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# Transcript of Michael Hecht, Ph.D.

**Date:** August 26, 2025
**Case:** Merck Sharp & Dohme LLC -v- Halozyme Inc. (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

Halozyme EX2076
Merck v. Halozyme
PGR2025-00050

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

- - - - - - - - - - - - - - x

MERCK SHARP & DOHME LLC, : Case Nos.

Petitioner, : PGR2025-00003; 00004;

v. : 00006; 00009

HALOZYME, INC., : U.S. Patent Nos.

Patent Owner. : 11,952,600; 12,018,298;

- - - - - - - - - - - - - - x 12,152,262; 12,123,035

Videotaped Deposition of MICHAEL HECHT, Ph.D.

Washington, DC

Tuesday, August 26, 2025

9:10 a.m.

Job No. 596628

Pages: 1 - 308

Reported by: Janet A. Hamilton, RDR

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C O N T E N T S

EXAMINATION OF MICHAEL HECHT, Ph.D. PAGE

By Ms. Martin 9

E X H I B I T S

(Pre-marked and Retained by Counsel)

Exhibit 1003 58

Declaration of Michael Hecht, Ph.D.

PGR2025-00003

US Patent No. 11,952,600

Exhibit 1003 58

Declaration of Michael Hecht, Ph.D.

PGR2025-00004

US Patent No. 12,018,298

Exhibit 1003 58

Declaration of Michael Hecht, Ph.D.

PGR2025-00006

US Patent No. 12,152,262

Exhibit 1003 58

Declaration of Michael Hecht, Ph.D.

PGR2025-00009

US Patent No. 12,123,035

E X H I B I T S C O N T I N U E D

| | PAGE |
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| Exhibit 1001<br>US Patent No. 11,952,600 | 187 |
| Exhibit 1010<br>Paper by Ling Zhang: Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues | 216 |
| Exhibit 1013<br>Paper by Gregory Frost: Recombinant human hyaluronidase: An enabling platform for subcutaneous drug and fluid administration | 228 |
| Exhibit 1018<br>Paper by Roberto Chica: Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design | 280 |
| Exhibit 1059<br>Review Paper from Matti Leisola: Opportunities and challenges | 287 |

THE VIDEOGRAPHER: Here begins Media Number 1 in the videotaped deposition of Dr. Michael Hecht in the matter of Merck Sharp & Dohme LLC v. Halozyme, Inc. in the United States Patent and Trademark Office, case number PGR2025-00003; 0004; 0006; 0009. 09:09:41 09:09:43 09:09:45 09:09:49 09:09:54 09:10:00

Today's date is August 26, 2025. The time on the video monitor is 9:10 a.m. The videographer today is Adam Schuman, representing Planet Depos. This video deposition is taking place at 1501 K Street, Northwest, Suite 600, Washington, DC 20005. 09:10:09 09:10:15 09:10:20 09:10:22 09:10:25 09:10:34

Would counsel please voice identify themselves and state whom they represent. 09:10:37 09:10:39

MS. MARTIN: Lauren Martin from Quinn Emanuel on behalf of Halozyme. And with me I have Zhen Cui, Zach Summers, both from Quinn Emanuel, and then Trey Powers and Eldora Ellison, both from Sterne Kessler. 09:10:41 09:10:42 09:10:46 09:10:51 09:10:55

MR. KUSHAN: Jeff Kushan from Sidley Austin for Merck. With me is Christine Engen from Sidley Austin, Mark Stewart for Merck, and 09:10:57 09:10:59 09:11:02

Katherine Helm from Dechert. 09:11:05

THE VIDEOGRAPHER: The court reporter 09:11:08
today is Jan Hamilton representing Planet Depos. 09:11:08

The witness will now be sworn. 09:11:11

P R O C E E D I N G S

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MICHAEL HECHT, Ph.D.,
a witness herein, being duly sworn, testified as follows:

EXAMINATION BY COUNSEL FOR THE PATENT OWNER 09:11:27
BY MS. MARTIN: 09:11:27

Q Good morning, Dr. Hecht. 09:11:28

A Hi. 09:11:29

Q Can you please state your full name and 09:11:30
address for the record? 09:11:32

A I am Michael Hecht. Sometimes I use a 09:11:33
middle initial H. 09:11:36

My home address is what you're asking for? 09:11:38

Q Home or work. 09:11:42

A Oh, well, my home address is 1571 Great 09:11:43
Road, Skillman, New Jersey. 09:11:48

Q Are you employed? 09:11:50

A I am employed by Princeton University. 09:11:51
Q How long have you been at Princeton? 09:11:53
A Since January 1990. 09:11:55
Q And what do you do at Princeton? 09:11:58
A I am a professor in the chemistry 09:12:01
department. And in that job, I teach courses, and 09:12:03
I run a research lab and various other things on 09:12:08
campus, but those are the primary. 09:12:12
Q Have you ever been deposed before? 09:12:15
A 30 years ago. Not since. 09:12:18
Q And what was the context of that 09:12:23
deposition? What kind of trial? 09:12:25
A That was a biopharmaceutical trial. 09:12:27
Q Were you serving -- 09:12:30
A Well, it didn't -- it ended up not being a 09:12:32
trial. It ended up being an arbitration. So, 09:12:35
formally, it was not a trial, but it was a 09:12:37
biopharmaceutical case. 09:12:40
Q So you were deposed in the context of a 09:12:40
biopharmaceutical arbitration about 30 years 09:12:42
ago -- 09:12:45
A Right. 09:12:45

Q -- is that right? 09:12:45
A That's right.
Q So, like, in 1995-ish? 09:12:47
A Yeah. Either '95 or early '96, but yeah. 09:12:49
Q And what was the -- well, strike that. 09:12:55
Were you serving as an expert witness in 09:12:57
that matter? 09:12:59
A Yes. 09:13:00
Q Do you recall who the parties were? 09:13:01
A Yes. 09:13:04
Q Who were the parties? 09:13:04
A Amgen and Johnson & Johnson or one of the 09:13:06
companies under Johnson & Johnson. 09:13:12
Q And who were you testifying on behalf of? 09:13:15
A I was working with Amgen. 09:13:17
Q What was the subject matter, generally, of 09:13:22
that matter? 09:13:25
A Erythropoietin, sometimes known as EPO. 09:13:27
And the issue was if one company had a patent on 09:13:33
the original molecule, to what extent were variant 09:13:40
MUTE molecules the same or different. 09:13:44
Q Did you testify at any arbitration 09:14:00

hearing? 09:14:03

A Yes. 09:14:05

Q So you testified at deposition and hearing for that arbitration? 09:14:07 09:14:11

A It was a long time ago, so let me think this through. 09:14:13 09:14:16

Yes, there was a deposition. And, yes, there was an arbitration, at both of which I spoke. 09:14:17 09:14:19 09:14:22

Q Aside from that proceeding, have you ever been deposed before? 09:14:26 09:14:29

A No. 09:14:32

Q Have you ever testified at trial aside from that arbitration? 09:14:34 09:14:36

A Sorry. Other than that, you said? 09:14:38

Q Mm-hmm. 09:14:40

A Have I ever testified at a trial. No. 09:14:41

Q Have you ever served as an expert witness apart from the arbitration and this matter? 09:14:44 09:14:46

A There was another case where I was asked to be involved, but that fizzled out pretty soon and never went to the level of, you know, 09:14:50 09:14:52 09:14:56

deposition or testifying or anything. It fizzled out. 09:15:01 09:15:05

Q Did you provide a report in that matter? 09:15:05

A No, never got to that point. 09:15:07

Q If at any point in the deposition you would like clarification regarding any of my questions, please ask me for clarification instead of your counsel. 09:15:28 09:15:31 09:15:33 09:15:37

Do you understand? 09:15:38

A Of course. 09:15:39

Q And as we go throughout the day, your counsel may object to some of my questions. But unless you are instructed not to answer, you still have to answer each question. 09:15:45 09:15:47 09:15:49 09:15:51

Do you understand? 09:15:53

A I understand, yeah. 09:15:55

Q I'll try to take a break around every hour or so. 09:15:57 09:15:59

But if at any time you feel like you need a break, please let me know, although I would ask if there's a question pending, you answer the question before we stop. 09:16:00 09:16:02 09:16:05 09:16:07

A Right. 09:16:09

Q Do you recall when you were first 09:16:12

contacted in connection with this matter? 09:16:14

A Yeah. It was last summer. 09:16:17

Q And do you recall who contacted you? 09:16:20

A Jeff. 09:16:22

Q What did you do to prepare for the 09:16:26

deposition today? 09:16:28

A I read numerous documents and reread 09:16:30

numerous documents and then had several meetings 09:16:36

with counsel, both in person and on Zoom. 09:16:42

Q When did you meet with counsel in person 09:17:00

to prepare for this deposition? 09:17:04

A Yesterday, last week. 09:17:07

You're speaking in person or both? 09:17:18

Q In person. 09:17:19

A In person, yesterday, last week, previous 09:17:20

week. There were a number of meetings. 09:17:25

Q Did you speak with anyone who's not a 09:17:32

lawyer to prepare for this deposition? 09:17:35

A No. 09:17:40

Q Did you speak with Dr. Park at all in 09:17:43

preparing for your deposition? 09:17:47
A No. 09:17:49
Q When was the last time you spoke with 09:17:50
Dr. Park? 09:17:52
A On Zoom. There were some Zoom sessions 09:17:57
months ago. I don't remember exactly when. Quite 09:18:07
a while ago, nothing recent. 09:18:12
Q Have you ever spoken with Dr. Park in 09:18:14
person? 09:18:16
A Not that I recall. It is possible we 09:18:20
bumped into each other at a conference 20 years 09:18:24
ago. I wouldn't rule that out because we're in 09:18:27
related fields. 09:18:30
But I don't recall ever meeting and -- not 09:18:31
that I recall, other than bumping into each other 09:18:34
at coffee at a conference 20 years ago or 09:18:38
something. 09:18:44
Q You understand that Dr. Park was deposed 09:18:46
in this matter? 09:18:48
A I understand that, yeah. 09:18:51
Q Did you read Dr. Park's deposition 09:18:52
transcript? 09:18:54

A No. 09:18:57

Q You listened to part of Dr. Park's deposition; correct? 09:19:00 09:19:02

A Briefly, yes. 09:19:03

Q Why did you listen to part of Dr. Park's deposition? 09:19:05 09:19:07

A I wanted to know what a deposition looks like. I just -- it was somewhat mysterious to me as I had only ever done it, as I said, you know, in 1995 or so and didn't remember much of that. 09:19:08 09:19:10 09:19:14 09:19:17

And so I was curious, like, what is this? What actually happens? 09:19:21 09:19:25

Q So you were curious to learn about what a deposition sounds like? 09:19:26 09:19:29

A Looks like, sounds like, yeah. What is the format of it, what goes on. 09:19:30 09:19:35

Q And did you rely on what you heard in Dr. Park's deposition to prepare for this deposition? 09:19:38 09:19:41 09:19:43

A No, not at all. 09:19:44

Q Did you rely on Dr. Park's testimony in forming any of your opinions in this case? 09:19:45 09:19:48

A Could you explain what you mean by -- do you mean testimony in the deposition? 09:19:52 09:19:54

Q Yes. 09:19:55

A Oh, no, no. 09:19:56

Q Did anything that Dr. Park say change any of your opinions in this case? 09:19:57 09:19:59

A Just to clarify, you mean what he said in the deposition? 09:20:01 09:20:04

Q Yes. 09:20:04

A No. 09:20:05

Q Okay. What's your research focus? 09:20:06

A I'm trying to be succinct. 09:20:16

Protein structure folding design, protein engineering, the impact of sequence changes on protein structure and function, yeah, combinatorial libraries of novel proteins. 09:20:20 09:20:25 09:20:32 09:20:41

Q Do you do any work with de novo proteins? 09:20:47

A Certainly do, yeah. 09:20:53

Q What's a de novo protein? 09:20:54

A Some people will define it somewhat differently. 09:21:00 09:21:03

But the way I like to define it is a 09:21:03

de novo protein is a protein that is, as the words mean, "de novo," it's new. It's not based on something in nature; it's not derived from anything in nature. It's made, designed from, and conceptualized from scratch. 09:21:06 09:21:11 09:21:14 09:21:17 09:21:22

Q Has your lab ever made a protein from scratch? 09:21:28 09:21:31

A Frequently. That's what we do. 09:21:33

Q How do you make a protein from scratch? 09:21:35

A How does one or how do -- well, okay. One could make it by solid-phase synthesis, right? That's laborious. 09:21:44 09:21:48 09:21:54

What we typically do is we make synthetic DNA or collections of synthetic DNA, piece them together to make artificial genes and then put those genes in a host cell -- typically E. coli -- and then have the host cell express the protein, and if all goes well, purify the proteins after that's done, lyse the cell and purify the proteins. 09:21:55 09:21:59 09:22:03 09:22:07 09:22:13 09:22:17 09:22:21 09:22:26

Q What is solid-phase synthesis? 09:22:27

A We don't do solid-phase synthesis. But 09:22:31

what it is, is -- it's basically the organic chemist's way of making proteins, not using cells, but rather, piecing together the protein amino acid by amino acid. 09:22:35 09:22:36 09:22:39 09:22:43

It's called solid phase because it's done where the terminus of the growing chain is attached to a resin. There's lots of reasons for doing that, but I'll be concise, yeah. 09:22:47 09:22:49 09:22:51 09:22:54

Q How do you arrive at the sequence that you use for your artificial -- artificial gene in your artificial protein? 09:23:04 09:23:07 09:23:11

A I've worked on many projects in that realm, so it's -- it's a bit tricky to answer. There are many answers. Try be more specific. What -- 09:23:17 09:23:19 09:23:24 09:23:31

Q In your work have you designed a sequence for a de novo protein that then you express to obtain the de novo protein? 09:23:34 09:23:37 09:23:41

A We have designed collections of sequences, large libraries of sequences, that we then make genes to encode. In other projects we choose a particular sequence that we want to make, do all 09:23:46 09:23:50 09:23:56 09:24:02

kinds of stuff. 09:24:08

Q So there have been instances where you've chosen a particular sequence that you want to make? 09:24:19 09:24:21 09:24:24

A Have -- yes. There are instances where we choose a particular sequence we want to make, sometimes a natural sequence, sometimes a de novo sequence. 09:24:25 09:24:31 09:24:35 09:24:38

But it's many years. There's been lots of projects. 09:24:39 09:24:41

Q Can de novo proteins have enzymatic activity? 09:24:49 09:24:53

A Can they? Is that the question? 09:24:54

Q Yes. 09:24:56

A Yes. 09:24:56

Q Have you generated a de novo protein with enzymatic activity in your lab? 09:24:58 09:25:02

A We, in fact, have published on de novo proteins that have enzymatic activity. 09:25:04 09:25:11

Q What's the purpose of generating a de novo protein? 09:25:18 09:25:21

A There are a number of ways of looking at 09:25:31

that. From a purely intellectual level, it's motivated by that which nature shows us is that which nature shows us. Are there other things out there that might be possible? It's a -- it's driven by curiosity. That's one answer. 09:25:34 09:25:46 09:25:52 09:25:56 09:25:59

In other situations, people might be making or figuring out how to make novel proteins as an initial step towards something useful. So it could be basic science curiosity. It could be leaning towards something more applied. 09:26:05 09:26:09 09:26:13 09:26:18 09:26:22

Q And how long have you been working with de novo proteins? 09:26:25 09:26:28

A Been working with proteins for half a century. Been working with de novo proteins since my postdoc. Long time ago. 09:26:30 09:26:40 09:26:43

Q And you generated the de novo protein called Felix; right? 09:26:46 09:26:49

A Right. In my postdoctoral work, that's what I worked on. 09:26:52 09:26:55

Q And that was in the 1990s? 09:26:56

A The publication came out in 1990, I think, but it was worked on even a few years before that. 09:27:04 09:27:08

Q And that was a completely novel amino acid sequence that then folded into a novel protein that you called Felix? 09:27:11 09:27:16 09:27:20

A Correct. 09:27:27

Q Do you recall how you arrived at the amino acid sequence for Felix? 09:27:30 09:27:35

A In fact, the story there was the sequence had been arrived at by my collaborators before I started doing the lab work. I was not -- technically, I was not involved in the actual design of that sequence. 09:27:37 09:27:41 09:27:43 09:27:46 09:27:49

Q Have you ever solved a protein crystal structure? 09:27:57 09:27:59

A Not with -- not me personally, no. 09:28:01

Q Have you ever analyzed a solved protein crystal structure? 09:28:04 09:28:07

A I have looked at many solved structures, yeah. 09:28:10 09:28:13

Q Why do you look at a solved structure? 09:28:13

A To learn about it, to understand it, to think about it, to take next steps in a research program, to understand whatever questions 09:28:24 09:28:27 09:28:34

you're -- you're trying to understand. 09:28:40

Q Is there information that you can glean from a solved protein crystal structure about the role of particular amino acids in the structure? 09:28:45 09:28:47 09:28:53

A Often, yeah. 09:29:00

Q Is there information you can obtain from a solved protein crystal structure about the secondary structure, the secondary structures in the protein? 09:29:06 09:29:09 09:29:11 09:29:17

A Yes. 09:29:18

Q What type of information about secondary structures can you obtain from a crystal structure? 09:29:21 09:29:23 09:29:26

A When you look at a crystal structure, you can see which sections of the polypeptide chain are in an alpha helix, which sections are in a beta sheet, which sections are in a loop, and so forth, which amino acids are in those secondary structures, yeah. 09:29:30 09:29:34 09:29:39 09:29:43 09:29:49 09:29:54

Q And you can also glean information regarding how the secondary structures interact with each other to form a tertiary structure; 09:30:02 09:30:04 09:30:10

correct? 09:30:15

A You can get information about how the protein folds from looking at its final folded structure, yeah. 09:30:15 09:30:19 09:30:23

Q Can you get information about which portions, which amino acid -- or sorry, strike that. Let me start again. 09:30:26 09:30:29 09:30:33

Can you obtain information regarding the residues that are involved in holding the various secondary structures in place to form the tertiary structure? 09:30:34 09:30:37 09:30:43 09:30:46

A You can look at a solved, an experimentally solved structure, and you can see interactions that stabilize the structure. 09:30:51 09:30:56 09:31:03

However, that's not the whole story. You would also want to -- if you want to know about stability, you would also perform stability studies, which are different from looking at a static structure. 09:31:08 09:31:10 09:31:12 09:31:15 09:31:18

Q When you talk about stability, a protein stability, what do you mean? 09:31:18 09:31:22

A In this context, when I'm talking about 09:31:27

protein stability, I'm talking about the free energy difference between a folded state and an unfolded state. 09:31:30 09:31:34 09:31:37

So stability is -- is a measure of the free energy difference between those two states. 09:31:38 09:31:41

Q Is that the delta G? 09:31:43

A Yeah. 09:31:46

Q And how do you -- how do you quantify the energy difference between a folded state and an unfolded state? 09:31:47 09:31:54 09:31:57

A The delta G. 09:31:57

Q Yes. 09:31:59

A There are a number of ways of doing it. We've done lots of experiments like that. You can look at stability by differential scanning calorimetry, which is a direct thermodynamic measurement. 09:31:59 09:32:01 09:32:06 09:32:11 09:32:14

You can take the folded protein, subject it to things that would unfold the protein, such as elevated temperature or denaturants like urea. 09:32:15 09:32:18 09:32:22

Then you can measure the folding transition and you can extrapolate back from that 09:32:29 09:32:30

measurement what the delta G is separating the folded state and the unfolded state. 09:32:33 09:32:35

Those are two ways of doing it. You could also do things with NMR. There's a bunch of very rigorous ways or there are several rigorous ways of assessing stability of a protein. 09:32:38 09:32:41 09:32:47 09:32:51

Q And those methods would allow you to calculate the delta G? 09:32:54 09:32:56

A In most cases, if the experiments work out smoothly, yeah. 09:32:57 09:32:59

Q Are there ways of assessing protein stability in a qualitative way that would not allow you to calculate delta G? 09:33:00 09:33:02 09:33:05

MR. KUSHAN: Objection. Form. 09:33:09

A I'm -- the question is kind of a difficult one because you're asking can you assess something without really assessing it. I'm not sure I understand what you mean. 09:33:18 09:33:23 09:33:27 09:33:30

Q Okay. When you refer to protein stability, are you always talking about the delta G value, the difference between -- an energy between the folded structure and nonfolded 09:33:30 09:33:39 09:33:42 09:33:45

structure? 09:33:48

A That's how I describe it when I teach 09:33:48

about this subject. I frequently put exactly that 09:33:51

on the board when I'm teaching about protein 09:33:54

stability, the delta G stuff. 09:33:57

Q Is the term "stability" used more broadly 09:33:59

in the field to refer to something more 09:34:03

qualitative than delta G? 09:34:08

A I am really hesitant to comment on about 09:34:10

how other people use a term. 09:34:12

Q Okay. Are there particular guidelines 09:34:14

that scientists use when designing a de novo 09:34:23

protein? 09:34:26

A This is a field that really just arose in 09:34:33

the past few decades and has kind of exploded, and 09:34:38

there are numerous different approaches that 09:34:43

people use. 09:34:44

Q What types of approaches? 09:34:46

A For making novel proteins? 09:34:51

Q Yes. 09:34:53

A The -- yeah, I mean the Nobel Prize last 09:34:54

year went, in part, to a group that does protein 09:35:21

design. And the write-up of that, which I think 09:35:24
is one of our linked documents -- the write-up to 09:35:29
that gave a background on approaches, starting 09:35:36
with an approach that Bill DeGrado used, which was 09:35:41
very sort of simplistic, minimalist design of, you 09:35:46
know, this amino acid likes to be in helices, so 09:35:52
I'll put it in helices, very simplistic. 09:35:57

But it was pioneering. It was written up 09:36:00
in the Nobel Prize stuff. Then that moved on to 09:36:03
our work, which was quoted as well, which talks 09:36:06
about making combinatorial libraries by patterning 09:36:08
polar and nonpolar amino acids to generate 09:36:15
structures, which generated structures but not 09:36:19
with high resolution, not with precision at all 09:36:22
but, nonetheless, it sort of was a guideline. 09:36:25

That same write-up talked about some work 09:36:28
by a fellow named Steve Mayo at Caltech, which was 09:36:31
the first computational approach to protein design 09:36:35
and then led to the work by David Baker, which was 09:36:38
awarded the Nobel Prize, which was also 09:36:42
computational protein design. 09:36:45

And then since then, there's been a lot of 09:36:48

other approaches, many based on AI. So there are many approaches. That's all I'm trying to get across is that it's not one answer. 09:36:52 09:36:58 09:37:01

Q And you mention that in your lab, you had an approach where you generated combinatorial libraries of sequences by patterning nonpolar and polar residues, and that's because when you pattern the nonpolar and polar residues, you can generate sequences that will have alpha helices; is that right? 09:37:05 09:37:09 09:37:13 09:37:16 09:37:18 09:37:22 09:37:27

A You can favor that structure. It doesn't always work, right, so you can make such libraries that are biased toward a particular outcome. Doesn't always work. You have large collections. Some succeed; some fail. 09:37:27 09:37:29 09:37:34 09:37:39 09:37:42

Q And then you would screen your library for desired function and then test the resulting protein? 09:37:44 09:37:47 09:37:49

A The original legwork was basically just aimed at structure and asking: Do these things fold at all, with no -- at the outset, no thought for structure, even -- I mean, no thought for 09:37:51 09:37:54 09:37:58 09:38:03

function. Just asking: Okay, you made a library with this patterning. Do any of them fold? Do a lot of them fold? 09:38:06 09:38:12 09:38:16

It was a very low resolution approach. 09:38:18

Q But the answer was yes, right, many of them folded? 09:38:21 09:38:24

A The answer is, yes, many of them collapsed into alpha helical structures. Most of those collapsed into alpha helical structures but were dynamic. They were not unique structures; they were not -- not the kind of thing where you could solve an x-ray crystal structure. 09:38:25 09:38:27 09:38:35 09:38:38 09:38:41 09:38:43

Q Can you explain what you mean by a dynamic structure? 09:38:45 09:38:48

A That it's not -- I usually do this with physical illustrations, but I need words here. 09:38:55 09:39:01

When I say it's a dynamic structure, I'm saying that the chain may have collapsed, and it's not -- it's not cooked spaghetti. So it may have collapsed into a globular structure, but it's dynamic in the sense that the atoms are not fixed in place in terms of precise X, Y, and Z 09:39:08 09:39:12 09:39:19 09:39:23 09:39:27 09:39:31

coordinates, but, rather, they're dynamic; they move. It's not a precise structure; it's fluctuating over time. So in many cases, our libraries would lead to that. 09:39:35 09:39:37 09:39:42 09:39:46

Q Well, isn't that true of all proteins; that all proteins are in constant motion, moving over time, not in a static image that you see in a crystal structure? 09:39:49 09:39:52 09:39:56 09:39:59

A This feels like my course. 09:40:00

It's a matter of scale; it's a matter of time scale. To the extreme, if you're not at absolute zero, everything's moving, right. But it's a matter of time scale on how much they're moving. 09:40:02 09:40:05 09:40:08 09:40:12 09:40:16

So some proteins are more rigid than others, which, you know, at room temperature, let's say. The ones I'm speaking of that are very dynamic are too dynamic to even get a crystal structure. 09:40:18 09:40:22 09:40:28 09:40:33 09:40:36

There's a term for this called molten globule. They're globular; they've collapsed. But they're molten in that they're like a liquid, 09:40:40 09:40:45 09:40:47

fluctuating. 09:40:50

Q Do you perform sequence alignments in your work? 09:40:51 09:40:58

A My lab certainly has done that kind of stuff, sure. 09:41:02 09:41:04

Q Do you generate homology models in your lab? 09:41:06 09:41:11

MR. KUSHAN: Objection. Form. 09:41:12

A If we're working with truly de novo sequences, then the term homology is a bit squishy because homology usually refers to ancestry, and if a protein is de novo and not from nature, then by definition it has no ancestry. 09:41:31 09:41:33 09:41:39 09:41:42 09:41:46

But we do sequence alignments, and we are certainly comfortable with modeling the structure of a protein by similarity to others. 09:41:50 09:41:56 09:42:03

Q How would you go about modeling the structure of a protein by similarity to others? 09:42:14 09:42:17

A The way we do it now is using technology that wasn't around at the time of the case we're discussing, using some of the AI methods that arose in the past few years. 09:42:53 09:42:57 09:43:01 09:43:07

Q So the way that you do it now, for example, maybe you would use AlphaFold? 09:43:10 09:43:13

A Yeah. 09:43:15

Q Okay. And AlphaFold wasn't around in 2011? 09:43:15 09:43:21

A Correct. 09:43:22

Q Could you use SWISS-MODEL? 09:43:26

A I'm sorry? 09:43:29

Q Could you use SWISS-MODEL? 09:43:30

A One could, yeah. 09:43:32

Q So it's possible to perform a sequence alignment for one of your de novo proteins and to generate a model using AlphaFold for that de novo protein; is that right? 09:43:36 09:43:41 09:43:46 09:43:52

MR. KUSHAN: Objection. Foundation. 09:43:53

A One would use AlphaFold. I mean, that's today. It's really different from what was done then. 09:44:06 09:44:10 09:44:13

Now AlphaFold is -- you know, it's an AI thing. People pop it in, and magic happens and something comes out. That's very different from what was going on 15 years ago. 09:44:13 09:44:15 09:44:18 09:44:21

Q Well, that wasn't my question. 09:44:23

My question was, could you? We've 09:44:25

established that AlphaFold wasn't around in 2011. 09:44:29

So today could you perform a sequence 09:44:31

alignment for one of your de novo proteins and 09:44:35

generate a model using AlphaFold -- 09:44:39

(The reporter requested clarification.)

Q Sorry. -- and generate a model using

AlphaFold for that de novo protein? 09:44:41

MR. KUSHAN: Objection. Foundation. 09:44:44

A Could you? It's two separate things. 09:44:51

Could you align sequences in a collection 09:44:56

of proteins? You could do that. 09:44:58

Could you have AlphaFold predict a 09:45:01

structure today, not then? You could do that. 09:45:05

Q Okay. And when AlphaFold predicts the 09:45:11

structure, would AlphaFold be basing that 09:45:15

structure off of other solved structures, or would 09:45:18

the AlphaFold be creating a de novo structure for 09:45:21

your de novo protein? 09:45:24

MR. KUSHAN: Objection to form. 09:45:26

Objection. Foundation. 09:45:28

A I am not real comfortable discussing what's under the hood for AlphaFold. I'm not an AI specialist. 09:45:31 09:45:34 09:45:37

Q So you don't know how AlphaFold works? 09:45:39

A Not in detail, no. 09:45:42

Q Do you know how it works in general? 09:45:44

A That it harvests -- like AI is, it harvests -- I mean, it's a bit of a black box, but it harvests data from known sequence -- from massive amounts of known sequences and structures. 09:45:46 09:45:50 09:45:53 09:45:56

Q In your work in your -- sorry. Strike that. 09:46:05 09:46:08

In your lab do you generate models, structural models, for your de novo proteins? 09:46:08 09:46:16

A We will feed a sequence into AlphaFold and ask it to predict a structure. 09:46:28 09:46:32

Q Why do you do that? 09:46:34

A Why do you do that? Because you're interested in what the structure looks like. I mean, yeah. It's... 09:46:35 09:46:43 09:46:45

Q Why are you interested in what the structure looks like? 09:46:48 09:46:50

A Because we study proteins. I mean... 09:46:51
Q Can you obtain information from the 09:46:55
structural model? 09:46:58
A Yeah. You can obtain the structure. 09:46:59
Q What type of information does that give 09:47:01
you? 09:47:02
A The structure. 09:47:03
Q And what type of information does the 09:47:04
structure give you? 09:47:06
A The structure. 09:47:07
Q Is there anything else that you can get 09:47:07
from the structure other than the picture of what 09:47:10
it looks like? 09:47:12
MR. KUSHAN: Objection. Form. 09:47:19
A If you're trying to see the structure, 09:47:20
then you could solve it by x-ray crystallography. 09:47:25
You could predict it with AlphaFold because your 09:47:32
goal is to see the structure, to assess what is 09:47:35
the structure of this -- of the sequence. 09:47:38
Q But why are you trying to assess what the 09:47:39
structure is of the sequence? 09:47:41
A Because we study protein structure. 09:47:43

Q And so what do you learn from -- what types of things can you learn from the model that you generate? 09:47:47 09:47:49 09:47:53

MR. KUSHAN: Objection. Foundation. 09:47:56

A What you learn is the structure in all of its intricacies and details. If the prediction is high resolution, then you learn high resolution information about the structure. 09:48:00 09:48:05 09:48:07 09:48:11

Q And that would include the tertiary structure and the secondary structures? 09:48:12 09:48:15

A If you did an AlphaFold prediction of a sequence and it worked, you know, things were going well, you -- it would feed back; it would give you the structure. And that would tell you where the atoms are in three-dimensional space. 09:48:22 09:48:26 09:48:28 09:48:33 09:48:37

And from that, you would infer -- from that, you would see what's in an alpha helix, what's in a beta sheet, what's in a loop. You would see the structure. 09:48:40 09:48:43 09:48:48 09:48:52

Q So from the model you would see what residues are in an alpha helix, what residues are in a beta sheet, and what residues are in a loop 09:48:54 09:48:58 09:49:02

for the protein that you modeled? 09:49:05

A If the AlphaFold prediction was working 09:49:07

well, that's what you would see. 09:49:10

Q Have you ever used MODELLER? 09:49:13

A My students have. 09:49:16

I mean, I'm -- I'm -- I've been fortunate 09:49:18

to work for years with, you know, teams of really 09:49:23

talented students, and so what will happen is I'll 09:49:27

say, you know, Make a model; let's look at it. 09:49:30

Q Were your students using MODELLER in the 09:49:34

2011 time frame? 09:49:37

A I think so. I'm not always sure exactly 09:49:43

how they -- how they model something. 09:49:46

Q Were your students using MODELLER in the 09:49:49

context of de novo proteins in the 2011 time 09:49:51

frame? 09:49:55

A Some, but not so much, because in many 09:50:13

cases we already knew that our novel proteins were 09:50:18

dynamic and modeling them would have been a 09:50:21

stretch because they would have been dynamic. 09:50:27

Q And is that because they don't form a 09:50:40

sufficiently fixed structure that a model would 09:50:46

give you information about, you know, what the structure would look like most of the time because they're so dynamic they're moving all the time? 09:50:49 09:50:51 09:50:53

MR. KUSHAN: Objection to form. 09:50:55

A Yeah, I'll just summarize by saying that in those combinatorial libraries of novel sequences, it was squishier territory, both intellectually and in terms of the protein itself than would be, say, with a fully evolved natural protein that forms a unique structure. 09:51:02 09:51:05 09:51:10 09:51:17 09:51:20 09:51:22

Q Over the course of your career, you've solved the crystal structure of some of your de novo proteins, right? 09:51:35 09:51:37 09:51:39

A In collaboration with crystallographers, we've -- yeah, there have been some. 09:51:42 09:51:44

Q So not all of the de novo proteins you've generated have been dynamic? 09:51:47 09:51:50

A That's correct. We occasionally find some that are reasonably rigid. 09:51:51 09:51:53

Q But it's possible that in the 2011 time frame your students used MODELLER to generate models of de novo proteins? 09:52:00 09:52:02 09:52:06

A It's possible. I can't remember what every, you know, what everybody was doing. Yeah. We certainly -- you know, as a group, were aware and comfortable with those technologies being available, yeah. 09:52:09 09:52:10 09:52:14 09:52:17 09:52:19

Q What about SWISS-MODEL? Have you used SWISS-MODEL? 09:52:21 09:52:24

A Same thing. I mean, I -- you know, I think students in my lab were aware of what technologies were around and would have used what was available. 09:52:24 09:52:27 09:52:29 09:52:31

Q So is it fair to say that the 2011 time frame your students may have been generating structural models of de novo proteins? 09:52:32 09:52:35 09:52:39

MR. KUSHAN: Objection to foundation. 09:52:52

A It's fair to say they would have been attempting to generate models. That does not mean those models were necessarily correct. 09:52:56 09:53:00 09:53:04

Q Is it possible to evaluate a model for reliability? 09:53:35 09:53:38

A It's possible to evaluate a model for reliability, and depending on the model, the 09:53:47 09:53:50

sequence and the time frame, your evaluation may or may not be solid. 09:53:53 09:53:58

Q So if you were to generate a model for a de novo protein in 2011, by definition, that de novo protein did not evolve from anything else, so you're not basing your model on a homologous sequence; is that right? 09:54:02 09:54:12 09:54:15 09:54:18 09:54:23

MR. KUSHAN: Objection to form. Also objection to foundation. 09:54:25 09:54:28

A You might be basing your model on sequences from library that are similar but not homologous because homologous, the word assumes ancestry, and these proteins were -- have no ancestry. 09:54:32 09:54:35 09:54:39 09:54:44 09:54:47

Q When you say a sequence is similar, are you referring to a percent identity? 09:54:56 09:54:58

A Percent identity, yeah. A sequence alignment, in looking at the identity or similarity of the amino acids. Yeah. 09:55:02 09:55:06 09:55:09

Q And what identity would you say makes a, make two protein sequences similar? 09:55:12 09:55:15

A Make them what? 09:55:18

Q Similar? 09:55:19

MR. KUSHAN: Objection to form. 09:55:20

Objection. Foundation. 09:55:21

A It depends on the context. I mean it's 09:55:25

just -- if you're dealing with evolved proteins 09:55:28

that are homologous, it's a different situation 09:55:33

from if you're dealing with proteins that were in 09:55:38

a designed library. It's -- it's just different. 09:55:42

So it depends on the context. 09:55:47

Q What sequence identity would you say that 09:55:54

evolved -- I'm sorry. Strike that. 09:55:57

What sequence identity would you say would 09:56:00

make two homologous proteins similar? 09:56:02

A Homologous proteins. 09:56:06

Q Yes. 09:56:07

A Natural proteins. 09:56:08

Q Yes. 09:56:09

A That evolve from a common ancestry. 09:56:09

I'm hesitant to put a number on it, but if 09:56:21

they are proteins with similar biological 09:56:27

functions, similar activities, evolved from common 09:56:29

ancestry, similar physical properties, then you 09:56:33

can be fairly confident that they're likely to fold in a similar structure. 09:56:38 09:56:41

And so then if you had sequence identity, it would be more permissive then than if you were just pulling out arbitrary sequences that you didn't know of them having common ancestry or common function. 09:56:44 09:56:48 09:56:51 09:56:55 09:56:57

So again, it depends. 09:56:58

Q Would you say sequences that are 40 percent identical, homologous sequences that are 40 percent identical are similar? 09:57:05 09:57:08 09:57:11

MR. KUSHAN: Objection. Foundation. 09:57:14

A You asked me if they're 40 percent similar, would they be similar? I think that's -- 09:57:17 09:57:19

