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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I N D E X

Deposition of:	Direct	Cross	Redirect	Recross
GREGORY PETSKO, PhD				
By Mr. Kushan				

E X H I B I T S

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Exhibit 1124	Spreadsheet	13
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*Original exhibits retained by USLegal
** Documents quoted on the record are transcribed as read.

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P R O C E E D I N G S

THE VIDEOGRAPHER: We are now on the record. Today's date is December 4, 2025, and the time on the monitor is 9:10 a.m.

This is the video-recorded deposition of Gregory Petsko. This is being taken in the matter of Merck Sharp & Dohme LLC versus Halozyme, Inc.

This proceeding is being held at Quinn Emanuel Urquhart & Sullivan, LLP, 111 Huntington Avenue, in Boston, Massachusetts.

My name is Alex Jandrow, and I am a legal videographer on behalf of US Legal Support.

The court reporter is Kathy Tevnan.

Counsel will introduce themselves for the record, and the witness will be sworn.

MR. KUSHAN: Jeff Kushan of Sidley Austin, for the petitioner. With me is Amy Mahan, Ryan Mulligan, Chelsea Himes, and Leif Peterson, from Sidley; and Brian Goldberg from Dechert.

MS. MARTIN: Lauren Martin from Quinn Emanuel on behalf of Halozyme. With me I have Elliot Choi, also from Quinn Emanuel; Eldora Ellison from Sterne Kessler, and Josh Mack from

Halozyme.

GREGORY PETSKO, Ph.D.,

a witness called for examination by counsel for the Petitioner, being first duly sworn, was examined and testified as follows:

DIRECT EXAMINATION

BY MR. KUSHAN:

Q. Dr. Petsko, can you state your full name for the record.

A. Gregory A. Petsko.

Q. And where do you reside?

A. Currently at 17 Commonwealth Avenue in Boston.

Q. Do you have a work affiliation presently?

A. Yes. I am professor of neurology at Harvard Medical School, and also professor of neurology at Brigham and Women's Hospital, which is an affiliated hospital to the medical school.

Q. Okay. You have been deposed before, right?

A. Yes.

Q. Do you know how many times?

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You can say a lot, that would be fine.

A. I -- it's certainly probably at least ten.

Q. Okay. Okay.

So as you know, in the course of the deposition, I will present questions to you. You can answer my questions. Your counsel may object to the questions. They will be short objections. Unless she's instructed you not to answer for a privilege basis, you have to answer my question.

You understand that?

A. I do.

Q. Okay. If I give you a question and it's imprecise or you don't understand, you just let me know. I will try to give you a better question. Okay?

A. Thank you.

Q. You understand you are under oath and your testimony today must be truthful, right?

A. I do.

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

A. No.

Q. Okay. Also, if I need to have a conversation with your counsel I may ask that you

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step out of the room, but I will try to limit when I need to do that.

A. I will limp out of the room, but yes.

Q. I will -- and you can wheel out of the room if you like. I am happy -- happy to accommodate you as you need be.

When were you first contacted about scheduling this deposition?

A. Scheduling of this deposition, probably a few months before the deposition. The time kept changing, but this particular scheduling, probably a few months ago.

Q. Okay. And I understand that you just had -- you said you had recent knee surgery?

A. Yeah, just a few weeks ago.

Q. Okay.

A. Total knee replacement. Right knee.

Q. All right. So we will make sure we do take breaks every hour at least. If you need to take a break more frequently than that, just let me know.

A. Appreciate it.

Q. One thing we do want to make sure we do is just the back and forth of questioning, it is always great if you can wait until my question

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ends before you answer it so that it gets captured accurately in the transcript. Okay?

Do you understand that you have provided four declarations in four different proceedings in the patent office that are the subject of the deposition today?

A. I do.

Q. Okay. And I see you -- are those your four declarations you brought with you?

A. They are.

Q. Are there any markings or notes in those?

A. No.

Q. Great. So that will avoid us having to move a lot of paper around. We will just go ahead and use your copies of the depo- -- of the declarations.

Because there are four proceedings, I am going to ask that you use the -- what's called Exhibit 2007, which is your declaration in the PGR 2025-00003 proceeding.

A. That's the '600 patent.

Q. Correct.

A. Yes.

Q. We can use that for the references today. If there is an answer you would give that's

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different based on the other three proceedings, please let me know. Otherwise, I will just treat your answer as being applicable to the four declarations. Is that all right?

A. Thank you.

Q. If you could turn to your declaration in the 003 proceeding. Just go to page 226 and verify that's your signature at the end of the declaration.

A. It is.

Q. And do you see there's a block of text above your signature?

A. Yes.

Q. And you understand that's the statement you made about assuring that the testimony is accurate and truthful?

A. Yes.

Q. And you -- did you carefully review your declaration before you signed the declaration?

A. Oh, yes.

Q. Okay. Are you aware of any errors in your declarations?

A. Not that I'm aware of.

Q. Okay. Did you personally draft the 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.

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MS. MARTIN: Okay.

MR. KUSHAN: This is just the first tab of the spreadsheet. So we're going to introduce this as a new exhibit, if that's all right, 1124. It's the same exhibit as the spreadsheet that we received from counsel.

(Exhibit 1124, Spreadsheet, marked for identification.)

BY MR. KUSHAN:

Q. This was originally -- this is tab -- the first tab of what is Exhibit 2166 in the proceeding.

Do you recognize this spreadsheet?

A. Yes, I think so.

Q. Okay. Great.

Did you prepare this spreadsheet?

A. Myself directly? No. I don't work with Excel.

Q. Okay. So you were given an Excel worksheet, and then you reviewed it?

A. Yes.

Q. All right. We'll just put that away for a minute, and you can leave it. I just wanted -- I just wanted to make sure that you saw this was a new document. I just want to make sure you're

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comfortable, and it's the exhibit that you are familiar with.

A. Yeah. As you say, the print is small, but we'll work with that.

Q. Perfect.

You understand there are four different patents that are at issue in these four proceedings; is that right?

A. I do.

Q. Okay. I'm going to introduce these. They're already marked as Exhibit 1001 in each of the four proceedings. I'm going to hand you the '600 patent first.

And again, for the same reasons -- for the same reasons about your declarations, we'll use the '600 patent. I'm also going to use another document.

This is the '298 patent.

This is the '262 patent.

A. Thank you.

Q. And I'm providing these in case you need to look at any of the different patents. We decided we'll use the '600 patent as the reference point.

And this is the '035 patent.

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Have you reviewed all these patents?
A. I've read all those -- all of them.
Q. And you understand that the body of patents are the same roughly or mostly and at the very end there are different sets of claims in each patent?
A. That is my understanding.
Q. Okay. Great.
And you know that the four patents have some -- the claims are directed to mutations at particular locations in the PH20 protein. Each patent has a different location that has been focused on in the claims. You understand that?
A. Yes, I do.
Q. Okay. So for the '600 patent, it's position 320; for the '298 patent, it's position 313; for the '262 patent, it's position 317; and for the '035 patent, it's position 312.
And these are positions in the mature polypeptide sequence of human PH20. You understand that?
A. Yes.
Q. I used the word "mature polypeptide." Do you know what that means?
A. Yes, I do. I understand the sequence

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numbering issue.

Q. Perfect. It took me a while.

All right. Is it fair to say that the declarations you prepared regarding these four patents are expressing the same opinions across the four patents except for any issues specific to those positions that may be raised by each of the four patents?

A. Yes, I believe so.

Q. Okay. Great.

MR. KUSHAN: Let me introduce the last large pile of paper. This is Exhibit 1026. This is U.S. Patent Application No. 13/68 -- 694,731. We'll call that the '731 application.

BY MR. KUSHAN:

Q. And what I'd like you to do is put that down and go back to the '600 patent.

And if you look at the '600 patent, on the second page of the patent, you'll see a text block over here titled "Related U.S. Application Data" (indicating).

A. Yes.

Q. All right. And if you go to the very bottom of that paragraph, you'll see a reference. It says "which is a division of application

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No. 13/694,731 filed on Dec. 28, 2012."

Do you see that line?

A. I do.

Q. That's referring to this new Exhibit 1026 that I've just handed to you.

The 1026 application is the application that was filed with the patent office in December of 2012. It eventually turned into all these different patents.

What I'd like you to do today is use the contents of the application, the '731 application, for my questions because it has the common disclosure with all the other patents, and it's an easier thing for me to work with. Okay?

All right. If I use the word "common disclosure" today, I'm referring to the shared contents of the '731 application and all these four patents. Okay? Is that -- so when you hear that word, it's just referring to the part of the patents and the application that are in common, which is the bulk of it.

A. You're referring to the specification?

Q. The specification, the drawings in those documents, those are what I'm referring to as the

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common disclosure. Okay?

I wanted to make sure we all had the same foundation of what I'm referring to so the -- hopefully we'll have clearer questions.

If you could go to your declaration now, and go to paragraph 24 of your declaration.

A. Yes.

Q. This is -- you've stated in paragraph 24 that you have reviewed documents, references that are listed as exhibits in an exhibit list. And that exhibit list is on page 224 of your declaration. And you can take a look at the exhibit list on page 20 -- 224.

A. Yes, I see it.

Q. So you reviewed all of those exhibits that are listed?

A. Yes, I've looked at all of them.

Q. Okay. Were there any other documents or information that you reviewed that are not listed on that exhibit list?

A. To the best of my ability, there are not.

Q. Did you review the institution decisions from the patent trial and appeal board in these four proceedings?

A. Not -- not particularly, no.

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Q. All right. Did you review a declaration from Dr. Melanie Simpson that was filed in these proceedings?

A. I do not believe I've ever seen that declaration. I have seen declarations from Dr. Hecht and Dr. Park.

Q. Okay. Have you spoken with Dr. Simpson?

A. No.

Q. Did you review a declaration from Dr. Gary Cherr?

A. Again, I think the answer is no. There's a paper I believe where Dr. Cherr was the first author. That I certainly looked at.

Q. Okay. Did you speak with Dr. Cherr?

A. No.

Q. Have you reviewed a declaration from Dr. James Moon -- Dr. James Moon?

A. No.

Q. Have you spoken with Dr. Moon?

A. No.

Q. Have you reviewed transcripts from depositions of Dr. Moon or Dr. Cherr?

A. No.

Q. Okay. You did review deposition transcripts from Dr. Hecht?

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A. I reviewed the declaration and also there were transcripts of the depositions.
Q. Okay.
A. Yes.
Q. You're not offering any opinions on any of the statements of -- that have been made by Dr. Simpson, Cherr, or Moon in these proceedings?
A. Not as far as I know.
Q. Okay. Have you spoken with any scientists from Halozyme?
A. No.
Q. Have you reviewed any experimental records generated by Halozyme scientists that are not contained in the patents?
A. No.
Q. All right. So you mentioned you had reviewed the declarations from Dr. Sheldon Park and from Dr. Michael Hecht?
A. Yes.
Q. And you reviewed the entirety of their declarations?
A. Yes.
Q. Did you review the appendices that were in Dr. Park's declaration?
A. I looked at those. Some of them are

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common to the appendices in my declaration. That's -- the ones that were different, I did look at them.

Q. All right. When you -- so you mentioned you reviewed transcripts. Did you -- from Dr. Hecht and Dr. Park. Did you review the entire transcript, or did you just review particular sections of it?

A. As far as I know, I was given the entire transcript, and I read what I was given.

Q. Okay. Great.

Could you go to page -- page 10 and 11 of your declaration?

A. Yes.

Q. And there are two paragraphs. Just look at paragraphs 25 and 27.

A. Yes.

Q. These are paragraphs that are referring to a person of ordinary skill in the art, or something which is abbreviated POSA.

Did you use the definition of the POSA that is in your declaration at paragraph 25 in forming your opinions in this proceeding?

A. I applied that definition. I was asked to do so.

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Q. Okay. Great.

And do you see that in paragraph 27 there are a few different dates referenced in that paragraph?

A. Yes.

Q. And is your testimony as to the views of the person of skill in the art the same across that spectrum of time between December of 2011 and December of 2012?

A. Yes.

Q. If any of my questions today -- today raise or cause you to give me a different answer based on a different time point in that spectrum of time just let me know.

A. I will ask you one in return.

Q. Sure.

A. Is the December 28, 2012, date specifically referring to this large document you just handed me?

Q. Yes. So that -- so that application was the one that was filed on December 28th of 2012. There were two earlier applications filed in -- starting in December of 2011. So I just want to make sure that your -- your answers are addressing that spectrum of time. If there is

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

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Q. Okay. Human PH20 catalyzes the hydrolysis of hyaluronic acid, right?
A. Also called hyaluronan, yes.
Q. It is also called -- sometimes referred to as HA, right?
A. Yes.
Q. So if I say any of those words we are referring to the same kind -- structure?
A. Perhaps we should clarify one thing.
Q. Sure.
A. HA could also refer to a subunit of the larger polymer. That's used in the literature as well.
Q. Okay.
A. Typically a disaccharide.
Q. So you -- so HA would be a disaccharide or -- or an oligomer?
A. It could be the disaccharide, it could be the whole polymer, depending on the context. There's no agreed-upon notation as far as I know.
Q. What's the best word for you to refer to --
A. I think if we just -- if the -- if it is obvious from the context I'm not worried.
Q. Okay.

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A. If it isn't, I will ask; or you can ask, if it is relevant to you.
Q. Perfect.
So hyaluronic acid is also called a substrate for the PH20 enzyme, right?
A. Yes.
Q. On the PH20 protein, there are positions that will bind to the substrate; is that right?
A. Yes.
Q. And that substrate binding is part of the requirements for the enzyme to catalyze the PH20 -- I'm sorry -- to catalyze the hyaluronic acid; is that right?
A. The hydrolysis of hyaluronic acid is what I think you were trying to say.
Q. It was. Thank you.
A. Okay. Yes.
Q. Are you aware of any other functions associated with human PH20?
A. Yes.
Q. What are they?
A. It can also catalyze the hydrolysis of chondroitin, albeit less efficiently.
Q. Is there other -- any other functional capability you identified as being associated

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with human PH20?

A. I think I would like a clarification of what you are implying by function. That's a broad term.

Q. Yeah, that's always a complicated word, "function."

If you look at page 109 of your declaration in paragraph 213?

A. Okay.

Q. You mentioned that PH20 is possibly involved in interactions with proteins on the surface of an egg. So that would be a binding capability of the protein that would interact with the protein on the egg, right?

A. It is a speculative binding capability. I don't know that it's been demonstrated experimentally in vivo.

Q. Did you look for any literature that documents the phenomenon of PH20 binding to the -- to a protein on the surface of the egg?

A. No.

Q. If that was a functional property of the PH20 protein, would you expect that to be associated with a particular region of the protein?

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A. At least one, but it may be associated with more than one region.

Q. All right. Would that require there to be a particular structure on the surface of the protein to cause that binding?

A. There would be a binding site, what's called a binding site, which is formed by a particular structure. And there would be one or more than one.

Q. Okay. All right. Would a -- and are you aware there are five human hyaluronidase proteins?

A. I know that five have been discovered so far.

Q. And I'm speaking specifically of the human variants.

A. Yes.

Q. What's the word you use to refer to human variants of a protein that are from the same family?

A. You would -- you would call them paralogs in the genome. You could call them that, but I think if we talk -- talk about them as variant proteins in the same family, that's okay. The complication comes in the use of the word

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"variant" in genetics also can mean a particular point mutation in the wild-type sequence. But since I think we are talking here about protein mutations more than the gene itself, if we refer to those as mutants then we can use variant the way you've used it. And I -- I think without any ambiguity.

Q. Okay. Are the five hyaluronidase proteins homologous proteins?

A. So the definition of the word "homologous," should we talk about that?

Q. Sure. Go ahead. What's your understanding of the meaning of homologous?

A. Homologous means related by divergent evolution from a common ancestor.

Q. And based on that terminology, would you consider -- do you believe a POSA would consider the five human hyaluronidase proteins --

(Reporter clarification requested.)

BY MR. KUSHAN:

Q. Based on that clarification, do you believe a POSA would consider the five human hyaluronidase proteins to be homologous proteins?

A. Yes.

Q. Did you investigate the differences

between the human hyaluronidase proteins?
A. I did. I looked at the alignment of sequences.
Q. Do they have the same C-terminal structures?
A. No. They -- they differ.
Q. Do they have functional differences?
A. Yes. Some do.
Q. Are some enzymes in that family not capable of hydrolyzing hyaluronic acid?
A. Yes.
Q. Do you know the amount of sequence identity between PH20 and the other four?
A. Off the top of my head, no; but I seem to recall it is in the 30 to 40 percent range, typically.
Q. When you investigated this family of homologous human hyaluronidase proteins, was it important to your decisions in this case that they were homologous proteins but had different structures and different activities?
A. I can't agree with the statement you made.
Q. What -- what is wrong with my statement?
A. The statement "different structures" is

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too general of a statement. I -- we would need to get more specific.

Q. All right. So was it important to your decisions in this case that the five human hyaluronidase proteins have different C-terminal structures?

A. Only in one or two occasions. In general, that was not -- that was not -- only on one or two occasions.

Q. What were -- what were those occasions that prompted that --

A. When -- when we considered issues such as, for example, the EGF domain.

Q. So was the EGF domain something that was present in all of those five human hyaluronidase proteins?

A. No.

Q. No?

A. No. Sorry. I'm sorry. You said the correct thing. I misspoke.

Q. Okay.

A. The human proteins, yes. I was also including bee venom, and I shouldn't have.

Q. Is the Hyal-EGF domain present in mammalian proteins -- mammalian hyaluronidase

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proteins?

A. Say that again, please.

Q. Sure.

Is the Hyal-EGF -- let's make sure we are on the same page. I am referring to this term "Hyal-EGF domain." Do you remember that was the term that I think was referred to in the Chao paper?

A. It was.

Q. Okay. So the Hyal-EGF domain, is that a domain that's present in mammalian hyaluronidase proteins?

A. Yes.

Q. Okay. It's in -- it's present in the five human hyaluronidase proteins?

A. No. I think there's one that lacks it because it's a truncated protein.

Q. Okay. Is the Hyal-EGF domain present in the Hyal-1 and PH20 proteins?

A. I think so.

Q. All right. So let's go with some really basic concepts. What is the primary structure of a protein?

A. It is the amino acid sequence of a protein.

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Q. What's a polypeptide?

