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Transcript of Michael Hecht, Ph.D.

Date: August 26, 2025

Case: Merck Sharp & Dohme LLC -v- Halozyme Inc. (PTAB)

Planet Depos

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

Halozyme EX2076
Merck v. Halozyme
PGR2025-00039

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3 - - - - - x

4 MERCK SHARP & DOHME LLC, : Case Nos.

5 Petitioner, : PGR2025-00003; 00004;

6 v. : 00006; 00009

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

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

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

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11
12
13 Videotaped Deposition of MICHAEL HECHT, Ph.D.

14 Washington, DC

15 Tuesday, August 26, 2025

16 9:10 a.m.

17
18
19
20 Job No. 596628

21 Pages: 1 - 308

22 Reported by: Janet A. Hamilton, RDR

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18 Public in and for the District of Columbia.
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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
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Declaration of Michael Hecht, Ph.D.

PGR2025-00003

US Patent No. 11,952,600

Exhibit 1003	58
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Declaration of Michael Hecht, Ph.D.

PGR2025-00004

US Patent No. 12,018,298

Exhibit 1003	58
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Declaration of Michael Hecht, Ph.D.

PGR2025-00006

US Patent No. 12,152,262

Exhibit 1003	58
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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

Exhibit 1001 187

US Patent No. 11,952,600

Exhibit 1010 216

Paper by Ling Zhang: Hyaluronidase Activity
of Human Hyal1 Requires Active Site Acidic
and Tyrosine Residues

Exhibit 1013 228

Paper by Gregory Frost: Recombinant human
hyaluronidase: An enabling platform for
subcutaneous drug and fluid administration

Exhibit 1018 280

Paper by Roberto Chica: Semi-rational
approaches to engineering enzyme activity:
combining the benefits of directed evolution
and rational design

Exhibit 1059 287

Review Paper from Matti Leisola: Opportunities
and challenges

Transcript of Michael Hecht, Ph.D.
Conducted on August 26, 2025

8

1	THE VIDEOGRAPHER: Here begins Media	09:09:41
2	Number 1 in the videotaped deposition of	09:09:43
3	Dr. Michael Hecht in the matter of Merck Sharp &	09:09:45
4	Dohme LLC v. Halozyme, Inc. in the United States	09:09:49
5	Patent and Trademark Office, case number	09:09:54
6	PGR2025-00003; 0004; 0006; 0009.	09:10:00
7	Today's date is August 26, 2025. The time	09:10:09
8	on the video monitor is 9:10 a.m. The	09:10:15
9	videographer today is Adam Schuman, representing	09:10:20
10	Planet Depos. This video deposition is taking	09:10:22
11	place at 1501 K Street, Northwest, Suite 600,	09:10:25
12	Washington, DC 20005.	09:10:34
13	Would counsel please voice identify	09:10:37
14	themselves and state whom they represent.	09:10:39
15	MS. MARTIN: Lauren Martin from Quinn	09:10:41
16	Emanuel on behalf of Halozyme. And with me I have	09:10:42
17	Zhen Cui, Zach Summers, both from Quinn Emanuel,	09:10:46
18	and then Trey Powers and Eldora Ellison, both from	09:10:51
19	Sterne Kessler.	09:10:55
20	MR. KUSHAN: Jeff Kushan from Sidley	09:10:57
21	Austin for Merck. With me is Christine Engen from	09:10:59
22	Sidley Austin, Mark Stewart for Merck, and	09:11:02

Transcript of Michael Hecht, Ph.D.
Conducted on August 26, 2025

9

1 Katherine Helm from Dechert.

09:11:05

2 THE VIDEOGRAPHER: The court reporter
3 today is Jan Hamilton representing Planet Depos.

09:11:08

09:11:08

4 The witness will now be sworn.

09:11:11

5 P R O C E E D I N G S

6 -----

7 MICHAEL HECHT, Ph.D.,

8 a witness herein, being duly sworn, testified as
9 follows:

10 EXAMINATION BY COUNSEL FOR THE PATENT OWNER

09:11:27

11 BY MS. MARTIN:

09:11:27

12 Q Good morning, Dr. Hecht.

09:11:28

13 A Hi.

09:11:29

14 Q Can you please state your full name and
15 address for the record?

09:11:30

09:11:32

16 A I am Michael Hecht. Sometimes I use a
17 middle initial H.

09:11:33

09:11:36

18 My home address is what you're asking for?

09:11:38

19 Q Home or work.

09:11:42

20 A Oh, well, my home address is 1571 Great
21 Road, Skillman, New Jersey.

09:11:43

09:11:48

22 Q Are you employed?

09:11:50

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Transcript of Michael Hecht, Ph.D.
Conducted on August 26, 2025

10

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

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

1	hearing?	09:14:03
2	A Yes.	09:14:05
3	Q So you testified at deposition and hearing	09:14:07
4	for that arbitration?	09:14:11
5	A It was a long time ago, so let me think	09:14:13
6	this through.	09:14:16
7	Yes, there was a deposition. And, yes,	09:14:17
8	there was an arbitration, at both of which I	09:14:19
9	spoke.	09:14:22
10	Q Aside from that proceeding, have you ever	09:14:26
11	been deposed before?	09:14:29
12	A No.	09:14:32
13	Q Have you ever testified at trial aside	09:14:34
14	from that arbitration?	09:14:36
15	A Sorry. Other than that, you said?	09:14:38
16	Q Mm-hmm.	09:14:40
17	A Have I ever testified at a trial. No.	09:14:41
18	Q Have you ever served as an expert witness	09:14:44
19	apart from the arbitration and this matter?	09:14:46
20	A There was another case where I was asked	09:14:50
21	to be involved, but that fizzled out pretty soon	09:14:52
22	and never went to the level of, you know,	09:14:56

1	deposition or testifying or anything. It fizzled	09:15:01
2	out.	09:15:05
3	Q Did you provide a report in that matter?	09:15:05
4	A No, never got to that point.	09:15:07
5	Q If at any point in the deposition you	09:15:28
6	would like clarification regarding any of my	09:15:31
7	questions, please ask me for clarification instead	09:15:33
8	of your counsel.	09:15:37
9	Do you understand?	09:15:38
10	A Of course.	09:15:39
11	Q And as we go throughout the day, your	09:15:45
12	counsel may object to some of my questions. But	09:15:47
13	unless you are instructed not to answer, you still	09:15:49
14	have to answer each question.	09:15:51
15	Do you understand?	09:15:53
16	A I understand, yeah.	09:15:55
17	Q I'll try to take a break around every hour	09:15:57
18	or so.	09:15:59
19	But if at any time you feel like you need	09:16:00
20	a break, please let me know, although I would ask	09:16:02
21	if there's a question pending, you answer the	09:16:05
22	question before we stop.	09:16:07

Transcript of Michael Hecht, Ph.D.
Conducted on August 26, 2025

14

1	A Right.	09:16:09
2	Q Do you recall when you were first	09:16:12
3	contacted in connection with this matter?	09:16:14
4	A Yeah. It was last summer.	09:16:17
5	Q And do you recall who contacted you?	09:16:20
6	A Jeff.	09:16:22
7	Q What did you do to prepare for the	09:16:26
8	deposition today?	09:16:28
9	A I read numerous documents and reread	09:16:30
10	numerous documents and then had several meetings	09:16:36
11	with counsel, both in person and on Zoom.	09:16:42
12	Q When did you meet with counsel in person	09:17:00
13	to prepare for this deposition?	09:17:04
14	A Yesterday, last week.	09:17:07
15	You're speaking in person or both?	09:17:18
16	Q In person.	09:17:19
17	A In person, yesterday, last week, previous	09:17:20
18	week. There were a number of meetings.	09:17:25
19	Q Did you speak with anyone who's not a	09:17:32
20	lawyer to prepare for this deposition?	09:17:35
21	A No.	09:17:40
22	Q Did you speak with Dr. Park at all in	09:17:43

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

1	A	No.	09:18:57
2	Q	You listened to part of Dr. Park's	09:19:00
3		deposition; correct?	09:19:02
4	A	Briefly, yes.	09:19:03
5	Q	Why did you listen to part of Dr. Park's	09:19:05
6		deposition?	09:19:07
7	A	I wanted to know what a deposition looks	09:19:08
8		like. I just -- it was somewhat mysterious to me	09:19:10
9		as I had only ever done it, as I said, you know,	09:19:14
10		in 1995 or so and didn't remember much of that.	09:19:17
11		And so I was curious, like, what is this?	09:19:21
12		What actually happens?	09:19:25
13	Q	So you were curious to learn about what a	09:19:26
14		deposition sounds like?	09:19:29
15	A	Looks like, sounds like, yeah. What is	09:19:30
16		the format of it, what goes on.	09:19:35
17	Q	And did you rely on what you heard in	09:19:38
18		Dr. Park's deposition to prepare for this	09:19:41
19		deposition?	09:19:43
20	A	No, not at all.	09:19:44
21	Q	Did you rely on Dr. Park's testimony in	09:19:45
22		forming any of your opinions in this case?	09:19:48

1	A	Could you explain what you mean by -- do	09:19:52
2		you mean testimony in the deposition?	09:19:54
3	Q	Yes.	09:19:55
4	A	Oh, no, no.	09:19:56
5	Q	Did anything that Dr. Park say change any	09:19:57
6		of your opinions in this case?	09:19:59
7	A	Just to clarify, you mean what he said in	09:20:01
8		the deposition?	09:20:04
9	Q	Yes.	09:20:04
10	A	No.	09:20:05
11	Q	Okay. What's your research focus?	09:20:06
12	A	I'm trying to be succinct.	09:20:16
13		Protein structure folding design, protein	09:20:20
14		engineering, the impact of sequence changes on	09:20:25
15		protein structure and function, yeah,	09:20:32
16		combinatorial libraries of novel proteins.	09:20:41
17	Q	Do you do any work with de novo proteins?	09:20:47
18	A	Certainly do, yeah.	09:20:53
19	Q	What's a de novo protein?	09:20:54
20	A	Some people will define it somewhat	09:21:00
21		differently.	09:21:03
22		But the way I like to define it is a	09:21:03

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1	kinds of stuff.	09:24:08
2	Q So there have been instances where you've	09:24:19
3	chosen a particular sequence that you want to	09:24:21
4	make?	09:24:24
5	A Have -- yes. There are instances where we	09:24:25
6	choose a particular sequence we want to make,	09:24:31
7	sometimes a natural sequence, sometimes a de novo	09:24:35
8	sequence.	09:24:38
9	But it's many years. There's been lots of	09:24:39
10	projects.	09:24:41
11	Q Can de novo proteins have enzymatic	09:24:49
12	activity?	09:24:53
13	A Can they? Is that the question?	09:24:54
14	Q Yes.	09:24:56
15	A Yes.	09:24:56
16	Q Have you generated a de novo protein with	09:24:58
17	enzymatic activity in your lab?	09:25:02
18	A We, in fact, have published on de novo	09:25:04
19	proteins that have enzymatic activity.	09:25:11
20	Q What's the purpose of generating a de novo	09:25:18
21	protein?	09:25:21
22	A There are a number of ways of looking at	09:25:31

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

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

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

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

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

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

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

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

1	Q And that was a completely novel amino acid	09:27:11
2	sequence that then folded into a novel protein	09:27:16
3	that you called Felix?	09:27:20
4	A Correct.	09:27:27
5	Q Do you recall how you arrived at the amino	09:27:30
6	acid sequence for Felix?	09:27:35
7	A In fact, the story there was the sequence	09:27:37
8	had been arrived at by my collaborators before I	09:27:41
9	started doing the lab work. I was not --	09:27:43
10	technically, I was not involved in the actual	09:27:46
11	design of that sequence.	09:27:49
12	Q Have you ever solved a protein crystal	09:27:57
13	structure?	09:27:59
14	A Not with -- not me personally, no.	09:28:01
15	Q Have you ever analyzed a solved protein	09:28:04
16	crystal structure?	09:28:07
17	A I have looked at many solved structures,	09:28:10
18	yeah.	09:28:13
19	Q Why do you look at a solved structure?	09:28:13
20	A To learn about it, to understand it, to	09:28:24
21	think about it, to take next steps in a research	09:28:27
22	program, to understand whatever questions	09:28:34

1	you're -- you're trying to understand.	09:28:40
2	Q Is there information that you can glean	09:28:45
3	from a solved protein crystal structure about the	09:28:47
4	role of particular amino acids in the structure?	09:28:53
5	A Often, yeah.	09:29:00
6	Q Is there information you can obtain from a	09:29:06
7	solved protein crystal structure about the	09:29:09
8	secondary structure, the secondary structures in	09:29:11
9	the protein?	09:29:17
10	A Yes.	09:29:18
11	Q What type of information about secondary	09:29:21
12	structures can you obtain from a crystal	09:29:23
13	structure?	09:29:26
14	A When you look at a crystal structure, you	09:29:30
15	can see which sections of the polypeptide chain	09:29:34
16	are in an alpha helix, which sections are in a	09:29:39
17	beta sheet, which sections are in a loop, and so	09:29:43
18	forth, which amino acids are in those secondary	09:29:49
19	structures, yeah.	09:29:54
20	Q And you can also glean information	09:30:02
21	regarding how the secondary structures interact	09:30:04
22	with each other to form a tertiary structure;	09:30:10

1	correct?	09:30:15
2	A You can get information about how the	09:30:15
3	protein folds from looking at its final folded	09:30:19
4	structure, yeah.	09:30:23
5	Q Can you get information about which	09:30:26
6	portions, which amino acid -- or sorry, strike	09:30:29
7	that. Let me start again.	09:30:33
8	Can you obtain information regarding the	09:30:34
9	residues that are involved in holding the various	09:30:37
10	secondary structures in place to form the tertiary	09:30:43
11	structure?	09:30:46
12	A You can look at a solved, an	09:30:51
13	experimentally solved structure, and you can see	09:30:56
14	interactions that stabilize the structure.	09:31:03
15	However, that's not the whole story. You	09:31:08
16	would also want to -- if you want to know about	09:31:10
17	stability, you would also perform stability	09:31:12
18	studies, which are different from looking at a	09:31:15
19	static structure.	09:31:18
20	Q When you talk about stability, a protein	09:31:18
21	stability, what do you mean?	09:31:22
22	A In this context, when I'm talking about	09:31:27

1	protein stability, I'm talking about the free	09:31:30
2	energy difference between a folded state and an	09:31:34
3	unfolded state.	09:31:37
4	So stability is -- is a measure of the	09:31:38
5	free energy difference between those two states.	09:31:41
6	Q Is that the delta G?	09:31:43
7	A Yeah.	09:31:46
8	Q And how do you -- how do you quantify the	09:31:47
9	energy difference between a folded state and an	09:31:54
10	unfolded state?	09:31:57
11	A The delta G.	09:31:57
12	Q Yes.	09:31:59
13	A There are a number of ways of doing it.	09:31:59
14	We've done lots of experiments like that. You can	09:32:01
15	look at stability by differential scanning	09:32:06
16	calorimetry, which is a direct thermodynamic	09:32:11
17	measurement.	09:32:14
18	You can take the folded protein, subject	09:32:15
19	it to things that would unfold the protein, such	09:32:18
20	as elevated temperature or denaturants like urea.	09:32:22
21	Then you can measure the folding	09:32:29
22	transition and you can extrapolate back from that	09:32:30

1	measurement what the delta G is separating the	09:32:33
2	folded state and the unfolded state.	09:32:35
3	Those are two ways of doing it. You could	09:32:38
4	also do things with NMR. There's a bunch of very	09:32:41
5	rigorous ways or there are several rigorous ways	09:32:47
6	of assessing stability of a protein.	09:32:51
7	Q And those methods would allow you to	09:32:54
8	calculate the delta G?	09:32:56
9	A In most cases, if the experiments work out	09:32:57
10	smoothly, yeah.	09:32:59
11	Q Are there ways of assessing protein	09:33:00
12	stability in a qualitative way that would not	09:33:02
13	allow you to calculate delta G?	09:33:05
14	MR. KUSHAN: Objection. Form.	09:33:09
15	A I'm -- the question is kind of a difficult	09:33:18
16	one because you're asking can you assess something	09:33:23
17	without really assessing it. I'm not sure I	09:33:27
18	understand what you mean.	09:33:30
19	Q Okay. When you refer to protein	09:33:30
20	stability, are you always talking about the	09:33:39
21	delta G value, the difference between -- an energy	09:33:42
22	between the folded structure and nonfolded	09:33:45

1	structure?	09:33:48
2	A That's how I describe it when I teach	09:33:48
3	about this subject. I frequently put exactly that	09:33:51
4	on the board when I'm teaching about protein	09:33:54
5	stability, the delta G stuff.	09:33:57
6	Q Is the term "stability" used more broadly	09:33:59
7	in the field to refer to something more	09:34:03
8	qualitative than delta G?	09:34:08
9	A I am really hesitant to comment on about	09:34:10
10	how other people use a term.	09:34:12
11	Q Okay. Are there particular guidelines	09:34:14
12	that scientists use when designing a de novo	09:34:23
13	protein?	09:34:26
14	A This is a field that really just arose in	09:34:33
15	the past few decades and has kind of exploded, and	09:34:38
16	there are numerous different approaches that	09:34:43
17	people use.	09:34:44
18	Q What types of approaches?	09:34:46
19	A For making novel proteins?	09:34:51
20	Q Yes.	09:34:53
21	A The -- yeah, I mean the Nobel Prize last	09:34:54
22	year went, in part, to a group that does protein	09:35:21

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

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

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

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

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

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

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

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

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

1	function. Just asking: Okay, you made a library	09:38:06
2	with this patterning. Do any of them fold? Do a	09:38:12
3	lot of them fold?	09:38:16
4	It was a very low resolution approach.	09:38:18
5	Q But the answer was yes, right, many of	09:38:21
6	them folded?	09:38:24
7	A The answer is, yes, many of them collapsed	09:38:25
8	into alpha helical structures. Most of those	09:38:27
9	collapsed into alpha helical structures but were	09:38:35
10	dynamic. They were not unique structures; they	09:38:38
11	were not -- not the kind of thing where you could	09:38:41
12	solve an x-ray crystal structure.	09:38:43
13	Q Can you explain what you mean by a dynamic	09:38:45
14	structure?	09:38:48
15	A That it's not -- I usually do this with	09:38:55
16	physical illustrations, but I need words here.	09:39:01
17	When I say it's a dynamic structure, I'm	09:39:08
18	saying that the chain may have collapsed, and it's	09:39:12
19	not -- it's not cooked spaghetti. So it may have	09:39:19
20	collapsed into a globular structure, but it's	09:39:23
21	dynamic in the sense that the atoms are not fixed	09:39:27
22	in place in terms of precise X, Y, and Z	09:39:31

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

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

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

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

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

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

1	fluctuating.	09:40:50
2	Q Do you perform sequence alignments in your	09:40:51
3	work?	09:40:58
4	A My lab certainly has done that kind of	09:41:02
5	stuff, sure.	09:41:04
6	Q Do you generate homology models in your	09:41:06
7	lab?	09:41:11
8	MR. KUSHAN: Objection. Form.	09:41:12
9	A If we're working with truly de novo	09:41:31
10	sequences, then the term homology is a bit squishy	09:41:33
11	because homology usually refers to ancestry, and	09:41:39
12	if a protein is de novo and not from nature, then	09:41:42
13	by definition it has no ancestry.	09:41:46
14	But we do sequence alignments, and we are	09:41:50
15	certainly comfortable with modeling the structure	09:41:56
16	of a protein by similarity to others.	09:42:03
17	Q How would you go about modeling the	09:42:14
18	structure of a protein by similarity to others?	09:42:17
19	A The way we do it now is using technology	09:42:53
20	that wasn't around at the time of the case we're	09:42:57
21	discussing, using some of the AI methods that	09:43:01
22	arose in the past few years.	09:43:07

1	Q So the way that you do it now, for	09:43:10
2	example, maybe you would use AlphaFold?	09:43:13
3	A Yeah.	09:43:15
4	Q Okay. And AlphaFold wasn't around in	09:43:15
5	2011?	09:43:21
6	A Correct.	09:43:22
7	Q Could you use SWISS-MODEL?	09:43:26
8	A I'm sorry?	09:43:29
9	Q Could you use SWISS-MODEL?	09:43:30
10	A One could, yeah.	09:43:32
11	Q So it's possible to perform a sequence	09:43:36
12	alignment for one of your de novo proteins and to	09:43:41
13	generate a model using AlphaFold for that de novo	09:43:46
14	protein; is that right?	09:43:52
15	MR. KUSHAN: Objection. Foundation.	09:43:53
16	A One would use AlphaFold. I mean, that's	09:44:06
17	today. It's really different from what was done	09:44:10
18	then.	09:44:13
19	Now AlphaFold is -- you know, it's an AI	09:44:13
20	thing. People pop it in, and magic happens and	09:44:15
21	something comes out. That's very different from	09:44:18
22	what was going on 15 years ago.	09:44:21

1	Q Well, that wasn't my question.	09:44:23
2	My question was, could you? We've	09:44:25
3	established that AlphaFold wasn't around in 2011.	09:44:29
4	So today could you perform a sequence	09:44:31
5	alignment for one of your de novo proteins and	09:44:35
6	generate a model using AlphaFold --	09:44:39
7	(The reporter requested clarification.)	
8	Q Sorry. -- and generate a model using	
9	AlphaFold for that de novo protein?	09:44:41
10	MR. KUSHAN: Objection. Foundation.	09:44:44
11	A Could you? It's two separate things.	09:44:51
12	Could you align sequences in a collection	09:44:56
13	of proteins? You could do that.	09:44:58
14	Could you have AlphaFold predict a	09:45:01
15	structure today, not then? You could do that.	09:45:05
16	Q Okay. And when AlphaFold predicts the	09:45:11
17	structure, would AlphaFold be basing that	09:45:15
18	structure off of other solved structures, or would	09:45:18
19	the AlphaFold be creating a de novo structure for	09:45:21
20	your de novo protein?	09:45:24
21	MR. KUSHAN: Objection to form.	09:45:26
22	Objection. Foundation.	09:45:28

1	A I am not real comfortable discussing	09:45:31
2	what's under the hood for AlphaFold. I'm not an	09:45:34
3	AI specialist.	09:45:37
4	Q So you don't know how AlphaFold works?	09:45:39
5	A Not in detail, no.	09:45:42
6	Q Do you know how it works in general?	09:45:44
7	A That it harvests -- like AI is, it	09:45:46
8	harvests -- I mean, it's a bit of a black box, but	09:45:50
9	it harvests data from known sequence -- from	09:45:53
10	massive amounts of known sequences and structures.	09:45:56
11	Q In your work in your -- sorry. Strike	09:46:05
12	that.	09:46:08
13	In your lab do you generate models,	09:46:08
14	structural models, for your de novo proteins?	09:46:16
15	A We will feed a sequence into AlphaFold and	09:46:28
16	ask it to predict a structure.	09:46:32
17	Q Why do you do that?	09:46:34
18	A Why do you do that? Because you're	09:46:35
19	interested in what the structure looks like. I	09:46:43
20	mean, yeah. It's...	09:46:45
21	Q Why are you interested in what the	09:46:48
22	structure looks like?	09:46:50

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

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

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

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

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

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

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

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

1	for the protein that you modeled?	09:49:05
2	A If the AlphaFold prediction was working	09:49:07
3	well, that's what you would see.	09:49:10
4	Q Have you ever used MODELLER?	09:49:13
5	A My students have.	09:49:16
6	I mean, I'm -- I'm -- I've been fortunate	09:49:18
7	to work for years with, you know, teams of really	09:49:23
8	talented students, and so what will happen is I'll	09:49:27
9	say, you know, Make a model; let's look at it.	09:49:30
10	Q Were your students using MODELLER in the	09:49:34
11	2011 time frame?	09:49:37
12	A I think so. I'm not always sure exactly	09:49:43
13	how they -- how they model something.	09:49:46
14	Q Were your students using MODELLER in the	09:49:49
15	context of de novo proteins in the 2011 time	09:49:51
16	frame?	09:49:55
17	A Some, but not so much, because in many	09:50:13
18	cases we already knew that our novel proteins were	09:50:18
19	dynamic and modeling them would have been a	09:50:21
20	stretch because they would have been dynamic.	09:50:27
21	Q And is that because they don't form a	09:50:40
22	sufficiently fixed structure that a model would	09:50:46

1	give you information about, you know, what the	09:50:49
2	structure would look like most of the time because	09:50:51
3	they're so dynamic they're moving all the time?	09:50:53
4	MR. KUSHAN: Objection to form.	09:50:55
5	A Yeah, I'll just summarize by saying that	09:51:02
6	in those combinatorial libraries of novel	09:51:05
7	sequences, it was squishier territory, both	09:51:10
8	intellectually and in terms of the protein itself	09:51:17
9	than would be, say, with a fully evolved natural	09:51:20
10	protein that forms a unique structure.	09:51:22
11	Q Over the course of your career, you've	09:51:35
12	solved the crystal structure of some of your	09:51:37
13	de novo proteins, right?	09:51:39
14	A In collaboration with crystallographers,	09:51:42
15	we've -- yeah, there have been some.	09:51:44
16	Q So not all of the de novo proteins you've	09:51:47
17	generated have been dynamic?	09:51:50
18	A That's correct. We occasionally find some	09:51:51
19	that are reasonably rigid.	09:51:53
20	Q But it's possible that in the 2011 time	09:52:00
21	frame your students used MODELLER to generate	09:52:02
22	models of de novo proteins?	09:52:06

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 A Make them what? 09:55:18

1	Q Similar?	09:55:19
2	MR. KUSHAN: Objection to form.	09:55:20
3	Objection. Foundation.	09:55:21
4	A It depends on the context. I mean it's	09:55:25
5	just -- if you're dealing with evolved proteins	09:55:28
6	that are homologous, it's a different situation	09:55:33
7	from if you're dealing with proteins that were in	09:55:38
8	a designed library. It's -- it's just different.	09:55:42
9	So it depends on the context.	09:55:47
10	Q What sequence identity would you say that	09:55:54
11	evolved -- I'm sorry. Strike that.	09:55:57
12	What sequence identity would you say would	09:56:00
13	make two homologous proteins similar?	09:56:02
14	A Homologous proteins.	09:56:06
15	Q Yes.	09:56:07
16	A Natural proteins.	09:56:08
17	Q Yes.	09:56:09
18	A That evolve from a common ancestry.	09:56:09
19	I'm hesitant to put a number on it, but if	09:56:21
20	they are proteins with similar biological	09:56:27
21	functions, similar activities, evolved from common	09:56:29
22	ancestry, similar physical properties, then you	09:56:33

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

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

8 So again, it depends. 09:56:58

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

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

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

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

17 MR. KUSHAN: Objection. 09:57:25

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

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

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

1	natural protein sequences?	09:58:22
2	A We thought about that. Way back when we	09:58:26
3	first started this we highlighted that our	09:58:29
4	sequences were de novo in the sense that they had	09:58:31
5	negligible runs of sequence identity with anything	09:58:37
6	in nature, and so we didn't bother aligning them	09:58:40
7	to anything in nature after that because why	09:58:44
8	should we? They're not natural.	09:58:47
9	In fact, we highlighted that they're not	09:58:58
10	similar to natural systems.	09:59:00
11	Q Are you aware of any instances where your	09:59:32
12	students used MODELLER or SWISS-MODEL to generate	09:59:35
13	a model of a de novo protein?	09:59:39
14	A You know, like I said before, in the --	09:59:43
15	you mean today or you mean in 2010, 2011, 2012	09:59:47
16	or --	09:59:52
17	Q The 2011 time frame.	09:59:52
18	A So in that period, people would	09:59:55
19	occasionally model one of our novel sequences and	10:00:01
20	show me a picture. I'm not certain which	10:00:05
21	computational method they used.	10:00:09
22	Q And do you know what the purpose was for	10:00:14

1	modeling the sequence and showing you the picture?	10:00:17
2	A Because we're interested in protein	10:00:21
3	structure. We want to see what they look like.	10:00:23
4	You model the structure because you're interested	10:00:24
5	in the structure.	10:00:26
6	Q Does the model give you any useful	10:00:27
7	information about the sequence?	10:00:30
8	A The model, in those cases, gives you a	10:00:31
9	model. In those cases, with these de novo	10:00:34
10	proteins, it gives you a -- something to look at	10:00:40
11	and think about. You're not certain if it's	10:00:44
12	correct or not because there is no homology to	10:00:46
13	work with. There's only these collections of	10:00:49
14	novel proteins that have some level of sequence	10:00:53
15	similarity.	10:00:57
16	So it's very different from working with	10:01:00
17	natural proteins. It's like a -- it's a whole	10:01:02
18	different way of thinking about stuff.	10:01:04
19	Q And when you say that there's no homology	10:01:06
20	to work with, you mean there is no natural protein	10:01:10
21	with a solved crystal structure and known function	10:01:13
22	that you can go from?	10:01:15

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

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

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

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

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

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

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

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

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

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

1	are consistent with activity give you a hint on	10:04:40
2	what's consistent with structure?	10:04:42
3	A It's protein chemistry 101. Is that	10:04:56
4	structure -- that function depend upon structure.	10:04:59
5	Q And you said homology is profoundly	10:05:06
6	important to model building; correct?	10:05:10
7	A Yes. Model building as we're discussing	10:05:17
8	that, right. I'm not talking about AI methods	10:05:20
9	now, for sure.	10:05:23
10	Q Correct. Yes.	10:05:25
11	And, again, why is it profoundly	10:05:26
12	important?	10:05:28
13	A I just said that, is that by looking at	10:05:29
14	homologous proteins that have made it through the	10:05:33
15	evolutionary experiment, you're seeing what	10:05:41
16	sequences are consistent with biological function.	10:05:43
17	And since function depends upon structure,	10:05:48
18	you're also seeing what sequences are -- are	10:05:51
19	consistent with structure. And since you're	10:05:54
20	asking about building models of structure, it's	10:05:57
21	kind of important.	10:06:00
22	Q So having a homologous protein is helpful	10:06:03

1 for building a structural model? 10:06:10

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

3 A Having in front of you a collection of 10:06:19

4 homologous sequences is very beneficial for 10:06:21

5 modeling three-dimensional structures, yeah. 10:06:28

6 Q And is it even more beneficial if you have 10:06:35

7 solved crystal structures for some of those 10:06:38

8 homologous sequences? 10:06:40

9 A It's very much beneficial to have 10:06:43

10 experimentally determined structure for some of 10:06:47

11 those proteins, yeah. 10:06:49

12 Q Because if you have an experimentally 10:06:51

13 determined structure for a homologous sequence, 10:06:53

14 then you can use that experimentally determined 10:06:56

15 structure as the basis to build the model for your 10:06:59

16 sequence; is that right? 10:07:02

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

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

19 foundation. 10:07:08

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

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

22 Q Yeah. 10:07:17

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

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

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

10 Q And what other inputs? 10:07:38

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

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

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

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

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

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

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

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

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

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

1	identity, one can model one on the other even	10:10:38
2	without dozens of other ones.	10:10:40
3	Q And why is that the case?	10:10:46
4	A You have a sequence in structure that's	10:11:01
5	been determined. And you know what it is. It's a	10:11:04
6	particular enzyme. You know what its function is.	10:11:09
7	You have another sequence when you don't	10:11:13
8	yet have the determined structure, okay, but it	10:11:17
9	has considerable sequence identity and it has	10:11:24
10	considerable biological overlap and it has	10:11:28
11	homology.	10:11:31
12	Then you can infer that since it has the	10:11:34
13	same activity and since it has so many positions	10:11:38
14	where the sequence is identical, then it's	10:11:43
15	reasonable to infer from that that it will form a	10:11:47
16	very similar structure because structure is a	10:11:51
17	foundation for function, and sequence is the	10:11:56
18	foundation for structure and function.	10:12:00
19	And so if the sequences are nearly	10:12:02
20	identical, the ancestry is common, and the	10:12:07
21	activity is more or less the same, then it's quite	10:12:10
22	reasonable to say that, Oh, it will also have the	10:12:14

1	same 3D structure, and one can model it	10:12:17
2	accordingly, even in the absence of a whole zoo of	10:12:22
3	other related sequences.	10:12:25
4	Q And those principles were well known in	10:12:34
5	the 2011 time frame; is that right?	10:12:36
6	A Oh, yeah, yeah, yeah.	10:12:37
7	Q Apart from this matter, have you done any	10:13:23
8	work with Merck?	10:13:25
9	A Not that I recall, no, nothing	10:13:35
10	significant.	10:13:38
11	Q Has Merck ever funded research in your	10:13:39
12	lab?	10:13:42
13	A No.	10:13:43
14	Q Have you ever done any consulting work for	10:13:50
15	Merck?	10:13:53
16	A No.	10:13:56
17	Q Apart from this matter, have you ever	10:14:00
18	worked with Dr. Park?	10:14:02
19	A So he had a book some years that had a	10:14:05
20	bunch -- some years ago, that had -- you probably	10:14:09
21	know -- that had a bunch of articles in it, one of	10:14:10
22	which was co-authored by me.	10:14:12

1	To be honest, I don't remember much about	10:14:14
2	that. Somebody asked us to submit a chapter. We	10:14:16
3	submitted a chapter.	10:14:18
4	I may have talked to him on the phone. We	10:14:19
5	may have met at a meeting. I don't remember. It	10:14:22
6	wasn't profound.	10:14:24
7	Q Have you ever heard of a company called	10:14:27
8	Alteogen?	10:14:30
9	A Say again?	10:14:31
10	Q Have you ever heard of a company called	10:14:32
11	Alteogen?	10:14:34
12	A I think so. I think I've heard of that in	10:14:36
13	passing in -- in the past year through working on	10:14:38
14	this case.	10:14:41
15	But I'm not sure I know much else about	10:14:43
16	it. I've never Googled it, so...	10:14:46
17	Q Apart from your work on this case, have	10:14:48
18	you ever heard of Alteogen?	10:14:50
19	A No, no, no.	10:14:52
20	Q So they don't fund any of your research?	10:14:53
21	A No.	10:14:57
22	Q Are you a named inventor on any patents?	10:14:57

1	A	On any patents? No.	10:15:01
2	Q	No?	10:15:03
3		Have you ever filed a patent application?	10:15:04
4	A	I have in a rather amateur and clueless	10:15:10
5		way. The university, Princeton, has but nothing	10:15:18
6		that ever went very far.	10:15:21
7	Q	Do you know if those patent applications	10:15:22
8		are still being prosecuted?	10:15:24
9	A	There was something we -- that the	10:15:27
10		intellectual property office at Princeton	10:15:31
11		submitted a few years ago that I've never heard	10:15:34
12		anything back on that. I don't know if it fizzled	10:15:36
13		out.	10:15:39
14		I was, to be honest, not super involved in	10:15:40
15		it. It was my postdoc and grad students who	10:15:43
16		wanted to move forward with it. And I said, Okay,	10:15:44
17		do what you want.	10:15:47
18		I kind of felt it was never going to be	10:15:50
19		commercially viable, so it wasn't really	10:15:52
20		worthwhile, but they wanted to pursue it.	10:15:55
21	Q	Have you ever actually -- strike that.	10:15:58
22		All right. So we've probably been going	10:16:10

1	for a little over an hour.	10:16:13
2	Do you want to take a quick break?	10:16:14
3	A Sure.	10:16:16
4	You want to take a break?	10:16:17
5	Q Mm-hmm.	10:16:18
6	A Bathroom break. Okay.	10:16:18
7	THE VIDEOGRAPHER: We are going off the	10:16:19
8	record. The time is 10:16 a.m.	10:16:21
9	(A recess was taken.)	10:16:23
10	THE VIDEOGRAPHER: We are back on the	10:35:31
11	record. The time is 10:35 a.m.	10:35:33
12	BY MS. MARTIN:	10:35:36
13	Q Welcome back, Dr. Hecht.	10:35:37
14	A Very good.	10:35:39
15	Q Did you speak with anyone during the break	10:35:40
16	about the substance of your testimony?	10:35:42
17	A No.	10:35:44
18	Q Would you say that a 40 percent sequence	10:35:48
19	identity for homologous sequences is sufficient to	10:35:52
20	generate a homology model?	10:35:56
21	MR. KUSHAN: Objection. Foundation.	10:36:00
22	Objection as to form.	10:36:02

1	A I don't want to generalize to all possible	10:36:12
2	situations, but I would say in many cases, yes.	10:36:14
3	Q All right. So we're going to mark your	10:36:19
4	exhibits, although they've already been marked in	10:36:28
5	this proceeding -- or your declarations, sorry.	10:36:31
6	So the first one --	10:36:41
7	A Wait. These were -- oh, okay.	10:36:42
8	These are all for me, this whole pile?	10:36:44
9	Q Yes, whole pile. All four at the same	10:36:47
10	time.	10:36:49
11	So for the record, first one is	10:36:52
12	Declaration of Michael Hecht, Ph.D. from PGR2025	10:36:58
13	Matter 3 regarding US Patent No. 11,952,600. And	10:37:04
14	that is in the -- in PGR Matter 3, that is Exhibit	10:37:10
15	1003.	10:37:16
16	And then in Matter -- PGR2025 Matter 4,	10:37:19
17	regarding US Patent No. 12,018,298, Declaration of	10:37:25
18	Michael Hecht, Ph.D., and that's Exhibit 1003.	10:37:31
19	And then in Matter -- PGR2025 Matter 6	10:37:37
20	regarding US Patent No. 12,152,262, the	10:37:41
21	Declaration of Michael Hecht, Ph.D., and that's	10:37:47
22	Exhibit 1003 in Matter 6.	10:37:50

1	And then finally, in PGR2025 Matter 9, US	10:37:54
2	Patent No. 12,123,035, Declaration of Michael	10:37:59
3	Hecht, Ph.D. and that's Exhibit 1003.	10:38:06
4	(Exhibit 1003 was introduced for	
5	identification.)	
6	BY MS. MARTIN:	
7	Q So Dr. Hecht, can you please confirm that	10:38:09
8	these are the four declarations that you've	10:38:12
9	submitted in each of these proceedings?	10:38:15
10	A I haven't seen every page, but they	10:38:20
11	certainly look that way.	10:38:22
12	Q And you signed each of these declarations;	10:38:26
13	correct?	10:38:30
14	A Correct.	10:38:30
15	Q All right. So your declaration for	10:38:35
16	Matter 3, Exhibit 1003, can you please turn to	10:38:53
17	page 123?	10:38:58
18	A Sorry, what page?	10:39:01
19	Q Page 123.	10:39:03
20	A Okay.	10:39:12
21	Q And page 123 and 124 has your exhibit	10:39:13
22	list; is that correct?	10:39:18

