAN: All right. Why don't we
4 take a break now. We can stay on the record for
5 our conversation.
6 Do you mind if we have you step out, or
7 should we just -- I don't want to -- I don't want
8 to make you move if you are uncomfortable.
9 THE WITNESS: No, I don't have a problem.
10 I am only wondering whether you are actually
11 expecting me to still return.
12 MR. KUSHAN: I am expecting you to
13 return.
14 THE WITNESS: Then you are expecting a
15 lot.
16 MR. KUSHAN: Thank you.
17 THE VIDEOGRAPHER: Microphone.
18 THE WITNESS: Yup.
19 MS. MARTIN: You should take your --
20 THE WITNESS: Yes, I should.
21 THE VIDEOGRAPHER: Are we staying on the
22 video record?
23 MS. MARTIN: Yeah. I don't really care
24 about the video record. We are staying on the
25 record.

THE WITNESS: You will need to know where to find me, I will probably be in the food area, general open area there.

MS. MARTIN: Okay.

THE VIDEOGRAPHER: Going off the video record at 5:04.

(Witness leaves room)

MR. KUSHAN: So we asked for, what, six weeks to have you produce the information associated with the production of this AutoDock Vina model. There are -- there is -- the witness's work product is embedded on top of pdb files returned by the AutoDock Vina tool and used to illustrate his vision of the docking areas on the protein. Then you have a number of opinions based on that. I am wondering why you didn't give us the pdb files.

MS. MARTIN: Okay. As a general matter, right, your witness, Dr. Park, is the one who generated the original pdb file, using SWISS-MODEL, of PH20. You did not give us that pdb file.

I am going to finish. Okay? Thank you.

All right. So he generated the original model. He also generated the spreadsheet.

1 Right? And he went through -- and it sounds like
2 from his testimony he went through and he
3 generated a whole bunch of SWISS-MODEL pdb files
4 for his analysis of every single different
5 mutation he looked at. And you produced exactly
6 zero, zero pdb files to us. Right?
7 So Dr. Park generated, let's say,
8 hundreds of pdb files as part of his analysis.
9 And he also had SWISS-MODEL -- I'm sorry,
10 SWISS-MODEL -- he also had PyMOL session files
11 that he shared over Zoom with Dr. Hecht and
12 counsel, and he went through and he discussed all
13 of -- they both discussed all of their opinions
14 on these PyMOL session files on Zoom, and we got
15 exactly zero pdb files. And also, zero PyMOL
16 session files.
17 So because your experts generated
18 hundreds of such files and gave us zero of them,
19 we were not expecting you, right, to think that
20 we were going to be giving you pdb files.
21 Because it seemed like the -- since you are the
22 ones who went first here, the order of the day or
23 the order of proceedings was that we weren't
24 going to be giving pdb files.
25 Now, Dr. Petsko -- and I just want to

1 make sure that we're really clear on what he said
2 because I think you mischaracterized his
3 testimony, and so I want to make sure that you
4 understood what he said, which is literally like
5 if you take the picture that you were looking at
6 in his declaration, and I'm sorry, I don't
7 remember what the -- oh, here it is.
8 So the page 165, right, like he was
9 saying that if you take your SWISS -- or
10 Dr. Park's SWISS-MODEL and you orient it this
11 way, like you turn it in PyMOL and you orient it,
12 like and you turn on -- you turn on the surface
13 view, right? You orient it so that it looks like
14 this, then you can tell where these patches are.
15 That's what he was saying.
16 So he's not saying that you needed the
17 pdb file to be able to do this analysis. He's
18 saying you just turn it in PyMOL, and then you
19 can figure out where these balls are sitting
20 (indicating).
21 MR. KUSHAN: So let me -- let me just
22 point out that I wasn't asking for every pdb
23 file. You and I had a conversation, I think it's
24 even embedded in the e-mail chain, that we're not
25 asking for the pdb files because you can generate