A. A polypeptide is a chain of amino acids linked by amide bonds formed between the carboxyl and one amino acid and the amino end of another amino acid. This process is repeated indefinitely to form a longer polymer called a polypeptide.

Q. Is there a difference between a polypeptide and a protein in the terminology you use?

A. Sometimes. It's a sloppy terminology. So you will sometimes find in the literature people will refer to things of 50 or so amino acids and less in length as a polypeptide rather than a protein.

This gets complicated when you're dealing with hormones like insulin, which are right around that number, and which usually gets referred to as a protein. So it is not a hard-and-fast terminology.

Q. Do -- do the two terms -- are they used interchangeably?

A. Frequently by people. Okay.

Q. Would you use the word "polypeptide" to refer to something which has a three-dimensional

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structure, or would you use a protein term to use that -- to connect that reference to structure?

A. Unfortunately, that's also sloppy. You could imagine using polypeptide to refer to something that doesn't have a structure, that's just a linear polymer. But it's not -- it's not established as a term that way. It gets used that way sometimes. Other times, it's simply a synonym for protein.

Q. If some of my questions today use the two words "polypeptide" or "protein" in a way that you think has some significance as a difference between the two, just let me know because if -- you'll see there are -- those two words very frequently in the documents.

A. Yes. You should do the same if I use them in a way that's not clear. Because as I said, this is sloppy on the part of scientists unfortunately.

Q. Okay. What is a protein secondary structure?

A. So there are elements of what are called secondary structure that involve hydrogen bond interactions between amino acids in the primary structure.

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Two of these elements of secondary structure involve hydrogen bonds between residues that are literally next to each other in the sequence. Those are called alpha helices, because of the shape that they make, or beta turns, because of the shape they make.

The other kind of secondary structure element is what's called a strand of a beta sheet. And when you have more than one strand, it's called a beta sheet. They can be parallel or antiparallel, and they involve hydrogen bonds between residues that are distant -- more distant from one another in the sequence. They're not consecutive. Okay?

Those three elements of structure constitute the well-known secondary structure features of proteins. And most proteins contain a mixture of those, although some are purely helical, for example.

Q. And in the protein structure, these secondary structures are interspersed with other sequences which are not as defined or rigid in their structure; is that right?

A. Yes. That's exactly the right way to put it. They are loops. We call them often loops.

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They can of indeterminate length. You can have very large loops. You can have small loops. And those are not classified technically as secondary structure.

Q. And then just the last one is: What's the -- what is a protein's tertiary structure?

A. So these individual secondary structure elements can be visualized as independent entities. The tertiary structure involves how the protein folds up to bring all of those elements together to make a compact structure. It isn't always globular, but it's more compact than when it's a linear sequence.

And the interactions between those elements are what hold the whole globular protein together.

Q. So is it fair to say that the tertiary structure is the structure that results from the folding and arrangement and packing of all of these different secondary structures and other unstructured regions of the protein into a final state of a structure?

A. To a relatively stable state. You can have situations where there are more than one tertiary structure, depending on conditions.

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Q. So I'm going to try to say this correctly, but if I said "for a polypeptide to function as a protein," is that a phrase that makes sense to you?

A. It does now that we've gone over the terminology, yes.

Q. All right. For a polypeptide to function as a protein, it must be able to form a stable tertiary structure under physiological conditions; is that right?

A. No. Unfortunately, it's not.

Q. Okay. What's wrong with that statement?

A. It doesn't apply to all polypeptide/proteins. We now know that there are a number of proteins in virtually all living organisms that are intrinsically disordered.

Namely, on a time-average basis, they do not seem to have either any secondary structure or tertiary structure, and yet they exist in the living organism and the organism pres- -- has preserved this over evolution.

Q. Is the human PH20 protein a protein that forms a stable tertiary structure under physiological conditions?

A. Fortunately, yes.

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

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would have to talk about it differently, yes.

Q. We've used the word "folding," and I've also seen the word "fold" used as a noun. Is the -- is a protein fold the protein's tertiary structure?

A. Usually. Occasionally, it could refer to the secondary structures, but usually that's context obvious.

Q. All right. So "fold" could refer to the fold of a discrete domain in a protein structure?

A. Yes.

Q. Okay. So if I say -- if a scientist uses the word "fold" generally in connection with the protein, that's when they would be referring to the entire tertiary structure?

A. Normally, that would be the default interpretation.

Q. Okay. So when a protein like PH20 folds, does it proceed through intermediate states or structures before it reaches its final folded tertiary state?

A. It's thought to for all proteins that fold, but it has not been determined experimentally for PH20, as far as I know.

Q. When -- and just generally for those

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proteins that do proceed through intermediate states, those are transient states in the process of folding before the protein adopts its final tertiary structure; is that right?

A. Under normal physiological conditions, yes.

Q. And the intermediate structures or intermediate states have different three-dimensional shapes compared to the final structure?

A. It depends on what you mean by different. I like to think of it in terms of altitude. All right? For some of these intermediates, if you looked at them from 1,000 feet, you wouldn't be able to tell that they were different from the final folded protein. But nevertheless, there would be differences, which would be clear if you got closer.

For others, even at 1,000 feet of altitude, they don't look like a final folded protein. So there are multiple intermediates, and their difference from the final folded protein is not the same.

Q. I'm going to use my hands because sometimes, when we speak of structure, it's hard

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to do it with words.

Is there -- is it -- is it possible that the intermediate states are not as tightly packed as the final protein structure?

A. So you're using your hands correctly. Okay?

That's -- there is something called a molten globule, which is an intermediate in the folding of many proteins, some people believe nearly all proteins. A molten globule may have most of the same secondary structure elements that the final folded protein has, but they have not yet coalesced into a compact form. Instead, they are like you did with your hands, they are somewhat separated and very loosely interacted.

Yes, that is a possible structure of an intermediate in the folding of many proteins.

Q. So when you introduced mutations into a naturally occurring protein, does -- can that set of -- or can those mutations cause the protein to misfold relative to the naturally occurring protein?

A. Occasionally. Okay. For some mutations. It is usually not the case for most mutation.

Q. Do the number of changes that are made to

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the amino acid sequence effect how frequently those misfolding events occur in the protein?

A. It can. It's probably protein dependent.

Q. Is it fair to say that even a single amino acid change can prevent a protein like PH20 from adopting its normal finally folded state?

MS. MARTIN: Object to form.

A. It's known for some proteins that there are single amino acid mutations that appear to result in the production of no stably folded protein. Whether that happens by the process you are -- you are trying to indicate is not -- not always clear. It could simply involve the failure of the protein to exit from the endoplasmic reticulum. For example, the protein might still be mostly folded.

So the number of mutations that have been made in proteins across the spectrum of proteins that have been mutated where a single point mutation causes the inability of protein to fold at all, that's a pretty small number.

Q. Is it possible that a mutation will cause the protein, at least a portion of the protein, to have a different structure relative -- different local structure relative to the native

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protein structure?

A. That has happened in some cases. Nearly all of the cases with which I am familiar involve proteins that are flexible, that have multiple domains whose relative arrangements are not terribly tight. That would not be the case for PH20.

Q. Can mutations cause proteins to aggregate?

A. Yes. Sickle cell hemoglobin is one example.

Q. And you study aggregation frequently in your own research; is that right?

A. We encounter aggregation in our own research. But yes, we have studied it as well.

Q. You are not trying to cause aggregation?

A. No. In the case of my work on neurodegenerative diseases like Alzheimer's, we are trying to prevent it.

Q. Can aggregation occur during the process of protein folding if there has been a mutation to the protein?

A. It can occur even if there hasn't been a mutation in the protein depending on the external conditions. Okay. But usually, that's

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concentration dependent. And it typically requires nonphysiological concentrations.

Q. Can aggregation occur within the cell during transcription/translation?

A. Yes. It can. And often, that's the result of overexpression that occurs because of, say, a promoter mutation.

Q. Can it occur because a mutation causes a different rate of folding or different pattern of folding inside the cell?

A. That will take some -- some discussion if you want a complete answer because the rate and patterns of folding involve rather different things.

Proteins have to fold within a defined time period, otherwise a partially folded protein might accidentally get degraded while it hasn't got enough time to complete the folding. There are proteins, for example, that if they -- if they weren't protected from that in some fashion, would literally take minutes to hours to fold -- to be synthesized, much less fold. So that's an issue.

As far as the pattern of folding is concerned, I think I need to understand what you

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mean by that word.

Q. So when a protein is folding as it's being translated -- maybe we should start with that point. So transcription takes it from DNA to the RNA, then RNA is the translation into the protein sequence where it assembles the amino acid sequence, right? So far so good?

A. So far so good.

Q. Okay. During the process of translation, is folding beginning as the protein is being translated inside the cell?

A. So nobody knows that for sure. Experiments that were done suggest yes. But it is complicated because antibodies were used to detect the folded form of the protein, and the antibody could be inducing the folding. All right. But what evidence there is suggests that the protein probably starts to fold during synthesis.

Q. So you have a native protein which has occurred in an organism because it's survived this evolutionary pressure. So that's a stable protein. It is a protein that has persisted over many years and now is -- is something which yields a stable structure in the final folded

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

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Q. And if that happens, that is something that may cause the protein to either not fold in the time span we referred to earlier that would cause it to be degraded by the cell, right? That's one possibility?

A. That's one possibility. It doesn't seem to be the most common thing that can happen.

Q. Is there some -- another bad outcome?

A. It's hard to know whether you would always call it bad. But the most common result of a mutation that affects what you would call folding affects the stability of the folded protein not the ability of the protein to reach that state. That is, by far, the most common.

Q. Okay. Just at a high level, what causes proteins to aggregate?

A. So there are a number of factors. One is concentration. All right? Some proteins you can concentrate them until you are blue in the face and they will not aggregate. But other proteins, at certain threshold concentration, may aggregate. And what keeps them from doing so in the cell is that they are at a lower concentration. That's one thing.

Another thing is -- I will use again

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sickle cell hemoglobin as an example. A mutation in the protein might create a patch that didn't exist before that allows the protein to self-associate. And that can form an aggregation. In the case of sickle cell hemoglobin, it forms filaments.

Q. So those -- those interactions, those are hydrophobic patches that become exposed on the surface of the protein?

A. Or that are created on the surface, yes. Those are the most common ways that you would see that kind of aggregation, would be hydrophobic.

Q. And when those interactions occur, those are basically random interactions between the locations on the proteins that are interacting with each other, right?

A. No. It can be, but in the case of sickle cell hemoglobin it is an extremely precise interaction.

Q. So I was -- so if I -- I am trying to make sure I understand.

The hydrophobic patches that may be exposed by a mutation, they can interact with any other hydrophobic patch of another molecule that is in the environment of that protein, right?

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

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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

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to digestion and they can accumulate.

Q. Is protein aggregation a concern for pharmaceutical development?

A. It is, but more commonly for issues of storage and immunogenicity than for efficacy. Usually the proteins that are employed pharmaceutically -- I am thinking of things like antibodies. All right? -- have been carefully developed so that they don't have that kind of problem. But on long-term storage, if the temperature changes or something goes wrong, you can have some misfolding and aggregation. And that can be an issue.

Q. And just the phenomenon of aggregation of a protein in solution, you're aware of that, that's the context we just were discussing. Can aggregates form that eventually become particulates?

A. Oh, yes. You can get -- you can get turbidity as a way of determining that aggregation has occurred. But you can also have aggregates that are completely soluble.

Q. If an enzyme like PH20 started to form aggregates because of mutations, just take that hypothetical, would the -- if it forms

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aggregates, is the enzyme able to be enzymatically active when it's in the aggregate?

A. It could be.

Q. Is it possible it might not be?

A. That's also possible. It would depend on the nature of the aggregation.

MR. KUSHAN: You know, you said you wanted -- you had another 20 minutes in you, but I would actually suggest we take a break now, if that's okay with you.

THE WITNESS: It's okay with me.

MR. KUSHAN: All right.

THE VIDEOGRAPHER: All right. Going off record at 10:04.

(Recess taken)

THE VIDEOGRAPHER: Back on record at 10:20.

BY MR. KUSHAN:

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

A. About the case, no.

Q. All right. If you can go to your declaration, and go to page 123, paragraph 241.

A. Wait a moment. Page 123. What was the paragraph number again?

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Q. 241.
A. Okay.
Q. And do you see in paragraph 241 you reproduced claim 1 of the '600 patent?
A. Yes.
Q. All right. In the first line of the claim, there is -- you see there are the words "modified PH20 polypeptide"?
A. Yes.
Q. So this claim is directed to modified PH20 polypeptides, right?
A. Yes.
Q. Okay. And look at the first paragraph under that. That's a paragraph that is requiring the modified PH20 polypeptide to have 95 percent sequence identity with one of a list of referenced sequences, right?
A. No. It's at least 95 percent.
Q. At least 95. So 95 percent or higher sequence identity?
A. Yes.
Q. Okay.
MS. MARTIN: I'm sorry. Can we go off the record for one second?
MR. KUSHAN: Sure.

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THE VIDEOGRAPHER: All right. Going off record at 10:22.

(Recess taken)

THE VIDEOGRAPHER: Back on record at 10:23.

BY MR. KUSHAN:

Q. We were just starting to talk about paragraph (a) of the claim, and you've clarified that it specifies that the modified PH20 polypeptide has at least 95 percent sequence identity.

A. Yes.

Q. And those are a sequence identity relative to a number of referenced sequences, right?

A. Yes.

Q. And do you understand that those sequences are wild-type human PH20 polypeptide sequences?

A. Yes.

Q. Do you understand that they have varying truncations at the C-terminus?

A. Yes.

Q. Okay. So they are between 430 residues to 465 residues in length?

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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?

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

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"to maximize identical residues, and wherein terminal gaps are treated as non-identical," so depending on how you line up the sequences. But basically, yes.

Q. So anywhere across the let's say -- Sequence ID 3 is a 447 residue protein, right? Do you remember that?

A. Yes.

Q. Okay. So let's go with Seq ID 3 for a minute. So in Seq ID 3, that means this language in the claim would allow the substitutions to occur at anywhere from position 1 to 447 in the sequence?

A. Excluding position 320, yes.

Q. Yes. All right. Does any language in the claim restrict what amino acid could be put into the sequence as a substitution of a wild-type sequence -- of a wild-type residue?

A. Not as far as I know.

Q. And nothing in the claim language prohibits deletions from occurring within the polypeptide sequence?

A. Let me look again. I think that's right.

Q. Okay. So do you agree that these claims are defining sets of different modified PH20

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polypeptides?

MS. MARTIN: Object to form.

A. I wouldn't use the term "sets."

Q. What word -- what word would you use?

A. I would use -- I would say that this claim defines a genus of proteins.

Q. Right. So you're familiar with the terminology of genus and species in the context of patents?

A. I've been given the information about that over the years, yes.

Q. Okay. So claim 1 is defining a genus of modified poly- -- PH20 polypeptides, right?

A. Yes.

Q. And one -- and one of those would be a species of modified PH20 polypeptide?

A. That's one of the terms that's used.

Q. Okay. Great.

Do you know how many different species of modified PH20 polypeptides are captured by the language of claim 1?

A. I haven't calculated that myself.

Q. Are you aware that Dr. Park calculated that number?

A. Yes.

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

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changes down to 17 were made. And that lower number is 6.14 times 1049 different polypeptide sequences?

A. Yes.

Q. All right. I may use that number, 6.14 times 1049, as an approximation of the scale of this genus; is that fair?

A. Sure.

Q. So we're in agreement that at least 1049 or greater different amino acid sequences would meet the requirements of, one, having 95 percent sequence identity to Sequence ID No. 3 and, two, including one of the four alternative amino acids at position 320?

MS. MARTIN: Object to form.

A. Assuming there are no errors in the calculation, that's the number that's given in this table. But I need you to repeat the various criteria that you mentioned, please.

BY MR. KUSHAN:

Q. Sure.

The criteria are that the modified PH20 polypeptide sequence has 95 percent sequence identity to Seq ID No. 3, and that it includes one of four alternative amino acids at

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position 320.

And my question was: That's at least 1049, and likely greater, as a number?

MS. MARTIN: Same objection.

A. I can't accept the statement "likely greater." I haven't done the calculation.

BY MR. KUSHAN:

Q. All right. So if we want to just go back.

So if you look at the second row of the table on page 96 from Dr. Park's declaration. So that's assuming that the reference sequences has 447 amino acids, which is the length of the Seq ID No. 3, right?

A. Yes.

Q. All right. And 22 changes reflects 95 percent sequence identity of the polypeptide sequence with 447 amino acids?

A. Yes, I think that's right.

Q. And then you see in the third column, position 320, there are four options as the parameter there?

A. Yes.

Q. Okay. And so based on those parameters of the 447 amino acid sequence, 95 percent

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sequence identity, along with 22 changes and four options at position 320, that translates into 1.5 times 1063 different polypeptide sequences, right?

A. Assuming there are no errors in the calculation. I haven't verified it.

Q. Okay. And you don't have a basis for, today, disputing that number as accurate?

A. As I said, I don't disagree.

Q. Could you go to your declaration again and go to paragraph -- I'm sorry -- page 125, paragraph 244.

A. Paragraph?

Q. 244?

A. Yes.

Q. You state in paragraph 244 your opinion that neither claim 1 nor claim 21 expressly refer to any hyaluronidase activity or any required level of activity.

In the genus of polypeptides that are defined by claim 1, would you agree that there are enzymatically active, properly folded, modified PH20 polypeptides?

A. Yes.

Q. Okay. And so some number of those 1049 -plus polypeptide sequences will be properly

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folded PH20 proteins that are enzymatically active?

A. Yes.

Q. Do you know how many?

A. No.

Q. Do you have an approximation that you can come up with of how many might be?

A. Not an approximation, no.

Q. Do you think it's closer to the 1049 scale, or some smaller number?

A. I think it's a lot of them.

Q. What does that mean?

A. A large number.

Q. Is that, like, 100,000?

A. Well, on the scale of 1049, that would not be a large number. I think it's a large number. But I don't know how large.

Q. So you have -- you have a perception it's a large number. Can you just put me on -- somewhere on that scale of 0 to 1049 --

A. No. I don't think that level of speculation is appropriate.

Q. Do you agree that there are a large number of polypeptide sequences that are not properly folded within that set of protein

sequences?

A. Now I feel like asking you what you mean by "a large number." But the answer is: I don't know how large that number is.

Q. How would a person of ordinary skill in the art determine what that number is in the 2011, 2012 timeframe; of -- of active, properly folded PH20 polypeptides?