1	Q Okay. Do you understand that trial has	10:40:45
2	been instituted in Matter 3?	10:40:57
3	A Do I understand what?	10:40:59
4	Q That trial has been instituted by the --	10:41:00
5	by the PTAB in Matter 3?	10:41:03
6	A I don't know what that means.	10:41:07
7	Q Okay. Have you read the institution	10:41:08
8	decision that the PTAB issued in connection with	10:41:11
9	Matter 3?	10:41:16
10	A I have not read it. I have a copy of it	10:41:17
11	and I've glanced at it, but I have not read it.	10:41:20
12	Q So you received a copy of the institution	10:41:22
13	decision?	10:41:24
14	A I received a copy of it, but I have not	10:41:25
15	read it page by page, no.	10:41:28
16	Q Did you read any -- did you glance at it?	10:41:29
17	A I glanced at it.	10:41:32
18	Q Do you recall anything that you saw?	10:41:33
19	A I saw some things -- we discussed some	10:41:35
20	things where they seem to have seen things in this	10:41:39
21	declaration and found them to be reasonable.	10:41:43
22	MR. KUSHAN: Doctor, I don't want to --	10:41:46

1	make sure you understand you're not to reveal	10:41:48
2	communications with counsel.	10:41:50
3	THE WITNESS: Okay.	10:41:51
4	Q Did you receive all four institution	10:42:02
5	decisions for each of these matters?	10:42:05
6	A I received a spiral-bound folder that I	10:42:09
7	think contains all four of them.	10:42:13
8	Q In paper form?	10:42:15
9	A Mm-hmm, yes.	10:42:16
10	Q Did you glance at all four of them?	10:42:18
11	A Barely.	10:42:21
12	Q Okay. So let's turn in your declaration	10:42:36
13	for Matter 3 to paragraph 11.	10:42:42
14	So in providing your opinions in this	10:43:05
15	matter, you used the time frame before December	10:43:09
16	29, 2011; is that right?	10:43:16
17	A That's what's written here.	10:43:18
18	Q Is that accurate?	10:43:20
19	A I would say that the relevant science that	10:43:25
20	was happening in the period of '11 --	10:43:33
21	Q Well, that's not my question, Dr. Hecht.	10:43:38
22	My question is --	10:43:41

1	MR. KUSHAN: I'm sorry. Were you finished	10:43:41
2	with your answer?	10:43:43
3	A Well, no. Go ahead. Then we can get back	10:43:44
4	to it.	10:43:46
5	Q Okay. So because you were about to	10:43:46
6	actually give me the answer to a different	10:43:49
7	question. The question that I asked you is -- is	10:43:51
8	you used the time frame before December 29th,	10:43:56
9	2011. That's what you stated in your declaration	10:44:00
10	when you performed your analysis. That's what's	10:44:03
11	written in paragraph 11 in your declaration; is	10:44:06
12	that right?	10:44:10
13	A That's what's written.	10:44:10
14	Q Okay. Thank you. And -- okay. And the	10:44:11
15	technical field at issue in this case concerns	10:44:24
16	protein structures and modifications of them; is	10:44:26
17	that correct?	10:44:31
18	A Correct.	10:44:31
19	Q So paragraph 13 provides the definition of	10:44:40
20	the person of ordinary skill in the art; is that	10:44:43
21	right?	10:44:48
22	A That's what it says, yeah.	10:44:48

1	Q And if I use the term POSA, do you	10:44:49
2	understand that that refers to person of ordinary	10:44:52
3	skill in the art?	10:44:54
4	A Okay.	10:44:55
5	Q Okay. You qualified as a person of	10:44:56
6	ordinary skill in the art in 2011; right?	10:45:14
7	A Yes.	10:45:16
8	Q Do you agree that a POSA would have been	10:45:21
9	able to consult with someone with hyaluronidase	10:45:24
10	experience as part of a multi-disciplinary team in	10:45:28
11	2011?	10:45:31
12	MR. KUSHAN: Objection. Foundation.	10:45:34
13	A Are you asking if somebody would be able	10:45:38
14	to talk to somebody else?	10:45:41
15	Q Yes.	10:45:43
16	A Yes. Anybody can talk to anybody else.	10:45:47
17	Q So a POSA would have been able to speak	10:45:51
18	with someone with hyaluronidase experience as part	10:45:55
19	of a multi-disciplinary team in the 2011 time	10:46:01
20	frame?	10:46:03
21	A As I said, I believe anybody in the --	10:46:08
22	you're asking a hypothetical question, and the	10:46:12

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

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

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

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

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

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

13 A I have not. 10:46:56

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

15 A Five. 10:47:05

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

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

19 Q Most of them do? 10:47:16

20 A Mm-hmm. 10:47:17

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

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

1	Q What's the function of PH20?	10:47:22
2	MR. KUSHAN: Objection. Form.	10:47:30
3	A As a biological protein, it could have	10:47:39
4	multiple functions, but it is a high -- it is an	10:47:42
5	enzyme with that specified activity. It also	10:47:45
6	exists on sperm and is involved in the function of	10:47:49
7	sperm.	10:47:52
8	Q So PH20 does cleave hyaluronic acid;	10:48:03
9	right?	10:48:08
10	A Yes.	10:48:08
11	Q And do you know the mechanism of action by	10:48:12
12	which PH20 cleaves hyaluronic acid?	10:48:15
13	A I've read papers that demonstrate that	10:48:20
14	mechanism. I have not memorized them.	10:48:22
15	Q And if you turn to paragraph 77, which is	10:48:25
16	the bottom of page 38, top of page 39.	10:48:45
17	A Okay.	10:48:49
18	Q The second sentence in that paragraph,	10:48:54
19	starting at the top of page 39, says that, "PH20	10:48:57
20	selectively catalyzes the hydrolysis of beta 1,4	10:49:01
21	glycosidic bonds in hyaluronan, also called	10:49:07
22	hyaluronic acid"; right?	10:49:10

1	A I see that.	10:49:12
2	Q So PH20's mechanism of action is that it	10:49:12
3	catalyzes the hydrolysis of the beta 1,4	10:49:17
4	glycosidic bonds in hyaluronic acid?	10:49:22
5	A That's what it says.	10:49:25
6	Q And is that the mechanism of action?	10:49:26
7	A That's what it says, yeah.	10:49:27
8	Q So is it fair to say that PH20, like other	10:49:29
9	hyaluronidases that cleave hyaluronic acid, do so	10:49:35
10	by hydrolyzing the beta 1,4 glycosidic bonds?	10:49:40
11	A PH20 selectively catalyze the hydrolysis	10:49:46
12	of the beta 1,4 glycosidic bonds in hyaluronic	10:49:50
13	acid, yeah.	10:49:54
14	Q Do you know if other hyaluronidases that	10:49:55
15	cleave hyaluronic acid also function using that	10:50:00
16	same mechanism of action?	10:50:01
17	A Yes. There are others that do.	10:50:04
18	Q Does HYAL1 cleave hyaluronic acid using	10:50:07
19	that same mechanism of action?	10:50:13
20	A I'm not going to remember -- I think so,	10:50:14
21	but I'm not going to remember the nomenclature of	10:50:17
22	which one. But I'm pretty sure it does, yeah.	10:50:19

1	Q Okay. Apart from your work in this	10:50:24
2	matter, have you ever analyzed any structure of a	10:50:25
3	hyaluronidase?	10:50:28
4	A Not prior to this work.	10:50:32
5	Q Have you ever performed an assay to	10:50:38
6	measure hyaluronidase activity?	10:50:40
7	A I have not measured hyaluronidase	10:50:46
8	activity.	10:50:49
9	Q Do you have experience running ELISA	10:50:51
10	assays?	10:50:54
11	A Long time ago.	10:50:59
12	Q Do you use ELISA assays in your lab?	10:51:02
13	A Not regularly.	10:51:05
14	Q So then you've never performed a	10:51:21
15	hyaluronic acid-coated microplate assay; is that	10:51:30
16	correct?	10:51:34
17	A I have not.	10:51:34
18	Q Have you ever measured enzymatic activity	10:51:37
19	using the Morgan-Elson color reaction?	10:51:40
20	A I have not.	10:51:44
21	Q Are you familiar with using	10:51:53
22	turbidity-reducing units as a measure of enzymatic	10:51:56

1	activity?	10:52:00
2	A I'm familiar with that, yes.	10:52:01
3	Q Do you use turbidity-reducing units in	10:52:02
4	work in your lab to characterize enzymatic	10:52:07
5	activity?	10:52:09
6	A At the moment, no.	10:52:26
7	But I -- over the course of the last half	10:52:27
8	century, it's -- yeah, might have. I'm certainly	10:52:31
9	familiar with it.	10:52:34
10	Q Can you explain what a turbidity-reducing	10:52:35
11	unit is?	10:52:41
12	A If one has a substrate that produces a	10:52:44
13	sample that's turbid and then if one has a	10:52:50
14	catalyst -- specifically, in this case, an	10:52:56
15	enzyme -- that degrades that substrate to produce	10:52:59
16	a product that's soluble and not turbid, then you	10:53:05
17	can monitor the progress of the reaction by	10:53:10
18	monitoring the diminished turbidity over the	10:53:14
19	course of time.	10:53:17
20	Q So do turbidity-reducing units refer to	10:54:14
21	the amount of enzyme that will reduce turbidity in	10:54:21
22	a solution by a certain amount over a particular	10:54:27

1	period of time?	10:54:33
2	MR. KUSHAN: Objection. Foundation.	10:54:33
3	A I would not say it refers to the amount of	10:54:36
4	enzyme.	10:54:38
5	It's a measurement of activity, which	10:54:39
6	could arise from having more enzyme -- more	10:54:43
7	activity could arise from having more enzyme or	10:54:46
8	the same amount of enzyme with higher specific	10:54:49
9	activity.	10:54:52
10	So what you said is not precisely correct.	10:54:54
11	Q Did anyone besides counsel assist you in	10:55:08
12	your analysis in these matters?	10:55:13
13	A Park.	10:55:17
14	Q Anyone else?	10:55:18
15	A No.	10:55:19
16	Q No one in your lab?	10:55:19
17	A No.	10:55:22
18	Q Okay. Did you collaborate with Dr. Park	10:55:23
19	in reaching your opinions in these matters?	10:55:28
20	MR. KUSHAN: Objection. Form.	10:55:36
21	A Park and I met on Zoom several times and	10:55:42
22	discussed the science involved. And in that sense	10:55:47

1	it was collaborative in terms of discussing the	10:55:52
2	science.	10:55:55
3	Q About how many Zooms would you say you had	10:55:57
4	with Dr. Park?	10:55:59
5	A More than one, less than five.	10:56:04
6	Q And do you recall roughly when those took	10:56:07
7	place?	10:56:13
8	A Many months ago.	10:56:13
9	Q Do you recall about for how long each Zoom	10:56:14
10	lasted?	10:56:17
11	A More than an hour, less than three.	10:56:22
12	Q Okay. And what did you discuss with	10:56:26
13	Dr. Park on those Zooms?	10:56:28
14	A Sequence, structure, homology,	10:56:40
15	mutagenesis, stability of hyaluronidases,	10:56:47
16	specifically PH20.	10:56:56
17	Q And what did you discuss about sequence,	10:57:00
18	structure, homology, and mutagenesis of PH20?	10:57:03
19	A We looked at sequence alignments. We	10:57:19
20	looked at 3D structures on the computer screen.	10:57:27
21	We looked at possible mutations. We	10:57:34
22	looked at the structures around such possible	10:57:41

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1	potential impact of the mutation on secondary	11:02:43
2	structure?	11:02:51
3	A I'm not going to generalize and say every	11:02:54
4	time, everything you look at, that's true.	11:02:58
5	But I will say that you can make a more	11:03:01
6	cogent analysis if you look at the structure and	11:03:06
7	the environment than if you didn't.	11:03:10
8	Q Well, if you have an amino acid that's in,	11:03:12
9	for example, an alpha helix and you're considering	11:03:14
10	changing that amino acid to an amino acid that is	11:03:17
11	known to be intolerant in alpha helices, then that	11:03:22
12	would give you potential, important information in	11:03:26
13	evaluating the likely impact of the substitution;	11:03:28
14	is that right?	11:03:32
15	MR. KUSHAN: Objection. Foundation. Also	11:03:32
16	objection as to form.	11:03:34
17	A I got distracted.	11:03:40
18	So you're saying if you look at an amino	11:03:41
19	acid in an alpha helix.	11:03:44
20	Continue your question.	11:03:45
21	Q Look at an amino acid in an alpha helix.	11:03:46
22	Then the fact that that amino acid is in	11:03:48

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

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

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

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

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

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

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

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

1	A	Correct.	11:05:49
2	Q	Can you explain how that sequence	11:05:50
3		alignment factored into the analysis in terms of	11:05:53
4		evaluating potential mutations?	11:05:57
5	A	Yeah. I mean, I think that's -- you know,	11:06:00
6		it's in the document here.	11:06:02
7		It's also -- I mean, it's elaborated quite	11:06:11
8		extensively in Park's document. We can look at	11:06:14
9		data if you want.	11:06:17
10		But you're asking how does sequence	11:06:17
11		alignment bear on the consideration of mutations?	11:06:20
12	Q	Yes.	11:06:24
13	A	Okay. Well, the section that begins on	11:06:26
14		page 102 and goes for many pages after that talks	11:07:14
15		about substitutions in non-essential regions.	11:07:37
16		And so an understanding of non-essential	11:07:44
17		regions -- discussion of non-essential regions is	11:07:53
18		based on -- starts by looking at sequence	11:08:09
19		alignments. Essential and non-essential regions	11:08:16
20		starts by looking at sequence alignments.	11:08:20
21		Yeah, there it is on page 109. That's	11:08:25
22		what I was looking for.	11:08:27

1 Q So how does the position of an amino acid
2 in a sequence alignment, how does that tell you
3 whether a potential mutation at that position --
4 or the potential impact of a mutation at that
5 position?

6 MR. KUSHAN: Objection to form.

7 A So on page 109, it says, "The Skilled
8 Artisan Would Have Identified Non-Essential
9 Regions in PH20 and Suitable Amino Acid
10 Substitutions Using a Multiple Sequence Alignment
11 of Homologous Hyaluronidase Proteins."

12 So the discussion starts by identifying
13 non-essential regions. And as it says, "The
14 skilled artisan would have understood that these
15 non-essential regions to be regions between --
16 between the conserved residues," (as read), okay,
17 in other words, not the conserved residues, okay.

18 The non-conserved residues would be deemed
19 as non-essential. And, therefore, if one is
20 considering making mutations, one would look for
21 these sequence alignments to assess what's
22 essential and what's not.

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

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

8 A We -- 11:10:12

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

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

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

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

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

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

1	of this case to refer to positions in an amino	11:10:57
2	acid alignment?	11:11:00
3	A Over the course of 50 years, probably.	11:11:03
4	Q And when you use those terms in your work,	11:11:05
5	what do they mean?	11:11:08
6	A When we say something is essential, we're	11:11:47
7	saying that that thing needs to be there. It is	11:11:50
8	essential for the property of interest.	11:11:55
9	When we say something is not essential,	11:12:00
10	we're saying that particular thing is not	11:12:02
11	essential for the property of interest.	11:12:06
12	Q And is that how you used those terms in	11:12:14
13	your analysis in this matter?	11:12:17
14	MR. KUSHAN: Objection. Foundation.	11:12:23
15	A I -- I mean, in this matter, we're looking	11:12:34
16	at the data to assess what -- which amino acids,	11:12:40
17	at which positions, would appear to be essential	11:12:50
18	for the property of interest, yeah.	11:12:54
19	Q What's the property of interest?	11:12:57
20	A In this case, the property of interest is	11:12:59
21	the enzymatic activity of this protein.	11:13:05
22	Q Now, all of the sequences in the alignment	11:13:09

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

2 A But the sequence in this alignment fold 11:13:19

3 into similar structures, and that structure is 11:13:23

4 essential for the activity that we are 11:13:28

5 considering. 11:13:32

6 Q How do you know that the sequences in the 11:13:34

7 alignment all fold into similar structures? 11:13:36

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

9 A It's something we discussed before. When 11:14:03

10 you have a family of homologous proteins that 11:14:05

11 share common ancestry and share considerable 11:14:13

12 sequence identity, share evolutionary history, and 11:14:21

13 in most cases share enzymatic activity, then one 11:14:28

14 infers from that that they're going to share 11:14:34

15 structure. 11:14:37

16 Q So you testified a few minutes ago -- and 11:14:55

17 I'm reading your testimony. "By looking at the 11:14:58

18 sequence comparisons and by also looking at the 11:15:01

19 structure in three dimensions, one can become more 11:15:03

20 educated about what the likelihood is, what the 11:15:06

21 impact is likely to be from making a particular 11:15:09

22 mutation." 11:15:11

1 Do you recall that testimony? 11:15:12

2 A Mm-hmm. 11:15:13

3 Q So my question is: What does the sequence 11:15:14

4 comparison -- what information does the sequence 11:15:18

5 comparison give you that helps you to become more 11:15:20

6 educated about what the likelihood is, or the 11:15:23

7 impact would be, from making a particular 11:15:25

8 mutation? 11:15:27

9 A The sequence comparison, as I was 11:15:56

10 suggesting before, is -- provides you with the 11:16:06

11 results of the biggest possible experiment, and 11:16:13

12 that is evolution on earth, which in principle has 11:16:16

13 sampled many, many, many sequences. Okay. 11:16:21

14 And those that persist in evolution are 11:16:23

15 those that are tolerated, and that informs us 11:16:28

16 about which positions are suitable for changes and 11:16:35

17 which positions where a change is not tolerated, 11:16:47

18 therefore not seen in the current homologous 11:16:53

19 proteins because it was not tolerated and weeded 11:16:57

20 out by eons of evolution. 11:17:02

21 So that's how the sequence alignments 11:17:08

22 informs us about all those things you asked. Yes. 11:17:10

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

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

4 Q Okay. 11:17:31

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

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

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

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

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

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

20 Q Yes. 11:18:29

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

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

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

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

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

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

1	various mutations?	11:20:49
2	And that's what he shared.	11:20:52
3	Q And how did he share the impact of making	11:20:58
4	various mutations with you? In what format did he	11:21:03
5	share that information?	11:21:07
6	A We discussed it on Zoom and I've looked at	11:21:07
7	his declaration.	11:21:10
8	Q Okay. Do you know if he generated any	11:21:11
9	other documents that provide the results of his	11:21:13
10	analysis?	11:21:16
11	A Not that I have seen. I have seen his	11:21:17
12	declaration. I wouldn't know if there are other	11:21:24
13	documents or not.	11:21:26
14	Q So you said that Dr. Park, in his	11:22:01
15	analysis, looked at, if he went through the PH20	11:22:12
16	sequence and structure, what kinds of mutations	11:22:15
17	would be tolerated.	11:22:17
18	Do you know -- do you have a sense of how	11:22:19
19	many mutations Dr. Park considered in his	11:22:22
20	analysis?	11:22:24
21	A A lot. He started by doing un, you know,	11:22:25
22	unbiased analysis. After he had aligned	11:22:37

1	everything and after he had put the structure up	11:22:40
2	on the screen, he went through amino acid by amino	11:22:42
3	acid, from start to finish, and said, Okay, what's	11:22:46
4	happening here? What's happening here? What's	11:22:48
5	allowed here? What's tolerated here?	11:22:51
6	And went through all of it.	11:22:55
7	Q So he went through and analyzed every	11:23:00
8	single -- potential substitutions at every single	11:23:03
9	position in PH20?	11:23:06
10	MR. KUSHAN: Objection. Foundation.	11:23:14
11	A By discussing what's essential and not	11:23:16
12	essential, he looked at each position and said,	11:23:19
13	Huh. What would happen, if it's	11:23:23
14	non-essential/essential, if mutations were made	11:23:26
15	here.	11:23:28
16	It's not to say he had looked at every	11:23:28
17	possible of the 19 substitutions at every	11:23:30
18	position, but he considered each position and	11:23:34
19	looked at its environment and its -- its	11:23:38
20	environment, both sequence and structurally, and	11:23:41
21	considered the possibility of making mutations at	11:23:44
22	those positions.	11:23:49

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

2 A It's in his declaration, and we had 11:23:53
3 discussions, but it's elaborated in his 11:23:57
4 declaration. 11:23:59

5 Q So in your discussions, did you go through 11:24:00
6 and look at every single position on PH20 and 11:24:03
7 discuss potential changes at every position? 11:24:06

8 A We discussed the global approach of 11:24:09
9 considering what's conserved, what's not 11:24:12
10 conserved, what's essential, what's not essential. 11:24:15

11 We did not do a PyMOL of every single side 11:24:18
12 chain at every -- yeah, every single side chain 11:24:22
13 substitution at every position. That would have 11:24:25
14 taken, you know, weeks. 11:24:28

15 But we discussed the approach, and then we 11:24:29
16 looked at representative examples. 11:24:31

17 Q And who selected the representative 11:24:36
18 examples? 11:24:39

19 A I saw what he showed me. I didn't say, 11:24:43
20 Oh, show me this, show me that. 11:24:46

21 You know, we went into the stuff that he 11:24:48
22 had. 11:24:53

1 Q So he just, to the best of your knowledge, 11:24:53
2 randomly picked examples and showed them to you 11:24:56
3 and you discussed them on PyMOL -- with PyMOL? 11:24:59
4 A I think, in the overall initial project, 11:25:03
5 he went through all -- everything, right? Looked 11:25:06
6 at it position by position by position and 11:25:09
7 considered, you know, is this position 11:25:13
8 evolutionarily conserved? Is this position, you 11:25:17
9 know, whatever. 11:25:21
10 And then after having done that, he was 11:25:21
11 asked to focus upon and show me certain examples. 11:25:25
12 Q Did you ask him to focus on and show you 11:25:42
13 certain examples, or was that instruction from 11:25:46
14 someone else? 11:25:48
15 A I did not say to him, Please show me 11:26:01
16 Position 23, although I did ask him questions. If 11:26:04
17 he had something on the screen, I'd say, What 11:26:09
18 about this over there? What about this next to 11:26:12
19 this other amino acid? 11:26:15
20 And he would then highlight it and we 11:26:18
21 would talk about it. 11:26:20
22 Q Okay. So earlier this morning we had 11:26:21

1	talked a little bit about SWISS-MODEL and	11:26:38
2	MODELLER.	11:26:41
3	Do you recall that?	11:26:42
4	A We talked about that, yeah.	11:26:42
5	Q SWISS-MODEL and MODELLER were both	11:26:45
6	available in 2011; right?	11:26:48
7	A Right.	11:26:50
8	Q And PyMOL was available in 2011?	11:26:53
9	A Right.	11:26:56
10	Q And Chimera also was available in 20 --	11:26:56
11	A I'm sorry. I didn't hear.	11:26:59
12	Q Chimera.	11:27:00
13	A I think so, yeah.	11:27:01
14	Q Okay. And Chimera was a -- was that a	11:27:02
15	structure visualization program?	11:27:05
16	A I haven't used Chimera, so I'm not going	11:27:07
17	to comment on that.	11:27:11
18	Q Okay. In 2011, the crystal structure for	11:27:12
19	bee venom hyaluronidase -- or strike that.	11:27:26
20	As of 2011, the crystal structure for bee	11:27:32
21	venom hyaluronidase and HYAL1, the crystal	11:27:36
22	structures for both of those proteins had been	11:27:40

1	solved; is that right?	11:27:42
2	A Right. Prior to '11, yes.	11:27:43
3	Q Okay. So as of 2011, the secondary	11:27:46
4	structures in bee venom hyaluronidase and HYAL1	11:27:48
5	were known; is that right?	11:27:54
6	A Correct.	11:27:57
7	Q And as of 2011, the sites of conserved	11:28:03
8	amino acids in PH20 and HYAL1 were known; right?	11:28:09
9	MR. KUSHAN: Objection. Form. Also	11:28:16
10	objection as to foundation.	11:28:17
11	A Yeah. On 40 -- page 43 in the declaration	11:28:22
12	explicitly shows how those sequences are related	11:28:26
13	and also alludes to the secondary structure that	11:28:31
14	you were asking about a moment ago in page 41, 42,	11:28:34
15	and 43 from the paper by Chao, et al.	11:28:40
16	Q So the alignment from Chao, et al., you	11:28:59
17	have reproduced that alignment on page 43 of your	11:29:06
18	declaration; is that right?	11:29:09
19	A That's right. That's just a screenshot --	11:29:09
20	Q Okay.	
21	A -- or -- yeah, okay. Yeah.	11:29:13
22	Q That -- the Chao alignment that's on page	11:29:14

1 43 in your declaration identifies the secondary
2 structures and sites of conserved amino acid in
3 both PH20 and HYAL1; correct?

11:29:20

11:29:24

11:29:27

4 A And the other sequences in there.

11:29:29

5 Q So the alignment from Chao on page 43 of
6 your declaration identifies the secondary
7 structures and sites of conserved amino acids in
8 HYAL1, HYAL2, HYAL3, HYAL4, and PH20; is that
9 right?

11:29:35

11:29:40

11:29:42

11:29:46

11:29:51

10 A That's what the figure shows.

11:29:51

11 Q So the secondary structures in HYAL1,
12 HYAL2, HYAL3, HYAL4, and PH20 were all known as of
13 2011?

11:29:53

11:29:57

11:30:03

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

11:30:03

11:30:06

11:30:11

11:30:14

11:30:21

19 What's shown in this figure are the five
20 sequences, the conserved amino acids, the
21 cysteines and such things, the active site amino
22 acids.

11:30:28

11:30:33

11:30:39

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

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

9 A Where are you reading? 11:31:14

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

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

13 Yes. 11:31:36

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

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

17 Q Yes. 11:31:42

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

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

21 THE REPORTER: Slow down, please.

22 A Sorry.

1 "For example, its sequence alignment 11:31:51
2 identified secondary structures and sites of 11:31:53
3 conserved amino acids in both PH20 and HYAL1." 11:31:55
4 Yeah, I'm satisfied with that sentence. 11:32:02
5 Q Okay. So, again, just to clarify, the 11:32:04
6 Chao sequence alignment identified secondary 11:32:07
7 structures and sites of conserved amino acids in 11:32:10
8 both PH20 and HYAL1; correct? 11:32:13
9 A Right. But to be clear, the HYAL1 is from 11:32:15
10 the crystal structure; the PH20 is based on 11:32:19
11 homology because the structure of PH20 was not 11:32:25
12 known at that point. 11:32:30
13 So the word "identified" here is 11:32:32
14 identified from the crystal structure in their 11:32:35
15 protein and identified -- or, you know, aligned 11:32:37
16 for the PH20. 11:32:44
17 Q Based on -- and aligned for PH20 based on 11:32:46
18 the homology between PH20 and HYAL1? 11:32:49
19 A That's based on sequence similarity, 11:32:53
20 which, in turn, is based on homology, which is 11:32:56
21 shown in that figure. 11:32:58
22 Q Okay. And the HYAL1 crystal structure in 11:33:00

1	Chao provided a template that one could use to	11:33:28
2	create a PH20 homology model; is that right?	11:33:31
3	A Correct.	11:33:34
4	Q So a POSA in 2011 seeking to evaluate	11:33:35
5	potential substitutions in PH20 would have	11:33:42
6	generated a homology model using HYAL1 as the	11:33:46
7	template; is that right?	11:33:49
8	A Correct.	11:33:53
9	Q So in 2011 a POSA seeking to evaluate	11:34:12
10	potential substitutions in PH20 likely to be	11:34:16
11	tolerated would have generated a homology model;	11:34:20
12	is that right?	11:34:29
13	A Yes. Among other things, yes.	11:34:29
14	Q And the POSA would have used that homology	11:34:30
15	model to evaluate the particular substitutions?	11:34:33
16	A Would have used the homology model and	11:34:38
17	also used other input.	11:34:40
18	Q And what other input?	11:34:41
19	A As we said before, the sequence alignment	11:34:43
20	of many sequences, not just those in the figure,	11:34:45
21	and just expertise and experience in the field of	11:34:51
22	protein structure and engineering and mutagenesis.	11:34:56

1	Q Also can you please turn to paragraph 88.	11:35:26
2	In paragraph 88, you say, "...a number" --	11:35:44
3	"...before 2011, a number of residues within the	11:35:47
4	region of the catalytic site in PH20 or HYAL1 had	11:35:50
5	been experimentally shown to be necessary or	11:35:54
6	important to the catalytic activity of	11:35:57
7	hyaluronidases"; is that right?	11:36:00
8	A Okay.	11:36:01
9	Q And then you refer to three papers:	11:36:04
10	Arming, Zhang, and Chao; right?	11:36:09
11	A Okay. Let's read that again.	11:36:15
12	Okay.	11:36:30
13	Q So you agree that in paragraph 88 you	11:36:30
14	refer to Arming, Zhang, and Chao?	11:36:33
15	A Those three papers are mentioned in that	11:36:38
16	paragraph, yeah.	11:36:41
17	Q Okay. We've probably been going for	11:36:43
18	another hour.	11:36:46
19	Do you want to take a break?	11:36:46
20	A Sure.	11:36:48
21	Q All right.	11:36:49
22	THE VIDEOGRAPHER: We are going off the	11:36:49

1	record. The time is 11:36 a.m.	11:36:50
2	(A recess was taken.)	12:04:10
3	THE VIDEOGRAPHER: We are back on the	12:04:10
4	record. The time is 12:04 p.m.	12:04:15
5	BY MS. MARTIN:	12:04:18
6	Q Welcome back, Dr. Hecht.	12:04:20
7	A Hey.	12:04:23
8	Q Doctor, did you speak with anyone during	12:04:23
9	the break regarding the substance of your	12:04:25
10	testimony?	12:04:27
11	A No.	12:04:27
12	Q So can you please turn in your declaration	12:04:27
13	to paragraph 88?	12:04:29
14	A Okay.	12:04:35
15	Q And so the first sentence in paragraph 88,	12:04:38
16	you say that, "...before 2011, a number of	12:04:44
17	residues within the region of the catalytic site	12:04:47
18	on -- in PH20 or HYAL1 had been experimentally	12:04:51
19	shown to be necessary or important to the	12:04:54
20	catalytic activity of hyaluronidases"; right?	12:04:57
21	A Right. I see that.	12:05:01
22	Q So what do you mean by the "region of the	12:05:02

1	catalytic site"?	12:05:04
2	A So, in enzymes -- so proteins are large	12:05:20
3	molecules, macromolecules, that are folded in	12:05:36
4	particular structures.	12:05:40
5	And if the protein is an enzyme, it will	12:05:42
6	typically have a -- it will have a site where the	12:05:46
7	enzyme performs a catalysis. And that's what's	12:05:50
8	being considered here necessary important for	12:05:54
9	the -- so region of the catalytic site is what	12:05:58
10	that's referring to.	12:06:02
11	And so if the catalytic site is the part	12:06:03
12	of the protein, the site where the catalysis	12:06:07
13	happens, that's what we're talking about there.	12:06:11
14	Q So the catalytic site is the area on the	12:06:14
15	protein where the catalysis happens?	12:06:18
16	MR. KUSHAN: Objection. Form.	12:06:24
17	A The catalytic site -- in general	12:06:28
18	textbooks -- sometimes also called the active	12:06:31
19	site, in general textbooks refers to that --	12:06:35
20	wouldn't say area -- but volume of the protein	12:06:40
21	where the essential chemistry happens.	12:06:43
22	But that's not to say that everything else	12:06:46

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

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

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

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

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

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

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

1 it's a picture above paragraph 83, and the picture
2 above paragraph 82, but that whole part of the
3 declaration, pages 41 and pages 42, after Chao, et
4 al., solved that structure, published it, okay,
5 that's -- well, you can see that on the top of
6 page 41.

7 So by comparing the HYAL1 structure that
8 they had solved with the bee venom structure that
9 had been reported previously, these two similar
10 homologous proteins had structural similarity as
11 shown in the figure on page 41.

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

17 So those are catalytic sites.

18 Q And in the -- in Chao's alignment, which
19 is on page 43, the three key catalytic residues
20 are colored in red; is that right?

21 A Yeah. The legend says three key catalytic
22 residues are colored in red. But that does not

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

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

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

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

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

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

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

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

9 of the region of the catalytic site? 12:10:37

10 A So -- 12:10:45

11 MR. KUSHAN: Sorry. Objection to form. 12:10:46

12 A So the EGF region is shown or diagram -- 12:10:51

13 well, shown and diagrammed on pages 44 and 45. 12:10:56

14 Maybe elsewhere also, but we can stick with those. 12:11:05

15 And your question is -- is whether the EGF region 12:11:09

16 is -- 12:11:15

17 Q Whether the EGF-like domain is in the 12:11:17

18 region of the active site. 12:11:20

19 A It's not directly in the active site, 12:11:22

20 okay. But one should not conclude for that, that 12:11:27

21 it's irrelevant for activity. 12:11:32

22 Q Well, that's not the question. The 12:11:35

1 question is: Is it in the region of the active 12:11:38
2 site? 12:11:41

3 A Region is a nebulous term. How many 12:11:42
4 angstroms do you mean by region? I mean it's -- 12:11:47
5 it's -- I think we can see in page 40 -- no, yeah, 12:11:50
6 page 44, Figure 4B, taken from the Chao, et al. 12:12:02
7 paper, one can see -- well, actually I like Figure 12:12:10
8 2A, it's a little easier to see there, Figure 2A 12:12:15
9 has an arrow pointing to the active site. And by 12:12:17
10 the definitions we discussed before, it's typical 12:12:20
11 for active site to refer to the actual amino acid 12:12:24
12 side chains that perform the catalysis. 12:12:29

13 The EGF-like domain is in yellow on the 12:12:33
14 bottom of Figure 2A. And so is it in the region? 12:12:36
15 It's not -- it depends if you define region as 5 12:12:39
16 angstroms or 10 angstroms or whatever. It's part 12:12:44
17 of the same protein. It's not contributing 12:12:47
18 catalytic atoms to direct mechanism, but it has 12:12:50
19 been shown that deleting it will be deleterious 12:12:54
20 for activity. 12:12:58

21 Q Okay. So just to be clear, "region" is 12:13:00
22 the nebulous word that you used in paragraph 88 in 12:13:05

1 your declaration. 12:13:09

2 And I'm just trying to understand that 12:13:09

3 when you -- in the first sentence, in paragraph 12:13:11

4 88, when you refer to the region of the catalytic 12:13:14

5 site, if you intended to encompass, within that 12:13:16

6 description, the EGF domain which you have at the 12:13:20

7 very end of the second sentence in paragraph 88? 12:13:23

8 A I think paragraph 88 talks about -- in the 12:13:49

9 first sentence, I would interpret that to be 12:13:53

10 region as being close to the catalytic site. I 12:13:55

11 don't want to give a cutoff in the number of 12:13:59

12 angstroms, but it's close. 12:14:01

13 And the later part of that paragraph 12:14:03

14 discusses the Hyal-EGF domain, which is further 12:14:07

15 away. I think the point of that paragraph is 12:14:13

16 residues and mutations had been observed that 12:14:16

17 impact activity in a number of places. 12:14:21

18 Q Okay. So you weren't intending to suggest 12:14:26

19 that the residues that you were listing were all 12:14:28

20 in the region of the catalytic site? 12:14:30

21 MR. KUSHAN: I'm sorry. Objection. 12:14:34

22 Foundation. 12:14:36

1 A I mean, again, I'm -- if you were to ask a 12:14:37
2 question about this on a final exam in a course, 12:14:45
3 you would have to define "region." You would say, 12:14:48
4 you know, is it two angstroms or 10 angstroms or 12:14:51
5 20 angstroms? 12:14:55

6 So -- but I think the point is that 12:14:56
7 residues that are close to the catalytic site or 12:14:58
8 in the catalytic site had been shown by mutation 12:15:02
9 to be important. 12:15:08

10 And also, later in the paragraph, 12:15:09
11 mutations -- later in the paragraph and elsewhere 12:15:16
12 in the document we describe mutations that are 12:15:21
13 elsewhere in the protein. 12:15:24

14 The point is that mutations can disable 12:15:26
15 activity if they're in the actual catalytic atoms, 12:15:29
16 but it's also possible to disable activity with 12:15:34
17 mutations that are not in the catalytic atoms. 12:15:38

18 Q So Arming, the Arming paper, that was a 12:15:51
19 mutagenesis study that involved PH20; right? 12:15:55

20 A I would want to see that paper before I 12:16:02
21 make any serious comments about it because there's 12:16:04
22 a sentence here. But, you know, I want to look at 12:16:07

1	that paper before we actually talked about the	12:16:12
2	details in it.	12:16:16
3	Q Did you read the Arming paper when you	12:16:17
4	were --	12:16:19
5	A Oh, of course I looked at that paper.	12:16:20
6	Q So I think --	12:16:22
7	A That was a while ago.	12:16:23
8	Q Let's look at paragraph 79. See if that	12:16:25
9	helps.	12:16:27
10	A I'm sorry.	
11	Q Actually, no. Paragraph 78.	12:16:34
12	A Okay.	12:16:59
13	Q So does paragraph 78 refresh your	12:16:59
14	recollection that Arming involved mutagenesis of	12:17:02
15	PH20?	12:17:05
16	A Yeah. Arming made mutations in PH20.	12:17:06
17	That's what -- yeah.	12:17:10
18	Q Okay. So then turning back to paragraph	12:17:11
19	88. In paragraph 88, you say that Arming, which	12:17:21
20	we just established involved PH20, identified	12:17:27
21	positions D111, E113, R176, E249 and R252;	12:17:30
22	correct?	12:17:40

1 A Okay. 12:17:40

2 Q And the mutagenesis study in Arming showed 12:17:44
3 that those -- that those residues at those 12:17:47
4 positions were necessary or important to catalytic 12:17:51
5 activity; is that right? 12:17:56