Q No, 40 percent identical, would they be considered similar? 09:57:20 09:57:24

MR. KUSHAN: Objection. 09:57:25

A Would what be considered similar? The sequences? 09:57:26 09:57:28

Q Strike that. Let me -- 09:57:30

In your lab do you perform sequence alignments aligning your de novo proteins to 09:58:17 09:58:18

natural protein sequences? 09:58:22

A We thought about that. Way back when we 09:58:26

first started this we highlighted that our 09:58:29

sequences were de novo in the sense that they had 09:58:31

negligible runs of sequence identity with anything 09:58:37

in nature, and so we didn't bother aligning them 09:58:40

to anything in nature after that because why 09:58:44

should we? They're not natural. 09:58:47

In fact, we highlighted that they're not 09:58:58

similar to natural systems. 09:59:00

Q Are you aware of any instances where your 09:59:32

students used MODELLER or SWISS-MODEL to generate 09:59:35

a model of a de novo protein? 09:59:39

A You know, like I said before, in the -- 09:59:43

you mean today or you mean in 2010, 2011, 2012 09:59:47

or -- 09:59:52

Q The 2011 time frame. 09:59:52

A So in that period, people would 09:59:55

occasionally model one of our novel sequences and 10:00:01

show me a picture. I'm not certain which 10:00:05

computational method they used. 10:00:09

Q And do you know what the purpose was for 10:00:14

modeling the sequence and showing you the picture? 10:00:17

A Because we're interested in protein 10:00:21

structure. We want to see what they look like. 10:00:23

You model the structure because you're interested 10:00:24

in the structure. 10:00:26

Q Does the model give you any useful 10:00:27

information about the sequence? 10:00:30

A The model, in those cases, gives you a 10:00:31

model. In those cases, with these de novo 10:00:34

proteins, it gives you a -- something to look at 10:00:40

and think about. You're not certain if it's 10:00:44

correct or not because there is no homology to 10:00:46

work with. There's only these collections of 10:00:49

novel proteins that have some level of sequence 10:00:53

similarity. 10:00:57

So it's very different from working with 10:01:00

natural proteins. It's like a -- it's a whole 10:01:02

different way of thinking about stuff. 10:01:04

Q And when you say that there's no homology 10:01:06

to work with, you mean there is no natural protein 10:01:10

with a solved crystal structure and known function 10:01:13

that you can go from? 10:01:15

A Well, homology is defined with a common ancestry, and so if the proteins are in, by intent de novo and unrelated to natural proteins, then by definition and by intent, there's no common ancestry, there's no ancestry, there's no -- there's none of that. There's no homology. 10:01:17 10:01:21 10:01:25 10:01:29 10:01:32 10:01:34

People often mistake those words of homology and sequence similarity. It's not the same thing. Homology implies evolutionary relatedness. And the de novo proteins, by definition, do not have evolutionary relatedness to anything in the biosphere. 10:01:37 10:01:40 10:01:42 10:01:45 10:01:48 10:01:51

Q So why does it -- you said there was no homology to work with. Why do you care about homology if homology is just ancestral relatedness? 10:01:58 10:02:00 10:02:02 10:02:06

A Because when you're model building, okay -- okay. Homology, as defined by evolutionary relatedness and common ancestry, is the result of the biggest experiment ever done, and that is the experiment done by Darwinian evolution. 10:02:07 10:02:11 10:02:22 10:02:26 10:02:30 10:02:35

And so homology tells you that sequences share common ancestry and that if there are changes, they have been tolerated by evolution. So the evolutionary experiment is telling you about what is tolerated and what's not. 10:02:36 10:02:41 10:02:45 10:02:49 10:02:53

Very different from matching up sequences in my lab. We have no idea what's tolerated and what's not tolerated because they've not been evolved, there's not been a selection. Very different. 10:02:58 10:03:03 10:03:06 10:03:08 10:03:11

Q What is -- what does homology have to do with model building? 10:03:22 10:03:26

A A lot. It's -- homology, as I said a moment ago, is the data, the result from this massive experiment done in nature that says what amino acids are consistent with activity. 10:03:27 10:03:54 10:03:58 10:04:06

If you understand what amino acids are consistent with activity gives you a hint on what's consistent with structure. Therefore, homology is profoundly important for structural modeling. 10:04:13 10:04:17 10:04:20 10:04:22 10:04:29

Q Why would understanding what amino acids 10:04:36

are consistent with activity give you a hint on what's consistent with structure? 10:04:40 10:04:42

A It's protein chemistry 101. Is that structure -- that function depend upon structure. 10:04:56 10:04:59

Q And you said homology is profoundly important to model building; correct? 10:05:06 10:05:10

A Yes. Model building as we're discussing that, right. I'm not talking about AI methods now, for sure. 10:05:17 10:05:20 10:05:23

Q Correct. Yes. 10:05:25

And, again, why is it profoundly important? 10:05:26 10:05:28

A I just said that, is that by looking at homologous proteins that have made it through the evolutionary experiment, you're seeing what sequences are consistent with biological function. 10:05:29 10:05:33 10:05:41 10:05:43

And since function depends upon structure, you're also seeing what sequences are -- are consistent with structure. And since you're asking about building models of structure, it's kind of important. 10:05:48 10:05:51 10:05:54 10:05:57 10:06:00

Q So having a homologous protein is helpful 10:06:03

for building a structural model? 10:06:10

MR. KUSHAN: Objection. Form. 10:06:13

A Having in front of you a collection of homologous sequences is very beneficial for modeling three-dimensional structures, yeah. 10:06:19 10:06:21 10:06:28

Q And is it even more beneficial if you have solved crystal structures for some of those homologous sequences? 10:06:35 10:06:38 10:06:40

A It's very much beneficial to have experimentally determined structure for some of those proteins, yeah. 10:06:43 10:06:47 10:06:49

Q Because if you have an experimentally determined structure for a homologous sequence, then you can use that experimentally determined structure as the basis to build the model for your sequence; is that right? 10:06:51 10:06:53 10:06:56 10:06:59 10:07:02

MR. KUSHAN: Objection -- sorry. 10:07:04

Objection. Form. Also, objection as to foundation. 10:07:06 10:07:08

A Now I lost where the question was. 10:07:12

Why don't you do it again. Sorry. 10:07:16

Q Yeah. 10:07:17

Because if you have an experimentally determined structure for a homologous sequence, then you can use that experimentally determined structure as the basis to build the model for your sequence? 10:07:18 10:07:20 10:07:22 10:07:24 10:07:27

MR. KUSHAN: Objection to form. 10:07:28

A That would be input for your model building. There would be other inputs as well, but that would be input. 10:07:29 10:07:32 10:07:37

Q And what other inputs? 10:07:38

A The set of homologous sequences that you have would be important. 10:07:44 10:07:51

The range of sequences in that collection of homologous sequences, that goes into your system. 10:07:54 10:07:56 10:08:00

And a known structure, experimentally determined structure, would go into it as well. 10:08:01 10:08:05

Q And the range of sequences in the collection of homologous sequences is helpful because it gives you information about which amino acids are tolerated at which position; is that right? 10:08:14 10:08:16 10:08:19 10:08:21 10:08:25

A It gives you some insight into that, yeah. 10:08:25

Q Is it helpful to know the range of amino acids that are tolerated at a particular position in a protein when you're building a model? 10:08:35 10:08:39 10:08:42

A When building a model, it's helpful to line -- it's important, it's crucial, to be able to line up the sequence of interest with the sequence and structure of the protein whose structure has been experimentally determined. 10:09:18 10:09:22 10:09:25 10:09:29 10:09:32

Q And it's important to have a set of homologous sequences when you're building a model in part because the homologous sequences are natural sequences that are expressed in nature and you know that they form actual, functional proteins; is that right? 10:09:52 10:09:56 10:09:59 10:10:04 10:10:07 10:10:10

A More data is always better, but it's not -- it is also done to have -- it's also the case that one has a sequence and a structure, right. They're different. 10:10:14 10:10:18 10:10:23 10:10:27

You have the sequence of Protein A and the sequence and structure of Protein B. And if they're homologous and have good sequence 10:10:29 10:10:31 10:10:35

identity, one can model one on the other even without dozens of other ones. 10:10:38 10:10:40

Q And why is that the case? 10:10:46

A You have a sequence in structure that's been determined. And you know what it is. It's a particular enzyme. You know what its function is. 10:11:01 10:11:04 10:11:09

You have another sequence when you don't yet have the determined structure, okay, but it has considerable sequence identity and it has considerable biological overlap and it has homology. 10:11:13 10:11:17 10:11:24 10:11:28 10:11:31

Then you can infer that since it has the same activity and since it has so many positions where the sequence is identical, then it's reasonable to infer from that that it will form a very similar structure because structure is a foundation for function, and sequence is the foundation for structure and function. 10:11:34 10:11:38 10:11:43 10:11:47 10:11:51 10:11:56 10:12:00

And so if the sequences are nearly identical, the ancestry is common, and the activity is more or less the same, then it's quite reasonable to say that, Oh, it will also have the 10:12:02 10:12:07 10:12:10 10:12:14

same 3D structure, and one can model it accordingly, even in the absence of a whole zoo of other related sequences. 10:12:17 10:12:22 10:12:25

Q And those principles were well known in the 2011 time frame; is that right? 10:12:34 10:12:36

A Oh, yeah, yeah, yeah. 10:12:37

Q Apart from this matter, have you done any work with Merck? 10:13:23 10:13:25

A Not that I recall, no, nothing significant. 10:13:35 10:13:38

Q Has Merck ever funded research in your lab? 10:13:39 10:13:42

A No. 10:13:43

Q Have you ever done any consulting work for Merck? 10:13:50 10:13:53

A No. 10:13:56

Q Apart from this matter, have you ever worked with Dr. Park? 10:14:00 10:14:02

A So he had a book some years that had a bunch -- some years ago, that had -- you probably know -- that had a bunch of articles in it, one of which was co-authored by me. 10:14:05 10:14:09 10:14:10 10:14:12

To be honest, I don't remember much about that. Somebody asked us to submit a chapter. We submitted a chapter. 10:14:14 10:14:16 10:14:18

I may have talked to him on the phone. We may have met at a meeting. I don't remember. It wasn't profound. 10:14:19 10:14:22 10:14:24

Q Have you ever heard of a company called Alteogen? 10:14:27 10:14:30

A Say again? 10:14:31

Q Have you ever heard of a company called Alteogen? 10:14:32 10:14:34

A I think so. I think I've heard of that in passing in -- in the past year through working on this case. 10:14:36 10:14:38 10:14:41

But I'm not sure I know much else about it. I've never Googled it, so... 10:14:43 10:14:46

Q Apart from your work on this case, have you ever heard of Alteogen? 10:14:48 10:14:50

A No, no, no. 10:14:52

Q So they don't fund any of your research? 10:14:53

A No. 10:14:57

Q Are you a named inventor on any patents? 10:14:57

A On any patents? No. 10:15:01

Q No? 10:15:03

Have you ever filed a patent application? 10:15:04

A I have in a rather amateur and clueless way. The university, Princeton, has but nothing that ever went very far. 10:15:10 10:15:18 10:15:21

Q Do you know if those patent applications are still being prosecuted? 10:15:22 10:15:24

A There was something we -- that the intellectual property office at Princeton submitted a few years ago that I've never heard anything back on that. I don't know if it fizzled out. 10:15:27 10:15:31 10:15:34 10:15:36 10:15:39

I was, to be honest, not super involved in it. It was my postdoc and grad students who wanted to move forward with it. And I said, Okay, do what you want. 10:15:40 10:15:43 10:15:44 10:15:47

I kind of felt it was never going to be commercially viable, so it wasn't really worthwhile, but they wanted to pursue it. 10:15:50 10:15:52 10:15:55

Q Have you ever actually -- strike that. 10:15:58

All right. So we've probably been going 10:16:10

for a little over an hour. 10:16:13

Do you want to take a quick break? 10:16:14

A Sure. 10:16:16

You want to take a break? 10:16:17

Q Mm-hmm. 10:16:18

A Bathroom break. Okay. 10:16:18

THE VIDEOGRAPHER: We are going off the record. The time is 10:16 a.m. 10:16:19 10:16:21

(A recess was taken.) 10:16:23

THE VIDEOGRAPHER: We are back on the record. The time is 10:35 a.m. 10:35:31 10:35:33

BY MS. MARTIN: 10:35:36

Q Welcome back, Dr. Hecht. 10:35:37

A Very good. 10:35:39

Q Did you speak with anyone during the break about the substance of your testimony? 10:35:40 10:35:42

A No. 10:35:44

Q Would you say that a 40 percent sequence identity for homologous sequences is sufficient to generate a homology model? 10:35:48 10:35:52 10:35:56

MR. KUSHAN: Objection. Foundation. Objection as to form. 10:36:00 10:36:02

A I don't want to generalize to all possible situations, but I would say in many cases, yes. 10:36:12 10:36:14

Q All right. So we're going to mark your exhibits, although they've already been marked in this proceeding -- or your declarations, sorry. 10:36:19 10:36:28 10:36:31

So the first one -- 10:36:41

A Wait. These were -- oh, okay. 10:36:42

These are all for me, this whole pile? 10:36:44

Q Yes, whole pile. All four at the same time. 10:36:47 10:36:49

So for the record, first one is Declaration of Michael Hecht, Ph.D. from PGR2025 Matter 3 regarding US Patent No. 11,952,600. And that is in the -- in PGR Matter 3, that is Exhibit 1003. 10:36:52 10:36:58 10:37:04 10:37:10 10:37:16

And then in Matter -- PGR2025 Matter 4, regarding US Patent No. 12,018,298, Declaration of Michael Hecht, Ph.D., and that's Exhibit 1003. 10:37:19 10:37:25 10:37:31

And then in Matter -- PGR2025 Matter 6 regarding US Patent No. 12,152,262, the Declaration of Michael Hecht, Ph.D., and that's Exhibit 1003 in Matter 6. 10:37:37 10:37:41 10:37:47 10:37:50

And then finally, in PGR2025 Matter 9, US Patent No. 12,123,035, Declaration of Michael Hecht, Ph.D. and that's Exhibit 1003. 10:37:54 10:37:59 10:38:06

(Exhibit 1003 was introduced for identification.)

BY MS. MARTIN:

Q So Dr. Hecht, can you please confirm that these are the four declarations that you've submitted in each of these proceedings? 10:38:09 10:38:12 10:38:15

A I haven't seen every page, but they certainly look that way. 10:38:20 10:38:22

Q And you signed each of these declarations; correct? 10:38:26 10:38:30

A Correct. 10:38:30

Q All right. So your declaration for Matter 3, Exhibit 1003, can you please turn to page 123? 10:38:35 10:38:53 10:38:58

A Sorry, what page? 10:39:01

Q Page 123. 10:39:03

A Okay. 10:39:12

Q And page 123 and 124 has your exhibit list; is that correct? 10:39:13 10:39:18

A Correct. 10:39:19

Q You listed all of the materials you considered in forming your opinions set forth in your declaration for Matter 3 in the exhibit list in your declaration; is that right? 10:39:22 10:39:25 10:39:29 10:39:32

A I listed items that were considered. That's not a complete and exhaustive list, but it's a list of things I considered. 10:39:34 10:39:43 10:39:45

Q Are there documents that you considered in forming your opinion that are not listed on your exhibit list? 10:39:48 10:39:50 10:39:53

A I mean, a whole career of documents. 10:39:54

Q Is it fair to say that all the documents that are cited in your declaration are on your exhibit list? 10:40:09 10:40:11 10:40:14

A I think so. I would -- you know, I don't want to answer with absolute certainty without going back and listing every one. But it looks that way, yes. 10:40:23 10:40:26 10:40:29 10:40:34

Q And you executed your declaration in Matter 3 on November 12, 2024; is that right? 10:40:35 10:40:37

A That's when I signed it, yes. 10:40:41

Q Okay. Do you understand that trial has been instituted in Matter 3? 10:40:45 10:40:57

A Do I understand what? 10:40:59

Q That trial has been instituted by the -- by the PTAB in Matter 3? 10:41:00 10:41:03

A I don't know what that means. 10:41:07

Q Okay. Have you read the institution decision that the PTAB issued in connection with Matter 3? 10:41:08 10:41:11 10:41:16

A I have not read it. I have a copy of it and I've glanced at it, but I have not read it. 10:41:17 10:41:20

Q So you received a copy of the institution decision? 10:41:22 10:41:24

A I received a copy of it, but I have not read it page by page, no. 10:41:25 10:41:28

Q Did you read any -- did you glance at it? 10:41:29

A I glanced at it. 10:41:32

Q Do you recall anything that you saw? 10:41:33

A I saw some things -- we discussed some things where they seem to have seen things in this declaration and found them to be reasonable. 10:41:35 10:41:39 10:41:43

MR. KUSHAN: Doctor, I don't want to -- 10:41:46

make sure you understand you're not to reveal communications with counsel. 10:41:48 10:41:50

THE WITNESS: Okay. 10:41:51

Q Did you receive all four institution decisions for each of these matters? 10:42:02 10:42:05

A I received a spiral-bound folder that I think contains all four of them. 10:42:09 10:42:13

Q In paper form? 10:42:15

A Mm-hmm, yes. 10:42:16

Q Did you glance at all four of them? 10:42:18

A Barely. 10:42:21

Q Okay. So let's turn in your declaration for Matter 3 to paragraph 11. 10:42:36 10:42:42

So in providing your opinions in this matter, you used the time frame before December 29, 2011; is that right? 10:43:05 10:43:09 10:43:16

A That's what's written here. 10:43:18

Q Is that accurate? 10:43:20

A I would say that the relevant science that was happening in the period of '11 -- 10:43:25 10:43:33

Q Well, that's not my question, Dr. Hecht. My question is -- 10:43:38 10:43:41

MR. KUSHAN: I'm sorry. Were you finished with your answer? 10:43:41 10:43:43

A Well, no. Go ahead. Then we can get back to it. 10:43:44 10:43:46

Q Okay. So because you were about to actually give me the answer to a different question. The question that I asked you is -- is you used the time frame before December 29th, 2011. That's what you stated in your declaration when you performed your analysis. That's what's written in paragraph 11 in your declaration; is that right? 10:43:46 10:43:49 10:43:51 10:43:56 10:44:00 10:44:03 10:44:06 10:44:10

A That's what's written. 10:44:10

Q Okay. Thank you. And -- okay. And the technical field at issue in this case concerns protein structures and modifications of them; is that correct? 10:44:11 10:44:24 10:44:26 10:44:31

A Correct. 10:44:31

Q So paragraph 13 provides the definition of the person of ordinary skill in the art; is that right? 10:44:40 10:44:43 10:44:48

A That's what it says, yeah. 10:44:48

Q And if I use the term POSA, do you understand that that refers to person of ordinary skill in the art? 10:44:49 10:44:52 10:44:54

A Okay. 10:44:55

Q Okay. You qualified as a person of ordinary skill in the art in 2011; right? 10:44:56 10:45:14

A Yes. 10:45:16

Q Do you agree that a POSA would have been able to consult with someone with hyaluronidase experience as part of a multi-disciplinary team in 2011? 10:45:21 10:45:24 10:45:28 10:45:31

MR. KUSHAN: Objection. Foundation. 10:45:34

A Are you asking if somebody would be able to talk to somebody else? 10:45:38 10:45:41

Q Yes. 10:45:43

A Yes. Anybody can talk to anybody else. 10:45:47

Q So a POSA would have been able to speak with someone with hyaluronidase experience as part of a multi-disciplinary team in the 2011 time frame? 10:45:51 10:45:55 10:46:01 10:46:03

A As I said, I believe anybody in the -- you're asking a hypothetical question, and the 10:46:08 10:46:12

hypothetical answer is yes, anybody could talk to anybody else. 10:46:15 10:46:18

Q And when you performed your analysis in this case, you did not consult with anyone having hyaluronidase experience in forming your opinions; is that right? 10:46:19 10:46:25 10:46:29 10:46:37

A I did not consult with anybody who had worked on hyaluronidase. 10:46:37 10:46:40

Q Have you done any work with hyaluronidases outside of this matter? 10:46:46 10:46:50

A No, not outside this matter, no. 10:46:51

Q Have you ever worked with PH20? 10:46:53

A I have not. 10:46:56

Q How many human hyaluronidases are there? 10:47:00

A Five. 10:47:05

Q And which ones cleave hyaluronic acid? 10:47:06

A I don't recall exactly, but they're -- most of them do. 10:47:12 10:47:15

Q Most of them do? 10:47:16

A Mm-hmm. 10:47:17

Q But there are some that do not? 10:47:17

A That's my recollection. 10:47:19

Q What's the function of PH20? 10:47:22

MR. KUSHAN: Objection. Form. 10:47:30

A As a biological protein, it could have multiple functions, but it is a high -- it is an enzyme with that specified activity. It also exists on sperm and is involved in the function of sperm. 10:47:39 10:47:42 10:47:45 10:47:49 10:47:52

Q So PH20 does cleave hyaluronic acid; right? 10:48:03 10:48:08

A Yes. 10:48:08

Q And do you know the mechanism of action by which PH20 cleaves hyaluronic acid? 10:48:12 10:48:15

A I've read papers that demonstrate that mechanism. I have not memorized them. 10:48:20 10:48:22

Q And if you turn to paragraph 77, which is the bottom of page 38, top of page 39. 10:48:25 10:48:45

A Okay. 10:48:49

Q The second sentence in that paragraph, starting at the top of page 39, says that, "PH20 selectively catalyzes the hydrolysis of beta 1,4 glycosidic bonds in hyaluronan, also called hyaluronic acid"; right? 10:48:54 10:48:57 10:49:01 10:49:07 10:49:10

A I see that. 10:49:12

Q So PH20's mechanism of action is that it catalyzes the hydrolysis of the beta 1,4 glycosidic bonds in hyaluronic acid? 10:49:12 10:49:17 10:49:22

A That's what it says. 10:49:25

Q And is that the mechanism of action? 10:49:26

A That's what it says, yeah. 10:49:27

Q So is it fair to say that PH20, like other hyaluronidases that cleave hyaluronic acid, do so by hydrolyzing the beta 1,4 glycosidic bonds? 10:49:29 10:49:35 10:49:40

A PH20 selectively catalyze the hydrolysis of the beta 1,4 glycosidic bonds in hyaluronic acid, yeah. 10:49:46 10:49:50 10:49:54

Q Do you know if other hyaluronidases that cleave hyaluronic acid also function using that same mechanism of action? 10:49:55 10:50:00 10:50:01

A Yes. There are others that do. 10:50:04

Q Does HYAL1 cleave hyaluronic acid using that same mechanism of action? 10:50:07 10:50:13

A I'm not going to remember -- I think so, but I'm not going to remember the nomenclature of which one. But I'm pretty sure it does, yeah. 10:50:14 10:50:17 10:50:19

Q Okay. Apart from your work in this matter, have you ever analyzed any structure of a hyaluronidase? 10:50:24 10:50:25 10:50:28

A Not prior to this work. 10:50:32

Q Have you ever performed an assay to measure hyaluronidase activity? 10:50:38 10:50:40

A I have not measured hyaluronidase activity. 10:50:46 10:50:49

Q Do you have experience running ELISA assays? 10:50:51 10:50:54

A Long time ago. 10:50:59

Q Do you use ELISA assays in your lab? 10:51:02

A Not regularly. 10:51:05

Q So then you've never performed a hyaluronic acid-coated microplate assay; is that correct? 10:51:21 10:51:30 10:51:34

A I have not. 10:51:34

Q Have you ever measured enzymatic activity using the Morgan-Elson color reaction? 10:51:37 10:51:40

A I have not. 10:51:44

Q Are you familiar with using turbidity-reducing units as a measure of enzymatic 10:51:53 10:51:56

activity? 10:52:00

A I'm familiar with that, yes. 10:52:01

Q Do you use turbidity-reducing units in work in your lab to characterize enzymatic activity? 10:52:02 10:52:07 10:52:09

A At the moment, no. 10:52:26

But I -- over the course of the last half century, it's -- yeah, might have. I'm certainly familiar with it. 10:52:27 10:52:31 10:52:34

Q Can you explain what a turbidity-reducing unit is? 10:52:35 10:52:41

A If one has a substrate that produces a sample that's turbid and then if one has a catalyst -- specifically, in this case, an enzyme -- that degrades that substrate to produce a product that's soluble and not turbid, then you can monitor the progress of the reaction by monitoring the diminished turbidity over the course of time. 10:52:44 10:52:50 10:52:56 10:52:59 10:53:05 10:53:10 10:53:14 10:53:17

Q So do turbidity-reducing units refer to the amount of enzyme that will reduce turbidity in a solution by a certain amount over a particular 10:54:14 10:54:21 10:54:27

period of time? 10:54:33

MR. KUSHAN: Objection. Foundation. 10:54:33

A I would not say it refers to the amount of 10:54:36

enzyme. 10:54:38

It's a measurement of activity, which 10:54:39

could arise from having more enzyme -- more 10:54:43

activity could arise from having more enzyme or 10:54:46

the same amount of enzyme with higher specific 10:54:49

activity. 10:54:52

So what you said is not precisely correct. 10:54:54

Q Did anyone besides counsel assist you in 10:55:08

your analysis in these matters? 10:55:13

A Park. 10:55:17

Q Anyone else? 10:55:18

A No. 10:55:19

Q No one in your lab? 10:55:19

A No. 10:55:22

Q Okay. Did you collaborate with Dr. Park 10:55:23

in reaching your opinions in these matters? 10:55:28

MR. KUSHAN: Objection. Form. 10:55:36

A Park and I met on Zoom several times and 10:55:42

discussed the science involved. And in that sense 10:55:47

it was collaborative in terms of discussing the science. 10:55:52 10:55:55

Q About how many Zooms would you say you had with Dr. Park? 10:55:57 10:55:59

A More than one, less than five. 10:56:04

Q And do you recall roughly when those took place? 10:56:07 10:56:13

A Many months ago. 10:56:13

Q Do you recall about for how long each Zoom lasted? 10:56:14 10:56:17

A More than an hour, less than three. 10:56:22

Q Okay. And what did you discuss with Dr. Park on those Zooms? 10:56:26 10:56:28

A Sequence, structure, homology, mutagenesis, stability of hyaluronidases, specifically PH20. 10:56:40 10:56:47 10:56:56

Q And what did you discuss about sequence, structure, homology, and mutagenesis of PH20? 10:57:00 10:57:03

A We looked at sequence alignments. We looked at 3D structures on the computer screen. 10:57:19 10:57:27

We looked at possible mutations. We looked at the structures around such possible 10:57:34 10:57:41

mutations, and discussions around those topics. 10:57:43

Q Do you recall what specific mutations you discussed with Dr. Park? 10:57:57 10:58:00

A Well, the conversation started out by discussing broad topics: which positions are conserved, which positions are not conserved, which positions are likely to be tolerant or obvious, which positions are likely to be sensitive to substitution. 10:58:05 10:58:09 10:58:15 10:58:19 10:58:22 10:58:24

Very broadly, that was a part of the conversation. After that we also discussed specific examples of particular positions in the sequence structure and particular mutations at those positions. 10:58:25 10:58:33 10:58:39 10:58:44 10:58:49

Q When you say you look at the structures around such possible mutations, do you mean you looked at the environment around a possible mutation in the PH20 model in PyMOL? 10:59:01 10:59:04 10:59:06 10:59:09

A Yeah, we looked in PyMOL. We looked at the overall structure. We moved it around and, you know, looked at it, the structural model. 10:59:17 10:59:19 10:59:25

Then, on occasion, we would zoom in to a 10:59:30

particular position, position X, Y, Z. We would look at the side chain in the protein at that position. 10:59:33 10:59:38 10:59:41

We would discuss its environment, three-dimensional environment. We also had discussed its sequence position relative to homologous proteins. 10:59:42 10:59:44 10:59:48 10:59:51

Then we would consider possible mutations at that position. We would look at the structure modeled of those mutations and look in the neighborhood around there and then have a geeky discussion about protein structure and stability. 10:59:53 10:59:59 11:00:05 11:00:08 11:00:15

Q So why were you examining the environment around each potential mutation in PyMOL? 11:00:20 11:00:24

A Location, location, location. I mean, it's basically -- one could make a mutation in the abstract of this amino acid to that amino acid. If you do that in the abstract, it's pretty difficult to say anything intelligent about that. 11:00:34 11:00:37 11:00:44 11:00:52 11:00:57

However, if you look at it in the context of its physical chemical environment in the protein and in the context of its homologous 11:01:00 11:01:02 11:01:07

environment sequence space, then you're better able to come up with an assessment of the properties of a potential mutation. 11:01:11 11:01:14 11:01:18

And the location of the position of interest matters, and the location of other amino acids in that neighborhood matters. 11:01:23 11:01:27 11:01:30

Q And that's because you can evaluate the potential change in interactions that would result from substituting the wild-type amino acid with a different amino acid? 11:01:41 11:01:47 11:01:52 11:01:55

A By looking at the sequence comparisons and by also looking at the structure in three dimensions, one can become more educated about what the likelihood is -- what the impact is likely to be from making a particular mutation. 11:01:58 11:02:01 11:02:04 11:02:10 11:02:15

Q And that's because you can evaluate -- when you look at the structure in three dimensions and the sequence comparison, you can evaluate the potential impact of the mutation on the protein structure; right? 11:02:20 11:02:24 11:02:27 11:02:30 11:02:34

A That's what I said, yeah. 11:02:35

Q And, in particular, you can evaluate the 11:02:40

potential impact of the mutation on secondary structure? 11:02:43 11:02:51

A I'm not going to generalize and say every time, everything you look at, that's true. 11:02:54 11:02:58

But I will say that you can make a more cogent analysis if you look at the structure and the environment than if you didn't. 11:03:01 11:03:06 11:03:10

Q Well, if you have an amino acid that's in, for example, an alpha helix and you're considering changing that amino acid to an amino acid that is known to be intolerant in alpha helices, then that would give you potential, important information in evaluating the likely impact of the substitution; is that right? 11:03:12 11:03:14 11:03:17 11:03:22 11:03:26 11:03:28 11:03:32

MR. KUSHAN: Objection. Foundation. Also objection as to form. 11:03:32 11:03:34

A I got distracted. 11:03:40

So you're saying if you look at an amino acid in an alpha helix. 11:03:41 11:03:44

Continue your question. 11:03:45

Q Look at an amino acid in an alpha helix. 11:03:46

Then the fact that that amino acid is in 11:03:48

an alpha helix -- and the residues around it give you important information in evaluating what other residues you might be able to put in that position; right? 11:03:51 11:03:54 11:03:57 11:03:59

A You're always better off with more input. 11:04:01

So if you look at it, you get more information than if you didn't look at it, yeah. 11:04:04 11:04:05

Q Why did you have these discussions with Dr. Park regarding the structure in PyMOL? 11:04:27 11:04:40

A The core issues in this case deal with making changes in a sequence. 11:05:06 11:05:10

And to understand the impact of changes in the sequence, it's wise to look at the sequence and look at the structure to have a more informed -- to be able to make a more informed analysis of what would the impact be of such changes. 11:05:14 11:05:17 11:05:21 11:05:25 11:05:28 11:05:32

Q You mention that you also discussed the sequence alignment. 11:05:36 11:05:39

Was that the alignment that Dr. Park generated of the PH20 sequence with the other homologous sequences? 11:05:42 11:05:44 11:05:47

A Correct. 11:05:49

Q Can you explain how that sequence 11:05:50

alignment factored into the analysis in terms of 11:05:53

evaluating potential mutations? 11:05:57

A Yeah. I mean, I think that's -- you know, 11:06:00

it's in the document here. 11:06:02

It's also -- I mean, it's elaborated quite 11:06:11

extensively in Park's document. We can look at 11:06:14

data if you want. 11:06:17

But you're asking how does sequence 11:06:17

alignment bear on the consideration of mutations? 11:06:20

Q Yes. 11:06:24

A Okay. Well, the section that begins on 11:06:26

page 102 and goes for many pages after that talks 11:07:14

about substitutions in non-essential regions. 11:07:37

And so an understanding of non-essential 11:07:44

regions -- discussion of non-essential regions is 11:07:53

based on -- starts by looking at sequence 11:08:09

alignments. Essential and non-essential regions 11:08:16

starts by looking at sequence alignments. 11:08:20

Yeah, there it is on page 109. That's 11:08:25

what I was looking for. 11:08:27

Q So how does the position of an amino acid in a sequence alignment, how does that tell you whether a potential mutation at that position -- or the potential impact of a mutation at that position? 11:08:30 11:08:32 11:08:38 11:08:40 11:08:43

MR. KUSHAN: Objection to form. 11:08:45

A So on page 109, it says, "The Skilled Artisan Would Have Identified Non-Essential Regions in PH20 and Suitable Amino Acid Substitutions Using a Multiple Sequence Alignment of Homologous Hyaluronidase Proteins." 11:08:49 11:08:52 11:08:55 11:09:00 11:09:03

So the discussion starts by identifying non-essential regions. And as it says, "The skilled artisan would have understood that these non-essential regions to be regions between -- between the conserved residues," (as read), okay, in other words, not the conserved residues, okay. 11:09:06 11:09:08 11:09:17 11:09:19 11:09:22 11:09:26

The non-conserved residues would be deemed as non-essential. And, therefore, if one is considering making mutations, one would look for these sequence alignments to assess what's essential and what's not. 11:09:30 11:09:32 11:09:37 11:09:42 11:09:48

Q So when you talked to Dr. Park on Zoom and you looked at the sequence alignments and you looked at PyMOL, did you use the sequence alignments and the PyMOL structure in order to -- and the PyMOL structure in order to evaluate potential substitutions? 11:09:49 11:09:53 11:09:55 11:10:02 11:10:05 11:10:08

I thought that that's what you said. 11:10:10

A We -- 11:10:12

MR. KUSHAN: Objection. Sorry. Objection to foundation. Go ahead. 11:10:13 11:10:16

A Repeat the question, then. Sorry. 11:10:17

Q When you talked to Dr. Park on Zoom and you looked at the sequence alignments and you looked at PyMOL, did you use the sequence alignments and the PyMOL structure in order to evaluate potential substitutions? 11:10:20 11:10:22 11:10:24 11:10:26 11:10:29

I thought that that's what you said. 11:10:30

A We looked at sequence alignments to assess what's essential and non-essential. Okay. And then followed up by looking at PyMOL. 11:10:33 11:10:39 11:10:47

Q Okay. Do -- have you used the term essential and non-essential in your work outside 11:10:52 11:10:54

of this case to refer to positions in an amino acid alignment? 11:10:57 11:11:00

A Over the course of 50 years, probably. 11:11:03

Q And when you use those terms in your work, what do they mean? 11:11:05 11:11:08

A When we say something is essential, we're saying that that thing needs to be there. It is essential for the property of interest. 11:11:47 11:11:50 11:11:55

When we say something is not essential, we're saying that particular thing is not essential for the property of interest. 11:12:00 11:12:02 11:12:06

Q And is that how you used those terms in your analysis in this matter? 11:12:14 11:12:17

MR. KUSHAN: Objection. Foundation. 11:12:23

A I -- I mean, in this matter, we're looking at the data to assess what -- which amino acids, at which positions, would appear to be essential for the property of interest, yeah. 11:12:34 11:12:40 11:12:50 11:12:54

Q What's the property of interest? 11:12:57

A In this case, the property of interest is the enzymatic activity of this protein. 11:12:59 11:13:05

Q Now, all of the sequences in the alignment 11:13:09

don't have enzymatic activity; right? 11:13:11

A But the sequence in this alignment fold into similar structures, and that structure is essential for the activity that we are considering. 11:13:19 11:13:23 11:13:28 11:13:32

Q How do you know that the sequences in the alignment all fold into similar structures? 11:13:34 11:13:36

MR. KUSHAN: Objection to form. 11:13:44

A It's something we discussed before. When you have a family of homologous proteins that share common ancestry and share considerable sequence identity, share evolutionary history, and in most cases share enzymatic activity, then one infers from that that they're going to share structure. 11:14:03 11:14:05 11:14:13 11:14:21 11:14:28 11:14:34 11:14:37

Q So you testified a few minutes ago -- and I'm reading your testimony. "By looking at the sequence comparisons and by also looking at the structure in three dimensions, one can become more educated about what the likelihood is, what the impact is likely to be from making a particular mutation." 11:14:55 11:14:58 11:15:01 11:15:03 11:15:06 11:15:09 11:15:11

Do you recall that testimony? 11:15:12

A Mm-hmm. 11:15:13

Q So my question is: What does the sequence comparison -- what information does the sequence comparison give you that helps you to become more educated about what the likelihood is, or the impact would be, from making a particular mutation? 11:15:14 11:15:18 11:15:20 11:15:23 11:15:25 11:15:27

A The sequence comparison, as I was suggesting before, is -- provides you with the results of the biggest possible experiment, and that is evolution on earth, which in principle has sampled many, many, many sequences. Okay. 11:15:56 11:16:06 11:16:13 11:16:16 11:16:21

And those that persist in evolution are those that are tolerated, and that informs us about which positions are suitable for changes and which positions where a change is not tolerated, therefore not seen in the current homologous proteins because it was not tolerated and weeded out by eons of evolution. 11:16:23 11:16:28 11:16:35 11:16:47 11:16:53 11:16:57 11:17:02

So that's how the sequence alignments informs us about all those things you asked. Yes. 11:17:08 11:17:10

Q Do you recall if you spoke with Dr. Park before or after you signed your declarations? 11:17:14 11:17:22

A As I recall, both. 11:17:27

Q Okay. 11:17:31

A Well, there were several declarations and there were several conversations. So yeah, both. 11:17:31 11:17:33

Q Okay. And did you rely on Dr. -- the information that Dr. Park provided to you in those discussions in reaching your opinions in these matters? 11:17:36 11:17:42 11:17:46 11:17:48

MR. KUSHAN: Objection to form. 11:17:51

A The discussions with Park are certainly a component of the science that I took in to reach my opinions. They're not the only component, but they're certainly a component. 11:17:57 11:18:02 11:18:05 11:18:09

Q Okay. And as you understand it, what was Dr. Park's analysis in this matter? What did he do? 11:18:11 11:18:19 11:18:25

A What was his pro -- project? 11:18:27

Q Yes. 11:18:29

A So Park is skilled in these kinds of computational approaches, and he -- what did he do 11:18:51 11:18:54

is he looked at what sequences, what homologous sequences were available in that time frame that we're discussing. 11:19:01 11:19:09 11:19:11

