Transcript of Michael Hecht, Ph.D.

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

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

MERCK SHARP & DOHME LLC, : Case Nos.

Petitioner, : PGR2025-00003; 00004;

v. : 00006; 00009

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

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

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

Videotaped Deposition of MICHAEL HECHT, Ph.D.

Washington, DC

Tuesday, August 26, 2025

9:10 a.m.

Job No. 596628

Pages: 1 - 308

Reported by: Janet A. Hamilton, RDR

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22 ADAM SCHUMAN, Videographer

1 C O N T E N T S

2 EXAMINATION OF MICHAEL HECHT, Ph.D. PAGE

3 By Ms. Martin 9

4

5 E X H I B I T S

6 (Pre-marked and Retained by Counsel)

7 Exhibit 1003 58

8 Declaration of Michael Hecht, Ph.D.

9 PGR2025-00003

10 US Patent No. 11,952,600

11 Exhibit 1003 58

12 Declaration of Michael Hecht, Ph.D.

13 PGR2025-00004

14 US Patent No. 12,018,298

15 Exhibit 1003 58

16 Declaration of Michael Hecht, Ph.D.

17 PGR2025-00006

18 US Patent No. 12,152,262

19 Exhibit 1003 58

20 Declaration of Michael Hecht, Ph.D.

21 PGR2025-00009

22 US Patent No. 12,123,035

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

2 PAGE

3 Exhibit 1001 187

4 US Patent No. 11,952,600

5 Exhibit 1010 216

6 Paper by Ling Zhang: Hyaluronidase Activity

7 of Human Hyal1 Requires Active Site Acidic

8 and Tyrosine Residues

9 Exhibit 1013 228

10 Paper by Gregory Frost: Recombinant human

11 hyaluronidase: An enabling platform for

12 subcutaneous drug and fluid administration

13 Exhibit 1018 280

14 Paper by Roberto Chica: Semi-rational

15 approaches to engineering enzyme activity:

16 combining the benefits of directed evolution

17 and rational design

18 Exhibit 1059 287

19 Review Paper from Matti Leisola: Opportunities

20 and challenges

21

22

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

1 Katherine Helm from Dechert. 09:11:05
2 THE VIDEOGRAPHER: The court reporter 09:11:08
3 today is Jan Hamilton representing Planet Depos. 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 09:11:30
15 address for the record? 09:11:32
16 A I am Michael Hecht. Sometimes I use a 09:11:33
17 middle initial H. 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 09:11:43
21 Road, Skillman, New Jersey. 09:11:48
22 Q Are you employed? 09:11:50

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

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

other approaches, many based on AI. So there are 09:36:52
many approaches. That's all I'm trying to get 09:36:58
across is that it's not one answer. 09:37:01
Q And you mention that in your lab, you had 09:37:05
an approach where you generated combinatorial 09:37:09
libraries of sequences by patterning nonpolar and 09:37:13
polar residues, and that's because when you 09:37:16
pattern the nonpolar and polar residues, you can 09:37:18
generate sequences that will have alpha helices; 09:37:22
is that right? 09:37:27
A You can favor that structure. It doesn't 09:37:27
always work, right, so you can make such libraries 09:37:29
that are biased toward a particular outcome. 09:37:34
Doesn't always work. You have large collections. 09:37:39
Some succeed; some fail. 09:37:42
Q And then you would screen your library for 09:37:44
desired function and then test the resulting 09:37:47
protein? 09:37:49
A The original legwork was basically just 09:37:51
aimed at structure and asking: Do these things 09:37:54
fold at all, with no -- at the outset, no thought 09:37:58
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 A Correct. 10:39:19
2 Q You listed all of the materials you 10:39:22
3 considered in forming your opinions set forth in 10:39:25
4 your declaration for Matter 3 in the exhibit list 10:39:29
5 in your declaration; is that right? 10:39:32
6 A I listed items that were considered. 10:39:34
7 That's not a complete and exhaustive list, but 10:39:43
8 it's a list of things I considered. 10:39:45
9 Q Are there documents that you considered in 10:39:48
10 forming your opinion that are not listed on your 10:39:50
11 exhibit list? 10:39:53
12 A I mean, a whole career of documents. 10:39:54
13 Q Is it fair to say that all the documents 10:40:09
14 that are cited in your declaration are on your 10:40:11
15 exhibit list? 10:40:14
16 A I think so. I would -- you know, I don't 10:40:23
17 want to answer with absolute certainty without 10:40:26
18 going back and listing every one. But it looks 10:40:29
19 that way, yes. 10:40:34
20 Q And you executed your declaration in 10:40:35
21 Matter 3 on November 12, 2024; is that right? 10:40:37
22 A That's when I signed it, yes. 10:40:41