6 A They were important for activity -- 12:17:57

7 MR. KUSHAN: Sorry. Objection to 12:18:00
8 foundation. 12:18:02

9 Q So in 2011 a POSA would have expected that 12:18:03
10 changing all five of those amino acids -- D111, 12:18:14
11 E113, R176, E249 and R252 -- that would have 12:18:21
12 resulted in an inactive PH20. 12:18:26

13 Is that a fair assumption? 12:18:29

14 MR. KUSHAN: Objection. Foundation. 12:18:31

15 A I don't think it's a fair assumption to 12:18:34
16 say it would be inactive in total. I think what 12:18:36
17 it said here is that they are important, and I 12:18:41
18 expect those mutations would have an impact. I 12:18:44
19 don't recall whether they were knocked out 12:18:49
20 completely. 12:18:51

21 Q Oh, so you have to look at Arming to 12:18:51
22 see -- 12:18:53

1	A Uh-huh.	12:18:54
2	Q -- if they were?	12:18:54
3	A Yes.	12:18:58
4	Q Okay. Well, if you look in paragraph 78,	12:18:58
5	paragraph 78 says that three of the mutants for	12:19:18
6	113, 249 and 252 were devoid of enzymatic	12:19:31
7	activity, while two other mutants at 111 and 176	12:19:38
8	had residual activities in the range of one to a	12:19:43
9	few percent of wild-type.	12:19:47
10	A Okay. Let me -- okay. Okay. I'm seeing	12:19:50
11	what you're reading.	12:20:44
12	Q So do you know which specific residue is	12:20:47
13	the proton donor for the hydrolysis reaction that	12:21:03
14	PH20 catalyzes?	12:21:08
15	A I don't remember that off the top of my	12:21:10
16	head.	12:21:12
17	Q Did you know it when you were doing your	12:21:12
18	analysis in this case?	12:21:14
19	A I read that paper, yeah.	12:21:15
20	Q So would you agree that a mutation, if	12:21:52
21	Arming teaches that a particular mutant was devoid	12:21:55
22	of enzymatic activity, that that mutant was	12:21:58

1	inactive?	12:22:01
2	A You said if it's devoid of activity, that	12:22:04
3	means it's inactive?	12:22:06
4	Q Yes.	12:22:08
5	A Yeah.	12:22:09
6	Q Okay. And if a particular mutant had	12:22:09
7	residual activity in the range of one to a few	12:22:13
8	percent of activity, would you think -- would you	12:22:15
9	consider that PH20 mutant to be inactive?	12:22:17
10	MR. KUSHAN: Objection. Foundation.	12:22:21
11	A You're saying 1 to 2 percent, would one	12:22:28
12	consider that active or not active?	12:22:32
13	Q Yes.	12:22:34
14	A So in the common disclosure, they make a	12:22:35
15	different dividing line than what you just said.	12:22:40
16	They typically divide it -- they say inactive is	12:22:43
17	below 20 percent.	12:22:47
18	So that's their choice of where they're	12:22:49
19	drawing the line. There are -- there are other	12:22:53
20	situations where having a little bit of activity,	12:23:00
21	1 or 2 percent, would be considered sufficient for	12:23:05
22	a particular purpose.	12:23:08

1 So it's where you choose to draw the line 12:23:10
2 between active and inactive. But 1 or 2 12:23:12
3 percent -- yeah, I'll just leave that, yeah. It's 12:23:16
4 where you choose to draw the line of what you 12:23:19
5 consider inactive. Is it 10 percent, 20 percent, 12:23:22
6 1 percent, 2 percent? 12:23:28

7 Q So you said that you were a POSA as of 12:23:29
8 2011; right? 12:23:31

9 A That I was what? 12:23:32

10 Q A POSA as of 2011? 12:23:33

11 A Yeah, I did. 12:23:35

12 Q So as a POSA, as of 2011, would you 12:23:35
13 consider a PH20 that has 1 to a few percent of 12:23:38
14 activity to be active or inactive? 12:23:42

15 A 1 to 2 percent? 12:23:44

16 Q Yes. 12:23:46

17 MR. KUSHAN: Objection. Foundation. 12:23:47

18 A Having considered as having 1 or 2 percent 12:23:48
19 activity, I don't think this is a -- this is not a 12:23:52
20 binary, yes/no issue. It's a quantitative issue. 12:23:54

21 Q Okay. And when -- when Arming says that 12:24:05
22 the mutants at the 113, 249, and 252 positions 12:24:10

1	were devoid of enzymatic activity --	12:24:16
2	A Where are you reading? I'm sorry, which	12:24:19
3	paragraph?	12:24:20
4	Q 78.	12:24:20
5	A Yes. Okay, devoid of activity.	12:24:25
6	Q Would you understand that to mean zero	12:24:26
7	activity?	12:24:29
8	A I would understand that to mean that	12:24:30
9	within the range of what their laboratory	12:24:33
10	experiment is able to detect, they were not able	12:24:36
11	to detect enzyme activity.	12:24:40
12	But different experiments have different	12:24:43
13	sensitivities. So, you know, as an experimental	12:24:45
14	scientist, one has to say that if it's reported as	12:24:48
15	devoid of activity, that's understood to mean	12:24:52
16	devoid of measurable activity in the assay as done	12:24:55
17	in that study.	12:25:00
18	Q So as a POSA reading the Arming paper in	12:25:12
19	2011, would you have concluded that the three	12:25:15
20	mutants that Arming teaches were devoid of	12:25:18
21	enzymatic activity, that those mutants were	12:25:20
22	inactive?	12:25:25

1 MR. KUSHAN: Objection. Form. Also 12:25:26
2 objection as to foundation. 12:25:28

3 A I would conclude what I just said, that 12:25:34
4 they were devoid of measurable activity in the 12:25:37
5 assay and the sensitivity of the assay that those 12:25:41
6 scientists were able to do. 12:25:45

7 This is something I actually have 12:25:49
8 expertise in because we make novel proteins. And 12:25:50
9 if we're looking for activity, the levels of 12:25:54
10 activity we see are often very, very low. And so 12:25:57
11 sometimes for us, in a novel protein, that level 12:26:02
12 of activity, we would jump up and down and say, 12:26:06
13 Oh, it's active, whereas that level of activity 12:26:10
14 for a natural protein would be, Oh, that's 12:26:14
15 inactive. 12:26:17

16 So it's -- context matters. It's not 12:26:18
17 absolute yes or no. There's a continuum. 12:26:22

18 Q So the amount of activity -- the amount of 12:26:25
19 activity that's useful really depends on the 12:26:29
20 context for which you intend to use the protein? 12:26:32

21 A The amount of activity you measure depends 12:26:36
22 on your measurement and the -- whether you define 12:26:38

1 that as a hit or a miss, as active or inactive, 12:26:42
2 depends on what you're using it for, what 12:26:47
3 your sensitivity of your measurement is, the 12:26:51
4 accuracy of your measurement is, what the 12:26:54
5 reproducibility is. 12:26:58

6 But I would say that it's a continuous 12:27:01
7 scale; that people sometimes put a bar -- as they 12:27:03
8 did in the common disclosure, they put a bar at 20 12:27:05
9 percent or 40 percent or whatever. 12:27:08

10 But the reality of the world is it's a 12:27:10
11 continuum. You know, what can you measure? How 12:27:13
12 sensitive is your assay? 12:27:16

13 Q Would you consider ELISA to be a sensitive 12:27:17
14 assay? 12:27:21

15 A ELISAs are sensitive -- I mean, it depends 12:27:28
16 what you're using them for. It's -- yes, it's a 12:27:32
17 sensitive assay, but how sensitive relative to 12:27:34
18 what for what activity? 12:27:37

19 Q If you're trying to identify a very, very 12:27:41
20 low level of activity, like you were talking about 12:27:45
21 in your lab, would you use an ELISA to do that? 12:27:49

22 MR. KUSHAN: Objection. Foundation. 12:27:56

1	A It's -- it's a -- it's just like a -- too	12:28:02
2	general a question. It's -- it depends on what	12:28:05
3	you're -- what the -- what you're looking for. It	12:28:11
4	depends how -- it depends what your enzyme is. It	12:28:14
5	depends what your -- yeah, it depends on a lot.	12:28:17
6	It's more -- I would say it's more	12:28:20
7	sensitive than the turbidity assay we looked at	12:28:21
8	earlier.	12:28:25
9	Q Okay. So you -- you agree that there is a	12:28:26
10	residue on PH20 that is the proton donor in the	12:29:09
11	hydrolysis reaction.	12:29:14
12	You just don't remember which one it is;	12:29:16
13	is that right?	12:29:18
14	MR. KUSHAN: Objection. Foundation.	12:29:18
15	A I would like to have that paper in front	12:29:24
16	of me to look at the catalytic mechanism.	12:29:26
17	I mean, I remember the catalytic	12:29:30
18	mechanism. You know, there was substrate-assisted	12:29:31
19	catalysis, which is kind of cool. I remember that	12:29:34
20	part. But I don't remember the details of which	12:29:36
21	amino acid did what.	12:29:38
22	Q Okay. All right. So the results, the	12:29:39

1	mutagenesis results in Arming that we talked about	12:29:58
2	in paragraph 78, a POSA could have looked at those	12:30:01
3	positions in the homology model to evaluate the --	12:30:13
4	their position in the structure; is that right?	12:30:23
5	MR. KUSHAN: Objection. Foundation.	12:30:27
6	A One could have looked at those positions	12:30:34
7	in the model to look at where they are in the	12:30:41
8	structure. One could look at those positions for	12:30:46
9	the wild-type sequence and say, Here's where they	12:30:49
10	are in the structure. One could point at them.	12:30:52
11	Q And one could also look at the mutagenesis	12:31:03
12	results achieved for HYAL1 on the HYAL1 structure,	12:31:07
13	right, to identify where those -- where those	12:31:13
14	residues appear in the structure?	12:31:14
15	A Well, you say one could look at the	12:31:17
16	mutagenesis. I would be more precise and say one	12:31:19
17	could look at the amino acid at the position in	12:31:24
18	the protein where the mutagenesis was performed.	12:31:27
19	It doesn't look at mutagenesis per se.	12:31:30
20	One looks at the atoms in the structure,	12:31:33
21	but one could look at position 27 or 132 or	12:31:36
22	whatever in the structure.	12:31:40

1 Q And by doing that, one could identify 12:31:47
2 potential explanations for the functional results 12:31:54
3 that were seen; is that right? 12:31:57

4 MR. KUSHAN: Objection. Foundation. 12:31:59

5 A One could use the structural analysis as 12:32:08
6 input to understand -- this is always the case. 12:32:15
7 One could look at the structure on the computer 12:32:19
8 and use that as input to interpret the observed 12:32:22
9 experimental result in the laboratory. 12:32:28

10 Q And how would you look at the structure on 12:32:41
11 the computer and use that -- how would you use 12:32:43
12 that as input to interpret the observed 12:32:45
13 experimental result in the laboratory? 12:32:48

14 A I would look at the environment of that 12:32:55
15 position, you know, position number 322, whatever. 12:32:58

16 I would look at the chemical environment 12:33:04
17 of that position with respect to its interactions 12:33:06
18 with other amino acids, with respect to its 12:33:12
19 interactions with, you know, water, solvent, or 12:33:16
20 buried. 12:33:20

21 I would look at its interactions with 12:33:21
22 respect to the putative active site. I would look 12:33:27

1 at its position -- at its position with respect 12:33:33
2 to, as shown on page 41, with respect to 12:33:35
3 the hyaluronic acid, you know, being docked in 12:33:44
4 there. 12:33:47

5 I would look at its position with respect 12:33:47
6 to the -- I think I already said this, but I'll 12:33:50
7 say it, again -- the putative active site in the 12:33:52
8 picture on page 42. 12:33:56

9 I would look at its position with respect 12:33:58
10 to the various interactions that are listed 12:34:02
11 somewhere earlier on in the -- this document about 12:34:05
12 the types of interactions that are formed -- 12:34:08
13 hydrogen bonds, electrostatic -- here we go, on 12:34:12
14 page 26 -- I would look at its position with 12:34:15
15 respect to -- page 26. 12:34:19

16 Q Page -- sorry, 20-what? 12:34:20

17 A Page 26, sorry. 12:34:21

18 Q 26. 12:34:23

19 A I would look at its position on the 12:34:24
20 structure with respect to its neighbors. And you 12:34:27
21 see A is hydrogen bonds; B is ionic interactions; 12:34:30
22 C is Van der Waals forces; D is hydrophobic 12:34:34

1 interactions; onward, pi-pi interactions; 12:34:38
2 cation-pi interactions. 12:34:42

3 So if one were interested in a particular 12:34:44
4 mutation, I would look at that location, position, 12:34:47
5 whatever number, with all these issues in mind: 12:34:50
6 its solvent exposure; its proximity to other amino 12:34:56
7 acids; that list of interactions I just read off; 12:35:02
8 its -- its atoms, whether or not those atoms 12:35:06
9 perform the catalysis or are they near the 12:35:11
10 catalytic site, or do they bind to the -- at a 12:35:15
11 hyaluronic acid? All those things. 12:35:20

12 I think that's what you were asking, 12:35:22
13 but -- yeah. 12:35:24

14 Q So how would that analysis assist you 12:35:24
15 in -- to -- how would that analysis assist you to 12:35:26
16 interpret the observed, experimental result in the 12:35:34
17 laboratory? 12:35:36

18 A I think I already said that; that if the 12:35:45
19 wild-type amino acid that's been deleted, removed, 12:35:53
20 replaced, if the structure shows that wild-type 12:35:58
21 amino acid has atoms that are involved in 12:36:03
22 catalysis, I would look at that and say, Oh, 12:36:08

1 making mutations in those atoms would impact the 12:36:12
2 actual catalytic chemistry. 12:36:16

3 Conversely, if it were elsewhere and it 12:36:21
4 was in a buried position, very well packed and 12:36:25
5 making lots of interactions, I would infer that 12:36:28
6 its impact is based on those structural features 12:36:31
7 separate from the actual catalytic chemistry. 12:36:36

8 And, you know, I could go on and on about 12:36:38
9 that, but that's how you do it. 12:36:41

10 Q Okay. So if you have a functional result 12:36:52
11 that shows you that a particular substitution has 12:36:54
12 a deleterious impact on function and you can look 12:37:00
13 at the structure -- you can look at the position 12:37:04
14 of that residue in the structure, and you can try 12:37:06
15 to understand what it is about that residue in 12:37:08
16 that position that potentially resulted in the 12:37:11
17 loss of function that you saw in the lab? 12:37:14

18 A As you said -- 12:37:16

19 MR. KUSHAN: Sorry. 12:37:17

20 A -- "try to understand." 12:37:17

21 MR. KUSHAN: Sorry. 12:37:18

22 Objection. Form. Also objection as to 12:37:19

1	foundation.	12:37:22
2	Q Is that right?	12:37:22
3	A You would try to understand. I'm not	12:37:23
4	saying you would absolutely know. You would use	12:37:26
5	that information to try to understand.	12:37:28
6	Q But that information, the structural	12:37:29
7	information, gives you potential insight into an	12:37:32
8	explanation for the result that you saw?	12:37:37
9	MR. KUSHAN: Objection. Foundation. Also	12:37:40
10	objection as to form.	12:37:42
11	A It gives you -- has the potential to give	12:37:44
12	you insight. Just different from saying it gives	12:37:47
13	you a perfect answer.	12:37:51
14	Q Have you ever gotten a perfect answer in	12:38:08
15	your research?	12:38:10
16	A Ha. Of course not.	12:38:12
17	Q Do you expect to get a perfect answer in	12:38:14
18	your research?	12:38:18
19	A Do you want to talk philosophy or theology	12:38:22
20	or science? I mean, this is -- you know, I don't	12:38:25
21	think perfection is an achievable thing in this	12:38:36
22	world.	12:38:39

1	Q Okay.	12:38:40
2	A You know, as I said before, things are on	12:38:48
3	a continuum. It's not binary, yes, no, perfect,	12:38:52
4	flawed. Things are on a continuum.	12:38:58
5	Q So as we talked earlier this morning about	12:39:01
6	non-essential and essential residues; right?	12:39:04
7	A We did.	12:39:09
8	Q So just to clarify some terminology. If	12:39:13
9	you're talking about a non-essential residue, is	12:39:17
10	it fair to say that the rest of the residues --	12:39:21
11	A The what, sorry?	12:39:23
12	Q The rest of the residues, the ones that	12:39:24
13	are not non-essential, would those be termed	12:39:26
14	essential residues?	12:39:29
15	MR. KUSHAN: Objection. Foundation.	12:39:33
16	A I'm in the section of the declaration that	12:39:45
17	starts on page 102 goes into pretty long	12:39:51
18	conversation about essential versus non-essential	12:39:55
19	regions.	12:40:01
20	But as we're discussing before -- and it's	12:40:04
21	the real world. By and large, I think it's pretty	12:40:08
22	solid to talk about essential versus non-essential	12:40:15

1 regions, but, you know, it's not perfect versus 12:40:17
2 dismal. There are going to be some amino acids 12:40:22
3 that are -- it's a little mushy. You can get away 12:40:25
4 with things. 12:40:28

5 But by and large, these are two distinct 12:40:29
6 regions that you can look at, based on all the 12:40:32
7 things written here. 12:40:35

8 Q Okay. So maybe let's turn to paragraph 12:40:47
9 208. And so in the second sentence in 208, you 12:40:51
10 say, "The skilled artisan would have understood 12:41:08
11 these non-essential regions to be the regions 12:41:10
12 between the conserved residues within PH20, which 12:41:13
13 are residues that are generally considered 12:41:17
14 essential to the structure and function of 12:41:20
15 proteins like hyaluronidase enzymes." 12:41:23

16 Is that right? 12:41:25

17 A Okay. 12:41:26

18 Q So is it fair to say that the conserved 12:41:27
19 residues in Dr. Park's sequence alignment, those 12:41:31
20 conserved residues, the one that are not termed 12:41:36
21 non-essential, you would refer to those as 12:41:40
22 essential residues? 12:41:43

1 A Dr. Park's analysis, and our thinking 12:41:45
2 about this is that, that one can look at the 12:41:52
3 protein and sequence and structure, and one can 12:42:02
4 infer from that that some positions are considered 12:42:06
5 essential. Others are considered non-essential. 12:42:12
6 Yeah. 12:42:18

7 Q And residues that are considered essential 12:42:20
8 are essential to the structure and function of the 12:42:25
9 protein; is that right? 12:42:27

10 A To the structure and function. Let's 12:42:35
11 realize function is a broad term, but yeah. 12:42:39

12 Q What do you mean when you say "function is 12:42:42
13 a broad term"? 12:42:44

14 A What I mean is that, if at the end of the 12:42:46
15 day your experiment is reporting on the measured 12:42:50
16 enzyme activity, that's the function you're 12:42:54
17 focusing your mind on, but you may get a negative 12:42:58
18 result because the protein failed to express, 12:43:01
19 failed to fold, failed to secrete. 12:43:04

20 And so all those are part of the steps 12:43:08
21 that ultimately lead to the function that you were 12:43:11
22 measuring in the laboratory. 12:43:14

1 Q Okay. Well, if it's a homology model and 12:43:29
2 you're talking about essential residues in the 12:43:40
3 homology model, you're talking about residues that 12:43:42
4 have not mutated, right, over time, so you're not 12:43:45
5 talking about function in the laboratory or 12:43:50
6 function measured in a test in a laboratory. 12:43:54
7 You're talking about the effect of evolution over 12:43:56
8 time? 12:43:59

9 MR. KUSHAN: Objection to form. 12:44:02

10 A Right. I mean, the person skilled in the 12:44:11
11 art in that situation is inferring essential 12:44:13
12 versus non-essential. 12:44:18

13 If you're trying to focus on the 12:44:19
14 evolutionary point, person of skill in the art is 12:44:21
15 inferring from evolution, the grand experiment, is 12:44:25
16 inferring that if something varies all over the 12:44:33
17 place over the course of essential, over the 12:44:38
18 course of evolution, then that amino acid at that 12:44:41
19 position is not essential, as shown by the results 12:44:46
20 of natural selection. It was not essential. It 12:44:51
21 was changed. 12:44:55

22 Q All right. So let's turn to paragraph 15. 12:45:18

1	A	Sorry. Paragraph --	12:45:23
2	Q	15?	12:45:24
3	A	The beginning, okay.	12:45:25
4	Q	So full-length human PH20 contains 509	12:45:38
5		amino acids; is that right?	12:45:45
6	A	That's what it says, yep.	12:45:46
7	Q	And the first 35 amino acids of that	12:45:51
8		sequence are a signal sequence that is truncated;	12:45:59
9		is that right?	12:46:08
10	A	What was the last word you said?	12:46:08
11	Q	A signal sequence that is truncated?	12:46:09
12	A	No, not truncated, no. Truncated usually	12:46:12
13		refers to something else.	12:46:28
14	Q	The signal sequence that is removed?	12:46:30
15	A	Okay.	12:46:33
16	Q	Okay. So the first 35 amino acids in the	12:46:33
17		509 amino acid sequence of PH20 refers to a signal	12:46:39
18		sequence that is removed?	12:46:43
19	A	Right. That is removed in -- in biology,	12:46:45
20		yeah.	12:46:49
21	Q	Okay. And so in your declaration, when	12:46:49
22		you use the term mature PH20, you're referring to	12:46:52

1	PH20 without the signal sequence?	12:46:56
2	A Correct, after the signal sequence has	12:47:00
3	been removed.	12:47:03
4	Q So that's Positions 36 through 509?	12:47:04
5	A I'm looking at the numbers. Yeah.	12:47:08
6	Q Okay. And if you, as you say in subpart	12:47:13
7	(b) of paragraph 15, if you were to start the	12:47:22
8	numbering of your mature PH20 sequence at 1, then	12:47:26
9	that would end at 474; right?	12:47:30
10	A That's what it says, yeah.	12:47:51
11	Q So let's turn to paragraph 89.	12:48:12
12	MR. KUSHAN: Can whoever joined just	12:48:21
13	announce themselves?	12:48:24
14	MR. MACK: Yes. This is Josh Mack,	12:48:27
15	in-house for Halozyme.	12:48:30
16	MR. KUSHAN: Thank you.	12:48:35
17	A Paragraph 89?	12:48:36
18	Q Yes. So paragraph 89, you refer to the	12:48:39
19	'429 patent; is that right?	12:48:51
20	A Right. That's what it says.	12:48:53
21	Q And the '429 patent issued in 2010;	12:48:56
22	correct?	12:49:04

1	A That's what it says, yep.	12:49:04
2	Q And the '429 patent taught that soluble	12:49:08
3	active PH20 could be obtained by truncating the	12:49:11
4	sequence just before the start of the GPI anchor	12:49:14
5	sequence at position 483?	12:49:17
6	A That's what it says.	12:49:20
7	Q Actually, let's see. So let's mark the	12:49:41
8	patents.	12:49:59
9	Can you get the -- all right. Let's go to	12:50:02
10	paragraph 114 in your declaration. Okay.	12:50:55
11	So you reviewed the claims of the '600	12:51:19
12	patent in your analysis; is that right?	12:51:22
13	A I indeed looked at them, yes.	12:51:25
14	Q Okay. Before your analysis in this matter	12:51:27
15	had you ever read a patent claim?	12:51:33
16	A As you mentioned earlier, some people in	12:51:41
17	my lab, we filed -- we -- Princeton's intellectual	12:51:44
18	property office filed something for us a couple of	12:51:51
19	years ago, so I would have looked at that.	12:51:53
20	When I was involved in that case 30 years	12:51:55
21	ago with Amgen, I would have looked at it then.	12:51:58
22	It's conceivable I've seen claims other times but	12:52:08

1 never really studied them. 12:52:11

2 Q Do you understand what the purpose of a 12:52:12

3 patent claim is? 12:52:14

4 A I'm not an attorney. I don't understand 12:52:16

5 them the way everybody else in this room does, but 12:52:18

6 I have some understanding. 12:52:20

7 Q And what's your understanding? 12:52:22

8 A That a patent is typically a large book of 12:52:26

9 paper that's describing stuff that's -- and the 12:52:31

10 claims come at the end where the person applying 12:52:37

11 for the patent is explicitly stating what they are 12:52:41

12 trying -- what they're attempting to claim as 12:52:45

13 their own. 12:52:48

14 Q So the patent claim is the part of the 12:52:58

15 patent where the inventor is trying, or attempting 12:53:01

16 to claim their invention as their own. 12:53:05

17 Is that what you said? 12:53:11

18 A Yes. 12:53:13

19 Q Okay. Do you understand that a patent 12:53:14

20 claim conveys a property right? 12:53:19

21 A Conveys a property right. Is that what 12:53:25

22 you said? 12:53:29

1	Q Yes.	12:53:30
2	A I'm not an attorney. I don't want to -- I	12:53:30
3	don't feel comfortable defining those terms.	12:53:34
4	Q Okay. Did you, as part of your analysis	12:53:36
5	in this case, evaluate the scope of the claims in	12:53:41
6	the '600 patent?	12:53:45
7	A I looked at those, and I evaluated them at	12:53:50
8	the level that a nonattorney would do.	12:53:54
9	Q What does that mean?	12:53:58
10	A Just that, that I'm not -- I'm not an	12:53:59
11	attorney with years of law school and legal	12:54:02
12	experience on claim construction or claim	12:54:04
13	interpretation.	12:54:07
14	But I -- I evaluated these claims based on	12:54:09
15	some guidance I had about what's -- what the law	12:54:14
16	is about patents and patent claims.	12:54:17
17	Q So you were provided law, explanation of	12:54:19
18	the law in terms of how to interpret patent	12:54:22
19	claims?	12:54:25
20	A I was provided some level of -- I mean,	12:54:26
21	that's here in the -- in the document on -- okay,	12:54:32
22	starting on page 9, there are a few key pages	12:54:43

1 about legal principles that summarize some of the 12:54:46
2 guidance that I had been given. 12:54:54

3 Q And none of those paragraphs have anything 12:54:57
4 to do with claim construction; is that right? 12:54:59

5 MR. KUSHAN: Objection. Foundation. 12:55:01

6 A As I said, what starts on paragraph 9 is a 12:55:04
7 list of some of the guidance I have been given. I 12:55:08
8 didn't say it was all the guidance I had been 12:55:11
9 given. 12:55:14

10 Q Okay. So going back to paragraph 114 on 12:55:14
11 page 62. So did you reach an opinion, construing 12:55:19
12 the claim, the terms in Claim 1 of the '600 12:55:27
13 patent? 12:55:32

14 A I reached an opinion about how best to 12:55:35
15 interpret what's written in these claims. 12:55:40

16 Q And how did you go about deciding how best 12:55:43
17 to interpret what's written in the claims? 12:55:47

18 A I read them many, many times and then some 12:55:55
19 more and thought about what would a person of 12:55:59
20 skill in the art, what would a scientist, what 12:56:05
21 would a protein engineer -- how would such a 12:56:09
22 person interpret what this text is trying to 12:56:14

1 claim. 12:56:20

2 Q And were you provided any guidance in 12:56:20
3 terms of the legal framework for how to 12:56:24
4 determine -- for how to determine the patent 12:56:27
5 claim? 12:56:34

6 MR. KUSHAN: Objection. Form. 12:56:35

7 A I was -- as I said over and over again, 12:56:39
8 I'm not an attorney. And so my, you know, 12:56:42
9 experience with -- I'm not going to write claims. 12:56:45
10 I'm not going to do that. 12:56:49

11 I'm not an attorney. However, I was 12:56:51
12 provided some guidance about, for example, you 12:56:53
13 know, what is a dependent claim? How are claims 12:56:58
14 organized? 12:57:05

15 I was told to look at these texts and try 12:57:05
16 to view them as what would a person of skill in 12:57:08
17 the art with reasonable common sense -- how would 12:57:10
18 such a person look at this. Yeah. 12:57:14

19 Q So why didn't you put that legal framework 12:57:19
20 in your declaration? 12:57:22

21 A I think what I -- what I said before is 12:57:26
22 that the -- the list at the beginning, wherever we 12:57:28

1 were a moment ago, of -- where did we go -- legal 12:57:36
2 principles on page 9 lists some of the legal 12:57:39
3 principles that I was taught early on in the 12:57:43
4 discussions by counsel. 12:57:49

5 But I'll also say that -- to everybody in 12:57:52
6 the room, this is a legal case. And so legal 12:57:57
7 issues are all over it. And since I have no 12:57:59
8 experience with legal issues, part of the ongoing 12:58:03
9 conversation is, you know, how does -- what are 12:58:07
10 the legal issues that guide the interpretation of 12:58:10
11 claims or guide the -- how claims -- what claims 12:58:16
12 mean in the legal system. 12:58:20

13 Q And you didn't provide any of the -- your 12:58:21
14 explanation for your understanding of any of the 12:58:27
15 legal issues that guide interpretation of claims 12:58:30
16 in the legal system in your declaration? 12:58:33

17 MR. KUSHAN: Objection. Foundation. 12:58:36

18 A I didn't write sections about the legal 12:58:45
19 issues associated with reading claims. 12:58:51

20 I mostly used common sense with some 12:58:56
21 advice about -- you know, the example I keep 12:59:03
22 getting back to is what is a dependent claim? 12:59:06

1 That's a -- it's a legal concept that I would not
2 have known about before this.

3 So in reading about the science and the
4 proteins, there's person of skill in the art using
5 their -- their skill in the art, thinking about
6 the text there.

7 But in terms of legal issues such as what
8 depends upon what, I needed guidance to understand
9 that.

10 Q And were there any steps that you followed
11 in your claim construction analysis besides
12 reading the claims?

13 A Without reading the claims?

14 Q Besides reading the claims.

15 A Oh, sorry, besides reading the claims.

16 I read the claims from the perspective of
17 somebody who spent half a century in a field of
18 protein sequence, protein engineering, protein
19 mutations.

20 And so, you know, as a person skilled in
21 the art, I read the text that's copied on page 62
22 from the perspective of somebody who spent a

1	lifetime thinking about amino acid sequences and	13:00:16
2	modification of amino acid sequences and the	13:00:24
3	impact of such modifications. Yeah.	13:00:25
4	Q So as part of your analysis, did you	13:00:35
5	evaluate the scope of the claims, meaning what	13:00:46
6	they cover?	13:00:51
7	A Yes.	13:00:56
8	Q So did you evaluate what modified PH20	13:00:58
9	polypeptides fall within the scope of the claims?	13:01:08
10	A Gave considerable thought to the idea that	13:01:21
11	there is -- that Claim 1 is talking about a vast	13:01:30
12	possible collection; gave considerable thought to	13:01:35
13	that and gave considerable thought to -- yeah, to	13:01:39
14	what's covered there, to what the claims appear to	13:01:48
15	be claiming to somebody reading this.	13:01:58
16	Q All right. So probably been going for	13:02:03
17	another hour.	13:02:06
18	Do you want to break for lunch?	13:02:07
19	MR. KUSHAN: Sure.	13:02:09
20	THE VIDEOGRAPHER: We are going off the	13:02:10
21	record. The time is 1:02 p.m.	13:02:12
22	(A recess was taken.)	14:03:27

1	THE VIDEOGRAPHER: We are back on the	14:03:27
2	record. The time is 2:03 p.m.	14:03:36
3	BY MS. MARTIN:	14:03:39
4	Q Welcome back, Dr. Hecht.	14:03:43
5	A Hi.	14:03:45
6	Q Could you please turn in your declaration	14:03:46
7	to paragraph 114.	14:03:48
8	A Okay.	14:03:59
9	Q And paragraph 114 has Claim 1 of the '600	14:04:01
10	patent; right?	14:04:07
11	A Right.	14:04:08
12	Q And Claim 1 is directed to a modified PH20	14:04:17
13	polypeptide that meets two requirements; is that	14:04:22
14	right?	14:04:25
15	MR. KUSHAN: Objection. Foundation.	14:04:25
16	A There's an A, B, and a C there. So I'm	14:04:37
17	not sure how you want to divide it up, into two or	14:04:41
18	three, but it meets some requirements.	14:04:48
19	Q Okay. So Claim 1 requires that the	14:04:49
20	sequence is at least 95 percent identical to one	14:04:52
21	of the recited sequences; is that right?	14:04:57
22	A That's what it says, yeah.	14:04:59

1 Q And then, second, the aspartic acid at 14:05:02
2 position 320 must be replaced with one of four 14:05:08
3 amino acids, either histidine, lysine, arginine, 14:05:10
4 or serine; is that right? 14:05:15

5 A That's what it says, yeah. 14:05:16

6 Q So Claim 1 requires 95 percent identity 14:05:18
7 and a change at position 320 to histidine, lysine, 14:05:21
8 arginine, or serine; is that right? 14:05:26

9 MR. KUSHAN: Objection. Foundation. 14:05:30

10 A Right. Section (a) says at least 95 14:05:36
11 percent residues the sequence are identical to 14:05:39
12 various ID numbers. 14:05:45

13 And (b) says the sequence has an amino 14:05:48
14 acid modification corresponding to position 320 14:05:57
15 with particular reference sequence, and that 14:06:03
16 modification is a replacement of the original 14:06:09
17 amino acid by H, K, R, or S. 14:06:11

18 Q So the number of additional changes in 14:06:16
19 PH20 that each claim permits besides the 14:06:32
20 replacement at position 320, that's defined via 14:06:35
21 percentage sequence identity calculation; is that 14:06:40
22 right? 14:06:44

1 A Yeah. The text says at least 95 percent, 14:06:44
2 and so that's a -- that's a calculation relative 14:06:47
3 to the ID, the sequence ID. 14:06:50

4 Q And that calculation involves counting the 14:06:53
5 total number of changes in the modified PH20 14:06:56
6 relative to the unmodified sequence and then 14:07:00
7 dividing that number by the total number of amino 14:07:02
8 acids in the unmodified PH20 sequence? 14:07:05

9 A Well, that would be the opposite. You 14:07:10
10 said "counting the changes." And, really, if you 14:07:15
11 want 95 percent, you're counting the ones that are 14:07:17
12 not changed. 5 percent would be the ones that are 14:07:20
13 changed. 14:07:23

14 Q Okay. Do you agree that Claim 1 in the 14:07:24
15 '600 patent, as written, covers any PH20 14:07:46
16 polypeptide that is 95 percent identical to SEQ 14:07:50
17 ID number 3 and in which the aspartic acid at 14:07:55
18 position 320 is a histidine, lysine, arginine, or 14:07:58
19 a serine? 14:08:07

20 MR. KUSHAN: Objection. Foundation. 14:08:08

21 A Yeah. 14:08:14

22 As I read this text or as I've read this 14:08:15

1 text many times and tried to interpret it from the 14:08:19
2 perspective of somebody who's, you know, expert in 14:08:22
3 the field, skilled in the art, and based on what 14:08:27
4 was taught in the '429 patent, I would interpret 14:08:34
5 it as that the people who put together this patent 14:08:45
6 would be seeking modified PH20 polypeptides that 14:08:51
7 have some utility and, therefore, that are active. 14:08:58

8 Wherein the position 320 change is as we 14:09:05
9 discussed, and there are up to, in this case let's 14:09:10
10 say 5 percent of the sequences of the residues 14:09:15
11 would be changed beyond that, and that those would 14:09:21
12 be leading to some proteins that have activity 14:09:24
13 that are useful. 14:09:31

14 Q So when you interpreted the scope of Claim 14:09:36
15 1 in the '600 patent, first you considered what 14:09:40
16 was taught in the '429 patent because that -- you 14:09:43
17 had said that; right? 14:09:47

18 A Well, I was aware of '429 patent. 14:09:50

19 But I think perhaps more importantly, I 14:09:56
20 was thinking of the '600 patent that this claim is 14:10:01
21 attached to. 14:10:05

22 Q Okay. Okay. So when you said "'429 14:10:06

1	patent," you meant the '600 patent?	14:10:10
2	A Yeah.	14:10:12
3	Q Okay. Just making sure.	14:10:12
4	A Yeah. So these numbers are, you know, not	14:10:14
5	numbers that are -- I'm using every day, but,	14:10:17
6	yeah, the '600 patent.	14:10:20
7	Q Okay.	
8	A The one that the claim is attached to.	14:10:22
9	Q Okay. So when you set about to analyze	14:10:24
10	the meaning of Claim 1 of the '600 patent and to	14:10:28
11	construe that claim, you -- you thought about the	14:10:32
12	people who put together the patent and whether	14:10:42
13	they would be -- and the fact that, in your view,	14:10:45
14	they were seeking to claim modified PH20	14:10:48
15	polypeptides that would have some utility; is that	14:10:51
16	right?	14:10:54
17	A And also -- and perhaps more	14:10:54
18	importantly -- reading it from the perspective of	14:10:56
19	somebody who would be skilled in the art and --	14:10:59
20	you know, because the text is attempting to claim	14:11:01
21	something. And there's an audience, and I'm	14:11:05
22	thinking the audience is somebody who is skilled	14:11:07

1 in the art. 14:11:10

2 And what are they claiming to this 14:11:11

3 audience who are skilled in the art of protein 14:11:13

4 engineering and would be seeking to make something 14:11:17

5 that has utility? 14:11:19

6 Q So, in your view, the '600 Patent Claim 1 14:11:25

7 is limited to sequences that you believe have 14:11:45

8 utility? 14:11:48

9 A Is limited to sequences that I believe 14:11:54

10 have utility, which are those that are 14:11:57

11 enzymatically active. 14:12:00

12 Q And so you -- in your -- it's your 14:12:02

13 testimony that a skilled person, a person skilled 14:12:05

14 in the art, reading Claim 1 of the '600 patent 14:12:07

15 would interpret Claim 1 of the '600 patent to be 14:12:10

16 limited to those polypeptides that that skilled 14:12:13

17 person believes are useful? 14:12:15

18 A Right, that -- that those proteins have 14:12:21

19 utility, that they're useful, which in the current 14:12:28

20 situation, since we're talking about an enzyme 14:12:32

21 with hyaluronidase activity, I would interpret 14:12:35

22 that as modified polypeptides that have 14:12:40

1	hyaluronidase activity.	14:12:45
2	Q So where in Claim 1 do you see the words	14:12:45
3	"hyaluronidase activity"?	14:12:50
4	A I see it in the common disclosure to which	14:13:03
5	this is attached.	14:13:08
6	Q Well, that wasn't the question. The	14:13:09
7	question was --	14:13:10
8	A I understand.	14:13:11
9	Q -- where in the claim do you see those	14:13:11
10	words?	14:13:14
11	A Okay. I -- right. The words are not	14:13:14
12	there, but I think the implication is there by the	14:13:18
13	specification of a specific set here, H, K, R and	14:13:23
14	S at 320 which the -- which the patent, you know,	14:13:30
15	the write-up describes as active.	14:13:38
16	Q All right. So I want to be very, very	14:13:42
17	clear here. Okay. So you understand, because you	14:13:44
18	were -- strike that. Let me start again.	14:13:50
19	You are construing the scope of Claim 1 of	14:13:52
20	the '600 patent; correct?	14:13:56
21	A I am reading that text and thinking about	14:14:00
22	what would somebody who was in the field as a	14:14:03