He found those sequences. He used the appropriate computational methods to align those sequences. Based on that alignment he assessed -- he assessed which parts are essential, which are non-essential. 11:19:14 11:19:23 11:19:26 11:19:43 11:19:51

He did that by looking at what substitutions occur and these many different positions at many different -- yeah, many different amino acids, many different positions. 11:19:54 11:19:58 11:20:01 11:20:06

He estimated what's essential and what's non-essential. He then, with that information -- oh, and then he looked at what positions are, you know, what amino acids occur at which positions in the zoo of different sequences. 11:20:09 11:20:11 11:20:17 11:20:19 11:20:24

And then he went beyond that and said, Okay. If I now go through the PH20 sequence and structure, what kinds of mutations would be tolerated? What would be the -- I'll say more generally: What would be the impact of making 11:20:27 11:20:31 11:20:41 11:20:44 11:20:47

various mutations? 11:20:49

And that's what he shared. 11:20:52

Q And how did he share the impact of making various mutations with you? In what format did he share that information? 11:20:58 11:21:03 11:21:07

A We discussed it on Zoom and I've looked at his declaration. 11:21:07 11:21:10

Q Okay. Do you know if he generated any other documents that provide the results of his analysis? 11:21:11 11:21:13 11:21:16

A Not that I have seen. I have seen his declaration. I wouldn't know if there are other documents or not. 11:21:17 11:21:24 11:21:26

Q So you said that Dr. Park, in his analysis, looked at, if he went through the PH20 sequence and structure, what kinds of mutations would be tolerated. 11:22:01 11:22:12 11:22:15 11:22:17

Do you know -- do you have a sense of how many mutations Dr. Park considered in his analysis? 11:22:19 11:22:22 11:22:24

A A lot. He started by doing un, you know, unbiased analysis. After he had aligned 11:22:25 11:22:37

everything and after he had put the structure up on the screen, he went through amino acid by amino acid, from start to finish, and said, Okay, what's happening here? What's happening here? What's allowed here? What's tolerated here? 11:22:40 11:22:42 11:22:46 11:22:48 11:22:51

And went through all of it. 11:22:55

Q So he went through and analyzed every single -- potential substitutions at every single position in PH20? 11:23:00 11:23:03 11:23:06

MR. KUSHAN: Objection. Foundation. 11:23:14

A By discussing what's essential and not essential, he looked at each position and said, Huh. What would happen, if it's non-essential/essential, if mutations were made here. 11:23:16 11:23:19 11:23:23 11:23:26 11:23:28

It's not to say he had looked at every possible of the 19 substitutions at every position, but he considered each position and looked at its environment and its -- its environment, both sequence and structurally, and considered the possibility of making mutations at those positions. 11:23:28 11:23:30 11:23:34 11:23:38 11:23:41 11:23:44 11:23:49

Q And how do you know that? 11:23:50

A It's in his declaration, and we had 11:23:53

discussions, but it's elaborated in his 11:23:57

declaration. 11:23:59

Q So in your discussions, did you go through 11:24:00

and look at every single position on PH20 and 11:24:03

discuss potential changes at every position? 11:24:06

A We discussed the global approach of 11:24:09

considering what's conserved, what's not 11:24:12

conserved, what's essential, what's not essential. 11:24:15

We did not do a PyMOL of every single side 11:24:18

chain at every -- yeah, every single side chain 11:24:22

substitution at every position. That would have 11:24:25

taken, you know, weeks. 11:24:28

But we discussed the approach, and then we 11:24:29

looked at representative examples. 11:24:31

Q And who selected the representative 11:24:36

examples? 11:24:39

A I saw what he showed me. I didn't say, 11:24:43

Oh, show me this, show me that. 11:24:46

You know, we went into the stuff that he 11:24:48

had. 11:24:53

Q So he just, to the best of your knowledge, randomly picked examples and showed them to you and you discussed them on PyMOL -- with PyMOL? 11:24:53 11:24:56 11:24:59

A I think, in the overall initial project, he went through all -- everything, right? Looked at it position by position by position and considered, you know, is this position evolutionarily conserved? Is this position, you know, whatever. 11:25:03 11:25:06 11:25:09 11:25:13 11:25:17 11:25:21

And then after having done that, he was asked to focus upon and show me certain examples. 11:25:21 11:25:25

Q Did you ask him to focus on and show you certain examples, or was that instruction from someone else? 11:25:42 11:25:46 11:25:48

A I did not say to him, Please show me Position 23, although I did ask him questions. If he had something on the screen, I'd say, What about this over there? What about this next to this other amino acid? 11:26:01 11:26:04 11:26:09 11:26:12 11:26:15

And he would then highlight it and we would talk about it. 11:26:18 11:26:20

Q Okay. So earlier this morning we had 11:26:21

talked a little bit about SWISS-MODEL and MODELLER. 11:26:38 11:26:41

Do you recall that? 11:26:42

A We talked about that, yeah. 11:26:42

Q SWISS-MODEL and MODELLER were both available in 2011; right? 11:26:45 11:26:48

A Right. 11:26:50

Q And PyMOL was available in 2011? 11:26:53

A Right. 11:26:56

Q And Chimera also was available in 20 -- 11:26:56

A I'm sorry. I didn't hear. 11:26:59

Q Chimera. 11:27:00

A I think so, yeah. 11:27:01

Q Okay. And Chimera was a -- was that a structure visualization program? 11:27:02 11:27:05

A I haven't used Chimera, so I'm not going to comment on that. 11:27:07 11:27:11

Q Okay. In 2011, the crystal structure for bee venom hyaluronidase -- or strike that. 11:27:12 11:27:26

As of 2011, the crystal structure for bee venom hyaluronidase and HYAL1, the crystal structures for both of those proteins had been 11:27:32 11:27:36 11:27:40

solved; is that right? 11:27:42

A Right. Prior to '11, yes. 11:27:43

Q Okay. So as of 2011, the secondary 11:27:46

structures in bee venom hyaluronidase and HYAL1 11:27:48

were known; is that right? 11:27:54

A Correct. 11:27:57

Q And as of 2011, the sites of conserved 11:28:03

amino acids in PH20 and HYAL1 were known; right? 11:28:09

MR. KUSHAN: Objection. Form. Also 11:28:16

objection as to foundation. 11:28:17

A Yeah. On 40 -- page 43 in the declaration 11:28:22

explicitly shows how those sequences are related 11:28:26

and also alludes to the secondary structure that 11:28:31

you were asking about a moment ago in page 41, 42, 11:28:34

and 43 from the paper by Chao, et al. 11:28:40

Q So the alignment from Chao, et al., you 11:28:59

have reproduced that alignment on page 43 of your 11:29:06

declaration; is that right? 11:29:09

A That's right. That's just a screenshot -- 11:29:09

Q Okay.

A -- or -- yeah, okay. Yeah. 11:29:13

Q That -- the Chao alignment that's on page 11:29:14

43 in your declaration identifies the secondary structures and sites of conserved amino acid in both PH20 and HYAL1; correct? 11:29:20 11:29:24 11:29:27

A And the other sequences in there. 11:29:29

Q So the alignment from Chao on page 43 of your declaration identifies the secondary structures and sites of conserved amino acids in HYAL1, HYAL2, HYAL3, HYAL4, and PH20; is that right? 11:29:35 11:29:40 11:29:42 11:29:46 11:29:51

A That's what the figure shows. 11:29:51

Q So the secondary structures in HYAL1, HYAL2, HYAL3, HYAL4, and PH20 were all known as of 2011? 11:29:53 11:29:57 11:30:03

A As you pointed out, the crystal structures of HYAL1 and bee venom, which is not shown on this picture, those crystal structures were known. And as we've discussed numerous times, one then models other sequences based on those structures. 11:30:03 11:30:06 11:30:11 11:30:14 11:30:21

What's shown in this figure are the five sequences, the conserved amino acids, the cysteines and such things, the active site amino acids. 11:30:28 11:30:33 11:30:39

And then the squiggly lines above the sequence and the arrows above the sequence refer to the secondary structure in the Chao paper, which is the HYAL1 protein. 11:30:44 11:30:48 11:30:52 11:30:56

Q You state in your declaration that the Chao sequence alignment identified secondary structures in sites of conserved amino acids in both PH20 and HYAL1; correct? 11:31:04 11:31:07 11:31:10 11:31:12

A Where are you reading? 11:31:14

Q Paragraph 86. Second paragraph in paragraph 86 -- 11:31:16 11:31:32

A No. I'm with you. I'm just reading it. 11:31:34

Yes. 11:31:36

Q And that statement is accurate? 11:31:36

A The statement -- the sentence that begins with "for example"? 11:31:39 11:31:42

Q Yes. 11:31:42

A Okay. I'll read it again. 11:31:43

"Its sequence alignment identified secondary structures in" -- 11:31:45 11:31:46

THE REPORTER: Slow down, please.

A Sorry.

"For example, its sequence alignment identified secondary structures and sites of conserved amino acids in both PH20 and HYAL1." 11:31:51 11:31:53 11:31:55

Yeah, I'm satisfied with that sentence. 11:32:02

Q Okay. So, again, just to clarify, the Chao sequence alignment identified secondary structures and sites of conserved amino acids in both PH20 and HYAL1; correct? 11:32:04 11:32:07 11:32:10 11:32:13

A Right. But to be clear, the HYAL1 is from the crystal structure; the PH20 is based on homology because the structure of PH20 was not known at that point. 11:32:15 11:32:19 11:32:25 11:32:30

So the word "identified" here is identified from the crystal structure in their protein and identified -- or, you know, aligned for the PH20. 11:32:32 11:32:35 11:32:37 11:32:44

Q Based on -- and aligned for PH20 based on the homology between PH20 and HYAL1? 11:32:46 11:32:49

A That's based on sequence similarity, which, in turn, is based on homology, which is shown in that figure. 11:32:53 11:32:56 11:32:58

Q Okay. And the HYAL1 crystal structure in 11:33:00

Chao provided a template that one could use to create a PH20 homology model; is that right? 11:33:28 11:33:31

A Correct. 11:33:34

Q So a POSA in 2011 seeking to evaluate potential substitutions in PH20 would have generated a homology model using HYAL1 as the template; is that right? 11:33:35 11:33:42 11:33:46 11:33:49

A Correct. 11:33:53

Q So in 2011 a POSA seeking to evaluate potential substitutions in PH20 likely to be tolerated would have generated a homology model; is that right? 11:34:12 11:34:16 11:34:20 11:34:29

A Yes. Among other things, yes. 11:34:29

Q And the POSA would have used that homology model to evaluate the particular substitutions? 11:34:30 11:34:33

A Would have used the homology model and also used other input. 11:34:38 11:34:40

Q And what other input? 11:34:41

A As we said before, the sequence alignment of many sequences, not just those in the figure, and just expertise and experience in the field of protein structure and engineering and mutagenesis. 11:34:43 11:34:45 11:34:51 11:34:56

Q Also can you please turn to paragraph 88. 11:35:26

In paragraph 88, you say, "...a number" -- 11:35:44

"...before 2011, a number of residues within the 11:35:47

region of the catalytic site in PH20 or HYAL1 had 11:35:50

been experimentally shown to be necessary or 11:35:54

important to the catalytic activity of 11:35:57

hyaluronidases"; is that right? 11:36:00

A Okay. 11:36:01

Q And then you refer to three papers: 11:36:04

Arming, Zhang, and Chao; right? 11:36:09

A Okay. Let's read that again. 11:36:15

Okay. 11:36:30

Q So you agree that in paragraph 88 you 11:36:30

refer to Arming, Zhang, and Chao? 11:36:33

A Those three papers are mentioned in that 11:36:38

paragraph, yeah. 11:36:41

Q Okay. We've probably been going for 11:36:43

another hour. 11:36:46

Do you want to take a break? 11:36:46

A Sure. 11:36:48

Q All right. 11:36:49

THE VIDEOGRAPHER: We are going off the 11:36:49

record. The time is 11:36 a.m. 11:36:50

(A recess was taken.) 12:04:10

THE VIDEOGRAPHER: We are back on the record. The time is 12:04 p.m. 12:04:10 12:04:15

BY MS. MARTIN: 12:04:18

Q Welcome back, Dr. Hecht. 12:04:20

A Hey. 12:04:23

Q Doctor, did you speak with anyone during the break regarding the substance of your testimony? 12:04:23 12:04:25 12:04:27

A No. 12:04:27

Q So can you please turn in your declaration to paragraph 88? 12:04:27 12:04:29

A Okay. 12:04:35

Q And so the first sentence in paragraph 88, you say that, "...before 2011, a number of residues within the region of the catalytic site on -- in PH20 or HYAL1 had been experimentally shown to be necessary or important to the catalytic activity of hyaluronidases"; right? 12:04:38 12:04:44 12:04:47 12:04:51 12:04:54 12:04:57

A Right. I see that. 12:05:01

Q So what do you mean by the "region of the 12:05:02

catalytic site"? 12:05:04

A So, in enzymes -- so proteins are large 12:05:20

molecules, macromolecules, that are folded in 12:05:36

particular structures. 12:05:40

And if the protein is an enzyme, it will 12:05:42

typically have a -- it will have a site where the 12:05:46

enzyme performs a catalysis. And that's what's 12:05:50

being considered here necessary important for 12:05:54

the -- so region of the catalytic site is what 12:05:58

that's referring to. 12:06:02

And so if the catalytic site is the part 12:06:03

of the protein, the site where the catalysis 12:06:07

happens, that's what we're talking about there. 12:06:11

Q So the catalytic site is the area on the 12:06:14

protein where the catalysis happens? 12:06:18

MR. KUSHAN: Objection. Form. 12:06:24

A The catalytic site -- in general 12:06:28

textbooks -- sometimes also called the active 12:06:31

site, in general textbooks refers to that -- 12:06:35

wouldn't say area -- but volume of the protein 12:06:40

where the essential chemistry happens. 12:06:43

But that's not to say that everything else 12:06:46

doesn't matter, but that's where the catalytic atoms typically reside. 12:06:50 12:06:55

Q And so what -- what's the region of the catalytic site? 12:06:57 12:07:00

A Neighborhood around there. And, again, this is not a black-and-white definition. 12:07:02 12:07:06

But it's -- you have a catalytic site, let's say, and at the narrowest definition would be the those atoms actually performing the catalytic chemistry. 12:07:11 12:07:14 12:07:18 12:07:21

But, surely, the region around there is going to be important as well because it holds the atoms in the proper position. So the region is their neighborhood. 12:07:25 12:07:28 12:07:30 12:07:34

Q So the residues that you identify in paragraph 88, are those residues all part of the -- the region or the neighborhood of the catalytic site on PH20 or HYAL1? 12:07:45 12:07:48 12:07:56 12:07:57

A I'd have to go back and look at the Arming paper and the Zhang paper and the Chao paper to answer that precisely. But, you know, I'll highlight that on paragraph 83 -- well, actually, 12:08:05 12:08:08 12:08:15 12:08:19

it's a picture above paragraph 83, and the picture above paragraph 82, but that whole part of the declaration, pages 41 and pages 42, after Chao, et al., solved that structure, published it, okay, that's -- well, you can see that on the top of page 41. 12:08:24 12:08:32 12:08:37 12:08:44 12:08:47 12:08:50

So by comparing the HYAL1 structure that they had solved with the bee venom structure that had been reported previously, these two similar homologous proteins had structural similarity as shown in the figure on page 41. 12:08:52 12:08:58 12:09:01 12:09:06 12:09:10

And then with those structures in hand, paragraph 82 says they compared the catalytic sites and found that they too show extensive structural similarity. And that's shown in the figure on page 41 and 42. 12:09:12 12:09:15 12:09:18 12:09:22 12:09:26

So those are catalytic sites. 12:09:32

Q And in the -- in Chao's alignment, which is on page 43, the three key catalytic residues are colored in red; is that right? 12:09:37 12:09:43 12:09:52

A Yeah. The legend says three key catalytic residues are colored in red. But that does not 12:09:55 12:09:58

mean that nothing else matters. Right? 12:10:04

Q But is it fair to conclude from that 12:10:07

disclosure that the residues that are colored in 12:10:11

red are key to the catalysis reaction? 12:10:13

A Well, that's the wording. It says "Key 12:10:21

catalytic residue," so that's their wording. So 12:10:24

you asked if they're key. That's what they say. 12:10:28

Q Do you think that the EGF domain is part 12:10:32

of the region of the catalytic site? 12:10:37

A So -- 12:10:45

MR. KUSHAN: Sorry. Objection to form. 12:10:46

A So the EGF region is shown or diagram -- 12:10:51

well, shown and diagrammed on pages 44 and 45. 12:10:56

Maybe elsewhere also, but we can stick with those. 12:11:05

And your question is -- is whether the EGF region 12:11:09

is -- 12:11:15

Q Whether the EGF-like domain is in the 12:11:17

region of the active site. 12:11:20

A It's not directly in the active site, 12:11:22

okay. But one should not conclude for that, that 12:11:27

it's irrelevant for activity. 12:11:32

Q Well, that's not the question. The 12:11:35

question is: Is it in the region of the active site? 12:11:38 12:11:41

A Region is a nebulous term. How many angstroms do you mean by region? I mean it's -- it's -- I think we can see in page 40 -- no, yeah, page 44, Figure 4B, taken from the Chao, et al. paper, one can see -- well, actually I like Figure 2A, it's a little easier to see there, Figure 2A has an arrow pointing to the active site. And by the definitions we discussed before, it's typical for active site to refer to the actual amino acid side chains that perform the catalysis. 12:11:42 12:11:47 12:11:50 12:12:02 12:12:10 12:12:15 12:12:17 12:12:20 12:12:24 12:12:29

The EGF-like domain is in yellow on the bottom of Figure 2A. And so is it in the region? It's not -- it depends if you define region as 5 angstroms or 10 angstroms or whatever. It's part of the same protein. It's not contributing catalytic atoms to direct mechanism, but it has been shown that deleting it will be deleterious for activity. 12:12:33 12:12:36 12:12:39 12:12:44 12:12:47 12:12:50 12:12:54 12:12:58

Q Okay. So just to be clear, "region" is the nebulous word that you used in paragraph 88 in 12:13:00 12:13:05

your declaration. 12:13:09

And I'm just trying to understand that 12:13:09

when you -- in the first sentence, in paragraph 12:13:11

88, when you refer to the region of the catalytic 12:13:14

site, if you intended to encompass, within that 12:13:16

description, the EGF domain which you have at the 12:13:20

very end of the second sentence in paragraph 88? 12:13:23

A I think paragraph 88 talks about -- in the 12:13:49

first sentence, I would interpret that to be 12:13:53

region as being close to the catalytic site. I 12:13:55

don't want to give a cutoff in the number of 12:13:59

angstroms, but it's close. 12:14:01

And the later part of that paragraph 12:14:03

discusses the Hyal-EGF domain, which is further 12:14:07

away. I think the point of that paragraph is 12:14:13

residues and mutations had been observed that 12:14:16

impact activity in a number of places. 12:14:21

Q Okay. So you weren't intending to suggest 12:14:26

that the residues that you were listing were all 12:14:28

in the region of the catalytic site? 12:14:30

MR. KUSHAN: I'm sorry. Objection. 12:14:34

Foundation. 12:14:36

A I mean, again, I'm -- if you were to ask a question about this on a final exam in a course, you would have to define "region." You would say, you know, is it two angstroms or 10 angstroms or 20 angstroms? 12:14:37 12:14:45 12:14:48 12:14:51 12:14:55

So -- but I think the point is that residues that are close to the catalytic site or in the catalytic site had been shown by mutation to be important. 12:14:56 12:14:58 12:15:02 12:15:08

And also, later in the paragraph, mutations -- later in the paragraph and elsewhere in the document we describe mutations that are elsewhere in the protein. 12:15:09 12:15:16 12:15:21 12:15:24

The point is that mutations can disable activity if they're in the actual catalytic atoms, but it's also possible to disable activity with mutations that are not in the catalytic atoms. 12:15:26 12:15:29 12:15:34 12:15:38

Q So Arming, the Arming paper, that was a mutagenesis study that involved PH20; right? 12:15:51 12:15:55

A I would want to see that paper before I make any serious comments about it because there's a sentence here. But, you know, I want to look at 12:16:02 12:16:04 12:16:07

that paper before we actually talked about the details in it. 12:16:12 12:16:16

Q Did you read the Arming paper when you were -- 12:16:17 12:16:19

A Oh, of course I looked at that paper. 12:16:20

Q So I think -- 12:16:22

A That was a while ago. 12:16:23

Q Let's look at paragraph 79. See if that helps. 12:16:25 12:16:27

A I'm sorry.

Q Actually, no. Paragraph 78. 12:16:34

A Okay. 12:16:59

Q So does paragraph 78 refresh your recollection that Arming involved mutagenesis of PH20? 12:16:59 12:17:02 12:17:05

A Yeah. Arming made mutations in PH20. That's what -- yeah. 12:17:06 12:17:10

Q Okay. So then turning back to paragraph 88. In paragraph 88, you say that Arming, which we just established involved PH20, identified positions D111, E113, R176, E249 and R252; correct? 12:17:11 12:17:21 12:17:27 12:17:30 12:17:40

A Okay. 12:17:40

Q And the mutagenesis study in Arming showed 12:17:44

that those -- that those residues at those 12:17:47

positions were necessary or important to catalytic 12:17:51

activity; is that right? 12:17:56

A They were important for activity -- 12:17:57

MR. KUSHAN: Sorry. Objection to 12:18:00

foundation. 12:18:02

Q So in 2011 a POSA would have expected that 12:18:03

changing all five of those amino acids -- D111, 12:18:14

E113, R176, E249 and R252 -- that would have 12:18:21

resulted in an inactive PH20. 12:18:26

Is that a fair assumption? 12:18:29

MR. KUSHAN: Objection. Foundation. 12:18:31

A I don't think it's a fair assumption to 12:18:34

say it would be inactive in total. I think what 12:18:36

it said here is that they are important, and I 12:18:41

expect those mutations would have an impact. I 12:18:44

don't recall whether they were knocked out 12:18:49

completely. 12:18:51

Q Oh, so you have to look at Arming to 12:18:51

see -- 12:18:53

A Uh-huh. 12:18:54

Q -- if they were? 12:18:54

A Yes. 12:18:58

Q Okay. Well, if you look in paragraph 78, 12:18:58

paragraph 78 says that three of the mutants for 12:19:18

113, 249 and 252 were devoid of enzymatic 12:19:31

activity, while two other mutants at 111 and 176 12:19:38

had residual activities in the range of one to a 12:19:43

few percent of wild-type. 12:19:47

A Okay. Let me -- okay. Okay. I'm seeing 12:19:50

what you're reading. 12:20:44

Q So do you know which specific residue is 12:20:47

the proton donor for the hydrolysis reaction that 12:21:03

PH20 catalyzes? 12:21:08

A I don't remember that off the top of my 12:21:10

head. 12:21:12

Q Did you know it when you were doing your 12:21:12

analysis in this case? 12:21:14

A I read that paper, yeah. 12:21:15

Q So would you agree that a mutation, if 12:21:52

Arming teaches that a particular mutant was devoid 12:21:55

of enzymatic activity, that that mutant was 12:21:58

inactive? 12:22:01

A You said if it's devoid of activity, that means it's inactive? 12:22:04 12:22:06

Q Yes. 12:22:08

A Yeah. 12:22:09

Q Okay. And if a particular mutant had residual activity in the range of one to a few percent of activity, would you think -- would you consider that PH20 mutant to be inactive? 12:22:09 12:22:13 12:22:15 12:22:17

MR. KUSHAN: Objection. Foundation. 12:22:21

A You're saying 1 to 2 percent, would one consider that active or not active? 12:22:28 12:22:32

Q Yes. 12:22:34

A So in the common disclosure, they make a different dividing line than what you just said. They typically divide it -- they say inactive is below 20 percent. 12:22:35 12:22:40 12:22:43 12:22:47

So that's their choice of where they're drawing the line. There are -- there are other situations where having a little bit of activity, 1 or 2 percent, would be considered sufficient for a particular purpose. 12:22:49 12:22:53 12:23:00 12:23:05 12:23:08

So it's where you choose to draw the line between active and inactive. But 1 or 2 percent -- yeah, I'll just leave that, yeah. It's where you choose to draw the line of what you consider inactive. Is it 10 percent, 20 percent, 1 percent, 2 percent? 12:23:10 12:23:12 12:23:16 12:23:19 12:23:22 12:23:28

Q So you said that you were a POSA as of 2011; right? 12:23:29 12:23:31

A That I was what? 12:23:32

Q A POSA as of 2011? 12:23:33

A Yeah, I did. 12:23:35

Q So as a POSA, as of 2011, would you consider a PH20 that has 1 to a few percent of activity to be active or inactive? 12:23:35 12:23:38 12:23:42

A 1 to 2 percent? 12:23:44

Q Yes. 12:23:46

MR. KUSHAN: Objection. Foundation. 12:23:47

A Having considered as having 1 or 2 percent activity, I don't think this is a -- this is not a binary, yes/no issue. It's a quantitative issue. 12:23:48 12:23:52 12:23:54

Q Okay. And when -- when Arming says that the mutants at the 113, 249, and 252 positions 12:24:05 12:24:10

were devoid of enzymatic activity -- 12:24:16

A Where are you reading? I'm sorry, which 12:24:19

paragraph? 12:24:20

Q 78. 12:24:20

A Yes. Okay, devoid of activity. 12:24:25

Q Would you understand that to mean zero 12:24:26

activity? 12:24:29

A I would understand that to mean that 12:24:30

within the range of what their laboratory 12:24:33

experiment is able to detect, they were not able 12:24:36

to detect enzyme activity. 12:24:40

But different experiments have different 12:24:43

sensitivities. So, you know, as an experimental 12:24:45

scientist, one has to say that if it's reported as 12:24:48

devoid of activity, that's understood to mean 12:24:52

devoid of measurable activity in the assay as done 12:24:55

in that study. 12:25:00

Q So as a POSA reading the Arming paper in 12:25:12

2011, would you have concluded that the three 12:25:15

mutants that Arming teaches were devoid of 12:25:18

enzymatic activity, that those mutants were 12:25:20

inactive? 12:25:25

MR. KUSHAN: Objection. Form. Also objection as to foundation. 12:25:26 12:25:28

A I would conclude what I just said, that they were devoid of measurable activity in the assay and the sensitivity of the assay that those scientists were able to do. 12:25:34 12:25:37 12:25:41 12:25:45

This is something I actually have expertise in because we make novel proteins. And if we're looking for activity, the levels of activity we see are often very, very low. And so sometimes for us, in a novel protein, that level of activity, we would jump up and down and say, Oh, it's active, whereas that level of activity for a natural protein would be, Oh, that's inactive. 12:25:49 12:25:50 12:25:54 12:25:57 12:26:02 12:26:06 12:26:10 12:26:14 12:26:17

So it's -- context matters. It's not absolute yes or no. There's a continuum. 12:26:18 12:26:22

Q So the amount of activity -- the amount of activity that's useful really depends on the context for which you intend to use the protein? 12:26:25 12:26:29 12:26:32

A The amount of activity you measure depends on your measurement and the -- whether you define 12:26:36 12:26:38

that as a hit or a miss, as active or inactive, depends on what you're using it for, what your sensitivity of your measurement is, the accuracy of your measurement is, what the reproducibility is. 12:26:42 12:26:47 12:26:51 12:26:54 12:26:58

But I would say that it's a continuous scale; that people sometimes put a bar -- as they did in the common disclosure, they put a bar at 20 percent or 40 percent or whatever. 12:27:01 12:27:03 12:27:05 12:27:08

But the reality of the world is it's a continuum. You know, what can you measure? How sensitive is your assay? 12:27:10 12:27:13 12:27:16

Q Would you consider ELISA to be a sensitive assay? 12:27:17 12:27:21

A ELISAs are sensitive -- I mean, it depends what you're using them for. It's -- yes, it's a sensitive assay, but how sensitive relative to what for what activity? 12:27:28 12:27:32 12:27:34 12:27:37

Q If you're trying to identify a very, very low level of activity, like you were talking about in your lab, would you use an ELISA to do that? 12:27:41 12:27:45 12:27:49

MR. KUSHAN: Objection. Foundation. 12:27:56

A It's -- it's a -- it's just like a -- too general a question. It's -- it depends on what you're -- what the -- what you're looking for. It depends how -- it depends what your enzyme is. It depends what your -- yeah, it depends on a lot. 12:28:02 12:28:05 12:28:11 12:28:14 12:28:17

It's more -- I would say it's more sensitive than the turbidity assay we looked at earlier. 12:28:20 12:28:21 12:28:25

Q Okay. So you -- you agree that there is a residue on PH20 that is the proton donor in the hydrolysis reaction. 12:28:26 12:29:09 12:29:14

You just don't remember which one it is; is that right? 12:29:16 12:29:18

MR. KUSHAN: Objection. Foundation. 12:29:18

A I would like to have that paper in front of me to look at the catalytic mechanism. 12:29:24 12:29:26

I mean, I remember the catalytic mechanism. You know, there was substrate-assisted catalysis, which is kind of cool. I remember that part. But I don't remember the details of which amino acid did what. 12:29:30 12:29:31 12:29:34 12:29:36 12:29:38

Q Okay. All right. So the results, the 12:29:39

mutagenesis results in Arming that we talked about in paragraph 78, a POSA could have looked at those positions in the homology model to evaluate the -- their position in the structure; is that right? 12:29:58 12:30:01 12:30:13 12:30:23

MR. KUSHAN: Objection. Foundation. 12:30:27

A One could have looked at those positions in the model to look at where they are in the structure. One could look at those positions for the wild-type sequence and say, Here's where they are in the structure. One could point at them. 12:30:34 12:30:41 12:30:46 12:30:49 12:30:52

Q And one could also look at the mutagenesis results achieved for HYAL1 on the HYAL1 structure, right, to identify where those -- where those residues appear in the structure? 12:31:03 12:31:07 12:31:13 12:31:14

A Well, you say one could look at the mutagenesis. I would be more precise and say one could look at the amino acid at the position in the protein where the mutagenesis was performed. It doesn't look at mutagenesis per se. 12:31:17 12:31:19 12:31:24 12:31:27 12:31:30

One looks at the atoms in the structure, but one could look at position 27 or 132 or whatever in the structure. 12:31:33 12:31:36 12:31:40

Q And by doing that, one could identify potential explanations for the functional results that were seen; is that right? 12:31:47 12:31:54 12:31:57

MR. KUSHAN: Objection. Foundation. 12:31:59

A One could use the structural analysis as input to understand -- this is always the case. One could look at the structure on the computer and use that as input to interpret the observed experimental result in the laboratory. 12:32:08 12:32:15 12:32:19 12:32:22 12:32:28

Q And how would you look at the structure on the computer and use that -- how would you use that as input to interpret the observed experimental result in the laboratory? 12:32:41 12:32:43 12:32:45 12:32:48

A I would look at the environment of that position, you know, position number 322, whatever. 12:32:55 12:32:58

I would look at the chemical environment of that position with respect to its interactions with other amino acids, with respect to its interactions with, you know, water, solvent, or buried. 12:33:04 12:33:06 12:33:12 12:33:16 12:33:20

I would look at its interactions with respect to the putative active site. I would look 12:33:21 12:33:27

at its position -- at its position with respect 12:33:33
to, as shown on page 41, with respect to 12:33:35
the hyaluronic acid, you know, being docked in 12:33:44
there. 12:33:47
I would look at its position with respect 12:33:47
to the -- I think I already said this, but I'll 12:33:50
say it, again -- the putative active site in the 12:33:52
picture on page 42. 12:33:56
I would look at its position with respect 12:33:58
to the various interactions that are listed 12:34:02
somewhere earlier on in the -- this document about 12:34:05
the types of interactions that are formed -- 12:34:08
hydrogen bonds, electrostatic -- here we go, on 12:34:12
page 26 -- I would look at its position with 12:34:15
respect to -- page 26. 12:34:19
Q Page -- sorry, 20-what? 12:34:20
A Page 26, sorry. 12:34:21
Q 26. 12:34:23
A I would look at its position on the 12:34:24
structure with respect to its neighbors. And you 12:34:27
see A is hydrogen bonds; B is ionic interactions; 12:34:30
C is Van der Waals forces; D is hydrophobic 12:34:34

interactions; onward, pi-pi interactions; 12:34:38
cation-pi interactions. 12:34:42
So if one were interested in a particular 12:34:44
mutation, I would look at that location, position, 12:34:47
whatever number, with all these issues in mind: 12:34:50
its solvent exposure; its proximity to other amino 12:34:56
acids; that list of interactions I just read off; 12:35:02
its -- its atoms, whether or not those atoms 12:35:06
perform the catalysis or are they near the 12:35:11
catalytic site, or do they bind to the -- at a 12:35:15
hyaluronic acid? All those things. 12:35:20
I think that's what you were asking, 12:35:22
but -- yeah. 12:35:24
Q So how would that analysis assist you 12:35:24
in -- to -- how would that analysis assist you to 12:35:26
interpret the observed, experimental result in the 12:35:34
laboratory? 12:35:36
A I think I already said that; that if the 12:35:45
wild-type amino acid that's been deleted, removed, 12:35:53
replaced, if the structure shows that wild-type 12:35:58
amino acid has atoms that are involved in 12:36:03
catalysis, I would look at that and say, Oh, 12:36:08

making mutations in those atoms would impact the actual catalytic chemistry. 12:36:12 12:36:16

Conversely, if it were elsewhere and it was in a buried position, very well packed and making lots of interactions, I would infer that its impact is based on those structural features separate from the actual catalytic chemistry. 12:36:21 12:36:25 12:36:28 12:36:31 12:36:36

And, you know, I could go on and on about that, but that's how you do it. 12:36:38 12:36:41

Q Okay. So if you have a functional result that shows you that a particular substitution has a deleterious impact on function and you can look at the structure -- you can look at the position of that residue in the structure, and you can try to understand what it is about that residue in that position that potentially resulted in the loss of function that you saw in the lab? 12:36:52 12:36:54 12:37:00 12:37:04 12:37:06 12:37:08 12:37:11 12:37:14

A As you said -- 12:37:16

MR. KUSHAN: Sorry. 12:37:17

A -- "try to understand."