MS. MARTIN: Object to form.

A. A person of ordinary skill in the art wouldn't do that.

BY MR. KUSHAN:

Q. That's a slightly different answer -- or slightly different question. We will talk -- I think that's a question you address in your declaration about whether someone would go down that path. I just want to have a starting point here of understanding.

If someone were asked in 2011 or 2012 and they were a person of ordinary skill in the art, and they were asked to determine the number of PH20 polypeptides in that genus of claim 1, that were properly folded and enzymatically active, how would they go about doing that?

MS. MARTIN: Object to form.

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A. They wouldn't even go about doing that.
BY MR. KUSHAN:
Q. Can you -- again, my question is, I am asking that person to do that. And I am asking you to tell me how they would do that.
A. What I'm saying is that would be their answer. They would say, I am not -- I won't do that because there isn't a simple way to do that.
Q. Is it possible to calculate that number, in 2011, 2012?
A. I don't believe so.
Q. Is it possible to experimentally determine which ones are properly folded and enzymatically active in 2011 or 2012?
MS. MARTIN: Object to form.
A. Not from experimenting on the entire ensemble.
BY MR. KUSHAN:
Q. Could you go to page 188, paragraph 390, of your declaration.
A. Page 188?
Q. Yes.
A. Yes. Which paragraph?
Q. 390.
A. Yes.

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Q. So at paragraph 390, you state your opinion that: "POSAs understand that the set of claim modified PH20 polypeptides that satisfy the claims share many common structural features."

A. Um-hmm.

Q. Then if I could have you, the next paragraph, paragraph 391. You say there that the claimed modified PH20 polypeptides that fold are a limited set of structurally homogeneous proteins.

A. Yes.

Q. So you're explaining in these two paragraphs that within -- or that claim 1 is directed to a set of modified PH20 polypeptides that are -- have particular structural features, right?

A. They have structural features in common.

Q. Structural features in common.

Can you list for me what the common structural features are of that set?

A. So every protein in that set, every protein in that set will contain an amino acid sequence that is at least 95 percent identical to the amino acid sequence of one of the reference proteins referred to in the claims. All right?

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That's a common structural feature. It limits the space that those, that that sequence, that the proteins can have.

Q. Is that the only common structural feature?

A. That is the structural feature that is most common to all of them. They have additional ones that is common -- there's another one that's common to all of them. They will all have a particular amino acid substations at residue 320, which is one of only three residues. That's another common structural feature.

Q. Are there other common structural features shared by this set?

A. Those are the two that are most common to -- that are common to all the members of the set.

Q. If you could go to paragraph 395 of your declaration.

A. Um-hmm.

Q. That's on page 190.

A. Um-hmm.

Q. Is one of the common structural features of the claimed modified polypeptides the set of critical residues that enable them to fold and

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function that are conserved?

A. Not all of the sequences in this genus will have all of those residues. But most, many of them, most of them will. And those will share that common feature. Those that do.

Q. So these are, these are the conserve residues in, that you might see in an alignment of homologous PH20 polypeptides, right?

A. Yes.

Q. Sometimes those are called invariant residues because they don't change in the position as to the identity of the amino acid among the homologous proteins, right?

A. Yes, that's how they are referred to frequently.

Q. Would you also refer to them as essential residues?

A. No. That would usually involve a bit more discussion. You would refer to them as a variant or sometimes conserved.

Q. Are those conserved or invariant residues essential to form the structure of the fold of the protein?

A. Many of them will be.

Q. Are some of those conserved residues

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essential for the protein to exhibit its enzymatic activity?

A. Some will be.

Q. If you can look at paragraph 396.

A. Yes.

Q. Once you've looked at that, is another common structural feature of the claimed modified polypeptides that they all have the same alpha-beta barrel fold?

A. No. You don't know that for certain. But you do know that a vast number of them will have the alpha -- that alpha-beta barrel fold because of the requirement of 95 percent sequence identity with proteins that do have the -- that alpha-beta barrel fold.

Q. Are you speaking of the alpha-beta fold that is the one observed in the human PH20 protein?

A. I'm speaking of that specific alpha-beta barrel fold. It's a subset of a common alpha-beta barrel super family.

Q. All right. And just so I'm -- I make sure I am clear about this in my own mind.

Is the alpha-beta barrel fold of the human PH20 polypeptide, is that also called the

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tertiary structure of the human PH20 polypeptide?
A. It's part of the tertiary structure because there are other elements in the protein besides that particular subdomain, if you will. But yes, it is part of the tertiary structure.
Q. So is it fair to say that -- that a portion of the amino acid sequence of the human PH20 polypeptide is responsible for creating the alpha-beta barrel fold in the PH20 protein?
A. I wouldn't use that terminology, no.
Q. How would you explain the relationship between the part of the sequence in the part that causes the folded protein?
A. You used the phrase "responsible for creating." That's an active verb.
Q. Right.
A. Okay? I would say that there was a particular sequence in the complete sequence of the protein that is -- what's the exact word I want to use? -- that is contained within the alpha-beta barrel fold. Okay?
The way you phrased it, it implied a mechanism, and I don't think we want to do that.
Q. The amino acid sequence, the primary structure of a protein, will dictate the ultimate

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tertiary structure of the protein, right?

A. Under most circumstance, yes.

Q. So when you're referring to the relationship between the amino acid sequence and the alpha-beta barrel fold of PH20, is it fair to say that the amino acid sequence in its entirety is going to be responsible for creating the tertiary structure that represents that alpha-beta barrel fold of PH20?

A. The amino acid sequence of the protein in its entirety, okay, is responsible for the entirety of the tertiary structure. Within that, there is a set of residues that is compatible with an alpha-beta barrel fold and adopts that fold. Okay.

Q. All right. If you look at paragraph 400 of your declaration, and you can look at paragraph -- pages 191 to 192.

A. Yup.

Q. So you have an observation that you've -- illustrating the alpha -- common alpha-beta barrel fold as wild-type PH20.

Just a clarification, when you're saying wild-type PH20 there, you're referring to wild-type human PH20, right?

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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

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helix that's going at a slant, that would be an additional tertiary structure component that isn't necessarily part of the alpha-beta barrel per se. The alpha-beta barrel fold can accommodate a lot of things around it, and inserted into it, in some cases.

Q. So when you refer to the common structural features of the claimed modified PH20 polypeptides -- and you can go back to --

A. Um-hmm.

Q. -- paragraph 396, if you wish.

A. Yes.

Q. -- you say one of the common structural features is this alpha-beta barrel fold, right?

A. Yes.

Q. And is that shared by all of the mem- -- species in the genus?

A. It's shared by all of the species in the genus that give a stable protein fold.

Q. Is it possible to know which portion of the genus will produce that stable fold that gives rise to that structure?

MS. MARTIN: Object to form.

A. If you look at the sequences, you can tell whether or not you have significant changes

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in the residues that make up the alpha-beta barrel fold, and that will give you a way of predicting whether or not that fold is likely to be preserved in that particular variant.

BY MR. KUSHAN:

Q. Are those residues you just referred to the set of the variant residues that are shared by PH20 proteins that are homologous to each other?

A. Oh, those are some, but there are many others that will accommodate -- can be accommodated in this fold. It is a very tolerant fold.

Q. Did you -- okay. I'm just trying to understand.

How would a person of skill in the art looking at the information in the '600 patent or the common disclosure know which positions are necessary for creating the alpha-beta barrel fold?

A. Well, again, I'm not comfortable with some of the words you're using. I wouldn't say "creating," for example.

If you want to -- if you want to know whether a particular sequence is compatible with

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the alpha-beta barrel fold, you could do that relatively easily, both in terms of a multiple sequence alignment, to show you what might be still possible, but you can also, and it's the first thing I would do, is look at the data in the patent to see if those particular sequence changes have been explored for those residues and if those residues retained -- if those sequences retained activity. All right? So that's -- that's one of the first things you would do.

But you also know that very few protein folds have been studied as extensively as this one. All right? And so there is a wide amount of information available about the tolerance of a fold like this for sub- -- amino acid substitutions. You can also draw on that previous information.

Q. So if I'm looking to identify a set of positions in the PH20 polypeptide sequence that -- I'm going to use the word "enable the sequence to adopt."

A. That will do.

Q. Okay. So if I'm looking for the positions that will enable the modified PH20 polypeptide sequence to adopt the alpha-beta

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barrel fold, has the patent identified which positions will cause the sequence to do that?

A. The pat- -- the patent has identified a large number of those positions, yes.

Q. And how does it -- what part of the patent is doing that?

A. The part where you look at whether or not a substi- -- a set of substitutions where it retains activity. All right? "Activity" in this case is a proxy for forming a proper fold. All right? You can't have activity without the proper fold.

So if you look at that, you can say this position, for example, is completely tolerant. All 15 substitutions that were tried still retained activity. That will tell you that that particular position can be substituted more or less whenever you want. Another position might be completely intolerant. That will tell you something as well.

You know how those positions map onto the alpha-beta barrel fold because you have the homology model of the PH20 structure.

Q. So let me parse those points a bit.

So one thing you mentioned was that the

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proteins that have retained activity, those are the proteins that you can say have adopted the alpha-beta barrel fold?

A. You would be comfortable saying that, right.

Q. For a protein that is not active, can you assume that the protein has adopted an alpha-beta barrel fold?

A. In some cases, you can assume it probably has if those are, for example, substitutions directly at the catalytic site. In other cases, you may not be able to be as sure.

Q. So unless it's a mutation that has been identified at a position that's responsible for the catalysis of hyaluronic acid, there's a question mark that would exist in your mind as to whether that mutation -- that mutated protein has properly folded?

MS. MARTIN: Object to form.

A. I wouldn't phrase it in terms of a question mark.

Q. Right.

A. I would say your prediction might have a different degree of confidence, but you would still in most cases, given the data in the

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patent, be able to make the prediction with some level of confidence.

Q. So let me give you a better question because I think the last one I asked was not a good question, not well formed.

So what I'm asking is, in the previous question and your previous answer, you had indicated that there is a set of positions in the protein that you would be able to have a higher confidence that that mutant with that change at that position would be folded because it was a position involved in catalysis, right?

A. No, not exactly.

Q. All right.

A. What I've tried to say was, there are a set of positions of -- that occur within the alpha-beta barrel fold itself, and those positions, if they retained activity, immediately tell you that the fold must still be essentially intact. All right? But that doesn't necessarily mean those residues are directly involved in catalysis. They're reporting on the structure in that case. Okay? Some may be directly involved in catalysis. Most will not be.

The structure function relationship is --

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enables you to go beyond just the question of chemical capability.

Q. Can I have you go to page 17 and paragraph 51 of your declaration.

A. Yup.

Q. So you say in paragraph 51, "The POSA would have understood that properly folded PH20s adopt the same tertiary structure-an alpha-beta barrel fold."

And then you say, "The claimed modified PH20s," the -- "that fold" in parenthesis, "thus share this fundamental common structure," and then in paren, "the PH20 alpha-beta barrel fold."

So in one of your previous answers, you confirmed that when you use a phrase like "the PH20 alpha-beta barrel fold," that's the one in the tertiary structure of the human PH20 protein, right?

A. Yes.

Q. And then you are saying that there is a subset of proteins within the genus that will fold to have that structure, right?

A. I'm saying that many of the pro- -- the sequences in the genus will fold, and when they fold, they will have that structure. Okay.

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Q. Do you believe that most of the PH20 mutants that were tested and classified as inactive mutants in the patent have properly folded to possess the alpha-beta barrel fold?

A. I can't give you a relative estimate. What I can say is, from years of experience in mutating enzymes and looking at them, just because a mutation has no activity or low activity doesn't mean it has disrupted the fold.

Q. It may have a mutation that induces aggregation, for example?

A. Yes. Although, that you can probably -- you know, you may be able to make a guess about that.

But the most common things are more complicated and more subtle. They involve, for example, action at a distance. You could have a mutation that changes the electrostatic potential of the protein at the active site even though it's not in the active site, for example. But it would still have exactly the same fold. We see that sort of thing often.

Q. Are there sets of changes that might be made that could induce a change in the structure of the protein to prevent it from having the same

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alpha-beta barrel fold as in the PH20 native protein?

A. I think that would be very difficult for this family of proteins. Okay.

Q. So if I put a -- took a stretch of 50 amino acids within a region that has one of the alpha helices and I changed 15 amino acids --

A. Change how much?

Q. Changed 15 amino acids with --

A. 1-5 or 5-O?

Q. -- 1-5 within the 5 --

A. Um-hmm.

Q. -- within the 5-0 length of the alpha helical structure, is that a scenario that could disrupt the alpha helix structure?

A. It could, but you would probably be able to assess that from the nature of the changes.

Q. If it did disrupt the alpha helical structure, could that disrupt the alpha-beta barrel fold?

A. Maybe, maybe not. So remember when we looked at the picture of the structure, one of the things we noted was that there were other helices that were not directly part of the alpha-beta barrel fold.

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Could you have a scenario where you might partially disrupt one of those helices while retaining the alpha-beta barrel fold, which is where the activity is primarily localized? Yes, you can absolutely imagine that.

Q. Is the -- is it possible to know, without actually making that mutation that I just described, whether it will properly fold or not properly fold?

MS. MARTIN: Object to form.

A. It's possible to predict with a very high degree of confidence for many mutations whether they will do that.

BY MR. KUSHAN:

Q. In the one that I was just describing that had the consequence of disrupting one of the alpha helices involved in the alpha-beta barrel fold, could you predict for that example whether that disruption would prevent folding of that mutant?

MS. MARTIN: Object to form.

A. Quite possibly. Depending on where in the structure the -- that helix was and how it was likely to be disrupted, yes, you would have a chance to do that.

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BY MR. KUSHAN:

Q. And you would know what percentage confidence that you have about that prediction?

A. I wouldn't quantify it in terms of an absolute percentage. I think you could say whether it was more likely than not or more highly likely than not. I think you could make statements like that in many cases.

Q. Is it your view that --

A. Sorry. I wanted to add one thing.

Q. Sure.

A. Which is, what part of the reason for that confluence in the data in the patent which allows you to understand the structure function relationship for this protein at a level that's much higher than that for most proteins.

Q. Is the dataset that you refer to in the patent, does that dataset include mutants that incorporated more than one amino acid change in them?

A. There were a few of those.

Q. Were those the ones that related to the glucosylation sites of the protein?

A. Those, certainly.

Q. Were there other changes -- any other

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examples of modified PH20 polypeptide that had more than one substitution?

A. Modified in terms of the experiments in the patent, or modified in terms of looking at sequences of other P- -- other PH20-related enzymes?

Q. For the former.

A. I don't think so.

Q. So that dataset, that was the basis of your -- call it a tolerance assessment, that dataset consists of modified PH20 polypeptides that have one amino acid change?

A. That's one of the datasets in the patent. But remember, there are also sequences of related PH20s from other organisms. That's additional information.

Q. And the other sequences from other organisms, those are all naturally occurring PH20 polypeptides?

A. As far as I know.

Q. Okay. Is there experimental characterization of the enzymatic activity of those proteins in the -- or the common disclosure?

A. Not as far as I know.

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Q. So those -- those proteins, those other nonhuman PH20 proteins that were referenced, that you are -- you are using those as examples of polypeptide sequences that are different than the human polypeptide sequence that folded to proteins that exhibit PH20 activity?

A. Yes. My shorthand would be nature's experiments.

Q. Got it.

Do you know how many of those nonhuman, naturally occurring proteins fall within the scope of the claims?

A. In the total ensemble of known sequences, no. For the ones that are mentioned in the patent, like the gibbon and so forth, those all fall within the scope of the claims except for the residue 320.

Q. Is it correct that there is three of those sequences that fall within the scope of the claim?

A. I think there were at least three, yeah.

Q. You have the chimp, gibbon, and --

A. Orangutan.

Q. -- orangutan? Yes.

A. Yeah, those are the ones I remember, but

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I'm trying to remember if there was another one, but those are the ones I remember. You asked me, I think, if they were active.

Q. Let's -- let's take it in two steps. So one question was just whether the -- the genus of modified PH20 polypeptides, that very large genus, most of those you believe will fold into a protein that will adopt the alpha-beta barrel fold of the human PH20 protein?

A. That is my prediction.

Q. That prediction is based on the naturally occurring PH20 proteins from other species in combination with the -- the data from the mutagenesis library of single mutants in the common disclosure?

A. Plus my understanding of the properties of the alpha-beta barrel fold. Which, as you know, go back a long way.

Q. And we use these words like "most," but we still don't know what that number mean -- what that means as a number or percentage of the genus size, right?

A. I am not trying to calculate an exact number.

Q. And you can't give the proportion of the

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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

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activity. Rather, I am using enzymatic activity as a proxy for a properly folded protein."

So that first point sounds like something you mentioned earlier where if you saw that a mutant was active, you had -- you would infer that it has properly folded?

A. Yes.

Q. Okay. And the other point you make in Footnote 12 is that: "Secretion is another proxy that could be used for a properly folded protein; proteins that do not fold will not generally" -- "generally will not be secreted."

Right?

A. Yes.

Q. So if a protein fails to secrete, you would infer that protein was not properly folded?

A. No. There are other reasons why it might not secrete.

Q. So --

A. But if it does secrete, I would infer that it was probably properly folded.

Q. If it secreted and showed no activity, would you assume it is properly folded?

A. Yes, it still could be.

Q. What would cause it to not exhibit

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activity after it had been secreted?

A. Mutation at the active site residue would do it every time.

Q. Would a -- is it also possible that the protein had a mutation that caused it to not remain stable and unfold once it's in -- outside of the cell?

A. So -- okay. The extracellular environment is harsh. That's one reason this protein has disulfide bridges. So mutations in the disulfide bridges could, in fact, have the effect that you are talking about. And you could still retain a large part of the fold but it would not be as precise as you would want -- as it would need to be to have activity outside the cell. You could imagine things like that.

There is a vast difference in the -- what's the word I want to use? -- insults that a protein must suffer on the outside of the cell versus the more protective environment inside the cell. So when you are dealing with a secreted protein, one of the things you usually find is that that protein is stable, has evolved to be stable; and therefore, has evolved to be fairly tolerant of things that can happen to it and

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retain its stabi- -- it's fold because it needs to be.

Q. So if I -- if I understand you, there is one kind of mutation that you can rationalize as explaining the lack of activity of a secreted, mutated PH20 polypeptide, and that is one which affects the -- one of those residues involved in catalysis or hydrolysis?