1 protein engineer, and more specifically, working 14:14:10
2 in the biopharmaceutical area, how would such a 14:14:13
3 person interpret this. 14:14:18

4 And my sense is, they would not interpret 14:14:20
5 it as a claim to grab on to stuff that was 14:14:25
6 useless. I would interpret it as they would 14:14:30
7 interpret -- I would see it as they would 14:14:32
8 interpret it as a claim to claim things that are 14:14:35
9 useful. 14:14:37

10 And in this case, since the whole issue 14:14:39
11 here is about hyaluronidase, I would interpret 14:14:43
12 that as that they're useful as hyaluronidase 14:14:45
13 enzymes. 14:14:48

14 Q Do you understand that claim construction 14:14:50
15 is a question of law? 14:14:52

16 A Claim construction is a -- of course there 14:14:59
17 are legal issues. 14:15:02

18 Q Okay. 14:15:03

19 A But there's also the claim is attached to 14:15:04
20 the patent, the whole patent, and there's -- which 14:15:07
21 itself talks a great deal about active and 14:15:11
22 inactive variants. 14:15:14

1 Q Do you understand what the term claim 14:15:17
2 construction means? 14:15:18

3 A I'm not an attorney. I can talk about my 14:15:20
4 interpretation and my reading of the claim. But 14:15:24
5 as a nonattorney, I don't want to talk about 14:15:27
6 construction because I think that's a legal term 14:15:30
7 that I -- 14:15:31

8 Q Okay. 14:15:32

9 A -- that I'm not comfortable with. I can 14:15:32
10 interpret, but I can't construct it. 14:15:34

11 Q You understand that interpreting a patent 14:15:36
12 claim and deciding what that patent claim covers, 14:15:38
13 that that exercise is a question of law? 14:15:41

14 A I understand that interpretation is, is a 14:15:45
15 central, is an intellectual thing, that you have a 14:15:48
16 text in front of you and you interpret it. 14:15:51

17 Q So you understand that it's the job of the 14:15:53
18 Court to interpret the scope of the patent claims 14:15:55
19 based on the standards that the law provides; 14:16:00
20 right? 14:16:04

21 A In the context of what somebody skilled in 14:16:04
22 the art would read it, how somebody skilled in the 14:16:08

1 art would read it. 14:16:11

2 Q So is your understanding that a Court 14:16:12

3 interprets a patent claim not in the context of 14:16:15

4 the legal principles that govern claim 14:16:21

5 construction, but rather in the context of how a 14:16:23

6 skilled person reads the claim? 14:16:25

7 MR. KUSHAN: Objection. Foundation. 14:16:27

8 Objection to form. 14:16:29

9 A I didn't say that. I didn't say "rather." 14:16:30

10 Q So -- because the question was: The Court 14:16:33

11 interprets claims, right, based on the legal 14:16:41

12 standards; is that right? 14:16:46

13 A Based on legal standards, of course. And 14:16:49

14 also based on how somebody skilled in the art of 14:16:54

15 the field would read it. 14:16:57

16 Q Okay. And so your testimony is that 14:16:59

17 someone skilled in the art would read this claim 14:17:03

18 as limited to things, to limit it to polypeptides 14:17:06

19 that you believe are useful in the context of 14:17:11

20 hyaluronidase activity because this case is about 14:17:16

21 hyaluronidase activity? 14:17:19

22 MR. KUSHAN: Objection. Foundation. 14:17:20

1 Objection to form. 14:17:22

2 A And because I've been made aware, as it 14:17:24
3 says in the legal principles upfront, that for 14:17:28
4 something to be patentable, it has to have some 14:17:32
5 level of utility. 14:17:36

6 Q Okay. But for something to be patentable, 14:17:40
7 it has to have a level of utility. And as a 14:17:43
8 result, you interpret the claim as limited to only 14:17:46
9 those embodiments that are useful? 14:17:48

10 Well, actually, no. Strike that. 14:17:53

11 You understand that in order for something 14:17:55
12 to be patentable, it has to have utility. And as 14:17:58
13 a result, you limit the claim to only those 14:18:00
14 embodiments that you believe are useful? 14:18:03

15 MR. KUSHAN: Objection. Foundation. 14:18:06
16 Objection as to form. 14:18:08

17 A That I see as being useful from the 14:18:13
18 perspective of somebody skilled in the art, and I 14:18:16
19 would suggest that in the situation anybody 14:18:20
20 skilled in the art would assume that these claims 14:18:24
21 are going after something useful, right. That's 14:18:28
22 the legal thing. It has to have utility, right? 14:18:32

1	Legally it has to have utility.	14:18:34
2	And somebody skilled in the art would say	14:18:36
3	random polypeptides, arbitrary polypeptides that	14:18:39
4	have no activity, which have no utility. Right?	14:18:44
5	The law says it needs to be patentable, it	14:18:48
6	needs to have utility, okay, and someone skilled	14:18:51
7	in the art would say that for a collection which	14:18:55
8	is not described in detail, but a massive	14:19:02
9	collection, for members of that collection to have	14:19:05
10	utility, they would need to be active.	14:19:09
11	Q So it's your understanding of patent law	14:19:13
12	that every single embodiment that falls within the	14:19:17
13	scope of the claims must have enzymatic activity	14:19:20
14	in order for the patent claim to be valid?	14:19:23
15	MR. KUSHAN: Objection. Sorry.	14:19:33
16	A I think I talk about this somewhere.	14:19:35
17	MR. KUSHAN: Go ahead.	14:19:39
18	Q So --	14:20:41
19	A No.	14:20:43
20	Q No, I'm going to --	14:20:43
21	MR. KUSHAN: Are you withdrawing the	14:20:45
22	question?	14:20:47

1	Q Yeah, I'm going to withdraw the question.	14:20:48
2	So Dr. Hecht --	14:20:50
3	A Mm-hmm.	14:20:51
4	Q -- in your view, does -- in order for	14:20:52
5	Claim 1 to have utility, in your view, every	14:20:56
6	single polypeptide that falls within the scope of	14:21:02
7	Claim 1 has to be active?	14:21:06
8	A That was an ambiguous question. You asked	14:21:08
9	me if the claim has utility. I was talking about	14:21:10
10	the proteins having utility.	14:21:13
11	Q Do you understand -- strike that. Okay.	14:21:16
12	When you interpret Claim 1, you -- you	14:21:19
13	require that Claim 1, that only polypeptides that	14:21:23
14	have enzymatic activity satisfy Claim 1; right?	14:21:29
15	A My interpretation that polypep- -- only	14:21:38
16	polypeptides that have enzymatic activity fit into	14:21:41
17	Claim 1.	14:21:45
18	Q Okay. So a polypeptide that satisfies the	14:21:46
19	sequence identity requirements of Claim 1 and that	14:21:50
20	has the required mutation at position 320 does not	14:21:54
21	meet Claim 1 if it is not -- if it doesn't have	14:21:58
22	enzymatic activity; is that right?	14:22:01

1 A My reading of this as somebody who is 14:22:13
2 skilled in the art and is aware of protein 14:22:16
3 engineering, and aware of the engineering of 14:22:19
4 proteins for biopharmaceutical applications, based 14:22:24
5 on that reading, I would interpret this as the -- 14:22:29
6 that the sequences claimed by Claim 1 must have 14:22:33
7 utility because that's what the law is, that they 14:22:38
8 must have some level of utility. 14:22:41

9 I've been informed that's -- that's the 14:22:43
10 law. You can't patent garbage. And therefore, I 14:22:45
11 would infer that they would have activity, and I 14:22:48
12 would also, from just looking at the claim itself, 14:22:52
13 say that if the authors of the claim were trying 14:22:56
14 to grab, claim all sorts of crap, then they 14:23:02
15 wouldn't have incorporated sections B and C, which 14:23:09
16 lead one down the pathway of activity. Right? 14:23:13

17 Because the body of the patent, the common 14:23:18
18 disclosure, is -- most of the common disclosure is 14:23:20
19 about active versus inactive proteins, okay? And 14:23:27
20 the common disclosure provides -- it basically 14:23:33
21 divides the world of modified PH20s into two 14:23:39
22 classes: Those that are active, and those that 14:23:45

1	are not active.	14:23:47
2	And it spends pages and pages and pages	14:23:49
3	talking about that and delineating or, you know,	14:23:53
4	listing -- I shouldn't say delineating -- listing	14:23:57
5	those that are active and those that are not	14:24:00
6	active.	14:24:03
7	And it talks about the replacements that	14:24:03
8	we've mentioned at position 320, presents data	14:24:06
9	suggesting those are active, okay.	14:24:10
10	And given that it divides the world of	14:24:14
11	mutations in PH20 into these two classes, okay,	14:24:20
12	which it sort of describes as mutually exclusive,	14:24:25
13	okay, based on the presence or absence of	14:24:28
14	activity, it's -- and it -- it explains that those	14:24:33
15	substitutions that we mentioned at 320 are in fact	14:24:38
16	active as shown in table on one of the pages,	14:24:41
17	shown on Table 1, page 69, given that the common	14:24:45
18	disclosure describes extensive experiments that	14:24:52
19	are aimed at differentiating between active and	14:24:57
20	inactive proteins.	14:25:01
21	And then it chooses, in the claim, Claim	14:25:04
22	1, to explicitly list those that it has proved are	14:25:08

1 active. It seems kind of nuts to think that it
2 would choose those and it would list those that
3 are active if it were trying to claim stuff that
4 were not active.

5 Why would it list those if it were trying
6 to do that? It focuses the reader's attention on
7 these, these mutations at 320, which it says in
8 the table, Table 9 on page 69, are good. They're
9 active.

10 And so it's -- the logic here is that the
11 body of the patent goes into great depth about
12 splitting the possible proteins into two classes:
13 Active and inactive. And then the claim focuses
14 on those -- four examples of those that in fact
15 have enhanced activity. And that, to my eye,
16 seems to be leading the reader, who would be, you
17 know, protein engineer, seems to be leading the
18 reader to make things that are active.

19 That's superimposed on what you were
20 referring to, the legal issues, where I've been
21 informed that legal issues say that you're -- that
22 patents should be directed at something that has

14:25:14

14:25:20

14:25:23

14:25:29

14:25:30

14:25:32

14:25:38

14:25:42

14:25:47

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

14:26:25

14:26:28

14:26:30

14:26:34

1 utility. 14:26:37

2 So for all those reasons, it seems to me 14:26:37
3 that's what Claim 1 is -- is leading to. 14:26:40

4 Q All right. Now, it's not just any 14:26:46
5 activity; right? It has to be -- 14:26:52

6 A It's hyaluronidase activity. 14:26:54

7 Q Oh. 14:26:56

8 A Yeah. 14:26:56

9 Q But not just any hyaluronidase activity 14:26:57
10 either; right? 40 percent hyaluronidase activity; 14:27:00
11 is that right? 14:27:04

12 MR. KUSHAN: Objection. Foundation. 14:27:04

13 A Based on the body of the patent, that 14:27:25
14 seems to be where they're going because they are 14:27:28
15 pretty emphatic about drawing a line. 14:27:30

16 You know, as we said earlier, activity is 14:27:35
17 a continuous thing. It's not binary, yes or no. 14:27:37

18 But in the body of the patent, they draw a 14:27:41
19 line at 40 percent active, and they're basically 14:27:50
20 listing active mutants. I mean, there's some 14:27:55
21 ambiguity and some irreproducibility in the data. 14:28:01

22 But putting that aside for the moment, 14:28:05

1 they are listing in tables proteins that are 14:28:06
2 greater than 40 percent active. And they're 14:28:11
3 calling that a class of mutants. And they're 14:28:15
4 listing others as not active, calling that a 14:28:18
5 separate class, okay, so... 14:28:21

6 Q So it's your testimony that a modified 14:28:26
7 PH20 polypeptide that is, let's say, 99 percent 14:28:31
8 identical to SEQ ID NO. 3 and has the mutation at 14:28:37
9 position 320 from, let's say, D to K, that that 14:28:42
10 modified PH20 polypeptide does not necessarily 14:28:47
11 fall within the scope of Claim 1; is that right? 14:28:52

12 A Are you saying it's active or not active? 14:28:58

13 Q Well, I didn't say. 14:29:00

14 A Okay. My interpretation of it is that 14:29:02
15 because of the body of the patent -- 14:29:05

16 Q Sir, it's a yes-or-no question. 14:29:08

17 Does that polypeptide fall within the 14:29:10
18 scope of the claim; yes or no? 14:29:12

19 MR. KUSHAN: Please let him answer the 14:29:14
20 question. 14:29:16

21 A I am confused. 14:29:16

22 Where are we? 14:29:17

1	Q Okay. You have a modified PH20	14:29:18
2	polypeptide, okay? It is 99 percent identical to	14:29:22
3	SEQ ID NO. 3, and it has a mutation at position	14:29:26
4	320 from a D to a K, okay?	14:29:30
5	The question is: If that's all the	14:29:32
6	information that you have, do you know whether	14:29:35
7	that polypeptide falls within the scope of Claim	14:29:38
8	1; yes or no?	14:29:41
9	A I would say you don't know until you	14:29:44
10	assess its activity.	14:29:47
11	Q And how do you go about assessing its	14:29:48
12	activity?	14:29:52
13	A That's the point. You need to -- you need	14:29:59
14	to actually describe how to make it; you need to	14:30:03
15	make it; and you need to test it. You can't say,	14:30:08
16	Oh, I'm claiming the world that I don't know	14:30:12
17	anything about.	14:30:14
18	Q Okay. Well, the question was: Does this	14:30:17
19	polypeptide satisfy the claim? Not, can you,	14:30:19
20	Dr. Hecht, claim anything in the world that you	14:30:23
21	don't know anything about?	14:30:25
22	MR. KUSHAN: Objection. Form.	14:30:27

1	Q So --	14:30:29
2	MR. KUSHAN: Objection. Foundation.	14:30:30
3	A My point is that the claim -- not me, the	14:30:33
4	claim -- cannot claim -- you know, it says here	14:30:37
5	that it's -- give me a moment to find the piece I	14:30:44
6	was looking for.	14:30:49
7	Basically, what I'm looking for here is	14:31:34
8	that I've been informed that it's not sufficient	14:31:37
9	to draw a fence around -- all right.	14:31:40
10	It's on page 10, that merely drawing --	14:31:45
11	this is a quote: "...been informed that" -- this	14:31:48
12	is at the end of paragraph 26: "I have been	14:31:51
13	informed that a description that is 'merely	14:31:53
14	drawing a fence around the outer limits of a	14:31:56
15	purported genus is not an adequate substitute for	14:31:59
16	describing a variety of materials constituting the	14:32:03
17	genus and showing that one has invented a genus	14:32:06
18	and not just a species.'"	14:32:09
19	So just drawing a fence around a	14:32:10
20	statistical possibility with no information about	14:32:17
21	what's in that fence with respect to utility or	14:32:24
22	activity is not sufficient and is not a substitute	14:32:29

1 for describing the -- for what they call written 14:32:37
2 description requirement; that drawing a fence 14:32:44
3 cannot replace the written description of what's 14:32:47
4 in there, what its properties are, whether it's 14:32:50
5 active, and that I've been informed that utility 14:32:55
6 is a crucial part of making something valid to be 14:33:01
7 claimed. And just drawing a fence around all 14:33:09
8 humans in the State of Maryland -- and you 14:33:15
9 can't -- I mean, that's a ridiculous example. 14:33:18

10 But you can't just draw a fence around all 14:33:20
11 of everything without showing how to make it, what 14:33:22
12 its properties are, whether it has utility; that 14:33:27
13 that's not sufficient for patentability. 14:33:32

14 Q All right. I want to unpack that. 14:33:36

15 So, first, in the -- to be clear, the 14:33:39
16 legal principle section of your declaration, you 14:33:52
17 say nothing about utility; right? 14:33:55

18 The word "utility" does not appear in the 14:33:59
19 paragraphs 23 to 32 of your declaration? 14:34:02

20 A It definitely appears in the declaration 14:34:05
21 somewhere. I'm not sure where, but it definitely 14:34:07
22 appears in the declaration somewhere. 14:34:09

1 Q Okay. Not in the legal -- not in the 14:34:11
2 legal standard section? 14:34:13

3 A But it appears in the declaration where 14:34:14
4 we're talking about -- as I said earlier, there 14:34:16
5 are legal issues that bear on this document that 14:34:19
6 may not actually be seen in pages 9 to 12. 14:34:22

7 Q And if you look in your table of contents, 14:34:27
8 right, if we go through -- we go through the 14:34:31
9 various opinions that you've given in this case, 14:34:37
10 none of those opinions are on whether the patent 14:34:42
11 is valid on utility grounds; right? 14:34:45

12 MR. KUSHAN: Objection. Foundation. 14:34:49

13 A The concept of utility and usefulness 14:34:58
14 is -- is in here. I mean, it would take -- it 14:35:04
15 might take us a while to find without a word 14:35:06
16 search, but it's in here somewhere. 14:35:08

17 Q Okay. So you understand -- strike that. 14:35:10

18 Okay. So you understand that Claim 1 of 14:35:14
19 the '600 patent is a genus claim, meaning that it 14:35:23
20 covers more than one embodiment; right? 14:35:28

21 A I am -- as we discussed before, Claim 1 14:35:33
22 talks about this 95 percent identity and thereby 14:35:38

1 is attempting to draw a fence around a vast, vast 14:35:42
2 number of sequences. 14:35:46

3 Q Okay. So it's your understanding of the 14:35:47
4 law -- it's your understanding of the law, 14:35:53
5 Dr. Hecht, that in order to satisfy the utility 14:36:02
6 requirement, every single one of the sequences 14:36:06
7 that falls within the scope of Claim 1 must have 14:36:09
8 enzymatic activity? 14:36:13

9 MR. KUSHAN: Objection. Foundation. 14:36:14
10 Objection as to form. 14:36:16

11 A My understanding of the law is that for 14:36:27
12 something to be claimed legitimately, it must have 14:36:30
13 some utility. 14:36:35

14 Q But you're using the word "something"; 14:36:36
15 right? That is a vague -- 14:36:39

16 A Sure -- 14:36:40

17 (Overlapping speakers/crosstalk) 14:36:41

18 Q That is a vague -- 14:36:41

19 A Yeah, yeah, yeah. So -- 14:36:43

20 Q And -- 14:36:44

21 A My understanding -- well, wait. Hold on. 14:36:45

22 You asked about my -- 14:36:46

1	Q Yes.	14:36:47
2	A -- understanding of the law.	14:36:47
3	Q Mm-hmm.	14:36:49
4	A I'm not a lawyer.	14:36:50
5	My understanding of the law is that for	14:36:51
6	some thing -- it's law -- to be claimed, it must	14:36:54
7	have some use or some utility. That's what I	14:36:55
8	said.	14:36:58
9	Q Okay. And I'm just trying to understand	14:36:58
10	if something is -- something is singular or	14:37:01
11	plural, meaning if it's a genus that covers more	14:37:04
12	than one thing -- multiple things, multiple	14:37:06
13	somethings -- within the scope of the claim, if	14:37:10
14	every single embodiment has to have enzymatic	14:37:13
15	activity in order to meet the legal requirement?	14:37:17
16	MR. KUSHAN: Objection. Form.	14:37:19
17	A It is my understanding that in order for	14:37:32
18	something to be patentable, it has to be well	14:37:38
19	described. And in that description, there are, in	14:37:42
20	this case, molecular structures, properties, and	14:37:48
21	activity.	14:37:52
22	And so it's my understanding that if one	14:37:53

1 attempts to claim a vast collection, one must 14:37:56
2 claim those that -- that those are -- that are 14:38:00
3 active. 14:38:03

4 That's my -- that's my -- that's my 14:38:04
5 reading of it because I don't see how it would 14:38:05
6 make sense to claim garbage that has no utility. 14:38:09

7 Q So what if it were the case that inactive 14:38:16
8 polypeptides did have some utility to someone, 14:38:20
9 perhaps not you, but to someone? Would it be 14:38:23
10 okay, then, for the patent claim to cover those 14:38:26
11 inactive polypeptides? 14:38:28

12 MR. KUSHAN: Objection. Foundation. 14:38:33
13 Objection as to form. 14:38:36

14 A You're saying if -- if it had zero 14:38:43
15 hyaluronidase activity, right? Is that what 14:38:49
16 you're going with? 14:38:53

17 Q Well, you said it had about 40 percent 14:38:54
18 activity, so... 14:38:57

19 A Okay. Well, let's -- let's say it's 14:38:57
20 inactive. We'll go back to your question. 14:38:59

21 Q Okay. 14:39:01

22 A Let's say it had inactive hyaluronidase 14:39:02

1 activity. If it had some other utility, then that 14:39:05
2 would be -- that would be utility; that would -- 14:39:17
3 that would be okay. 14:39:21

4 Q Okay. So if it, in fact, is the case that 14:39:22
5 PH20 polypeptides that don't have hyaluronidase 14:39:28
6 activity are useful for some other purpose, then 14:39:32
7 those inactive polypeptides can fall within the 14:39:35
8 scope of Claim 1; is that right? 14:39:40

9 A Is that a hypothetical? 14:39:41

10 MR. KUSHAN: Objection -- sorry. 14:39:42

11 Q No. It's a question.

12 MR. KUSHAN: Objection as to foundation. 14:39:43

13 A I'm sorry? 14:39:47

14 Q It's a question. 14:39:47

15 MR. KUSHAN: Objection to foundation. 14:39:48

16 Objection as to form. 14:39:50

17 A Well, it was a hypothetical. You're 14:39:51
18 saying if they had some other activity, some other 14:39:53
19 utility, I do not know of any convincing case that 14:39:56
20 it -- I've worked with a lot of proteins and for a 14:40:02
21 lot of years. 14:40:07

22 If something is unfolded, degraded, not 14:40:07

1 secreted, not expressed, it's hard to imagine they 14:40:12
2 would have utility. 14:40:14

3 Q So you assume that all PH20 polypeptides 14:40:27
4 that don't have enzymatic activity are unfolded, 14:40:31
5 degraded, not secreted, and/or not expressed, and 14:40:34
6 that's why they're not useful? 14:40:37

7 MR. KUSHAN: Objection. Foundation. 14:40:39
8 Objection -- 14:40:41

9 A I didn't say that. I said I am -- that if 14:40:41
10 they were -- I know I said that I have seen in my 14:40:45
11 career lots of sequences that are unfolded, not 14:40:49
12 secreted, degraded and so forth. 14:40:54

13 And my expectation is, in a collection 14:40:56
14 which, you know, if we look at that table that 14:41:03
15 outlines what the numbers are, but the numbers are 14:41:06
16 the collection is the hypothetical collection, 10 14:41:08
17 to the 50th sequences, 10 to the 60th sequences, 14:41:13
18 and a staggering number, and my expectation is 14:41:17
19 that among that hypothetical collection, some will 14:41:21
20 be active as hyaluronidase activities. Some will 14:41:26
21 be folded but inactive. But if you're making 20 14:41:36
22 or so mutations, you're going to end up with many, 14:41:38

1 many, many, many sequences that fail to express,
2 that are degraded by the cell, that fail to
3 secrete, or even if they pass all of those bars,
4 they're going to misfold and aggregate.

5 So among the collection of sequences that
6 do not deliver high levels, or whatever level you
7 want to set of activity, they won't all be folded,
8 things that fail at catalysis, they will be lots
9 of other messy things.

10 And so for those reasons, it's hard for me
11 to fathom that a claim would include so many
12 different forms of things that are basically
13 useless garbage.

14 I mean, I've had a lot of useless garbage
15 in my life. I've seen that. You throw them away
16 pretty quickly.

17 Q Okay. So you interpret Claim 1 to require
18 hyaluronidase activity because even though the
19 literal scope, the literal language in Claim 1
20 covers PH20 polypeptides that meet the sequence
21 identity limitation and have the requisite change
22 at position 320, you require the claim to require

14:41:42

14:41:48

14:41:52

14:41:56

14:42:00

14:42:05

14:42:09

14:42:12

14:42:17

14:42:18

14:42:22

14:42:30

14:42:32

14:42:34

14:42:38

14:42:41

14:42:42

14:42:46

14:42:49

14:42:56

14:43:00

14:43:03

1 hyaluronidase activity because of -- in your view,
2 every single polypeptide that falls within the
3 scope of the claim needs to have some sort of
4 utility in order for the claim to be patentable?

5 MR. KUSHAN: Objection. Form. Objection
6 as to foundation.

7 A It's -- yeah, it's my understanding that
8 in order for the claim to be legitimate, it must
9 claim proteins that have utility because that
10 which doesn't have utility, I've been taught, is
11 not patentable.

12 Q Okay. So it's your understanding, from
13 counsel, that if the claim covers polypeptides
14 that do not have activity, the claim is invalid?

15 MR. KUSHAN: Objection. Foundation.
16 Objection as to form.

17 A As we said at the outset, my
18 interpretation of this is the claim is -- is
19 targeting those which are active because I think
20 that's how someone skilled in the art would read
21 it, because the claim goes to the effort of
22 starting with mutations at position 320 that

1 render the protein active. 14:44:53

2 And therefore, it seems baffling that one 14:44:56

3 would focus on that mutation which enhances 14:45:00

4 activity and then make additional mutations to 14:45:05

5 destroy it. That just doesn't seem reasonable. 14:45:10

6 In a sense, it's like there's a fork in 14:45:14

7 the road. You could be making mutations. You 14:45:16

8 make your first mutation at 320. You've chosen 14:45:19

9 the fork in the road to go towards enzymatically 14:45:24

10 active proteins. 14:45:28

11 Who would then go and delete ten amino 14:45:29

12 acids to destroy -- you know, delete 10 amino 14:45:33

13 acids, including the active site, to destroy 14:45:37

14 activity, and then say, Oh, that's part of the 14:45:39

15 claim. We're going to do that too. It doesn't 14:45:42

16 make any sense. 14:45:45

17 Q Do you interpret the claim to require that 14:45:50

18 the first change you make in the sequence is 320? 14:45:53

19 A The claim requires that change be there. 14:46:07

20 I don't think it's relevant if you make one first 14:46:11

21 and make the other -- intellectually, yes. 14:46:14

22 Intellectually, the claim says "make this." 14:46:20

1 But the claim does not give any written 14:46:22
2 description of how and where and which the other 14:46:24
3 one should be. It's very explicit about 320, 14:46:27
4 okay. 14:46:33

5 So intellectually, it doesn't make any 14:46:33
6 sense to me that one would follow the guidance of 14:46:36
7 the claim, make that one, and then, Oh, let's just 14:46:39
8 also make, you know, 10 to the 50th other changes, 14:46:45
9 which include, according to the text of the 14:46:49
10 patent, deletions and just all kinds of stuff 14:46:56
11 that's going to destroy it. 14:46:58

12 Q So because in your view it wouldn't make 14:47:00
13 sense for the skilled person to make changes in a 14:47:01
14 protein that are going to destroy the activity of 14:47:04
15 the protein; in your view the claim does not cover 14:47:06
16 inactive proteins? 14:47:09

17 MR. KUSHAN: Objection. Foundation. 14:47:10

18 A Well, many reasons. That because it 14:47:14
19 doesn't make sense that one would choose this 320 14:47:17
20 mutation that's more active, and then go on to add 14:47:24
21 all sorts of destructive mutations. That doesn't 14:47:29
22 make sense, especially as it's attached to the 14:47:32

1 '600 patent, which basically gives a set of 14:47:39
2 instructions on how to -- well, it's not really 14:47:45
3 instructions, but it gives a set -- it gives a 14:47:49
4 great description -- not great -- a lengthy 14:47:51
5 description -- sorry -- gives a lengthy 14:47:54
6 description that proteins fall into these two 14:47:56
7 classes, okay. 14:48:00

8 And it talks about, it focuses on the ones 14:48:02
9 that, you know, let's go after -- it focuses on 14:48:08
10 what -- those that are active. Even if something 14:48:12
11 is inactive, it retests them. It's looking for 14:48:14
12 activity, okay, and it talks about those active 14:48:17
13 mutants have a utility, have a use as enzymes. 14:48:20

14 And so, for that reason, it just seems 14:48:25
15 that once they specifically lay out that -- the 14:48:29
16 requirement, right? They're putting it in as a 14:48:35
17 requirement that it have that 320 change. 14:48:39

18 It doesn't make sense that one would 14:48:43
19 choose that fork in the road to make something 14:48:45
20 active and then destroy what you've made. 14:48:48

21 It just -- I mean I -- I've been working 14:48:52
22 protein engineering forever. It just doesn't make 14:48:57

1	sense to me that anybody would do that.	14:48:59
2	Q Okay. So let's -- does Claim 1 cover	14:49:01
3	enzymatically inactive polypeptides? Yes or no?	14:49:05
4	A Give me a second. What it says in the	14:49:12
5	claim -- I'm on page 68. "The claim would be	14:49:21
6	understood to concern active mutant PH20 modified	14:49:24
7	polypeptides."	14:49:30
8	Q All right. Well, the question was: Does	14:49:31
9	Claim 1 cover enzymatically inactive polypeptides?	14:49:32
10	Yes or no?	14:49:37
11	MR. KUSHAN: Objection. Form. Objection.	14:49:37
12	Foundation.	14:49:39
13	A I would say that that claim does not	14:49:46
14	capture inactive mutants.	14:49:50
15	Q And, but if those mutants were shown --	14:49:56
16	sorry, strike that.	14:50:01
17	If there was some utility for the inactive	14:50:02
18	mutants, then in your view Claim 1 could cover	14:50:05
19	them. You just don't think that they're useful.	14:50:08
20	So in your view, Claim 1 does not cover them?	14:50:10
21	MR. KUSHAN: Objection. Foundation.	14:50:14
22	Objection as to form.	14:50:15

1	A	Sorry. Say that again.	14:50:27
2	Q	The --	14:50:39
3	A	Yeah.	14:50:41
4	Q	Let's try this a different way. So let's	14:50:44
5		say you have a polypeptide with 99 percent	14:50:47
6		sequence identity and mutation -- 99 percent	14:50:50
7		sequence identity to SEQ ID 3, and you have a	14:50:55
8		mutation D320 to K, right? And let's say that	14:50:58
9		protein has 39 percent hyaluronidase activity.	14:51:05
10		Does it fall within the scope of Claim 1?	14:51:09
11	A	I -- I think that it -- I mean, I'm not	14:51:14
12		sure where one would -- they draw the line at 40	14:51:18
13		percent, but I think more broadly, the point is	14:51:20
14		they say, in the body of the patent, that a	14:51:24
15		modified PH20 polypeptide has modifications as	14:51:27
16		long as resulting modified polypeptide exhibits	14:51:33
17		hyaluronidase activity.	14:51:36
18		So the body of the patent says frequently	14:51:37
19		that a modified PH20 polypeptide or a variant PH20	14:51:41
20		polypeptide so long as it exhibits hyaluronidase	14:51:48
21		activity.	14:51:51
22	Q	You understand that you can't read the	14:51:51

1	disclosure of the specification into the claim.	14:51:53
2	You understand that that's the basic fundamental	14:51:55
3	canon of claim construction?	14:51:58
4	MR. KUSHAN: Objection. Foundation.	14:52:00
5	Objection as to form.	14:52:01
6	Q Yes or no?	14:52:08
7	MR. KUSHAN: Objection as to form.	14:52:11
8	A I am reading the claims with the awareness	14:52:14
9	that they're attached to the disclosure, and so	14:52:19
10	the disclosure provides information that are the	14:52:22
11	foundation for the claims, and the disclosure	14:52:26
12	repeatedly says a modified PH20 polypeptide has	14:52:29
13	such and such amino acid changes, so long as a	14:52:36
14	resulting modified PH20 polypeptide exhibits	14:52:40
15	hyaluronidase activity.	14:52:43
16	Q And it also says -- the disclosure also	14:52:43
17	says that the modified PH20 polypeptide includes	14:52:46
18	various changes, so long as it doesn't have	14:52:50
19	hyaluronidase activity; right?	14:52:53
20	A Doesn't say --	14:52:54
21	Q That's what it says.	
22	A -- doesn't say so long as it doesn't have.	14:52:57

1	Q So long as it remains inactive?	14:52:59
2	A It doesn't use those -- so long as it	14:53:01
3	remains inactive? Is that a quote?	14:53:03
4	Q Are you telling me that the patent doesn't	14:53:05
5	disclose inactive -- does not have a section --	14:53:08
6	A No, it doesn't say that it's modified so	14:53:10
7	long as it's inactive. That's not -- I can't	14:53:12
8	imagine it would say that. So long as it's	14:53:15
9	inactive?	14:53:17
10	Q You don't think the bullet says that?	14:53:18
11	A I don't think that there's a language	14:53:19
12	saying so long as it's inactive, that it's	14:53:21
13	defining and modifying polypeptides so long as	14:53:26
14	it's inactive.	14:53:28
15	Q So you don't think that -- you don't think	14:53:29
16	the '600 patent discloses, as a class of	14:53:31
17	embodiments, inactive PH20 polypeptides?	14:53:34
18	MR. KUSHAN: Objection. Foundation.	14:53:38
19	Objection as to form.	14:53:39
20	A Sorry. You were talking about the disclo-	14:53:41
21	-- you're talking about the body of the patent or	14:53:43
22	the claim? I lost you there.	14:53:46

1 Q The body of the patent. 14:53:46

2 A Okay. Go ahead. 14:53:47

3 Q You don't think that the body of the 14:53:48

4 patent discloses a class of embodiments that are 14:53:49

5 inactive PH20 polypeptides? 14:53:52

6 A The body of the patent talks about -- it 14:53:55

7 has tables of inactive polypeptides, okay. It has 14:53:58

8 tables of inactive polypeptides. 14:54:03

9 And the way that's -- the way that's 14:54:06

10 presented to somebody in the field reading it, 14:54:09

11 it's pretty clear that they're trying to show that 14:54:12

12 one can make mutations, get active ones and 14:54:16

13 inactive ones. And their goal is to go after 14:54:20

14 activity. 14:54:24

15 Q Okay. But the specification uses the term 14:54:25

16 modified PH20 polypeptide to refer to both active 14:54:28

17 and inactive PH20 polypeptides; correct? 14:54:32

18 MR. KUSHAN: Objection. Foundation. 14:54:36

19 A On page 70, there are -- 70 and 71, there 14:54:39

20 are numerous quotes where the patent says modified 14:54:45

21 polypep- -- PH polypeptide -- so referring to a 14:54:53

22 PH20 polypeptide -- refers to a PH20 polypeptide

1 have to look at the text. I'm looking at the text 14:56:12
2 that I have quoted here, which was put in the -- 14:56:15
3 in the -- in this document. 14:56:18

4 And these were put in this document to 14:56:19
5 emphasize that the common disclosure repeatedly 14:56:24
6 talks about so long as, so long as. 14:56:31

7 You know, you can make -- I mean, here's 14:56:34
8 another one: "In particular example, the amino 14:56:37
9 acid replacements can be at the corresponding 14:56:40
10 positions in a PH20 polypeptide as set forth in 14:56:42
11 any of sequence ID numbers" -- I won't read all 14:56:46
12 the numbers, many numbers -- "variants having at 14:56:49
13 least" -- and then it goes through percentages, 75 14:56:52
14 percent up to 99 percent or more -- "so long as 14:56:55
15 the resulting modified PH20 polypeptide exhibits 14:56:59
16 at least 40 percent of the hyaluronidase 14:57:02
17 activity." 14:57:04

18 So there in that case it's saying -- it's 14:57:05
19 explicitly saying that the replacements can be at 14:57:08
20 various positions in various percentages so long 14:57:12
21 as it exhibits at least 40 percent. 14:57:17

22 Q So you're reading that 40 percent, at 14:57:21

1	least 40 percent -- you're reading that from the	14:57:24
2	specification into the claims; yes or no?	14:57:25
3	MR. KUSHAN: Objection. Foundation.	14:57:28
4	Objection as to form.	14:57:29
5	A That's a legal term. I don't know what	14:57:33
6	you mean "reading into the claim."	14:57:35
7	Q Okay.	14:57:36
8	A But I am interpreting the claim where the	14:57:37
9	claim talks about modified, right, the language of	14:57:39
10	the claim, which I don't have at my fingertips	14:57:44
11	here.	14:57:47
12	But it -- the language of the claim talks	14:57:47
13	about modified PH20 polypeptides. If one wants to	14:57:49
14	know what modified PH20 polypeptides -- what does	14:57:55
15	that mean, okay, then the sensible thing to do is	14:58:00
16	to look at the body of the patent where they	14:58:05
17	explicitly say, so long as the resulting modified	14:58:07
18	PH20 polypeptide exhibits at least 40 percent.	14:58:11
19	Q But if you only want to look at the part	14:58:15
20	of the patent specification that helps you,	14:58:17
21	right -- you don't want to look at the part of the	14:58:19
22	patent specification that uses modified PH20	14:58:21

1	polypeptide to refer to inactive --	14:58:24
2	MR. KUSHAN: Objection. Foundation.	14:58:28
3	Q -- polypeptides. You already explained --	
4	sorry, strike that. We can go ahead and move on.	14:58:30
5	So I don't think you ever answered my	14:58:37
6	question, which is -- so we're going to do a	14:58:39
7	yes-or-no question deal here.	14:58:43
8	So 95 percent sequence identity to SEQ ID	14:58:45
9	NO. 3, and the change from D320 from D to K, okay,	14:58:49
10	and it has 39 percent enzymatic activity.	14:58:53
11	Does that polypeptide satisfy Claim 1 of	14:58:56
12	the '600 patent; yes, no, or I don't know?	14:59:01
13	MR. KUSHAN: Objection. Form.	14:59:02
14	A If it's fully inactive, I would say no.	14:59:08
15	39 percent is a bit close to the 40 percent. But	14:59:11
16	if it's fully inactive, I would say no.	14:59:13
17	Q Okay. But I didn't say fully inactive. I	14:59:18
18	said 39 percent.	14:59:18
19	So 39 percent; yes or no?	14:59:20
20	A Technically, no.	14:59:21
21	Q Okay. And you agree with me that nothing	14:59:23
22	in the text of Claim 1 says anything about 40	14:59:24