MR. KUSHAN: Sorry. 12:37:18

Objection. Form. Also objection as to 12:37:19

foundation. 12:37:22

Q Is that right? 12:37:22

A You would try to understand. I'm not saying you would absolutely know. You would use that information to try to understand. 12:37:23 12:37:26 12:37:28

Q But that information, the structural information, gives you potential insight into an explanation for the result that you saw? 12:37:29 12:37:32 12:37:37

MR. KUSHAN: Objection. Foundation. Also objection as to form. 12:37:40 12:37:42

A It gives you -- has the potential to give you insight. Just different from saying it gives you a perfect answer. 12:37:44 12:37:47 12:37:51

Q Have you ever gotten a perfect answer in your research? 12:38:08 12:38:10

A Ha. Of course not. 12:38:12

Q Do you expect to get a perfect answer in your research? 12:38:14 12:38:18

A Do you want to talk philosophy or theology or science? I mean, this is -- you know, I don't think perfection is an achievable thing in this world. 12:38:22 12:38:25 12:38:36 12:38:39

Q Okay. 12:38:40

A You know, as I said before, things are on 12:38:48

a continuum. It's not binary, yes, no, perfect, 12:38:52

flawed. Things are on a continuum. 12:38:58

Q So as we talked earlier this morning about 12:39:01

non-essential and essential residues; right? 12:39:04

A We did. 12:39:09

Q So just to clarify some terminology. If 12:39:13

you're talking about a non-essential residue, is 12:39:17

it fair to say that the rest of the residues -- 12:39:21

A The what, sorry? 12:39:23

Q The rest of the residues, the ones that 12:39:24

are not non-essential, would those be termed 12:39:26

essential residues? 12:39:29

MR. KUSHAN: Objection. Foundation. 12:39:33

A I'm in the section of the declaration that 12:39:45

starts on page 102 goes into pretty long 12:39:51

conversation about essential versus non-essential 12:39:55

regions. 12:40:01

But as we're discussing before -- and it's 12:40:04

the real world. By and large, I think it's pretty 12:40:08

solid to talk about essential versus non-essential 12:40:15

regions, but, you know, it's not perfect versus dismal. There are going to be some amino acids that are -- it's a little mushy. You can get away with things. 12:40:17 12:40:22 12:40:25 12:40:28

But by and large, these are two distinct regions that you can look at, based on all the things written here. 12:40:29 12:40:32 12:40:35

Q Okay. So maybe let's turn to paragraph 208. And so in the second sentence in 208, you say, "The skilled artisan would have understood these non-essential regions to be the regions between the conserved residues within PH20, which are residues that are generally considered essential to the structure and function of proteins like hyaluronidase enzymes." 12:40:47 12:40:51 12:41:08 12:41:10 12:41:13 12:41:17 12:41:20 12:41:23

Is that right? 12:41:25

A Okay. 12:41:26

Q So is it fair to say that the conserved residues in Dr. Park's sequence alignment, those conserved residues, the one that are not termed non-essential, you would refer to those as essential residues? 12:41:27 12:41:31 12:41:36 12:41:40 12:41:43

A Dr. Park's analysis, and our thinking about this is that, that one can look at the protein and sequence and structure, and one can infer from that that some positions are considered essential. Others are considered non-essential. Yeah. 12:41:45 12:41:52 12:42:02 12:42:06 12:42:12 12:42:18

Q And residues that are considered essential are essential to the structure and function of the protein; is that right? 12:42:20 12:42:25 12:42:27

A To the structure and function. Let's realize function is a broad term, but yeah. 12:42:35 12:42:39

Q What do you mean when you say "function is a broad term"? 12:42:42 12:42:44

A What I mean is that, if at the end of the day your experiment is reporting on the measured enzyme activity, that's the function you're focusing your mind on, but you may get a negative result because the protein failed to express, failed to fold, failed to secrete. 12:42:46 12:42:50 12:42:54 12:42:58 12:43:01 12:43:04

And so all those are part of the steps that ultimately lead to the function that you were measuring in the laboratory. 12:43:08 12:43:11 12:43:14

Q Okay. Well, if it's a homology model and you're talking about essential residues in the homology model, you're talking about residues that have not mutated, right, over time, so you're not talking about function in the laboratory or function measured in a test in a laboratory. You're talking about the effect of evolution over time? 12:43:29 12:43:40 12:43:42 12:43:45 12:43:50 12:43:54 12:43:56 12:43:59

MR. KUSHAN: Objection to form. 12:44:02

A Right. I mean, the person skilled in the art in that situation is inferring essential versus non-essential. 12:44:11 12:44:13 12:44:18

If you're trying to focus on the evolutionary point, person of skill in the art is inferring from evolution, the grand experiment, is inferring that if something varies all over the place over the course of essential, over the course of evolution, then that amino acid at that position is not essential, as shown by the results of natural selection. It was not essential. It was changed. 12:44:19 12:44:21 12:44:25 12:44:33 12:44:38 12:44:41 12:44:46 12:44:51 12:44:55

Q All right. So let's turn to paragraph 15. 12:45:18

A Sorry. Paragraph -- 12:45:23
Q 15? 12:45:24
A The beginning, okay. 12:45:25
Q So full-length human PH20 contains 509 amino acids; is that right? 12:45:38
A That's what it says, yep. 12:45:45
Q And the first 35 amino acids of that sequence are a signal sequence that is truncated; is that right? 12:45:46
A What was the last word you said? 12:45:59
Q A signal sequence that is truncated? 12:46:08
A No, not truncated, no. Truncated usually refers to something else. 12:46:08
Q The signal sequence that is removed? 12:46:09
A Okay. 12:46:12
Q Okay. So the first 35 amino acids in the 509 amino acid sequence of PH20 refers to a signal sequence that is removed? 12:46:28
A Right. That is removed in -- in biology, yeah. 12:46:30
Q Okay. And so in your declaration, when you use the term mature PH20, you're referring to 12:46:33 12:46:39 12:46:43 12:46:45 12:46:49 12:46:49 12:46:52

PH20 without the signal sequence? 12:46:56

A Correct, after the signal sequence has been removed. 12:47:00 12:47:03

Q So that's Positions 36 through 509? 12:47:04

A I'm looking at the numbers. Yeah. 12:47:08

Q Okay. And if you, as you say in subpart (b) of paragraph 15, if you were to start the numbering of your mature PH20 sequence at 1, then that would end at 474; right? 12:47:13 12:47:22 12:47:26 12:47:30

A That's what it says, yeah. 12:47:51

Q So let's turn to paragraph 89. 12:48:12

MR. KUSHAN: Can whoever joined just announce themselves? 12:48:21 12:48:24

MR. MACK: Yes. This is Josh Mack, in-house for Halozyme. 12:48:27 12:48:30

MR. KUSHAN: Thank you. 12:48:35

A Paragraph 89? 12:48:36

Q Yes. So paragraph 89, you refer to the '429 patent; is that right? 12:48:39 12:48:51

A Right. That's what it says. 12:48:53

Q And the '429 patent issued in 2010; correct? 12:48:56 12:49:04

A That's what it says, yep. 12:49:04

Q And the '429 patent taught that soluble 12:49:08

active PH20 could be obtained by truncating the 12:49:11

sequence just before the start of the GPI anchor 12:49:14

sequence at position 483? 12:49:17

A That's what it says. 12:49:20

Q Actually, let's see. So let's mark the 12:49:41

patents. 12:49:59

Can you get the -- all right. Let's go to 12:50:02

paragraph 114 in your declaration. Okay. 12:50:55

So you reviewed the claims of the '600 12:51:19

patent in your analysis; is that right? 12:51:22

A I indeed looked at them, yes. 12:51:25

Q Okay. Before your analysis in this matter 12:51:27

had you ever read a patent claim? 12:51:33

A As you mentioned earlier, some people in 12:51:41

my lab, we filed -- we -- Princeton's intellectual 12:51:44

property office filed something for us a couple of 12:51:51

years ago, so I would have looked at that. 12:51:53

When I was involved in that case 30 years 12:51:55

ago with Amgen, I would have looked at it then. 12:51:58

It's conceivable I've seen claims other times but 12:52:08

never really studied them. 12:52:11

Q Do you understand what the purpose of a patent claim is? 12:52:12 12:52:14

A I'm not an attorney. I don't understand them the way everybody else in this room does, but I have some understanding. 12:52:16 12:52:18 12:52:20

Q And what's your understanding? 12:52:22

A That a patent is typically a large book of paper that's describing stuff that's -- and the claims come at the end where the person applying for the patent is explicitly stating what they are trying -- what they're attempting to claim as their own. 12:52:26 12:52:31 12:52:37 12:52:41 12:52:45 12:52:48

Q So the patent claim is the part of the patent where the inventor is trying, or attempting to claim their invention as their own. 12:52:58 12:53:01 12:53:05

Is that what you said? 12:53:11

A Yes. 12:53:13

Q Okay. Do you understand that a patent claim conveys a property right? 12:53:14 12:53:19

A Conveys a property right. Is that what you said? 12:53:25 12:53:29

Q Yes. 12:53:30

A I'm not an attorney. I don't want to -- I don't feel comfortable defining those terms. 12:53:30 12:53:34

Q Okay. Did you, as part of your analysis in this case, evaluate the scope of the claims in the '600 patent? 12:53:36 12:53:41 12:53:45

A I looked at those, and I evaluated them at the level that a nonattorney would do. 12:53:50 12:53:54

Q What does that mean? 12:53:58

A Just that, that I'm not -- I'm not an attorney with years of law school and legal experience on claim construction or claim interpretation. 12:53:59 12:54:02 12:54:04 12:54:07

But I -- I evaluated these claims based on some guidance I had about what's -- what the law is about patents and patent claims. 12:54:09 12:54:14 12:54:17

Q So you were provided law, explanation of the law in terms of how to interpret patent claims? 12:54:19 12:54:22 12:54:25

A I was provided some level of -- I mean, that's here in the -- in the document on -- okay, starting on page 9, there are a few key pages 12:54:26 12:54:32 12:54:43

about legal principles that summarize some of the guidance that I had been given. 12:54:46 12:54:54

Q And none of those paragraphs have anything to do with claim construction; is that right? 12:54:57 12:54:59

MR. KUSHAN: Objection. Foundation. 12:55:01

A As I said, what starts on paragraph 9 is a list of some of the guidance I have been given. I didn't say it was all the guidance I had been given. 12:55:04 12:55:08 12:55:11 12:55:14

Q Okay. So going back to paragraph 114 on page 62. So did you reach an opinion, construing the claim, the terms in Claim 1 of the '600 patent? 12:55:14 12:55:19 12:55:27 12:55:32

A I reached an opinion about how best to interpret what's written in these claims. 12:55:35 12:55:40

Q And how did you go about deciding how best to interpret what's written in the claims? 12:55:43 12:55:47

A I read them many, many times and then some more and thought about what would a person of skill in the art, what would a scientist, what would a protein engineer -- how would such a person interpret what this text is trying to 12:55:55 12:55:59 12:56:05 12:56:09 12:56:14

claim. 12:56:20

Q And were you provided any guidance in 12:56:20

terms of the legal framework for how to 12:56:24

determine -- for how to determine the patent 12:56:27

claim? 12:56:34

MR. KUSHAN: Objection. Form. 12:56:35

A I was -- as I said over and over again, 12:56:39

I'm not an attorney. And so my, you know, 12:56:42

experience with -- I'm not going to write claims. 12:56:45

I'm not going to do that. 12:56:49

I'm not an attorney. However, I was 12:56:51

provided some guidance about, for example, you 12:56:53

know, what is a dependent claim? How are claims 12:56:58

organized? 12:57:05

I was told to look at these texts and try 12:57:05

to view them as what would a person of skill in 12:57:08

the art with reasonable common sense -- how would 12:57:10

such a person look at this. Yeah. 12:57:14

Q So why didn't you put that legal framework 12:57:19

in your declaration? 12:57:22

A I think what I -- what I said before is 12:57:26

that the -- the list at the beginning, wherever we 12:57:28

were a moment ago, of -- where did we go -- legal principles on page 9 lists some of the legal principles that I was taught early on in the discussions by counsel. 12:57:36 12:57:39 12:57:43 12:57:49

But I'll also say that -- to everybody in the room, this is a legal case. And so legal issues are all over it. And since I have no experience with legal issues, part of the ongoing conversation is, you know, how does -- what are the legal issues that guide the interpretation of claims or guide the -- how claims -- what claims mean in the legal system. 12:57:52 12:57:57 12:57:59 12:58:03 12:58:07 12:58:10 12:58:16 12:58:20

Q And you didn't provide any of the -- your explanation for your understanding of any of the legal issues that guide interpretation of claims in the legal system in your declaration? 12:58:21 12:58:27 12:58:30 12:58:33

MR. KUSHAN: Objection. Foundation. 12:58:36

A I didn't write sections about the legal issues associated with reading claims. 12:58:45 12:58:51

I mostly used common sense with some advice about -- you know, the example I keep getting back to is what is a dependent claim? 12:58:56 12:59:03 12:59:06

That's a -- it's a legal concept that I would not have known about before this. 12:59:10 12:59:12

So in reading about the science and the proteins, there's person of skill in the art using their -- their skill in the art, thinking about the text there. 12:59:15 12:59:17 12:59:20 12:59:23

But in terms of legal issues such as what depends upon what, I needed guidance to understand that. 12:59:26 12:59:28 12:59:32

Q And were there any steps that you followed in your claim construction analysis besides reading the claims? 12:59:32 12:59:34 12:59:37

A Without reading the claims? 12:59:39

Q Besides reading the claims. 12:59:41

A Oh, sorry, besides reading the claims. 12:59:43

I read the claims from the perspective of somebody who spent half a century in a field of protein sequence, protein engineering, protein mutations. 12:59:53 12:59:56 13:00:00 13:00:05

And so, you know, as a person skilled in the art, I read the text that's copied on page 62 from the perspective of somebody who spent a 13:00:06 13:00:09 13:00:13

lifetime thinking about amino acid sequences and modification of amino acid sequences and the impact of such modifications. Yeah. 13:00:16 13:00:24 13:00:25

Q So as part of your analysis, did you evaluate the scope of the claims, meaning what they cover? 13:00:35 13:00:46 13:00:51

A Yes. 13:00:56

Q So did you evaluate what modified PH20 polypeptides fall within the scope of the claims? 13:00:58 13:01:08

A Gave considerable thought to the idea that there is -- that Claim 1 is talking about a vast possible collection; gave considerable thought to that and gave considerable thought to -- yeah, to what's covered there, to what the claims appear to be claiming to somebody reading this. 13:01:21 13:01:30 13:01:35 13:01:39 13:01:48 13:01:58

Q All right. So probably been going for another hour. 13:02:03 13:02:06

Do you want to break for lunch? 13:02:07

MR. KUSHAN: Sure. 13:02:09

THE VIDEOGRAPHER: We are going off the record. The time is 1:02 p.m. 13:02:10 13:02:12

(A recess was taken.) 14:03:27

THE VIDEOGRAPHER: We are back on the record. The time is 2:03 p.m. 14:03:27 14:03:36

BY MS. MARTIN: 14:03:39

Q Welcome back, Dr. Hecht. 14:03:43

A Hi. 14:03:45

Q Could you please turn in your declaration to paragraph 114. 14:03:46 14:03:48

A Okay. 14:03:59

Q And paragraph 114 has Claim 1 of the '600 patent; right? 14:04:01 14:04:07

A Right. 14:04:08

Q And Claim 1 is directed to a modified PH20 polypeptide that meets two requirements; is that right? 14:04:17 14:04:22 14:04:25

MR. KUSHAN: Objection. Foundation. 14:04:25

A There's an A, B, and a C there. So I'm not sure how you want to divide it up, into two or three, but it meets some requirements. 14:04:37 14:04:41 14:04:48

Q Okay. So Claim 1 requires that the sequence is at least 95 percent identical to one of the recited sequences; is that right? 14:04:49 14:04:52 14:04:57

A That's what it says, yeah. 14:04:59

Q And then, second, the aspartic acid at position 320 must be replaced with one of four amino acids, either histidine, lysine, arginine, or serine; is that right? 14:05:02 14:05:08 14:05:10 14:05:15

A That's what it says, yeah. 14:05:16

Q So Claim 1 requires 95 percent identity and a change at position 320 to histidine, lysine, arginine, or serine; is that right? 14:05:18 14:05:21 14:05:26

MR. KUSHAN: Objection. Foundation. 14:05:30

A Right. Section (a) says at least 95 percent residues the sequence are identical to various ID numbers. 14:05:36 14:05:39 14:05:45

And (b) says the sequence has an amino acid modification corresponding to position 320 with particular reference sequence, and that modification is a replacement of the original amino acid by H, K, R, or S. 14:05:48 14:05:57 14:06:03 14:06:09 14:06:11

Q So the number of additional changes in PH20 that each claim permits besides the replacement at position 320, that's defined via percentage sequence identity calculation; is that right? 14:06:16 14:06:32 14:06:35 14:06:40 14:06:44

A Yeah. The text says at least 95 percent, and so that's a -- that's a calculation relative to the ID, the sequence ID. 14:06:44 14:06:47 14:06:50

Q And that calculation involves counting the total number of changes in the modified PH20 relative to the unmodified sequence and then dividing that number by the total number of amino acids in the unmodified PH20 sequence? 14:06:53 14:06:56 14:07:00 14:07:02 14:07:05

A Well, that would be the opposite. You said "counting the changes." And, really, if you want 95 percent, you're counting the ones that are not changed. 5 percent would be the ones that are changed. 14:07:10 14:07:15 14:07:17 14:07:20 14:07:23

Q Okay. Do you agree that Claim 1 in the '600 patent, as written, covers any PH20 polypeptide that is 95 percent identical to SEQ ID number 3 and in which the aspartic acid at position 320 is a histidine, lysine, arginine, or a serine? 14:07:24 14:07:46 14:07:50 14:07:55 14:07:58 14:08:07

MR. KUSHAN: Objection. Foundation. 14:08:08

A Yeah. 14:08:14

As I read this text or as I've read this 14:08:15

text many times and tried to interpret it from the perspective of somebody who's, you know, expert in the field, skilled in the art, and based on what was taught in the '429 patent, I would interpret it as that the people who put together this patent would be seeking modified PH20 polypeptides that have some utility and, therefore, that are active. 14:08:19 14:08:22 14:08:27 14:08:34 14:08:45 14:08:51 14:08:58

Wherein the position 320 change is as we discussed, and there are up to, in this case let's say 5 percent of the sequences of the residues would be changed beyond that, and that those would be leading to some proteins that have activity that are useful. 14:09:05 14:09:10 14:09:15 14:09:21 14:09:24 14:09:31

Q So when you interpreted the scope of Claim 1 in the '600 patent, first you considered what was taught in the '429 patent because that -- you had said that; right? 14:09:36 14:09:40 14:09:43 14:09:47

A Well, I was aware of '429 patent. 14:09:50

But I think perhaps more importantly, I was thinking of the '600 patent that this claim is attached to. 14:09:56 14:10:01 14:10:05

Q Okay. Okay. So when you said "'429 14:10:06

patent," you meant the '600 patent? 14:10:10
A Yeah. 14:10:12
Q Okay. Just making sure. 14:10:12
A Yeah. So these numbers are, you know, not 14:10:14
numbers that are -- I'm using every day, but, 14:10:17
yeah, the '600 patent. 14:10:20
Q Okay.
A The one that the claim is attached to. 14:10:22
Q Okay. So when you set about to analyze 14:10:24
the meaning of Claim 1 of the '600 patent and to 14:10:28
construe that claim, you -- you thought about the 14:10:32
people who put together the patent and whether 14:10:42
they would be -- and the fact that, in your view, 14:10:45
they were seeking to claim modified PH20 14:10:48
polypeptides that would have some utility; is that 14:10:51
right? 14:10:54
A And also -- and perhaps more 14:10:54
importantly -- reading it from the perspective of 14:10:56
somebody who would be skilled in the art and -- 14:10:59
you know, because the text is attempting to claim 14:11:01
something. And there's an audience, and I'm 14:11:05
thinking the audience is somebody who is skilled 14:11:07

in the art. 14:11:10

And what are they claiming to this audience who are skilled in the art of protein engineering and would be seeking to make something that has utility? 14:11:11 14:11:13 14:11:17 14:11:19

Q So, in your view, the '600 Patent Claim 1 is limited to sequences that you believe have utility? 14:11:25 14:11:45 14:11:48

A Is limited to sequences that I believe have utility, which are those that are enzymatically active. 14:11:54 14:11:57 14:12:00

Q And so you -- in your -- it's your testimony that a skilled person, a person skilled in the art, reading Claim 1 of the '600 patent would interpret Claim 1 of the '600 patent to be limited to those polypeptides that that skilled person believes are useful? 14:12:02 14:12:05 14:12:07 14:12:10 14:12:13 14:12:15

A Right, that -- that those proteins have utility, that they're useful, which in the current situation, since we're talking about an enzyme with hyaluronidase activity, I would interpret that as modified polypeptides that have 14:12:21 14:12:28 14:12:32 14:12:35 14:12:40

hyaluronidase activity. 14:12:45

Q So where in Claim 1 do you see the words 14:12:45

"hyaluronidase activity"? 14:12:50

A I see it in the common disclosure to which 14:13:03

this is attached. 14:13:08

Q Well, that wasn't the question. The 14:13:09

question was -- 14:13:10

A I understand. 14:13:11

Q -- where in the claim do you see those 14:13:11

words? 14:13:14

A Okay. I -- right. The words are not 14:13:14

there, but I think the implication is there by the 14:13:18

specification of a specific set here, H, K, R and 14:13:23

S at 320 which the -- which the patent, you know, 14:13:30

the write-up describes as active. 14:13:38

Q All right. So I want to be very, very 14:13:42

clear here. Okay. So you understand, because you 14:13:44

were -- strike that. Let me start again. 14:13:50

You are construing the scope of Claim 1 of 14:13:52

the '600 patent; correct? 14:13:56

A I am reading that text and thinking about 14:14:00

what would somebody who was in the field as a 14:14:03

protein engineer, and more specifically, working in the biopharmaceutical area, how would such a person interpret this. 14:14:10 14:14:13 14:14:18

And my sense is, they would not interpret it as a claim to grab on to stuff that was useless. I would interpret it as they would interpret -- I would see it as they would interpret it as a claim to claim things that are useful. 14:14:20 14:14:25 14:14:30 14:14:32 14:14:35 14:14:37

And in this case, since the whole issue here is about hyaluronidase, I would interpret that as that they're useful as hyaluronidase enzymes. 14:14:39 14:14:43 14:14:45 14:14:48

Q Do you understand that claim construction is a question of law? 14:14:50 14:14:52

A Claim construction is a -- of course there are legal issues. 14:14:59 14:15:02

Q Okay. 14:15:03

A But there's also the claim is attached to the patent, the whole patent, and there's -- which itself talks a great deal about active and inactive variants. 14:15:04 14:15:07 14:15:11 14:15:14

Q Do you understand what the term claim construction means? 14:15:17 14:15:18

A I'm not an attorney. I can talk about my interpretation and my reading of the claim. But as a nonattorney, I don't want to talk about construction because I think that's a legal term that I -- 14:15:20 14:15:24 14:15:27 14:15:30 14:15:31

Q Okay. 14:15:32

A -- that I'm not comfortable with. I can interpret, but I can't construct it. 14:15:32 14:15:34

Q You understand that interpreting a patent claim and deciding what that patent claim covers, that that exercise is a question of law? 14:15:36 14:15:38 14:15:41

A I understand that interpretation is, is a central, is an intellectual thing, that you have a text in front of you and you interpret it. 14:15:45 14:15:48 14:15:51

Q So you understand that it's the job of the Court to interpret the scope of the patent claims based on the standards that the law provides; right? 14:15:53 14:15:55 14:16:00 14:16:04

A In the context of what somebody skilled in the art would read it, how somebody skilled in the 14:16:04 14:16:08

art would read it. 14:16:11

Q So is your understanding that a Court interprets a patent claim not in the context of the legal principles that govern claim construction, but rather in the context of how a skilled person reads the claim? 14:16:12 14:16:15 14:16:21 14:16:23 14:16:25

MR. KUSHAN: Objection. Foundation. Objection to form. 14:16:27 14:16:29

A I didn't say that. I didn't say "rather." 14:16:30

Q So -- because the question was: The Court interprets claims, right, based on the legal standards; is that right? 14:16:33 14:16:41 14:16:46

A Based on legal standards, of course. And also based on how somebody skilled in the art of the field would read it. 14:16:49 14:16:54 14:16:57

Q Okay. And so your testimony is that someone skilled in the art would read this claim as limited to things, to limit it to polypeptides that you believe are useful in the context of hyaluronidase activity because this case is about hyaluronidase activity? 14:16:59 14:17:03 14:17:06 14:17:11 14:17:16 14:17:19

MR. KUSHAN: Objection. Foundation. 14:17:20

Objection to form. 14:17:22

A And because I've been made aware, as it says in the legal principles upfront, that for something to be patentable, it has to have some level of utility. 14:17:24 14:17:28 14:17:32 14:17:36

Q Okay. But for something to be patentable, it has to have a level of utility. And as a result, you interpret the claim as limited to only those embodiments that are useful? 14:17:40 14:17:43 14:17:46 14:17:48

Well, actually, no. Strike that. 14:17:53

You understand that in order for something to be patentable, it has to have utility. And as a result, you limit the claim to only those embodiments that you believe are useful? 14:17:55 14:17:58 14:18:00 14:18:03

MR. KUSHAN: Objection. Foundation. Objection as to form. 14:18:06 14:18:08

A That I see as being useful from the perspective of somebody skilled in the art, and I would suggest that in the situation anybody skilled in the art would assume that these claims are going after something useful, right. That's the legal thing. It has to have utility, right? 14:18:13 14:18:16 14:18:20 14:18:24 14:18:28 14:18:32

Legally it has to have utility. 14:18:34

And somebody skilled in the art would say 14:18:36

random polypeptides, arbitrary polypeptides that 14:18:39

have no activity, which have no utility. Right? 14:18:44

The law says it needs to be patentable, it 14:18:48

needs to have utility, okay, and someone skilled 14:18:51

in the art would say that for a collection which 14:18:55

is not described in detail, but a massive 14:19:02

collection, for members of that collection to have 14:19:05

utility, they would need to be active. 14:19:09

Q So it's your understanding of patent law 14:19:13

that every single embodiment that falls within the 14:19:17

scope of the claims must have enzymatic activity 14:19:20

in order for the patent claim to be valid? 14:19:23

MR. KUSHAN: Objection. Sorry. 14:19:33

A I think I talk about this somewhere. 14:19:35

MR. KUSHAN: Go ahead. 14:19:39

Q So -- 14:20:41

A No. 14:20:43

Q No, I'm going to -- 14:20:43

MR. KUSHAN: Are you withdrawing the 14:20:45

question? 14:20:47

Q Yeah, I'm going to withdraw the question. 14:20:48

So Dr. Hecht -- 14:20:50

A Mm-hmm. 14:20:51

Q -- in your view, does -- in order for 14:20:52

Claim 1 to have utility, in your view, every 14:20:56

single polypeptide that falls within the scope of 14:21:02

Claim 1 has to be active? 14:21:06

A That was an ambiguous question. You asked 14:21:08

me if the claim has utility. I was talking about 14:21:10

the proteins having utility. 14:21:13

Q Do you understand -- strike that. Okay. 14:21:16

When you interpret Claim 1, you -- you 14:21:19

require that Claim 1, that only polypeptides that 14:21:23

have enzymatic activity satisfy Claim 1; right? 14:21:29

A My interpretation that polypep- -- only 14:21:38

polypeptides that have enzymatic activity fit into 14:21:41

Claim 1. 14:21:45

Q Okay. So a polypeptide that satisfies the 14:21:46

sequence identity requirements of Claim 1 and that 14:21:50

has the required mutation at position 320 does not 14:21:54

meet Claim 1 if it is not -- if it doesn't have 14:21:58

enzymatic activity; is that right? 14:22:01

A My reading of this as somebody who is skilled in the art and is aware of protein engineering, and aware of the engineering of proteins for biopharmaceutical applications, based on that reading, I would interpret this as the -- that the sequences claimed by Claim 1 must have utility because that's what the law is, that they must have some level of utility. 14:22:13 14:22:16 14:22:19 14:22:24 14:22:29 14:22:33 14:22:38 14:22:41

I've been informed that's -- that's the law. You can't patent garbage. And therefore, I would infer that they would have activity, and I would also, from just looking at the claim itself, say that if the authors of the claim were trying to grab, claim all sorts of crap, then they wouldn't have incorporated sections B and C, which lead one down the pathway of activity. Right? 14:22:43 14:22:45 14:22:48 14:22:52 14:22:56 14:23:02 14:23:09 14:23:13

Because the body of the patent, the common disclosure, is -- most of the common disclosure is about active versus inactive proteins, okay? And the common disclosure provides -- it basically divides the world of modified PH20s into two classes: Those that are active, and those that 14:23:18 14:23:20 14:23:27 14:23:33 14:23:39 14:23:45

are not active. 14:23:47

And it spends pages and pages and pages 14:23:49

talking about that and delineating or, you know, 14:23:53

listing -- I shouldn't say delineating -- listing 14:23:57

those that are active and those that are not 14:24:00

active. 14:24:03

And it talks about the replacements that 14:24:03

we've mentioned at position 320, presents data 14:24:06

suggesting those are active, okay. 14:24:10

And given that it divides the world of 14:24:14

mutations in PH20 into these two classes, okay, 14:24:20

which it sort of describes as mutually exclusive, 14:24:25

okay, based on the presence or absence of 14:24:28

activity, it's -- and it -- it explains that those 14:24:33

substitutions that we mentioned at 320 are in fact 14:24:38

active as shown in table on one of the pages, 14:24:41

shown on Table 1, page 69, given that the common 14:24:45

disclosure describes extensive experiments that 14:24:52

are aimed at differentiating between active and 14:24:57

inactive proteins. 14:25:01

And then it chooses, in the claim, Claim 14:25:04

1, to explicitly list those that it has proved are 14:25:08

active. It seems kind of nuts to think that it would choose those and it would list those that are active if it were trying to claim stuff that were not active. 14:25:14 14:25:20 14:25:23 14:25:29

Why would it list those if it were trying to do that? It focuses the reader's attention on these, these mutations at 320, which it says in the table, Table 9 on page 69, are good. They're active. 14:25:30 14:25:32 14:25:38 14:25:42 14:25:47

And so it's -- the logic here is that the body of the patent goes into great depth about splitting the possible proteins into two classes: Active and inactive. And then the claim focuses on those -- four examples of those that in fact have enhanced activity. And that, to my eye, seems to be leading the reader, who would be, you know, protein engineer, seems to be leading the reader to make things that are active. 14:25:47 14:25:52 14:25:59 14:26:03 14:26:06 14:26:10 14:26:13 14:26:17 14:26:21

That's superimposed on what you were referring to, the legal issues, where I've been informed that legal issues say that you're -- that patents should be directed at something that has 14:26:25 14:26:28 14:26:30 14:26:34

utility. 14:26:37

So for all those reasons, it seems to me 14:26:37

that's what Claim 1 is -- is leading to. 14:26:40

Q All right. Now, it's not just any 14:26:46

activity; right? It has to be -- 14:26:52

A It's hyaluronidase activity. 14:26:54

Q Oh. 14:26:56

A Yeah. 14:26:56

Q But not just any hyaluronidase activity 14:26:57

either; right? 40 percent hyaluronidase activity; 14:27:00

is that right? 14:27:04

MR. KUSHAN: Objection. Foundation. 14:27:04

A Based on the body of the patent, that 14:27:25

seems to be where they're going because they are 14:27:28

pretty emphatic about drawing a line. 14:27:30

You know, as we said earlier, activity is 14:27:35

a continuous thing. It's not binary, yes or no. 14:27:37

But in the body of the patent, they draw a 14:27:41

line at 40 percent active, and they're basically 14:27:50

listing active mutants. I mean, there's some 14:27:55

ambiguity and some irreproducibility in the data. 14:28:01

But putting that aside for the moment, 14:28:05

they are listing in tables proteins that are greater than 40 percent active. And they're calling that a class of mutants. And they're listing others as not active, calling that a separate class, okay, so... 14:28:06 14:28:11 14:28:15 14:28:18 14:28:21

Q So it's your testimony that a modified PH20 polypeptide that is, let's say, 99 percent identical to SEQ ID NO. 3 and has the mutation at position 320 from, let's say, D to K, that that modified PH20 polypeptide does not necessarily fall within the scope of Claim 1; is that right? 14:28:26 14:28:31 14:28:37 14:28:42 14:28:47 14:28:52

A Are you saying it's active or not active? 14:28:58

Q Well, I didn't say. 14:29:00

A Okay. My interpretation of it is that because of the body of the patent -- 14:29:02 14:29:05

Q Sir, it's a yes-or-no question. 14:29:08

Does that polypeptide fall within the scope of the claim; yes or no? 14:29:10 14:29:12

MR. KUSHAN: Please let him answer the question. 14:29:14 14:29:16

A I am confused. 14:29:16

Where are we? 14:29:17

Q Okay. You have a modified PH20 polypeptide, okay? It is 99 percent identical to SEQ ID NO. 3, and it has a mutation at position 320 from a D to a K, okay? 14:29:18 14:29:22 14:29:26 14:29:30

The question is: If that's all the information that you have, do you know whether that polypeptide falls within the scope of Claim 1; yes or no? 14:29:32 14:29:35 14:29:38 14:29:41

A I would say you don't know until you assess its activity. 14:29:44 14:29:47

Q And how do you go about assessing its activity? 14:29:48 14:29:52

A That's the point. You need to -- you need to actually describe how to make it; you need to make it; and you need to test it. You can't say, Oh, I'm claiming the world that I don't know anything about. 14:29:59 14:30:03 14:30:08 14:30:12 14:30:14

Q Okay. Well, the question was: Does this polypeptide satisfy the claim? Not, can you, Dr. Hecht, claim anything in the world that you don't know anything about? 14:30:17 14:30:19 14:30:23 14:30:25

MR. KUSHAN: Objection. Form. 14:30:27

Q So -- 14:30:29

MR. KUSHAN: Objection. Foundation. 14:30:30

A My point is that the claim -- not me, the 14:30:33
claim -- cannot claim -- you know, it says here 14:30:37
that it's -- give me a moment to find the piece I 14:30:44
was looking for. 14:30:49

Basically, what I'm looking for here is 14:31:34
that I've been informed that it's not sufficient 14:31:37
to draw a fence around -- all right. 14:31:40

It's on page 10, that merely drawing -- 14:31:45
this is a quote: "...been informed that" -- this 14:31:48
is at the end of paragraph 26: "I have been 14:31:51
informed that a description that is 'merely 14:31:53
drawing a fence around the outer limits of a 14:31:56
purported genus is not an adequate substitute for 14:31:59
describing a variety of materials constituting the 14:32:03
genus and showing that one has invented a genus 14:32:06
and not just a species.'" 14:32:09

So just drawing a fence around a 14:32:10
statistical possibility with no information about 14:32:17
what's in that fence with respect to utility or 14:32:24
activity is not sufficient and is not a substitute 14:32:29

for describing the -- for what they call written description requirement; that drawing a fence cannot replace the written description of what's in there, what its properties are, whether it's active, and that I've been informed that utility is a crucial part of making something valid to be claimed. And just drawing a fence around all humans in the State of Maryland -- and you can't -- I mean, that's a ridiculous example. 14:32:37 14:32:44 14:32:47 14:32:50 14:32:55 14:33:01 14:33:09 14:33:15 14:33:18

But you can't just draw a fence around all of everything without showing how to make it, what its properties are, whether it has utility; that that's not sufficient for patentability. 14:33:20 14:33:22 14:33:27 14:33:32

Q All right. I want to unpack that. 14:33:36

So, first, in the -- to be clear, the legal principle section of your declaration, you say nothing about utility; right? 14:33:39 14:33:52 14:33:55

The word "utility" does not appear in the paragraphs 23 to 32 of your declaration? 14:33:59 14:34:02

A It definitely appears in the declaration somewhere. I'm not sure where, but it definitely appears in the declaration somewhere. 14:34:05 14:34:07 14:34:09

Q Okay. Not in the legal -- not in the legal standard section? 14:34:11 14:34:13

A But it appears in the declaration where we're talking about -- as I said earlier, there are legal issues that bear on this document that may not actually be seen in pages 9 to 12. 14:34:14 14:34:16 14:34:19 14:34:22

Q And if you look in your table of contents, right, if we go through -- we go through the various opinions that you've given in this case, none of those opinions are on whether the patent is valid on utility grounds; right? 14:34:27 14:34:31 14:34:37 14:34:42 14:34:45

MR. KUSHAN: Objection. Foundation. 14:34:49

A The concept of utility and usefulness is -- is in here. I mean, it would take -- it might take us a while to find without a word search, but it's in here somewhere. 14:34:58 14:35:04 14:35:06 14:35:08

Q Okay. So you understand -- strike that. 14:35:10

Okay. So you understand that Claim 1 of the '600 patent is a genus claim, meaning that it covers more than one embodiment; right? 14:35:14 14:35:23 14:35:28

A I am -- as we discussed before, Claim 1 talks about this 95 percent identity and thereby 14:35:33 14:35:38

is attempting to draw a fence around a vast, vast number of sequences. 14:35:42 14:35:46

Q Okay. So it's your understanding of the law -- it's your understanding of the law, Dr. Hecht, that in order to satisfy the utility requirement, every single one of the sequences that falls within the scope of Claim 1 must have enzymatic activity? 14:35:47 14:35:53 14:36:02 14:36:06 14:36:09 14:36:13

MR. KUSHAN: Objection. Foundation. Objection as to form. 14:36:14 14:36:16

A My understanding of the law is that for something to be claimed legitimately, it must have some utility. 14:36:27 14:36:30 14:36:35

Q But you're using the word "something"; right? That is a vague -- 14:36:36 14:36:39

A Sure -- 14:36:40

(Overlapping speakers/crosstalk) 14:36:41

Q That is a vague -- 14:36:41

A Yeah, yeah, yeah. So -- 14:36:43

Q And -- 14:36:44

A My understanding -- well, wait. Hold on. 14:36:45

You asked about my -- 14:36:46

Q Yes. 14:36:47
A -- understanding of the law. 14:36:47
Q Mm-hmm. 14:36:49
A I'm not a lawyer. 14:36:50
My understanding of the law is that for 14:36:51
some thing -- it's law -- to be claimed, it must 14:36:54
have some use or some utility. That's what I 14:36:55
said. 14:36:58
Q Okay. And I'm just trying to understand 14:36:58
if something is -- something is singular or 14:37:01
plural, meaning if it's a genus that covers more 14:37:04
than one thing -- multiple things, multiple 14:37:06
somethings -- within the scope of the claim, if 14:37:10
every single embodiment has to have enzymatic 14:37:13
activity in order to meet the legal requirement? 14:37:17
MR. KUSHAN: Objection. Form. 14:37:19
A It is my understanding that in order for 14:37:32
something to be patentable, it has to be well 14:37:38
described. And in that description, there are, in 14:37:42
this case, molecular structures, properties, and 14:37:48
activity. 14:37:52
And so it's my understanding that if one 14:37:53

attempts to claim a vast collection, one must claim those that -- that those are -- that are active. 14:37:56 14:38:00 14:38:03

That's my -- that's my -- that's my reading of it because I don't see how it would make sense to claim garbage that has no utility. 14:38:04 14:38:05 14:38:09

Q So what if it were the case that inactive polypeptides did have some utility to someone, perhaps not you, but to someone? Would it be okay, then, for the patent claim to cover those inactive polypeptides? 14:38:16 14:38:20 14:38:23 14:38:26 14:38:28

MR. KUSHAN: Objection. Foundation. Objection as to form. 14:38:33 14:38:36

A You're saying if -- if it had zero hyaluronidase activity, right? Is that what you're going with? 14:38:43 14:38:49 14:38:53

Q Well, you said it had about 40 percent activity, so... 14:38:54 14:38:57

A Okay. Well, let's -- let's say it's inactive. We'll go back to your question. 14:38:57 14:38:59

Q Okay. 14:39:01

A Let's say it had inactive hyaluronidase 14:39:02

activity. If it had some other utility, then that would be -- that would be utility; that would -- that would be okay. 14:39:05 14:39:17 14:39:21

Q Okay. So if it, in fact, is the case that PH20 polypeptides that don't have hyaluronidase activity are useful for some other purpose, then those inactive polypeptides can fall within the scope of Claim 1; is that right? 14:39:22 14:39:28 14:39:32 14:39:35 14:39:40

A Is that a hypothetical? 14:39:41

MR. KUSHAN: Objection -- sorry. 14:39:42

Q No. It's a question.