A. That's one of the mutations I can envision. There are others.

Q. And the -- the other, I think, we talked about it earlier, mutations that were made to the invariant residues of the protein that are found across the homologous protein set?

A. That's another.

Q. Okay. The other category, I think, were residues that you indicated a person wouldn't understand or associated with the alpha-beta barrel fold structure?

A. That's third. But there are others.

Q. What are -- what are other ones?

A. For example, I mentioned earlier long-range interactions. Usually of the electrostatic type. Those are often -- it is often possible to determine that that's likely

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what happened by the nature of a substitution in its location.

Q. And the disruption of that long-range electrostatic interaction would cause the protein to no longer adopt the PH20 alpha-beta barrel fold?

A. Quite the opposite.

Q. Quite the opposite.

A. We'd still have the alpha-beta barrel fold, but it would have an effect at the active site that would perturb it's catalytic activity without directly modifying the amino acids in the active site.

Q. So that scenario is one where the spatial positioning of the atoms that are involved in hydrolysis in the catalysis activity of the protein have shifted somehow so --

A. No. That's yet another category, which we can talk about. No, it's actually more a question of the chemical nature of the residue. So for example, there is a glutamic acid residue in the active site as of hyaluronic base. It must be able to donate a proton to the substrate in the catalytic mechanism.

That requires that it's pKa be

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appropriate with respect to the environment. Let's say, the extracellular environment of pH 7.4. All right? That glutamic acid must have a pKa that would allow it to function as a proton donor at pH 7.4. You could have a change distant from that site that perturbs the electrostatic environment of the glutamic acid such that its position would be the same. Okay? The residues around it would be the same. But the local -- there would be a kind of local pH effect, all right, that would alter the ability of that glutamic acid to donate a proton. There are many examples of things like this in enzymology. All right.

And the other you mentioned was changing the position of the substrate in the active site. For an enzyme like this that has a polymeric substrate, yes, that's easily possible. All right. If you have the polymers bound in more than one place on the enzyme you could have mutations at one of those other sites that shifts the position of the polymer in the active site slightly, and it wouldn't take much. And yet, the alpha-beta barrel fold is perfectly preserved.

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Q. So is -- just so I am clear, the -- the alpha-beta barrel fold structure does not include, in your mind, these variations in the structure of the protein that may affect the enzymatic activity of the protein or ligand binding or substrate binding?

A. It certainly includes them in the sense that the alpha-beta barrel is still there.

Q. That was a bad question.

I am trying to --

A. Is that because it was a good answer?

Q. No, it was --

A. Okay.

Q. -- because it was a bad question. It was an imprecise question.

A. All right.

Q. The -- the point I am trying to understand is these changes that cause a loss of activity, they have -- if you positioned that changed protein, that mutated protein, and overlaid it on the structure of the human PH20 protein, is it likely that individual residues have shifted in the spatial positioning of them relative to the native protein?

A. Maybe a few, but not many. And the

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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.

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Q. So is it your view that the set of proteins within this genus that constitute the alpha-beta-barrel-fold-possessing species, they can accommodate variations in the structure relative to the native PH20 tertiary structure but would still retain something you would describe as an alpha-beta barrel fold structure?

A. The way I would phrase it is that the common structural feature is one of the things that is most likely to be preserved throughout this genus and that the common -- specifically, the common structural feature of the alpha-beta barrel part of the fold.

Q. When you reviewed the common disclosure, did you see a description of the PH20 polypeptides that used alpha-beta barrel fold to describe it?

A. Not in the -- I looked at this actually. Not in the text of the specification, but the structure of the bee venom hyaluronidase was referenced in the patent application.

Q. Do -- do you recall if you saw the words "alpha-beta barrel fold" in the comment section?

A. I don't recall whether they were or not.

MS. MARTIN: So we've been going for about another hour. Greg, do you want another

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break?

THE WITNESS: Let's do 10 to 15 more minutes, then we'll break.

MS. MARTIN: Okay.

THE WITNESS: Unless other people need it.

MR. KUSHAN: Let me ask maybe just one or two questions, then we'll take a break. Maybe five minutes.

THE WITNESS: Fine with me.

MS. MARTIN: Okay.

BY MR. KUSHAN:

Q. So we talked before about protein -- cells can degrade proteins that have misfolded, right?

A. Sometimes.

Q. All right. But there's like -- there's a -- I've heard the word "garbage collection pathways" or "protein degradation pathways" in this --

(Simultaneous crosstalk)

A. "Trash compactor" has been used as well.

Yeah. So it -- but it depends on the -- on what's happened to the protein. Right? And what protein it is.

So there are proteins that misfold that

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you can't get rid of, and there are other proteins that misfold that you can get rid of like that (indicating). And it depends on the molecule, and it -- sometimes it can even depend on the organism.

Q. Is one of the reasons they get degraded that they're misfolded, the proteins?

A. Yes, that's one of the reasons.

Q. Is it a common reason they get degraded?

A. I -- yeah, probably.

Q. Have you heard the term "intrinsic stability" be used in connection with protein structure?

A. Yes.

Q. What does that mean?

A. Well, it -- it's another one of these somewhat sloppy terms in that it can be context dependent.

For some people, it means the ability of a protein that you've made and purified to withstand some denaturing conditions in a test tube. For other people, it means the property of the protein in the cell to withstand stress conditions and so forth. And for yet other people, it may mean the protein being in an

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organism that is itself able to withstand say extreme temperatures.

So it's -- it's -- you've got to be precise if you use it.

Q. So that term kind of across all three of these meanings is referring to the -- kind of the energy state of the protein confirmation and it being in an energy state that permits it to stay folded as opposed to pushing it over to become unfolded; is that what --

A. I hope you mean free energy.

Q. Free energy, yes, that's exactly what I mean.

A. Okay. Because if you meant other, it's not true.

Q. Correct. So let's recast that question to be in the context of free energy.

Is the protein's intrinsic stability in the context of it having -- sorry. I'm not sure -- I can do a better job asking this question. Let me try.

Does a protein's ability to resist thermal unfolding reflect its intrinsic stability?

A. Okay. That's a -- that's a better

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question. I'll give you a better answer than I would have maybe had to give in the other case.

Sometimes yes. Often yes. Not always. All right? The intrinsic -- if you want to define the term correctly, as I said, it gets used sloppy, intrinsic stability of a protein is the difference in free energy between the folded form of the protein and the unfolded form of the protein. All right?

So that can change not only because you can lose stability of the folded form, but you can -- that can change because you can gain stability of the unfolded form. And it matters which that is sometimes, and a careful scientist who studies protein folding and stability always has to keep that in mind, that you're dealing with a difference between a state that you can not only measure but in many cases visualize with crystallography and a state that isn't one state but that it's a distribution of unfolded forms.

And yet the stability -- the ability of that particular state to exist and how much of it exists in that form is critical to the stability of the protein, even though it's not -- I'm sorry. I'm -- I'm not going to ramble anymore.

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Do you see what I mean?

Q. Yes.

A. Okay.

Q. So is it fair to say that the protein's free -- net free energy of stabilization is the composite of all of the different influences that contribute positive or negative to that stability of the protein?

A. Yes. Compared with the stability of the unfolded form.

Q. And is it possible for mutations made to the protein to shift the net-free-energy level to cause a protein to go from -- that had a tendency to be stable at one temperature to be unstable at that temperature with the mutations in it?

A. Yes. In case of some mutations, it is. That will depend to some extent on how intrinsically stable a fold is.

Q. Are you aware of instances where two or three mutations to a protein can shift that thermal stability of a protein that intrinsic?

A. Yes.

Q. Would introducing 15 or 20 changes into a protein structure as mutations be more likely to shift the thermal stability of the protein?

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

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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.

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Q. So your testimony is that a person of ordinary skill in the art in the 2011-2012 timeframe would be able to predict the change to a protein's net free energy of stabilization associated with a set of 10 or 15 or 20 mutations?

A. No. They would not be able to predict the number. They would be able to get a sense of whether those were likely to be destabilizing or not.

Q. Likely to be destabilizing to the point that they would cause a protein to tend toward unfolding?

A. Depending on the nature of the mutations and their locations, possibly.

Q. So you'd have to assess each one and reach this conclusion from inspection of it within a structure of the protein?

MS. MARTIN: Object to form.

A. Each protein family in particular, and maybe some of the proteins within the family, is going to be a case that you need to think about.

But in the case of PH20, you have the patent data. Okay? That's a tremendous amount of information that allows you to become more confident in the kind of predictions you're

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talking about.
Q. Does the common disclosure report experimental testing of the thermal stability of any mutants?
A. It talks about the stability of some of the mutants, yes.
Q. Two of them, right?
A. Yes.
MS. MARTIN: So then we can --
MR. KUSHAN: Yeah, I was going to -- I was going to say we can take a break. Why don't we -- why don't we take the break now and then we can resume this conversation, if that makes sense.
MS. MARTIN: Yeah.
THE WITNESS: Fine with me.
THE VIDEOGRAPHER: All right. Going off record at 11:26.
(Recess taken)
THE VIDEOGRAPHER: Back on record at 11:50.
BY MR. KUSHAN:
Q. Dr. Petsko, did you speak with counsel during the last break?
A. Not about the case, no.

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

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Q. Sorry. Sorry -- 1- -- 169.
A. Sorry.
Q. That was my bad.
A. And paragraph was 346?
Q. Correct.
A. Okay. I'm there.
Q. Okay. You say that: "POSAs modify existing proteins for a purpose."
Could you just explain what purposes that a POSA would modify a PH20 for?
A. There are a number of them. They might want to increase activity. Okay. They might want to abolish activity, in some cases, to retain a protein that binds hyaluronic acid but doesn't hydrolyze it. They might want to abolish binding as well as activity. They might want to actually, deliberately, misfold the protein for purposes of creating antibodies at a higher rate of efficiency than you can through the folding protein. Those would be some of the reasons.
You might want to improve stability to temperature. You might want to improve stability to certain denaturing preservatives.
Q. So for those various purposes, would 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.

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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

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to identify from the genus proteins that contain the properties you are interested in.

BY MR. KUSHAN:

Q. Do they also contain -- do they give you, as a POSA -- sorry. Let me start over.

The properties you are interested in, are you referring to the increase stability-type property?

A. The sort of things we talked about.

Q. So basically a feature or an attribute of the resulting mutated protein, that's what you are referring to by "properties you are interested in"?

A. Yes.

Q. Okay.

A. Usually.

Q. And then what you are saying is that the data in the patent allows somebody who is a person of ordinary skill to select combinations of mutations that will deliver those desired properties in a particular mutant?

A. That's correct.

Q. So the patent, in your view, and data in the patent in particular, is giving the ability of a skilled person to select combinations that

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they could then put together and test to see if they have the properties that they are looking for?

MS. MARTIN: Object to form.

A. Remember, you are not only talking about combinations, for one thing. Might be a single substitution is all you require. In fact, in a number of cases it probably will be.

As far as testing is concerned, it depends -- right? -- again, on what you want to do. What you can do, however, is predict, with a high degree of likelihood, that the changes that you make are going to have properties of the kind you are interested in.

Q. And that's true from the individual single mutants -- sorry.

So you can reach that conclusion by looking at single mutants and you extrapolate that data for the single mutant to combinations of mutations?

A. In some cases, many cases, maybe most cases, yes, because you also, remember, have the structure. So you know where those mutations are as well as what they are.

Q. So do you -- is there -- was there a

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published structure, experimentally determined structure, of PH20 in 2011 or 2012?

A. PH20, no, but there was the bee venom structure in 2012. It was -- Hyal-1 was available, I think, in 2012. I don't know the -- I can't remember the year of publication but I think I'm right that that structure was available in 2012.

Q. That was published in the Chao paper?

A. Yeah, that's right. I can't -- I just can't remember the date of publication.

Q. Did you use the bee venom structure or the Hyal-1 structure to produce the PH20 model you used?

A. Hyal-1 was the -- was the structure that was used. The bee venom structure was used to compare with Hyal-1 and the PH20 structure. And also, to look at the interactions of hyaluronic acid with those models because the bee venom structure, if you will recall, has hyaluronic acid dimer present in the protein.

Q. Does the patent provide examples of particular combinations of mutations that are correlated to PH20 proteins with desired properties such as increased activity or

increased stability?

A. The main combinations referred to have to do with the glycosylation. I don't remember that any of those increased the activity. I don't know if the stability was measured. Solubility of those can effect -- I think that might have been looked at but I don't remember that either. So no, I don't think so.

Q. So your opinion is that a POSA could use the data from testing single mutants in the patent to select 15 or 20 substitutions in the PH20 sequence, and you would be able to predict whether that mutated 15 or 20 residue-mutated PH20 will exhibit the activity that you are hoping to get?

A. My opinion is that you could do so. My opinion is also that you would almost never do so. You would probably rarely, if ever, make that many substitutions. You wouldn't need to.

Q. Have you used the word "protein space" to describe kind of the universe of protein variants that might be the subject of an investigation?

A. I don't know that I've used the word "protein space." If I have, confirmational space might have been a better choice. But I think we

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mean the same thing when we are talking about that.

Q. Yeah. So I am trying to see if there is a word that correlates to the genus -- although you used the genus definition, which may be fine. What I'm trying to get to is, in that genus of claim 1 of the '600 patent, and you said this earlier, it's -- you don't have an ability to kind of draw these lines about how much of it is active mutant, inactive mutant, etc.

What I'm trying to understand is, within that genus, how much of it is made up of multiply modified PH20s as compared to singly modified single mutant?

A. I haven't done that calculation. The genus is defined in the claims.

Q. Right.

A. So claim 1 will tell you what you have to do.

Q. So if you just look at the universe of modified PH20 polypeptides that have one amino acid substitution in the 447 residue sequence, I think there are probably around 9,000 species in that genus, right?

A. I don't know. Thousands sounds right,

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but I don't know.

Q. So if you look at the entire genus that it has a set of changes that can include up to 21 or 22 mutations, the portion of the genus that is reflected in the dataset is a tiny, tiny fraction of that genus, right?

MS. MARTIN: Object to form.

A. So the -- what is reflected in the patent is a subset. Okay. Which has a particular number of mutations. A few thousand. Sounds about right.

The real question is: What about the information content? The information content of that particular set of substitutions is enormous. And when combined with the structural information from modeling the PH20 structure, it allows you to visualize and make predictions about much more of the dataset than just what you see here.

BY MR. KUSHAN:

Q. So using that dataset, the person could predict which combinations might yield an active form of a mutated PH20 polypeptide let's say with 15 changes to it?

A. You could, but as I said, you would not tend to do that. A person of skill in the art

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would tend to only be interested in a much smaller number of mutations, because you can almost certainly get where you want to go that way.

Q. So a POSA is not interested in trying to practice the entire scope of this genus, they would focus on a portion of it, right?

MS. MARTIN: Object to form.

A. A POSA would have the capability of both visualizing and practicing the full scope of the claims if they needed to. They could -- that is to say, they could look at any particular type of variant that fit the claim and they could make that variant and they would be able to predict beforehand what that variant might do with a -- in many cases, on a high degree of confidence.

Q. And they could do that for 1049 -- a number that -- I'm sorry. They can do that for a number of modified PH20 polypeptides that approaches 1049 different sequences?

A. They can do that for any member of the 1049 sequences that they wish to examine. Okay? A person of skill in the art would do it that way.

Q. If you had to estimate the portion of the

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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)

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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

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

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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.

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(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

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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

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declaration. Go to para- -- page 53 --
A. Um-hmm.
Q. -- paragraph 127.
A. Um-hmm.
Q. And in paragraph 127, you're referencing Chao to support your views about similarities shared by human Hyal-1 and then PH20 and bee venom hyaluronidase, right?
A. Um-hmm.
Q. Right?
A. Yes.
Q. So go to pages 61 and 63 and take a look at paragraphs 141 and 143. So just skim --
A. Um-hmm.
Q. -- skim 141 and 143, and then tell me when you're done.
A. Yes.
Q. So here you were relying on Chao to support similarities about the active site clefts in three hyaluronidases.
A. I think I need to know what you mean by relied on.
Q. You're -- you're using the Hyal-1 structure and -- to help understand what the -- what that cleft looks like as a structure, right?

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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?

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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 --
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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

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HyalEGF-like Domain"?

A. Yes.

Q. And is Chao confirming in this paragraph that the Hyal-EGF domain is present in all mammalian hyaluronidases?

A. Let me read this.

Q. Sure.

(Pause)

A. Yes, although he does mention the additional cysteine residues in Hyal-3 and PH20.

BY MR. KUSHAN:

Q. Do you recall if Chao identified a particular pattern of amino acids that is present in mammalian hyaluronidases that is necessary to form the Hyal-EGF domain?

A. I thought he did but let me take a look.

Q. Go back, I think -- go back to page 6912 in the left column. It is the second full paragraph.

A. Yup.

Q. So did Chao indicate that there is a particular pattern of amino acids that occurs that is --

A. You are not talking about alternative splice transcripts. I am not looking at the

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right place.
Q. No. Look at 6912 in the paragraph that starts "Human Hyal-1."
A. Ah, okay.
Q. And then go down --
A. So the second full paragraph. I have got it.
Q. Yeah, yeah.
A. All right.
Q. Just let me know when you finish reading that.
A. Give me a second.
Q. Of course.
(Pause)
A. Yes. He is referring only to the pattern of cysteine residues. Okay. He is not -- in this paragraph, he is not looking at any of the other amino acids in the domain.
BY MR. KUSHAN:
Q. He is also referring to the spacing of the residues, right?
A. Yes, that's what I mean by the pattern.
Q. He also says that there are particular amino acids that have character, like the hydrophobic residue is an "a" in the pattern,

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right?
A. Yes.
Q. And that there is -- "x" is denoting any residues that's showing a tolerance to the position next to the hydrophobic one after that cysteine, right?
A. That's right.
Q. But overall, he is making it fairly clear that there is a characteristic pattern that is found in the sequence that is associated with the Hyal-EGF domain?
A. Yes, and that pattern is primarily established by the disulfide bridges.
(Reporter clarification requested.)
A. That pattern is primarily established by the disulfide bridges.
BY MR. KUSHAN:
Q. And the gaps can vary in length?
A. It would seem so.
Q. All right. Chao was the first to report this characteristic pattern, do you --
A. I don't know that.
Q. Well, at least he thinks he does, I think.
A. I don't think so. Because he refers to

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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?