1	percent hyaluronidase activity; right?	14:59:27
2	MR. KUSHAN: Objection. Foundation.	14:59:30
3	Objection as to form.	14:59:31
4	A The words "hyaluronidase activity" do not	14:59:48
5	appear in that quoted text.	14:59:50
6	Q And the words "40 percent hyaluronidase	14:59:59
7	activity" also do not appear in the text of Claim	15:00:03
8	1; correct?	15:00:06
9	A Correct.	15:00:08
10	Q Okay. So, similarly, if you have a	15:00:10
11	modified PH20 polypeptide that is 99 percent	15:00:14
12	identical to SEQ ID NO. 3 and has the mutation	15:00:19
13	D320K and it has 35 percent hyaluronidase	15:00:24
14	activity -- so 99 percent sequence identity, D320K	15:00:30
15	mutation, 35 percent hyaluronidase activity does	15:00:37
16	not fall within the scope of Claim 1; correct?	15:00:41
17	A Correct.	15:00:44
18	Q Okay.	15:00:45
19	MR. KUSHAN: Objection. Foundation.	15:00:45
20	Objection. Form.	15:00:47
21	A Correct.	15:00:48
22	Q Thank you.	15:00:49

1	So when you performed your claim	15:00:52
2	construction analysis, you applied a test for	15:00:54
3	utility; right?	15:00:58
4	A Wait. Wait a second.	15:01:01
5	On the previous thing, the point is the	15:01:03
6	claim talks about a modified PH20 polypeptide,	15:01:06
7	okay, and I'm interpreting what those words mean	15:01:10
8	in light of the common disclosure, which defines	15:01:14
9	that as so long as a resulting modified exhibits	15:01:18
10	40 percent activity. That's why that's there.	15:01:24
11	I'm interpreting what the words "modified	15:01:27
12	PH20 polypeptide" -- what that means.	15:01:30
13	Q Okay. So it's your testimony that the	15:01:32
14	common disclosure defines the term modified PH20	15:01:34
15	polypeptide to mean a modified polypeptide that	15:01:38
16	exhibits at least 40 percent activity?	15:01:45
17	A Okay --	
18	Q That 40 percent activity is part of the	15:01:48
19	definition of modified PH20 polypeptide; right?	15:01:50
20	MR. KUSHAN: Objection. Foundation.	15:01:54
21	Objection as to form.	15:01:57
22	A I'm saying that based on what's quoted on	15:01:59

1 pages 70 and 71 of the declaration, which quote 15:02:02
2 how it defines "modified" -- what -- how it 15:02:06
3 defines what a modified PH20 polypeptide is, where 15:02:11
4 it says that modified PH20 polypeptide is -- blah, 15:02:15
5 blah, blah, blah -- so long as the resulting 15:02:20
6 modified PH20 polypeptide exhibits hyaluronidase 15:02:22
7 activity. 15:02:26

8 Q Well, you said 40 percent, though -- 15:02:26

9 A Yeah, but --

10 Q That 40 percent --

11 (Overlapping speakers/crosstalk)

12 (The reporter requested clarification.) 15:02:33

13 Q Sorry. Yeah, I know. One at a time. I'm 15:02:33
14 sorry.

15 I just want to be clear that when you say 15:02:33

16 the definition -- in the specification for 15:02:35

17 modified PH20 polypeptide, you're saying the 15:02:38

18 definition for modified PH20 polypeptide in the 15:02:40

19 specification requires at least 40 percent 15:02:43

20 activity? 15:02:46

21 MR. KUSHAN: Objection. Foundation. 15:02:47

22 Objection as to form. 15:02:48

1	A I think we'd be best off going to pages 70	15:02:52
2	and 71 where this is -- the quotes are spelled	15:02:55
3	out.	15:02:58
4	Q And, again, I just want to make sure that	15:03:03
5	I understand your testimony that the definition of	15:03:08
6	modified PH20 polypeptide requires at least 40	15:03:11
7	percent activity.	15:03:15
8	MR. KUSHAN: Objection. Foundation.	15:03:17
9	Objection as to form.	15:03:19
10	A On page 20 -- sorry. On page 70, there is	15:03:25
11	a quote.	15:03:33
12	It says, "As used herein, 'modified PH20	15:03:34
13	polypeptide' or 'variant PH20 polypeptide' refers	15:03:37
14	to PH20 polypeptide that contains at least one	15:03:41
15	amino acid modification" -- and so forth.	15:03:46
16	And then it says, "A modified PH20	15:03:48
17	polypeptide can have up to 150 amino acid	15:03:51
18	replacements, so long as the resulting modified	15:03:54
19	PH20 polypeptide exhibits hyaluronidase activity."	15:03:58
20	Okay. The next paragraph says, "The	15:04:01
21	modifications described herein can be in any PH20	15:04:04
22	polypeptide, including -- including precursor,	15:04:09

1	mature, or C-terminal truncated forms, so long as	15:04:13
2	the modified form exhibits hyaluronidase	15:04:17
3	activity."	15:04:20
4	So they're defining the modification there	15:04:20
5	with "so long as it exhibits activity," okay.	15:04:23
6	The next one is about truncations, which	15:04:26
7	is a particular kind of modification. And "The	15:04:29
8	C-terminal truncation can be a truncation or	15:04:32
9	deletion of 8 to 50 or more amino acids	15:04:36
10	C-terminus, so long as the resulting C-terminally	15:04:39
11	truncated polypeptide exhibits hyaluronidase	15:04:44
12	activity and secreted from cells."	15:04:47
13	And then the next two, which are now on	15:04:49
14	page 71, are similar quotes; however, in those	15:04:51
15	next two in the bold face type, it says, "so	15:04:55
16	long" -- it's more specific about the activity,	15:04:59
17	and it says, "so long as the resulting modified	15:05:01
18	PH20 polypeptide exhibits at least 40 percent of	15:05:05
19	the hyaluronidase activity."	15:05:08
20	And it says that again in another text.	15:05:10
21	We're toward the end of paragraph 129. So in all	15:05:14
22	those exam- -- excuse me.	15:05:20

1	In all those examples, the patent	15:05:21
2	disclosure is giving us guidance on how to	15:05:23
3	translate the words modified PH20 polypeptide.	15:05:28
4	Those are the words that are -- the first few	15:05:33
5	words of Claim 1, a modified PH20 polypeptide.	15:05:37
6	And so the body of the patent, as I just	15:05:42
7	read to you on pages 70 and 71, the body of the	15:05:45
8	patent translates the words modified PH20	15:05:50
9	polypeptide, and that translation is telling the	15:05:56
10	reader that these exhibit hyaluronidase activity.	15:05:59
11	In some cases it says generically they	15:06:02
12	exhibit hyaluronidase activity. In other cases it	15:06:05
13	says specifically at least 40 percent.	15:06:08
14	So that's the core -- that's one of the	15:06:11
15	cores -- there are several cores, but that's the	15:06:15
16	core of my reading of Claim 1, is that I'm	15:06:18
17	interpreting what the word modified PH20	15:06:21
18	polypeptide means in -- in light of the quotes	15:06:25
19	taken from the common disclosure, as -- as	15:06:29
20	reproduced on pages 70 and 71.	15:06:34
21	Q So would you -- do you consider the quotes	15:06:38
22	on pages 70 and 71 to be a definition of the term	15:06:41

1 modified PH20 polypeptide? 15:06:45

2 A They are presenting it that way. When you 15:06:48

3 start a paragraph with, "As used herein, modified 15:06:51

4 PH20 polypeptide," blah, blah, blah, "refers to," 15:06:55

5 I think that's their way of defining what that 15:06:59

6 term means. 15:07:02

7 When you say, you know, "a blah, blah, 15:07:03

8 blah refers to," that's basically what -- what you 15:07:08

9 do when you're defining, interpreting, translating 15:07:11

10 a word. That's what they're doing here. 15:07:15

11 Q And so in your view, every single one of 15:07:18

12 these paragraphs, only the first of which starts 15:07:20

13 with the phrase "as used herein," every single one 15:07:23

14 of these paragraphs is a definition of modified 15:07:26

15 PH20? 15:07:29

16 A Well, the first one certainly sounds that 15:07:29

17 way. The others are guiding us how to read that 15:07:31

18 words -- those words. The first one is worded as, 15:07:41

19 "As used herein," this refers to. 15:07:45

20 That is similar to, you know, the way one 15:07:49

21 defines terms, you know, as you did before, where 15:07:54

22 you used an acronym for a person skilled in the 15:07:58

1 art. You said I will use, you know, the 15:08:00

2 abbreviation. 15:08:04

3 Q POSA? 15:08:04

4 A As blah, blah, blah. You were basically 15:08:05

5 alerting me of what the usage is and what it 15:08:06

6 means. By similar logic, that paragraph on page 15:08:10

7 70 says, "As used herein, modified PH20 15:08:17

8 polypeptide, da da da da da, so long as it's 15:08:21

9 active hyaluronidase activity." 15:08:25

10 So if I read the first words of Claim 1, I 15:08:26

11 am guided by how the patent itself defines this. 15:08:30

12 Okay. 15:08:36

13 Q And so the sentence that we've established 15:08:39

14 is the definition, reads, "As used herein modified 15:08:43

15 PH20 polypeptide, or variant PH20 polypeptide, 15:08:46

16 refers to a PH20 polypeptide that contains at 15:08:50

17 least one amino acid modification such as at least 15:08:53

18 one amino acid replacement as described herein, 15:08:57

19 and its sequence of amino acids compared to a 15:09:00

20 reference unmodified PH20 polypeptide, period." 15:09:02

21 That is the definition; correct? 15:09:05

22 MR. KUSHAN: Objection. 15:09:07

1	A No, it keeps going.	15:09:08
2	MR. KUSHAN: Objection. Foundation.	15:09:10
3	Objection as to form.	15:09:11
4	Q Well, it keeps going for another 180	15:09:15
5	pages. You only include one other sentence after	15:09:18
6	that sentence. So are you saying that the	15:09:20
7	definition is these two sentences?	15:09:22
8	Does it include what comes below those two	15:09:26
9	sentences? How are you drawing the line between	15:09:28
10	what's a definition and what's not a definition?	15:09:30
11	A Because the first sentence that you just	15:09:39
12	read is, "as used herein," okay, a modified PH20	15:09:42
13	polypeptide, okay. And then it continues saying a	15:09:48
14	modified PH20 -- that it's -- it's now giving us	15:09:52
15	more detail and saying it can have up to 150 amino	15:09:59
16	acid replacements, so long as the resulting	15:10:04
17	modified PH20 polypeptide exhibits hyaluronidase	15:10:06
18	activity.	15:10:10
19	Q So you think that the claims cover any	15:10:13
20	modified PH20 polypeptide with up to 150 amino	15:10:16
21	acid replacements?	15:10:21
22	A Well, the claims, as we said, talk about	15:10:24

1 whatever those numbers were, 95 percent. 15:10:28

2 Q But in the specification that you say, 15:10:33

3 that you're relying on to interpret the claims, 15:10:38

4 it's not limited to 95 percent; right? It talks 15:10:42

5 about, for example, on page 71, 75 percent, 80 15:10:45

6 percent, 81 percent, 82 percent, and so on and so 15:10:49

7 on, in sequence identity. 15:10:54

8 So why is it the case that you're sticking 15:10:55

9 with the 95 percent sequence identity that's in 15:10:57

10 the claim? You're not changing the 95 percent 15:10:59

11 number based on what's in the spec, but you're 15:11:01

12 changing -- 15:11:02

13 A Well -- 15:11:02

14 Q -- other terms based on what's in the 15:11:02

15 spec. 15:11:05

16 MR. KUSHAN: Objection. Foundation. 15:11:05

17 A I don't think I need help to interpret 15:11:07

18 what 95 percent means. That's a math -- that's a 15:11:08

19 math issue. 15:11:11

20 Q But you need help to interpret what 15:11:13

21 modified PH20 polypeptide means? 15:11:14

22 A Yes. 15:11:17

1	Q Okay. So the skilled person would not	15:11:17
2	understand what the term modified PH20 polypeptide	15:11:18
3	means --	15:11:22
4	MR. KUSHAN: Objection.	15:11:22
5	Q -- without looking at the specification?	15:11:22
6	MR. KUSHAN: Objection. Foundation.	15:11:25
7	Objection as to form.	15:11:26
8	Q Does the skilled person, the skilled	15:11:34
9	person, in general -- withdraw the question.	15:11:37
10	Does the skilled person have a general	15:11:39
11	understanding of the phrase "PH20 polypeptide"?	15:11:40
12	A The disclosure enumerates various sequence	15:11:56
13	IDs, and that's important, right?	15:12:05
14	So it enumerates various sequence IDs of	15:12:07
15	PH20 polypeptide. Okay. I don't think the fraud	15:12:14
16	PH20 polypeptide, you know, is enumerated there.	15:12:17
17	It enumerates specific ones, okay, because it	15:12:22
18	wants to explain what it means there.	15:12:25
19	Q If you saw the phrase "modified PH20	15:12:29
20	polypeptide" outside the context of this patent,	15:12:31
21	is it your testimony that you would have no idea	15:12:33
22	what that phrase meant?	15:12:35

1 A I would say for the sake of a -- in 15:13:04
2 general, I would have a sense of where that's 15:13:07
3 going. But I would say for the sake of a patent 15:13:09
4 claim, one has to be more specific, right? 15:13:11

5 Because the patent claim talks about 95 15:13:15
6 percent. And so it's -- it's limiting what's 15:13:20
7 meant by modified, okay. 15:13:24

8 Likewise, the common disclosure is 15:13:30
9 limiting what's meant by modified PH20 when it 15:13:31
10 goes on to say "so long as it's active." 15:13:36

11 Q So you applied your understanding of the 15:13:40
12 term modified PH20 polypeptide as requiring at 15:13:43
13 least 40 percent activity, you applied that 15:13:48
14 understanding consistently in your analysis of 15:13:50
15 written description, enablement and utility; is 15:13:52
16 that right? 15:13:58

17 MR. KUSHAN: Objection. Foundation. 15:13:58

18 A I think there's too much going on at once. 15:14:04
19 I think we might be due for a break. We've been 15:14:08
20 going for over an hour now. 15:14:11

21 Q Okay. Well, a question is pending. So 15:14:12
22 can you please answer the question? 15:14:14

1 A Sorry? 15:14:15

2 Q There's a question pending. Can you
3 please answer the question?

4 A Okay. So why not re-ask it. 15:14:18

5 Q All right. 15:14:18

6 You applied your understanding of the term 15:14:18

7 modified PH20 polypeptide as requiring at least 40 15:14:21

8 percent activity consistently in your analysis of 15:14:23

9 written description, enablement and utility in 15:14:26

10 your analysis; is that right? 15:14:29

11 A I've applied the definition of requiring 15:14:31

12 hyaluronidase activity in interpreting this claim, 15:14:36

13 yeah. Is that what you're asking? 15:14:41

14 Q Consistently throughout your declaration. 15:14:44

15 MR. KUSHAN: Objection. Foundation. 15:14:49

16 A As pertains to what's being claimed in 15:14:59

17 Claim 1, yeah. 15:15:02

18 Q Okay. And it's not just hyaluronidase 15:15:02

19 activity -- 15:15:05

20 MR. KUSHAN: Sorry. He asked for a break. 15:15:06

21 Can we take a break? 15:15:07

22 Q Can I just clarify? Because he only 15:15:10

1 answered part of my question. I would just like 15:15:12
2 an answer to that question. 15:15:16

3 Not just hyaluronidase activity, but 40 15:15:17
4 percent hyaluronidase activity, consistently 15:15:19
5 throughout your declaration? 15:15:21

6 MR. KUSHAN: Objection. Foundation. 15:15:24
7 Objection as to form. 15:15:26

8 A I am saying that, based on what they say 15:15:31
9 here, which is hyaluronidase activity, in one case 15:15:34
10 or two cases, they limit that to 40 percent, as 15:15:37
11 compared to the other cases where they generically 15:15:42
12 say "activity." 15:15:46

13 Q Okay. So let's take a break. 15:15:48

14 THE VIDEOGRAPHER: We are going off the 15:15:51
15 record. The time is 3:15 p.m. 15:15:53

16 (A recess was taken.) 15:15:56

17 THE VIDEOGRAPHER: We are back on the 15:49:02
18 record. The time is 3:49 p.m. 15:49:10

19 BY MS. MARTIN: 15:49:13

20 Q All right. So we're going to mark another 15:49:16
21 exhibit. This is Exhibit 1001, which is the '600 15:49:18
22 patent. 15:49:31

1 (Exhibit 1001 was introduced for
2 identification.)

3 Q Dr. Hecht, the '600 patent is one of the 15:49:37
4 patents you analyzed in this matter; right? 15:49:40

5 A Right. 15:49:42

6 Q That's the patent that we've been talking 15:49:42
7 about? 15:49:45

8 A Right. 15:49:45

9 Q Okay. And before the break, I believe you 15:49:47
10 testified that the skilled person would look in 15:49:52
11 the specification as to how the inventors used the 15:49:55
12 term modified PH20 polypeptide when interpreting 15:49:58
13 the claims; right? 15:50:03

14 MR. KUSHAN: Objection. Foundation. 15:50:04

15 A Yeah, right. 15:50:06

16 Q And I asked you before the break if the 15:50:09
17 term modified PH20 polypeptide was used in the 15:50:16
18 specification to refer to inactive polypeptides. 15:50:21

19 A And I said that I didn't know the patent 15:50:25
20 by heart, or something like that. I'll say that 15:50:27
21 now. 15:50:29

22 Q So let's turn to Column 119, which is on 15:50:30

1	page 87.	15:50:43
2	A Sorry, column what? 1 --	15:50:46
3	Q 119, which is on page 87, 119.	15:50:49
4	A I'm sorry. Column 119.	15:50:59
5	Q Yeah. Do you see the number 2, Inactive	15:51:15
6	Mutants, in Column 119?	15:51:20
7	A Yeah.	15:51:22
8	Q And under that, it says, "Provided herein	15:51:22
9	are modified PH20 polypeptides that contain one or	15:51:25
10	more amino acid replacements in a PH20 polypeptide	15:51:29
11	that are inactive, whereby the polypeptides do not	15:51:33
12	exhibit hyaluronidase activity or exhibit low or	15:51:40
13	diminished hyaluronidase activity"; correct?	15:51:43
14	A I see that, yeah.	15:51:44
15	Q And it continues: "The modified PH20	15:51:45
16	polypeptides provided herein that are inactive	15:51:49
17	generally exhibit less than 20 percent, such as	15:51:51
18	less than 10 percent, of the hyaluronidase	15:51:54
19	activity of a wildtype or reference PH20	15:51:56
20	polypeptide, such as the peptide -- polypeptide	15:52:00
21	set forth in SEQ ID NO. 3 or 7"; correct?	15:52:07
22	A I see where you're at, yeah.	15:52:07

1 Q So, in fact, the patent specification uses 15:52:09
2 the term modified PH20 polypeptides to refer to 15:52:11
3 inactive polypeptides; right? 15:52:14

4 A I see that. It seems contradictory. It 15:52:15
5 seems the patent is using contradictory language 15:52:19
6 in that elsewhere it says, "modified so long as 15:52:22
7 active" whereas here it seems to use it in a 15:52:26
8 different way. Seems contradictory. 15:52:29

9 Q So the patent uses the term modified PH20 15:52:32
10 polypeptide to refer to both active and inactive? 15:52:36

11 A Right. The language is -- as I said, it 15:52:39
12 seems contradictory to me. 15:52:42

13 Q And when you interpreted the claim, you 15:52:45
14 selected the portions of the specification that 15:52:46
15 refer to active modified PH20 polypeptides. 15:52:49

16 And so you -- you interpreted modified 15:52:52
17 PH20 polypeptides to be limited to actives; right? 15:52:59

18 MR. KUSHAN: Objection. Foundation. 15:53:02
19 Objection also as to form. 15:53:03

20 A That was one piece of my interpretation. 15:53:04

21 There were two or three or four others 15:53:07
22 about why I interpret Claim 1 to be referring to 15:53:11

1 active -- active enzymes. 15:53:16

2 Q Did you consider the fact that the 15:53:17

3 specification uses the term modified PH20 15:53:19

4 polypeptide to refer to inactive PH20s in your 15:53:22

5 claim construction analysis? 15:53:26

6 A I considered the quotes I mentioned to you 15:53:33

7 earlier, where it says, "so long as." 15:53:35

8 I did not consider this because it seemed 15:53:38

9 contradictory. But my interpretation of the 15:53:40

10 claim, referring to active, was also based on 15:53:44

11 several other things, which I can go into. 15:53:48

12 Q Okay. So just to confirm, you did not 15:53:50

13 consider the disclosure in the specification in 15:53:53

14 which the term modified PH20 polypeptide is used 15:53:56

15 to refer to inactive mutants -- 15:53:59

16 MR. KUSHAN: Objection --

17 Q -- in the claim construction analysis? 15:54:02

18 MR. KUSHAN: Objection. Foundation. 15:54:05

19 Objection also as to form. 15:54:06

20 A Right. I did not base my interpretation 15:54:25

21 on the paragraph you read. 15:54:27

22 I based it on other factors, which have to 15:54:28

1 do with how -- about utility and about how it 15:54:33
2 just -- how the patent makes an effort to 15:54:39
3 distinguish between active and inactive and how 15:54:42
4 it -- only the active ones had utility and also 15:54:47
5 how it seems to choose to take this fork in the 15:54:51
6 road towards activity, and it makes no sense that 15:54:54
7 they would then destroy the activity that they had 15:54:56
8 succeeded in preserving or enhancing with that 320 15:55:01
9 mutation. So my interpretation was based on the 15:55:05
10 issue of how "modified" is defined and all those 15:55:09
11 other factors. 15:55:12

12 Q So you said that modified PH20 -- I'm 15:55:21
13 sorry, strike that. 15:55:27

14 You just referred to how modified PH20 15:55:27
15 polypeptide is defined, which suggests that you 15:55:29
16 understand the term modified PH20 polypeptide to 15:55:34
17 be defined as limited to actives. 15:55:36

18 But as we just saw, right, the 15:55:39
19 specification, in fact, uses the termed modified 15:55:43
20 PH20 polypeptides to refer to inactives? 15:55:46

21 A Right. As I said, I think it seems to 15:55:48
22 contradict itself because it seems elsewhere to 15:55:50

1 define it, as I read earlier. And then in the 15:55:54
2 paragraph you read, it seems to violate that 15:55:57
3 definition. 15:55:59

4 It says "as used herein" on my 15:56:00
5 declaration, page 70, which appears, to me, to be 15:56:05
6 a definition of how it is used herein and so -- 15:56:08
7 which says, "so long as the resulting polypeptides 15:56:12
8 exhibit hyaluronidase activity." That seemed a 15:56:17
9 pretty strong statement to me in terms of how it 15:56:18
10 is used herein whereas the paragraph you read 15:56:21
11 seems to contradict that. 15:56:24

12 That is somewhat baffling that they would 15:56:26
13 contradict how they say "as used herein." 15:56:28
14 Nonetheless, I think my interpretation of Claim 1 15:56:32
15 stands on several other pretty strong arguments as 15:56:36
16 well. 15:56:48

17 Q And just to confirm, you applied your 15:56:48
18 understanding of modified PH20 polypeptides 15:56:50
19 requiring at least 40 percent activity -- you 15:56:55
20 applied that interpretation consistently in your 15:56:57
21 written description, enablement, and utility 15:57:00
22 analysis; right? 15:57:03

1	MR. KUSHAN: Objection. Foundation.	15:57:04
2	Objection also to form.	15:57:06
3	A Sorry. When there's two people speaking,	15:57:11
4	I lose the question.	15:57:13
5	Repeat it, would you?	15:57:14
6	Q You applied your understanding of the term	15:57:14
7	modified PH20 polypeptide as requiring at least 40	15:57:17
8	percent hyaluronidase activity consistently in	15:57:20
9	doing the written description and enablement	15:57:23
10	analysis in your declaration; correct?	15:57:27
11	A As requiring activity, yes. I don't think	15:57:28
12	I necessarily fixated on 40 percent, but as	15:57:31
13	requiring activity.	15:57:34
14	Q So you interpret the claim as requiring 40	15:57:35
15	percent activity, but when you did your written	15:57:38
16	description and enablement analysis, you did not	15:57:41
17	require the claim -- you did not interpret the	15:57:44
18	claim to require 40 percent activity?	15:57:46
19	MR. KUSHAN: Objection. Foundation.	15:57:48
20	Objection as to form.	15:57:49
21	A I said that I interpret the claim as	15:57:52
22	requiring enzyme activity. I don't think I	15:57:56

1	fixated on whether it was 40 percent or 39 percent	15:57:59
2	or 50 percent --	15:58:03
3	Q So --	15:58:04
4	A -- but as requiring activity.	15:58:05
5	Q -- before the break, you testified that	15:58:06
6	the claim required 40 percent activity.	15:58:08
7	And now you're saying the claim does not	15:58:10
8	require 40 percent activity?	15:58:12
9	A My understanding is the claim requires	15:58:13
10	activity. 40 percent is a number that they use in	15:58:15
11	their experiments. I am not going to fixate on	15:58:18
12	that number.	15:58:22
13	Q So I just want to understand your	15:58:23
14	testimony because it's changing throughout the	15:58:25
15	day.	15:58:29
16	Can you tell me one way or the other	15:58:29
17	whether Claim 1 of the '600 patent requires 40	15:58:31
18	percent activity?	15:58:34
19	MR. KUSHAN: Objection. Foundation.	15:58:36
20	Objection as to form.	15:58:38
21	A My understanding is that it requires real	15:58:41
22	activity, not just 1 or 2 percent.	15:58:46

1 The authors of the patent have decided 15:58:49
2 that 40 percent is the cutoff. So if they're 15:58:53
3 choosing 40 percent as the cutoff, let's use that. 15:58:57

4 Q Okay. Does the claim require that any 15:59:01
5 additional substitutions beyond 320 improve the 15:59:38
6 activity above and beyond that which was seen with 15:59:42
7 the first mutation at 320? 15:59:47

8 MR. KUSHAN: Objection to form. 15:59:52

9 A My understanding of the claim is it 15:59:56
10 requires hyaluronidase activity; my understanding 16:00:00
11 is it does not explicitly require more than the 16:00:02
12 single mutant at 320. 16:00:06

13 That's already active, and I think other 16:00:08
14 mutations that were active would be included fine. 16:00:11

15 Q So if you have your 320 change and then 16:00:15
16 you add another change, another mutation, you're 16:00:20
17 not saying that the second mutation needs to 16:00:27
18 improve activity above and beyond the activity 16:00:31
19 achieved with the first -- with the 320 mutation? 16:00:33

20 A Right, yes. My understanding is based on 16:00:49
21 the idea that if you destroy activity and render 16:00:51
22 the protein inactive, that would have no utility 16:00:55

1 and, therefore, would -- would not count. 16:00:58

2 However, I think the patent is trying to 16:01:02

3 claim -- is trying to claim a diversity of 16:01:04

4 sequences that are active. It's not describing 16:01:06

5 them in detail, but that's, you know -- right. 16:01:11

6 Q So as I understood your testimony before 16:01:15

7 the break, you said that the claim element 16:01:19

8 requiring a change at 320 was intended to show 16:01:23

9 activity. 16:01:27

10 If that's the case, then what is your 16:01:29

11 interpretation for why the inventors used a 95 16:01:31

12 percent sequence identity claim language? 16:01:35

13 MR. KUSHAN: Objection. Foundation. 16:01:37

14 Objection also as to form. 16:01:39

15 A The inventors are trying to capture a 16:01:45

16 genus. They're not giving a substantial, written 16:01:47

17 description of that genus, but they're attempting 16:01:54

18 to capture that. 16:01:56

19 Q So did you consider written description of 16:01:59

20 the genus when you were construing the claim? 16:02:01

21 A When I was looking at the claim and trying 16:02:11

22 to interpret it, I -- yes, I've thought about the 16:02:13

1	concept of written description, representative	16:02:16
2	examples, enablement, and stuff like that. Yeah.	16:02:20
3	Q And did the concepts of written	16:02:23
4	description, representative examples, and	16:02:26
5	enablement inform your construction of the claim?	16:02:30
6	A Interpretation. I don't construct --	16:02:31
7	Q Interpretation --	16:02:34
8	A Okay.	
9	Q Interpretation of the claim?	16:02:34
10	A It influenced how I read the claim and how	16:02:50
11	I understood what they were attempting to go after	16:02:53
12	and whether it was legitimate or not.	16:02:56
13	Q Why is that?	16:02:58
14	A Well, let me -- let me go into that.	16:03:01
15	Because I was taught, informed, that a	16:03:22
16	written description must either provide a -- well,	16:03:26
17	I'm on page 10 -- must either describe a	16:03:30
18	representative number of species falling within	16:03:33
19	the scope of the genus. I felt -- yeah, so that.	16:03:37
20	Or structural features common to members	16:03:43
21	of the genus, such as one skilled in the art could	16:03:46
22	visualize or recognize members of the genus, okay.	16:03:49

1 And I was informed, as I'm reading here, 16:03:53
2 that adequate, written description of a genus of 16:03:57
3 polypeptides requires a precise definition, such 16:04:00
4 as by structure, formula, chemical name, physical 16:04:04
5 properties, or other properties of species falling 16:04:10
6 within a genus, sufficient to distinguish the 16:04:12
7 genus from other materials. 16:04:15

8 And, moreover, that merely drawing a fence 16:04:17
9 around the outer limits of the proposed genus is 16:04:21
10 not adequate substitute from describing a variety 16:04:24
11 of materials in the genus, and showing that one 16:04:27
12 has invented a genus and not just a species. 16:04:31

13 So that's -- yeah, that was -- that played 16:04:35
14 a role in how I read and understood Claim 1 and 16:04:40
15 whether it was legitimate or not. 16:04:46

16 Q When you said legitimate or not, what does 16:04:49
17 that mean? 16:04:51

18 A Whether it met -- whether it met the -- 16:04:52
19 the dis- -- the requirements. 16:04:55

20 Q So did you perform your written 16:05:00
21 description analysis before you interpreted the 16:05:02
22 scope of the claim? 16:05:05

1 MR. KUSHAN: Objection. Foundation. 16:05:07

2 A As I'm not an attorney, there was 16:05:14

3 considerable amount of learning and studying 16:05:17

4 involved. I didn't read the claims in isolation. 16:05:19

5 I didn't read the common disclosure in isolation. 16:05:21

6 I read all of them several times before I had the 16:05:24

7 ability to understand what's going on and analyze 16:05:28

8 it and learn the legal principles. 16:05:32

9 Q In your declaration, did you apply an 16:05:35

10 interpretation of Claim 1 that requires 40 percent 16:05:38

11 activity? 16:05:41

12 A Didn't we discuss that already? That in 16:05:52

13 my interpretation of Claim 1, my understanding was 16:05:55

14 that Claim 1 is aiming to capture proteins with 16:05:59

15 utility, which in this case means those that have 16:06:04

16 enzymatic activity. 16:06:07

17 Q Would you consider an amino acid sequence 16:06:24

18 to be a formula? 16:06:27

19 A It's not the same thing. An amino acid 16:06:35

20 sequence is an amino acid sequence. 16:06:38

21 Q So when you say, written description -- 16:06:40

22 "Adequate written description of a genus of 16:06:46

1 polypeptides requires a precise definition such as 16:06:48
2 by structure, formula, chemical name, physical 16:06:52
3 properties or other properties," which one of 16:06:55
4 those amino acid sequence falls in one of those 16:06:58
5 categories? And if so, which one? 16:07:00

6 A Well, well -- my concern is that structure 16:07:02
7 is not depicted. Physical properties and other 16:07:05
8 properties are not described for this 10 to the 16:07:09
9 60th different sequences, right? 16:07:17

10 There's no written description of a 16:07:22
11 representative sample of 10 to the 60th proteins. 16:07:28
12 There's no written description of do they fold, 16:07:32
13 how do I design them so they might fold? How does 16:07:35
14 the information in the common disclosure about the 16:07:39
15 6,000 mutants that they made, how does that enable 16:07:42
16 discovery of further -- of further proteins in 16:07:47
17 this class? There's no -- there's no information 16:07:52
18 on how to move forward. 16:07:54

19 There's no description of the properties 16:07:56
20 of those, you know, as I said earlier, some of 16:07:58
21 them are going to be folded, some will be 16:08:02
22 unfolded, some will be aggregated. 16:08:05

1	There's no description of any of that.	16:08:07
2	There's just a drawing a fence around a vast	16:08:09
3	hypothetical universe or genus without any written	16:08:11
4	description of their properties.	16:08:15
5	Q So --	16:08:16
6	A Or -- yeah.	16:08:17
7	Q So it's your understanding that in order	16:08:18
8	to claim a genus of proteins, you have to describe	16:08:20
9	the properties of all of the proteins in the	16:08:23
10	genus?	16:08:27
11	A Of a representative sampling.	16:08:28
12	Q Now, the text that you're -- strike that.	16:08:30
13	Let me start again.	16:08:35
14	The text is, "Requires a precise	16:08:36
15	definition, such as by structure, formula,	16:08:38
16	chemical name, physical properties or other	16:08:41
17	properties, of species falling within the genus	16:08:42
18	sufficient to distinguish the genus from other	16:08:45
19	materials."	16:08:48
20	Do you see that that is the sentence?	16:08:49
21	A I read what you read.	16:08:50
22	Q Okay. And do you see that the word	16:08:51

1 "representative" does not appear at all in that 16:08:53
2 sentence? 16:08:56

3 A Right. But I've been instructed that 16:08:57
4 representative sampling is an important -- is 16:09:01
5 important. 16:09:03

6 Q So you have to satisfy the representative 16:09:04
7 species test in order to satisfy the written 16:09:07
8 description requirement? 16:09:10

9 MR. KUSHAN: Objection. Foundation. Also 16:09:14
10 objection as to form. 16:09:17

11 A I would say that in order to claim a 16:09:22
12 genus, one would have to provide written 16:09:25
13 description and enablement, not necessarily for 16:09:29
14 every single one, but for a representative 16:09:33
15 sampling of the collection. And that would be 16:09:36
16 required beyond simply, you know, drawing a fence 16:09:39
17 around a hypothetical 10 to the 50th different 16:09:42
18 sequences. 16:09:46

19 Q Okay. So your understanding of the law is 16:09:47
20 that you have to have a representative -- you have 16:09:50
21 to describe the properties of a representative 16:09:52
22 number of species that are encompassed in the 16:09:55

1	claim?	16:09:58
2	MR. KUSHAN: Objection. Foundation.	16:09:59
3	A One would have to describe and list a	16:10:02
4	representative bunch of them with respect to	16:10:06
5	actual sequences, properties, activity, enablement	16:10:10
6	of how to make something that's active, whereas my	16:10:16
7	sense was that the '600 patent lists a minuscule	16:10:21
8	and highly biased sample of what would be within	16:10:30
9	that fence, in the sense that it only lists single	16:10:33
10	amino acid substitutions while at the same time	16:10:39
11	it's attempting to claim things that have 20 or	16:10:42
12	more substitutions.	16:10:47
13	It's attempting to claim, you know, 10 to	16:10:48
14	the 50th different sequences with anywhere between	16:10:52
15	1 and 20 substitutions. And yet it doesn't	16:10:55
16	present any information, either in terms of	16:10:58
17	description or enablement, about that collection.	16:11:02
18	Q Okay. I want to be very clear. Can you	16:11:06
19	tell from an amino acid sequence whether that	16:11:14
20	amino acid sequence is 95 percent identical to,	16:11:20
21	for example, SEQ ID 3 or not?	16:11:25
22	A One can do that, yes.	16:11:28

1 Q So an amino acid sequence of a polypeptide 16:11:29
2 gives you enough information to tell whether that 16:11:32
3 amino acid sequence is 95 percent identical to, 16:11:35
4 for example, SEQ ID 3; correct? 16:11:40

5 A The sequence tells you whether, what 16:11:43
6 percentage is identical, yes. 16:11:45

7 Q And the sequence would also tell you 16:11:46
8 whether there's a mutation at position 320; 16:11:49
9 correct? 16:11:52

10 A That it would. 16:11:52

11 Q So an amino acid sequence, by itself, 16:11:53
12 gives you enough information to tell whether that 16:11:56
13 amino acid sequence is 95 percent identical to SEQ 16:11:59
14 ID NO. 3 and whether that sequence has a mutation 16:12:04
15 at position 320; correct? 16:12:06

16 A Yes, but that's all it tells you. It 16:12:08
17 doesn't tell you anything about active, 16:12:12
18 precipitated, aggregated, folded. 16:12:14

19 It doesn't tell you anything. 16:12:19

20 Q And so the claim requires the protein to 16:12:20
21 be not precipitated? 16:12:24

22 A Correct. If it's precipitated, it won't 16:12:27

1	be active.	16:12:30
2	Q So modified PH20 polypeptide requires the	16:12:31
3	protein to be soluble; is that right?	16:12:37
4	A The point we discussed earlier was that it	16:12:41
5	requires the protein to have hyaluronidase	16:12:43
6	activity. And for the most part, almost totally,	16:12:46
7	if it's precipitated, that would indicate it's	16:12:52
8	unfolded, aggregated. And if it's unfolded and	16:12:56
9	aggregated, that would not be active. So that	16:12:59
10	would fall outside of the limit.	16:13:03
11	Q Okay. I just want to understand what you	16:13:05
12	mean by precipitated. So if something is	16:13:06
13	precipitated, that would mean it's not soluble?	16:13:10
14	A Let me elaborate on that.	16:13:13
15	Q Okay.	16:13:14
16	A As used herein, the word precipitated, in	16:13:15
17	my thinking about this, is that a protein, a	16:13:19
18	mutant protein, has been made. The protein is	16:13:23
19	unstable, fails to fold.	16:13:26
20	That unfolded or misfolded polypeptide, in	16:13:30
21	its unfolded or misfolded state, would aggregate	16:13:36
22	with other copies of the unfolded or misfolded	16:13:40