MR. KUSHAN: Objection as to foundation. 14:39:43

A I'm sorry? 14:39:47

Q It's a question. 14:39:47

MR. KUSHAN: Objection to foundation. Objection as to form. 14:39:48 14:39:50

A Well, it was a hypothetical. You're saying if they had some other activity, some other utility, I do not know of any convincing case that it -- I've worked with a lot of proteins and for a lot of years. 14:39:51 14:39:53 14:39:56 14:40:02 14:40:07

If something is unfolded, degraded, not 14:40:07

secreted, not expressed, it's hard to imagine they would have utility. 14:40:12 14:40:14

Q So you assume that all PH20 polypeptides that don't have enzymatic activity are unfolded, degraded, not secreted, and/or not expressed, and that's why they're not useful? 14:40:27 14:40:31 14:40:34 14:40:37

MR. KUSHAN: Objection. Foundation. Objection -- 14:40:39 14:40:41

A I didn't say that. I said I am -- that if they were -- I know I said that I have seen in my career lots of sequences that are unfolded, not secreted, degraded and so forth. 14:40:41 14:40:45 14:40:49 14:40:54

And my expectation is, in a collection which, you know, if we look at that table that outlines what the numbers are, but the numbers are the collection is the hypothetical collection, 10 to the 50th sequences, 10 to the 60th sequences, and a staggering number, and my expectation is that among that hypothetical collection, some will be active as hyaluronidase activities. Some will be folded but inactive. But if you're making 20 or so mutations, you're going to end up with many, 14:40:56 14:41:03 14:41:06 14:41:08 14:41:13 14:41:17 14:41:21 14:41:26 14:41:36 14:41:38

many, many, many sequences that fail to express, that are degraded by the cell, that fail to secrete, or even if they pass all of those bars, they're going to misfold and aggregate. 14:41:42 14:41:48 14:41:52 14:41:56

So among the collection of sequences that do not deliver high levels, or whatever level you want to set of activity, they won't all be folded, things that fail at catalysis, they will be lots of other messy things. 14:42:00 14:42:05 14:42:09 14:42:12 14:42:17

And so for those reasons, it's hard for me to fathom that a claim would include so many different forms of things that are basically useless garbage. 14:42:18 14:42:22 14:42:30 14:42:32

I mean, I've had a lot of useless garbage in my life. I've seen that. You throw them away pretty quickly. 14:42:34 14:42:38 14:42:41

Q Okay. So you interpret Claim 1 to require hyaluronidase activity because even though the literal scope, the literal language in Claim 1 covers PH20 polypeptides that meet the sequence identity limitation and have the requisite change at position 320, you require the claim to require 14:42:42 14:42:46 14:42:49 14:42:56 14:43:00 14:43:03

hyaluronidase activity because of -- in your view, every single polypeptide that falls within the scope of the claim needs to have some sort of utility in order for the claim to be patentable? 14:43:10 14:43:16 14:43:21 14:43:23

MR. KUSHAN: Objection. Form. Objection as to foundation. 14:43:27 14:43:29

A It's -- yeah, it's my understanding that in order for the claim to be legitimate, it must claim proteins that have utility because that which doesn't have utility, I've been taught, is not patentable. 14:43:33 14:43:44 14:43:53 14:43:58 14:44:03

Q Okay. So it's your understanding, from counsel, that if the claim covers polypeptides that do not have activity, the claim is invalid? 14:44:05 14:44:07 14:44:13

MR. KUSHAN: Objection. Foundation. Objection as to form. 14:44:17 14:44:20

A As we said at the outset, my interpretation of this is the claim is -- is targeting those which are active because I think that's how someone skilled in the art would read it, because the claim goes to the effort of starting with mutations at position 320 that 14:44:32 14:44:35 14:44:38 14:44:41 14:44:44 14:44:49

render the protein active. 14:44:53

And therefore, it seems baffling that one would focus on that mutation which enhances activity and then make additional mutations to destroy it. That just doesn't seem reasonable. 14:44:56 14:45:00 14:45:05 14:45:10

In a sense, it's like there's a fork in the road. You could be making mutations. You make your first mutation at 320. You've chosen the fork in the road to go towards enzymatically active proteins. 14:45:14 14:45:16 14:45:19 14:45:24 14:45:28

Who would then go and delete ten amino acids to destroy -- you know, delete 10 amino acids, including the active site, to destroy activity, and then say, Oh, that's part of the claim. We're going to do that too. It doesn't make any sense. 14:45:29 14:45:33 14:45:37 14:45:39 14:45:42 14:45:45

Q Do you interpret the claim to require that the first change you make in the sequence is 320? 14:45:50 14:45:53

A The claim requires that change be there. I don't think it's relevant if you make one first and make the other -- intellectually, yes. Intellectually, the claim says "make this." 14:46:07 14:46:11 14:46:14 14:46:20

But the claim does not give any written description of how and where and which the other one should be. It's very explicit about 320, okay. 14:46:22 14:46:24 14:46:27 14:46:33

So intellectually, it doesn't make any sense to me that one would follow the guidance of the claim, make that one, and then, Oh, let's just also make, you know, 10 to the 50th other changes, which include, according to the text of the patent, deletions and just all kinds of stuff that's going to destroy it. 14:46:33 14:46:36 14:46:39 14:46:45 14:46:49 14:46:56 14:46:58

Q So because in your view it wouldn't make sense for the skilled person to make changes in a protein that are going to destroy the activity of the protein; in your view the claim does not cover inactive proteins? 14:47:00 14:47:01 14:47:04 14:47:06 14:47:09

MR. KUSHAN: Objection. Foundation. 14:47:10

A Well, many reasons. That because it doesn't make sense that one would choose this 320 mutation that's more active, and then go on to add all sorts of destructive mutations. That doesn't make sense, especially as it's attached to the 14:47:14 14:47:17 14:47:24 14:47:29 14:47:32

'600 patent, which basically gives a set of instructions on how to -- well, it's not really instructions, but it gives a set -- it gives a great description -- not great -- a lengthy description -- sorry -- gives a lengthy description that proteins fall into these two classes, okay. 14:47:39 14:47:45 14:47:49 14:47:51 14:47:54 14:47:56 14:48:00

And it talks about, it focuses on the ones that, you know, let's go after -- it focuses on what -- those that are active. Even if something is inactive, it retests them. It's looking for activity, okay, and it talks about those active mutants have a utility, have a use as enzymes. 14:48:02 14:48:08 14:48:12 14:48:14 14:48:17 14:48:20

And so, for that reason, it just seems that once they specifically lay out that -- the requirement, right? They're putting it in as a requirement that it have that 320 change. 14:48:25 14:48:29 14:48:35 14:48:39

It doesn't make sense that one would choose that fork in the road to make something active and then destroy what you've made. 14:48:43 14:48:45 14:48:48

It just -- I mean I -- I've been working protein engineering forever. It just doesn't make 14:48:52 14:48:57

sense to me that anybody would do that. 14:48:59

Q Okay. So let's -- does Claim 1 cover 14:49:01

enzymatically inactive polypeptides? Yes or no? 14:49:05

A Give me a second. What it says in the 14:49:12

claim -- I'm on page 68. "The claim would be 14:49:21

understood to concern active mutant PH20 modified 14:49:24

polypeptides." 14:49:30

Q All right. Well, the question was: Does 14:49:31

Claim 1 cover enzymatically inactive polypeptides? 14:49:32

Yes or no? 14:49:37

MR. KUSHAN: Objection. Form. Objection. 14:49:37

Foundation. 14:49:39

A I would say that that claim does not 14:49:46

capture inactive mutants. 14:49:50

Q And, but if those mutants were shown -- 14:49:56

sorry, strike that. 14:50:01

If there was some utility for the inactive 14:50:02

mutants, then in your view Claim 1 could cover 14:50:05

them. You just don't think that they're useful. 14:50:08

So in your view, Claim 1 does not cover them? 14:50:10

MR. KUSHAN: Objection. Foundation. 14:50:14

Objection as to form. 14:50:15

A Sorry. Say that again. 14:50:27

Q The -- 14:50:39

A Yeah. 14:50:41

Q Let's try this a different way. So let's say you have a polypeptide with 99 percent sequence identity and mutation -- 99 percent sequence identity to SEQ ID 3, and you have a mutation D320 to K, right? And let's say that protein has 39 percent hyaluronidase activity. 14:50:44 14:50:47 14:50:50 14:50:55 14:50:58 14:51:05

Does it fall within the scope of Claim 1? 14:51:09

A I -- I think that it -- I mean, I'm not sure where one would -- they draw the line at 40 percent, but I think more broadly, the point is they say, in the body of the patent, that a modified PH20 polypeptide has modifications as long as resulting modified polypeptide exhibits hyaluronidase activity. 14:51:14 14:51:18 14:51:20 14:51:24 14:51:27 14:51:33 14:51:36

So the body of the patent says frequently that a modified PH20 polypeptide or a variant PH20 polypeptide so long as it exhibits hyaluronidase activity. 14:51:37 14:51:41 14:51:48 14:51:51

Q You understand that you can't read the 14:51:51

disclosure of the specification into the claim. 14:51:53
You understand that that's the basic fundamental 14:51:55
canon of claim construction? 14:51:58
MR. KUSHAN: Objection. Foundation. 14:52:00
Objection as to form. 14:52:01
Q Yes or no? 14:52:08
MR. KUSHAN: Objection as to form. 14:52:11
A I am reading the claims with the awareness 14:52:14
that they're attached to the disclosure, and so 14:52:19
the disclosure provides information that are the 14:52:22
foundation for the claims, and the disclosure 14:52:26
repeatedly says a modified PH20 polypeptide has 14:52:29
such and such amino acid changes, so long as a 14:52:36
resulting modified PH20 polypeptide exhibits 14:52:40
hyaluronidase activity. 14:52:43
Q And it also says -- the disclosure also 14:52:43
says that the modified PH20 polypeptide includes 14:52:46
various changes, so long as it doesn't have 14:52:50
hyaluronidase activity; right? 14:52:53
A Doesn't say -- 14:52:54
Q That's what it says.
A -- doesn't say so long as it doesn't have. 14:52:57

Q So long as it remains inactive? 14:52:59

A It doesn't use those -- so long as it 14:53:01

remains inactive? Is that a quote? 14:53:03

Q Are you telling me that the patent doesn't 14:53:05

disclose inactive -- does not have a section -- 14:53:08

A No, it doesn't say that it's modified so 14:53:10

long as it's inactive. That's not -- I can't 14:53:12

imagine it would say that. So long as it's 14:53:15

inactive? 14:53:17

Q You don't think the bullet says that? 14:53:18

A I don't think that there's a language 14:53:19

saying so long as it's inactive, that it's 14:53:21

defining and modifying polypeptides so long as 14:53:26

it's inactive. 14:53:28

Q So you don't think that -- you don't think 14:53:29

the '600 patent discloses, as a class of 14:53:31

embodiments, inactive PH20 polypeptides? 14:53:34

MR. KUSHAN: Objection. Foundation. 14:53:38

Objection as to form. 14:53:39

A Sorry. You were talking about the disclo- 14:53:41

-- you're talking about the body of the patent or 14:53:43

the claim? I lost you there. 14:53:46

Q The body of the patent. 14:53:46

A Okay. Go ahead. 14:53:47

Q You don't think that the body of the patent discloses a class of embodiments that are inactive PH20 polypeptides? 14:53:48 14:53:49 14:53:52

A The body of the patent talks about -- it has tables of inactive polypeptides, okay. It has tables of inactive polypeptides. 14:53:55 14:53:58 14:54:03

And the way that's -- the way that's presented to somebody in the field reading it, it's pretty clear that they're trying to show that one can make mutations, get active ones and inactive ones. And their goal is to go after activity. 14:54:06 14:54:09 14:54:12 14:54:16 14:54:20 14:54:24

Q Okay. But the specification uses the term modified PH20 polypeptide to refer to both active and inactive PH20 polypeptides; correct? 14:54:25 14:54:28 14:54:32

MR. KUSHAN: Objection. Foundation. 14:54:36

A On page 70, there are -- 70 and 71, there are numerous quotes where the patent says modified polypep- -- PH polypeptide -- so referring to a PH20 polypeptide -- refers to a PH20 polypeptide 14:54:39 14:54:45 14:54:53

that contains at least one amino acid modification --

THE REPORTER: Slow down, please.

A I'm sorry.

"As used herein, 'modified PH20 polypeptide' or 'variant PH20 polypeptide' refers to a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide. A modified PH20 polypeptide can have up to 150 amino acids replacements" -- emphasized -- "so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." 14:55:05 14:55:07 14:55:12 14:55:16 14:55:19 14:55:23 14:55:26 14:55:31 14:55:36 14:55:38 14:55:41

Q Well, that didn't answer the question. 14:55:43

So the specification uses the term modified PH20 polypeptide to refer to both active and inactive PH20 polypeptides; yes, no, or I don't know? 14:55:45 14:55:47 14:55:51 14:56:00

MR. KUSHAN: Objection as to form. 14:56:00

A I think we'd have to look at it. We'd 14:56:09

have to look at the text. I'm looking at the text that I have quoted here, which was put in the -- in the -- in this document. 14:56:12 14:56:15 14:56:18

And these were put in this document to emphasize that the common disclosure repeatedly talks about so long as, so long as. 14:56:19 14:56:24 14:56:31

You know, you can make -- I mean, here's another one: "In particular example, the amino acid replacements can be at the corresponding positions in a PH20 polypeptide as set forth in any of sequence ID numbers" -- I won't read all the numbers, many numbers -- "variants having at least" -- and then it goes through percentages, 75 percent up to 99 percent or more -- "so long as the resulting modified PH20 polypeptide exhibits at least 40 percent of the hyaluronidase activity." 14:56:34 14:56:37 14:56:40 14:56:42 14:56:46 14:56:49 14:56:52 14:56:55 14:56:59 14:57:02 14:57:04

So there in that case it's saying -- it's explicitly saying that the replacements can be at various positions in various percentages so long as it exhibits at least 40 percent. 14:57:05 14:57:08 14:57:12 14:57:17

Q So you're reading that 40 percent, at 14:57:21

least 40 percent -- you're reading that from the specification into the claims; yes or no? 14:57:24 14:57:25

MR. KUSHAN: Objection. Foundation. Objection as to form. 14:57:28 14:57:29

A That's a legal term. I don't know what you mean "reading into the claim." 14:57:33 14:57:35

Q Okay. 14:57:36

A But I am interpreting the claim where the claim talks about modified, right, the language of the claim, which I don't have at my fingertips here. 14:57:37 14:57:39 14:57:44 14:57:47

But it -- the language of the claim talks about modified PH20 polypeptides. If one wants to know what modified PH20 polypeptides -- what does that mean, okay, then the sensible thing to do is to look at the body of the patent where they explicitly say, so long as the resulting modified PH20 polypeptide exhibits at least 40 percent. 14:57:47 14:57:49 14:57:55 14:58:00 14:58:05 14:58:07 14:58:11

Q But if you only want to look at the part of the patent specification that helps you, right -- you don't want to look at the part of the patent specification that uses modified PH20 14:58:15 14:58:17 14:58:19 14:58:21

polypeptide to refer to inactive -- 14:58:24

MR. KUSHAN: Objection. Foundation. 14:58:28

Q -- polypeptides. You already explained -- sorry, strike that. We can go ahead and move on. 14:58:30

So I don't think you ever answered my question, which is -- so we're going to do a yes-or-no question deal here. 14:58:37 14:58:39 14:58:43

So 95 percent sequence identity to SEQ ID NO. 3, and the change from D320 from D to K, okay, and it has 39 percent enzymatic activity. 14:58:45 14:58:49 14:58:53

Does that polypeptide satisfy Claim 1 of the '600 patent; yes, no, or I don't know? 14:58:56 14:59:01

MR. KUSHAN: Objection. Form. 14:59:02

A If it's fully inactive, I would say no. 39 percent is a bit close to the 40 percent. But if it's fully inactive, I would say no. 14:59:08 14:59:11 14:59:13

Q Okay. But I didn't say fully inactive. I said 39 percent. 14:59:18 14:59:18

So 39 percent; yes or no? 14:59:20

A Technically, no. 14:59:21

Q Okay. And you agree with me that nothing in the text of Claim 1 says anything about 40 14:59:23 14:59:24

percent hyaluronidase activity; right? 14:59:27

MR. KUSHAN: Objection. Foundation. 14:59:30

Objection as to form. 14:59:31

A The words "hyaluronidase activity" do not 14:59:48

appear in that quoted text. 14:59:50

Q And the words "40 percent hyaluronidase 14:59:59

activity" also do not appear in the text of Claim 15:00:03

1; correct? 15:00:06

A Correct. 15:00:08

Q Okay. So, similarly, if you have a 15:00:10

modified PH20 polypeptide that is 99 percent 15:00:14

identical to SEQ ID NO. 3 and has the mutation 15:00:19

D320K and it has 35 percent hyaluronidase 15:00:24

activity -- so 99 percent sequence identity, D320K 15:00:30

mutation, 35 percent hyaluronidase activity does 15:00:37

not fall within the scope of Claim 1; correct? 15:00:41

A Correct. 15:00:44

Q Okay. 15:00:45

MR. KUSHAN: Objection. Foundation. 15:00:45

Objection. Form. 15:00:47

A Correct. 15:00:48

Q Thank you. 15:00:49

So when you performed your claim construction analysis, you applied a test for utility; right? 15:00:52 15:00:54 15:00:58

A Wait. Wait a second. 15:01:01

On the previous thing, the point is the claim talks about a modified PH20 polypeptide, okay, and I'm interpreting what those words mean in light of the common disclosure, which defines that as so long as a resulting modified exhibits 40 percent activity. That's why that's there. 15:01:03 15:01:06 15:01:10 15:01:14 15:01:18 15:01:24

I'm interpreting what the words "modified PH20 polypeptide" -- what that means. 15:01:27 15:01:30

Q Okay. So it's your testimony that the common disclosure defines the term modified PH20 polypeptide to mean a modified polypeptide that exhibits at least 40 percent activity? 15:01:32 15:01:34 15:01:38 15:01:45

A Okay --

Q That 40 percent activity is part of the definition of modified PH20 polypeptide; right? 15:01:48 15:01:50

MR. KUSHAN: Objection. Foundation. Objection as to form. 15:01:54 15:01:57

A I'm saying that based on what's quoted on 15:01:59

pages 70 and 71 of the declaration, which quote how it defines "modified" -- what -- how it defines what a modified PH20 polypeptide is, where it says that modified PH20 polypeptide is -- blah, blah, blah, blah -- so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity. 15:02:02 15:02:06 15:02:11 15:02:15 15:02:20 15:02:22 15:02:26

Q Well, you said 40 percent, though -- 15:02:26

A Yeah, but --

Q That 40 percent --

(Overlapping speakers/crosstalk)

(The reporter requested clarification.) 15:02:33

Q Sorry. Yeah, I know. One at a time. I'm sorry. 15:02:33

I just want to be clear that when you say the definition -- in the specification for modified PH20 polypeptide, you're saying the definition for modified PH20 polypeptide in the specification requires at least 40 percent activity? 15:02:33 15:02:35 15:02:38 15:02:40 15:02:43 15:02:46

MR. KUSHAN: Objection. Foundation. Objection as to form. 15:02:47 15:02:48

A I think we'd be best off going to pages 70 and 71 where this is -- the quotes are spelled out. 15:02:52 15:02:55 15:02:58

Q And, again, I just want to make sure that I understand your testimony that the definition of modified PH20 polypeptide requires at least 40 percent activity. 15:03:03 15:03:08 15:03:11 15:03:15

MR. KUSHAN: Objection. Foundation. Objection as to form. 15:03:17 15:03:19

A On page 20 -- sorry. On page 70, there is a quote. 15:03:25 15:03:33

It says, "As used herein, 'modified PH20 polypeptide' or 'variant PH20 polypeptide' refers to PH20 polypeptide that contains at least one amino acid modification" -- and so forth. 15:03:34 15:03:37 15:03:41 15:03:46

And then it says, "A modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." 15:03:48 15:03:51 15:03:54 15:03:58

Okay. The next paragraph says, "The modifications described herein can be in any PH20 polypeptide, including -- including precursor, 15:04:01 15:04:04 15:04:09

mature, or C-terminal truncated forms, so long as the modified form exhibits hyaluronidase activity." 15:04:13 15:04:17 15:04:20

So they're defining the modification there with "so long as it exhibits activity," okay. 15:04:20 15:04:23

The next one is about truncations, which is a particular kind of modification. And "The C-terminal truncation can be a truncation or deletion of 8 to 50 or more amino acids C-terminus, so long as the resulting C-terminally truncated polypeptide exhibits hyaluronidase activity and secreted from cells." 15:04:26 15:04:29 15:04:32 15:04:36 15:04:39 15:04:44 15:04:47

And then the next two, which are now on page 71, are similar quotes; however, in those next two in the bold face type, it says, "so long" -- it's more specific about the activity, and it says, "so long as the resulting modified PH20 polypeptide exhibits at least 40 percent of the hyaluronidase activity." 15:04:49 15:04:51 15:04:55 15:04:59 15:05:01 15:05:05 15:05:08

And it says that again in another text. We're toward the end of paragraph 129. So in all those exam- -- excuse me. 15:05:10 15:05:14 15:05:20

In all those examples, the patent disclosure is giving us guidance on how to translate the words modified PH20 polypeptide. Those are the words that are -- the first few words of Claim 1, a modified PH20 polypeptide. 15:05:21 15:05:23 15:05:28 15:05:33 15:05:37

And so the body of the patent, as I just read to you on pages 70 and 71, the body of the patent translates the words modified PH20 polypeptide, and that translation is telling the reader that these exhibit hyaluronidase activity. 15:05:42 15:05:45 15:05:50 15:05:56 15:05:59

In some cases it says generically they exhibit hyaluronidase activity. In other cases it says specifically at least 40 percent. 15:06:02 15:06:05 15:06:08

So that's the core -- that's one of the cores -- there are several cores, but that's the core of my reading of Claim 1, is that I'm interpreting what the word modified PH20 polypeptide means in -- in light of the quotes taken from the common disclosure, as -- as reproduced on pages 70 and 71. 15:06:11 15:06:15 15:06:18 15:06:21 15:06:25 15:06:29 15:06:34

Q So would you -- do you consider the quotes on pages 70 and 71 to be a definition of the term 15:06:38 15:06:41

modified PH20 polypeptide? 15:06:45

A They are presenting it that way. When you 15:06:48

start a paragraph with, "As used herein, modified 15:06:51

PH20 polypeptide," blah, blah, blah, "refers to," 15:06:55

I think that's their way of defining what that 15:06:59

term means. 15:07:02

When you say, you know, "a blah, blah, 15:07:03

blah refers to," that's basically what -- what you 15:07:08

do when you're defining, interpreting, translating 15:07:11

a word. That's what they're doing here. 15:07:15

Q And so in your view, every single one of 15:07:18

these paragraphs, only the first of which starts 15:07:20

with the phrase "as used herein," every single one 15:07:23

of these paragraphs is a definition of modified 15:07:26

PH20? 15:07:29

A Well, the first one certainly sounds that 15:07:29

way. The others are guiding us how to read that 15:07:31

words -- those words. The first one is worded as, 15:07:41

"As used herein," this refers to. 15:07:45

That is similar to, you know, the way one 15:07:49

defines terms, you know, as you did before, where 15:07:54

you used an acronym for a person skilled in the 15:07:58

art. You said I will use, you know, the abbreviation. 15:08:00 15:08:04

Q POSA? 15:08:04

A As blah, blah, blah. You were basically alerting me of what the usage is and what it means. By similar logic, that paragraph on page 70 says, "As used herein, modified PH20 polypeptide, da da da da da, so long as it's active hyaluronidase activity." 15:08:05 15:08:06 15:08:10 15:08:17 15:08:21 15:08:25

So if I read the first words of Claim 1, I am guided by how the patent itself defines this. Okay. 15:08:26 15:08:30 15:08:36

Q And so the sentence that we've established is the definition, reads, "As used herein modified PH20 polypeptide, or variant PH20 polypeptide, refers to a PH20 polypeptide that contains at least one amino acid modification such as at least one amino acid replacement as described herein, and its sequence of amino acids compared to a reference unmodified PH20 polypeptide, period." 15:08:39 15:08:43 15:08:46 15:08:50 15:08:53 15:08:57 15:09:00 15:09:02

That is the definition; correct? 15:09:05

MR. KUSHAN: Objection. 15:09:07

A No, it keeps going. 15:09:08

MR. KUSHAN: Objection. Foundation. 15:09:10

Objection as to form. 15:09:11

Q Well, it keeps going for another 180 15:09:15

pages. You only include one other sentence after 15:09:18

that sentence. So are you saying that the 15:09:20

definition is these two sentences? 15:09:22

Does it include what comes below those two 15:09:26

sentences? How are you drawing the line between 15:09:28

what's a definition and what's not a definition? 15:09:30

A Because the first sentence that you just 15:09:39

read is, "as used herein," okay, a modified PH20 15:09:42

polypeptide, okay. And then it continues saying a 15:09:48

modified PH20 -- that it's -- it's now giving us 15:09:52

more detail and saying it can have up to 150 amino 15:09:59

acid replacements, so long as the resulting 15:10:04

modified PH20 polypeptide exhibits hyaluronidase 15:10:06

activity. 15:10:10

Q So you think that the claims cover any 15:10:13

modified PH20 polypeptide with up to 150 amino 15:10:16

acid replacements? 15:10:21

A Well, the claims, as we said, talk about 15:10:24

whatever those numbers were, 95 percent. 15:10:28

Q But in the specification that you say, 15:10:33

that you're relying on to interpret the claims, 15:10:38

it's not limited to 95 percent; right? It talks 15:10:42

about, for example, on page 71, 75 percent, 80 15:10:45

percent, 81 percent, 82 percent, and so on and so 15:10:49

on, in sequence identity. 15:10:54

So why is it the case that you're sticking 15:10:55

with the 95 percent sequence identity that's in 15:10:57

the claim? You're not changing the 95 percent 15:10:59

number based on what's in the spec, but you're 15:11:01

changing -- 15:11:02

A Well -- 15:11:02

Q -- other terms based on what's in the 15:11:02

spec. 15:11:05

MR. KUSHAN: Objection. Foundation. 15:11:05

A I don't think I need help to interpret 15:11:07

what 95 percent means. That's a math -- that's a 15:11:08

math issue. 15:11:11

Q But you need help to interpret what 15:11:13

modified PH20 polypeptide means? 15:11:14

A Yes. 15:11:17

Q Okay. So the skilled person would not understand what the term modified PH20 polypeptide means -- 15:11:17 15:11:18 15:11:22

MR. KUSHAN: Objection. 15:11:22

Q -- without looking at the specification? 15:11:22

MR. KUSHAN: Objection. Foundation. Objection as to form. 15:11:25 15:11:26

Q Does the skilled person, the skilled person, in general -- withdraw the question. 15:11:34 15:11:37

Does the skilled person have a general understanding of the phrase "PH20 polypeptide"? 15:11:39 15:11:40

A The disclosure enumerates various sequence IDs, and that's important, right? 15:11:56 15:12:05

So it enumerates various sequence IDs of PH20 polypeptide. Okay. I don't think the fraud PH20 polypeptide, you know, is enumerated there. It enumerates specific ones, okay, because it wants to explain what it means there. 15:12:07 15:12:14 15:12:17 15:12:22 15:12:25

Q If you saw the phrase "modified PH20 polypeptide" outside the context of this patent, is it your testimony that you would have no idea what that phrase meant? 15:12:29 15:12:31 15:12:33 15:12:35

A I would say for the sake of a -- in general, I would have a sense of where that's going. But I would say for the sake of a patent claim, one has to be more specific, right? 15:13:04 15:13:07 15:13:09 15:13:11

Because the patent claim talks about 95 percent. And so it's -- it's limiting what's meant by modified, okay. 15:13:15 15:13:20 15:13:24

Likewise, the common disclosure is limiting what's meant by modified PH20 when it goes on to say "so long as it's active." 15:13:30 15:13:31 15:13:36

Q So you applied your understanding of the term modified PH20 polypeptide as requiring at least 40 percent activity, you applied that understanding consistently in your analysis of written description, enablement and utility; is that right? 15:13:40 15:13:43 15:13:48 15:13:50 15:13:52 15:13:58

MR. KUSHAN: Objection. Foundation. 15:13:58

A I think there's too much going on at once. I think we might be due for a break. We've been going for over an hour now. 15:14:04 15:14:08 15:14:11

Q Okay. Well, a question is pending. So can you please answer the question? 15:14:12 15:14:14

A Sorry? 15:14:15

Q There's a question pending. Can you please answer the question?

A Okay. So why not re-ask it. 15:14:18

Q All right. 15:14:18

You applied your understanding of the term modified PH20 polypeptide as requiring at least 40 percent activity consistently in your analysis of written description, enablement and utility in your analysis; is that right? 15:14:18 15:14:21 15:14:23 15:14:26 15:14:29

A I've applied the definition of requiring hyaluronidase activity in interpreting this claim, yeah. Is that what you're asking? 15:14:31 15:14:36 15:14:41

Q Consistently throughout your declaration. 15:14:44

MR. KUSHAN: Objection. Foundation. 15:14:49

A As pertains to what's being claimed in Claim 1, yeah. 15:14:59 15:15:02

Q Okay. And it's not just hyaluronidase activity -- 15:15:02 15:15:05

MR. KUSHAN: Sorry. He asked for a break. Can we take a break? 15:15:06 15:15:07

Q Can I just clarify? Because he only 15:15:10

answered part of my question. I would just like an answer to that question. 15:15:12 15:15:16

Not just hyaluronidase activity, but 40 percent hyaluronidase activity, consistently throughout your declaration? 15:15:17 15:15:19 15:15:21

MR. KUSHAN: Objection. Foundation. Objection as to form. 15:15:24 15:15:26

A I am saying that, based on what they say here, which is hyaluronidase activity, in one case or two cases, they limit that to 40 percent, as compared to the other cases where they generically say "activity." 15:15:31 15:15:34 15:15:37 15:15:42 15:15:46

Q Okay. So let's take a break. 15:15:48

THE VIDEOGRAPHER: We are going off the record. The time is 3:15 p.m. 15:15:51 15:15:53

(A recess was taken.) 15:15:56

THE VIDEOGRAPHER: We are back on the record. The time is 3:49 p.m. 15:49:02 15:49:10

BY MS. MARTIN: 15:49:13

Q All right. So we're going to mark another exhibit. This is Exhibit 1001, which is the '600 patent. 15:49:16 15:49:18 15:49:31

(Exhibit 1001 was introduced for identification.)

Q Dr. Hecht, the '600 patent is one of the patents you analyzed in this matter; right? 15:49:37 15:49:40

A Right. 15:49:42

Q That's the patent that we've been talking about? 15:49:42 15:49:45

A Right. 15:49:45

Q Okay. And before the break, I believe you testified that the skilled person would look in the specification as to how the inventors used the term modified PH20 polypeptide when interpreting the claims; right? 15:49:47 15:49:52 15:49:55 15:49:58 15:50:03

MR. KUSHAN: Objection. Foundation. 15:50:04

A Yeah, right. 15:50:06

Q And I asked you before the break if the term modified PH20 polypeptide was used in the specification to refer to inactive polypeptides. 15:50:09 15:50:16 15:50:21

A And I said that I didn't know the patent by heart, or something like that. I'll say that now. 15:50:25 15:50:27 15:50:29

Q So let's turn to Column 119, which is on 15:50:30

page 87. 15:50:43

A Sorry, column what? 1 -- 15:50:46

Q 119, which is on page 87, 119. 15:50:49

A I'm sorry. Column 119. 15:50:59

Q Yeah. Do you see the number 2, Inactive Mutants, in Column 119? 15:51:15 15:51:20

A Yeah. 15:51:22

Q And under that, it says, "Provided herein are modified PH20 polypeptides that contain one or more amino acid replacements in a PH20 polypeptide that are inactive, whereby the polypeptides do not exhibit hyaluronidase activity or exhibit low or diminished hyaluronidase activity"; correct? 15:51:22 15:51:25 15:51:29 15:51:33 15:51:40 15:51:43

A I see that, yeah. 15:51:44

Q And it continues: "The modified PH20 polypeptides provided herein that are inactive generally exhibit less than 20 percent, such as less than 10 percent, of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the peptide -- polypeptide set forth in SEQ ID NO. 3 or 7"; correct? 15:51:45 15:51:49 15:51:51 15:51:54 15:51:56 15:52:00 15:52:07

A I see where you're at, yeah. 15:52:07

Q So, in fact, the patent specification uses the term modified PH20 polypeptides to refer to inactive polypeptides; right? 15:52:09 15:52:11 15:52:14

A I see that. It seems contradictory. It seems the patent is using contradictory language in that elsewhere it says, "modified so long as active" whereas here it seems to use it in a different way. Seems contradictory. 15:52:15 15:52:19 15:52:22 15:52:26 15:52:29

Q So the patent uses the term modified PH20 polypeptide to refer to both active and inactive? 15:52:32 15:52:36

A Right. The language is -- as I said, it seems contradictory to me. 15:52:39 15:52:42

Q And when you interpreted the claim, you selected the portions of the specification that refer to active modified PH20 polypeptides. 15:52:45 15:52:46 15:52:49

And so you -- you interpreted modified PH20 polypeptides to be limited to actives; right? 15:52:52 15:52:59

MR. KUSHAN: Objection. Foundation. Objection also as to form. 15:53:02 15:53:03

A That was one piece of my interpretation. 15:53:04

There were two or three or four others about why I interpret Claim 1 to be referring to 15:53:07 15:53:11

active -- active enzymes. 15:53:16

Q Did you consider the fact that the specification uses the term modified PH20 polypeptide to refer to inactive PH20s in your claim construction analysis? 15:53:17 15:53:19 15:53:22 15:53:26

A I considered the quotes I mentioned to you earlier, where it says, "so long as." 15:53:33 15:53:35

I did not consider this because it seemed contradictory. But my interpretation of the claim, referring to active, was also based on several other things, which I can go into. 15:53:38 15:53:40 15:53:44 15:53:48

Q Okay. So just to confirm, you did not consider the disclosure in the specification in which the term modified PH20 polypeptide is used to refer to inactive mutants -- 15:53:50 15:53:53 15:53:56 15:53:59

MR. KUSHAN: Objection --

Q -- in the claim construction analysis? 15:54:02

MR. KUSHAN: Objection. Foundation. Objection also as to form. 15:54:05 15:54:06

A Right. I did not base my interpretation on the paragraph you read. 15:54:25 15:54:27

I based it on other factors, which have to 15:54:28

do with how -- about utility and about how it just -- how the patent makes an effort to distinguish between active and inactive and how it -- only the active ones had utility and also how it seems to choose to take this fork in the road towards activity, and it makes no sense that they would then destroy the activity that they had succeeded in preserving or enhancing with that 320 mutation. So my interpretation was based on the issue of how "modified" is defined and all those other factors. 15:54:33 15:54:39 15:54:42 15:54:47 15:54:51 15:54:54 15:54:56 15:55:01 15:55:05 15:55:09 15:55:12

Q So you said that modified PH20 -- I'm sorry, strike that. 15:55:21 15:55:27

You just referred to how modified PH20 polypeptide is defined, which suggests that you understand the term modified PH20 polypeptide to be defined as limited to actives. 15:55:27 15:55:29 15:55:34 15:55:36

But as we just saw, right, the specification, in fact, uses the termed modified PH20 polypeptides to refer to inactives? 15:55:39 15:55:43 15:55:46

A Right. As I said, I think it seems to contradict itself because it seems elsewhere to 15:55:48 15:55:50

define it, as I read earlier. And then in the paragraph you read, it seems to violate that definition. 15:55:54 15:55:57 15:55:59

It says "as used herein" on my declaration, page 70, which appears, to me, to be a definition of how it is used herein and so -- which says, "so long as the resulting polypeptides exhibit hyaluronidase activity." That seemed a pretty strong statement to me in terms of how it is used herein whereas the paragraph you read seems to contradict that. 15:56:00 15:56:05 15:56:08 15:56:12 15:56:17 15:56:18 15:56:21 15:56:24

That is somewhat baffling that they would contradict how they say "as used herein." Nonetheless, I think my interpretation of Claim 1 stands on several other pretty strong arguments as well. 15:56:26 15:56:28 15:56:32 15:56:36 15:56:48

Q And just to confirm, you applied your understanding of modified PH20 polypeptides requiring at least 40 percent activity -- you applied that interpretation consistently in your written description, enablement, and utility analysis; right? 15:56:48 15:56:50 15:56:55 15:56:57 15:57:00 15:57:03

MR. KUSHAN: Objection. Foundation. Objection also to form. 15:57:04 15:57:06

A Sorry. When there's two people speaking, I lose the question. 15:57:11 15:57:13

Repeat it, would you? 15:57:14

Q You applied your understanding of the term modified PH20 polypeptide as requiring at least 40 percent hyaluronidase activity consistently in doing the written description and enablement analysis in your declaration; correct? 15:57:14 15:57:17 15:57:20 15:57:23 15:57:27

A As requiring activity, yes. I don't think I necessarily fixated on 40 percent, but as requiring activity. 15:57:28 15:57:31 15:57:34

Q So you interpret the claim as requiring 40 percent activity, but when you did your written description and enablement analysis, you did not require the claim -- you did not interpret the claim to require 40 percent activity? 15:57:35 15:57:38 15:57:41 15:57:44 15:57:46

MR. KUSHAN: Objection. Foundation. Objection as to form. 15:57:48 15:57:49

A I said that I interpret the claim as requiring enzyme activity. I don't think I 15:57:52 15:57:56

fixated on whether it was 40 percent or 39 percent or 50 percent -- 15:57:59 15:58:03

Q So -- 15:58:04

A -- but as requiring activity. 15:58:05

Q -- before the break, you testified that the claim required 40 percent activity. 15:58:06 15:58:08

And now you're saying the claim does not require 40 percent activity? 15:58:10 15:58:12

A My understanding is the claim requires activity. 40 percent is a number that they use in their experiments. I am not going to fixate on that number. 15:58:13 15:58:15 15:58:18 15:58:22

Q So I just want to understand your testimony because it's changing throughout the day. 15:58:23 15:58:25 15:58:29

Can you tell me one way or the other whether Claim 1 of the '600 patent requires 40 percent activity? 15:58:29 15:58:31 15:58:34

MR. KUSHAN: Objection. Foundation. Objection as to form. 15:58:36 15:58:38

A My understanding is that it requires real activity, not just 1 or 2 percent. 15:58:41 15:58:46

The authors of the patent have decided that 40 percent is the cutoff. So if they're choosing 40 percent as the cutoff, let's use that. 15:58:49 15:58:53 15:58:57

Q Okay. Does the claim require that any additional substitutions beyond 320 improve the activity above and beyond that which was seen with the first mutation at 320? 15:59:01 15:59:38 15:59:42 15:59:47

MR. KUSHAN: Objection to form. 15:59:52

A My understanding of the claim is it requires hyaluronidase activity; my understanding is it does not explicitly require more than the single mutant at 320. 15:59:56 16:00:00 16:00:02 16:00:06

That's already active, and I think other mutations that were active would be included fine. 16:00:08 16:00:11

Q So if you have your 320 change and then you add another change, another mutation, you're not saying that the second mutation needs to improve activity above and beyond the activity achieved with the first -- with the 320 mutation? 16:00:15 16:00:20 16:00:27 16:00:31 16:00:33

A Right, yes. My understanding is based on the idea that if you destroy activity and render the protein inactive, that would have no utility 16:00:49 16:00:51 16:00:55

and, therefore, would -- would not count. 16:00:58

However, I think the patent is trying to 16:01:02

claim -- is trying to claim a diversity of 16:01:04

sequences that are active. It's not describing 16:01:06

them in detail, but that's, you know -- right. 16:01:11

Q So as I understood your testimony before 16:01:15

the break, you said that the claim element 16:01:19

requiring a change at 320 was intended to show 16:01:23

activity. 16:01:27

If that's the case, then what is your 16:01:29

interpretation for why the inventors used a 95 16:01:31

percent sequence identity claim language? 16:01:35

MR. KUSHAN: Objection. Foundation. 16:01:37

Objection also as to form. 16:01:39

A The inventors are trying to capture a 16:01:45

genus. They're not giving a substantial, written 16:01:47

description of that genus, but they're attempting 16:01:54

to capture that. 16:01:56

Q So did you consider written description of 16:01:59

the genus when you were construing the claim? 16:02:01

A When I was looking at the claim and trying 16:02:11

to interpret it, I -- yes, I've thought about the 16:02:13

concept of written description, representative examples, enablement, and stuff like that. Yeah. 16:02:16 16:02:20

Q And did the concepts of written description, representative examples, and enablement inform your construction of the claim? 16:02:23 16:02:26 16:02:30

A Interpretation. I don't construct -- 16:02:31

Q Interpretation -- 16:02:34

A Okay.