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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

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disrupt one, you'd have an odd number of cysteines that can produce disulfide scrambling.

As far as the other residues are concerned, the implication here is that there is variability. But that variability is derived from comparing sequences of different EGF domains. It's almost certain that those will not encompass every possible substitution at each of those locations.

However, we have the patent. The patent does explore those locations in more detail. So the answer is, we can turn to the data in the patent for a better answer to the question.

Q. In your declaration, did you -- well, did you compare the mutation data in the patent to this region of the PH20 sequence and offer any opinions on how the data influences decision-making on changing this region of the protein?

A. Not explicitly.

Q. If a person of ordinary skill made a deletion within this region -- that is, the characteristic region associated with the Hyal-EGF -- could that disrupt the Hyal-EGF domain found in PH20?

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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

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tolerant.

And I have a little bit of support for that statement because of the bee venom protein, which lacks the domain completely but the rest of the fold is the same. So that suggests that it is certainly possible to remove vast chunks of that domain and not necessarily prevent the folding of the rest of the protein.

Q. In the human PH20 protein, the Hyal-EGF domain is part of its tertiary structure, right?

A. Yes.

Q. And is it also part of the -- it is necessary for the activity of the human PH20 protein, right?

A. Yes.

Q. Okay. Could you go to your declaration and look at page 107, paragraph 207.

A. Um-hmm.

Q. Here, you are indicating that another common structural feature shared by Hyal-1 and PH20 is the EGF -- Hyal-EGF domain, right?

A. Yes.

Q. So a POSA would recognize that the Hyal-EGF domain is one of the common structural features shared by the claimed modified

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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.

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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

where in the human PH20 sequence the Hyal EGF region is, did you?

A. I didn't have to figure it out. I could see it. Remember, I -- you displayed what displays the structure.

Q. Let me -- so let's focus on the amino acid sequence that creates -- or sorry, the amino acid sequence associated with that structure. You didn't identify the boundaries of the amino acid sequence?

A. I didn't have to because it's been done elsewhere in the literature (indicating).

Q. And so, for example, you could see that from the alignment in the Chao --

A. That's one place.

Q. Do you recall if Dr. Park also identified it?

A. I thought he did.

Q. Okay.

A. I can't point you to the paragraph.

Q. So, but you didn't look at the individual amino acid makeup or compare that to the mutational data of the sequence that correlates to the human PH20 Hyal-EGF domain as part of your work in this case?

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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.

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Q. And you're saying that "the Arming results are consistent with Zahn ... that the EGF motif appears to be required for enzymatic activity for both Hyal-1 and PH20," right?

A. Yes.

MR. KUSHAN: Okay. So let me introduce Zhang. This is Exhibit 1010.

A. Um-hmm.

BY MR. KUSHAN:

Q. Please confirm this is the Zhang paper that -- that you addressed in your declaration.

A. Yes.

Q. So Zhang reported experimental results from mutations of the Hyal-1 protein, right?

A. Yes.

Q. And --

A. This -- this is subsequent to the structure of the Hyal-1 protein.

Q. Yeah. So Zhang actually uses the Chao Hyal-1 structure to study and then performed mutations to the structure to compare the effect of predicted changes to actual changes?

A. Yes. It's more specific than that. They're probing the mechanism of catalysis.

Q. Got it. Could you go to page 9439 of

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Zhang?

A. Um-hmm.

Q. And in the right column there's a paragraph --

A. Um-hmm. The deletion?

Q. Yeah. There's a paragraph in -- what is that section? What does it say there -- I'm sorry. Was is the title there?

A. "Deletion of EGF-like domain," is that what you're referring to?

Q. Yeah. And it says "Abolishes Hyal-1 Activity Independently" --

A. Yes.

Q. -- "of Asparagine 350."

A. Yes.

Q. Okay.

A. That's the paragraph I assume you want.

Q. Okay. So Zhang attempted to produce a Hyal-1 mutant that deleted the entire Hyal-EGF domain?

A. Yes.

Q. And Zhang said that the transfected cells did not secrete the Hyal EGF truncation mutant, right?

A. That's right.

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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

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Hyal-EGF domain, right?

A. Well, evidently they didn't at this time. I don't know if it's been determined since.

Q. Right. And Zhang measured activity in -- from the lysed cells, and they recovered protein from the lysed cells, right?

A. Yes, I believe so.

Q. And they reported the activity being 6 percent from that recovered lysed cell?

A. I think that's right.

Q. All right.

A. And that's not zero, by the way.

Q. Right. So they -- the Zhang authors portray that level of activity as being -- as indicating the activity has been abolished, right?

A. Yeah. I don't know that a person of skill in the art would always accept that statement without some additional data.

Q. The Zhang author did?

A. Yes. And -- that's correct.

Q. If you can go to the paragraph we were referring to a minute ago at page 9439.

A. Excuse me. Can we go back to the previous question for one second?

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Q. Sure.

A. If we look at the last two sentences of that paragraph, it may be germane to what I just said. "The lysates showed ... 2.5 and ... 6.3% of wild-type activity for N350tr and L356tr, respectively, at the 125 µm amount of HA [sic]. Thus, loss of this domain is deleterious to both secretion and activity of Hyal-1, although the residual activity suggests the effect is indirect."

So that sort of gets at what I was trying to say.

Q. So --

(Simultaneous crosstalk)

A. Because there was residual activity that suggests that the effect of truncating the domain is not necessarily to abolish the folding of the rest of the protein.

Q. Why don't you look at page 9441.

A. Okay.

Q. And if you look up in the top right paragraph of 9441.

A. "It has been proposed"?

Q. Yes. Take a look -- just read that, and let me know when you're done.

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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."

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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

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forming an active protein. You're implying that that has to do with an alteration of mechanism. That suggests the chemical process of catalysis to me. I think that's a more specific conclusion that you're able to draw from these data.

Q. What if the mechanism contemplated it from the perspective of binding to the substrate and causing catalysis, so a broader perspective?

A. That's -- that's a -- that's a better conclusion to draw because it encompasses more possibilities that I think are consistent with the data.

Q. And in that setting, from that perspective, a person of skill in the art would believe that a Hyal EGF was necessary for that mechanistic capability?

A. Or something like that.

Q. Okay.

A. Yeah.

Q. All right. So going back to that one paragraph on 9439.

A. Wait. Where -- which document are we in?

Q. Sorry. We're back -- still with -- still with Zhang.

A. Okay. Which page?

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

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supernatant in the hyaluronidase and I got zero, it might indicate the protein had not secreted, right?

A. That would be the first conclusion you would check.

Q. All right. Let's go to page 132 of your declaration, paragraph 262.

A. Page 132?

Q. Yup.

A. Paragraph 262?

Q. Correct.

A. Okay.

Q. So -- bear with me for one second.

This is the part of your declaration where you are introducing the analysis you did of mutagenesis data in the patent, right?

A. Yes.

Q. Okay. And you relied on the data from that mutagenesis experiment which is reported in Tables 9 and 10 of the patent, right?

A. Yes.

Q. You said that the data are extremely useful because they show the tolerability of each position in PH20 to substitution, right?

A. Yes.

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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.

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Q. So is it fair to say that you could not have formed those opinions about the tolerability of individual positions in PH20 to modification without the mutagenesis data in the common disclosure?

A. I could not have formed that opinion for most of the residues in the protein without the mutagenesis data.

Q. Could you have formed opinions about some of those positions based on the multiple sequence alignment and homologous sequence information available before 2012?

A. You could have tried to do that. And in some cases, you would have a high probability of being right but it would be for a small number of residues.

So for example, the catalytic residues you probably pick up that way. The cysteines in the EGF domain you probably pick up that way. For most of the rest of the protein, no.

Q. All right. So you also relied on the classification of each mutant in the common disclosure as an active or inactive mutant to form your opinions on tolerability, right?

A. Yes.

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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.

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Q. All right.
A. For each of the colors that are used.
Q. Sure. So dark green indicates positions where all substitutions are tolerated, right?
A. That's correct.
Q. And that means 100 percent of the tested mutants were active mutants?
A. That's correct. And those -- that could be a variable -- that's a variable number for different amino acids, how many were tested.
Q. So that -- so that color is going to be true -- that dark green color is going to be true if you had seven mutants tested and all seven were active, as well as if you had 15 mutants tested and all 15 were active?
A. Correct.
Q. Light green means they are generally tolerant to change?
A. Specifically. Okay. Positions where 60 percent or more of the substitutions were tolerant are colored light green.
Q. Okay. And then no color means that between 30 and 60 percent of the tested mutants were active mutants, right?
A. Correct.

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Q. And you didn't offer opinions on the tolerability of those positions?

MS. MARTIN: Object to form.

A. No. I mean, that's not true. I considered those positions sometimes when I thought about what substitutions one might make or not make. The coloring is simply to give you an indication of where in the spectrum of tolerability to the mutations those particular residues fall.

Q. Let's look at the last couple of colors and see if we can make some sense. So orange, you said means generally intolerant of substitution, right?

A. Yes. That's less than 30 percent.

Q. And then, finally, red are positions that tolerate no changes, right?

A. Correct. So you can --

Q. And that's again -- sorry.

A. Sorry.

Q. So that's 100 percent of the tested mutants were inactive, regardless of the number of them?

A. Correct.

Q. So what I'm wondering is, in your

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description of these different colors, there is no characterization of tolerance for the 30 to 60 percent range that you had for all the other ranges, right?

A. It is an intermediate set of activity that was determined. Okay.

Q. So if you -- if you looked at one of those positions that is uncolored, can you characterize it as a position that is or isn't tolerant to change?

A. Then you would go back to the original data and look at the values for each of the individual mutants. That's what I implied earlier.

Q. So there's no --

A. But you wouldn't use this alone (indicating).

Q. So from -- from this table, from the coloring, you wouldn't associate kind of a degree of tolerability, generally, to that position that is at 30 to 60 percent range?

A. You would know that it was in the range but you would want to know what it is specifically.

Q. So some changes were tolerated and some

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changes weren't?

A. Some changes were more tolerated, if you will, than others. Produced a different level of activity than others. You would want to look at that carefully.

Q. So in -- in the table you have presented, in those classifications that are used in the coloring of them, they don't reflect some metric of how many mutants were tested at a position, right?

A. No, they don't reflect the absolute number of mutations at each position.

Q. There is also no indicator or factor that's built into your coloring scheme that reflects the character of the change of the amino acids at these positions that were -- that were substituted. So going from a wild type to -- like, take an example, if the wild type is a hydrophobic residue, you don't have a metric that's evaluating in your table how big of a change could be tolerated as to other kinds of amino acids?

A. In this table, no. But the data exists in the patent to get that information very easily.

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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?

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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

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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.

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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

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scheme is the same coloring scheme you used in your table.

A. Let me make sure that that's true. I believe it is.

(Pause)

A. Yes, I believe that's correct.

BY MR. KUSHAN:

Q. All right, let's go back to 135 and 6, which is your table.

A. Okay.

Q. So I want to understand the designation of these positions as dark green. That's 100 percent tolerated, right?

A. It's 100 percent tolerant for the mut- -- substitutions that were made.

Q. Okay. If I had an instance where I had only seven substitutions that were tested --

A. Um-hmm.

Q. -- and all of them are active, is it -- is it fair to infer that all 19 choices that could be put in that position also would be tolerated?

A. You -- it might. It would depend on what those seven were.

Q. Did you --

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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

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PH20 mutant regardless of how many changes or where those changes were in the protein?

A. Most of the time, yes. If the other changes were in adjacent residues, residues in contact with that one, then you would want to look at the structure.

Q. Okay. So that's something you'd have to kind of do on a case-by-case basis?

A. You would do that on a case-by-case basis when you were trying to make the mutants that had the purposes that you intended.

Q. All right. If I picked 15 of the dark green spots to mutate --

A. Okay.

Q. -- is it your view that a protein that had those 15 mutations in them would fold, regardless of which amino acids were put in each position?

A. That would depend on which mutations you picked. If you picked a mutation that only had -- a residue that was only mutated to one or two others, you might be hesitant to make that prediction without first checking with the structure.

Say that residue was on the surface of

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the protein, sticking out into the solvent, and making no contact with any other residue in the protein. Then even though you only had two mutations at that position, you might well be justified in assuming that you could make many, if not all, substitutions at that position and they would tend to be tolerated.

But it depends -- as I said, it's context dependent, context in this case being structure.

MS. MARTIN: So we -- sorry. We've been going for almost an hour exactly. So, Greg, do you need a break?

THE WITNESS: I'm okay for another few minutes.

MR. KUSHAN: Yeah. Why don't we just -- I think just a couple more questions and we can take a break.

MS. MARTIN: All right.

BY MR. KUSHAN:

Q. So is there -- just kind of a surrogate of evaluating tolerability, is there some number of substitutions above which you would feel that the position had been interrogated enough to support the position being, for example, highly tolerant or likely tolerant to change?

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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

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whether or not those would give you the same result until you looked at the structure. Okay?

If those residues, the other 17 mutations, are in a site that's not in contact with the rest of the protein much, but not in a buried region of the protein, then you might be justified in saying phenylalanine, tyrosine, and tryptophan will almost certainly be tolerated as well. But if the packing around it is somewhat different from that, then you might need to think about it some more.

The -- you see, you don't want to just use this. You want to use all the data in the patent. The patent has a lot of data. You want to use all of it in making sensible decisions. That's what a person of skill in the art would do.

Q. And again, so that the -- what you're saying is that a person of skill in the art would need to take this table, look at the character of changes in individual mutations, study it in the context of the position you're contemplating changing, and then make judgments with all that data to say, yes, this one is a substitution I believe would be tolerated?

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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 --

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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

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to interact with the one that you've substituted?

A. Solvent, neighboring residues, but in some cases, also the secondary structure that you're in, that can make a difference, for example.

Q. So a residue that might be tolerated in an unstructured loop might not be tolerated if it is part of an alpha helical sequence?

A. Perhaps. Or if it is at the end of an alpha helix its charge may matter because of what is called helix cAMPing effect. A person of skill in the art knows all these things. And a person of skill in the art will make use of that knowledge together with the data in the patent.

Q. So using that kind of understanding of assessment of interactions and environment, a person of skill could conclude that a particular amino acid substitution would be tolerated at a particular position?

A. I think you would be able to make that prediction with a high degree of confidence for most of the mutations, yes.

MR. KUSHAN: All right. If you want to take a break, we can take a break now.

THE WITNESS: That's fine.

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

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under the sun. BLAST would then give you sequences that had various levels of identity, all right, not similarity, but identity to your sequence. It would attempt to do so by minimizing the number of insertions and gaps in the alignment.

You would then tend to use cutoffs. All right? 40 percent identity, or whatever. And look at those alignments. And in most cases, unless there were a lot of gaps of things, you could be comfortable in saying that this sequence with 40 percent identity or more to PH20 is part of a family of PH20-related enzymes. And so you would then begin to use that in multiple sequence alignments. And you would pull other sequences out in the same way.

Q. Okay. That's helpful.

Just to confirm, when -- when the BLAST algorithms are selecting sequences for homology they are not just doing kind of a 40 percent overall identity, they are doing -- kind of checking segments or regions and looking for those segments to have a sufficient level of identity?

A. Yes. They start by doing local

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alignments and then extend it over the -- the whole protein. And that was what was done in 2011. There have now been some refinements to the algorithm. If you did it today, you might get a few more additional proteins showing up. But in general, the -- that technology was well developed.

Q. I want you to look at pages 36 to 37 of your declaration in paragraph 91.

A. Yes.

Q. So you see on -- there is an image of a multiple sequence alignment, I think, on page 92, right?

A. I am looking at page 36. Is that what you are talking about?

Q. I'm sorry. It's 37.

A. Right. Paragraph 92?

Q. Yeah.

A. Okay.

Q. So that's -- that's the picture out of your textbook, right?

A. Yes.

Q. And this is a multiple sequence alignment of homologous proteins?

A. Yes, and that would have been done around

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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

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these homologous proteins, right?

A. Usually, yes.

Q. Could a POSA know whether one of the conserved positions was going to be necessary for those structure and activity without experimental testing?

A. Say that again, please.

Q. Could a POSA have known from the position of a conserved residue whether it was important for both structure and activity without testing?

A. Conserve -- position where? In the sequence or position in the structure?

Q. So having just the sequence, the conserved sequence position, a person looking at that conserved residue at that position in the sequence, could they know whether that one was going to be important for both structure and activity without testing?

A. Unless one of the proteins in question were a protein for which there was three-dimensional structural information; or, or for which experiments had been done that identified one or more residues as being essential for activity, for example. And that was often done before structures.

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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

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change?
A. Not given the information in the patent. They would look at the information in the patent.
Q. Let's just go back --
A. Because this is a restricted range of residues.
Q. Sorry. My question was not great because I was focusing mostly -- I wanted it in the context of an MSA.
If all they had was an MSA of the homologous proteins, would a person of skill in the art avoid the positions that were conserved?
MS. MARTIN: Objection. Scope.
BY MR. KUSHAN:
Q. When making modifications.
MS. MARTIN: Objection. Scope.
A. When you're making modifications, it depends on the purpose. So if your purpose was to identify catalytically important residues you might focus on the residues that were conserved, not avoid them. So it will depend on the purpose.
BY MR. KUSHAN:
Q. If I am trying to make enzymatically active mutants that have a change to them --

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

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BY MR. KUSHAN:

Q. Would a person of ordinary skill in the art who is trying to make an enzymatically active PH20 have believed that they could modify a position that is not a conserved residue and expect that PH20 to retain its activity?

MS. MARTIN: Object to form.

A. It is probably too general a question to give you a good answer to. All right?

BY MR. KUSHAN:

Q. So if I have mutational data combined with an MSA, so I have mutated a bunch of different positions, I am equipped as a person of skill in the art with a number of positions, have lost activity because of a mutation, and then I have my MSA in this, which is identifying conserved residues.

Does the combination of those two things give the person, collectively, more information than just the MSA?

MS. MARTIN: Objection. Scope.

A. So the multiple sequence alignment is limited in its nature because there are lots of reasons why residues get selected in evolution, including the frequency with which codons can

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change, for example.

You would -- the mutational data when it is on the scale of what's in this patent, all right, is where you would tend to start (indicating).

Q. The -- in -- before 2012 and before 2011, there were studies that had identified through single point mutations effects on PH20 structure and activity, right?