1 those, you can color them yourself. That's --
2 that's not what we're asking for.
3 We were asking for the output of the tool
4 which positioned the molecules on the pdb file,
5 which then allows you to figure out where the
6 molecules are interacting with the portions of
7 the protein.
8 It would have taken you a click to do
9 that, and I don't understand why there is any
10 confusion about -- I mean, I think there was an
11 exchange we had where I was very clear we weren't
12 asking for pdb files, we weren't asking for
13 colored pdb files, because we know that's
14 something that you can just recreate from visual
15 inspection of the document.
16 We wanted to have the information that
17 allowed us to understand where those molecules
18 were on the protein, and we wanted the output of
19 the tool, which is what we said from day one.
20 The output of the tool is not the picture
21 we're looking at. The output of the tool is the
22 pdb files in complex with the molecules. That's
23 the narrow thing we asked for.
24 When you -- finally you responded, you
25 gave us something which you must know was not

1 responsive to the thing we asked for.
2 MS. MARTIN: No. We --
3 MR. KUSHAN: This exhibit which we've
4 introduced is useless as a point of information
5 to deduce the locations of those interactions.
6 These are -- these are -- these are the
7 pdb files. They're just a list of the pdb files.
8 If you had provided them, we would have not have
9 had a conversation. It's very simple.
10 When an ex- -- when a -- when a witness
11 does an experiment and uses the information to
12 support their opinions, you're supposed to give
13 us the information they created associated with
14 that experiment. That's what we asked for. You
15 didn't provide it. We believe we're entitled to
16 relief. We're going to pursue that with the
17 board.
18 MS. MARTIN: I still actually -- so this
19 is the first -- I sent this e-mail to you on --
20 this is so small. I sent this --
21 MR. KUSHAN: We had to understand -- we
22 had to understand what use he was making of this
23 information. And it's now -- he has a very long
24 explanation of his use of the information. We
25 believe it's -- he's relying on it to make a

1 point, that if he's making the point, he's
2 relying on the experimental work he did.
3 MS. MARTIN: Well, the point -- the point
4 that he's making in his declaration is literally
5 based on the figures in his declaration, right?
6 Like he gave you these figures when he was served
7 with this declaration in whatever, September.
8 MR. KUSHAN: Well, we stated our
9 positions. I don't know how long you want to
10 keep talking at each other.
11 MS. MARTIN: No, I do actually because
12 this is -- I just want to make really clear for
13 the record that I sent this e-mail on
14 October 27th, right? And it is now December 4th,
15 and you never respond -- you did not respond to
16 this e-mail, so we understood this to have been
17 resolved.
18 If you had an issue with what we
19 provided, which frankly is -- like you asked for
20 the output, and so -- and the in- -- no, you
21 asked for the input and the output, and you got
22 the input, right? You got the input, and you got
23 the output. And if you had a problem with that
24 or if it wasn't specifically what you were asking
25 for, you should have e-mailed, you should have

1 responded sometime in the -- you know.
2 MR. KUSHAN: So the -- so the three times
3 I asked for it, you wanted me to go like six or
4 seven or ten?
5 MS. MARTIN: No. If you had answered --
6 MR. KUSHAN: What was -- how many times
7 do I -- so, Lauren, how many times would I have
8 to ask for it before you handed over the
9 information?
10 MS. MARTIN: No. If this wasn't --
11 MR. KUSHAN: Just tell me.
12 MS. MARTIN: We gave you the information.
13 MR. KUSHAN: Just give me a number. Ten?
14 MS. MARTIN: You're not answering --
15 MR. KUSHAN: Did you want to ask -- did
16 you only want to provide it like the day before
17 the deposition?
18 MS. MARTIN: Okay. See, like now you're
19 getting --
20 MR. KUSHAN: I just need to understand.
21 I just need to understand where the line is you
22 think is -- and you believe this was sufficient?
23 MS. MARTIN: If we gave you information
24 in response to your request and you do not
25 respond to it, we assume it's been resolved.