Q Interpretation of the claim? 16:02:34

A It influenced how I read the claim and how I understood what they were attempting to go after and whether it was legitimate or not. 16:02:50 16:02:53 16:02:56

Q Why is that? 16:02:58

A Well, let me -- let me go into that. 16:03:01

Because I was taught, informed, that a written description must either provide a -- well, I'm on page 10 -- must either describe a representative number of species falling within the scope of the genus. I felt -- yeah, so that. 16:03:22 16:03:26 16:03:30 16:03:33 16:03:37

Or structural features common to members of the genus, such as one skilled in the art could visualize or recognize members of the genus, okay. 16:03:43 16:03:46 16:03:49

And I was informed, as I'm reading here, that adequate, written description of a genus of polypeptides requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties of species falling within a genus, sufficient to distinguish the genus from other materials. 16:03:53 16:03:57 16:04:00 16:04:04 16:04:10 16:04:12 16:04:15

And, moreover, that merely drawing a fence around the outer limits of the proposed genus is not adequate substitute from describing a variety of materials in the genus, and showing that one has invented a genus and not just a species. 16:04:17 16:04:21 16:04:24 16:04:27 16:04:31

So that's -- yeah, that was -- that played a role in how I read and understood Claim 1 and whether it was legitimate or not. 16:04:35 16:04:40 16:04:46

Q When you said legitimate or not, what does that mean? 16:04:49 16:04:51

A Whether it met -- whether it met the -- the dis- -- the requirements. 16:04:52 16:04:55

Q So did you perform your written description analysis before you interpreted the scope of the claim? 16:05:00 16:05:02 16:05:05

MR. KUSHAN: Objection. Foundation. 16:05:07

A As I'm not an attorney, there was considerable amount of learning and studying involved. I didn't read the claims in isolation. I didn't read the common disclosure in isolation. I read all of them several times before I had the ability to understand what's going on and analyze it and learn the legal principles. 16:05:14 16:05:17 16:05:19 16:05:21 16:05:24 16:05:28 16:05:32

Q In your declaration, did you apply an interpretation of Claim 1 that requires 40 percent activity? 16:05:35 16:05:38 16:05:41

A Didn't we discuss that already? That in my interpretation of Claim 1, my understanding was that Claim 1 is aiming to capture proteins with utility, which in this case means those that have enzymatic activity. 16:05:52 16:05:55 16:05:59 16:06:04 16:06:07

Q Would you consider an amino acid sequence to be a formula? 16:06:24 16:06:27

A It's not the same thing. An amino acid sequence is an amino acid sequence. 16:06:35 16:06:38

Q So when you say, written description -- "Adequate written description of a genus of 16:06:40 16:06:46

polypeptides requires a precise definition such as by structure, formula, chemical name, physical properties or other properties," which one of those amino acid sequence falls in one of those categories? And if so, which one? 16:06:48 16:06:52 16:06:55 16:06:58 16:07:00

A Well, well -- my concern is that structure is not depicted. Physical properties and other properties are not described for this 10 to the 60th different sequences, right? 16:07:02 16:07:05 16:07:09 16:07:17

There's no written description of a representative sample of 10 to the 60th proteins. There's no written description of do they fold, how do I design them so they might fold? How does the information in the common disclosure about the 6,000 mutants that they made, how does that enable discovery of further -- of further proteins in this class? There's no -- there's no information on how to move forward. 16:07:22 16:07:28 16:07:32 16:07:35 16:07:39 16:07:42 16:07:47 16:07:52 16:07:54

There's no description of the properties of those, you know, as I said earlier, some of them are going to be folded, some will be unfolded, some will be aggregated. 16:07:56 16:07:58 16:08:02 16:08:05

There's no description of any of that. There's just a drawing a fence around a vast hypothetical universe or genus without any written description of their properties. 16:08:07 16:08:09 16:08:11 16:08:15

Q So -- 16:08:16

A Or -- yeah. 16:08:17

Q So it's your understanding that in order to claim a genus of proteins, you have to describe the properties of all of the proteins in the genus? 16:08:18 16:08:20 16:08:23 16:08:27

A Of a representative sampling. 16:08:28

Q Now, the text that you're -- strike that. Let me start again. 16:08:30 16:08:35

The text is, "Requires a precise definition, such as by structure, formula, chemical name, physical properties or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." 16:08:36 16:08:38 16:08:41 16:08:42 16:08:45 16:08:48

Do you see that that is the sentence? 16:08:49

A I read what you read. 16:08:50

Q Okay. And do you see that the word 16:08:51

"representative" does not appear at all in that sentence? 16:08:53 16:08:56

A Right. But I've been instructed that representative sampling is an important -- is important. 16:08:57 16:09:01 16:09:03

Q So you have to satisfy the representative species test in order to satisfy the written description requirement? 16:09:04 16:09:07 16:09:10

MR. KUSHAN: Objection. Foundation. Also objection as to form. 16:09:14 16:09:17

A I would say that in order to claim a genus, one would have to provide written description and enablement, not necessarily for every single one, but for a representative sampling of the collection. And that would be required beyond simply, you know, drawing a fence around a hypothetical 10 to the 50th different sequences. 16:09:22 16:09:25 16:09:29 16:09:33 16:09:36 16:09:39 16:09:42 16:09:46

Q Okay. So your understanding of the law is that you have to have a representative -- you have to describe the properties of a representative number of species that are encompassed in the 16:09:47 16:09:50 16:09:52 16:09:55

claim? 16:09:58

MR. KUSHAN: Objection. Foundation. 16:09:59

A One would have to describe and list a representative bunch of them with respect to actual sequences, properties, activity, enablement of how to make something that's active, whereas my sense was that the '600 patent lists a minuscule and highly biased sample of what would be within that fence, in the sense that it only lists single amino acid substitutions while at the same time it's attempting to claim things that have 20 or more substitutions. 16:10:02 16:10:06 16:10:10 16:10:16 16:10:21 16:10:30 16:10:33 16:10:39 16:10:42 16:10:47

It's attempting to claim, you know, 10 to the 50th different sequences with anywhere between 1 and 20 substitutions. And yet it doesn't present any information, either in terms of description or enablement, about that collection. 16:10:48 16:10:52 16:10:55 16:10:58 16:11:02

Q Okay. I want to be very clear. Can you tell from an amino acid sequence whether that amino acid sequence is 95 percent identical to, for example, SEQ ID 3 or not? 16:11:06 16:11:14 16:11:20 16:11:25

A One can do that, yes. 16:11:28

Q So an amino acid sequence of a polypeptide gives you enough information to tell whether that amino acid sequence is 95 percent identical to, for example, SEQ ID 3; correct? 16:11:29 16:11:32 16:11:35 16:11:40

A The sequence tells you whether, what percentage is identical, yes. 16:11:43 16:11:45

Q And the sequence would also tell you whether there's a mutation at position 320; correct? 16:11:46 16:11:49 16:11:52

A That it would. 16:11:52

Q So an amino acid sequence, by itself, gives you enough information to tell whether that amino acid sequence is 95 percent identical to SEQ ID NO. 3 and whether that sequence has a mutation at position 320; correct? 16:11:53 16:11:56 16:11:59 16:12:04 16:12:06

A Yes, but that's all it tells you. It doesn't tell you anything about active, precipitated, aggregated, folded. 16:12:08 16:12:12 16:12:14

It doesn't tell you anything. 16:12:19

Q And so the claim requires the protein to be not precipitated? 16:12:20 16:12:24

A Correct. If it's precipitated, it won't 16:12:27

be active. 16:12:30

Q So modified PH20 polypeptide requires the protein to be soluble; is that right? 16:12:31 16:12:37

A The point we discussed earlier was that it requires the protein to have hyaluronidase activity. And for the most part, almost totally, if it's precipitated, that would indicate it's unfolded, aggregated. And if it's unfolded and aggregated, that would not be active. So that would fall outside of the limit. 16:12:41 16:12:43 16:12:46 16:12:52 16:12:56 16:12:59 16:13:03

Q Okay. I just want to understand what you mean by precipitated. So if something is precipitated, that would mean it's not soluble? 16:13:05 16:13:06 16:13:10

A Let me elaborate on that. 16:13:13

Q Okay. 16:13:14

A As used herein, the word precipitated, in my thinking about this, is that a protein, a mutant protein, has been made. The protein is unstable, fails to fold. 16:13:15 16:13:19 16:13:23 16:13:26

That unfolded or misfolded polypeptide, in its unfolded or misfolded state, would aggregate with other copies of the unfolded or misfolded 16:13:30 16:13:36 16:13:40

protein, and such aggregates would precipitate. And because they're not folded, they're not active. 16:13:43 16:13:47 16:13:52

So the fact that they precipitate is indicative of an aggregated, misfolded structure. And as we said earlier, folding is required for activity. So that's how I would look at that. We've had lots of those in my lab. If it precipitates, chances are it's not folded. 16:13:52 16:13:55 16:13:58 16:14:01 16:14:03 16:14:06

Q You used the phrase "drawing a fence" multiple times. What do you mean when you say "drawing a fence"? 16:14:09 16:14:12 16:14:14

A Yeah, so that's the end of paragraph 26. Give me a moment to try and come up with a clear way of describing that. I mean, this is language, you know, that was quoted from -- from the legal literature. 16:14:15 16:14:37 16:14:40 16:14:46 16:14:48

But as I'll interpret it here, it means that it's not sufficient to say, I claim everybody in this room, because they're within the boundaries of this room. That instead, one has to provide a description of what it is one is 16:14:49 16:14:57 16:15:02 16:15:06 16:15:09

claiming. 16:15:11

Maybe that metaphor is not good because we're not actually making things. But we'll use the broken metaphor. It's not sufficient to say I claim everything that is within the boundaries of these walls. 16:15:12 16:15:15 16:15:17 16:15:21 16:15:25

But instead, one has to actually demonstrate inventing something by enabling the making of that and describing the properties of that which one is making. 16:15:26 16:15:28 16:15:34 16:15:38

Q What does it mean to you to have invented something? 16:15:43 16:15:47

A What does it mean to invent something? 16:15:47

MR. KUSHAN: Objection. Foundation. Objection as to form. 16:15:50 16:15:54

A It means to invent -- to come up with something novel that has use that wasn't, you know, being used before. I mean, it's -- I noticed when you handed out this patent, it said "to promote the progress of science and useful arts." 16:16:05 16:16:19 16:16:26 16:16:34 16:16:39 16:16:42

There's a focus on useful stuff. So the 16:16:42

patent is patenting -- well, all right. So 16:16:46
inventing something -- my understanding of 16:16:48
inventing something that's patentable is coming up 16:16:50
with something novel that is useful. And that's, 16:16:53
you know, what we mean by inventing something. 16:16:59
Q Does it matter how you come up with the 16:17:01
something that is novel and useful? In other 16:17:04
words, do you have to actually engineer an amino 16:17:08
acid sequence from scratch, or can you identify 16:17:13
your novel and useful something by, for example, 16:17:16
screening? 16:17:20
MR. KUSHAN: Objection. Foundation. 16:17:24
A I have no objection to screening. It 16:17:37
has -- but it has to be done -- yeah. I have no 16:17:39
objection to screening. 16:17:43
So you come up with something useful, and 16:17:45
then you characterize it and provide -- you 16:17:48
provide a written description of how to make this 16:17:51
thing and what its properties are. Yeah. 16:17:54
Q How many properties do you have to 16:17:59
identify in order to have invented something? 16:18:01
MR. KUSHAN: Objection. Foundation. 16:18:04

Objection as to form. 16:18:05

A I would say enough properties so that 16:18:14

someone of -- skilled in the art knows what it is 16:18:18

and how it's used. 16:18:21

And in the case of a -- of macromolecules 16:18:29

like this, you know, you'd want to sequence; you'd 16:18:34

want to know something about its secondary 16:18:37

structure, its tertiary structure, its activity, 16:18:39

its solubility, you know, its protein properties. 16:18:45

Q So in order to -- in order to invent, for 16:18:47

example, a PH20 polypeptide, would you have to 16:18:51

disclose a crystal structure? 16:18:56

A Have to what? 16:18:57

Q Disclose a crystal structure of PH20? 16:18:58

A Of a -- of a mutant? What -- 16:19:03

Q Of PH20 in general? 16:19:04

MR. KUSHAN: Objection. Foundation. 16:19:06

A You would have to know enough about it so 16:19:23

that one could understand what it is that's 16:19:27

approaching with such and such activity with such 16:19:29

and such uses. Whether you needed a crystal 16:19:32

structure or not, my assumption is that would have 16:19:40

changed over the past many years. 16:19:45

But I think -- originally, I think people were able to claim without crystal structures if they had sufficient information about what the molecule was, sequence and utility, solubility, you know, stuff like that. 16:19:47 16:19:52 16:19:56 16:19:59 16:20:05

Nowadays I expect you would want to present a structure. I'm sure the standards have gone up. 16:20:06 16:20:08 16:20:11

Q So, in your view, does the fact that there's no crystal structure for PH20 disclosed in the patent, does that indicate that there was no invention in the patent because there's no crystal structure? 16:20:11 16:20:14 16:20:19 16:20:22 16:20:25

A No. I didn't say that, no. That was a long time ago. 16:20:26 16:20:30

Q So it's -- okay. Sorry, strike that. 16:20:33

Does Claim 1 of the '600 patent cover modified PH20 polypeptides that are not expressed in cells? 16:20:36 16:20:41 16:20:42

MR. KUSHAN: Objection. Foundation. 16:20:45

A All right. Does Claim 1 what? 16:20:48

Q Cover modified PH20 polypeptides that are not expressed in cells? 16:20:50 16:20:54

MR. KUSHAN: Objection. Foundation. 16:20:57

A Such as made by solid phase synthesis? 16:21:05

Q Yes. 16:21:10

A In the case of this patent, I think it wouldn't because I don't think you could make it in that -- in that period of time, I don't think you could have made it by -- by solid phase synthesis. It's a big protein. You couldn't do that. 16:21:11 16:21:14 16:21:16 16:21:17 16:21:21 16:21:25

Q Okay. Is it fair to say that you interpreted the claims of the '298 patent, the '262 patent, and the '035 patent also to require hyaluronidase activity? 16:21:25 16:22:16 16:22:21 16:22:25

A We should look at those specifically before we answer that question, right? 16:22:29 16:22:31

Q Okay. So let's start with -- 16:22:33

A Are the claims -- we can look at them in the context of the -- 16:22:39 16:22:43

Q So your declaration for Matter 4 is the '298 patent. 16:22:44 16:22:46

A Yeah, yeah, yeah, yeah. That's what I was about to say. So we can look at them in the context of the declaration right now, the four other patents. 16:22:47 16:22:49 16:22:52 16:22:54

Q Yep, correct. Okay. 16:22:55

Page 62 of your declaration for Matter 4. 16:23:08

A Wait. 16:23:11

Of? 16:23:12

Q For Matter 4. 16:23:12

A The '298 patent? 16:23:14

Q Yes. It's on page 62. 16:23:15

A Okay. 16:23:25

Q Okay. And on page 62 in paragraph 114 of your declaration in Matter 4, you have reproduced Claim 1 of the '298 patent; correct? 16:23:26 16:23:31 16:23:34

A Yes. 16:23:37

Q And in forming your opinions regarding Claim 1 of the '298 patent, did you interpret the '298 patent to require hyaluronidase activity? 16:23:38 16:23:41 16:23:45

A Let me read it once again just to make sure. 16:23:48 16:23:51

Yes. 16:24:16

Q All right. Did you interpret the claim to require at least 40 percent hyaluronidase activity? 16:24:16 16:24:17 16:24:24

A As I said earlier, I'm uncomfortable with fixating on that number. 16:24:24 16:24:31

The -- the authors of the patent have chosen that number, so I'll go along with it. But I -- you know, I'm not comfortable with fixating on that number. 16:24:32 16:24:34 16:24:39 16:24:42

Q So how much activity do you think is required to satisfy the claim? 16:24:44 16:24:46

A I would say enough activity to be useful in a biomedical application or in any application that uses this enzyme. And since I don't use this enzyme as a practitioner, I'm not sure how much activity is required. They seem to think 40 percent is a cutoff, so that seems reasonable. 16:25:01 16:25:06 16:25:10 16:25:13 16:25:16 16:25:18

But I'm very hesitant to say I know exactly what that number should be. I don't have experience in the clinical use of this enzyme, but enough activity to make it useful as a product. 16:25:22 16:25:24 16:25:26 16:25:29

Q Does it need to have enough activity to 16:25:36

make it useful as a commercial product in order to satisfy the claim? 16:25:39 16:25:42

MR. KUSHAN: Objection. Form. 16:25:44

A It needs to be useful -- it needs to be useful. It needs to be useful to somebody who uses hyaluronidase enzymes. 16:25:49 16:25:55 16:26:00

I understand most of those uses are clinical, but one could imagine others as well, right? Activity in a clinical setting might need to be above a certain bar, whereas if you're using the enzymes to create hyaluronic acid in a laboratory experiment, you could use a lower activity, and it would still degrade the polymer for you. But if you had no activity, it would be useless. 16:26:04 16:26:06 16:26:12 16:26:16 16:26:19 16:26:25 16:26:29 16:26:30 16:26:32

Q All right. So now let's go to the declaration for Matter 6, which is the '262 patent, and page 65 -- actually, no. 16:26:33 16:26:48 16:26:52

Page 66, sorry. 16:27:05

MR. KUSHAN: Page what? 16:27:08

A The '262 patent, page 66? 16:27:09

Q '262 patent, Matter 6 declaration, page 16:27:12

66. 16:27:16

A Okay. 16:27:16

Q All right. And that's Claim 1 of the '262 patent; right? 16:27:17 16:27:19

A Okay. I'll reread it just to be thorough. 16:27:20

Q Okay. 16:27:23

A Okay. 16:27:53

Q All right. So in your analysis regarding the '262 patent, did you interpret Claim 1 to require hyaluronidase activity? 16:27:55 16:28:00 16:28:05

A Yes. 16:28:06

Q Did you require Claim 1 to require enough hyaluronidase activity such that the modified polypeptide is useful? 16:28:09 16:28:14 16:28:19

A Thanks for wording it that way. 16:28:19

Q Okay.

A Yes. We're getting -- we're getting away from that 40 percent thing, but, yes, that it be useful. 16:28:21 16:28:24 16:28:28

Q All right. And then, finally, for Matter 9, the '035 patent. That's page 65 -- or I'm sorry, no. 16:28:28 16:28:35 16:28:49

Page 66, again. 16:28:49

A Okay. I'm going to reread it once again. 16:28:53

Formatting is different, so hang on a second. 16:28:56

Okay. 16:30:10

Q So in rendering your opinions regarding 16:30:11

the '035 patent, did you require the claims to 16:30:14

have hyaluronidase activity? 16:30:18

A Yes. 16:30:19

Q And, similarly, in your analysis in the 16:30:20

'035 patent, did you require the claims to have 16:30:24

sufficient hyaluronidase activity that the 16:30:27

modified PH20 polypeptide is useful? 16:30:31

A Yes. Useful, yes. 16:30:31

Q All right. All right. So now we're going 16:30:39

to mark another exhibit. This is Exhibit 1010. 16:30:48

MR. KUSHAN: Here. 16:31:18

(Exhibit 1010 was introduced for identification.)

Q Dr. Hecht, do you recognize Exhibit 1010 16:31:27

as the Zhang paper? 16:31:31

A Yes. I've seen this before. 16:31:32

Q And this is one of the papers that you 16:31:33

considered in forming your opinions in this case; right? 16:31:37 16:31:40

A Correct. 16:31:40

Q So a while ago this morning, we talked about the reaction mechanism for PH20. 16:31:41 16:31:44

And if you turn to page 9434, I believe you will find the reaction mechanism. 16:31:51 16:31:55

A Okay. 16:31:58

Q So, Dr. Hecht, on page 9434, is that the -- in Scheme 1, does the reaction mechanism displayed there, does that show the double displacement hydrolysis mechanism of action for the hyaluronidases? 16:32:59 16:33:03 16:33:07 16:33:09 16:33:14

A That's how they're describing it. 16:33:15

Q And in that reaction with respect to HYAL1 -- that's the glutamic acid 131 that functions as the proton donor; is that right? 16:33:18 16:33:23 16:33:27

A Okay. Yeah. 16:33:35

Q So glutamic acid 131 is directly involved in the hydrolysis reaction for -- with respect to HYAL1; is that right? 16:34:20 16:34:25 16:34:31

A That's what's shown in the figure, yeah. 16:34:31

Q And that glutamic acid 131, that corresponds to glutamic acid 113 in PH20; is that right? 16:34:37 16:34:41 16:34:46

A We'd have to look that up. 16:34:46

Q Look it up. 16:34:48

Okay. Can you turn to page 9436 in Zhang? 16:34:50

A Sorry. I was rereading parts of it. 9436. 16:35:04 16:35:08

Q Yes. 16:35:09

A Okay. 16:35:16

Q On 9436, do you see Figure 1? 16:35:17

A I do. 16:35:20

Q And in Figure 1, the Zhang authors have superimposed the hyaluronic acid tetramer from the bee venom structure onto the HYAL1 crystal structure; is that right? 16:35:20 16:35:25 16:35:31 16:35:34

A That's my understanding of it, yeah. 16:35:34

Q And in Figure 1B, they depict interactions between residues in the HYAL1 active site and the hyaluronic acid tetramer; is that right? 16:35:36 16:35:39 16:35:49

A That's what I see. 16:35:52

Q And do you see the glutamic acid 131 in 16:35:53

that figure? 16:35:57

A I do. 16:35:59

Q And do you see interactions between the glutamic acid 131 and the hyaluronic acid tetramer? 16:36:00 16:36:02 16:36:08

A I see that. 16:36:09

Q So can we keep this handy, but if you could turn in your Matter 3 declaration? 16:36:33 16:36:37

A That's the -- the '600 patent. 16:36:42

Q The '600 patent declaration. To paragraph -- actually, to page 46. 16:36:46 16:37:03

A Okay. 16:37:12

Q And on page 46, you have reproduced Table 1 from the Zhang paper; right? 16:37:14 16:37:18

A Yeah. Let me just -- I'd like to stare at it and see it with both documents. Okay. 16:37:20 16:37:23

Q And in the text on page 46, you say, "Zhang also showed that single substitution mutants at each of these identified positions in HYAL1 rendered the enzyme inactive or significantly reduced its hyaluronidase activity"; correct? 16:37:31 16:37:50 16:37:52 16:37:54 16:37:58 16:38:02

A That's what it says. 16:38:02

Q So Table 1 in the Zhang paper shows that single substitution mutants at various positions in HYAL1 inactivated or significantly reduced hyaluronidase activity; is that right? 16:38:04 16:38:08 16:38:13 16:38:18

A That's what it says, yeah. 16:38:18

Q So which of these mutants in Table 1 would you say are inactive? 16:38:31 16:38:34

A The ones that have less than 1 percent activity I would classify as inactive. The ones that have single-digit, 2, 3, 4 percent activity, I would classify as very low activity. 16:38:53 16:38:56 16:39:02 16:39:05

Q And when you say percent, are you talking about the column that has percent wild-type activity at 50 micromolar? 16:39:10 16:39:13 16:39:15

A Right. So let's go through that. So the first line there is the wild-type. That's defined as a hundred percent. Then the amino acid you were speaking of a little while ago was glutamate 131 or glutamate 131 changed to 2 glutamine, which is, in some situations, a subtle mutation. In this case it decreases activity by, what, a 16:39:19 16:39:21 16:39:23 16:39:26 16:39:30 16:39:34 16:39:37

thousand-fold. Okay. 16:39:44

And so I would say that's a -- that's 16:39:46

pretty dramatic. So .08, right, that's pretty 16:39:49

dramatic. So I would classify that as inactive. 16:39:54

And some of the ones below that that have 4 16:39:58

percent activity relative to the wild-type enzyme, 16:40:02

I would describe those as low activity. 16:40:04

Q Okay. If an enzyme has 4 percent 16:40:07

activity, would you consider that enzyme to be 16:40:21

useful? 16:40:24

A You say if it's 4 percent, would I 16:40:25

consider it useful? Was that your question? 16:40:27

Q Yes. 16:40:30

A Again, I -- I come from a -- my laboratory 16:40:33

and my research, throughout my -- most of my 16:40:37

career is working with novel proteins made from 16:40:39

scratch, and their activity levels are very low. 16:40:42

And so my understanding of this is 16:40:46

impacted by that experience. And so while 16:40:51

something that's 4 percent as active as the wild 16:40:53

types would probably, if you had a wild-type 16:40:58

enzyme, you probably would not want to pursue the 16:41:00

one that was only 4 percent active. But for academic studies, you might. 16:41:03 16:41:07

But if I were, you know, getting back to these patents, I would say that 4 percent is not something you'd want to pursue. 16:41:08 16:41:12 16:41:15

Q But if it's something that you might want to pursue for academic studies, then, it has the potential utility. Isn't that right? 16:41:19 16:41:21 16:41:25

MR. KUSHAN: Objection. Foundation. 16:41:27

A I -- okay. Let me restate that. For academic studies, yes. If it's something that a company sells for use in an academic lab as a reagent, that's a use. That's not what I was meaning. What I was meaning is in terms of basic research and understanding and something that's interesting, but I would say -- so let's be clear about that. 16:41:30 16:41:35 16:41:37 16:41:41 16:41:44 16:41:47 16:41:49 16:41:51

So something of low activity -- if you have a polymer such as hyaluronic acid, and you want to degrade it in a laboratory, some company might sell you a hyaluronidase that's only 5 percent as active as the natural one. And that 16:41:51 16:41:54 16:41:59 16:42:02 16:42:05

would be perfectly adequate. You would purchase it and use it perhaps. 16:42:09

That's a different example of -- when I say it's of academic interest, then I'm saying, oh, it's intellectually interesting as I try and tease apart which amino acids are doing what. I might want this data for intellectual interests, but I'm not using it for something. 16:42:11 16:42:12 16:42:18 16:42:20 16:42:25

Q So if a company were to sell, as a reagent, the hyaluronidase that's only 5 percent as active -- 16:42:28 16:42:32 16:42:35

A You say 5 percent, did you say? 16:42:35

Q Yes, 5 percent is active as wild-type, that would still be a use; right? That would still have utility? 16:42:37 16:42:40 16:42:42

A If a company were selling that as a laboratory reagent. Is that what you're saying? 16:42:43 16:42:45

Q Yes. 16:42:48

A I would say that's a low-activity protein, but it's not inactive. And that would be used. That's why before I was so uncomfortable with fixating on 40 percent. 16:42:48 16:42:51 16:42:55 16:42:56

Q When you -- I think you said that for your de novo protein work, you would see low activity. I'm just trying to get a sense of like what level of activity you're talking about when you say "low activity." 16:42:59 16:43:11 16:43:17 16:43:20 16:43:22

A It's kind of apples and oranges. We're not looking at hyaluronidase enzymes or things like that. We're looking at semi-random sequences and asking: Can a semi-random sequence that never existed before on planet earth possess any kind of catalytic activity beyond background? 16:43:24 16:43:27 16:43:30 16:43:33 16:43:38 16:43:41

And then if it has an activity that's even a thousand-fold lower than a natural enzyme, it's kind of cool, because it never arose in nature. 16:43:43 16:43:46 16:43:49

So it's intellectually kind of cool. It's useless, but it's intellectually cool. I would not attempt to patent such a thing. 16:43:52 16:43:55 16:44:01

Q All right. So you agree that the Zhang paper shows that mutating glutamate 131 to glutamine inactivated the HYAL1 protein; right? 16:44:04 16:44:16 16:44:24

A It reduced its activity by a thousand-fold so let's -- as I said many times, these things are 16:44:27 16:44:30

not binary. There's a continuum. So where we draw the line between activity and inactive is a decision. Okay. 16:44:34 16:44:37 16:44:40

So it -- it -- it ruined activity by a factor of a thousand. That's pretty dramatic. 16:44:41 16:44:45

Q And it makes sense that mutating glutamate 131 had a dramatic impact on activity because glutamate 131 is the proton donor in the hydrolysis reaction; right? 16:44:48 16:44:54 16:44:58 16:45:01

A Right. So the result depicted in Table 1 is entirely consistent with the mechanism showed in Scheme 1 and the structure shown in Figure 1. 16:45:02 16:45:05 16:45:08

Q So a POSA reading the Zhang paper would reasonably expect that if they were to mutate the glutamate 131 in HYAL1, that they would dramatically reduce the activity of the enzyme; right? 16:45:11 16:45:15 16:45:19 16:45:24 16:45:30

A I want to make sure I understood you. You're saying that who would expect this? 16:45:30 16:45:33

Q The POSA, POSA. 16:45:36

A Oh sorry. So a skilled person in the field -- 16:45:37 16:45:42

Q Skilled person. 16:45:42

A Yeah, sorry. Would -- repeat what you said. Would expect that if you made that mutation, that would diminish activity dramatically. 16:45:43 16:45:46 16:45:49 16:45:52

Q Yes. 16:45:53

A Oh, yeah, yeah, yeah, yeah, yeah. 16:45:54

Q So isn't it also the case that if a POSA -- or sorry. Strike that. 16:45:56 16:45:59

Isn't it also the case that a POSA would reasonably expect that if they were to change glutamate 131 and also change tyrosine 247 and also change aspartate 129 in HYAL1, they would dramatically reduce activity? 16:46:03 16:46:06 16:46:11 16:46:17 16:46:23

MR. KUSHAN: Objection. Foundation. Objection as to form. 16:46:25 16:46:27

A To clarify your question, are you saying doing them one at a time or you -- is that what you're asking? 16:46:30 16:46:32 16:46:36

Q All together. Changing them all at the same time. 16:46:36 16:46:38

A In the same molecule. One would expect if 16:46:38

one changed all three of those simultaneously, one would wind up with a protein that had zero activity or close to zero activity. Again, that's a continuum. I don't want to commit to zero, but maybe .0001 percent. 16:46:43 16:46:46 16:46:49 16:46:53 16:46:57

Q And adding on to that, the skilled person would expect that if they made five changes in HYAL1, they change 131, 247, 129, 202 and 245, they would reasonably expect that they would dramatically reduce the activity in the protein; right? 16:47:00 16:47:03 16:47:05 16:47:13 16:47:16 16:47:19

MR. KUSHAN: Objection. Foundation. Also objection as to form. 16:47:19 16:47:21

A Those were all you chose -- 16:47:24

Q Yes. 16:47:27

A -- from this table. 16:47:27

Q Yes. 16:47:28

A Yes. I would say that if one made mutations at all those -- if one made all these mutations simultaneously in the same sequence, one would anticipate a huge reduction in activity. 16:47:29 16:47:32 16:47:35 16:47:40

Q Okay. And why is that? 16:47:47

A I know why. I'm looking for words to best explain it. If you break something, it no longer performs its function or its function is diminished. If you break it simultaneously in five places, then its function is more dramatically diminished. 16:48:03 16:48:09 16:48:27 16:48:29 16:48:33 16:48:36

If you break a bone in your leg, you can maybe hobble along. If you break five bones, you won't. Sorry for the negative graphic, but yeah. 16:48:44 16:48:47 16:48:50

Q All right. So let's mark Exhibit 1013. 16:48:57

(Exhibit 1013 was introduced for identification.)

Q Dr. Hecht, do you recognize Exhibit 1013? 16:49:23

A The Frost paper. 16:49:26

Q Yes. Do you recognize -- sorry, strike that. 16:49:27 16:50:22

You relied on Exhibit 1013 in forming your opinions in this case? 16:50:23 16:50:26

A I looked, yeah. I looked at the Frost paper. That was part of my thinking about this project, yeah. 16:50:27 16:50:29 16:50:31

Q Okay. So let's go to page 432. And so 16:50:32

I'm actually going to point you to the first sentence on page 432. But that sentence starts on page 431, so -- or actually, no. It starts on page 430. 16:50:55 16:50:58 16:51:01 16:51:04

A Okay. 16:51:17

Q So the sentence on page 4 -- at the bottom of page 430 is: "Transfection of these deletion mutants into" -- and then continues on 432 -- "into Chinese Hamster Ovary (CHO) cells followed by screening for enzyme activity using microtiter-based enzyme assay with biotinylated hyaluronan revealed that soluble hyaluronidase activity could be recovered in the conditioned medium from deletion mutants terminating after Amino Acids 477 to 483"; is that right? 16:51:21 16:51:25 16:51:29 16:51:33 16:51:36 16:51:38 16:51:42 16:51:46 16:51:46 16:51:50

A That's what it says. 16:51:53

Q And then it continues: "Less than 10 percent activity was recovered when constructs terminated after amino acid 467 or when using the full-length PH20 cDNA"; right? 16:51:56 16:51:58 16:52:01 16:52:07

A Yeah. 16:52:09

Q Do you have an understanding as to what 16:52:11

the word "soluble" means in that paragraph? 16:52:14

A Let me -- let me go to the paragraph again. 16:52:17

Yes. 16:52:21

Q And what is your understanding of what the word "soluble" means in that paragraph? 16:52:48

A Yeah. This is different from what I was describing for solubility in our earlier discussion. 16:52:48

So this is basically that the stuff is -- is not attached to the -- the cell boundary, the membrane; that it's soluble. This is not an issue of unfolded and aggregated. 16:52:51

So, in this case it's secreted, and it's soluble in the medium. 16:52:53

Q Okay. And the Frost paper is teaching that mutants that terminate from amino acids 477 to 483 were soluble and exhibited hyaluronidase activity; is that right? 16:52:55

A Mm-hmm. 16:52:59

Q And the Frost paper is also teaching that mutants that terminated between 467 and 476 had 16:52:59 16:53:03 16:53:06 16:53:11 16:53:16 16:53:19 16:53:23 16:53:29 16:53:44 16:53:52 16:53:52 16:53:57 16:54:01

less than 10 percent activity; is that right? 16:54:09

A Well, they say less than 10 percent was recovered when constructs terminated after amino acid 467 or when using the full length. Yeah. 16:54:14 16:54:18 16:54:20

Q So would the skilled person reading the Frost paper understand that a PH20 construct that terminated, for example, at position 477 would be soluble and have hyaluronidase activity? 16:54:34 16:54:36 16:54:42 16:54:45

A The text says that it -- that the assay that they did revealed that soluble activity, hyaluronidase activity, could be recovered in the conditioned medium from deletion into terminating after amino acids 477 to 483. 16:54:50 16:54:54 16:54:58 16:55:00 16:55:01

I think that's what you're asking? 16:55:04

Q Yes. 16:55:06

A Yes. That's what it says, yes. 16:55:08

Q So can we turn in your declaration to paragraph 88? 16:55:47 16:55:49

A Yes. Let me get oriented here. Okay. I'm with you, paragraph 88. 16:55:54 16:56:14

Q All right. So we had looked at the -- at the Zhang Table 1, which is on page 46. 16:56:16 16:56:22

And now we're looking at paragraph 88, which is on page 47 of your declaration, just to orient you. 16:56:24 16:56:26 16:56:29

A Well, we're looking at paragraph 88, which is next to that. Yeah. 16:56:30 16:56:32

Q Yeah. Okay. 16:56:34

And so in paragraph 88, you say, "Zhang (EX1010) identified positions in HYAL1 corresponding to D111" -- I think that should be "E113, D184, S227, Y229, R246, W304, and N333 in PH20, as well as the Hyal-EGF domain from 337 to 409 in PH20"; is that right? 16:56:35 16:56:39 16:56:41 16:56:46 16:57:06 16:57:11

A Okay. 16:57:13

Q So is it fair to say that the mutations -- that you're talking about the mutations in Table 1 of Zhang, and you are correlating the amino acids from the HYAL1 sequence in Table 1 to the positions in PH20? 16:57:14 16:57:21 16:57:30 16:57:34 16:57:38

A That what you're saying -- yeah. I mean, what you're saying is identify positions of HYAL1 corresponding to -- blah, blah, blah, blah -- in PH20. 16:57:43 16:57:45 16:57:49 16:57:52

So I think that's what you're saying? 16:57:52

Q Yes. 16:57:54

All right. So do you know one way or the other whether the "D113" should be an "E113"? 16:58:09 16:58:14

A That's interesting. 16:58:18

If we look at the figure in the Zhang paper, there's a D and an E two positions apart. And so that seems consistent with what you're implying. 16:58:19 16:58:22 16:58:26 16:58:33

Q Mm-hmm, yes. 16:58:34

A I have to say I didn't notice that, but -- 16:58:34

Q Okay. 16:58:36

A -- good eyes. 16:58:37

Q And, similarly, actually, if you look at the preceding sentence, you say, "Arming identified positions D111, E113"? 16:58:39 16:58:41 16:58:43

A Yeah. That looks right. 16:58:47

Q Okay. So is it correct, then, that E113, the glutamate 113 in PH20, is the residue that is the proton donor in the catalytic reaction? 16:58:49 16:58:55 16:59:00

A Give me a second. 16:59:08

You're saying E113 in PH20? 16:59:12

Q Yes. 16:59:18

A It seems that way. I mean, I -- you know, 16:59:19

I'd have to -- that's what it seems to imply here. 16:59:21

I'd have to look them all up and line them up 16:59:24

again, but that's the logic here. 16:59:27

Q All right. So we've been going for 16:59:30

probably more than an hour. 16:59:32

Do you want to take another break? 16:59:34

A Sure. Can we make it a shorter break -- 16:59:35

THE VIDEOGRAPHER: We are going off the 16:59:37

record.