1	protein, and such aggregates would precipitate.	16:13:43
2	And because they're not folded, they're not	16:13:47
3	active.	16:13:52
4	So the fact that they precipitate is	16:13:52
5	indicative of an aggregated, misfolded structure.	16:13:55
6	And as we said earlier, folding is required for	16:13:58
7	activity. So that's how I would look at that.	16:14:01
8	We've had lots of those in my lab. If it	16:14:03
9	precipitates, chances are it's not folded.	16:14:06
10	Q You used the phrase "drawing a fence"	16:14:09
11	multiple times. What do you mean when you say	16:14:12
12	"drawing a fence"?	16:14:14
13	A Yeah, so that's the end of paragraph 26.	16:14:15
14	Give me a moment to try and come up with a clear	16:14:37
15	way of describing that. I mean, this is language,	16:14:40
16	you know, that was quoted from -- from the legal	16:14:46
17	literature.	16:14:48
18	But as I'll interpret it here, it means	16:14:49
19	that it's not sufficient to say, I claim everybody	16:14:57
20	in this room, because they're within the	16:15:02
21	boundaries of this room. That instead, one has to	16:15:06
22	provide a description of what it is one is	16:15:09

1 claiming. 16:15:11

2 Maybe that metaphor is not good because 16:15:12

3 we're not actually making things. But we'll use 16:15:15

4 the broken metaphor. It's not sufficient to say I 16:15:17

5 claim everything that is within the boundaries of 16:15:21

6 these walls. 16:15:25

7 But instead, one has to actually 16:15:26

8 demonstrate inventing something by enabling the 16:15:28

9 making of that and describing the properties of 16:15:34

10 that which one is making. 16:15:38

11 Q What does it mean to you to have invented 16:15:43

12 something? 16:15:47

13 A What does it mean to invent something? 16:15:47

14 MR. KUSHAN: Objection. Foundation. 16:15:50

15 Objection as to form. 16:15:54

16 A It means to invent -- to come up with 16:16:05

17 something novel that has use that wasn't, you 16:16:19

18 know, being used before. I mean, it's -- I 16:16:26

19 noticed when you handed out this patent, it said 16:16:34

20 "to promote the progress of science and useful 16:16:39

21 arts." 16:16:42

22 There's a focus on useful stuff. So the 16:16:42

1 patent is patenting -- well, all right. So 16:16:46
2 inventing something -- my understanding of 16:16:48
3 inventing something that's patentable is coming up 16:16:50
4 with something novel that is useful. And that's, 16:16:53
5 you know, what we mean by inventing something. 16:16:59

6 Q Does it matter how you come up with the 16:17:01
7 something that is novel and useful? In other 16:17:04
8 words, do you have to actually engineer an amino 16:17:08
9 acid sequence from scratch, or can you identify 16:17:13
10 your novel and useful something by, for example, 16:17:16
11 screening? 16:17:20

12 MR. KUSHAN: Objection. Foundation. 16:17:24

13 A I have no objection to screening. It 16:17:37
14 has -- but it has to be done -- yeah. I have no 16:17:39
15 objection to screening. 16:17:43

16 So you come up with something useful, and 16:17:45
17 then you characterize it and provide -- you 16:17:48
18 provide a written description of how to make this 16:17:51
19 thing and what its properties are. Yeah. 16:17:54

20 Q How many properties do you have to 16:17:59
21 identify in order to have invented something? 16:18:01

22 MR. KUSHAN: Objection. Foundation. 16:18:04

1 changed over the past many years. 16:19:45

2 But I think -- originally, I think people 16:19:47
3 were able to claim without crystal structures if 16:19:52
4 they had sufficient information about what the 16:19:56
5 molecule was, sequence and utility, solubility, 16:19:59
6 you know, stuff like that. 16:20:05

7 Nowadays I expect you would want to 16:20:06
8 present a structure. I'm sure the standards have 16:20:08
9 gone up. 16:20:11

10 Q So, in your view, does the fact that 16:20:11
11 there's no crystal structure for PH20 disclosed in 16:20:14
12 the patent, does that indicate that there was no 16:20:19
13 invention in the patent because there's no crystal 16:20:22
14 structure? 16:20:25

15 A No. I didn't say that, no. That was a 16:20:26
16 long time ago. 16:20:30

17 Q So it's -- okay. Sorry, strike that. 16:20:33

18 Does Claim 1 of the '600 patent cover 16:20:36
19 modified PH20 polypeptides that are not expressed 16:20:41
20 in cells? 16:20:42

21 MR. KUSHAN: Objection. Foundation. 16:20:45

22 A All right. Does Claim 1 what? 16:20:48

1	Q	Cover modified PH20 polypeptides that are	16:20:50
2		not expressed in cells?	16:20:54
3	MR. KUSHAN:	Objection. Foundation.	16:20:57
4	A	Such as made by solid phase synthesis?	16:21:05
5	Q	Yes.	16:21:10
6	A	In the case of this patent, I think it	16:21:11
7		wouldn't because I don't think you could make it	16:21:14
8		in that -- in that period of time, I don't think	16:21:16
9		you could have made it by -- by solid phase	16:21:17
10		synthesis. It's a big protein. You couldn't do	16:21:21
11		that.	16:21:25
12	Q	Okay. Is it fair to say that you	16:21:25
13		interpreted the claims of the '298 patent, the	16:22:16
14		'262 patent, and the '035 patent also to require	16:22:21
15		hyaluronidase activity?	16:22:25
16	A	We should look at those specifically	16:22:29
17		before we answer that question, right?	16:22:31
18	Q	Okay. So let's start with --	16:22:33
19	A	Are the claims -- we can look at them in	16:22:39
20		the context of the --	16:22:43
21	Q	So your declaration for Matter 4 is the	16:22:44
22		'298 patent.	16:22:46

1	A	Yeah, yeah, yeah, yeah. That's what I was	16:22:47
2		about to say. So we can look at them in the	16:22:49
3		context of the declaration right now, the four	16:22:52
4		other patents.	16:22:54
5	Q	Yep, correct. Okay.	16:22:55
6		Page 62 of your declaration for Matter 4.	16:23:08
7	A	Wait.	16:23:11
8		Of?	16:23:12
9	Q	For Matter 4.	16:23:12
10	A	The '298 patent?	16:23:14
11	Q	Yes. It's on page 62.	16:23:15
12	A	Okay.	16:23:25
13	Q	Okay. And on page 62 in paragraph 114 of	16:23:26
14		your declaration in Matter 4, you have reproduced	16:23:31
15		Claim 1 of the '298 patent; correct?	16:23:34
16	A	Yes.	16:23:37
17	Q	And in forming your opinions regarding	16:23:38
18		Claim 1 of the '298 patent, did you interpret the	16:23:41
19		'298 patent to require hyaluronidase activity?	16:23:45
20	A	Let me read it once again just to make	16:23:48
21		sure.	16:23:51
22		Yes.	16:24:16

1 Q All right. Did you interpret the claim to 16:24:16
2 require at least 40 percent hyaluronidase 16:24:17
3 activity? 16:24:24

4 A As I said earlier, I'm uncomfortable with 16:24:24
5 fixating on that number. 16:24:31

6 The -- the authors of the patent have 16:24:32
7 chosen that number, so I'll go along with it. But 16:24:34
8 I -- you know, I'm not comfortable with fixating 16:24:39
9 on that number. 16:24:42

10 Q So how much activity do you think is 16:24:44
11 required to satisfy the claim? 16:24:46

12 A I would say enough activity to be useful 16:25:01
13 in a biomedical application or in any application 16:25:06
14 that uses this enzyme. And since I don't use this 16:25:10
15 enzyme as a practitioner, I'm not sure how much 16:25:13
16 activity is required. They seem to think 40 16:25:16
17 percent is a cutoff, so that seems reasonable. 16:25:18

18 But I'm very hesitant to say I know 16:25:22
19 exactly what that number should be. I don't have 16:25:24
20 experience in the clinical use of this enzyme, but 16:25:26
21 enough activity to make it useful as a product. 16:25:29

22 Q Does it need to have enough activity to 16:25:36

1 make it useful as a commercial product in order to 16:25:39
2 satisfy the claim? 16:25:42

3 MR. KUSHAN: Objection. Form. 16:25:44

4 A It needs to be useful -- it needs to be 16:25:49
5 useful. It needs to be useful to somebody who 16:25:55
6 uses hyaluronidase enzymes. 16:26:00

7 I understand most of those uses are 16:26:04
8 clinical, but one could imagine others as well, 16:26:06
9 right? Activity in a clinical setting might need 16:26:12
10 to be above a certain bar, whereas if you're using 16:26:16
11 the enzymes to create hyaluronic acid in a 16:26:19
12 laboratory experiment, you could use a lower 16:26:25
13 activity, and it would still degrade the polymer 16:26:29
14 for you. But if you had no activity, it would be 16:26:30
15 useless. 16:26:32

16 Q All right. So now let's go to the 16:26:33
17 declaration for Matter 6, which is the '262 16:26:48
18 patent, and page 65 -- actually, no. 16:26:52

19 Page 66, sorry. 16:27:05

20 MR. KUSHAN: Page what? 16:27:08

21 A The '262 patent, page 66? 16:27:09

22 Q '262 patent, Matter 6 declaration, page 16:27:12

1	66.	16:27:16
2	A Okay.	16:27:16
3	Q All right. And that's Claim 1 of the '262	16:27:17
4	patent; right?	16:27:19
5	A Okay. I'll reread it just to be thorough.	16:27:20
6	Q Okay.	16:27:23
7	A Okay.	16:27:53
8	Q All right. So in your analysis regarding	16:27:55
9	the '262 patent, did you interpret Claim 1 to	16:28:00
10	require hyaluronidase activity?	16:28:05
11	A Yes.	16:28:06
12	Q Did you require Claim 1 to require enough	16:28:09
13	hyaluronidase activity such that the modified	16:28:14
14	polypeptide is useful?	16:28:19
15	A Thanks for wording it that way.	16:28:19
16	Q Okay.	
17	A Yes. We're getting -- we're getting away	16:28:21
18	from that 40 percent thing, but, yes, that it be	16:28:24
19	useful.	16:28:28
20	Q All right. And then, finally, for Matter	16:28:28
21	9, the '035 patent. That's page 65 -- or I'm	16:28:35
22	sorry, no.	16:28:49

1	Page 66, again.	16:28:49
2	A Okay. I'm going to reread it once again.	16:28:53
3	Formatting is different, so hang on a second.	16:28:56
4	Okay.	16:30:10
5	Q So in rendering your opinions regarding	16:30:11
6	the '035 patent, did you require the claims to	16:30:14
7	have hyaluronidase activity?	16:30:18
8	A Yes.	16:30:19
9	Q And, similarly, in your analysis in the	16:30:20
10	'035 patent, did you require the claims to have	16:30:24
11	sufficient hyaluronidase activity that the	16:30:27
12	modified PH20 polypeptide is useful?	16:30:31
13	A Yes. Useful, yes.	16:30:31
14	Q All right. All right. So now we're going	16:30:39
15	to mark another exhibit. This is Exhibit 1010.	16:30:48
16	MR. KUSHAN: Here.	16:31:18
17	(Exhibit 1010 was introduced for	
18	identification.)	
19	Q Dr. Hecht, do you recognize Exhibit 1010	16:31:27
20	as the Zhang paper?	16:31:31
21	A Yes. I've seen this before.	16:31:32
22	Q And this is one of the papers that you	16:31:33

1	considered in forming your opinions in this case;	16:31:37
2	right?	16:31:40
3	A Correct.	16:31:40
4	Q So a while ago this morning, we talked	16:31:41
5	about the reaction mechanism for PH20.	16:31:44
6	And if you turn to page 9434, I believe	16:31:51
7	you will find the reaction mechanism.	16:31:55
8	A Okay.	16:31:58
9	Q So, Dr. Hecht, on page 9434, is that	16:32:59
10	the -- in Scheme 1, does the reaction mechanism	16:33:03
11	displayed there, does that show the double	16:33:07
12	displacement hydrolysis mechanism of action for	16:33:09
13	the hyaluronidases?	16:33:14
14	A That's how they're describing it.	16:33:15
15	Q And in that reaction with respect to	16:33:18
16	HYAL1 -- that's the glutamic acid 131 that	16:33:23
17	functions as the proton donor; is that right?	16:33:27
18	A Okay. Yeah.	16:33:35
19	Q So glutamic acid 131 is directly involved	16:34:20
20	in the hydrolysis reaction for -- with respect to	16:34:25
21	HYAL1; is that right?	16:34:31
22	A That's what's shown in the figure, yeah.	16:34:31

1	Q And that glutamic acid 131, that	16:34:37
2	corresponds to glutamic acid 113 in PH20; is that	16:34:41
3	right?	16:34:46
4	A We'd have to look that up.	16:34:46
5	Q Look it up.	16:34:48
6	Okay. Can you turn to page 9436 in Zhang?	16:34:50
7	A Sorry. I was rereading parts of it.	16:35:04
8	9436.	16:35:08
9	Q Yes.	16:35:09
10	A Okay.	16:35:16
11	Q On 9436, do you see Figure 1?	16:35:17
12	A I do.	16:35:20
13	Q And in Figure 1, the Zhang authors have	16:35:20
14	superimposed the hyaluronic acid tetramer from the	16:35:25
15	bee venom structure onto the HYAL1 crystal	16:35:31
16	structure; is that right?	16:35:34
17	A That's my understanding of it, yeah.	16:35:34
18	Q And in Figure 1B, they depict interactions	16:35:36
19	between residues in the HYAL1 active site and the	16:35:39
20	hyaluronic acid tetramer; is that right?	16:35:49
21	A That's what I see.	16:35:52
22	Q And do you see the glutamic acid 131 in	16:35:53

1	that figure?	16:35:57
2	A I do.	16:35:59
3	Q And do you see interactions between the	16:36:00
4	glutamic acid 131 and the hyaluronic acid	16:36:02
5	tetramer?	16:36:08
6	A I see that.	16:36:09
7	Q So can we keep this handy, but if you	16:36:33
8	could turn in your Matter 3 declaration?	16:36:37
9	A That's the -- the '600 patent.	16:36:42
10	Q The '600 patent declaration. To	16:36:46
11	paragraph -- actually, to page 46.	16:37:03
12	A Okay.	16:37:12
13	Q And on page 46, you have reproduced	16:37:14
14	Table 1 from the Zhang paper; right?	16:37:18
15	A Yeah. Let me just -- I'd like to stare at	16:37:20
16	it and see it with both documents. Okay.	16:37:23
17	Q And in the text on page 46, you say,	16:37:31
18	"Zhang also showed that single substitution	16:37:50
19	mutants at each of these identified positions in	16:37:52
20	HYAL1 rendered the enzyme inactive or	16:37:54
21	significantly reduced its hyaluronidase activity";	16:37:58
22	correct?	16:38:02

1	A That's what it says.	16:38:02
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2	Q So Table 1 in the Zhang paper shows that	16:38:04
3	single substitution mutants at various positions	16:38:08
4	in HYAL1 inactivated or significantly reduced	16:38:13
5	hyaluronidase activity; is that right?	16:38:18

6	A That's what it says, yeah.	16:38:18
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7	Q So which of these mutants in Table 1 would	16:38:31
8	you say are inactive?	16:38:34

9	A The ones that have less than 1 percent	16:38:53
10	activity I would classify as inactive. The ones	16:38:56
11	that have single-digit, 2, 3, 4 percent activity,	16:39:02
12	I would classify as very low activity.	16:39:05

13	Q And when you say percent, are you talking	16:39:10
14	about the column that has percent wild-type	16:39:13
15	activity at 50 micromolar?	16:39:15

16	A Right. So let's go through that. So the	16:39:19
17	first line there is the wild-type. That's defined	16:39:21
18	as a hundred percent. Then the amino acid you	16:39:23
19	were speaking of a little while ago was glutamate	16:39:26
20	131 or glutamate 131 changed to 2 glutamine, which	16:39:30
21	is, in some situations, a subtle mutation. In	16:39:34
22	this case it decreases activity by, what, a	16:39:37

17	first line there is the wild-type. That's defined	16:39:21
18	as a hundred percent. Then the amino acid you	16:39:23

19	were speaking of a little while ago was glutamate	16:39:26
20	131 or glutamate 131 changed to 2 glutamine, which	16:39:30

21	is, in some situations, a subtle mutation. In	16:39:34
22	this case it decreases activity by, what, a	16:39:37

22	this case it decreases activity by, what, a	16:39:37
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1	thousand-fold. Okay.	16:39:44
2	And so I would say that's a -- that's	16:39:46
3	pretty dramatic. So .08, right, that's pretty	16:39:49
4	dramatic. So I would classify that as inactive.	16:39:54
5	And some of the ones below that that have 4	16:39:58
6	percent activity relative to the wild-type enzyme,	16:40:02
7	I would describe those as low activity.	16:40:04
8	Q Okay. If an enzyme has 4 percent	16:40:07
9	activity, would you consider that enzyme to be	16:40:21
10	useful?	16:40:24
11	A You say if it's 4 percent, would I	16:40:25
12	consider it useful? Was that your question?	16:40:27
13	Q Yes.	16:40:30
14	A Again, I -- I come from a -- my laboratory	16:40:33
15	and my research, throughout my -- most of my	16:40:37
16	career is working with novel proteins made from	16:40:39
17	scratch, and their activity levels are very low.	16:40:42
18	And so my understanding of this is	16:40:46
19	impacted by that experience. And so while	16:40:51
20	something that's 4 percent as active as the wild	16:40:53
21	types would probably, if you had a wild-type	16:40:58
22	enzyme, you probably would not want to pursue the	16:41:00

1 one that was only 4 percent active. But for 16:41:03
2 academic studies, you might. 16:41:07

3 But if I were, you know, getting back to 16:41:08
4 these patents, I would say that 4 percent is not 16:41:12
5 something you'd want to pursue. 16:41:15

6 Q But if it's something that you might want 16:41:19
7 to pursue for academic studies, then, it has the 16:41:21
8 potential utility. Isn't that right? 16:41:25

9 MR. KUSHAN: Objection. Foundation. 16:41:27

10 A I -- okay. Let me restate that. For 16:41:30
11 academic studies, yes. If it's something that a 16:41:35
12 company sells for use in an academic lab as a 16:41:37
13 reagent, that's a use. That's not what I was 16:41:41
14 meaning. What I was meaning is in terms of basic 16:41:44
15 research and understanding and something that's 16:41:47
16 interesting, but I would say -- so let's be clear 16:41:49
17 about that. 16:41:51

18 So something of low activity -- if you 16:41:51
19 have a polymer such as hyaluronic acid, and you 16:41:54
20 want to degrade it in a laboratory, some company 16:41:59
21 might sell you a hyaluronidase that's only 5 16:42:02
22 percent as active as the natural one. And that 16:42:05

1 would be perfectly adequate. You would purchase
2 it and use it perhaps.

3 That's a different example of -- when I
4 say it's of academic interest, then I'm saying,
5 oh, it's intellectually interesting as I try and
6 tease apart which amino acids are doing what. I
7 might want this data for intellectual interests,
8 but I'm not using it for something.

9 Q So if a company were to sell, as a
10 reagent, the hyaluronidase that's only 5 percent
11 as active --

12 A You say 5 percent, did you say?

13 Q Yes, 5 percent is active as wild-type,
14 that would still be a use; right? That would
15 still have utility?

16 A If a company were selling that as a
17 laboratory reagent. Is that what you're saying?

18 Q Yes.

19 A I would say that's a low-activity protein,
20 but it's not inactive. And that would be used.
21 That's why before I was so uncomfortable with
22 fixating on 40 percent.

1 Q When you -- I think you said that for your 16:42:59
2 de novo protein work, you would see low activity. 16:43:11
3 I'm just trying to get a sense of like what level 16:43:17
4 of activity you're talking about when you say "low 16:43:20
5 activity." 16:43:22

6 A It's kind of apples and oranges. We're 16:43:24
7 not looking at hyaluronidase enzymes or things 16:43:27
8 like that. We're looking at semi-random sequences 16:43:30
9 and asking: Can a semi-random sequence that never 16:43:33
10 existed before on planet earth possess any kind of 16:43:38
11 catalytic activity beyond background? 16:43:41

12 And then if it has an activity that's even 16:43:43
13 a thousand-fold lower than a natural enzyme, it's 16:43:46
14 kind of cool, because it never arose in nature. 16:43:49

15 So it's intellectually kind of cool. It's 16:43:52
16 useless, but it's intellectually cool. I would 16:43:55
17 not attempt to patent such a thing. 16:44:01

18 Q All right. So you agree that the Zhang 16:44:04
19 paper shows that mutating glutamate 131 to 16:44:16
20 glutamine inactivated the HYAL1 protein; right? 16:44:24

21 A It reduced its activity by a thousand-fold 16:44:27
22 so let's -- as I said many times, these things are 16:44:30

1 not binary. There's a continuum. So where we 16:44:34
2 draw the line between activity and inactive is a 16:44:37
3 decision. Okay. 16:44:40

4 So it -- it -- it ruined activity by a 16:44:41
5 factor of a thousand. That's pretty dramatic. 16:44:45

6 Q And it makes sense that mutating glutamate 16:44:48
7 131 had a dramatic impact on activity because 16:44:54
8 glutamate 131 is the proton donor in the 16:44:58
9 hydrolysis reaction; right? 16:45:01

10 A Right. So the result depicted in Table 1 16:45:02
11 is entirely consistent with the mechanism showed 16:45:05
12 in Scheme 1 and the structure shown in Figure 1. 16:45:08

13 Q So a POSA reading the Zhang paper would 16:45:11
14 reasonably expect that if they were to mutate the 16:45:15
15 glutamate 131 in HYAL1, that they would 16:45:19
16 dramatically reduce the activity of the enzyme; 16:45:24
17 right? 16:45:30

18 A I want to make sure I understood you. 16:45:30
19 You're saying that who would expect this? 16:45:33

20 Q The POSA, POSA. 16:45:36

21 A Oh sorry. So a skilled person in the 16:45:37
22 field -- 16:45:42

1	Q Skilled person.	16:45:42
2	A Yeah, sorry. Would -- repeat what you	16:45:43
3	said. Would expect that if you made that	16:45:46
4	mutation, that would diminish activity	16:45:49
5	dramatically.	16:45:52
6	Q Yes.	16:45:53
7	A Oh, yeah, yeah, yeah, yeah, yeah.	16:45:54
8	Q So isn't it also the case that if a	16:45:56
9	POSA -- or sorry. Strike that.	16:45:59
10	Isn't it also the case that a POSA would	16:46:03
11	reasonably expect that if they were to change	16:46:06
12	glutamate 131 and also change tyrosine 247 and	16:46:11
13	also change aspartate 129 in HYAL1, they would	16:46:17
14	dramatically reduce activity?	16:46:23
15	MR. KUSHAN: Objection. Foundation.	16:46:25
16	Objection as to form.	16:46:27
17	A To clarify your question, are you saying	16:46:30
18	doing them one at a time or you -- is that what	16:46:32
19	you're asking?	16:46:36
20	Q All together. Changing them all at the	16:46:36
21	same time.	16:46:38
22	A In the same molecule. One would expect if	16:46:38

1 one changed all three of those simultaneously, one 16:46:43
2 would wind up with a protein that had zero 16:46:46
3 activity or close to zero activity. Again, that's 16:46:49
4 a continuum. I don't want to commit to zero, but 16:46:53
5 maybe .0001 percent. 16:46:57

6 Q And adding on to that, the skilled person 16:47:00
7 would expect that if they made five changes in 16:47:03
8 HYAL1, they change 131, 247, 129, 202 and 245, 16:47:05
9 they would reasonably expect that they would 16:47:13
10 dramatically reduce the activity in the protein; 16:47:16
11 right? 16:47:19

12 MR. KUSHAN: Objection. Foundation. Also 16:47:19
13 objection as to form. 16:47:21

14 A Those were all you chose -- 16:47:24

15 Q Yes. 16:47:27

16 A -- from this table. 16:47:27

17 Q Yes. 16:47:28

18 A Yes. I would say that if one made 16:47:29
19 mutations at all those -- if one made all these 16:47:32
20 mutations simultaneously in the same sequence, one 16:47:35
21 would anticipate a huge reduction in activity. 16:47:40

22 Q Okay. And why is that? 16:47:47

1 A I know why. I'm looking for words to best 16:48:03
2 explain it. If you break something, it no longer 16:48:09
3 performs its function or its function is 16:48:27
4 diminished. If you break it simultaneously in 16:48:29
5 five places, then its function is more 16:48:33
6 dramatically diminished. 16:48:36

7 If you break a bone in your leg, you can 16:48:44
8 maybe hobble along. If you break five bones, you 16:48:47
9 won't. Sorry for the negative graphic, but yeah. 16:48:50

10 Q All right. So let's mark Exhibit 1013. 16:48:57

11 (Exhibit 1013 was introduced for
12 identification.)

13 Q Dr. Hecht, do you recognize Exhibit 1013? 16:49:23

14 A The Frost paper. 16:49:26

15 Q Yes. Do you recognize -- sorry, strike 16:49:27
16 that. 16:50:22

17 You relied on Exhibit 1013 in forming your 16:50:23
18 opinions in this case? 16:50:26

19 A I looked, yeah. I looked at the Frost 16:50:27
20 paper. That was part of my thinking about this 16:50:29
21 project, yeah. 16:50:31

22 Q Okay. So let's go to page 432. And so 16:50:32

1 I'm actually going to point you to the first 16:50:55
2 sentence on page 432. But that sentence starts on 16:50:58
3 page 431, so -- or actually, no. It starts on 16:51:01
4 page 430. 16:51:04

5 A Okay. 16:51:17

6 Q So the sentence on page 4 -- at the bottom 16:51:21
7 of page 430 is: "Transfection of these deletion 16:51:25
8 mutants into" -- and then continues on 432 -- 16:51:29
9 "into Chinese Hamster Ovary (CHO) cells followed 16:51:33
10 by screening for enzyme activity using 16:51:36
11 microtiter-based enzyme assay with biotinylated 16:51:38
12 hyaluronan revealed that soluble hyaluronidase 16:51:42
13 activity could be recovered in the conditioned 16:51:46
14 medium from deletion mutants terminating after 16:51:46
15 Amino Acids 477 to 483"; is that right? 16:51:50

16 A That's what it says. 16:51:53

17 Q And then it continues: "Less than 10 16:51:56
18 percent activity was recovered when constructs 16:51:58
19 terminated after amino acid 467 or when using the 16:52:01
20 full-length PH20 cDNA"; right? 16:52:07

21 A Yeah. 16:52:09

22 Q Do you have an understanding as to what 16:52:11

1	the word "soluble" means in that paragraph?	16:52:14
2	A Let me -- let me go to the paragraph	16:52:17
3	again.	16:52:21
4	Yes.	16:52:48
5	Q And what is your understanding of what the	16:52:48
6	word "soluble" means in that paragraph?	16:52:51
7	A Yeah. This is different from what I was	16:52:53
8	describing for solubility in our earlier	16:52:55
9	discussion.	16:52:59
10	So this is basically that the stuff is --	16:52:59
11	is not attached to the -- the cell boundary, the	16:53:03
12	membrane; that it's soluble. This is not an issue	16:53:06
13	of unfolded and aggregated.	16:53:11
14	So, in this case it's secreted, and it's	16:53:16
15	soluble in the medium.	16:53:19
16	Q Okay. And the Frost paper is teaching	16:53:23
17	that mutants that terminate from amino acids 477	16:53:29
18	to 483 were soluble and exhibited hyaluronidase	16:53:44
19	activity; is that right?	16:53:52
20	A Mm-hmm.	16:53:52
21	Q And the Frost paper is also teaching that	16:53:57
22	mutants that terminated between 467 and 476 had	16:54:01

1 less than 10 percent activity; is that right? 16:54:09

2 A Well, they say less than 10 percent was 16:54:14
3 recovered when constructs terminated after amino 16:54:18
4 acid 467 or when using the full length. Yeah. 16:54:20

5 Q So would the skilled person reading the 16:54:34
6 Frost paper understand that a PH20 construct that 16:54:36
7 terminated, for example, at position 477 would be 16:54:42
8 soluble and have hyaluronidase activity? 16:54:45

9 A The text says that it -- that the assay 16:54:50
10 that they did revealed that soluble activity, 16:54:54
11 hyaluronidase activity, could be recovered in the 16:54:58
12 conditioned medium from deletion into terminating 16:55:00
13 after amino acids 477 to 483. 16:55:01

14 I think that's what you're asking? 16:55:04

15 Q Yes. 16:55:06

16 A Yes. That's what it says, yes. 16:55:08

17 Q So can we turn in your declaration to 16:55:47
18 paragraph 88? 16:55:49

19 A Yes. Let me get oriented here. Okay. 16:55:54
20 I'm with you, paragraph 88. 16:56:14

21 Q All right. So we had looked at the -- at 16:56:16
22 the Zhang Table 1, which is on page 46. 16:56:22

1 And now we're looking at paragraph 88, 16:56:24
2 which is on page 47 of your declaration, just to 16:56:26
3 orient you. 16:56:29

4 A Well, we're looking at paragraph 88, which 16:56:30
5 is next to that. Yeah. 16:56:32

6 Q Yeah. Okay. 16:56:34

7 And so in paragraph 88, you say, "Zhang 16:56:35
8 (EX1010) identified positions in HYAL1 16:56:39
9 corresponding to D111" -- I think that should be 16:56:41
10 "E113, D184, S227, Y229, R246, W304, and N333 in 16:56:46
11 PH20, as well as the Hyal-EGF domain from 337 to 16:57:06
12 409 in PH20"; is that right? 16:57:11

13 A Okay. 16:57:13

14 Q So is it fair to say that the mutations -- 16:57:14
15 that you're talking about the mutations in Table 1 16:57:21
16 of Zhang, and you are correlating the amino acids 16:57:30
17 from the HYAL1 sequence in Table 1 to the 16:57:34
18 positions in PH20? 16:57:38

19 A That what you're saying -- yeah. I mean, 16:57:43
20 what you're saying is identify positions of HYAL1 16:57:45
21 corresponding to -- blah, blah, blah, blah -- in 16:57:49
22 PH20. 16:57:52

1	So I think that's what you're saying?	16:57:52
2	Q Yes.	16:57:54
3	All right. So do you know one way or the	16:58:09
4	other whether the "D113" should be an "E113"?	16:58:14
5	A That's interesting.	16:58:18
6	If we look at the figure in the Zhang	16:58:19
7	paper, there's a D and an E two positions apart.	16:58:22
8	And so that seems consistent with what you're	16:58:26
9	implying.	16:58:33
10	Q Mm-hmm, yes.	16:58:34
11	A I have to say I didn't notice that, but --	16:58:34
12	Q Okay.	16:58:36
13	A -- good eyes.	16:58:37
14	Q And, similarly, actually, if you look at	16:58:39
15	the preceding sentence, you say, "Arming	16:58:41
16	identified positions D111, E113"?	16:58:43
17	A Yeah. That looks right.	16:58:47
18	Q Okay. So is it correct, then, that E113,	16:58:49
19	the glutamate 113 in PH20, is the residue that is	16:58:55
20	the proton donor in the catalytic reaction?	16:59:00
21	A Give me a second.	16:59:08
22	You're saying E113 in PH20?	16:59:12

1	Q Yes.	16:59:18
2	A It seems that way. I mean, I -- you know,	16:59:19
3	I'd have to -- that's what it seems to imply here.	16:59:21
4	I'd have to look them all up and line them up	16:59:24
5	again, but that's the logic here.	16:59:27
6	Q All right. So we've been going for	16:59:30
7	probably more than an hour.	16:59:32
8	Do you want to take another break?	16:59:34
9	A Sure. Can we make it a shorter break --	16:59:35
10	THE VIDEOGRAPHER: We are going off the	16:59:37
11	record.	
12	A -- so we're not here until midnight.	
13	THE VIDEOGRAPHER: The time is 4:59.	16:59:39
14	(A recess was taken.)	17:17:32
15	THE VIDEOGRAPHER: We are back on the	17:17:32
16	record. The time is 5:18 p.m.	17:18:33
17	BY MS. MARTIN:	17:18:37
18	Q So, Dr. Hecht, would you agree that all	17:18:39
19	PH20s that have hyaluronidase activity -- that all	17:18:43
20	PH20s that have hyaluronidase activity cleave	17:18:50
21	hyaluronidase through a hydrolysis reaction?	17:18:56
22	MR. KUSHAN: Objection. Foundation.	17:18:58

1	Objection as to form.	17:19:01
2	A I would assume so. I have not, you know,	17:19:05
3	looked at all of them, but I would assume so.	17:19:09
4	Q So is it fair to say that all PH20s that	17:19:12
5	have a sequence that's 95 percent identical to SEQ	17:19:16
6	ID NO. 3 and that are active, that all of those	17:19:22
7	PH20s cleave hyaluronic acid through a hydrolysis	17:19:28
8	reaction?	17:19:35
9	MR. KUSHAN: Objection. Form.	17:19:35
10	A I can't add -- I mean, it's a reasonable	17:19:38
11	assumption, but until one does the experiment and	17:19:39
12	does the analysis, one doesn't know for sure.	17:19:43
13	It's sort of a classic thing in this field	17:19:46
14	is that these are all reasonable assumptions, but	17:19:48
15	you, nonetheless, want to confirm them.	17:19:50
16	Q So you think that there may be some other	17:19:54
17	mechanism of action other than a hydrolysis	17:19:56
18	reaction whereby PH20 with 95 percent sequence	17:19:59
19	identity to SEQ ID 3 cleaves hyaluronic acid?	17:20:02
20	A I'm aware of other enzyme systems where	17:20:13
21	people have mutated away an essential catalytic	17:20:16
22	residue, expecting to lose all activity, and then	17:20:21

1 found some small level of activity remaining, 17:20:25
2 thereby suggesting that binding and molecular 17:20:29
3 strain might have been sufficient to get a tiny 17:20:34
4 bit of activity, even when catalytic atoms are not 17:20:37
5 there. 17:20:40

6 So while your point is a good assumption, 17:20:41
7 I would not want to answer that in absolute terms. 17:20:44

8 Q Are you aware of any evidence with respect 17:21:00
9 to -- with respect to hyaluronidases, that if you 17:21:05
10 mutate the glutamic acid that is the proton donor 17:21:08
11 in the hydrolysis reaction, that they are still 17:21:14
12 able to cleave hyaluronic acid through some other 17:21:17
13 mechanism? 17:21:22

14 A The last two words, that -- 17:21:23

15 Q That they're still able to cleave 17:21:24
16 hyaluronic acid through some other mechanism? 17:21:30

17 A Well, you pointed out that the -- in the 17:21:33
18 Zhang paper that the mutation of glutamate 131 in 17:21:38
19 Table 1 of the Zhang paper produces an enzyme that 17:21:44
20 has very, very, very low activity, but it's not 17:21:48
21 zero. 17:21:52

22 And so that would lead the curious 17:21:53

1 individual to think, huh, maybe there's an 17:21:57
2 alternative mechanism in a situation where binding 17:22:01
3 is still present, but the catalytic atoms are no 17:22:04
4 longer present. Maybe it's still possible to 17:22:08
5 cleave by a mechanism where water substitutes for 17:22:10
6 the amino acid or whether just a mere strain of 17:22:16
7 binding would give some very, very low level of 17:22:20
8 cleavage, even in the absence of the original 17:22:23
9 catalytic mechanism. 17:22:27

10 So while I agree that your assumption is a 17:22:28
11 good one, I'd be hesitant to say that's an 17:22:31
12 absolute thing until one does a lot more study of 17:22:35
13 it. 17:22:37

14 As I said, I'm aware of other situations 17:22:38
15 in other enzymes where people mutated out the key 17:22:40
16 catalytic residue, assuming the enzyme would be a 17:22:46
17 hundred percent completely dead or, said 17:22:51
18 differently, having 0.000 level of activity, and 17:22:53
19 they saw, huh, it has some activity. 17:22:57

20 And that caused people to rethink the 17:23:00
21 simple assumption you were making; that is, you 17:23:02
22 know, if you, you know, kick out the hydrolytic 17:23:06

1 side chain, then you would lose it all. So, you 17:23:12
2 know, it's a good assumption, but I would want to 17:23:15
3 confirm it in a lab. 17:23:16

4 Q And how would you confirm it in the lab? 17:23:18

5 A Oh, goodness. Well, in this case, the 17:23:20
6 Zhang paper confirms that it's not completely 17:23:33
7 dead. 17:23:37

8 As we said, you know, the first entry in 17:23:37
9 that table, Table 1 of the Zhang paper, shows that 17:23:39
10 while, for practical purposes, this protein has no 17:23:44
11 activity, right, it's less than one one-thousandth 17:23:48
12 -- less than one one-thousandth -- it hasn't -- so 17:23:52
13 for practical perspective, it has no activity. 17:23:57

14 But, again, as I said earlier, from a 17:23:59
15 quote unquote, "academic" perspective, not for 17:24:01
16 use, but for intellect -- from an academic 17:24:03
17 perspective, the fact that it's not 0.000; that 17:24:08
18 it's 0.08 would lead one to believe that maybe 17:24:12
19 something else is going on. 17:24:15

20 What would I do to test that? Hmm, I'd 17:24:17
21 have to think about that. There's some isotope 17:24:28
22 experiments you could look at to see whether you 17:24:31

1	put a deuterium in there, whether a deuterium was	17:24:34
2	transferred. I don't know. I'd have to think	
3	about that. I don't want to -- I don't want to	17:24:39
4	say for sure what I would do to test that. But	17:24:41
5	you'd want to test it in a lab in some creative	17:24:42
6	way to figure out that even when you remove the	17:24:44
7	catalytic side chain that you still get some	17:24:48
8	amount of cleavage what's going on.	17:24:51
9	Q So you said that you didn't consider an	17:24:54
10	amino acid sequence to be a formula. Do you	17:25:25
11	consider an amino acid sequence to be a structural	17:25:27
12	feature?	17:25:29
13	MR. KUSHAN: Objection. Foundation.	17:25:31
14	A So with respect to formula, going to the	17:25:38
15	beginning of your comment, I mean you could have	17:25:40
16	the dipeptide glutamate lysine or lysine glutamate	17:25:45
17	that have the same chemical formula but they're	17:25:51
18	different things. So that's why I'm saying amino	17:25:54
19	acid sequence and formula are different.	17:25:57
20	Your next question was about structure?	17:26:00
21	So amino acid sequence is not a formula. It's	17:26:07
22	related but it's not the same thing.	17:26:10

1 Q Is amino acid sequence a structural 17:26:14
2 feature? 17:26:16

3 A Usually when chemists talk about 17:26:26
4 structure, they're thinking in three dimensions, 17:26:30
5 and so an amino acid sequence, you know, according 17:26:32
6 to the development of protein folding amino acid 17:26:35
7 sequence --

8 (The reporter requested clarification.)