MR. KUSHAN: No. You --

MS. MARTIN: If it was not resolved, you should have said -- you should have something sometime before right now.

MR. KUSHAN: All right. Well, we both said our -- stated our position. That's great. We'll raise it with the board and see whether relief is appropriate.

MS. MARTIN: What relief are you seeking?

MR. KUSHAN: I'll decide once we've assessed the nature of the evidence and the testimony that we got today. We'll go back, and we'll come back to you.

MS. MARTIN: And you also mischaracterized -- you also mischaracterized the paragraphs in his declaration, so we'll happily point that out as well.

MR. KUSHAN: Great. I love it. I look forward to that.

MS. MARTIN: Great.

MR. KUSHAN: So why don't we take our little break and then finish off.

Can you tell us where we are on the record?

THE VIDEOGRAPHER: 5 hours, 31 minutes.

1 (Recess taken)
2 THE VIDEOGRAPHER: Back on record at
3 5:23.
4 BY MR. KUSHAN:
5 Q. All right, Dr. Petsko. Can you go to
6 page 198 of your declaration and look at
7 paragraph 410?
8 A. Page -- paragraph 410?
9 Q. Yes.
10 A. Yes.
11 Q. So this is a section of your declaration
12 where you compared chimp, gibbon, orangutan, and
13 then three versions of PH20 with mutations at --
14 among 47, 131 through -- 47, 131, 219, and --
15 A. Yeah. I see it.
16 Q. Okay. So the first three are the
17 naturally occurring chimp, gibbon, orangutan PH20
18 with the D320 mutation inserted into it.
19 A. Yes.
20 Q. And then the last three are all based on
21 the PH20 sequence with those specified --
22 (Simultaneous crosstalk)
23 A. Yes. So again with D320K.
24 Q. With D320K plus those other -- and those
25 are all glycosylation sites, right?

A. The other two residues are glycosylate residues.

Q. All right. Could you go to paragraph 418 and look at the figure under 418, which is on page 3 -- 213?

A. Yes.

Q. So this is an overlay of the models into one perspective, right?

A. I'm sorry?

Q. This is an overlay of all of the seven models, right?

A. They've all been aligned to each other.

Q. All right. So all seven models were modeled using the Hyal-1 template, right?

A. They were all based on that template, yeah.

Q. And the first three are -- have one amino acid difference from their natural occurring sequence, right?

A. You mean the D320?

Q. Yes.

A. Um-hmm.

Q. And then the last four are the double or triple mutants plus D3 -- 320. So those are up to four changes relative to the PH20 wild type?

A. Yes.

Q. Okay. So based on your familiarity with SWISS-MODEL, would you expect very similar structures to be returned as the model sequences for all seven of those sequences?

A. Oh, yes.

Q. So when you were giving us an image of them overlaid, are there -- is there some significance to the fact that they are all very closely overlaid with their residue positions?

A. Well, there are two significances. One is to show that the modeling worked as expected, which is basically what you just asked me.

And the other is to show that the sequence differences between the orangutan, chimp, and so forth in the context of that modeling program did not produce any -- even really any significant local changes in the active site.

Q. Do you know if the SWISS-MODEL technique has the ability to differentiate structures in a way that would become visible when you're dealing with so similar set of parameters?

A. Small local changes, yes.

Q. Okay. And in the area that you're

1 showing us, those are alpha helical --
2 A. Well, that's the active site cleft, is
3 what I'm showing here.
4 Q. Okay. So to preserve the active site?
5 A. Yes.
6 Q. Did you address any other regions and
7 find anything of significance?
8 A. No.
9 Q. Okay. Could you turn to page 282 of the
10 '731 application.
11 A. 282?
12 Q. 282.
13 A. Okay. I'm there.
14 Q. This is the start of Example 5 where they
15 did this testing of certain of the active
16 mutants.
17 Could you look at page 303? Did they
18 call out any particular mutants --
19 A. I'm not there yet.
20 Q. Oh, sorry.
21 A. Okay.
22 Q. From the testing they did of increased
23 temperature and increased -- did the patent
24 identify any particular mutants?
25 A. Sorry. Please repeat that.