A -- so we're not here until midnight.

THE VIDEOGRAPHER: The time is 4:59. 16:59:39

(A recess was taken.) 17:17:32

THE VIDEOGRAPHER: We are back on the 17:17:32

record. The time is 5:18 p.m. 17:18:33

BY MS. MARTIN: 17:18:37

Q So, Dr. Hecht, would you agree that all 17:18:39

PH20s that have hyaluronidase activity -- that all 17:18:43

PH20s that have hyaluronidase activity cleave 17:18:50

hyaluronidase through a hydrolysis reaction? 17:18:56

MR. KUSHAN: Objection. Foundation. 17:18:58

Objection as to form. 17:19:01

A I would assume so. I have not, you know, 17:19:05

looked at all of them, but I would assume so. 17:19:09

Q So is it fair to say that all PH20s that 17:19:12

have a sequence that's 95 percent identical to SEQ 17:19:16

ID NO. 3 and that are active, that all of those 17:19:22

PH20s cleave hyaluronic acid through a hydrolysis 17:19:28

reaction? 17:19:35

MR. KUSHAN: Objection. Form. 17:19:35

A I can't add -- I mean, it's a reasonable 17:19:38

assumption, but until one does the experiment and 17:19:39

does the analysis, one doesn't know for sure. 17:19:43

It's sort of a classic thing in this field 17:19:46

is that these are all reasonable assumptions, but 17:19:48

you, nonetheless, want to confirm them. 17:19:50

Q So you think that there may be some other 17:19:54

mechanism of action other than a hydrolysis 17:19:56

reaction whereby PH20 with 95 percent sequence 17:19:59

identity to SEQ ID 3 cleaves hyaluronic acid? 17:20:02

A I'm aware of other enzyme systems where 17:20:13

people have mutated away an essential catalytic 17:20:16

residue, expecting to lose all activity, and then 17:20:21

found some small level of activity remaining, 17:20:25
thereby suggesting that binding and molecular 17:20:29
strain might have been sufficient to get a tiny 17:20:34
bit of activity, even when catalytic atoms are not 17:20:37
there. 17:20:40
So while your point is a good assumption, 17:20:41
I would not want to answer that in absolute terms. 17:20:44
Q Are you aware of any evidence with respect 17:21:00
to -- with respect to hyaluronidases, that if you 17:21:05
mutate the glutamic acid that is the proton donor 17:21:08
in the hydrolysis reaction, that they are still 17:21:14
able to cleave hyaluronic acid through some other 17:21:17
mechanism? 17:21:22
A The last two words, that -- 17:21:23
Q That they're still able to cleave 17:21:24
hyaluronic acid through some other mechanism? 17:21:30
A Well, you pointed out that the -- in the 17:21:33
Zhang paper that the mutation of glutamate 131 in 17:21:38
Table 1 of the Zhang paper produces an enzyme that 17:21:44
has very, very, very low activity, but it's not 17:21:48
zero. 17:21:52
And so that would lead the curious 17:21:53

individual to think, huh, maybe there's an alternative mechanism in a situation where binding is still present, but the catalytic atoms are no longer present. Maybe it's still possible to cleave by a mechanism where water substitutes for the amino acid or whether just a mere strain of binding would give some very, very low level of cleavage, even in the absence of the original catalytic mechanism. 17:21:57 17:22:01 17:22:04 17:22:08 17:22:10 17:22:16 17:22:20 17:22:23 17:22:27

So while I agree that your assumption is a good one, I'd be hesitant to say that's an absolute thing until one does a lot more study of it. 17:22:28 17:22:31 17:22:35 17:22:37

As I said, I'm aware of other situations in other enzymes where people mutated out the key catalytic residue, assuming the enzyme would be a hundred percent completely dead or, said differently, having 0.000 level of activity, and they saw, huh, it has some activity. 17:22:38 17:22:40 17:22:46 17:22:51 17:22:53 17:22:57

And that caused people to rethink the simple assumption you were making; that is, you know, if you, you know, kick out the hydrolytic 17:23:00 17:23:02 17:23:06

side chain, then you would lose it all. So, you know, it's a good assumption, but I would want to confirm it in a lab. 17:23:12 17:23:15 17:23:16

Q And how would you confirm it in the lab? 17:23:18

A Oh, goodness. Well, in this case, the Zhang paper confirms that it's not completely dead. 17:23:20 17:23:33 17:23:37

As we said, you know, the first entry in that table, Table 1 of the Zhang paper, shows that while, for practical purposes, this protein has no activity, right, it's less than one one-thousandth -- less than one one-thousandth -- it hasn't -- so for practical perspective, it has no activity. 17:23:37 17:23:39 17:23:44 17:23:48 17:23:52 17:23:57

But, again, as I said earlier, from a quote unquote, "academic" perspective, not for use, but for intellect -- from an academic perspective, the fact that it's not 0.000; that it's 0.08 would lead one to believe that maybe something else is going on. 17:23:59 17:24:01 17:24:03 17:24:08 17:24:12 17:24:15

What would I do to test that? Hmm, I'd have to think about that. There's some isotope experiments you could look at to see whether you 17:24:17 17:24:28 17:24:31

put a deuterium in there, whether a deuterium was transferred. I don't know. I'd have to think about that. I don't want to -- I don't want to say for sure what I would do to test that. But you'd want to test it in a lab in some creative way to figure out that even when you remove the catalytic side chain that you still get some amount of cleavage what's going on. 17:24:34 17:24:39 17:24:41 17:24:42 17:24:44 17:24:48 17:24:51

Q So you said that you didn't consider an amino acid sequence to be a formula. Do you consider an amino acid sequence to be a structural feature? 17:24:54 17:25:25 17:25:27 17:25:29

MR. KUSHAN: Objection. Foundation. 17:25:31

A So with respect to formula, going to the beginning of your comment, I mean you could have the dipeptide glutamate lysine or lysine glutamate that have the same chemical formula but they're different things. So that's why I'm saying amino acid sequence and formula are different. 17:25:38 17:25:40 17:25:45 17:25:51 17:25:54 17:25:57

Your next question was about structure? So amino acid sequence is not a formula. It's related but it's not the same thing. 17:26:00 17:26:07 17:26:10

Q Is amino acid sequence a structural feature? 17:26:14 17:26:16

A Usually when chemists talk about structure, they're thinking in three dimensions, and so an amino acid sequence, you know, according to the development of protein folding amino acid sequence -- 17:26:26 17:26:30 17:26:32 17:26:35

(The reporter requested clarification.)

A I'm sorry. When chemists think about structure, they're usually thinking about a three-dimensional structure, okay, and so an amino acid sequence is generally considered -- you know, when you write down the sequence on a piece of paper, that's linear. That's one dimensional. So the sequence in, in the way I just described is not synonymous with a structure which is three dimensional. It's related, you know. In protein folding the sequence gives rise to the three-dimensional structure but it's not synonymous. 17:26:40 17:26:49 17:26:51 17:26:54 17:26:58 17:27:01 17:27:04 17:27:08 17:27:13 17:27:15 17:27:17 17:27:21

Q Amino acid sequence is considered the primary structure in a protein; right? 17:27:22 17:27:25

A Yeah. I think that's a misuse of the word structure, but it's often described that way. I think the word structure, to my mind, connotes three dimensions. 17:27:27 17:27:29 17:27:31 17:27:36

Q Do proteins have a chemical formula? 17:27:49

A Do proteins what? 17:28:07

Q Have a chemical formula? 17:28:08

A You can write a chemical formula. Sure. It's not very interesting but you could add up all the atoms and count how many carbons are there, how many oxygens are there and so on. So you could do that. 17:28:10 17:28:13 17:28:16 17:28:19 17:28:21

It's -- as I said, it's not very interesting because, as I said, you could have many different sequences with the same chemical formula, same number of carbons and hydrogens and nitrogens and oxygens and so on, but they're completely different entities even though they have the same formula. 17:28:22 17:28:25 17:28:29 17:28:31 17:28:35 17:28:38 17:28:39

People who do mass spectrometry are, you know, might be concerned with the formula because they're counting atoms, but it's not very 17:28:45 17:28:47 17:28:49

informative. 17:28:53

Q What do you -- what do you consider to be undue experimentation? 17:29:03 17:29:05

MR. KUSHAN: Objection. Foundation. 17:29:08

A Once again, it's not binary. It's not -- it's not a fine line. This is reasonable experimentation. This is undue experimentation. But if we look at the extremes, something that my grad students could do in the course of their Ph.D. is reasonable. Something that would take a thousand people a thousand years is not. It's undue experimentation, and if you want to draw the line of ten people ten years? I don't know. There's a gradient. It's not a binary thing. 17:29:15 17:29:19 17:29:22 17:29:24 17:29:27 17:29:30 17:29:33 17:29:37 17:29:40 17:29:43

Q And what would you consider to be a research plan? 17:29:45 17:29:47

A A research plan is something that in the old days before funding collapsed a research plan would be something you would write up as a plan to the NSF or the NIH or the DoE or some private foundation as a plan for research where you're proposing to do certain things where you don't for 17:29:49 17:29:57 17:30:02 17:30:06 17:30:10 17:30:15

sure know what the answer will be where you have hypotheses that you'd like to test but you don't know the answer. Quite the contrary. You're asking for funding to support a research plan that would enable you to uncover the answer. 17:30:19 17:30:25 17:30:27 17:30:29 17:30:32

Q Okay. If a skilled person decides to make a modified PH20 polypeptide and they select which mutations to make, would you consider that to be rationale design? 17:30:35 17:30:48 17:30:52 17:30:55

A Could you talk a little louder? I don't hear that well. 17:30:55 17:30:57

Q Sorry. If a skilled person specifically selects which mutations to make in a modified PH20 polypeptide, would you consider that to be rational design? 17:30:58 17:31:01 17:31:05 17:31:07

MR. KUSHAN: Objection. Foundation. 17:31:10

A I have to say once again it's not binary. Yes, we can describe what rational design is and, yes, we can describe what directed evolution is, but there are lots of projects where there's some rational design and some directed evolution. 17:31:11 17:31:15 17:31:17 17:31:20 17:31:24

You know, in some extreme case you're 17:31:30

making random sequences and searching. It's a fishing expedition. In other cases you have a rational design atom by atom of one thing. That's an extreme as well, but much of science in this field is done by merging those two. So... 17:31:32 17:31:35 17:31:38 17:31:42 17:31:44

Q So you say that in paragraph 47 of your declaration. 17:31:51 17:31:55

A Paragraph 47. I'm with you. 17:32:10

Q "At a conceptual level there are two approaches for creating engineered proteins referred to as rational design and directed evolution"; right? 17:32:13 17:32:15 17:32:17 17:32:19

A Right, right. 17:32:20

Q And are those the only two approaches for creating engineered proteins? 17:32:21 17:32:23

A All right. So we're going to not be talking about the present where it's all done by machines, right, by AI, because nowadays it's AI is doing everything. So we're not talking about that. 17:32:31 17:32:34 17:32:36 17:32:45 17:32:47

Q Correct. 17:32:48

A We're back in -- 17:32:48

Q We're back in 2010, 2011. 17:32:49

A Okay. So we're back in 2010, 2011. I would say this is a description of -- you know, I keep coming back to this binary versus a gradation, but this is a description of two extremes of rational design and directed evolution. Those are really useful ways of looking at things, but, in fact, there are many approaches that combine these. 17:32:51 17:33:00 17:33:02 17:33:06 17:33:09 17:33:13 17:33:15 17:33:17

My own lab, for example, we are -- we do rational things, but we're also making large collections and selecting. So we do both, and the product -- not that we do either/or but we do things that incorporate features, both of rational design and of directed evolution and, you know, people do that. 17:33:19 17:33:22 17:33:26 17:33:28 17:33:31 17:33:35 17:33:38

Q So if a skilled person is selecting positions on PH20 to change -- 17:33:38 17:33:42

A Don't use the word selecting. That sounds like a Darwinian selection. You mean choosing. 17:33:45 17:33:48

Q Choosing? 17:33:51

A Okay.

Q A skilled person is choosing positions on PH20 to change and is choosing the substitutions that they're going to make -- 17:33:52 17:33:54 17:33:57

A Right, right, right. 17:33:58

Q -- to PH20, would that be classified as rational design? 17:33:59 17:34:03

MR. KUSHAN: Objection. Foundation. 17:34:05

A It depends. I mean is all choice in life rational? I mean sometimes they're choosing to make certain substitutions back in those days because, you know, the DNA oligos were easy to make or something like that. 17:34:15 17:34:24 17:34:26 17:34:29 17:34:35

But, so again, it's hard to be absolute in the answer, but if one is choosing to make one amino acid, one change based on the structural, structural and sequence analysis, I would call that rational design, yeah. 17:34:36 17:34:38 17:34:41 17:34:46 17:34:48

But if one makes a library or even a collection, let's say you make a collection of a hundred and then you select among them for those that have your desired property, then you're doing rationally biased evolution. 17:34:53 17:34:55 17:34:58 17:35:01 17:35:10

There's a combination of these approaches. I mean I think rational design and directed evolution are really great ways to talk about this as we do on these pages here, but I'm also highlighting that, you know, there are projects that do the best of both or the worst of both. 17:35:14 17:35:15 17:35:19 17:35:21 17:35:25 17:35:28

Q So let's turn in your declaration to your appendices, and in particular let's look at Appendix A-2. It starts at page 128. 17:35:54 17:36:01 17:36:04

A Page 128 you're at? 17:36:12

Q Yes. And the header is on 127 if that's helpful to orient you. 17:36:14 17:36:26

A Hmm? 17:36:28

Q The cover page is on page 127. 17:36:29

A Yeah, yeah. 17:36:32

Q Okay. So Appendix A-2 is a list of all of the -- well, it has a list of the positions in PH20, the wild-type amino acid at that position, and then the substitutions that retained activity, and this is taken from the data that's disclosed in the '600 patent; right? 17:36:33 17:36:45 17:36:47 17:36:50 17:36:56 17:36:59

A Right. And the tables mentioned here. 17:37:01

Q Okay. So for example, position 1, the wild-type amino acid is leucine; right? 17:37:03 17:37:09

A Right. 17:37:13

Q And for substituted amino acids you have one, two, three, four, five, six, seven, eight, nine, 10, 11, 12, 13, 14, 15 amino acids -- 17:37:13 17:37:17 17:37:20

A Okay. 17:37:23

Q -- that were substituted at position 1 and they maintained activity; is that right? 17:37:24 17:37:27

A Right. These are, you know, as a title on page 127 says, it's a composite list of active mutants from the source from the patent. So we -- I'm not going to go back and check each one right now, but assuming that's all correct, that suggests that those substitutions give rise to proteins that are active by the criteria defined in the patent. 17:37:31 17:37:35 17:37:41 17:37:44 17:37:46 17:37:48 17:37:53 17:37:55

Q Okay. Now the patent teaches the results of mutations at every single position from 1 to 447 in PH20; is that right? 17:37:56 17:38:07 17:38:13

A No. There's some gray areas in this which where they're -- right, there are some gray areas 17:38:15 17:38:17

in this table where they don't have data. 17:38:20

Q Well, but that's not because they weren't tested; right? That's because when they made mutations at those positions, the protein was inactive? 17:38:22 17:38:25 17:38:28 17:38:31

A I'd have to go back and look at that. I mean, I -- 17:38:32 17:38:34

Q Because it's in your next -- that's in your next -- 17:38:34 17:38:35

A Yeah, yeah --

Q -- appendix. 17:38:37

A -- yeah. I mean, this is a lot of data here. We have to go back and look at it. 17:38:38 17:38:39

Q So in Appendix A-3 which starts on 142, you see that position 16, which you had grayed out -- 17:38:42 17:38:48 17:38:52

A Right. 17:38:53

Q -- in fact, has a whole bunch of substitutions? 17:38:53 17:38:56

A Correct, a whole bunch of inactive substitutions, right. 17:38:57 17:38:59

Q All right. So you say in your footer in 17:39:01

Appendix A-2 on page 140 that gray filling is no mutants tested at respective PH20 position; right? 17:39:10 17:39:19

A Hold on. Hold on. 17:39:22

You're on page 140? 17:39:23

Q Yes. 17:39:25

A Okay. 17:39:30

Q Do you see that gray -- 17:39:31

A I see that. 17:39:33

Q Okay. And that's not accurate; right? 17:39:35

A From what we just looked at, I -- this seems to be an error. 17:39:37 17:39:40

Q Okay. So, in fact, the patent provides data at every single position from 1 to 447? 17:39:41 17:39:45

A I'd have to go back and --

MR. KUSHAN: Objection. Foundation.

A -- check that but, look at those. Okay. I mean, I'm not going to say for sure because I'd have to go back and look, but let's -- go ahead. 17:39:56 17:39:59 17:40:00

Q Okay. Now, you said in your declaration that the data in the patent are -- are the report of a random mutagenesis experiment; right? 17:40:02 17:40:14 17:40:18

A Okay. Yes. 17:40:28

Q But you didn't intend to suggest that the inventors only mutated random positions on PH20; right? 17:40:29 17:40:33 17:40:51

A Let's discuss what's meant by random, and let's discuss what's meant by targeted. 17:40:51 17:40:53

Usually, in this field, when one uses the word "targeted," one is saying, I'm targeting amino acid 27, or I'm targeting amino acids 27 through 37. That's targeting, like you target an archery target, where you're saying where you're going. 17:40:56 17:40:59 17:41:02 17:41:07 17:41:11 17:41:14

Randomness usually refers to saying, I'm not picking which amino acid to put in. In many experiments, it's both random in composition and in location. 17:41:14 17:41:18 17:41:23 17:41:26

In this case, it was not targeted, okay, in the sense that it was -- say they were exploring the entire sequence. So each experiment was targeted, but the summation of the entire study was not targeted. Okay. 17:41:30 17:41:34 17:41:39 17:41:41 17:41:44

And the choice of which amino acid was put in there was pretty much random. They weren't 17:41:47 17:41:51

saying, Oh, at position 17, I'm only going to put in phenylalanine. They're just allowing lots of things to go in there. 17:41:57 17:42:00 17:42:06

It's not a complete set. They did not try -- make every amino acid every position. That would be an obscene amount of work, but, you know, they made a lot. 17:42:06 17:42:09 17:42:10 17:42:12

Q So, again, when you said random -- when you used the phrase random mutagenesis, you weren't intending to suggest that the inventors only picked a handful of random positions on PH20 to test; right? 17:42:14 17:42:16 17:42:19 17:42:21 17:42:25

MR. KUSHAN: Objection. Form. 17:42:27

A I was -- quite the opposite. I was not -- I'm not suggesting that they targeted particular positions. Quite the opposite. 17:42:37 17:42:41 17:42:43

It was untargeted; it was the whole thing. And so, in that sense, it's not directed toward a particular location. And -- yeah. 17:42:45 17:42:47 17:42:50

Q And, similarly, you also did not intend to suggest that the inventors only provided data for one change at a time, one -- I'm sorry, strike 17:42:55 17:42:58 17:43:01

that. Let me start again. 17:43:05

You were not intending to suggest that the inventors only tested one substitution per position in PH20; correct? 17:43:06 17:43:09 17:43:12

A I'm -- I'm with you, but are you reading from a particular paragraph? 17:43:15 17:43:17

Q No. I'm just asking the question. 17:43:18

A Okay. So then re-ask it, please. 17:43:20

Q You are not intending to suggest that the inventors only tested one substitution per position in PH20; correct? 17:43:22 17:43:24 17:43:27

MR. KUSHAN: Objection. Form. 17:43:29

A You're implying what I said or suggested. 17:43:32

But I'll say now that, as we see from the table, the inventors tested -- they made and studied numerous possible substitutions at -- all over the place. 17:43:35 17:43:37 17:43:43 17:43:50

Q All over the place, meaning at every single position? 17:43:51 17:43:53

A It seems to be every single one. I don't want to go through and -- you know, there might be one missing that I'm not noticing. 17:43:53 17:43:56 17:43:59

But it looks like, you know, either every single one or almost every single one. I don't know. 17:44:01 17:44:04

Q Did you -- did you -- when you rendered your opinions in this case, did you examine whether or not the inventors tested substitutions at every single position? 17:44:06 17:44:08 17:44:10 17:44:13

A I knew that they had tested many positions. I don't think I concerned myself whether it was every single one. 17:44:16 17:44:20 17:44:22

But I knew it was either every single one or the vast, vast majority. 17:44:24 17:44:27

Q So let's look on page 128. 17:44:37

A 1 -- 17:44:43

Q 128. 17:44:45

A Okay. 17:44:46

Q And this is the active table; right? 17:44:46

A Okay. 17:44:49

Q All right. And so you can see, for example, positions 26 through 32. There are many amino acid substitutions that retained activity at those positions; right? 17:44:49 17:44:56 17:45:01 17:45:03

MR. KUSHAN: Objection. Form. 17:45:06

A The occurrence of these entries in this tables suggests that at the numbers you mentioned, many amino acids could be substituted these positions without destroying activity. 17:45:14 17:45:18 17:45:20 17:45:23

Q And many -- both conservative and nonconservative changes were tolerated without destroying activity; right? 17:45:26 17:45:34 17:45:37

MR. KUSHAN: Objection. Foundation. 17:45:40

A At some positions, such as the ones -- you're looking at the bottom of the table on page 128; right? 17:45:44 17:45:48 17:45:51

Q Mm-hmm. 17:45:52

A So at some positions -- the data demonstrate that at some positions, a diversity of amino acids were tolerated. This is what we would usually call -- you know, they're tolerant; they're tolerated, yeah. 17:45:53 17:45:55 17:45:59 17:46:01 17:46:04

Q So that particular position, for example, 26 to 32, is tolerant? 17:46:05 17:46:08

A That's what the data appear to show, right. 17:46:12 17:46:15

Q Okay. 17:46:15

A Now, they did not test all 20 amino acids at all those positions. So it's possible that some are not tolerated, but it looks rather permissive from what we have right here. 17:46:15 17:46:19 17:46:21 17:46:25

Q And the data show that at those positions, the protein is tolerant of a range of amino acids from, for example, at position 30, which started as aspartate, it tolerated arginine, glycine, histidine, lysine, leucine, glutamine, threonine, serine, tryptophan, for example. 17:46:27 17:46:33 17:46:36 17:46:38 17:46:44 17:46:50

That's a wide variety of amino acids; right? 17:46:52 17:46:56

A That's correct. 17:46:56

Q And the data on page 128 shows that other positions, for example, position 23, are less tolerant; right? 17:46:59 17:47:05 17:47:10

A That's right. 17:47:11

Q So position 23 only tolerated the change from E to D; right? 17:47:12 17:47:17

A That's what it shows. That's what the table says. 17:47:19 17:47:21

Q Similarly, if you look on page 129 in position 60, that position only tolerated a change from arginine to lysine; right? 17:47:26 17:47:30 17:47:36

A Correct. 17:47:39

Q And that would be considered a conservative substitution? 17:47:40 17:47:43

MR. KUSHAN: Objection. Foundation. 17:47:45

A In general, arginine to lysine is considered a mild or conservative substitution in most positions, not everyplace, everywhere, but usually. 17:47:48 17:47:50 17:47:53 17:47:57

Q So information about the tolerance of each position on PH20 to substitution is useful; right? 17:47:59 17:48:03

A All information is useful. Information is useful. 17:48:08 17:48:15

Q So, again, the information -- information regarding the tolerance of each one of the 447 amino acids that were tested, that's useful; right? 17:48:15 17:48:19 17:48:24 17:48:29

MR. KUSHAN: Objection -- 17:48:29

A Right -- 17:48:30

MR. KUSHAN: Wait. 17:48:30

THE WITNESS: Sorry.

MR. KUSHAN: Objection as to form. 17:48:31

A Keeping in mind here that one is looking 17:48:32
at single amino acid substitutions, where one 17:48:38
amino acid has replaced -- it has been replaced in 17:48:42
the context of an otherwise wild-type protein. 17:48:45

Q So are you saying that, in general, 17:48:51
knowledge about the tolerance of every single 17:48:56
position in PH20 is, in fact, useless? 17:48:58

A I didn't say that. 17:49:02

Q Okay. So you agree that it is useful? 17:49:04

A I said that. I said all knowledge is 17:49:05
useful. 17:49:07

Q And it's useful because it gives you 17:49:08
information about the extent to which each 17:49:09
position tolerates change and the extent -- and 17:49:12
the types of changes that each position may 17:49:17
tolerate? 17:49:20

MR. KUSHAN: Objection. Foundation. Also 17:49:20
objection as to form. 17:49:22

A It provides some insight about the 17:49:26
tolerance to substitution in the context of an 17:49:29

otherwise wild-type protein. 17:49:34

Q So you would agree that there are some positions in the protein -- and, actually, just to make sure that we're on the same page here, let's look at your inactives table, which, again, starts at page 142. 17:49:38 17:49:41 17:49:45 17:49:48 17:49:55

A Okay. 17:50:03

Q And the grayed-out positions -- and the grayed-out, yeah, positions in your inactives table, those are positions in which every single substitution tested was active? 17:50:03 17:50:06 17:50:09 17:50:12

And if you would like to double-check that for -- please go ahead, like, for example, position 24. 17:50:14 17:50:17 17:50:19

A So in the example, position 24, let's go back. That's what it looks like. Again, I'm not -- you know, unless we go and test every single one -- I don't want to commit to it, but position 24, what you said -- 17:50:21 17:50:24 17:50:27 17:50:30 17:50:33

Q Yeah.

A -- is consistent. 17:50:34

Q And, you know, similarly, position 28 to 17:50:35

32, they're grayed out in your inactives table, but you've got a whole lot of substitutions in your actives table? 17:50:37 17:50:40 17:50:43

A Okay. 17:50:44

Q All right. So fair to say that for positions 24 and 28 to 32, all of the substitutions that were tested maintained activity? 17:50:45 17:50:50 17:50:54 17:50:57

A Give me a second. 17:50:58

That's what the data show. 17:51:06

Q Okay. And, similarly, positions 146 to 148, which are on page 146 in your inactives table, every single position at those residues that was tested maintained activity? 17:51:08 17:51:27 17:51:40 17:51:43

And that is on page 132. 17:51:44

A Okay. 17:51:54

Q Is that right? 17:51:57

A That's what the data show for comparing the table on page 132 with the table on page 146, right? 17:51:59 17:52:03 17:52:08

That's what you're looking at? 17:52:08

Q Yes. 17:52:10

A Yeah.

Q All right. So is the fact that, for example, positions 146 and positions 28 tolerated every single substitution that was tested, would that be helpful to the POSA seeking to make a PH20 that had mutations at positions 146 and position 28? 17:52:13 17:52:15 17:52:20 17:52:23 17:52:29 17:52:32

MR. KUSHAN: Objection. Foundation. 17:52:32

A To make substitutions at those positions in this experiment at that position and in that experiment at that position, right, you're making them separately? What -- 17:52:41 17:52:47 17:52:50 17:52:53

Q No, no. 17:52:54

If a POSA wanted to make a PH20 where they made changes at position 1 -- I'm sorry -- at position 28 and position 46 [sic], would the knowledge that in this experiment -- 17:52:55 17:52:59 17:53:01 17:53:04

A Made those changes simultaneously -- 17:53:05

Q Yes, simultaneously.

A -- in the same molecule? 17:53:08

Q Yes.

A Is that what you're trying to say? 17:53:09

Q Yes. Yes. 17:53:11

A Okay. 17:53:11

Q Would the knowledge from the patent that position 28 and position 146 tolerated every single substitution that was tried at that position, would that be useful or not? 17:53:11 17:53:14 17:53:17 17:53:19

A You know, as I said before, all data is useful. You know, the more data you have, the more insight you gain and the more likely you can predict results. 17:53:23 17:53:26 17:53:28 17:53:34

But, yeah, I mean, the data are useful. It does not say that you can predict the future necessarily, but the data are useful, of course. All data are useful. 17:53:35 17:53:40 17:53:45 17:53:48

Q So is it your testimony that the data in the patent provide no information whatsoever that is useful to a POSA that is seeking to make, for example, a PH20 with 10 mutations, compared to wild-type? 17:54:34 17:54:43 17:54:47 17:54:51 17:54:55

A Once again, I'll say it's the continuum. Having zero data gives you zero insight; having more data gives you more insight. 17:55:04 17:55:10 17:55:12

That's not the same as saying that having X amount of data allows you to predict something accurately. 17:55:14 17:55:16 17:55:21

Q And when you think about having to predict something accurately, what level of certainty are you talking about? 17:55:24 17:55:27 17:55:29

MR. KUSHAN: Objection. Foundation. Also objection as to form. 17:55:31 17:55:33

A It's not really that way. It -- I mean, when you're trying to predict a structure, people ask what level of resolution are you accurate at. 17:55:40 17:55:45 17:55:48

If you're trying to predict a structure, the metric would be the resolution, the root mean square deviation of a location of the atoms. 17:55:51 17:55:53 17:55:56

So when you're evaluating how good a prediction is, you know, is it percentage? Is it angstroms, root mean square deviation? Is it level of activity? It kind of depends on what the -- what the project is. 17:55:59 17:56:03 17:56:11 17:56:15 17:56:17

Q So you were talking about having to predict something accurately if you're making a PH20 with 10 mutations. 17:56:20 17:56:24 17:56:27

What would --
A You said 10?
Q Yeah, with 10 mutation.
What exactly were you thinking that you would have to predict accurately?
A Okay. Okay. So if you're -- let's be clear here. If you're trying to make a -- if you're trying to take a protein -- this protein, PH20 -- and you're planning to make 10 mutations, in many cases even having the data here would not allow you to predict whether that protein would be active.
In some cases that data would be helpful. In -- it would be helpful, but it would probably in many cases not be sufficient to say, All right, I'm going to make this protein that has a whole bunch of mutations, and I'm going to know what's going to happen.
Having data is always better than not having data. But in this business having data doesn't necessarily allow you to predict with great confidence the result of, let's say,

making -- well, I go further -- 15 or 20 mutations? No. That would be really tough. 10, in some cases, it would be okay. In many cases it would not. 17:57:46 17:57:49 17:57:52 17:57:56

Q So when you say "in many cases it would not," what do -- like, what do you have in mind? 17:57:56 17:58:00

A I'm saying in many cases, even if you had at your, you know, at your fingers, if you hadn't had these tables that would facilitate with confidence making a protein with one mutation because it's already been done. 17:58:02 17:58:07 17:58:12 17:58:19 17:58:23

And so in that situation, you'd have high confidence that the mutation would be tolerated or not tolerated because you could know ahead of time because it's on the table. 17:58:25 17:58:28 17:58:34 17:58:38

If you made two simultaneous mutations, you -- your confidence would be not as high as if you were making one because you're making one. You're just copying what's already been done. 17:58:39 17:58:44 17:58:47 17:58:50

If you're making two, then you're inferring from the data that they might or might not be tolerated together. This brings up the 17:58:52 17:58:54 17:58:57

concept of cooperativity, right. 17:59:00

So in -- in -- when people make mutations 17:59:02

at different positions simultaneously and they're 17:59:10

assessing stability or they're assessing some 17:59:16

other function, they'll discuss independence 17:59:18

versus cooperativity. 17:59:22

And it is not always the case that sites 17:59:25

are independent. It is not always the case that 17:59:28

if I change that corner, it has an effect; and I 17:59:31

change that corner, it has an effect; and if I 17:59:34

change them both, I can just add that up. That 17:59:36

would suggest they're additive, and sometimes that 17:59:39

happens. 17:59:41

But sometimes there's cooperativity. So 17:59:42

I'll do it with corners on the floor. If I change 17:59:45

that corner and I change that corner 17:59:48

simultaneously, the wall would fall down. So it's 17:59:50

not additive, right, so there's cooperativity. 17:59:53

The two positions are cooperating together to 17:59:56

produce an outcome. And, therefore, the impact of 18:00:00

changing them is not the additive sum of the 18:00:02

individuals, right. Sometimes it is, but often 18:00:07

it's not. 18:00:08

Q So if you have information that one corner tolerated all, let's say, 15 substitutions that were tested and another corner also tested all -- or tolerated all 15 substitutions that were tested, would that give the skilled person a reasonable expectation that changing those two positions would produce a -- would retain -- at least retain some amount of activity? 18:00:09 18:00:16 18:00:19 18:00:23 18:00:26 18:00:28 18:00:31 18:00:36

MR. KUSHAN: Objection. Foundation. Objection as to form. 18:00:39 18:00:40

A Well, in the case of cooperativity, you would -- you could get caught surprised, right. I mean, I think the metaphor of holding up the wall is fine because if you -- it's a good metaphor because -- or in that Ta-Ka-Radi, you know, game where you're piling blocks on -- one on top of the other, if I pull out this support, it's tolerated; if I pull out that support, it's tolerated; if I pull them out both at the same time, boom, the whole thing falls down because there's a cooperative impact; that the two positions are 18:00:48 18:00:52 18:00:55 18:00:58 18:01:01 18:01:08 18:01:11 18:01:14 18:01:15 18:01:17 18:01:19

cooperating to do a function. 18:01:23

Q If you change two residues in two 18:01:26

separate, unstructured loops in a structure that 18:01:29

are nowhere near each other and both completely 18:01:32

tolerated all substitutions that were tested, 18:01:36

would you be surprised if somehow you inactivated 18:01:40

the protein and drove activity down to zero? 18:01:47

A So you're talking about an extreme case, 18:01:50

so let's talk about this. 18:01:52

So you have a loop over there and a loop 18:01:54

over there, and the data in these tables suggests 18:01:56

amino acid in the center of this loop and amino 18:02:00

acid in the center of that loop are both very 18:02:03

tolerant. Could you then be fairly confident you 18:02:05

could place them both at the same time? 18:02:09

That's a special case. I could easily 18:02:10

come up with special cases in the opposite 18:02:13

direction. 18:02:16

In that special case, you could be fairly 18:02:16

confident that you get away with it. In other 18:02:19

special cases where, for example, at a certain 18:02:22

position, I can insert a lysine on the surface and 18:02:31

it's fine. In another one I can insert a lysine on the surface, and it's fine. But if they happen to be close together, it won't be fine because they'll repel. 18:02:35 18:02:39 18:02:41 18:02:44

So it's very context dependent. Once you start making multiple mutations, it depends on the location -- context. It depends on the location, and it depends on structural cooperativity. 18:02:46 18:02:49 18:02:53 18:02:56

And, again, the pile of blocks is the best example. If you've ever played Ta-Ka-Radi, you pull out one block, the tower of blocks still holds because the other support is still there. You put it back; you pull out the other one, it still stands because the other one's still there. You pull them both out, it's down. 18:03:01 18:03:04 18:03:09 18:03:11 18:03:13 18:03:15 18:03:17

So it depends on the positioning whether there's -- cooperativity is -- I mean, it's -- you know, it's -- it's a source of allostery; it's the source of a lot of things. 18:03:20 18:03:24 18:03:27 18:03:31

But cooperativity means different -- that different positions are cooperating in such a way that the combination is not nearly the additive 18:03:32 18:03:34 18:03:37

sum of the two separately. 18:03:41

So that's where it gets more complicated 18:03:44

than just saying, Oh, the data in this table is 18:03:47

going to solve all my problems. The data in the 18:03:50

table has always -- or, you know, as I said, all 18:03:52

data are helpful. 18:03:55

But the data in these tables is not going 18:03:57

to always solve your problems if you're attempting 18:04:01

to make 10 changes. You can get into a situation 18:04:04

where two changes give rise to a cooperative 18:04:07

result, which means they're not just the additive 18:04:09

sum of the two. 18:04:12

Once you start making 10, the chances of 18:04:13

some sort of cooperativity go up. So sometimes 18:04:15

you'll get away with it, but many times you won't. 18:04:19

Q And you can -- you have a reasonable -- at 18:04:21

least a reasonable prediction of positions that 18:04:25

are likely to be cooperative, right, that would be 18:04:28

positions that are right next to each other on the 18:04:30

protein? 18:04:33

If you change 10 residues right in a row, 18:04:33

would you reasonably expect there to be some sort 18:04:37

of cooperative effect that's going to happen? 18:04:40

MR. KUSHAN: Objection. Foundation. 18:04:41

Objection as to form. 18:04:43

A So changing 10 residues in a row is an 18:04:45

extreme example, but it's -- but it's also 18:04:49

possible. 18:04:54

People have seen that their networks, what 18:04:55

sort of seem to be networks, that one -- I mean, 18:04:59

there have been some really cool, classic studies 18:05:02

where you look at the protein and you don't -- you 18:05:05

know, you look at the structure, and you don't 18:05:07

know where the cooperativity or where the networks 18:05:09

are until you start making mutations and you see 18:05:12

that there is some sort of cooperativity. 18:05:17

People also see things where two positions 18:05:23

coevolve; that as one changes -- position 22 18:05:26

changes throughout evolution, but it's always the 18:05:30

case that when 22 changes, 44 also changes. That 18:05:33

suggests that there's -- there's crosstalk between 18:05:38

them that you may not have noticed just by looking 18:05:40

at the 3D structure. 18:05:43

So it's -- you know, again, taking back to 18:05:46

15 years ago -- it's different now, but in that era, it would be hard to have a lot of confidence if I were trying to predict the outcome of making, you know, what they talk about here, 95 percent, which is changing 5 percent -- you know, 95 percent means you're changing 5 percent, right. 18:05:49 18:05:56 18:06:02 18:06:07 18:06:10 18:06:12

So it would be hard to have confidence on the outcome of an experiment where you simultaneously mutated 5 percent of the sequence. Sure, the data in the tables is always good to have. But even with that data, it would be hard to have strong confidence about what would happen if I simultaneously changed, say, 20 -- you know, 5 percent of the sequence. Yeah. 18:06:16 18:06:19 18:06:21 18:06:26 18:06:30 18:06:32 18:06:36 18:06:40

Q Are you saying it would be hard to have or difficult to have confidence in the -- for the result of every single polypeptide that you would test? 18:06:43 18:06:46 18:06:49 18:06:53

I mean, you agree that for at least some mutations that you could make within the scope of the claims, you could -- you could make some predictions based on the data in the patent; 18:06:53 18:06:58 18:07:01 18:07:04

right? 18:07:07

MR. KUSHAN: Objection -- 18:07:07

A We don't have that -- 18:07:08

MR. KUSHAN: Objection. Foundation. 18:07:09

Objection as to form. 18:07:10

Go ahead. 18:07:11

Q So you don't think that you could make any 18:07:11

predictions whatsoever using the data in the 18:07:13

patent regarding, you know, let's say you make 18:07:15

PH20 with two substitutions? 18:07:18

A Well, there's the issue of making 18:07:20

predictions versus having your predictions turn 18:07:22

out to be accurate, okay. So you can predict 18:07:25

whatever you want. 18:07:28

But whether your predictions would be 18:07:28

accurate -- you know, you make a hundred 18:07:32

predictions. Sometimes you get it right. 18:07:35

Q So you're requiring -- 18:07:38

A Sometimes you get it wrong. 18:07:39

Q You're requiring certainty? 18:07:40

MR. KUSHAN: Objection. 18:07:42

A I didn't say that -- 18:07:43

MR. KUSHAN: Form.