9 A I'm sorry. When chemists think about 17:26:40
10 structure, they're usually thinking about a 17:26:49
11 three-dimensional structure, okay, and so an amino 17:26:51
12 acid sequence is generally considered -- you know, 17:26:54
13 when you write down the sequence on a piece of 17:26:58
14 paper, that's linear. That's one dimensional. So 17:27:01
15 the sequence in, in the way I just described is 17:27:04
16 not synonymous with a structure which is three 17:27:08
17 dimensional. It's related, you know. In protein 17:27:13
18 folding the sequence gives rise to the 17:27:15
19 three-dimensional structure but it's not 17:27:17
20 synonymous. 17:27:21

21 Q Amino acid sequence is considered the 17:27:22
22 primary structure in a protein; right? 17:27:25

1 A Yeah. I think that's a misuse of the word
2 structure, but it's often described that way. I
3 think the word structure, to my mind, connotes
4 three dimensions.

5 Q Do proteins have a chemical formula? 17:27:49

6 A Do proteins what? 17:28:07

7 Q Have a chemical formula? 17:28:08

8 A You can write a chemical formula. Sure. 17:28:10

9 It's not very interesting but you could add up all 17:28:13

10 the atoms and count how many carbons are there, 17:28:16

11 how many oxygens are there and so on. So you 17:28:19

12 could do that. 17:28:21

13 It's -- as I said, it's not very 17:28:22

14 interesting because, as I said, you could have 17:28:25

15 many different sequences with the same chemical 17:28:29

16 formula, same number of carbons and hydrogens and 17:28:31

17 nitrogens and oxygens and so on, but they're 17:28:35

18 completely different entities even though they 17:28:38

19 have the same formula. 17:28:39

20 People who do mass spectrometry are, you 17:28:45

21 know, might be concerned with the formula because 17:28:47

22 they're counting atoms, but it's not very 17:28:49

1	informative.	17:28:53
2	Q What do you -- what do you consider to be	17:29:03
3	undue experimentation?	17:29:05
4	MR. KUSHAN: Objection. Foundation.	17:29:08
5	A Once again, it's not binary. It's not --	17:29:15
6	it's not a fine line. This is reasonable	17:29:19
7	experimentation. This is undue experimentation.	17:29:22
8	But if we look at the extremes, something that my	17:29:24
9	grad students could do in the course of their	17:29:27
10	Ph.D. is reasonable. Something that would take a	17:29:30
11	thousand people a thousand years is not. It's	17:29:33
12	undue experimentation, and if you want to draw the	17:29:37
13	line of ten people ten years? I don't know.	17:29:40
14	There's a gradient. It's not a binary thing.	17:29:43
15	Q And what would you consider to be a	17:29:45
16	research plan?	17:29:47
17	A A research plan is something that in the	17:29:49
18	old days before funding collapsed a research plan	17:29:57
19	would be something you would write up as a plan to	17:30:02
20	the NSF or the NIH or the DoE or some private	17:30:06
21	foundation as a plan for research where you're	17:30:10
22	proposing to do certain things where you don't for	17:30:15

1 sure know what the answer will be where you have 17:30:19
2 hypotheses that you'd like to test but you don't 17:30:25
3 know the answer. Quite the contrary. You're 17:30:27
4 asking for funding to support a research plan that 17:30:29
5 would enable you to uncover the answer. 17:30:32

6 Q Okay. If a skilled person decides to make 17:30:35
7 a modified PH20 polypeptide and they select which 17:30:48
8 mutations to make, would you consider that to be 17:30:52
9 rationale design? 17:30:55

10 A Could you talk a little louder? I don't 17:30:55
11 hear that well. 17:30:57

12 Q Sorry. If a skilled person specifically 17:30:58
13 selects which mutations to make in a modified PH20 17:31:01
14 polypeptide, would you consider that to be 17:31:05
15 rational design? 17:31:07

16 MR. KUSHAN: Objection. Foundation. 17:31:10

17 A I have to say once again it's not binary. 17:31:11
18 Yes, we can describe what rational design is and, 17:31:15
19 yes, we can describe what directed evolution is, 17:31:17
20 but there are lots of projects where there's some 17:31:20
21 rational design and some directed evolution. 17:31:24

22 You know, in some extreme case you're 17:31:30

1	making random sequences and searching. It's a	17:31:32
2	fishing expedition. In other cases you have a	17:31:35
3	rational design atom by atom of one thing. That's	17:31:38
4	an extreme as well, but much of science in this	17:31:42
5	field is done by merging those two. So...	17:31:44
6	Q So you say that in paragraph 47 of your	17:31:51
7	declaration.	17:31:55
8	A Paragraph 47. I'm with you.	17:32:10
9	Q "At a conceptual level there are two	17:32:13
10	approaches for creating engineered proteins	17:32:15
11	referred to as rational design and directed	17:32:17
12	evolution"; right?	17:32:19
13	A Right, right.	17:32:20
14	Q And are those the only two approaches for	17:32:21
15	creating engineered proteins?	17:32:23
16	A All right. So we're going to not be	17:32:31
17	talking about the present where it's all done by	17:32:34
18	machines, right, by AI, because nowadays it's AI	17:32:36
19	is doing everything. So we're not talking about	17:32:45
20	that.	17:32:47
21	Q Correct.	17:32:48
22	A We're back in --	17:32:48

1 Q We're back in 2010, 2011. 17:32:49

2 A Okay. So we're back in 2010, 2011. I 17:32:51

3 would say this is a description of -- you know, I 17:33:00

4 keep coming back to this binary versus a 17:33:02

5 gradation, but this is a description of two 17:33:06

6 extremes of rational design and directed 17:33:09

7 evolution. Those are really useful ways of 17:33:13

8 looking at things, but, in fact, there are many 17:33:15

9 approaches that combine these. 17:33:17

10 My own lab, for example, we are -- we do 17:33:19

11 rational things, but we're also making large 17:33:22

12 collections and selecting. So we do both, and the 17:33:26

13 product -- not that we do either/or but we do 17:33:28

14 things that incorporate features, both of rational 17:33:31

15 design and of directed evolution and, you know, 17:33:35

16 people do that. 17:33:38

17 Q So if a skilled person is selecting 17:33:38

18 positions on PH20 to change -- 17:33:42

19 A Don't use the word selecting. That sounds 17:33:45

20 like a Darwinian selection. You mean choosing. 17:33:48

21 Q Choosing? 17:33:51

22 A Okay.

1	Q A skilled person is choosing positions on	17:33:52
2	PH20 to change and is choosing the substitutions	17:33:54
3	that they're going to make --	17:33:57
4	A Right, right, right.	17:33:58
5	Q -- to PH20, would that be classified as	17:33:59
6	rational design?	17:34:03
7	MR. KUSHAN: Objection. Foundation.	17:34:05
8	A It depends. I mean is all choice in life	17:34:15
9	rational? I mean sometimes they're choosing to	17:34:24
10	make certain substitutions back in those days	17:34:26
11	because, you know, the DNA oligos were easy to	17:34:29
12	make or something like that.	17:34:35
13	But, so again, it's hard to be absolute in	17:34:36
14	the answer, but if one is choosing to make one	17:34:38
15	amino acid, one change based on the structural,	17:34:41
16	structural and sequence analysis, I would call	17:34:46
17	that rational design, yeah.	17:34:48
18	But if one makes a library or even a	17:34:53
19	collection, let's say you make a collection of a	17:34:55
20	hundred and then you select among them for those	17:34:58
21	that have your desired property, then you're doing	17:35:01
22	rationally biased evolution.	17:35:10

1	There's a combination of these approaches.	17:35:14
2	I mean I think rational design and directed	17:35:15
3	evolution are really great ways to talk about this	17:35:19
4	as we do on these pages here, but I'm also	17:35:21
5	highlighting that, you know, there are projects	17:35:25
6	that do the best of both or the worst of both.	17:35:28
7	Q So let's turn in your declaration to your	17:35:54
8	appendices, and in particular let's look at	17:36:01
9	Appendix A-2. It starts at page 128.	17:36:04
10	A Page 128 you're at?	17:36:12
11	Q Yes. And the header is on 127 if that's	17:36:14
12	helpful to orient you.	17:36:26
13	A Hmm?	17:36:28
14	Q The cover page is on page 127.	17:36:29
15	A Yeah, yeah.	17:36:32
16	Q Okay. So Appendix A-2 is a list of all of	17:36:33
17	the -- well, it has a list of the positions in	17:36:45
18	PH20, the wild-type amino acid at that position,	17:36:47
19	and then the substitutions that retained activity,	17:36:50
20	and this is taken from the data that's disclosed	17:36:56
21	in the '600 patent; right?	17:36:59
22	A Right. And the tables mentioned here.	17:37:01

1 Q Okay. So for example, position 1, the 17:37:03
2 wild-type amino acid is leucine; right? 17:37:09

3 A Right. 17:37:13

4 Q And for substituted amino acids you have 17:37:13
5 one, two, three, four, five, six, seven, eight, 17:37:17
6 nine, 10, 11, 12, 13, 14, 15 amino acids -- 17:37:20

7 A Okay. 17:37:23

8 Q -- that were substituted at position 1 and 17:37:24
9 they maintained activity; is that right? 17:37:27

10 A Right. These are, you know, as a title on 17:37:31
11 page 127 says, it's a composite list of active 17:37:35
12 mutants from the source from the patent. So we -- 17:37:41
13 I'm not going to go back and check each one right 17:37:44
14 now, but assuming that's all correct, that 17:37:46
15 suggests that those substitutions give rise to 17:37:48
16 proteins that are active by the criteria defined 17:37:53
17 in the patent. 17:37:55

18 Q Okay. Now the patent teaches the results 17:37:56
19 of mutations at every single position from 1 to 17:38:07
20 447 in PH20; is that right? 17:38:13

21 A No. There's some gray areas in this which 17:38:15
22 where they're -- right, there are some gray areas 17:38:17

1	in this table where they don't have data.	17:38:20
2	Q Well, but that's not because they weren't	17:38:22
3	tested; right? That's because when they made	17:38:25
4	mutations at those positions, the protein was	17:38:28
5	inactive?	17:38:31
6	A I'd have to go back and look at that. I	17:38:32
7	mean, I --	17:38:34
8	Q Because it's in your next -- that's in	17:38:34
9	your next --	17:38:35
10	A Yeah, yeah --	
11	Q -- appendix.	17:38:37
12	A -- yeah. I mean, this is a lot of data	17:38:38
13	here. We have to go back and look at it.	17:38:39
14	Q So in Appendix A-3 which starts on 142,	17:38:42
15	you see that position 16, which you had grayed	17:38:48
16	out --	17:38:52
17	A Right.	17:38:53
18	Q -- in fact, has a whole bunch of	17:38:53
19	substitutions?	17:38:56
20	A Correct, a whole bunch of inactive	17:38:57
21	substitutions, right.	17:38:59
22	Q All right. So you say in your footer in	17:39:01

1	Appendix A-2 on page 140 that gray filling is no	17:39:10
2	mutants tested at respective PH20 position; right?	17:39:19
3	A Hold on. Hold on.	17:39:22
4	You're on page 140?	17:39:23
5	Q Yes.	17:39:25
6	A Okay.	17:39:30
7	Q Do you see that gray --	17:39:31
8	A I see that.	17:39:33
9	Q Okay. And that's not accurate; right?	17:39:35
10	A From what we just looked at, I -- this	17:39:37
11	seems to be an error.	17:39:40
12	Q Okay. So, in fact, the patent provides	17:39:41
13	data at every single position from 1 to 447?	17:39:45
14	A I'd have to go back and --	
15	MR. KUSHAN: Objection. Foundation.	
16	A -- check that but, look at those. Okay.	17:39:56
17	I mean, I'm not going to say for sure because I'd	17:39:59
18	have to go back and look, but let's -- go ahead.	17:40:00
19	Q Okay. Now, you said in your declaration	17:40:02
20	that the data in the patent are -- are the report	17:40:14
21	of a random mutagenesis experiment; right?	17:40:18
22	A Okay. Yes.	17:40:28

1 Q But you didn't intend to suggest that the 17:40:29
2 inventors only mutated random positions on PH20; 17:40:33
3 right? 17:40:51

4 A Let's discuss what's meant by random, and 17:40:51
5 let's discuss what's meant by targeted. 17:40:53

6 Usually, in this field, when one uses the 17:40:56
7 word "targeted," one is saying, I'm targeting 17:40:59
8 amino acid 27, or I'm targeting amino acids 27 17:41:02
9 through 37. That's targeting, like you target an 17:41:07
10 archery target, where you're saying where you're 17:41:11
11 going. 17:41:14

12 Randomness usually refers to saying, I'm 17:41:14
13 not picking which amino acid to put in. In many 17:41:18
14 experiments, it's both random in composition and 17:41:23
15 in location. 17:41:26

16 In this case, it was not targeted, okay, 17:41:30
17 in the sense that it was -- say they were 17:41:34
18 exploring the entire sequence. So each experiment 17:41:39
19 was targeted, but the summation of the entire 17:41:41
20 study was not targeted. Okay. 17:41:44

21 And the choice of which amino acid was put 17:41:47
22 in there was pretty much random. They weren't 17:41:51

1 saying, Oh, at position 17, I'm only going to put 17:41:57
2 in phenylalanine. They're just allowing lots of 17:42:00
3 things to go in there. 17:42:06

4 It's not a complete set. They did not 17:42:06
5 try -- make every amino acid every position. That 17:42:09
6 would be an obscene amount of work, but, you know, 17:42:10
7 they made a lot. 17:42:12

8 Q So, again, when you said random -- when 17:42:14
9 you used the phrase random mutagenesis, you 17:42:16
10 weren't intending to suggest that the inventors 17:42:19
11 only picked a handful of random positions on PH20 17:42:21
12 to test; right? 17:42:25

13 MR. KUSHAN: Objection. Form. 17:42:27

14 A I was -- quite the opposite. I was not -- 17:42:37
15 I'm not suggesting that they targeted particular 17:42:41
16 positions. Quite the opposite. 17:42:43

17 It was untargeted; it was the whole thing. 17:42:45
18 And so, in that sense, it's not directed toward a 17:42:47
19 particular location. And -- yeah. 17:42:50

20 Q And, similarly, you also did not intend to 17:42:55
21 suggest that the inventors only provided data for 17:42:58
22 one change at a time, one -- I'm sorry, strike 17:43:01

1	that. Let me start again.	17:43:05
2	You were not intending to suggest that the	17:43:06
3	inventors only tested one substitution per	17:43:09
4	position in PH20; correct?	17:43:12
5	A I'm -- I'm with you, but are you reading	17:43:15
6	from a particular paragraph?	17:43:17
7	Q No. I'm just asking the question.	17:43:18
8	A Okay. So then re-ask it, please.	17:43:20
9	Q You are not intending to suggest that the	17:43:22
10	inventors only tested one substitution per	17:43:24
11	position in PH20; correct?	17:43:27
12	MR. KUSHAN: Objection. Form.	17:43:29
13	A You're implying what I said or suggested.	17:43:32
14	But I'll say now that, as we see from the	17:43:35
15	table, the inventors tested -- they made and	17:43:37
16	studied numerous possible substitutions at -- all	17:43:43
17	over the place.	17:43:50
18	Q All over the place, meaning at every	17:43:51
19	single position?	17:43:53
20	A It seems to be every single one. I don't	17:43:53
21	want to go through and -- you know, there might be	17:43:56
22	one missing that I'm not noticing.	17:43:59

1 But it looks like, you know, either every 17:44:01
2 single one or almost every single one. I don't 17:44:04
3 know.

4 Q Did you -- did you -- when you rendered 17:44:06
5 your opinions in this case, did you examine 17:44:08
6 whether or not the inventors tested substitutions 17:44:10
7 at every single position? 17:44:13

8 A I knew that they had tested many 17:44:16
9 positions. I don't think I concerned myself 17:44:20
10 whether it was every single one. 17:44:22

11 But I knew it was either every single one 17:44:24
12 or the vast, vast majority. 17:44:27

13 Q So let's look on page 128. 17:44:37

14 A 1 -- 17:44:43

15 Q 128. 17:44:45

16 A Okay. 17:44:46

17 Q And this is the active table; right? 17:44:46

18 A Okay. 17:44:49

19 Q All right. And so you can see, for 17:44:49
20 example, positions 26 through 32. There are many 17:44:56
21 amino acid substitutions that retained activity at 17:45:01
22 those positions; right? 17:45:03

1 MR. KUSHAN: Objection. Form. 17:45:06

2 A The occurrence of these entries in this 17:45:14
3 tables suggests that at the numbers you mentioned, 17:45:18
4 many amino acids could be substituted these 17:45:20
5 positions without destroying activity. 17:45:23

6 Q And many -- both conservative and 17:45:26
7 nonconservative changes were tolerated without 17:45:34
8 destroying activity; right? 17:45:37

9 MR. KUSHAN: Objection. Foundation. 17:45:40

10 A At some positions, such as the ones -- 17:45:44
11 you're looking at the bottom of the table on page 17:45:48
12 128; right? 17:45:51

13 Q Mm-hmm. 17:45:52

14 A So at some positions -- the data 17:45:53
15 demonstrate that at some positions, a diversity of 17:45:55
16 amino acids were tolerated. This is what we would 17:45:59
17 usually call -- you know, they're tolerant; 17:46:01
18 they're tolerated, yeah. 17:46:04

19 Q So that particular position, for example, 17:46:05
20 26 to 32, is tolerant? 17:46:08

21 A That's what the data appear to show, 17:46:12
22 right. 17:46:15

1 Q Okay. 17:46:15

2 A Now, they did not test all 20 amino acids 17:46:15
3 at all those positions. So it's possible that 17:46:19
4 some are not tolerated, but it looks rather 17:46:21
5 permissive from what we have right here. 17:46:25

6 Q And the data show that at those positions, 17:46:27
7 the protein is tolerant of a range of amino acids 17:46:33
8 from, for example, at position 30, which started 17:46:36
9 as aspartate, it tolerated arginine, glycine, 17:46:38
10 histidine, lysine, leucine, glutamine, threonine, 17:46:44
11 serine, tryptophan, for example. 17:46:50

12 That's a wide variety of amino acids; 17:46:52
13 right? 17:46:56

14 A That's correct. 17:46:56

15 Q And the data on page 128 shows that other 17:46:59
16 positions, for example, position 23, are less 17:47:05
17 tolerant; right? 17:47:10

18 A That's right. 17:47:11

19 Q So position 23 only tolerated the change 17:47:12
20 from E to D; right? 17:47:17

21 A That's what it shows. That's what the 17:47:19
22 table says. 17:47:21

1 Q Similarly, if you look on page 129 in 17:47:26
2 position 60, that position only tolerated a change 17:47:30
3 from arginine to lysine; right? 17:47:36

4 A Correct. 17:47:39

5 Q And that would be considered a 17:47:40
6 conservative substitution? 17:47:43

7 MR. KUSHAN: Objection. Foundation. 17:47:45

8 A In general, arginine to lysine is 17:47:48
9 considered a mild or conservative substitution in 17:47:50
10 most positions, not everyplace, everywhere, but 17:47:53
11 usually. 17:47:57

12 Q So information about the tolerance of each 17:47:59
13 position on PH20 to substitution is useful; right? 17:48:03

14 A All information is useful. Information is 17:48:08
15 useful. 17:48:15

16 Q So, again, the information -- information 17:48:15
17 regarding the tolerance of each one of the 447 17:48:19
18 amino acids that were tested, that's useful; 17:48:24
19 right? 17:48:29

20 MR. KUSHAN: Objection -- 17:48:29

21 A Right -- 17:48:30

22 MR. KUSHAN: Wait. 17:48:30

1 THE WITNESS: Sorry.

2 MR. KUSHAN: Objection as to form.

17:48:31

3 A Keeping in mind here that one is looking
4 at single amino acid substitutions, where one
5 amino acid has replaced -- it has been replaced in
6 the context of an otherwise wild-type protein.

17:48:32

17:48:38

17:48:42

17:48:45

7 Q So are you saying that, in general,
8 knowledge about the tolerance of every single
9 position in PH20 is, in fact, useless?

17:48:51

17:48:56

17:48:58

10 A I didn't say that.

17:49:02

11 Q Okay. So you agree that it is useful?

17:49:04

12 A I said that. I said all knowledge is
13 useful.

17:49:05

17:49:07

14 Q And it's useful because it gives you
15 information about the extent to which each
16 position tolerates change and the extent -- and
17 the types of changes that each position may
18 tolerate?

17:49:08

17:49:09

17:49:12

17:49:17

17:49:20

19 MR. KUSHAN: Objection. Foundation. Also
20 objection as to form.

17:49:20

17:49:22

21 A It provides some insight about the
22 tolerance to substitution in the context of an

17:49:26

17:49:29

1 otherwise wild-type protein. 17:49:34

2 Q So you would agree that there are some 17:49:38
3 positions in the protein -- and, actually, just to 17:49:41
4 make sure that we're on the same page here, let's 17:49:45
5 look at your inactives table, which, again, starts 17:49:48
6 at page 142. 17:49:55

7 A Okay. 17:50:03

8 Q And the grayed-out positions -- and the 17:50:03
9 grayed-out, yeah, positions in your inactives 17:50:06
10 table, those are positions in which every single 17:50:09
11 substitution tested was active? 17:50:12

12 And if you would like to double-check that 17:50:14
13 for -- please go ahead, like, for example, 17:50:17
14 position 24. 17:50:19

15 A So in the example, position 24, let's go 17:50:21
16 back. That's what it looks like. Again, I'm 17:50:24
17 not -- you know, unless we go and test every 17:50:27
18 single one -- I don't want to commit to it, but 17:50:30
19 position 24, what you said -- 17:50:33

20 Q Yeah.

21 A -- is consistent. 17:50:34

22 Q And, you know, similarly, position 28 to 17:50:35

1	32, they're grayed out in your inactives table,	17:50:37
2	but you've got a whole lot of substitutions in	17:50:40
3	your actives table?	17:50:43
4	A Okay.	17:50:44
5	Q All right. So fair to say that for	17:50:45
6	positions 24 and 28 to 32, all of the	17:50:50
7	substitutions that were tested maintained	17:50:54
8	activity?	17:50:57
9	A Give me a second.	17:50:58
10	That's what the data show.	17:51:06
11	Q Okay. And, similarly, positions 146 to	17:51:08
12	148, which are on page 146 in your inactives	17:51:27
13	table, every single position at those residues	17:51:40
14	that was tested maintained activity?	17:51:43
15	And that is on page 132.	17:51:44
16	A Okay.	17:51:54
17	Q Is that right?	17:51:57
18	A That's what the data show for comparing	17:51:59
19	the table on page 132 with the table on page 146,	17:52:03
20	right?	17:52:08
21	That's what you're looking at?	17:52:08
22	Q Yes.	17:52:10

1 A Yeah.

2 Q All right. So is the fact that, for 17:52:13
3 example, positions 146 and positions 28 tolerated 17:52:15
4 every single substitution that was tested, would 17:52:20
5 that be helpful to the POSA seeking to make a PH20 17:52:23
6 that had mutations at positions 146 and position 17:52:29
7 28? 17:52:32

8 MR. KUSHAN: Objection. Foundation. 17:52:32

9 A To make substitutions at those positions 17:52:41
10 in this experiment at that position and in that 17:52:47
11 experiment at that position, right, you're making 17:52:50
12 them separately? What -- 17:52:53

13 Q No, no. 17:52:54

14 If a POSA wanted to make a PH20 where they 17:52:55
15 made changes at position 1 -- I'm sorry -- at 17:52:59
16 position 28 and position 46 [sic], would the 17:53:01
17 knowledge that in this experiment -- 17:53:04

18 A Made those changes simultaneously -- 17:53:05

19 Q Yes, simultaneously.

20 A -- in the same molecule? 17:53:08

21 Q Yes.

22 A Is that what you're trying to say? 17:53:09

1 Q Yes. Yes. 17:53:11

2 A Okay. 17:53:11

3 Q Would the knowledge from the patent that 17:53:11

4 position 28 and position 146 tolerated every 17:53:14

5 single substitution that was tried at that 17:53:17

6 position, would that be useful or not? 17:53:19

7 A You know, as I said before, all data is 17:53:23

8 useful. You know, the more data you have, the 17:53:26

9 more insight you gain and the more likely you can 17:53:28

10 predict results. 17:53:34

11 But, yeah, I mean, the data are useful. 17:53:35

12 It does not say that you can predict the future 17:53:40

13 necessarily, but the data are useful, of course. 17:53:45

14 All data are useful. 17:53:48

15 Q So is it your testimony that the data in 17:54:34

16 the patent provide no information whatsoever that 17:54:43

17 is useful to a POSA that is seeking to make, for 17:54:47

18 example, a PH20 with 10 mutations, compared to 17:54:51

19 wild-type? 17:54:55

20 A Once again, I'll say it's the continuum. 17:55:04

21 Having zero data gives you zero insight; having 17:55:10

22 more data gives you more insight. 17:55:12

1 That's not the same as saying that having 17:55:14
2 X amount of data allows you to predict something 17:55:16
3 accurately. 17:55:21

4 Q And when you think about having to predict 17:55:24
5 something accurately, what level of certainty are 17:55:27
6 you talking about? 17:55:29

7 MR. KUSHAN: Objection. Foundation. Also 17:55:31
8 objection as to form. 17:55:33

9 A It's not really that way. It -- I mean, 17:55:40
10 when you're trying to predict a structure, people 17:55:45
11 ask what level of resolution are you accurate at. 17:55:48

12 If you're trying to predict a structure, 17:55:51
13 the metric would be the resolution, the root mean 17:55:53
14 square deviation of a location of the atoms. 17:55:56

15 So when you're evaluating how good a 17:55:59
16 prediction is, you know, is it percentage? Is it 17:56:03
17 angstroms, root mean square deviation? Is it 17:56:11
18 level of activity? It kind of depends on what 17:56:15
19 the -- what the project is. 17:56:17

20 Q So you were talking about having to 17:56:20
21 predict something accurately if you're making a 17:56:24
22 PH20 with 10 mutations. 17:56:27

1	What would --	17:56:29
2	A You said 10?	17:56:29
3	Q Yeah, with 10 mutation.	17:56:30
4	What exactly were you thinking that you	17:56:32
5	would have to predict accurately?	17:56:35
6	A Okay. Okay. So if you're -- let's be	17:56:36
7	clear here. If you're trying to make a -- if	17:56:38
8	you're trying to take a protein -- this protein,	17:56:41
9	PH20 -- and you're planning to make 10 mutations,	17:56:44
10	in many cases even having the data here would not	17:56:55
11	allow you to predict whether that protein would be	17:57:01
12	active.	17:57:08
13	In some cases that data would be helpful.	17:57:09
14	In -- it would be helpful, but it would probably	17:57:14
15	in many cases not be sufficient to say, All right,	17:57:17
16	I'm going to make this protein that has a whole	17:57:21
17	bunch of mutations, and I'm going to know what's	17:57:25
18	going to happen.	17:57:27
19	Having data is always better than not	17:57:31
20	having data. But in this business having data	17:57:33
21	doesn't necessarily allow you to predict with	17:57:38
22	great confidence the result of, let's say,	17:57:44

1	making -- well, I go further -- 15 or 20	17:57:46
2	mutations? No. That would be really tough. 10,	17:57:49
3	in some cases, it would be okay. In many cases it	17:57:52
4	would not.	17:57:56
5	Q So when you say "in many cases it would	17:57:56
6	not," what do -- like, what do you have in mind?	17:58:00
7	A I'm saying in many cases, even if you had	17:58:02
8	at your, you know, at your fingers, if you hadn't	17:58:07
9	had these tables that would facilitate with	17:58:12
10	confidence making a protein with one mutation	17:58:19
11	because it's already been done.	17:58:23
12	And so in that situation, you'd have high	17:58:25
13	confidence that the mutation would be tolerated or	17:58:28
14	not tolerated because you could know ahead of time	17:58:34
15	because it's on the table.	17:58:38
16	If you made two simultaneous mutations,	17:58:39
17	you -- your confidence would be not as high as if	17:58:44
18	you were making one because you're making one.	17:58:47
19	You're just copying what's already been done.	17:58:50
20	If you're making two, then you're	17:58:52
21	inferring from the data that they might or might	17:58:54
22	not be tolerated together. This brings up the	17:58:57

1	concept of cooperativity, right.	17:59:00
2	So in -- in -- when people make mutations	17:59:02
3	at different positions simultaneously and they're	17:59:10
4	assessing stability or they're assessing some	17:59:16
5	other function, they'll discuss independence	17:59:18
6	versus cooperativity.	17:59:22
7	And it is not always the case that sites	17:59:25
8	are independent. It is not always the case that	17:59:28
9	if I change that corner, it has an effect; and I	17:59:31
10	change that corner, it has an effect; and if I	17:59:34
11	change them both, I can just add that up. That	17:59:36
12	would suggest they're additive, and sometimes that	17:59:39
13	happens.	17:59:41
14	But sometimes there's cooperativity. So	17:59:42
15	I'll do it with corners on the floor. If I change	17:59:45
16	that corner and I change that corner	17:59:48
17	simultaneously, the wall would fall down. So it's	17:59:50
18	not additive, right, so there's cooperativity.	17:59:53
19	The two positions are cooperating together to	17:59:56
20	produce an outcome. And, therefore, the impact of	18:00:00
21	changing them is not the additive sum of the	18:00:02
22	individuals, right. Sometimes it is, but often	18:00:07

1	it's not.	18:00:08
2	Q So if you have information that one corner	18:00:09
3	tolerated all, let's say, 15 substitutions that	18:00:16
4	were tested and another corner also tested all --	18:00:19
5	or tolerated all 15 substitutions that were	18:00:23
6	tested, would that give the skilled person a	18:00:26
7	reasonable expectation that changing those two	18:00:28
8	positions would produce a -- would retain -- at	18:00:31
9	least retain some amount of activity?	18:00:36
10	MR. KUSHAN: Objection. Foundation.	18:00:39
11	Objection as to form.	18:00:40
12	A Well, in the case of cooperativity, you	18:00:48
13	would -- you could get caught surprised, right. I	18:00:52
14	mean, I think the metaphor of holding up the wall	18:00:55
15	is fine because if you -- it's a good metaphor	18:00:58
16	because -- or in that Ta-Ka-Radi, you know, game	18:01:01
17	where you're piling blocks on -- one on top of the	18:01:08
18	other, if I pull out this support, it's tolerated;	18:01:11
19	if I pull out that support, it's tolerated; if I	18:01:14
20	pull them out both at the same time, boom, the	18:01:15
21	whole thing falls down because there's a	18:01:17
22	cooperative impact; that the two positions are	18:01:19

1 cooperating to do a function. 18:01:23

2 Q If you change two residues in two 18:01:26

3 separate, unstructured loops in a structure that 18:01:29

4 are nowhere near each other and both completely 18:01:32

5 tolerated all substitutions that were tested, 18:01:36

6 would you be surprised if somehow you inactivated 18:01:40

7 the protein and drove activity down to zero? 18:01:47

8 A So you're talking about an extreme case, 18:01:50

9 so let's talk about this. 18:01:52

10 So you have a loop over there and a loop 18:01:54

11 over there, and the data in these tables suggests 18:01:56

12 amino acid in the center of this loop and amino 18:02:00

13 acid in the center of that loop are both very 18:02:03

14 tolerant. Could you then be fairly confident you 18:02:05

15 could place them both at the same time? 18:02:09

16 That's a special case. I could easily 18:02:10

17 come up with special cases in the opposite 18:02:13

18 direction. 18:02:16

19 In that special case, you could be fairly 18:02:16

20 confident that you get away with it. In other 18:02:19

21 special cases where, for example, at a certain 18:02:22

22 position, I can insert a lysine on the surface and 18:02:31

1 it's fine. In another one I can insert a lysine 18:02:35
2 on the surface, and it's fine. But if they happen 18:02:39
3 to be close together, it won't be fine because 18:02:41
4 they'll repel. 18:02:44

5 So it's very context dependent. Once you 18:02:46
6 start making multiple mutations, it depends on the 18:02:49
7 location -- context. It depends on the location, 18:02:53
8 and it depends on structural cooperativity. 18:02:56

9 And, again, the pile of blocks is the best 18:03:01
10 example. If you've ever played Ta-Ka-Radi, you 18:03:04
11 pull out one block, the tower of blocks still 18:03:09
12 holds because the other support is still there. 18:03:11
13 You put it back; you pull out the other one, it 18:03:13
14 still stands because the other one's still there. 18:03:15
15 You pull them both out, it's down. 18:03:17

16 So it depends on the positioning whether 18:03:20
17 there's -- cooperativity is -- I mean, it's -- you 18:03:24
18 know, it's -- it's a source of allostery; it's the 18:03:27
19 source of a lot of things. 18:03:31

20 But cooperativity means different -- that 18:03:32
21 different positions are cooperating in such a way 18:03:34
22 that the combination is not nearly the additive 18:03:37

1 sum of the two separately. 18:03:41

2 So that's where it gets more complicated 18:03:44

3 than just saying, Oh, the data in this table is 18:03:47

4 going to solve all my problems. The data in the 18:03:50

5 table has always -- or, you know, as I said, all 18:03:52

6 data are helpful. 18:03:55

7 But the data in these tables is not going 18:03:57

8 to always solve your problems if you're attempting 18:04:01

9 to make 10 changes. You can get into a situation 18:04:04

10 where two changes give rise to a cooperative 18:04:07

11 result, which means they're not just the additive 18:04:09

12 sum of the two. 18:04:12

13 Once you start making 10, the chances of 18:04:13

14 some sort of cooperativity go up. So sometimes 18:04:15

15 you'll get away with it, but many times you won't. 18:04:19

16 Q And you can -- you have a reasonable -- at 18:04:21

17 least a reasonable prediction of positions that 18:04:25

18 are likely to be cooperative, right, that would be 18:04:28

19 positions that are right next to each other on the 18:04:30

20 protein? 18:04:33

21 If you change 10 residues right in a row, 18:04:33

22 would you reasonably expect there to be some sort 18:04:37

1	of cooperative effect that's going to happen?	18:04:40
2	MR. KUSHAN: Objection. Foundation.	18:04:41
3	Objection as to form.	18:04:43
4	A So changing 10 residues in a row is an	18:04:45
5	extreme example, but it's -- but it's also	18:04:49
6	possible.	18:04:54
7	People have seen that their networks, what	18:04:55
8	sort of seem to be networks, that one -- I mean,	18:04:59
9	there have been some really cool, classic studies	18:05:02
10	where you look at the protein and you don't -- you	18:05:05
11	know, you look at the structure, and you don't	18:05:07
12	know where the cooperativity or where the networks	18:05:09
13	are until you start making mutations and you see	18:05:12
14	that there is some sort of cooperativity.	18:05:17
15	People also see things where two positions	18:05:23
16	coevolve; that as one changes -- position 22	18:05:26
17	changes throughout evolution, but it's always the	18:05:30
18	case that when 22 changes, 44 also changes. That	18:05:33
19	suggests that there's -- there's crosstalk between	18:05:38
20	them that you may not have noticed just by looking	18:05:40
21	at the 3D structure.	18:05:43
22	So it's -- you know, again, taking back to	18:05:46

1 15 years ago -- it's different now, but in that 18:05:49
2 era, it would be hard to have a lot of confidence 18:05:56
3 if I were trying to predict the outcome of making, 18:06:02
4 you know, what they talk about here, 95 percent, 18:06:07
5 which is changing 5 percent -- you know, 95 18:06:10
6 percent means you're changing 5 percent, right. 18:06:12

7 So it would be hard to have confidence on 18:06:16
8 the outcome of an experiment where you 18:06:19
9 simultaneously mutated 5 percent of the sequence. 18:06:21
10 Sure, the data in the tables is always good to 18:06:26
11 have. But even with that data, it would be hard 18:06:30
12 to have strong confidence about what would happen 18:06:32
13 if I simultaneously changed, say, 20 -- you know, 18:06:36
14 5 percent of the sequence. Yeah. 18:06:40

15 Q Are you saying it would be hard to have or 18:06:43
16 difficult to have confidence in the -- for the 18:06:46
17 result of every single polypeptide that you would 18:06:49
18 test? 18:06:53

19 I mean, you agree that for at least some 18:06:53
20 mutations that you could make within the scope of 18:06:58
21 the claims, you could -- you could make some 18:07:01
22 predictions based on the data in the patent; 18:07:04

1	right?	18:07:07
2	MR. KUSHAN: Objection --	18:07:07
3	A We don't have that --	18:07:08
4	MR. KUSHAN: Objection. Foundation.	18:07:09
5	Objection as to form.	18:07:10
6	Go ahead.	18:07:11
7	Q So you don't think that you could make any	18:07:11
8	predictions whatsoever using the data in the	18:07:13
9	patent regarding, you know, let's say you make	18:07:15
10	PH20 with two substitutions?	18:07:18
11	A Well, there's the issue of making	18:07:20
12	predictions versus having your predictions turn	18:07:22
13	out to be accurate, okay. So you can predict	18:07:25
14	whatever you want.	18:07:28
15	But whether your predictions would be	18:07:28
16	accurate -- you know, you make a hundred	18:07:32
17	predictions. Sometimes you get it right.	18:07:35
18	Q So you're requiring --	18:07:38
19	A Sometimes you get it wrong.	18:07:39
20	Q You're requiring certainty?	18:07:40
21	MR. KUSHAN: Objection.	18:07:42
22	A I didn't say that --	18:07:43

1 MR. KUSHAN: Form.

2 A I was requiring confidence.

18:07:43

3 Q What does confidence mean? Like 50
4 percent?

18:07:45

18:07:50

5 A Confidence means -- well, it depends on
6 the parameter. Confidence in a structure -- am I
7 confident that it's correct plus or minus two
8 angstroms? Or am I confident that it's correct
9 plus or minus two-tenths of an angstrom? If the
10 issue is activity, am I confident that it's still
11 as active as the original, or am I confident that
12 it has more than one one-thousandth of the
13 activity?