1 Q. Based on the information -- based on the
2 testing that was done of the mutants, did the
3 patent identify any particular mutants of
4 significance?
5 A. You mean F204P?
6 Q. I do. Did you look at -- when you
7 reviewed this, did you look at the results and
8 try to understand why they called out F204P?
9 A. I recall -- just a moment while I look at
10 what they said here.
11 (Pause)
12 A. So as I recall, it was very resistant to
13 creosol treatment. Whether it was the most
14 resistant I don't remember. But I do remember
15 that it was very resistant.
16 Q. So do you know if the patent addressed
17 the particular mutant any more in its
18 experimental work?
19 A. You mean any more than this?
20 Q. Yes.
21 A. I don't recall.
22 Q. Why don't we go through and look. Could
23 you go to page 303.
24 A. Yes.
25 Q. So this is a summary of the results with

1 F204P, but then they also did an additional
2 assay, and they tested it compared to the wild
3 type at the bottom of page 303.
4 A. Yes. You are talking about Table 13?
5 Q. Yes.
6 A. Yes.
7 Q. Then if you can look at page 309.
8 A. Just a moment. I am still looking at
9 304.
10 Q. Sure.
11 A. Okay. 309, did you say?
12 Q. Correct.
13 A. That's Table 15?
14 Q. Example 10 and Table -- Table 16.
15 A. Table 16. Just a moment. Okay.
16 Q. So they are testing the F204P mutant in
17 an additional experiment for stability with
18 insulin, right?
19 A. That's what the experiment is, yes.
20 Q. Could you go to page 311. Is there
21 another experiment where they tested the F204P
22 mutant?
23 A. You mean Example 11?
24 Q. Yes.
25 A. That's a different variant, right?

1 Q. The V58R variant, right?
2 A. Yes.
3 Q. So this is a second mutant that was
4 called out and tested in the patent?
5 A. Okay.
6 Q. If you look at Part B of Example 11 on
7 page 312, they are comparing the stability of
8 F204P and V58R; is that right?
9 A. Yes.
10 Q. So they are, again, looking at the F204P
11 alongside this one other mutant F -- V58 --
12 A. One moment. I am looking at Tables 21
13 and 22 first. Just one second.
14 Q. Sure.
15 A. Okay. Sorry. Now, what were you asking
16 me?
17 Q. So this part of the patent has an
18 experiment devoted to comparing these two
19 particular mutants?
20 A. You are talking about Table 23?
21 Q. Correct. Is that right?
22 A. I think so, yes.
23 Q. And then in Example 12, they are doing
24 experimenting to investigate expression of the
25 F204P using a lentivirus expression vector,

1 right?
2 A. Yes.
3 Q. And this was another way of making,
4 perhaps, more of the F204P mutant?
5 A. It could be a cheaper way than making it
6 at CHO cells, for example.
7 Q. But in Example 13, I think you mentioned
8 this earlier, this is a -- this is actually an
9 assessment of the stability of the F204P mutant,
10 right?
11 A. Hold on one second. Yes. These are
12 specific measures of secondary structure and what
13 they call melting temperature, but which I would
14 call thermal denaturization temperature.
15 Q. So this was a single mutant, and I think
16 in the experimental results they say that it had
17 an effect of changing the Tm of nine degrees?
18 A. Yes.
19 Q. Is that a significant change?
20 A. It can be. Depends on what you normally
21 see looking with the protein. But for some
22 proteins, that's a significant number.
23 Q. Do you have -- are you able to kind of
24 correlate that temperature change to a free
25 energy change?

A. No. People have done such extrapolations. They are not very accurate so I don't do them.

Q. Okay. So there is a technique called circular dichroism, which is mentioned in Example 13?

A. Yes.

Q. What is that?

A. It is a spectroscopic technique that measures the secondary structure content of a protein. It can be used in two ways. One, as a simple yes or no, to determine whether the protein has secondary structure and approximately how much.