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 11:08:30
2 in a sequence alignment, how does that tell you 11:08:32
3 whether a potential mutation at that position -- 11:08:38
4 or the potential impact of a mutation at that 11:08:40
5 position? 11:08:43
6 MR. KUSHAN: Objection to form. 11:08:45
7 A So on page 109, it says, "The Skilled 11:08:49
8 Artisan Would Have Identified Non-Essential 11:08:52
9 Regions in PH20 and Suitable Amino Acid 11:08:55
10 Substitutions Using a Multiple Sequence Alignment 11:09:00
11 of Homologous Hyaluronidase Proteins." 11:09:03
12 So the discussion starts by identifying 11:09:06
13 non-essential regions. And as it says, "The 11:09:08
14 skilled artisan would have understood that these 11:09:17
15 non-essential regions to be regions between -- 11:09:19
16 between the conserved residues," (as read), okay, 11:09:22
17 in other words, not the conserved residues, okay. 11:09:26
18 The non-conserved residues would be deemed 11:09:30
19 as non-essential. And, therefore, if one is 11:09:32
20 considering making mutations, one would look for 11:09:37
21 these sequence alignments to assess what's 11:09:42
22 essential and what's not. 11:09:48

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 11:29:20
2 structures and sites of conserved amino acid in 11:29:24
3 both PH20 and HYAL1; correct? 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 11:29:35
6 your declaration identifies the secondary 11:29:40
7 structures and sites of conserved amino acids in 11:29:42
8 HYAL1, HYAL2, HYAL3, HYAL4, and PH20; is that 11:29:46
9 right? 11:29:51
10 A That's what the figure shows. 11:29:51
11 Q So the secondary structures in HYAL1, 11:29:53
12 HYAL2, HYAL3, HYAL4, and PH20 were all known as of 11:29:57
13 2011? 11:30:03
14 A As you pointed out, the crystal structures 11:30:03
15 of HYAL1 and bee venom, which is not shown on this 11:30:06
16 picture, those crystal structures were known. And 11:30:11
17 as we've discussed numerous times, one then models 11:30:14
18 other sequences based on those structures. 11:30:21
19 What's shown in this figure are the five 11:30:28
20 sequences, the conserved amino acids, the 11:30:33
21 cysteines and such things, the active site amino 11:30:39
22 acids.

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 12:08:24
2 above paragraph 82, but that whole part of the 12:08:32
3 declaration, pages 41 and pages 42, after Chao, et 12:08:37
4 al., solved that structure, published it, okay, 12:08:44
5 that's -- well, you can see that on the top of 12:08:47
6 page 41. 12:08:50
7 So by comparing the HYAL1 structure that 12:08:52
8 they had solved with the bee venom structure that 12:08:58
9 had been reported previously, these two similar 12:09:01
10 homologous proteins had structural similarity as 12:09:06
11 shown in the figure on page 41. 12:09:10
12 And then with those structures in hand, 12:09:12
13 paragraph 82 says they compared the catalytic 12:09:15
14 sites and found that they too show extensive 12:09:18
15 structural similarity. And that's shown in the 12:09:22
16 figure on page 41 and 42. 12:09:26
17 So those are catalytic sites. 12:09:32
18 Q And in the -- in Chao's alignment, which 12:09:37
19 is on page 43, the three key catalytic residues 12:09:43
20 are colored in red; is that right? 12:09:52
21 A Yeah. The legend says three key catalytic 12:09:55
22 residues are colored in red. But that does not 12:09:58

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

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

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."
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

never really studied them. 12:52:11

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

patent claim is? 12:52:14

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

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

I have some understanding. 12:52:20

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

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

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

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

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

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

their own. 12:52:48

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

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

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

Is that what you said? 12:53:11

A Yes. 12:53:13

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

claim conveys a property right? 12:53:19

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

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 12:59:10
2 have known about before this. 12:59:12
3 So in reading about the science and the 12:59:15
4 proteins, there's person of skill in the art using 12:59:17
5 their -- their skill in the art, thinking about 12:59:20
6 the text there. 12:59:23
7 But in terms of legal issues such as what 12:59:26
8 depends upon what, I needed guidance to understand 12:59:28
9 that. 12:59:32
10 Q And were there any steps that you followed 12:59:32
11 in your claim construction analysis besides 12:59:34
12 reading the claims? 12:59:37
13 A Without reading the claims? 12:59:39
14 Q Besides reading the claims. 12:59:41
15 A Oh, sorry, besides reading the claims. 12:59:43
16 I read the claims from the perspective of 12:59:53
17 somebody who spent half a century in a field of 12:59:56
18 protein sequence, protein engineering, protein 13:00:00
19 mutations. 13:00:05
20 And so, you know, as a person skilled in 13:00:06
21 the art, I read the text that's copied on page 62 13:00:09
22 from the perspective of somebody who spent a 13:00:13