A. Yes.

Q. So that set of information would be useful to a skilled person trying to make modified PH20s, right?

A. Yes. Those you have maybe a half dozen or so residues, something like that.

Q. Could you go to Dr. Park's declaration again, which is 1004.

A. Thank you. Where?

Q. Go to pages 10 and 11.

A. Yes.

Q. And Dr. Park is describing kind of his methodology of what he did at pages 10 and 11 --

A. Um-hmm.

Q. -- paragraphs 27 to 29.

A. Um-hmm.

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Q. So he identified homologous PH20 -- proteins homologous to PH20 using a BLAST search, right?

A. Yes.

Q. And he aligned it into -- from a -- from multiple sequence alignment with Clustal Omega, and that was a conventional tool back then, right?

A. That's right. And I think he had about 90 sequences when all was said and done.

Q. Right. So those are steps that a person of skill in the art would have taken in the 2011 to 2012 timeframe if they were undertaking a study of protein for modifications?

A. Prior to the patent.

Q. Yes.

A. That's one of the things you could do.

Q. Okay. Go to paragraph 30. And do you see --

A. Yes.

Q. He's also referring to an Appendix D-3. Don't go there yet.

He's put a table on page 14 of what he's identified as the "largely invariant residues" in human PH20 from his MSA, right?

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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.

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Q. So you point out that the Y184 mutant had activity, and that is not one of the -- and that's at a position -- there was a mutant made from the wild type that went from tyrosine to tryptophan, right?

A. Yes.

Q. And that's at one of the positions Dr. Park had identified as one of these conserved residues, right?

A. That's a position that he's identified as a residue that cannot change.

Q. Right. And so did you -- that's one mutant out of the set that was tested in the patent, right?

A. One of those mutants had activity.

Q. Do you know how many mutants were tested at that position?

A. I don't remember. We could look it up.

Q. Why don't we do that. Why don't you look at this big sheet (indicating).

A. Um-hmm.

Q. And go to page 4. Are there page numbers on this?

A. 184.

Q. Yeah. 184, which --

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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?

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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.

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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

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proteins with invariant activity, invariant occurrence. In your mutation -- in your mutagenesis study, you have one that is not inactive.

A. Yes.

Q. Four unknowns --

A. Yes.

Q. -- or three -- there unknowns.

A. Yes.

Q. Okay. So that conserved residue readout is different, in your view, than the mutagenesis study at that position?

A. You're comparing apples to golf balls.

Q. Right.

A. Okay? They're very different. Because the one is in the context of a protein whose entire structure is subject to variation by evolution, but which, for most sequences, are going to be very similar to each other because they're going to be not so far apart on the evolutionary tree. Since you've a lot of sequences, then you're covering more of the evolutionary tree.

In this -- in a case of the mutagenesis data, you're doing something very precise.

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You're taking the same protein, mutating one residue, seeing what it does in the context of the wild-type sequence.

Q. What about the converse, where you look in the -- in the MSA data and you see 15 different amino acids occurring at that position.

A. Correct.

Q. Does that give a more comparable assessment of tolerability to the mutagenesis study that has also tested 15 amino acids at that same position?

A. So I got half the question, but it sounded like the two halves were the same, which means I must have misunderstood it. I apologize, but please try again.

Q. So one position -- there's one position that is looked at through the lens of MSA data.

A. Okay.

Q. Looking at the same --

A. And what do we see when we look at it?

Q. We see 15 different amino acids of various kinds being tolerated at that position in nature.

A. Okay.

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Q. And now I have a mutagenesis study that has studied the same position and has tested 15 alternative amino acids.

A. Same 15?

Q. Same 15.

Would you draw the same kind of conclusion about tolerability from the MSA data as you would from the mutagenesis data?

A. You would say that -- you could say that the two sets of data were consistent. All right? That's what you would say.

Q. If you concluded that the mutagenesis from the mutagenesis study, that it would be tolerated at that position, would you reach the same conclusion of being tolerated from the MSA data?

A. If you had the MSA data alone, you might not -- you might be a little more careful about drawing that conclusion, for the reasons I indicated. It's a very limited set of proteins you're looking at.

I think the MSA -- the mutational data, you're more comfortable in drawing a specific conclusion like that at that position under the conditions of the -- the way this study was done.

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Q. So you identify I believe three positions where there was variation in the set of positions that Dr. Park had identified as essential.
A. Um-hmm.
Q. Did you identify any other positions where --
A. Yeah, there was -- there were others. I just listed these.
Q. Where -- what other ones were they?
A. I don't remember. I'm sorry.
Q. So based on what you have in your declaration, 65 out of the 68 positions were consistent with what Dr. Park had reported in his --
A. I don't -- I can't say that.
Q. So is -- did you -- did you reach a conclusion before you completed your declarations that there were additional positions that were different in the conclusion of being conserved relative to Dr. Park's MSA analysis?
A. Yes. I believe there were more than three.
Q. Did you write it down anyplace?
A. Sorry. I did not.
Q. So as far as we know, from what you put

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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?

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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?

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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

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want it to have somewhat similar properties to the residues that were changed. Okay?

So if it were a large hydrophobic residue, you would want to know if the large hydrophobic residues tended to do that, for example.

Q. Are those types of changes you are speaking of called conservative changes?

A. They could be. But conservative can have different meanings in context. So it could mean a charge conservation only. It could mean a conservation of shape. It could mean a conservation of polarizability, or position in the structure could be important for what property you think is -- is a conservative property. But often, it will mean what you say.

Q. So if I understood the last answer you gave, kind of a chemical or size attribute of the residue in the context of the position is what you would look to to assess?

A. That's the first thing you would look at.

Q. All right. And is that -- the use of that perspective something that gives a predictable indicator of whether a substitution to a similar residue is going to be tolerated at

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

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Q. Sorry. Modified PH20 polypeptides that are incorporating multiple changes?

MS. MARTIN: Object to form.

A. I didn't say I wasn't able to do that.

BY MR. KUSHAN:

Q. So let me -- I am just trying to understand the restraint you are expressing about that last opinion.

Is the -- are you able to rely on the tolerance criteria that you laid out in your table to predict the effect of making multiple changes to PH20?

A. A person of skill in the art could use the information in that colored table together with the other information in the patent -- let's keep remembering we want to look at all of the data -- and could make predictions about multiple substitutions, yes.

Q. And these predictions, those are based on your comments about each individual mutation?

A. The individual -- the data for the individual mutations is one of the most important things you would take into consideration, yes.

Can we turn off the sound for a second?

MR. KUSHAN: Do you just want to take a

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break?

MS. MARTIN: Do you want to go off the record?

Yeah, let's take a break.

THE WITNESS: No, I am just getting rid of my leg wrappings.

THE VIDEOGRAPHER: You are fine.

(Discussion off the record)

THE WITNESS: Okay. I am good.

THE VIDEOGRAPHER: All set.

BY MR. KUSHAN:

Q. So if I could have you go to page 156, paragraph 323.

A. Yes.

Q. So in this paragraph, you are discussing substitutions at individual -- individual -- where the substitution --

In this paragraph, you are discussing substitutions that are in different parts of the protein?

A. I am discussing what criteria you might use in thinking about those, yes.

Q. All right. And what you say is, a person of ordinary skill, POSA, would expect that if substitutions were made at these -- at the light

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green residues in different parts of the protein, they would be independent of each other, and that that person would generally expect multiple independent changes to be tolerated.

A. I am talking about the distribution of the mutations in space. The structural space. If those are different -- if those are separated from each other in the structure there is a high degree of likelihood that they will operate independently.

Q. Can multiple changes to the protein in these -- I call them spatially distinct; is that fair?

A. Yes.

Q. So a POSA makes changes at spatially distinct regions of the protein. Is it possible that even as separate spatial, distinct regions --

(Reporter clarification requested)

(Discussion off the record)

A. Want me to do it for you?

BY MR. KUSHAN:

Q. I have a feeling you will.

So I am wondering if it's possible for a substitution made in spatially distinct parts of

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the protein can still unpredictably cause the protein to not tolerate both of those changes?

A. It can happen. It is less likely that it does happen.

Q. Do you have any sense of frequency with which it happens?

A. Not in any absolute terms. But as a general rule based on years of experience, they are more -- they are certainly more likely to be independent than not.

Q. So when you are inserting changes at different spatially distinct parts of the protein, can the mutations cause formation of intermediate states of the protein during the folding process relative to the native sequence?

A. Theoretically, yes. Practically, those are -- there are very few residues that do that in any given protein. And in some cases, none have been found.

Q. What -- what are the circumstances where it does happen?

A. There is not a rule of thumb. Because the folding pathways of different proteins are quite different.

Q. They are not really things that can be

easily characterized, right?

A. It's hard to -- it's hard to do the experiments. Okay. And it was thought, originally, that there might be a common pathway. Doesn't seem to be true.

Q. Can a -- can a set of mutations that are spatially -- in spatially distinct parts of the protein cause a particular combination of changes in the sequence to cause a --

If changes are made in spatially distinct regions of the protein substitutions, can the set of substitutions cause the protein to not fold?

A. It's been, it can happen but it is rare. For changes that are spatially distinct like that, it is rare.

Q. Do you -- can you predict when they will impact folding?

A. If you have a protein whose folded pathway has been characterized, yes. If you don't, it will depend to some extent on the protein. There are proteins that belong to families where one member of the family is folding pathway characterized. You might assume that that pathway is common. The short answer is, not easily.

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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.

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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

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naturally occurring protein sequence that is highly homologous to the sequence it is trying to model. That's the first thing it does. Okay?

It doesn't -- if it can't find one that covers the whole protein, it may look at various segments of it.

Q. So I -- there's two -- kind of two variables in the -- in my question here. So certainly there's a template that's going to be selected for a sequence that's submitted to SWISS-MODEL, right?

A. If it can find one, yes.

Q. All right. And then the sequence itself, does SWISS-MODEL factor into any of its assessment of the model whether that is a naturally occurring protein sequence as opposed to an artificial sequence?

A. I have no idea. But as of 2010, I think the only thing in the database SWISS-MODEL was using were naturally occurring sequences. I don't think there's an artificial sequence in it.

Q. Right. I'm still doing a poor job of explaining my question.

So I have two things that I'm matching. I have an amino acid sequence, and I have a

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solved structure that is a template structure that could be used by SWISS-MODEL.

A. Right.

Q. Right? So I have a sequence that has not yet been experimentally determined as to its structure.

A. Yes.

Q. And what I'm wondering is, when I put that sequence into the Swiss model algorithm, does SWISS-MODEL account for the fact that the sequence is a naturally occurring protein or if it's an artificial sequence?

A. No. SWISS-MODEL only looks for homologies. It doesn't look at the organism or a source of the protein, as far as I know.

Q. And if it were a naturally occurring protein, you'd know that protein folds, right?

A. Most of them. Not all of them.

Q. Sure. For the -- for the assumption I'm making here, this is a protein that you can, for example, isolate.

A. If it's an -- let's say it's an enzyme.

Q. So it's an enzyme that occurs naturally.

A. Then you'll -- then it faults.

Q. Okay. So you -- you have a sequence

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associated with a folded protein going into SWISS-MODEL to create a PH20 homology model, right?

A. Yes.

Q. Okay. So what I'm wondering is, if I send a sequence in for modeling to SWISS-MODEL that is an artificial sequence, that isn't one than has been demonstrated to fold and be functional, does SWISS-MODEL account for that in any way in the output of the model results?

A. Only in -- to the extent that it might not have very -- any significant sequence identity to the existing sequences in its database. But if it does, then SWISS-MODEL doesn't care where it comes from.

Q. So SWISS-MODEL -- when you run a job with SWISS-MODEL, you get a report back that gives you quality metrics of the model, right?

A. Um-hmm.

Q. And one of them is an overall quality score, right?

A. Yes.

Q. And the other perspective is a residue-by-residue quality metric?

A. A local quality.

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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

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came back when the -- I think this is the D320K PH20 model.

And in the middle of the page, you see this histogram with red and blue. That's the local quality score?

A. Yup.

Q. Okay. And when you're doing your assessments of modeling with the SWISS -- with the PH20 homology model, are you relying on essentially the portions of the local quality region that are kind of consistently either blue -- or, well, consistently blue?

A. You take the -- you trust those more. Okay?

The red ones are red for a variety of reasons. All right? If you just have an occasional red one here, it may simply mean that the sequence identity at that point was so different that it's not quite sure what might happen. But if you're looking at blocks of red residues, those tend to be loops, and loops in 2010 were not as well modeled by SWISS-MODEL as other parts of the structure.

Q. So it's fair to say that where you see those stretches of red, you're going to be a

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little bit more cautious about predicting the effective changes in that region?

A. On structure -- affect on structure, yes, yes. Um-hmm.

Q. Okay. When you formed your opinions in this case, did you consider the local quality or overall quality metrics of the model you created?

A. Yes. When I used the model, I did.

Q. All right. This is --

MR. KUSHAN: I'm going to introduce Exhibit 2183.

THE WITNESS: Thank you.

BY MR. KUSHAN:

Q. And this is the exhibit that was provided in this case. Did you create this printout?

A. Looks like it.

Q. I don't see any local quality scores on this.

A. We certainly calculated them.

Q. Were --

A. Okay?

Q. Did you --

A. You can't not calculate them. The program does it.

Q. Right. What I'm wondering is, did you

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

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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

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the question with 15 changes?

MS. MARTIN: Object to form.

A. A person of ordinary skill in the art probably wouldn't be doing that.

Q. And why not?

A. Because you wouldn't need to.

Q. You wouldn't need to?

A. Yeah. You'd be able to make -- you'd almost certainly be able to make the kinds of things you'd want to make with fewer changes than that.

Q. So you're saying that no one would make a PH20 protein with more than five changes?

A. No. I'm saying that you would rarely, rarely, make PH20 with 15 changes.

Q. Is that -- is that because it's unnecessary to achieve the purpose you're aiming for?

A. Yes.

Q. So is it also true that the more that you introduce as changes, the greater the likelihood is that it may have a problem such as folding or loss of activity?

MS. MARTIN: Object to form.

A. No. It will depend on where they are and

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what they are. The primary -- primary reason is a person of ordinary skill in the art would be more efficient than that.

BY MR. KUSHAN:

Q. But isn't it correct that each -- each position introduces some amount of unpredictability as to the effect of the folding on the protein, right?

A. No.

Q. No?

A. Because for some of these positions we have virtually every amino acid in the database, and so we know what they do.

Q. So in the database positions where you have, let's say, three or five mutants tested, for those positions are they different? Would that be a different answer?

A. They could be more unpredictable, it depends on what change you would make. A person of ordinary skill in the art would probably look at the changes that were made, and if they needed to change that residue at all -- and they might not choose to change that residue at all, but if they needed to change that residue at all, they would probably select an amino acid with

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properties similar to the ones that did whatever it is they wanted it to do.

MR. KUSHAN: Would you like to take a break? It has been a little bit more than an hour.

THE WITNESS: No. I am okay. The massage of the calfs helped.

MR. KUSHAN: Why don't -- why don't we take a break.

MS. MARTIN: Let's take a break.

THE WITNESS: Okay.

MR. KUSHAN: It won't be a long one.

THE VIDEOGRAPHER: Going off the record at 3:08.

(Recess taken)

THE VIDEOGRAPHER: Back on record at 3:30.

BY MR. KUSHAN:

Q. Dr. Petsko, did you discuss anything relating to the --

A. One second because I am now having trouble hearing.

THE WITNESS: Check to see -- let's see if that thing is turned on (indicating). That's on all right. It has got battery. Okay. Let

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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.

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BY MR. KUSHAN:

Q. So this is describing kind of how the patent classified the mutants into the different categories of active mutants or inactive mutants?

A. Yes.

Q. Okay. And an active mutant was -- well, first, each mutant was tested with two assays, right?

A. Yes.

Q. And if one of the assays had a score of 40 percent relative activity to the control, then it was classified as an active mutant, right?

A. 40 percent or greater.

Q. 40 percent or greater of the control. And then what was reported in the table, Table 9, was an average of the two activities?

A. Yes.

Q. Okay. So some of the instances are below 40 percent and they are still classified as active mutants?

A. That's correct. That's because one of the measurements was less.

Q. All right. There is two tables, a Table 3 and Table 9 that are devoted to active mutants and --

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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

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between Tables 9 and 10?

A. I don't recall.

Q. Did you look for any inconsistencies where perhaps a mutant was double counted, basically?

A. Yeah. I looked for that a little bit, but I don't know that I was completely systematic.

Q. If you had encountered any of those which were classifying as the same mutant as both active and inactive mutant, you couldn't really rely on that for your tolerance score card, right?

A. You might be cautious about that.

Q. Because that -- the classification based on the percentages are based on just how their -- how a mutant is classified, as an active or inactive, right?

A. Yes.

Q. So probably more cautious to take that off the table as --

(Simultaneous crosstalk)

A. You could take it off the table or you might look at some of those individually a little bit more carefully.

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Q. But for the -- just for your table, you would probably take it off that because --
A. You mean the summary table?
Q. Yes.
A. Yes, you might.
Q. Okay. I want you to go to the '731 application, which is the -- this one (indicating).
A. The big one.
Q. Yeah.
A. Yup.
Q. And you might want to take the binder clip off because it is hard to --
A. I -- I had that thought.
Q. Could you go to page 250.
A. Yes. You mean Example 4?
Q. Yes. And I just want to walk through this. In the active -- this is part of the patent that is describing the active mutants classification, right?
A. Yes.
Q. And it indicates that measured activity values for samples of positive controls were used to calculate the -- the percent activity values for all of the mutants, right?

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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?

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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

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the variability of the positive controls in the primary screen?

A. How was I to do that?

Q. For example, did you ask counsel, or --

A. No.

Q. All right. Just to be clear, the classifications in your table of the mutants rests on the data of each mutant as its activity readout?

A. You mean the color --

Q. Yes.

A. -- chart?

Q. Yes.

A. Yes, although we were also careful to look for trends. Okay? On the data. That's important.

Q. Trends in what sense?

A. In the sense that if you have -- you know, if the measurements don't agree they might -- they might be not agreeing but within the same general direction. All right? Increased activity, decreased activity. Those are the things you pay attention to.

Q. Sorry. I'm not quite understanding. Are you talking about in a positional stretch of

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

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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.

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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.

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

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

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variables that influence the readout of each mutant --

(Simultaneous crosstalk)

A. Two at least.

Q. Okay. Is the --

A. Yes.

Q. So you didn't attempt to calculate the range of activity that was observed in the positive control at either of the two temperatures?