Used in a slightly more sophisticated way, it can determine the rough percentage of alpha helix/beta sheet in a protein.

Q. Can you use that technique to compare the folded characteristics of two different proteins?

A. It is used for that sometimes.

Q. Okay. So this is an experiment that could have been done to show that a mutant PH20 more or less had the same secondary structures in tertiary structure of the PH20 protein?

A. It could be used to determine whether

they differ significantly or are they similar.

Q. Okay. And these are direct measurements of stability of the protein, right?

A. Yeah. I mean, you could -- you could say it's direct in the sense that it's a reporting of the confirmation of the protein.

Q. Okay. If you're comparing an experiment like this pair of experiments of circular dichroism and the measuring of the melting temperature, is that a more direct investigation of the stability of the protein than, for example, measuring activity effects of a mutant?

A. No, I wouldn't say so. I would simply say they are -- they are different experiments. You are getting at the same question in different ways.

Q. And for the activity measurements, that's derivative of the fact that the protein has folded?

A. Has a structure.

Q. Has a structure.

Could you --

A. And I think those results for the circular dichroism are in this section, correct?

Q. Yes.

Can you go to page 47 of Exhibit 1026, toward the front of the document.

A. Page 47?

Q. Yes.

A. Of the big document?

Q. Yes.

A. Um-hmm. Okay.

Q. Do you see a section called "Brief Description of the Figures"?

A. Yes.

Q. What I'd like you to do is keep that on one side of the -- in front of you so you can look at the brief description of the figures, and then I am going to make you go -- sorry -- to the very end of the document where the figures are located. Sorry. Figure 1 is at page 358.

A. I have it.

Q. Did you review Figure 1 when you prepared your report?

A. I remember reading it in the original patent. I assume it is the same figure.

Q. Yes.

If you look at the description of Figure 1, do you see that it's -- Figure 1 is, it's being depicted as the full-length PH20 sequence,

1 right?
2 A. 1's at 474, yes.
3 Q. Yes. That's the full length, including
4 the GPI anchor, right?
5 (Reporter clarification requested.)
6 BY MR. KUSHAN:
7 Q. The GPI anchor sequence?
8 A. Yes.
9 Q. And if you look at the description, it
10 says, somewhere around line 25, it begins -- or
11 26: "Exemplary, non-limiting positions for amino
12 acid replacements are indicated by highlighting"?
13 A. Yes.
14 Q. And then those positions are highlighted
15 in Figure 1 with kind of black shading, right?
16 A. Yes.
17 Q. Did you look at those positions that were
18 highlighted by the common disclosure in PH20?
19 A. I noted that they were highlighted.
20 Q. I'm going to give you a demonstrative I
21 prepared, which -- because I am horrible at
22 trying to figure out what the numbers of
23 positions as amino acids are in this sequence I
24 made a chart that I'm going to give to you and
25 introduce as Exhibit -- I assume we are at

1 Exhibit 1120s.
2 (Exhibit 1127, Chart created by Attorney
3 Kushan, marked for identification.)
4 BY MR. KUSHAN:
5 Q. This is just to help figure out what
6 these numbers are. It is not a perfect alignment
7 to the figure, but what I would like you to do is
8 see if you can find the F204 residue so we know
9 where that is.
10 A. I do. And I have.
11 Q. Okay. Can you use the demonstrative I
12 gave you to identify the -- sorry. Second page.
13 Could you go to the --
14 A. Second page of the demonstrative?
15 Q. Second page of the demonstrative.
16 And as you do that, just look at the
17 valine that is the last valine in the row that
18 ends 300. And just tell me what position number
19 is that --
20 A. You mean 302?
21 Q. No.
22 A. I'm sorry?
23 Q. The valine that's highlighted in the row
24 that ends 300.
25 A. Well, I am not seeing this. Let me see.