18:07:52

18:08:16

18:08:19

18:08:22

18:08:25

18:08:29

18:08:32

18:08:35

18:08:39

14 It's not -- again, it's not binary; it's
15 not black and white. But the point is that as you
16 make -- as you attempt to make many
17 simultaneous -- as you attempt to make many
18 simultaneous mutations, the data that you had that
19 made you comfortable to make one mutation would
20 make you way less comfortable to make an abundance
21 of mutations because of issues like cooperativity
22 and because of issues that the structure is

18:08:39

18:08:42

18:08:45

18:08:48

18:08:54

18:08:58

18:09:02

18:09:05

18:09:09

1 slightly altered by the first mutation and then 18:09:12
2 the second and the third and the fourth. And so 18:09:15
3 it's -- you know, it's just -- your level of 18:09:17
4 confidence goes down. 18:09:20

5 Also, I want to highlight that, you know, 18:09:26
6 many of the multiply altered proteins that the 18:09:28
7 claim attempts to capture also include deletions 18:09:36
8 and, you know, things that are really tough to 18:09:39
9 have confidence in how they would impact the 18:09:42
10 protein. 18:09:45

11 Q But a protein -- or the claims cover 18:09:47
12 deletions that would inactivate the protein; 18:09:50
13 right? 18:09:53

14 A I said the claims -- in defining percent 18:09:54
15 identity, the claims allow for deletions. That's 18:09:58
16 all I said. 18:10:02

17 I didn't say anything about what -- the 18:10:03
18 rest of your sentence. 18:10:08

19 Q Oh, so when you were talking about the 18:10:08
20 deletions, you're not talking about the deletions 18:10:10
21 that would inactivate the protein? 18:10:12

22 MR. KUSHAN: Objection. Foundation. Also 18:10:15

1	objection as to form.	18:10:17
2	A I'm saying when the claims -- I'm	18:10:19
3	saying -- all right. Leave the claims behind.	18:10:22
4	I'm saying when the scientist goes out to	18:10:24
5	make mutations and when the patent, the body of	18:10:28
6	the patent -- and forget the claims for a moment.	18:10:36
7	When the body of the patent talks about --	18:10:38
8	about modifications, okay, it's not limiting to --	18:10:42
9	when it says modifications, it's not limiting	18:10:51
10	itself to amino acid substitutions.	18:10:55
11	It's also -- in the word modifications,	18:10:57
12	it's also including deletions.	18:10:59
13	Q Okay. So can we take a break?	18:11:02
14	MR. KUSHAN: Sure.	18:11:06
15	THE VIDEOGRAPHER: We are going off the	18:11:07
16	record. The time is 6:11 p.m.	18:11:09
17	(A recess was taken.)	18:29:22
18	THE VIDEOGRAPHER: We are back on the	18:29:22
19	record. The time is 6:29 p.m.	18:29:38
20	BY MS. MARTIN:	18:29:40
21	Q Dr. Hecht, you said that you've never	18:29:43
22	worked with hyaluronidases before; correct?	18:29:44

1	A	Correct.	18:29:49
2	Q	And hyaluronidases are different than the	18:29:50
3		enzymes that you've worked with in your	18:29:53
4		laboratory?	18:29:55
5	A	I've not worked with hyaluronidases, I	18:29:59
6		mean, like I said, right.	18:30:01
7	Q	Do you know how much hyaluronidase	18:30:06
8		activity is required for clinical utility?	18:30:08
9	MR. KUSHAN:	Objection. Foundation.	18:30:11
10		Objection as to form.	18:30:12
11	A	One could look it up, but I don't know.	18:30:17
12	Q	And would you consider yourself to be an	18:30:20
13		expert in hyaluronidase?	18:30:24
14	A	No. I've not worked with it.	18:30:26
15	Q	Are you -- do you know of Andrej Sali?	18:30:30
16	A	I haven't seen him in years, but I know	18:30:38
17		the name.	18:30:40
18	Q	Do you consider him to be a respected	18:30:43
19		scientist?	18:30:48
20	MR. KUSHAN:	Objection. Foundation.	18:30:50
21	A	I mean, he certainly was. I haven't --	18:30:57
22		you know, I haven't seen him in years or thought	18:31:00

1 about him in years, but, certainly, back when he 18:31:02

2 was -- yeah, he was -- he was a known -- yeah. 18:31:06

3 Q Okay. What about John Moulton? Do you know 18:31:08

4 him? 18:31:15

5 A I know who he is, sure. 18:31:15

6 Q Is he a respected scientist? 18:31:17

7 A Yes. 18:31:18

8 Q Respected in the field? 18:31:19

9 A Sorry. Yes. Yeah. Sorry. I didn't hear 18:31:27

10 you. Yes. 18:31:29

11 Q Would you trust his work? 18:31:29

12 MR. KUSHAN: Objection. Foundation. 18:31:31

13 Objection as to form. 18:31:33

14 A It's a quirky question. I mean, with any 18:31:39

15 person, any author, any scientist, you don't want 18:31:47

16 to make a blanket statement like that. 18:31:51

17 But these were respected scientists, and I 18:31:54

18 would look at the work, and I would make my own 18:31:57

19 judgment. 18:32:02

20 Q What about Greg Petsko? 18:32:03

21 A He was on my thesis committee. I know who 18:32:07

22 he is. 18:32:10

1	Q Is he a respected scientist?	18:32:10
2	A Yes.	18:32:13
3	Q What about Roland Dunbrack?	18:32:16
4	A I know who he is. I've heard him speak.	18:32:21
5	I don't know him personally, but yeah.	18:32:23
6	Q Is he a respected scientist?	18:32:25
7	A Yes.	18:32:27
8	Q All right. So let's turn in your	18:32:29
9	declaration to paragraph 50.	18:32:42
10	A Sorry. Paragraph 50 or page 50?	18:33:09
11	Q Paragraph 50 --	18:33:12
12	A I'm sorry.	
13	Q -- page 20.	18:33:13
14	A I'm sorry. I was on the wrong one. Okay.	18:33:15
15	Q And paragraph 50, you say, "There were	18:33:18
16	limits to using rational design techniques in the	18:33:21
17	2011 time frame"; right?	18:33:24
18	A Mm-hmm.	18:33:25
19	Q And to support that statement, you cite to	18:33:26
20	Exhibit 1018, which is the Chica paper; is that	18:33:29
21	right?	18:33:32
22	A I know him too, yeah.	18:33:32

1	Q All right. So marking Exhibit 1018.	18:33:35
2	(Exhibit 1018 was introduced for	
3	identification.)	
4	Q Dr. Hecht, is -- Exhibit 1018, that's the	18:33:52
5	Chica paper that you cited in your declaration?	18:33:54
6	A Right.	18:33:57
7	Q Okay. And you're citing to page 378,	18:33:59
8	which is the first page; right?	18:34:08
9	A Okay.	18:34:10
10	Q And so the second full paragraph on page	18:34:14
11	378 that starts "Multiple approaches," do you see	18:34:22
12	that paragraph?	18:34:25
13	A I do.	18:34:25
14	Q And it's -- that sentence says, "Multiple	18:34:29
15	approaches have been developed to allow the	18:34:31
16	identification of mutant enzymes possessing	18:34:34
17	desirable qualities such as increased activity and	18:34:37
18	modified specificity, selectivity, or cofactor	18:34:39
19	binding"; is that right?	18:34:43
20	A I see that.	18:34:44
21	Q And the next sentence says, "The earliest	18:34:45
22	approach was rational design, which was used to	18:34:47

1	modify the specificity of enzymes"; is that right?	18:34:50
2	A I see that. I'm going to look at the	18:34:52
3	references for a second.	18:34:55
4	Okay.	18:35:01
5	Q And then the next sentence is the sentence	18:35:01
6	that you quote in your declaration, which is,	18:35:04
7	"This approach requires an in-depth knowledge of	18:35:06
8	the structural features of the enzyme active site	18:35:08
9	and their contribution to function"; correct?	18:35:11
10	A Okay.	18:35:13
11	Q And then it continues: "The complexity of	18:35:15
12	the structure-function relationship in enzymes has	18:35:18
13	proven to be a factor limiting the general	18:35:20
14	applicability of rational design"; is that right?	18:35:22
15	A Okay.	18:35:25
16	Q So when Chica is talking about rational	18:35:26
17	design in this paragraph, Chica's talking about	18:35:31
18	using rational design to modify the specificity of	18:35:35
19	enzymes; right?	18:35:38
20	MR. KUSHAN: Objection. Foundation. Also	18:35:39
21	to form.	18:35:49
22	A I mean, I want to highlight that the title	18:35:55

1 talks about semi-rational approaches, which is 18:35:59
2 sort of what I was saying before we took a break 18:36:02
3 that there are -- it's not just rational design 18:36:05
4 and not just directed evolution or laboratory 18:36:08
5 evolution. 18:36:10

6 There are also approaches that merge the 18:36:11
7 two of both directed evolution and rational 18:36:13
8 design, right. We talked about that before the 18:36:17
9 break. 18:36:19

10 Now getting back to the text where we are 18:36:20
11 now. So what the text says, earliest approach was 18:36:22
12 rational design, which was used to modify the 18:36:28
13 specificity of enzymes. Okay. Approach 18:36:30
14 required -- he's saying rational design requires 18:36:34
15 an in-depth knowledge. Yeah. Right. 18:36:37

16 What -- what's the question? 18:36:40

17 Q So in those sentences when he's talking 18:36:42
18 about rational design, he's talking about using 18:36:46
19 rational design to modify the specificity of 18:36:48
20 enzymes? 18:36:51

21 A In some cases, that was -- yeah. 18:36:51

22 Q He's not talking about using rational 18:36:53

1	design to make a modified PH20 polypeptide with 95	18:36:56
2	percent sequence identity in this paper, is he?	18:37:02
3	MR. KUSHAN: Objection -- objection.	18:37:04
4	Foundation.	18:37:05
5	A There is no mention of PH20 in the text we	18:37:08
6	just looked at.	18:37:11
7	Q So what does it mean to modify the	18:37:13
8	specificity of enzymes?	18:37:16
9	A Ah, to modify the specificity of enzymes.	18:37:18
10	If you look at reference number 5 at the	18:37:31
11	end of that paper, there's a paper from Perham's	18:37:34
12	lab. I remember when this was happening.	18:37:37
13	And the title of that was "Redesign of the	18:37:39
14	coenzyme specificity of a dehydrogenase by protein	18:37:41
15	engineering." In its day in 1990, that made a big	18:37:47
16	splash because they were redesigning an enzyme	18:37:50
17	such that the coenzyme it used, the cofactor it	18:37:53
18	used, was different from the natural one. That's	18:37:58
19	what they're citing in that example.	18:38:01
20	So that's modifying -- that's one example	18:38:04
21	of modifying specificity for a substrate or for a	18:38:08
22	cofactor.	18:38:12

1 Q So in that paragraph, Chica is teaching 18:38:19
2 that there are -- it's -- there are difficulties 18:38:23
3 associated with using rational design to change 18:38:24
4 the specificity for a substrate or a cofactor; 18:38:26
5 right? 18:38:44

6 A Well, he's doing both. He's highlighting 18:38:44
7 some very impressive successes with references 4 18:38:47
8 through 9 but, at the same time, highlighting that 18:38:50
9 the approach requires an in-depth knowledge of 18:38:54
10 structural features of the enzyme active site and 18:38:57
11 their contribution to function. 18:39:01

12 So he's both citing the successful 18:39:02
13 accomplishments and highlighting the limitations, 18:39:05
14 both. 18:39:08

15 Q Now the claims that you looked at in this 18:39:09
16 case, they don't require changing the specificity 18:39:12
17 of an enzyme for a substrate or a cofactor; right? 18:39:18

18 MR. KUSHAN: Objection. Foundation. 18:39:23

19 A That's correct; they don't. The claims do 18:39:34
20 not require altering the specificity for the 18:39:38
21 substrate or the cofactor, yeah. 18:39:42

22 Q So difficulties of using rational design 18:39:44

1 to change specificity for a substrate or a 18:39:47
2 cofactor are not relevant to practicing the 18:39:50
3 claims; right? 18:39:55

4 MR. KUSHAN: Objection. Foundation. 18:39:57

5 A I'm going to disagree with what you said. 18:40:02

6 I would say that Chica's comment is a 18:40:05
7 broad statement about the approach for rational 18:40:07
8 design. The approach, rational design, requires 18:40:10
9 an in-depth knowledge and so forth. And, 18:40:14
10 therefore, it has limitations. 18:40:18

11 The approach could be used to make altered 18:40:21
12 specificity for cofactors or substrates. The 18:40:26
13 approach could be used to try and make the same 18:40:31
14 specificity but with greater activity. The 18:40:34
15 approach could be used to make the same activity 18:40:38
16 and the same specificity but with a different 18:40:41
17 sequence with mutations. 18:40:44

18 The approach could be used for various 18:40:46
19 goals. Irrespective of the goal, the approach has 18:40:49
20 limitations, as he spells out, because it requires 18:40:53
21 an in-depth knowledge of the structural features 18:40:55
22 of what he says there: the, you know, structural 18:40:57

1 features of the enzyme, the active site, the
2 contribution to function.

3 So the rational design approach has
4 limitations because it requires a great deal of
5 input to -- a great deal of very solid input as a
6 foundation for the rational design.

7 And he's highlighting that in many cases
8 that in-depth knowledge, that input, is
9 incomplete. And, therefore, the rational design
10 approach is challenging, irrespective of whether
11 we're talking about modified specificity in the
12 top line of this column or whether we're talking
13 about making mutations for the same specificity in
14 hyaluronidase.

15 Either way, rational design is -- is
16 challenged by whether -- by how much information
17 and how much understanding, you know, from the
18 structure, the physical chemistry, the
19 interactions by -- you know, your understanding is
20 incomplete, and so your rational design is
21 constrained by an incomplete understanding.

22 Q Okay. Let's mark Exhibit 1059.

1 (Exhibit 1059 was introduced for
2 identification.)

3 I'm not sure how you say his name,
4 Leisola?

18:42:24

18:42:28

5 A I'm sorry. What?

18:42:28

6 Q I'm not sure how you say that name.

18:42:29

7 Is it Leisola?

18:42:30

8 A I don't know this person, so I won't
9 answer that.

18:42:32

18:42:34

10 Q Okay. So in any event, Exhibit 1059 is a
11 paper that you considered in rendering your
12 opinion in this case; right?

18:42:35

18:42:38

18:42:39

13 A It's one of the ones listed in here,
14 right?

18:42:40

18:42:43

15 Q Yeah.

18:42:43

16 You cite it, for example, in Footnote 17
17 on page 21 in your declaration.

18:42:44

18:42:45

18 A Page 21.

18:42:51

19 Q Yes.

18:42:52

20 A Okay. Okay.

18:42:53

21 Q Okay. So if you turn to page 1226 in
22 Exhibit 1059.

18:43:08

18:43:27

1 A Mm-hmm. 18:43:29

2 Q First full sentence: "At one end is an 18:43:30
3 approach commonly referred to as a rational 18:43:34
4 design, which aims to understand the principles of 18:43:37
5 protein structure and function well enough to 18:43:40
6 apply them in designing new properties or even 18:43:42
7 novel proteins using de novo design"; right? 18:43:45

8 A I see what you read, but I also want to 18:43:49
9 highlight the line before that, where they say 18:43:52
10 what I've been saying all day -- is that it's a 18:43:54
11 spec- -- is that it's a spectrum defined by two 18:43:57
12 extremes, right. It's a spectrum; it's not this 18:44:02
13 or that. It's a continuum. 18:44:05

14 Q So the continuum is what screening a 18:44:07
15 totally random library versus rationally selecting 18:44:09
16 the changes that you're going to make? I just 18:44:12
17 want to understand the continuum that you're 18:44:14
18 talking about. 18:44:17

19 MR. KUSHAN: Objection. Foundation. 18:44:18

20 A The continuum is at one extreme -- there 18:44:19
21 was a paper by Keith and Szostak -- Jack Szostak, 18:44:23
22 Nobel Prize winner for different things -- where 18:44:27

1 they made completely random sequences, and they 18:44:30
2 had something like 10 to the 12th random 18:44:33
3 sequences. They didn't use any kind of screener 18:44:36
4 selection that's relevant to today because you 18:44:39
5 can't screen 10 to the 12th in ways that we're 18:44:41
6 talking about today. 18:44:44

7 But they screened through 10 to the 12th 18:44:44
8 totally random sequences and selected for function 18:44:47
9 by 15 generations. That's the most extreme 18:44:52
10 example that I can think of of a laboratory 18:44:56
11 evolution with fully random sequences and fully 18:45:00
12 based on selection and screening, no rational 18:45:04
13 design. That's one extreme. 18:45:07

14 The other extreme is you have a very high 18:45:09
15 precision understanding and knowledge of your 18:45:12
16 target situation and using structural 18:45:15
17 understanding, physical chemistry, organic 18:45:20
18 chemistry, you say, I want that atom over there, 18:45:24
19 and I'm going to make this mutation to do that. 18:45:27

20 Those are the two extremes. And many 18:45:29
21 projects, most projects, are not at either of 18:45:31
22 those extremes. Sorry. 18:45:34

1 Q Is the first extreme, is that directed 18:45:37
2 evolution? 18:45:39

3 A Many, many, many projects are directed 18:45:41
4 evolution. Frances Arnold does directed 18:45:43
5 evolution. But with the Keith and Szostak, what 18:45:46
6 I'm describing is the most extreme example of that 18:45:50
7 because there was no rational input into their 18:45:53
8 sequences. They start out with fully random, 10 18:45:55
9 to the 12th random sequences. A lot of directed 18:45:58
10 evolution experiments start with -- you know, they 18:46:02
11 start with some rational input. 18:46:05

12 It varies. There's a whole -- there's a 18:46:08
13 whole spectrum of approaches. But, you know, it's 18:46:10
14 handy to conceptually imagine these two extremes: 18:46:21
15 the Keith and Szostak 10 to the 12th random 18:46:24
16 sequences on the one hand and the hypothetical 18:46:27
17 situation where you know every atom's position and 18:46:29
18 its role in catalysis and you know the stability 18:46:33
19 to the tenth of a kilocalorie or a hundredth of a 18:46:37
20 kilocalorie, you know, and you know the catalytic 18:46:42
21 mechanism and all of that, which is -- you know, 18:46:43
22 it's demanding. 18:46:46

1 As the Chica paper says, that's a 18:46:47
2 challenge to have that kind of precise and 18:46:50
3 accurate understanding that will allow that 18:46:52
4 perfect level of rational design. But in 18:46:53
5 principle that's what the extreme rational design 18:46:56
6 would be. 18:46:59

7 Q And would the extreme rational design 18:47:00
8 theoretically allow you to predict a novel protein 18:47:03
9 using de novo design? 18:47:06

10 MR. KUSHAN: Objection. Foundation. 18:47:10
11 Objection as to form. 18:47:11

12 A It's kind of a different question. 18:47:12

13 What we were talking about a moment ago is 18:47:14
14 making a single amino acid change in a protein 18:47:16
15 where you've got the structure known to less than 18:47:19
16 one angstrom resolution and you know the precise 18:47:24
17 catalytic mechanism and you know all this stuff. 18:47:27

18 What you asked a moment ago was de novo 18:47:30
19 protein design. As I said, now that's all being 18:47:32
20 done by machine. In the last couple years or four 18:47:35
21 years or whatever, that's all being done by AI. 18:47:39

22 Rational design, again, is -- there's a 18:47:43

1 spectrum. 18:47:46

2 And when Bill DeGrado started doing it or 18:47:46

3 when I was doing it as a postdoc, it was rational. 18:47:49

4 But holy moly, we were -- we were -- you know, we 18:47:52

5 didn't know that much. 18:47:54

6 Conversely, a really fully rational thing 18:47:56

7 is where you know everything at a very high level 18:48:00

8 of detail and you can design an atom by atom. 18:48:03

9 So I -- you know, sorry if I didn't quite 18:48:06

10 answer your question, but... 18:48:09

11 Q Practicing the claims that you've been 18:48:13

12 evaluating in this case does not require designing 18:48:16

13 new properties for hyaluronidases; correct? 18:48:20

14 MR. KUSHAN: Objection. Form. Objection 18:48:23

15 as to foundation. 18:48:25

16 A As I said before, it's not designing new 18:48:27

17 specificity or new cofactors. It's attempting to 18:48:30

18 design new sequences that have, in this case, 18:48:35

19 hyaluronidase activity. 18:48:41

20 So there's rational design. It depends on 18:48:42

21 what your goals are, right. You can rationally 18:48:47

22 design in principle. And let's say -- you can't 18:48:51

1 always get away with it, but in theory you can 18:48:53
2 rationally design a new sequence for a known 18:48:56
3 function, or you could rationally design an 18:48:59
4 altered function based on a known sequence. 18:49:02

5 I mean, there's a lot of ways of spinning 18:49:06
6 that. 18:49:08

7 Q Your opinions in this case are all 18:49:25
8 premised on your conclusion that the claims across 18:49:30
9 the four patents that you considered require 18:49:33
10 hyaluronidase activity; correct? 18:49:37

11 MR. KUSHAN: Objection. Foundation. 18:49:38

12 A You were asking, again, if I consider 18:49:42
13 Claim 1 to require hyaluronidase activity, as we 18:49:45
14 discussed earlier? 18:49:48

15 Q I'm saying the opinions that you rendered 18:49:49
16 regarding the four patents that you considered, 18:49:52
17 your opinions were all based on your assessment 18:49:54
18 that the claims that you considered required 18:49:58
19 hyaluronidase activity? 18:50:02

20 MR. KUSHAN: Objection. Foundation. 18:50:03

21 A I interpreted Claim 1 as requiring 18:50:05
22 hyaluronidase activity. 18:50:12

1 But there's 150 pages of opinions in 18:50:13
2 there, and not all of them are related to that 18:50:16
3 issue. 18:50:19

4 Q So did you evaluate whether the claims 18:50:20
5 would be valid if they didn't require 18:50:22
6 hyaluronidase activity? 18:50:25

7 A Ah. So you're proposing, what if the 18:50:30
8 claims did not require hyaluronidase activity? 18:50:35
9 And I would say there, it's still a very -- 18:50:40
10 there's still a -- an absence of a full, written 18:50:44
11 description or an enablement because -- I mean, 18:50:53
12 this is in here. I can go hunt it down. 18:50:59

13 But -- let me go find it. Okay. 18:51:02
14 Paragraph 135, even if the claims are interpreted 18:51:21
15 to encompass inactive mutants, they would still 18:51:26
16 include an immense number of active mutant 18:51:30
17 modified PH20 polypeptides.

18 As I discuss further below, it's my 18:51:35
19 opinion that the common disclosure does not 18:51:37
20 describe or enable this immense number of inactive 18:51:40
21 mutants. 18:51:42

22 In other words, even if you were to choose 18:51:43

1	to interpret Claim 1 as including or as	18:51:45
2	encompassing also inactive mutants, then,	18:51:48
3	nonetheless, the -- the -- the common disclosure	18:51:52
4	does not provide information on how to sort	18:52:02
5	through the immense collection of 10 to the 50th	18:52:12
6	or 10 to the 60th and know, among those that have	18:52:17
7	15 amino acid substitutions, which of those are	18:52:20
8	useful, right, and which of those are not.	18:52:24
9	So even if the claim were to -- even if,	18:52:27
10	which we're not granting necessarily. But even if	18:52:31
11	we were to say -- as it says in paragraph 135,	18:52:33
12	even if we were to interpret the claim as	18:52:37
13	including both active and inactive, in some ways,	18:52:41
14	it's even more difficult because then you have to	18:52:47
15	say, How do I sort through these and figure out	18:52:50
16	which ones have utility and which ones don't.	18:52:52
17	The common disclosure does not tell us	18:52:56
18	which ones have activity and which ones don't	18:52:58
19	beyond, you know, the 6,000 in those tables. The	18:53:01
20	common disclosure doesn't tell us which ones are	18:53:04
21	active and which ones aren't, okay, beyond those	18:53:08
22	few.	18:53:11

1 And even for those few it does describe, 18:53:11
2 it doesn't give us interpretations of why. And it 18:53:13
3 gives us no information on how to construct 18:53:17
4 sub-libraries from the 10 to the 60th. It does -- 18:53:22
5 it gives us no information on how to construct 18:53:25
6 sub-libraries. So there's no written description 18:53:28
7 of how to make sub-libraries that will include 18:53:30
8 the -- you know, that will allow us to find the 18:53:35
9 active ones. 18:53:37

10 And there's no enablement explaining -- 18:53:38
11 enabling the person of -- you know, expert in the 18:53:41
12 field -- enabling one to sort through, find, 18:53:45
13 produce, make those that will have activity and, 18:53:52
14 therefore, will be -- have utility. So -- 18:53:56

15 Q So -- 18:53:59

16 A -- yeah. 18:54:00

17 Q Okay. 18:54:00

18 A So even if one were to say the claims 18:54:01
19 encompassed both active and inactive, there's 18:54:03
20 still a serious problem in that there's no -- or 18:54:07
21 incomplete, very limited, written description of 18:54:13
22 how to find out, how to make, how to find active 18:54:16

1	modified proteins and how, or enable how to -- how	18:54:21
2	to find them. Yeah.	18:54:24
3	Q Okay.	18:54:25
4	MS. MARTIN: I'll move to strike that as	18:54:26
5	nonresponsive.	18:54:28
6	A Sorry?	18:54:28
7	Q I said move to strike as nonresponsive.	18:54:30
8	So it's your understanding there has to be	18:54:32
9	a --	18:54:34
10	MR. KUSHAN: Sorry. I'm going to object	18:54:34
11	to that. Sorry. That was an answer he gave in	18:54:36
12	response to your question. That's responsive.	18:54:40
13	Go ahead.	18:54:42
14	MS. MARTIN: Okay.	18:54:43
15	Q So it's your understanding that the patent	18:54:46
16	needs to disclose -- needs to disclose	18:54:51
17	sub-libraries in order to have sufficient, written	18:54:56
18	description and enablement support.	18:54:58
19	And it also needs to disclose some sort of	18:54:59
20	sorting mechanism for sorting between the	18:55:03
21	polypeptides that have what you consider to be	18:55:08
22	utility from those that you considered not to have	18:55:11

1 utility in order to satisfy the written 18:55:14

2 description and enablement requirement? 18:55:17

3 MR. KUSHAN: Objection. Foundation. 18:55:20

4 Objection to form. 18:55:22

5 A That it would need to provide guidance on 18:55:22

6 how to find proteins that have utility amidst this 18:55:27

7 hypothetical 10 to the 60th. And that guidance is 18:55:34

8 lacking. And in many cases, you know, it even 18:55:41

9 tells you to sort of ignore some of the guidance 18:55:46

10 that was in the common disclosure where the common 18:55:49

11 disclosure tells -- you know, says to avoid 18:55:51

12 changing certain residues and, you know. 18:55:55

13 And yet the attempt to draw a fence around 18:55:58

14 this entire universe of proteins is not providing 18:56:03

15 guidance on which ones to make us active ones and 18:56:10

16 which ones -- you know, and how to determine 18:56:17

17 they're active. There's -- there's no guidance. 18:56:19

18 Q So there's -- in all the data that you 18:56:21

19 looked at and all the data that you have in your 18:56:22

20 appendices, that provides absolutely no guidance 18:56:25

21 whatsoever to the skilled person seeking to make 18:56:30

22 the claimed modified PH20 polypeptides totally 18:56:34

1	left in the dark with no clue whatsoever what	18:56:38
2	potential changes they may make -- they may want	18:56:40
3	to make?	18:56:42
4	MR. KUSHAN: Objection. Foundation.	18:56:43
5	Objection as to form.	18:56:45
6	A With respect to the overall collection,	18:56:46
7	it's a grain of sand on a large beach. The tables	18:56:48
8	list 5- or 6,000 single substitutions. That's,	18:56:57
9	you know, five times ten to the third or six times	18:57:02
10	then to the third. That's compared to ten to the	18:57:05
11	50th or ten to the 60th. That's, like, nothing.	18:57:09
12	So --	18:57:14
13	Q So how many examples would the patent have	18:57:14
14	needed to provide to be representative, in your	18:57:16
15	view?	18:57:19
16	A Ah, it's not just how many. It's also	18:57:20
17	that the patent is saying you can change, let's	18:57:24
18	say, 5 percent of the sequence, which, depending	18:57:31
19	on which sequence you're looking at, is maybe, you	18:57:34
20	know, 20 substitutions. And so it's not how many	18:57:38
21	examples they should be providing. It's are they	18:57:42
22	representative?	18:57:45

1 And when you're dealing with a -- a 18:57:46
2 universe of single, double, triple, 5, 10, 20 18:57:51
3 substitutions and there are 10 to the 60th of 18:57:56
4 them, then it's not just that the number, 6,000 or 18:58:01
5 5,000, is such a small number. It's also that, in 18:58:05
6 terms of its type, it's not representative. It's 18:58:08
7 single changes. 18:58:10
8 And so that's not representative of the 20 18:58:11
9 substitutions that would arise based on 5 percent 18:58:16
10 changes. 18:58:22
11 Q You also -- 18:58:23
12 A That's not representative. 18:58:24
13 Yeah. 18:58:25
14 Q Sorry. 18:58:25
15 You also said that there's no disclosure, 18:58:27
16 there's no explanation for why -- there's no 18:58:30
17 explanation for the results that were achieved. 18:58:35
18 So is it your understanding to satisfy 18:58:38
19 written description and enablement requirement, 18:58:40
20 there has to be some sort of explanation in terms 18:58:43
21 of the structural impact of each of the 18:58:45
22 substitutions? 18:58:48

1	A Exactly.	18:58:48
2	So when Park went through the individual	18:58:49
3	amino acid substitutions that are on the last few	18:58:54
4	pages of each of my documents, it's a very, I	18:58:57
5	would say, erudite description of why this	18:59:05
6	mutation would likely be tolerated based on	18:59:09
7	sequence alignment, based on hydrogen bonds, based	18:59:12
8	on, you know, the model, the hydrogen bonds, the	18:59:17
9	accessible surface area, and all of that.	18:59:20
10	And so he's providing -- he's suggesting a	18:59:22
11	mutation and also providing an intellectual	18:59:26
12	underpinning for why that would work and thereby	18:59:31
13	guiding an expert in the field about what works	18:59:33
14	and what doesn't.	18:59:36
15	In contrast, the 5,000 or 6,000 things	18:59:39
16	listed in those tables are just lists with no	18:59:42
17	guidance about why something -- you know, you were	18:59:46
18	looking at before all these ones that failed to	18:59:49
19	work and all these ones that do work. There's no	18:59:51
20	guidance, right. There's nothing there. It	18:59:54
21	doesn't say whether, Oh, this works because, you	18:59:56
22	know, it's on the surface, whatever.	19:00:01

1 There's no guidance of -- for a 19:00:02
2 practitioner to learn from those lists and apply 19:00:05
3 them in any kind of rational design, right, in the 19:00:10
4 way that Park did. 19:00:14

5 Q So it's -- so Park did all of that just 19:00:15
6 based on what the -- based on a POSA's knowledge 19:00:18
7 in 2011; right? He was able to do that analysis? 19:00:20

8 A Based on the -- yeah. I mean, based on -- 19:00:28
9 you know, based on -- yeah, based on what was 19:00:34
10 known, what tools were available, what was known 19:00:38
11 in the field, what was available, and the, you 19:00:41
12 know, and the fact that he is very skilled at 19:00:45
13 this, but yeah. 19:00:46

14 Q Okay. So are you saying that the skilled 19:00:47
15 person couldn't actually interpret the data in the 19:00:51
16 patent and try to understand, based on the data in 19:00:53
17 the patent -- for example, if, you know, maybe 19:00:57
18 those positions are tolerated because they're on 19:00:59
19 the surface, or maybe they're not tolerated 19:01:02
20 because they're in the center of the protein. 19:01:04

21 Is that outside the realm of what the 19:01:05
22 skilled person could do? 19:01:07

1 A My understanding is the obligation is upon 19:01:08
2 the patent to provide a written description. It's 19:01:10
3 not upon the reader to provide a written 19:01:13
4 description. It's upon the patent to provide 19:01:18
5 enablement. It's not upon the reader of the 19:01:21
6 patent to provide enablement. 19:01:23

7 And the patent fails to do that. 19:01:25

8 Q So you're saying that the -- you're saying 19:01:27
9 that what the skilled person knew is not relevant 19:01:29
10 because it actually has to be spelled out in the 19:01:33
11 patent? 19:01:38

12 MR. KUSHAN: Objection. Foundation. 19:01:38
13 Objection to form. 19:01:40

14 A I'm saying that it is the obligation -- I 19:01:51
15 mean, you know, it's just what it says in this 19:01:54
16 part on legal principles -- is that -- is that -- 19:01:57
17 I'll be quick. I mean, I'll get to it right here. 19:02:01

18 It says that, "Patent disclosure should 19:02:04
19 provide" -- page -- paragraph 26 -- "should 19:02:09
20 provide a sufficient written description" -- and 19:02:12
21 so on. 19:02:17

22 And that "could be achieved by disclosure 19:02:19

1 that describes a representative number of species 19:02:22
2 and structural features." 19:02:25

3 It does not say that it is upon the reader 19:02:26
4 of the patent to figure out what's going on 19:02:32
5 because the reader happens to be in this field. 19:02:34
6 It says that it's upon the patent, the disclosure 19:02:37
7 requirement, to provide a written description. 19:02:41

8 And in paragraph 27, it's informed that 19:02:44
9 the second disclosure requirement, not a 19:02:47
10 requirement upon the reader, is that the 19:02:49
11 disclosure provide a description that enables a 19:02:52
12 skilled artisan to practice. 19:02:56

13 So, in this case, I would expect -- I 19:02:58
14 would -- you know, I think a requirement would be 19:02:59
15 that the disclosure would provide, as I said, a 19:03:01
16 description that enables the skilled artisan to 19:03:05
17 practice. 19:03:09

18 A data dump is not a teaching, okay? And 19:03:10
19 so those tables are a data dump. I mean, I talk 19:03:16
20 to my students about this all the time. A data 19:03:19
21 dump is not the same as a teaching. 19:03:21

22 And it's my understanding -- I'm not an 19:03:24

1 attorney, but it's my understanding that the 19:03:26
2 patent doesn't -- is supposed to be a teaching 19:03:28
3 that gives you a written description, and it gives 19:03:32
4 you a teaching that would enable you to, you know, 19:03:35
5 to do all the stuff. A data dump is not a 19:03:38
6 description, is not a teaching. 19:03:42

7 Q Because it provides no information? 19:03:44

8 A Sorry? 19:03:46

9 Q Because it provides no information? 19:03:47

10 A It provides information but no insight, no 19:03:49
11 guidance, right. That's what a data dump is. 19:03:51

12 Q Okay. I don't have any other questions. 19:03:56

13 MR. KUSHAN: Why don't we just take a 19:04:01
14 two-minute break, and we'll come back. 19:04:03

15 THE VIDEOGRAPHER: We are going off the 19:04:05
16 record. The time is 7:04 p.m. 19:04:07

17 (A recess was taken.) 19:07:38

18 THE VIDEOGRAPHER: We are back on the 19:07:38
19 record. The time is 7:07 p.m. 19:07:52

20 MR. KUSHAN: We have no questions. Thank
21 you.

22 MS. MARTIN: Wonderful.

1 THE VIDEOGRAPHER: We are going off the
2 record. The time is 7:08 p.m.

3 THE REPORTER: I want to grab transcript
4 orders.

5 MS. MARTIN: Oh, yeah. Expedited. So we
6 want, like, a rough today, if possible.

7 THE REPORTER: Sure. And the final
8 transcript?

9 MS. MARTIN: What's the quickest you can
10 do the final?

11 THE REPORTER: Thursday?

12 MS. MARTIN: Thursday sounds good.

13 THE REPORTER: Mr. Kushan?

14 MR. KUSHAN: Thursday.

15 (Off the record at 7:09 p.m.)
16
17
18
19
20
21
22

1 CERTIFICATE OF SHORTHAND REPORTER-NOTARY PUBLIC

2
3 I, Janet A. Hamilton, Registered Diplomate
4 Reporter and Notary Public within and for the
5 District of Columbia do hereby certify:

6 That MICHAEL HECHT, Ph.D., the witness whose
7 deposition is hereinbefore set forth, was duly
8 sworn by me before the commencement of such
9 deposition and that such deposition was taken
10 before me and is a true record of the testimony
11 given by such witness.

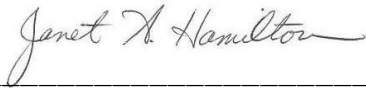
12 I further certify that the adverse party, Merck
13 Sharp & Dohme LLC, was represented by counsel at
14 the deposition.

15 I further certify that the deposition of
16 MICHAEL HECHT, Ph.D., occurred at the office of
17 Sidley Austin LLP, Washington, DC, on Tuesday,
18 August 26, 2025, commencing at 9:10 a.m. to 7:09
19 p.m.

20 I further certify the inspection, reading and
21 signing of said deposition was not discussed on
22 the record.

1 I further certify that I am not related to any
2 of the parties to this action by blood or
3 marriage, I am not employed by or an attorney to
4 any of the parties to this action, and that I am
5 in no way interested, financially or otherwise, in
6 the outcome of this matter.

7
8 IN WITNESS WHEREOF, I have hereunto set my hand
9 this 28th day of August, 2025.

10
11 
12 _____

13 My commission expires:

14 March 30, 2028

15 DISTRICT OF COLUMBIA
16
17
18
19
20
21
22

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