A I was requiring confidence. 18:07:43

Q What does confidence mean? Like 50 18:07:45

percent? 18:07:50

A Confidence means -- well, it depends on 18:07:52

the parameter. Confidence in a structure -- am I 18:08:16

confident that it's correct plus or minus two 18:08:19

angstroms? Or am I confident that it's correct 18:08:22

plus or minus two-tenths of an angstrom? If the 18:08:25

issue is activity, am I confident that it's still 18:08:29

as active as the original, or am I confident that 18:08:32

it has more than one one-thousandth of the 18:08:35

activity? 18:08:39

It's not -- again, it's not binary; it's 18:08:39

not black and white. But the point is that as you 18:08:42

make -- as you attempt to make many 18:08:45

simultaneous -- as you attempt to make many 18:08:48

simultaneous mutations, the data that you had that 18:08:54

made you comfortable to make one mutation would 18:08:58

make you way less comfortable to make an abundance 18:09:02

of mutations because of issues like cooperativity 18:09:05

and because of issues that the structure is 18:09:09

slightly altered by the first mutation and then the second and the third and the fourth. And so it's -- you know, it's just -- your level of confidence goes down. 18:09:12 18:09:15 18:09:17 18:09:20

Also, I want to highlight that, you know, many of the multiply altered proteins that the claim attempts to capture also include deletions and, you know, things that are really tough to have confidence in how they would impact the protein. 18:09:26 18:09:28 18:09:36 18:09:39 18:09:42 18:09:45

Q But a protein -- or the claims cover deletions that would inactivate the protein; right? 18:09:47 18:09:50 18:09:53

A I said the claims -- in defining percent identity, the claims allow for deletions. That's all I said. 18:09:54 18:09:58 18:10:02

I didn't say anything about what -- the rest of your sentence. 18:10:03 18:10:08

Q Oh, so when you were talking about the deletions, you're not talking about the deletions that would inactivate the protein? 18:10:08 18:10:10 18:10:12

MR. KUSHAN: Objection. Foundation. Also 18:10:15

objection as to form. 18:10:17

A I'm saying when the claims -- I'm 18:10:19

saying -- all right. Leave the claims behind. 18:10:22

I'm saying when the scientist goes out to 18:10:24

make mutations and when the patent, the body of 18:10:28

the patent -- and forget the claims for a moment. 18:10:36

When the body of the patent talks about -- 18:10:38

about modifications, okay, it's not limiting to -- 18:10:42

when it says modifications, it's not limiting 18:10:51

itself to amino acid substitutions. 18:10:55

It's also -- in the word modifications, 18:10:57

it's also including deletions. 18:10:59

Q Okay. So can we take a break? 18:11:02

MR. KUSHAN: Sure. 18:11:06

THE VIDEOGRAPHER: We are going off the 18:11:07

record. The time is 6:11 p.m. 18:11:09

(A recess was taken.) 18:29:22

THE VIDEOGRAPHER: We are back on the 18:29:22

record. The time is 6:29 p.m. 18:29:38

BY MS. MARTIN: 18:29:40

Q Dr. Hecht, you said that you've never 18:29:43

worked with hyaluronidases before; correct? 18:29:44

A Correct. 18:29:49

Q And hyaluronidases are different than the 18:29:50

enzymes that you've worked with in your 18:29:53

laboratory? 18:29:55

A I've not worked with hyaluronidases, I 18:29:59

mean, like I said, right. 18:30:01

Q Do you know how much hyaluronidase 18:30:06

activity is required for clinical utility? 18:30:08

MR. KUSHAN: Objection. Foundation. 18:30:11

Objection as to form. 18:30:12

A One could look it up, but I don't know. 18:30:17

Q And would you consider yourself to be an 18:30:20

expert in hyaluronidase? 18:30:24

A No. I've not worked with it. 18:30:26

Q Are you -- do you know of Andrej Sali? 18:30:30

A I haven't seen him in years, but I know 18:30:38

the name. 18:30:40

Q Do you consider him to be a respected 18:30:43

scientist? 18:30:48

MR. KUSHAN: Objection. Foundation. 18:30:50

A I mean, he certainly was. I haven't -- 18:30:57

you know, I haven't seen him in years or thought 18:31:00

about him in years, but, certainly, back when he was -- yeah, he was -- he was a known -- yeah. 18:31:02 18:31:06

Q Okay. What about John Moult? Do you know him? 18:31:08 18:31:15

A I know who he is, sure. 18:31:15

Q Is he a respected scientist? 18:31:17

A Yes. 18:31:18

Q Respected in the field? 18:31:19

A Sorry. Yes. Yeah. Sorry. I didn't hear you. Yes. 18:31:27 18:31:29

Q Would you trust his work? 18:31:29

MR. KUSHAN: Objection. Foundation. Objection as to form. 18:31:31 18:31:33

A It's a quirky question. I mean, with any person, any author, any scientist, you don't want to make a blanket statement like that. 18:31:39 18:31:47 18:31:51

But these were respected scientists, and I would look at the work, and I would make my own judgment. 18:31:54 18:31:57 18:32:02

Q What about Greg Petsko? 18:32:03

A He was on my thesis committee. I know who he is. 18:32:07 18:32:10

Q Is he a respected scientist? 18:32:10
A Yes. 18:32:13
Q What about Roland Dunbrack? 18:32:16
A I know who he is. I've heard him speak. 18:32:21
I don't know him personally, but yeah. 18:32:23
Q Is he a respected scientist? 18:32:25
A Yes. 18:32:27
Q All right. So let's turn in your 18:32:29
declaration to paragraph 50. 18:32:42
A Sorry. Paragraph 50 or page 50? 18:33:09
Q Paragraph 50 -- 18:33:12
A I'm sorry.
Q -- page 20. 18:33:13
A I'm sorry. I was on the wrong one. Okay. 18:33:15
Q And paragraph 50, you say, "There were 18:33:18
limits to using rational design techniques in the 18:33:21
2011 time frame"; right? 18:33:24
A Mm-hmm. 18:33:25
Q And to support that statement, you cite to 18:33:26
Exhibit 1018, which is the Chica paper; is that 18:33:29
right? 18:33:32
A I know him too, yeah. 18:33:32

Q All right. So marking Exhibit 1018. 18:33:35

(Exhibit 1018 was introduced for identification.)

Q Dr. Hecht, is -- Exhibit 1018, that's the Chica paper that you cited in your declaration? 18:33:52 18:33:54

A Right. 18:33:57

Q Okay. And you're citing to page 378, which is the first page; right? 18:33:59 18:34:08

A Okay. 18:34:10

Q And so the second full paragraph on page 378 that starts "Multiple approaches," do you see that paragraph? 18:34:14 18:34:22 18:34:25

A I do. 18:34:25

Q And it's -- that sentence says, "Multiple approaches have been developed to allow the identification of mutant enzymes possessing desirable qualities such as increased activity and modified specificity, selectivity, or cofactor binding"; is that right? 18:34:29 18:34:31 18:34:34 18:34:37 18:34:39 18:34:43

A I see that. 18:34:44

Q And the next sentence says, "The earliest approach was rational design, which was used to 18:34:45 18:34:47

modify the specificity of enzymes"; is that right? 18:34:50

A I see that. I'm going to look at the 18:34:52

references for a second. 18:34:55

Okay. 18:35:01

Q And then the next sentence is the sentence 18:35:01

that you quote in your declaration, which is, 18:35:04

"This approach requires an in-depth knowledge of 18:35:06

the structural features of the enzyme active site 18:35:08

and their contribution to function"; correct? 18:35:11

A Okay. 18:35:13

Q And then it continues: "The complexity of 18:35:15

the structure-function relationship in enzymes has 18:35:18

proven to be a factor limiting the general 18:35:20

applicability of rational design"; is that right? 18:35:22

A Okay. 18:35:25

Q So when Chica is talking about rational 18:35:26

design in this paragraph, Chica's talking about 18:35:31

using rational design to modify the specificity of 18:35:35

enzymes; right? 18:35:38

MR. KUSHAN: Objection. Foundation. Also 18:35:39

to form. 18:35:49

A I mean, I want to highlight that the title 18:35:55

talks about semi-rational approaches, which is sort of what I was saying before we took a break that there are -- it's not just rational design and not just directed evolution or laboratory evolution. 18:35:59 18:36:02 18:36:05 18:36:08 18:36:10

There are also approaches that merge the two of both directed evolution and rational design, right. We talked about that before the break. 18:36:11 18:36:13 18:36:17 18:36:19

Now getting back to the text where we are now. So what the text says, earliest approach was rational design, which was used to modify the specificity of enzymes. Okay. Approach required -- he's saying rational design requires an in-depth knowledge. Yeah. Right. 18:36:20 18:36:22 18:36:28 18:36:30 18:36:34 18:36:37

What -- what's the question? 18:36:40

Q So in those sentences when he's talking about rational design, he's talking about using rational design to modify the specificity of enzymes? 18:36:42 18:36:46 18:36:48 18:36:51

A In some cases, that was -- yeah. 18:36:51

Q He's not talking about using rational 18:36:53

design to make a modified PH20 polypeptide with 95 percent sequence identity in this paper, is he? 18:36:56 18:37:02

MR. KUSHAN: Objection -- objection. Foundation. 18:37:04 18:37:05

A There is no mention of PH20 in the text we just looked at. 18:37:08 18:37:11

Q So what does it mean to modify the specificity of enzymes? 18:37:13 18:37:16

A Ah, to modify the specificity of enzymes. 18:37:18

If you look at reference number 5 at the end of that paper, there's a paper from Perham's lab. I remember when this was happening. 18:37:31 18:37:34 18:37:37

And the title of that was "Redesign of the coenzyme specificity of a dehydrogenase by protein engineering." In its day in 1990, that made a big splash because they were redesigning an enzyme such that the coenzyme it used, the cofactor it used, was different from the natural one. That's what they're citing in that example. 18:37:39 18:37:41 18:37:47 18:37:50 18:37:53 18:37:58 18:38:01

So that's modifying -- that's one example of modifying specificity for a substrate or for a cofactor. 18:38:04 18:38:08 18:38:12

Q So in that paragraph, Chica is teaching that there are -- it's -- there are difficulties associated with using rational design to change the specificity for a substrate or a cofactor; right? 18:38:19 18:38:23 18:38:24 18:38:26 18:38:44

A Well, he's doing both. He's highlighting some very impressive successes with references 4 through 9 but, at the same time, highlighting that the approach requires an in-depth knowledge of structural features of the enzyme active site and their contribution to function. 18:38:44 18:38:47 18:38:50 18:38:54 18:38:57 18:39:01

So he's both citing the successful accomplishments and highlighting the limitations, both. 18:39:02 18:39:05 18:39:08

Q Now the claims that you looked at in this case, they don't require changing the specificity of an enzyme for a substrate or a cofactor; right? 18:39:09 18:39:12 18:39:18

MR. KUSHAN: Objection. Foundation. 18:39:23

A That's correct; they don't. The claims do not require altering the specificity for the substrate or the cofactor, yeah. 18:39:34 18:39:38 18:39:42

Q So difficulties of using rational design 18:39:44

to change specificity for a substrate or a cofactor are not relevant to practicing the claims; right? 18:39:47 18:39:50 18:39:55

MR. KUSHAN: Objection. Foundation. 18:39:57

A I'm going to disagree with what you said. 18:40:02

I would say that Chica's comment is a broad statement about the approach for rational design. The approach, rational design, requires an in-depth knowledge and so forth. And, therefore, it has limitations. 18:40:05 18:40:07 18:40:10 18:40:14 18:40:18

The approach could be used to make altered specificity for cofactors or substrates. The approach could be used to try and make the same specificity but with greater activity. The approach could be used to make the same activity and the same specificity but with a different sequence with mutations. 18:40:21 18:40:26 18:40:31 18:40:34 18:40:38 18:40:41 18:40:44

The approach could be used for various goals. Irrespective of the goal, the approach has limitations, as he spells out, because it requires an in-depth knowledge of the structural features of what he says there: the, you know, structural 18:40:46 18:40:49 18:40:53 18:40:55 18:40:57

features of the enzyme, the active site, the contribution to function. 18:41:01 18:41:03

So the rational design approach has limitations because it requires a great deal of input to -- a great deal of very solid input as a foundation for the rational design. 18:41:04 18:41:06 18:41:10 18:41:20

And he's highlighting that in many cases that in-depth knowledge, that input, is incomplete. And, therefore, the rational design approach is challenging, irrespective of whether we're talking about modified specificity in the top line of this column or whether we're talking about making mutations for the same specificity in hyaluronidase. 18:41:22 18:41:26 18:41:28 18:41:30 18:41:35 18:41:37 18:41:40 18:41:44

Either way, rational design is -- is challenged by whether -- by how much information and how much understanding, you know, from the structure, the physical chemistry, the interactions by -- you know, your understanding is incomplete, and so your rational design is constrained by an incomplete understanding. 18:41:44 18:41:47 18:41:49 18:41:53 18:41:55 18:41:57 18:42:01

Q Okay. Let's mark Exhibit 1059. 18:42:03

(Exhibit 1059 was introduced for identification.)

I'm not sure how you say his name, Leisola? 18:42:24 18:42:28

A I'm sorry. What? 18:42:28

Q I'm not sure how you say that name. 18:42:29

Is it Leisola? 18:42:30

A I don't know this person, so I won't answer that. 18:42:32 18:42:34

Q Okay. So in any event, Exhibit 1059 is a paper that you considered in rendering your opinion in this case; right? 18:42:35 18:42:38 18:42:39

A It's one of the ones listed in here, right? 18:42:40 18:42:43

Q Yeah. 18:42:43

You cite it, for example, in Footnote 17 on page 21 in your declaration. 18:42:44 18:42:45

A Page 21. 18:42:51

Q Yes. 18:42:52

A Okay. Okay. 18:42:53

Q Okay. So if you turn to page 1226 in Exhibit 1059. 18:43:08 18:43:27

A Mm-hmm. 18:43:29

Q First full sentence: "At one end is an approach commonly referred to as a rational design, which aims to understand the principles of protein structure and function well enough to apply them in designing new properties or even novel proteins using de novo design"; right? 18:43:30 18:43:34 18:43:37 18:43:40 18:43:42 18:43:45

A I see what you read, but I also want to highlight the line before that, where they say what I've been saying all day -- is that it's a spec- -- is that it's a spectrum defined by two extremes, right. It's a spectrum; it's not this or that. It's a continuum. 18:43:49 18:43:52 18:43:54 18:43:57 18:44:02 18:44:05

Q So the continuum is what screening a totally random library versus rationally selecting the changes that you're going to make? I just want to understand the continuum that you're talking about. 18:44:07 18:44:09 18:44:12 18:44:14 18:44:17

MR. KUSHAN: Objection. Foundation. 18:44:18

A The continuum is at one extreme -- there was a paper by Keith and Szostak -- Jack Szostak, Nobel Prize winner for different things -- where 18:44:19 18:44:23 18:44:27

they made completely random sequences, and they had something like 10 to the 12th random sequences. They didn't use any kind of screener selection that's relevant to today because you can't screen 10 to the 12th in ways that we're talking about today. 18:44:30 18:44:33 18:44:36 18:44:39 18:44:41 18:44:44

But they screened through 10 to the 12th totally random sequences and selected for function by 15 generations. That's the most extreme example that I can think of of a laboratory evolution with fully random sequences and fully based on selection and screening, no rational design. That's one extreme. 18:44:44 18:44:47 18:44:52 18:44:56 18:45:00 18:45:04 18:45:07

The other extreme is you have a very high precision understanding and knowledge of your target situation and using structural understanding, physical chemistry, organic chemistry, you say, I want that atom over there, and I'm going to make this mutation to do that. 18:45:09 18:45:12 18:45:15 18:45:20 18:45:24 18:45:27

Those are the two extremes. And many projects, most projects, are not at either of those extremes. Sorry. 18:45:29 18:45:31 18:45:34

Q Is the first extreme, is that directed evolution? 18:45:37 18:45:39

A Many, many, many projects are directed evolution. Frances Arnold does directed evolution. But with the Keith and Szostak, what I'm describing is the most extreme example of that because there was no rational input into their sequences. They start out with fully random, 10 to the 12th random sequences. A lot of directed evolution experiments start with -- you know, they start with some rational input. 18:45:41 18:45:43 18:45:46 18:45:50 18:45:53 18:45:55 18:45:58 18:46:02 18:46:05

It varies. There's a whole -- there's a whole spectrum of approaches. But, you know, it's handy to conceptually imagine these two extremes: the Keith and Szostak 10 to the 12th random sequences on the one hand and the hypothetical situation where you know every atom's position and its role in catalysis and you know the stability to the tenth of a kilocalorie or a hundredth of a kilocalorie, you know, and you know the catalytic mechanism and all of that, which is -- you know, it's demanding. 18:46:08 18:46:10 18:46:21 18:46:24 18:46:27 18:46:29 18:46:33 18:46:37 18:46:42 18:46:43 18:46:46

As the Chica paper says, that's a challenge to have that kind of precise and accurate understanding that will allow that perfect level of rational design. But in principle that's what the extreme rational design would be. 18:46:47 18:46:50 18:46:52 18:46:53 18:46:56 18:46:59

Q And would the extreme rational design theoretically allow you to predict a novel protein using de novo design? 18:47:00 18:47:03 18:47:06

MR. KUSHAN: Objection. Foundation. Objection as to form. 18:47:10 18:47:11

A It's kind of a different question. 18:47:12

What we were talking about a moment ago is making a single amino acid change in a protein where you've got the structure known to less than one angstrom resolution and you know the precise catalytic mechanism and you know all this stuff. 18:47:14 18:47:16 18:47:19 18:47:24 18:47:27

What you asked a moment ago was de novo protein design. As I said, now that's all being done by machine. In the last couple years or four years or whatever, that's all being done by AI. 18:47:30 18:47:32 18:47:35 18:47:39

Rational design, again, is -- there's a 18:47:43

spectrum. 18:47:46

And when Bill DeGrado started doing it or when I was doing it as a postdoc, it was rational. But holy moly, we were -- we were -- you know, we didn't know that much. 18:47:46 18:47:49 18:47:52 18:47:54

Conversely, a really fully rational thing is where you know everything at a very high level of detail and you can design an atom by atom. 18:47:56 18:48:00 18:48:03

So I -- you know, sorry if I didn't quite answer your question, but... 18:48:06 18:48:09

Q Practicing the claims that you've been evaluating in this case does not require designing new properties for hyaluronidases; correct? 18:48:13 18:48:16 18:48:20

MR. KUSHAN: Objection. Form. Objection as to foundation. 18:48:23 18:48:25

A As I said before, it's not designing new specificity or new cofactors. It's attempting to design new sequences that have, in this case, hyaluronidase activity. 18:48:27 18:48:30 18:48:35 18:48:41

So there's rational design. It depends on what your goals are, right. You can rationally design in principle. And let's say -- you can't 18:48:42 18:48:47 18:48:51

always get away with it, but in theory you can rationally design a new sequence for a known function, or you could rationally design an altered function based on a known sequence. 18:48:53 18:48:56 18:48:59 18:49:02

I mean, there's a lot of ways of spinning that. 18:49:06 18:49:08

Q Your opinions in this case are all premised on your conclusion that the claims across the four patents that you considered require hyaluronidase activity; correct? 18:49:25 18:49:30 18:49:33 18:49:37

MR. KUSHAN: Objection. Foundation. 18:49:38

A You were asking, again, if I consider Claim 1 to require hyaluronidase activity, as we discussed earlier? 18:49:42 18:49:45 18:49:48

Q I'm saying the opinions that you rendered regarding the four patents that you considered, your opinions were all based on your assessment that the claims that you considered required hyaluronidase activity? 18:49:49 18:49:52 18:49:54 18:49:58 18:50:02

MR. KUSHAN: Objection. Foundation. 18:50:03

A I interpreted Claim 1 as requiring hyaluronidase activity. 18:50:05 18:50:12

But there's 150 pages of opinions in there, and not all of them are related to that issue. 18:50:13 18:50:16 18:50:19

Q So did you evaluate whether the claims would be valid if they didn't require hyaluronidase activity? 18:50:20 18:50:22 18:50:25

A Ah. So you're proposing, what if the claims did not require hyaluronidase activity? And I would say there, it's still a very -- there's still a -- an absence of a full, written description or an enablement because -- I mean, this is in here. I can go hunt it down. 18:50:30 18:50:35 18:50:40 18:50:44 18:50:53 18:50:59

But -- let me go find it. Okay. Paragraph 135, even if the claims are interpreted to encompass inactive mutants, they would still include an immense number of active mutant modified PH20 polypeptides. 18:51:02 18:51:21 18:51:26 18:51:30

As I discuss further below, it's my opinion that the common disclosure does not describe or enable this immense number of inactive mutants. 18:51:35 18:51:37 18:51:40 18:51:42

In other words, even if you were to choose 18:51:43

to interpret Claim 1 as including or as encompassing also inactive mutants, then, nonetheless, the -- the -- the common disclosure does not provide information on how to sort through the immense collection of 10 to the 50th or 10 to the 60th and know, among those that have 15 amino acid substitutions, which of those are useful, right, and which of those are not. 18:51:45 18:51:48 18:51:52 18:52:02 18:52:12 18:52:17 18:52:20 18:52:24

So even if the claim were to -- even if, which we're not granting necessarily. But even if we were to say -- as it says in paragraph 135, even if we were to interpret the claim as including both active and inactive, in some ways, it's even more difficult because then you have to say, How do I sort through these and figure out which ones have utility and which ones don't. 18:52:27 18:52:31 18:52:33 18:52:37 18:52:41 18:52:47 18:52:50 18:52:52

The common disclosure does not tell us which ones have activity and which ones don't beyond, you know, the 6,000 in those tables. The common disclosure doesn't tell us which ones are active and which ones aren't, okay, beyond those few. 18:52:56 18:52:58 18:53:01 18:53:04 18:53:08 18:53:11

And even for those few it does describe, it doesn't give us interpretations of why. And it gives us no information on how to construct sub-libraries from the 10 to the 60th. It does -- it gives us no information on how to construct sub-libraries. So there's no written description of how to make sub-libraries that will include the -- you know, that will allow us to find the active ones. 18:53:11 18:53:13 18:53:17 18:53:22 18:53:25 18:53:28 18:53:30 18:53:35 18:53:37

And there's no enablement explaining -- enabling the person of -- you know, expert in the field -- enabling one to sort through, find, produce, make those that will have activity and, therefore, will be -- have utility. So -- 18:53:38 18:53:41 18:53:45 18:53:52 18:53:56

Q So -- 18:53:59

A -- yeah. 18:54:00

Q Okay. 18:54:00

A So even if one were to say the claims encompassed both active and inactive, there's still a serious problem in that there's no -- or incomplete, very limited, written description of how to find out, how to make, how to find active 18:54:01 18:54:03 18:54:07 18:54:13 18:54:16

modified proteins and how, or enable how to -- how to find them. Yeah. 18:54:21 18:54:24

Q Okay. 18:54:25

MS. MARTIN: I'll move to strike that as nonresponsive. 18:54:26 18:54:28

A Sorry? 18:54:28

Q I said move to strike as nonresponsive. 18:54:30

So it's your understanding there has to be a -- 18:54:32 18:54:34

MR. KUSHAN: Sorry. I'm going to object to that. Sorry. That was an answer he gave in response to your question. That's responsive. 18:54:34 18:54:36 18:54:40

Go ahead. 18:54:42

MS. MARTIN: Okay. 18:54:43

Q So it's your understanding that the patent needs to disclose -- needs to disclose sub-libraries in order to have sufficient, written description and enablement support. 18:54:46 18:54:51 18:54:56 18:54:58

And it also needs to disclose some sort of sorting mechanism for sorting between the polypeptides that have what you consider to be utility from those that you considered not to have 18:54:59 18:55:03 18:55:08 18:55:11

utility in order to satisfy the written description and enablement requirement? 18:55:14 18:55:17

MR. KUSHAN: Objection. Foundation. Objection to form. 18:55:20 18:55:22

A That it would need to provide guidance on how to find proteins that have utility amidst this hypothetical 10 to the 60th. And that guidance is lacking. And in many cases, you know, it even tells you to sort of ignore some of the guidance that was in the common disclosure where the common disclosure tells -- you know, says to avoid changing certain residues and, you know. 18:55:22 18:55:27 18:55:34 18:55:41 18:55:46 18:55:49 18:55:51 18:55:55

And yet the attempt to draw a fence around this entire universe of proteins is not providing guidance on which ones to make us active ones and which ones -- you know, and how to determine they're active. There's -- there's no guidance. 18:55:58 18:56:03 18:56:10 18:56:17 18:56:19

Q So there's -- in all the data that you looked at and all the data that you have in your appendices, that provides absolutely no guidance whatsoever to the skilled person seeking to make the claimed modified PH20 polypeptides totally 18:56:21 18:56:22 18:56:25 18:56:30 18:56:34

left in the dark with no clue whatsoever what potential changes they may make -- they may want to make? 18:56:38 18:56:40 18:56:42

MR. KUSHAN: Objection. Foundation. Objection as to form. 18:56:43 18:56:45

A With respect to the overall collection, it's a grain of sand on a large beach. The tables list 5- or 6,000 single substitutions. That's, you know, five times ten to the third or six times then to the third. That's compared to ten to the 50th or ten to the 60th. That's, like, nothing. So -- 18:56:46 18:56:48 18:56:57 18:57:02 18:57:05 18:57:09 18:57:14

Q So how many examples would the patent have needed to provide to be representative, in your view? 18:57:14 18:57:16 18:57:19

A Ah, it's not just how many. It's also that the patent is saying you can change, let's say, 5 percent of the sequence, which, depending on which sequence you're looking at, is maybe, you know, 20 substitutions. And so it's not how many examples they should be providing. It's are they representative? 18:57:20 18:57:24 18:57:31 18:57:34 18:57:38 18:57:42 18:57:45

And when you're dealing with a -- a universe of single, double, triple, 5, 10, 20 substitutions and there are 10 to the 60th of them, then it's not just that the number, 6,000 or 5,000, is such a small number. It's also that, in terms of its type, it's not representative. It's single changes. 18:57:46 18:57:51 18:57:56 18:58:01 18:58:05 18:58:08 18:58:10

And so that's not representative of the 20 substitutions that would arise based on 5 percent changes. 18:58:11 18:58:16 18:58:22

Q You also -- 18:58:23

A That's not representative. 18:58:24

Yeah. 18:58:25

Q Sorry. 18:58:25

You also said that there's no disclosure, there's no explanation for why -- there's no explanation for the results that were achieved. 18:58:27 18:58:30 18:58:35

So is it your understanding to satisfy written description and enablement requirement, there has to be some sort of explanation in terms of the structural impact of each of the substitutions? 18:58:38 18:58:40 18:58:43 18:58:45 18:58:48

A Exactly. 18:58:48

So when Park went through the individual 18:58:49
amino acid substitutions that are on the last few 18:58:54
pages of each of my documents, it's a very, I 18:58:57
would say, erudite description of why this 18:59:05
mutation would likely be tolerated based on 18:59:09
sequence alignment, based on hydrogen bonds, based 18:59:12
on, you know, the model, the hydrogen bonds, the 18:59:17
accessible surface area, and all of that. 18:59:20

And so he's providing -- he's suggesting a 18:59:22
mutation and also providing an intellectual 18:59:26
underpinning for why that would work and thereby 18:59:31
guiding an expert in the field about what works 18:59:33
and what doesn't. 18:59:36

In contrast, the 5,000 or 6,000 things 18:59:39
listed in those tables are just lists with no 18:59:42
guidance about why something -- you know, you were 18:59:46
looking at before all these ones that failed to 18:59:49
work and all these ones that do work. There's no 18:59:51
guidance, right. There's nothing there. It 18:59:54
doesn't say whether, Oh, this works because, you 18:59:56
know, it's on the surface, whatever. 19:00:01

There's no guidance of -- for a practitioner to learn from those lists and apply them in any kind of rational design, right, in the way that Park did. 19:00:02 19:00:05 19:00:10 19:00:14

Q So it's -- so Park did all of that just based on what the -- based on a POSA's knowledge in 2011; right? He was able to do that analysis? 19:00:15 19:00:18 19:00:20

A Based on the -- yeah. I mean, based on -- you know, based on -- yeah, based on what was known, what tools were available, what was known in the field, what was available, and the, you know, and the fact that he is very skilled at this, but yeah. 19:00:28 19:00:34 19:00:38 19:00:41 19:00:45 19:00:46

Q Okay. So are you saying that the skilled person couldn't actually interpret the data in the patent and try to understand, based on the data in the patent -- for example, if, you know, maybe those positions are tolerated because they're on the surface, or maybe they're not tolerated because they're in the center of the protein. 19:00:47 19:00:51 19:00:53 19:00:57 19:00:59 19:01:02 19:01:04

Is that outside the realm of what the skilled person could do? 19:01:05 19:01:07

A My understanding is the obligation is upon the patent to provide a written description. It's not upon the reader to provide a written description. It's upon the patent to provide enablement. It's not upon the reader of the patent to provide enablement. 19:01:08 19:01:10 19:01:13 19:01:18 19:01:21 19:01:23

And the patent fails to do that. 19:01:25

Q So you're saying that the -- you're saying that what the skilled person knew is not relevant because it actually has to be spelled out in the patent? 19:01:27 19:01:29 19:01:33 19:01:38

MR. KUSHAN: Objection. Foundation. Objection to form. 19:01:38 19:01:40

A I'm saying that it is the obligation -- I mean, you know, it's just what it says in this part on legal principles -- is that -- is that -- I'll be quick. I mean, I'll get to it right here. 19:01:51 19:01:54 19:01:57 19:02:01

It says that, "Patent disclosure should provide" -- page -- paragraph 26 -- "should provide a sufficient written description" -- and so on. 19:02:04 19:02:09 19:02:12 19:02:17

And that "could be achieved by disclosure 19:02:19

that describes a representative number of species and structural features." 19:02:22 19:02:25

It does not say that it is upon the reader of the patent to figure out what's going on because the reader happens to be in this field. It says that it's upon the patent, the disclosure requirement, to provide a written description. 19:02:26 19:02:32 19:02:34 19:02:37 19:02:41

And in paragraph 27, it's informed that the second disclosure requirement, not a requirement upon the reader, is that the disclosure provide a description that enables a skilled artisan to practice. 19:02:44 19:02:47 19:02:49 19:02:52 19:02:56

So, in this case, I would expect -- I would -- you know, I think a requirement would be that the disclosure would provide, as I said, a description that enables the skilled artisan to practice. 19:02:58 19:02:59 19:03:01 19:03:05 19:03:09

A data dump is not a teaching, okay? And so those tables are a data dump. I mean, I talk to my students about this all the time. A data dump is not the same as a teaching. 19:03:10 19:03:16 19:03:19 19:03:21

And it's my understanding -- I'm not an 19:03:24

attorney, but it's my understanding that the patent doesn't -- is supposed to be a teaching that gives you a written description, and it gives you a teaching that would enable you to, you know, to do all the stuff. A data dump is not a description, is not a teaching. 19:03:26 19:03:28 19:03:32 19:03:35 19:03:38 19:03:42

Q Because it provides no information? 19:03:44

A Sorry? 19:03:46

Q Because it provides no information? 19:03:47

A It provides information but no insight, no guidance, right. That's what a data dump is. 19:03:49 19:03:51

Q Okay. I don't have any other questions. 19:03:56

MR. KUSHAN: Why don't we just take a two-minute break, and we'll come back. 19:04:01 19:04:03

THE VIDEOGRAPHER: We are going off the record. The time is 7:04 p.m. 19:04:05 19:04:07

(A recess was taken.) 19:07:38

THE VIDEOGRAPHER: We are back on the record. The time is 7:07 p.m. 19:07:38 19:07:52

MR. KUSHAN: We have no questions. Thank you.

MS. MARTIN: Wonderful.

THE VIDEOGRAPHER: We are going off the record. The time is 7:08 p.m.

THE REPORTER: I want to grab transcript orders.

MS. MARTIN: Oh, yeah. Expedited. So we want, like, a rough today, if possible.

THE REPORTER: Sure. And the final transcript?

MS. MARTIN: What's the quickest you can do the final?

THE REPORTER: Thursday?

MS. MARTIN: Thursday sounds good.

THE REPORTER: Mr. Kushan?

MR. KUSHAN: Thursday.

(Off the record at 7:09 p.m.)

CERTIFICATE OF SHORTHAND REPORTER-NOTARY PUBLIC

I, Janet A. Hamilton, Registered Diplomate Reporter and Notary Public within and for the District of Columbia do hereby certify:

That MICHAEL HECHT, Ph.D., the witness whose deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition and that such deposition was taken before me and is a true record of the testimony given by such witness.

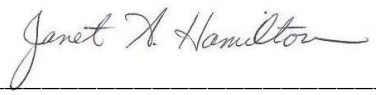
I further certify that the adverse party, Merck Sharp & Dohme LLC, was represented by counsel at the deposition.

I further certify that the deposition of MICHAEL HECHT, Ph.D., occurred at the office of Sidley Austin LLP, Washington, DC, on Tuesday, August 26, 2025, commencing at 9:10 a.m. to 7:09 p.m.

I further certify the inspection, reading and signing of said deposition was not discussed on the record.

I further certify that I am not related to any of the parties to this action by blood or marriage, I am not employed by or an attorney to any of the parties to this action, and that I am in no way interested, financially or otherwise, in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 28th day of August, 2025.



_____

My commission expires:

March 30, 2028

DISTRICT OF COLUMBIA

**A**
**a-2**
247:9, 247:16, 250:1
**a-3**
249:14
**abbreviation**
180:2
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