1 There is a valine highlighted at 277.
2 Q. Correct. That's what I'm just -- I just
3 want -- so that's valine 277. Then the next
4 highlighted residue, what is that?
5 A. The next highlighted residue appears to
6 be glutamine 347.
7 Q. So there are no highlighted residues
8 between positions 277 and 347?
9 A. I don't see them here. Let me check them
10 against the figure itself.
11 That seems to be the case.
12 Q. So the common disclosure in Figure 1
13 didn't highlight any mutants that were changed at
14 positions between 277 and position 347, right?
15 A. That's what -- they are not highlighted
16 on the figure.
17 Q. Right. The only two mutants that were
18 called out in the examples from stability testing
19 were the F204P and the V58L mutants, right?
20 A. Yes.
21 Q. And then in the figure in Example 4,
22 there was six mutants called out, and none of
23 them were in the region of 247 to 347, right?
24 A. As far as I can tell.
25 Q. Okay. So the patent hasn't called out

1 any particular mutants through any of these
2 specific examples that they've done elsewhere in
3 the patent?
4 A. I am not sure that I understand that. If
5 I read the legend to Figure 1, it says:
6 "Exemplary, non-limiting positions for amino acid
7 replacements are indicated by highlighting."
8 That's the only thing they say about
9 them. So I don't know why they chose to
10 highlight them. It just seemed residues they
11 were interested in for some reason.
12 Q. So the patent doesn't explain why these
13 particular mutants were highlighted?
14 A. Not in this part of the figure or
15 anything like that, no.
16 Q. If you were reading this patent, would
17 you be inclined to look up what happened with
18 these mutants as to why they were highlighted?
19 A. Not necessarily.
20 MR. KUSHAN: All right. So I don't think
21 we have any further questions.
22 THE WITNESS: Do you want your sheet
23 back?
24 MR. KUSHAN: That's an exhibit. She will
25 keep that.

MS. MARTIN: All right. So why don't we take a break?

THE VIDEOGRAPHER: All right. Going off record at 5:44.

(Recess taken)

THE VIDEOGRAPHER: Back on record at 5:49.

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

MR. KUSHAN: Great.

THE VIDEOGRAPHER: Going off record at 5:49.

(Whereupon, the deposition was concluded at 5:49 p.m.)

1 C E R T I F I C A T E

2 I, GREGORY PETSKO, PhD, do hereby certify
3 that I have read the foregoing transcript of my
4 testimony, and further certify that said
5 transcript is a true and accurate record of said
6 testimony (with the exception of the following
7 corrections listed below):
8 Page Line Correction
9
10
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16
17 GREGORY PETSKO, PhD
18 Sworn to and subscribed before me this
19 day of , 2025.
20
21 Notary Public
22 My commission expires:
23
24
25

COMMONWEALTH OF MASSACHUSETTS)
)
SUFFOLK, SS.)

I, Katherine A. Tevnan, Registered Merit Reporter, Certified Shorthand Reporter No. 129093 and Notary Public in and for the Commonwealth of Massachusetts, do hereby certify that GREGORY PETSKO, PhD, the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true record of the testimony given by the witness.

I further certify that I am neither related to or employed by any of the parties or counsel to this action, nor am I financially interested in the outcome of this action.

In witness whereof, I have hereunto set my hand and seal this 7th day of December, 2025.

Katherine A. Tevnan

Katherine A. Tevnan,
Registered Merit Reporter
CSR # 129093

Notary Public
My commission expires March 10, 2028

1 *** ERRATA SHEET ***

2 NAME OF CASE: Merck Sharp V. Halozyme

3 DATE OF DEPOSITION: December 4, 2025
NAME OF WITNESS: GREGORY PETSKO, Ph.D.
4 PAGE LINE FROM TO REASON

5 _____|_____|_____|_____|_____

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17 _____|_____|_____|_____|_____

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19 _____|_____|_____|_____|_____

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21 _____

22 Subscribed and sworn before me

23 this____day of_____,20__.

24 _____ _____
(Notary Public) My Commission Expires:
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53:8 54:16
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