A. No. I did not think that was appropriate.

Q. Did you review Dr. Hecht's analysis of the positive control data?

A. I -- I recall it, but I don't recall it in detail.

Q. Do you recall his conclusion about the variability in the positive control?

A. I know he concluded that it was variable, but I don't remember his -- his numerical answer.

Q. Okay. And you're not offering any different opinions relative to Dr. Hecht on that point, are you?

MS. MARTIN: Objection. Scope.

A. I'm not offering an opinion on that,

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period.
Q. Okay. All right. Could you go back to page 251?
A. 251. Yes.
Q. And look at the paragraph that goes from line 14 to 20.
A. Line?
Q. 14 to 20.
A. Okay. Um-hmm. Um-hmm.
Q. So this is reporting that over 600 tested mutants exhibit activity that's increased relative to wild type, right?
A. Yes.
Q. And then it starts walking through some more specific observations?
A. Um-hmm.
Q. It says 536 mutants exhibited 120 percent or greater activity, right? And then 75 exhibited 300 percent or greater activity?
A. Um-hmm.
Q. There weren't any other percentage thresholds that the patent called out, right?
A. No. I think that's right.
Q. Okay. And then it goes through and identifies one, two, three, four, five --

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six specific mutants, right?
A. I'm sorry?
Q. It identifies six specific mutants as active mutants in this section, right?
A. They say "in particular," yes.
Q. So there's two at position 69?
A. Yes.
Q. And three at position 170 -- or sorry, position 70.
A. 70.
Q. Yeah. And then one at 127 -- or sorry. I'm doing bad math here.
A. Um-hmm.
Q. Position 271, right?
A. Yes.
Q. Okay. So these are the six that the patents calls out as examples of active mutants, right?
A. Yes.
Q. Okay. It didn't call out any mutants that had an activity of 500 percent, right?
A. If it's 22-fold, it's bigger than 500 percent.
Q. Right.
Does this part of the common disclosure

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highlight any substitutions at positions between 300 and 325 of the --

(Simultaneous crosstalk)

A. I don't remember if it does. I'd have to look.

Q. All right.

A. Between which residues again?

Q. It -- there's no -- in this section, where they're discussing the results of the activity classifications, they're not calling out anything in the 300 to 325 range?

A. You mean residue range?

Q. Right.

A. 300 through --

Q. In the narrative. Not in the table, in the narrative.

A. Oh, yes, that's right.

Q. Okay.

A. But it -- there -- there -- there -- there are some in the table, yes.

Q. Can I ask you to go back to Example 2, which is -- starts at page 219?

A. Yes.

Q. All right. So -- and you're familiar with this experimental description, right?

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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

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of codon bias influencing the volume of the expression of the different proteins?

A. Yes. Although, I thought they used codon optimization.

Q. For both? For --

A. I don't know that.

Q. Okay. If the ratio of expression of the SEAP in the particular mutant varied in that cell, that would affect kind of the rating of activity of the mutant, right?

A. It could unless you normalized, but they do normalize.

Q. And they normalize against a standard curve, right?

A. Yes.

Q. Okay. Could I ask you to turn to page 130? Sorry.

A. 130?

Q. Hold on -- hold on one second.

Could you go to your declaration for a minute?

A. Yup.

Q. Go to page --

A. Wait a moment.

Q. Sure.

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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.

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Q. What I'm asking is: Do you know if the mutant proteins in each well were characterized or tested in any manner as part of the primary screen?

A. I have to double-check. I think I do.

Q. Yeah, go ahead and look at -- this is at 248.

A. Pardon?

Q. You can go to 248.

A. I am going to, to make sure I'm right. I mean the primary screen.

Q. The primary screen was the source of the values of activity, right?

A. No, I know. They then carried out a activity assay.

Q. Right.

A. Is that what you asked?

Q. Yeah, I am just confirming they didn't try to detect the presence of the mutant protein in individual wells that were assayed, the supernatants that were assayed, right? There wasn't a step in the assay process that confirmed an amount or presence of the mutant PH20, right?

A. I don't know that. It is not reported, but I don't know if there was or not.

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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

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see there, there is a paragraph that starts "The transfected variant or wildtype PH20 supernatants."

A. I haven't found it yet. This is on page 248?

Q. Yup.

A. This is on 248?

Q. Yes.

A. Which paragraph?

Q. Hold on for a second. Do you see paragraph that starts "Transfected variant or wildtype PH20 supernatant" on page 249 --

A. There is -- that's not in any paragraphs on -- are we in the patent or my declaration?

Q. We are in the patent.

A. I don't see that.

Q. Turn the page.

A. It is page 249 in the copy I have.

Q. Got it. Perfect.

A. Okay.

Q. Do you see the paragraph starting --

A. I do.

Q. -- "Transfected variant or wildtype PH20 supernatants"?

A. Yes.

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Q. So they prepared them with the diluent buffer, right, was the first step. They took a sample of the supernatant and they put it in diluent buffer, right?

A. Yes.

Q. And then at the bottom last sentence, they said: "One hundred microliters of each standard and sample were transferred to the assay plates and incubated for approximately 1.5 hours."

This is where they are testing the mutant for activity against the substrate, right?

A. Yes.

Q. Okay.

A. Which is in a -- which is bound to the microplate.

Q. Correct. If you go to the next page.

A. Um-hmm.

Q. After this incubation step, they wash the plates, right?

A. Yes.

Q. And then they put in an agent to realize the color, basically, of each assay which is the measurement -- the basis of the measurement of the activity, right, it is a colorimetric assay?

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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,

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right?
A. Yes.
Q. And do you know if the SEAP activity was detected from the same sample, the supernatant as the PH20 activity, or did they test different samples of supernatant?
A. I don't know that they say.
Q. Would that have an effect on this normalization process?
A. Depends on how robust the data are.
Q. The patent doesn't give any information on -- on that parameter, right?
A. I don't recall any.
Q. Could you go to page 250, then go to line 26 of page 250?
A. Yes. Starting with "the criteria for".
Q. Exactly. Did you -- did you review this part of the experimental protocol?
A. I read it, yes.
Q. What -- what are they -- so they are using one criteria for the high throughput assay as a -- using the SEAP signal, right?
A. Yes.
Q. And then the other signal that they are using is for the control PH20, right?

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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

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plate.

Q. So you used two samples of positive control or two different positive controls?

A. Yes. Well, it depends on the assay and the protein. Sometimes you can't. Sometimes you can. If you can do two different positive controls, we would do it.

Q. If -- at a minimum, you would do two samples of a positive control?

A. Yes.

Q. Okay. Do you do any negative controls?

A. Always, when we can. All right?

Q. Do you know if they used a negative control in this assay?

A. I don't. I would hope that they did but I don't.

Q. All right. So based on the protocol that was followed, is it correct that no steps in the screening process for the primary assay confirmed there was mutant PH20 in the tested supernatants?

A. If you are getting activity, I think that's...

Q. So activity would be a readout that's a positive signal that there is a mutant there, right?

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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

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clear the threshold?
A. Yes.
Q. All right. Can you -- could you go to page 272 of Exhibit 1026.
A. Yes.
Q. This is a description of the inactive mutant assay, right?
A. Um-hmm.
Q. So the inactive mutants were tested not only at 96 hours after transfection, they were then tested again the next day?
A. Yes.
Q. We don't know how many exact hours, we presume when you just say 12 hours later?
A. Yes.
Q. Okay. So all of the inactive mutants had two measurements for activity?
A. Yes.
Q. The Table 10, does that show the values that were measured for the inactive mutants at either of those measurements?
A. It lists the mutants.
Q. It just lists the mutants. So it doesn't give you any activity values for any of the active --

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(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

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point and then 18 percent activity at the whatever -- 12 hours later. You'd have two data points showing that this protein is exhibiting activity?

A. The same activity.

Q. Would you conclude that protein, that inactive mutant, had folded properly?

A. It's not an inactive protein necessarily if it has 18 percent activity. If you -- if you make a cutoff of 20 percent, then you call it inactive. If your cutoff is 15 percent, you might call it active. But you -- what you would say is that it was a reproducible result.

Q. You would -- you would also -- because you could see there was activity being exhibited by the mutant, it's in a state that would be likely folded and has some -- I don't know how to -- how you would characterize it, but it's meaningful information to you that there is activity associated with that inactive mutant?

A. Usually. But again, be careful about what we mean by inactive. All right? We may not be talking about the same thing.

Q. Sure. In -- in the table, you wouldn't be able to differentiate that inactive mutant

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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.

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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

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the absence of additives?

Q. I'm actually focused on, are -- were there any experiments done besides the one we've looked at which tested the activity of the inactive mutants?

A. I don't see any.

Q. So the only description of the inactive mutants that describes their kind of status, you know, classification was the example -- sorry, Example 4 in Table 10?

A. I believe that's correct.

Q. Okay. All right.

So based on the information in the patent that experimentally characterized the inactive mutants, from what you can tell, if an inactive -- sorry, if a mutant PH20 polypeptide was not secreted by the transfected cell, that would give a rating of activity below 20 percent?

A. Yes.

Q. And so that -- that mutant would be classified as an inactive mutant?

A. That would be -- would be classified as inactive.

Q. And then if a mutant was secreted by the cell, but within 96 hours after it was

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transected, that mutant, 100 percent aggregated, and that also would give you a result which would result in that mutant being classified as an inactive mutant?

A. Yes. Although that's rare -- that's a rare phenomenon, relatively speaking.

Q. Okay. And then I have the two examples of the mutant that had an 18 percent activity that -- it's an 18 percent activity at 96 hours, and then an 18 percent activity at -- 12 hours later. That's also being classified as an inactive mutant?

A. If the cutoff was 20 percent, yes.

Q. Correct. If I had an inactive mutant that had 18 percent activity at that first reading and then 0 percent activity at the 12-hour point, that also would be classified as an inactive mutant, right?

A. Yes, that would be classified --

Q. Would you differentiate the two 18 percent mutants I just mentioned?

A. No, not necessarily. Again, it would depend on your cutoff.

Q. Sorry. Let me make you a better question.

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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.

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Q. So the variation of the assay in terms of the activity variation is something that would influence these classifications that are made in the patent?

A. It would -- it would certainly -- it would certainly need to be considered in the way you looked at the data. Okay?

Q. And that's not possible for the dataset of the inactive mutants, which are classified only by falling below the threshold?

A. Yes, that's correct.

Q. Did you -- so there were -- not all of the mutants that were produced were classified as an inactive or active mutant, right? If you want to go to Example 2, I believe. Look at page -- it starts at 219, but goes to --

A. I have it.

Q. -- page 220.

A. Yes.

Q. So all -- all the mutants that were made and tested are listed in Table 8, right?

A. As far as I know.

Q. And the number of those mutants is larger than the number of total mutants that are active and inactive mutants in Tables 9 and 10, right?

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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

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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.

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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 --

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A. They are in the top of the active site cleft.

Q. Okay. So go to page -- paragraph 335.

A. Yes.

Q. And this is the section of your report where you're explaining that you used a tool called AutoDock Vina to explore locations on the surface of the protein where hyaluronic acid might interact, right?

A. Yes, that's Vina, but yes.

Q. Okay. AutoDock Vina. Okay.

And the motivation for this was your belief that it might be possible that residues in hyaluronic acid bind to PH20 outside the active site. This is a quote in paragraph 335, just want to check if that was a typo. The sentence you say: "Residues in HA bind to PH20 outside of the active site groove."

Did you mean to say HA interacts with residues in PH20 outside the active site groove?

A. Yes.

Q. Okay. Good. I just -- I thought that's what you meant. I just wanted to make sure.

A. Yes.

Q. All right. And this thought you had

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prompted you to do an investigation to determine if the red-colored surface exposed regions are predicted to be HA binding sites?

A. Yes. There were -- that was the motivation for the calculation.

Q. Okay. So this is an analysis that you did which is not in the patent. This is an analysis you did?

A. No.

Q. Okay.

A. This is a demonstration of what the data in the patent might be useful for. One of the things it might be useful for.

Q. So what are you using from the patent to do the AutoDock Vina experiment?

A. So I'm not using anything in the patent to do the AutoDock calculation. All right? I'm using the data in the patent to interpret what the AutoDock calculation is telling me.

Q. And is the AutoDock calculation telling you things like the -- which residues are interacting with hyaluronic acid?

A. Not that specifically. The docking is not accurate enough to find a single position for something as small as hyaluronic acid in a

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particular pocket. It will tend to find what it calls "poses," but which I call "states," for the hyaluronic acid.

So it may be sometimes here, sometimes here, sometimes here. But always in the same pocket. And so you wouldn't want to use it to state exactly that residues X, Y, or Z are going to specifically interact with hyaluronic acid. In this case, it was a more general question. The patches of residues on the surface that are intolerant of mutations are interesting because they are patches. And because they are on the surface. And the question is, is it possible that hyaluronic acid might like to sit there, at least if you give it a chance to computationally.

Q. How does the AutoDock Vina tool tell you if it does or doesn't interact with one of those residues?

A. So you have to view it in a particular way. You want to give the hyaluronic acid the opportunity to explore the entire protein. You also want to do so excluding the active site because unless you run a very, very long docking simulation you will tend to get mostly results in the active site. That's what, obviously, it is

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supposed to be.

So I did that. I gave it the whole protein to look at, but to exclude the active site, and to ask the simple question: Do I get any positions on the rest of the protein where the hyaluronic acid dimer, disaccharide, does that particular molecule like to sit there more often than -- more often than it does other places?

I mean, it'll -- you are bombarding the whole surface of the protein with hyaluronic acid, but you are asking does it find a potential stability in certain areas more than in others. All right?

And you generally will run more than one simulation because there is a certain randomness to the parameters and you want to give it a chance to look at several sets of parameters. I did that. And then you take the results, you aggregate them. You say for all of the different simulations of docking that I run, where do I see the hyaluronic acid on the surface of the protein? And then I attempted to illustrate that further along.

Q. So that illustration above paragraph 338

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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

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determine whether a ligand is possibly binding at a site. One is shape complementary. It has to fit. Right? If it doesn't fit, it is not going to do that.

Does that fit perfectly? If the site is larger, then it might -- and the site could accommodate, say, a tetrasaccharide, but if I gave it a disaccharide, you are going to see it in multiple positions.

It also attempts to calculate an interaction energy. That calculation is crude, and the interaction energy is virtually useless except to indicate that the interactions are more favorable than unfavorable. So the interaction energy would be calculated to be bad if, for example, the only docked position put a positively charged residue on the ligand next to a positively charged residue on the protein.

But you would get a negative interaction energy if it was positive with negative. The energy function is not accurate enough to allow you to discriminate between positions, to say that this pose is more accurate -- is more likely than this pose, or to say that this site is more likely than that site. It only tells you that

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something is, in general, favorable relative to the rest of the protein.

Q. So what I'm trying to understand is -- and this is -- at a first level -- there is two levels of comprehension I'm seeking. One is simple and one is more complicated.

A. Okay.

Q. So my simple comprehension I'm aiming to achieve is why -- what are the places on this image that the molecules are sitting on? You reached a conclusion somehow to place them --

A. No, AutoDock Vine has placed them.

Q. So are -- what are you -- are you getting back from AutoDock Vina a pdb model with the molecule sitting on them?

A. That's exactly right. I am getting back the pdb model with almost no modifications. In some cases, it may allow the residues in the pocket to move just a tiny bit. And I'm getting the -- all the positions that the ligand finds on the protein where it can make a favorable energy of interaction. Okay?

So you can see -- if you look at the first figure, the one at the top. There are three sites shown there pretty clearly. In each

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case there is a whole bunch of little stick figures. Those are the different orientations of the HA dimer that you can see in that pocket, but they are all favorable orientations.

And what you can see is that the rest of the protein doesn't have any HA dimers in it at all. This is where it wants to go. Again, computationally, with really crude functions.

Q. So if I had the pdb model with the -- kind of the array of HA molecules complexed on it, I could then look and see which of the particular residues on PH20 that are the location of these spots?

A. But those -- but given how much disorder there is in the HA positions, right, you would not -- you could see there are many different --

Q. Sure.

A. You would never say, oh, this position is making a hydrogen bond to that part of HA. You would never say that.

Q. Yeah, I -- just to be clear, I am just trying to understand what -- kind of what region of residues --

A. That you could do.

Q. -- so the -- okay. Great. So I could

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have used the pdb model with the -- that I got back from AutoDock Vina to identify the regions in the PH20 protein where the HA molecules interacted?

A. PyMOL will even do that for you if you ask it to.

Q. Okay.

A. By the way, the lower one is informative on that page, because you can see at the very low left there is one spot where it looks like there is maybe only one or two molecules of HA have bound there.

Do you see that?

Q. Um-hmm.

A. So that's not an obviously good binding site. It just happens to be something that came up with a slightly negative energy.

Q. Okay.

A. The others are striking because so many positions are possible for the HA there. Suggesting that a significantly sized HA chain could bind in that position.

Q. As far as I can tell, I'm looking at your declaration, it looks like you are using this kind of analytical output of the tool to form

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opinions in paragraphs 338, 339, 340, 341, and 342; is that -- can you confirm that's right?

MS. MARTIN: Object to -- object to form.

A. I wouldn't call them opinions. I am testing a hypothesis, and wondering whether the computation gives me any evidence that the hypothesis may have some valid -- value.

BY MR. KUSHAN:

Q. Sure. But I am just looking at your declaration, and the part of your declaration that is related to the work you have performed with AutoDock Vina. It looks like it runs up to paragraph 342, and it starts around paragraph 3- -- 335.

A. Um-hmm.

MS. MARTIN: Object to form. Object to form.

BY MR. KUSHAN:

Q. So 335 to 342 represent the statements you made in your declaration relating to your AutoDock Vina work?

A. This is --

MS. MARTIN: Object to form.

A. I think I need you to say that again because --

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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.)

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MR. KUSHAN: It's a revision exhibit, which is an e-mail chain correspondence between me and counsel for Halozyme in the first three pages.

THE WITNESS: Thank you.

BY MR. KUSHAN:

Q. So, Dr. Petsko, in the first three pages of this document are images and text that was provided to us by counsel for Halozyme which represent the -- a response to the request we made for the information that was produced by the AutoDock Vina tool and the work you did related to it.

A. Are you sure you couldn't have made the text smaller?

Q. I -- I am not sure that having -- making it bigger may it -- may have given you any further insight. But what I'm trying to understand is, this information that we received back from counsel for Halozyme, this is not providing the information that was in the -- the pdb files, right?

A. It illustrates what was in the pdb files.

Q. It illustrates it. It doesn't give us the positional numbers of the residues that are

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

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invariant residues, which ones -- which ones were always active, which ones were always inactive, and so forth. The red color here indicates that those residues were, when mutated, inactive.

Q. Is -- I'm looking at these images. I see a lot of different hyaluronic acid molecules sitting in different spots. Did you superimpose all of the pdb structures together to create that?

A. Yes. But it -- but each pdb structure will have more than one hyaluronic acid orientation.

Q. And so this is -- this is a composite of all the pdbs?

A. Yes. But they'll be -- they're essentially identical.

Q. All right.

A. You would not be able to tell a significant difference except an occasional residue position here or there.

Q. All right. And did you save this like a PyMOL session file that captured all of this illustrated information?

A. I don't remember whether I saved it as a session file or not, but you can, sure.

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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 --

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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

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was first established experimentally by others, that this enzyme is not processive. What I mean by that is it doesn't sit on hyaluronic acid and, like Pac-Man, chew one residue at a time all the way along the chain. It doesn't do that.

It finds a particular site, binds anywhere on the polymer, cuts there, and then the moment it is cut, it dissociates and randomly binds somewhere else and cuts. Okay? So that's a hit-and-run, if you will, binding.

Oddly enough, for most enzymes that operate on polymers, that's most often what happens. The processive -- there are processive enzymes, but they're not the most common. So it turns out that's what hyaluronidase does, it hits and runs.

But if you think about that from an enzymologist's point of view, it's not very efficient to make a cut and then wander off somewhere and sometime later find the same or another hyaluronic -- hyaluronic acid molecule, bind and cut, defuse off, wander around some more, and so forth.

So my hypothesis that I wanted to test was the hypothesis that the enzyme might be

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smarter than that, might actually bind hyaluronic acid in more than one place, not just the active site. But so that when it cut and the product dissociated from the active site, it remained tethered to the polymer and therefore could do a one- or two-dimensional search for another cleavage site rather than search three-dimensional space after it wandered somewhere. That could, in principle, give you a considerable increase in the efficiency of catalysis. All right?

So I simply asked the question, are there sites on this protein that would accommodate a model like that? And if they were, are they sites that, when mutated, affect the activity of the enzyme? And to my delight, both seemed to be true. That doesn't mean the hypothesis was right, but it's evidence in favor of it possibly being correct.

Q. Okay. Could I have you look at paragraph 251 in your declaration, which is on page 128?

A. Yup.

Q. And you're quoting part of the patent disclosure, the common disclosure.

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

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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.

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Q. That's something that you could have determined by looking at the results of your AutoDock Vina experiment and comparing it to this information in the patent?

A. I could have.

Q. But you didn't?

A. I didn't. I treated it as an independent calculation.

Q. All right. So your opinions relating to the hyaluron and binding interactions with PH20 are not based on this observation --

A. That's correct.

Q. Are you aware of any publications prior to December of 2012 that provide the same information that you obtained by the work you did with the AutoDock Vina tool?

A. No, I am not.

MR. KUSHAN: All right. So we are going to have to have a conversation after we excuse the witness. I have a couple of other topics I want to get through. I am going to make -- I am going to reiterate our objections to the use of this information, and there definitely has been prejudice caused by the failure to produce the information prior to his deposition. We will be

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addressing that with the board.

MS. MARTIN: Well, we can have a discussion about it on the record.

Do you want to do it now, or would you like to wait until after we're done?

MR. KUSHAN: We can do it after we are done.

MS. MARTIN: All right. On the record after we -- but on the record, correct? Because you just grossly mischaracterized what he said.

MR. KUSHAN: Well, we will have that conversation.

MS. MARTIN: Fine.

BY MR. KUSHAN:

Q. All right. Could you go to paragraph 120 of your declaration, which is on page 50.

A. Yes.

Q. The -- this is a paragraph where you mention a tool called Modeller?

A. Yes.

Q. Did you use Modeller to do any of the work that you performed in the course of preparing your declarations?

A. No.

Q. Did you use the Rosetta tool for any --

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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

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right? For sequences that were on the order of 30, 40 percent identical for certain proteins.

And so at one point, I went through a systematic test of -- we -- we coded the Alpha algorithm monitor on our machine and went through a systematic test of the proteins of interest in my lab, and a variety of other proteins that I had access to the coordinates of, to see how bad some of the errors were.

This was one of the proteins I used.

Q. And what was your conclusion?

A. Actually, AlphaFold did just fine with PH20, if you compared it with the much later determined cryo-EM structure of PH20. And it also matched the PH20 model from SWISS-MODEL pretty well.

Q. Did you also look at the cryo-EM model that had been published in 2025?

A. For the purpose of the comparison with AlphaFold, yes.

Q. In the process of comparing those two structures, did you look at particular regions of the protein?

A. No. No, it was an overall assessment.

Q. What was the takeaway you had from that

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

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Proteins: Structure, Function, and Bioinformatics. It's dated 16 -- well, it's a June 2025 publication.

A. It appeared in -- it was accepted in December of 2024.

Q. So the citation is Volume 93, pages 1067 to 1073, dated 2025.

A. Yes, it appeared earlier in 2025.

Q. Is this the paper that has -- made reference to the structures that you looked at?

A. This is a paper that describes the cryo-EM structure of that protein, yes.

Q. All right. Could you go to the first pages of the document.

A. The first page?

Q. Yes.

A. Yes.

Q. Do you see who the authors are?

A. Yes.

Q. Do you see what the affiliation is of the authors?

A. Yes, they are from Korea.

Q. And what's the company they are affiliated with?

A. Alteogen, maybe. If that's a company, I

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don't know. They are certainly in some of the university-type labs. Is that the one you are talking about?

Q. Yes. Have you ever heard of Alteogen?

A. Nope. Never heard of them. That's -- which authors? Is it just -- that's three of the authors are from there. I don't know -- I don't know them and I don't know the company.

Q. So these are the individuals who actually determined the structure experimentally of PH20?

A. I don't know that. If you were to just go by the author list, you would say it would be probably the first author and the last author who are all at Daejeon.

Q. Right. I am just -- this is the first publication of the experimentally determined structure of PH20?

A. Correct. But what you -- the trouble with this kind of thing for a scientist trying to figure out who did what --

Q. I don't need that granularity. It came from this group of scientists, right?

A. Yes.

Q. So the Alteogen scientists are the ones who determined this experimentally determined

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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

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determined experimentally the structure of PH20?

A. I don't know.

MR. KUSHAN: All right. Why don't we take a break now. We can stay on the record for our conversation.

Do you mind if we have you step out, or should we just -- I don't want to -- I don't want to make you move if you are uncomfortable.

THE WITNESS: No, I don't have a problem. I am only wondering whether you are actually expecting me to still return.

MR. KUSHAN: I am expecting you to return.

THE WITNESS: Then you are expecting a lot.

MR. KUSHAN: Thank you.

THE VIDEOGRAPHER: Microphone.

THE WITNESS: Yup.

MS. MARTIN: You should take your --

THE WITNESS: Yes, I should.

THE VIDEOGRAPHER: Are we staying on the video record?

MS. MARTIN: Yeah. I don't really care about the video record. We are staying on the record.

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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.

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Right? And he went through -- and it sounds like from his testimony he went through and he generated a whole bunch of SWISS-MODEL pdb files for his analysis of every single different mutation he looked at. And you produced exactly zero, zero pdb files to us. Right?

So Dr. Park generated, let's say, hundreds of pdb files as part of his analysis. And he also had SWISS-MODEL -- I'm sorry, SWISS-MODEL -- he also had PyMOL session files that he shared over Zoom with Dr. Hecht and counsel, and he went through and he discussed all of -- they both discussed all of their opinions on these PyMOL session files on Zoom, and we got exactly zero pdb files. And also, zero PyMOL session files.

So because your experts generated hundreds of such files and gave us zero of them, we were not expecting you, right, to think that we were going to be giving you pdb files. Because it seemed like the -- since you are the ones who went first here, the order of the day or the order of proceedings was that we weren't going to be giving pdb files.

Now, Dr. Petsko -- and I just want to

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make sure that we're really clear on what he said because I think you mischaracterized his testimony, and so I want to make sure that you understood what he said, which is literally like if you take the picture that you were looking at in his declaration, and I'm sorry, I don't remember what the -- oh, here it is.

So the page 165, right, like he was saying that if you take your SWISS -- or Dr. Park's SWISS-MODEL and you orient it this way, like you turn it in PyMOL and you orient it, like and you turn on -- you turn on the surface view, right? You orient it so that it looks like this, then you can tell where these patches are. That's what he was saying.

So he's not saying that you needed the pdb file to be able to do this analysis. He's saying you just turn it in PyMOL, and then you can figure out where these balls are sitting (indicating).

MR. KUSHAN: So let me -- let me just point out that I wasn't asking for every pdb file. You and I had a conversation, I think it's even embedded in the e-mail chain, that we're not asking for the pdb files because you can generate

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those, you can color them yourself. That's -- that's not what we're asking for.

We were asking for the output of the tool which positioned the molecules on the pdb file, which then allows you to figure out where the molecules are interacting with the portions of the protein.

It would have taken you a click to do that, and I don't understand why there is any confusion about -- I mean, I think there was an exchange we had where I was very clear we weren't asking for pdb files, we weren't asking for colored pdb files, because we know that's something that you can just recreate from visual inspection of the document.

We wanted to have the information that allowed us to understand where those molecules were on the protein, and we wanted the output of the tool, which is what we said from day one.

The output of the tool is not the picture we're looking at. The output of the tool is the pdb files in complex with the molecules. That's the narrow thing we asked for.

When you -- finally you responded, you gave us something which you must know was not

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responsive to the thing we asked for.

MS. MARTIN: No. We --

MR. KUSHAN: This exhibit which we've introduced is useless as a point of information to deduce the locations of those interactions.

These are -- these are -- these are the pdb files. They're just a list of the pdb files. If you had provided them, we would have not have had a conversation. It's very simple.

When an ex- -- when a -- when a witness does an experiment and uses the information to support their opinions, you're supposed to give us the information they created associated with that experiment. That's what we asked for. You didn't provide it. We believe we're entitled to relief. We're going to pursue that with the board.

MS. MARTIN: I still actually -- so this is the first -- I sent this e-mail to you on -- this is so small. I sent this --

MR. KUSHAN: We had to understand -- we had to understand what use he was making of this information. And it's now -- he has a very long explanation of his use of the information. We believe it's -- he's relying on it to make a

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point, that if he's making the point, he's relying on the experimental work he did.

MS. MARTIN: Well, the point -- the point that he's making in his declaration is literally based on the figures in his declaration, right? Like he gave you these figures when he was served with this declaration in whatever, September.

MR. KUSHAN: Well, we stated our positions. I don't know how long you want to keep talking at each other.

MS. MARTIN: No, I do actually because this is -- I just want to make really clear for the record that I sent this e-mail on October 27th, right? And it is now December 4th, and you never respond -- you did not respond to this e-mail, so we understood this to have been resolved.

If you had an issue with what we provided, which frankly is -- like you asked for the output, and so -- and the in- -- no, you asked for the input and the output, and you got the input, right? You got the input, and you got the output. And if you had a problem with that or if it wasn't specifically what you were asking for, you should have e-mailed, you should have

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responded sometime in the -- you know.
MR. KUSHAN: So the -- so the three times I asked for it, you wanted me to go like six or seven or ten?
MS. MARTIN: No. If you had answered --
MR. KUSHAN: What was -- how many times do I -- so, Lauren, how many times would I have to ask for it before you handed over the information?
MS. MARTIN: No. If this wasn't --
MR. KUSHAN: Just tell me.
MS. MARTIN: We gave you the information.
MR. KUSHAN: Just give me a number. Ten?
MS. MARTIN: You're not answering --
MR. KUSHAN: Did you want to ask -- did you only want to provide it like the day before the deposition?
MS. MARTIN: Okay. See, like now you're getting --
MR. KUSHAN: I just need to understand. I just need to understand where the line is you think is -- and you believe this was sufficient?
MS. MARTIN: If we gave you information in response to your request and you do not respond to it, we assume it's been resolved.

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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.

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

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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?

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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

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showing us, those are alpha helical --

A. Well, that's the active site cleft, is what I'm showing here.

Q. Okay. So to preserve the active site?

A. Yes.

Q. Did you address any other regions and find anything of significance?

A. No.

Q. Okay. Could you turn to page 282 of the '731 application.

A. 282?

Q. 282.

A. Okay. I'm there.

Q. This is the start of Example 5 where they did this testing of certain of the active mutants.

Could you look at page 303? Did they call out any particular mutants --

A. I'm not there yet.

Q. Oh, sorry.

A. Okay.

Q. From the testing they did of increased temperature and increased -- did the patent identify any particular mutants?

A. Sorry. Please repeat that.

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Q. Based on the information -- based on the testing that was done of the mutants, did the patent identify any particular mutants of significance?
A. You mean F204P?
Q. I do. Did you look at -- when you reviewed this, did you look at the results and try to understand why they called out F204P?
A. I recall -- just a moment while I look at what they said here.
(Pause)
A. So as I recall, it was very resistant to creosol treatment. Whether it was the most resistant I don't remember. But I do remember that it was very resistant.
Q. So do you know if the patent addressed the particular mutant any more in its experimental work?
A. You mean any more than this?
Q. Yes.
A. I don't recall.
Q. Why don't we go through and look. Could you go to page 303.
A. Yes.
Q. So this is a summary of the results with

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F204P, but then they also did an additional assay, and they tested it compared to the wild type at the bottom of page 303.

A. Yes. You are talking about Table 13?

Q. Yes.

A. Yes.

Q. Then if you can look at page 309.

A. Just a moment. I am still looking at 304.

Q. Sure.

A. Okay. 309, did you say?

Q. Correct.

A. That's Table 15?

Q. Example 10 and Table -- Table 16.

A. Table 16. Just a moment. Okay.

Q. So they are testing the F204P mutant in an additional experiment for stability with insulin, right?

A. That's what the experiment is, yes.

Q. Could you go to page 311. Is there another experiment where they tested the F204P mutant?

A. You mean Example 11?

Q. Yes.

A. That's a different variant, right?

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

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right?

A. Yes.

Q. And this was another way of making, perhaps, more of the F204P mutant?

A. It could be a cheaper way than making it at CHO cells, for example.

Q. But in Example 13, I think you mentioned this earlier, this is a -- this is actually an assessment of the stability of the F204P mutant, right?

A. Hold on one second. Yes. These are specific measures of secondary structure and what they call melting temperature, but which I would call thermal denaturization temperature.

Q. So this was a single mutant, and I think in the experimental results they say that it had an effect of changing the Tm of nine degrees?

A. Yes.

Q. Is that a significant change?

A. It can be. Depends on what you normally see looking with the protein. But for some proteins, that's a significant number.

Q. Do you have -- are you able to kind of correlate that temperature change to a free energy change?

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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

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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.

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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,

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

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Exhibit 1120s.

(Exhibit 1127, Chart created by Attorney Kushan, marked for identification.)

BY MR. KUSHAN:

Q. This is just to help figure out what these numbers are. It is not a perfect alignment to the figure, but what I would like you to do is see if you can find the F204 residue so we know where that is.

A. I do. And I have.

Q. Okay. Can you use the demonstrative I gave you to identify the -- sorry. Second page. Could you go to the --

A. Second page of the demonstrative?

Q. Second page of the demonstrative.

And as you do that, just look at the valine that is the last valine in the row that ends 300. And just tell me what position number is that --

A. You mean 302?

Q. No.

A. I'm sorry?

Q. The valine that's highlighted in the row that ends 300.

A. Well, I am not seeing this. Let me see.

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There is a valine highlighted at 277.

Q. Correct. That's what I'm just -- I just want -- so that's valine 277. Then the next highlighted residue, what is that?

A. The next highlighted residue appears to be glutamine 347.

Q. So there are no highlighted residues between positions 277 and 347?

A. I don't see them here. Let me check them against the figure itself.

That seems to be the case.

Q. So the common disclosure in Figure 1 didn't highlight any mutants that were changed at positions between 277 and position 347, right?

A. That's what -- they are not highlighted on the figure.

Q. Right. The only two mutants that were called out in the examples from stability testing were the F204P and the V58L mutants, right?

A. Yes.

Q. And then in the figure in Example 4, there was six mutants called out, and none of them were in the region of 247 to 347, right?

A. As far as I can tell.

Q. Okay. So the patent hasn't called out

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any particular mutants through any of these specific examples that they've done elsewhere in the patent?

A. I am not sure that I understand that. If I read the legend to Figure 1, it says: "Exemplary, non-limiting positions for amino acid replacements are indicated by highlighting."

That's the only thing they say about them. So I don't know why they chose to highlight them. It just seemed residues they were interested in for some reason.

Q. So the patent doesn't explain why these particular mutants were highlighted?

A. Not in this part of the figure or anything like that, no.

Q. If you were reading this patent, would you be inclined to look up what happened with these mutants as to why they were highlighted?

A. Not necessarily.

MR. KUSHAN: All right. So I don't think we have any further questions.

THE WITNESS: Do you want your sheet back?

MR. KUSHAN: That's an exhibit. She will keep that.

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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.)

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C E R T I F I C A T E

I, GREGORY PETSKO, PhD, do hereby certify that I have read the foregoing transcript of my testimony, and further certify that said transcript is a true and accurate record of said testimony (with the exception of the following corrections listed below):

Page	Line	Correction

GREGORY PETSKO, PhD

Sworn to and subscribed before me this day of , 2025.

Notary Public
My commission expires:

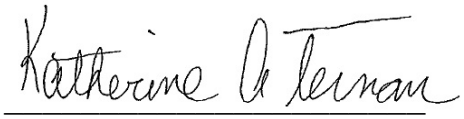
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COMMONWEALTH OF MASSACHUSETTS)
)
SUFFOLK, SS.)

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,
Registered Merit Reporter
CSR # 129093

Notary Public
My commission expires March 10, 2028

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*** ERRATA SHEET ***

NAME OF CASE: Merck Sharp V. Halozyme

DATE OF DEPOSITION: December 4, 2025
NAME OF WITNESS: GREGORY PETSKO, Ph.D.

PAGE	LINE	FROM	TO	REASON

_____

Subscribed and sworn before me

this____day of_____,20__.

_____ _____
(Notary Public) My Commission Expires:

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