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 14:25:14
2 would choose those and it would list those that 14:25:20
3 are active if it were trying to claim stuff that 14:25:23
4 were not active. 14:25:29
5 Why would it list those if it were trying 14:25:30
6 to do that? It focuses the reader's attention on 14:25:32
7 these, these mutations at 320, which it says in 14:25:38
8 the table, Table 9 on page 69, are good. They're 14:25:42
9 active. 14:25:47
10 And so it's -- the logic here is that the 14:25:47
11 body of the patent goes into great depth about 14:25:52
12 splitting the possible proteins into two classes: 14:25:59
13 Active and inactive. And then the claim focuses 14:26:03
14 on those -- four examples of those that in fact 14:26:06
15 have enhanced activity. And that, to my eye, 14:26:10
16 seems to be leading the reader, who would be, you 14:26:13
17 know, protein engineer, seems to be leading the 14:26:17
18 reader to make things that are active. 14:26:21
19 That's superimposed on what you were 14:26:25
20 referring to, the legal issues, where I've been 14:26:28
21 informed that legal issues say that you're -- that 14:26:30
22 patents should be directed at something that has 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, 14:41:42
2 that are degraded by the cell, that fail to 14:41:48
3 secrete, or even if they pass all of those bars, 14:41:52
4 they're going to misfold and aggregate. 14:41:56
5 So among the collection of sequences that 14:42:00
6 do not deliver high levels, or whatever level you 14:42:05
7 want to set of activity, they won't all be folded, 14:42:09
8 things that fail at catalysis, they will be lots 14:42:12
9 of other messy things. 14:42:17
10 And so for those reasons, it's hard for me 14:42:18
11 to fathom that a claim would include so many 14:42:22
12 different forms of things that are basically 14:42:30
13 useless garbage. 14:42:32
14 I mean, I've had a lot of useless garbage 14:42:34
15 in my life. I've seen that. You throw them away 14:42:38
16 pretty quickly. 14:42:41
17 Q Okay. So you interpret Claim 1 to require 14:42:42
18 hyaluronidase activity because even though the 14:42:46
19 literal scope, the literal language in Claim 1 14:42:49
20 covers PH20 polypeptides that meet the sequence 14:42:56
21 identity limitation and have the requisite change 14:43:00
22 at position 320, you require the claim to require 14:43:03

1 hyaluronidase activity because of -- in your view, 14:43:10
2 every single polypeptide that falls within the 14:43:16
3 scope of the claim needs to have some sort of 14:43:21
4 utility in order for the claim to be patentable? 14:43:23
5 MR. KUSHAN: Objection. Form. Objection 14:43:27
6 as to foundation. 14:43:29
7 A It's -- yeah, it's my understanding that 14:43:33
8 in order for the claim to be legitimate, it must 14:43:44
9 claim proteins that have utility because that 14:43:53
10 which doesn't have utility, I've been taught, is 14:43:58
11 not patentable. 14:44:03
12 Q Okay. So it's your understanding, from 14:44:05
13 counsel, that if the claim covers polypeptides 14:44:07
14 that do not have activity, the claim is invalid? 14:44:13
15 MR. KUSHAN: Objection. Foundation. 14:44:17
16 Objection as to form. 14:44:20
17 A As we said at the outset, my 14:44:32
18 interpretation of this is the claim is -- is 14:44:35
19 targeting those which are active because I think 14:44:38
20 that's how someone skilled in the art would read 14:44:41
21 it, because the claim goes to the effort of 14:44:44
22 starting with mutations at position 320 that 14:44:49

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 that contains at least one amino acid
2 modification --
3 THE REPORTER: Slow down, please.
4 A I'm sorry.
5 "As used herein, 'modified PH20 14:55:05
6 polypeptide' or 'variant PH20 polypeptide' refers 14:55:07
7 to a PH20 polypeptide that contains at least one 14:55:12
8 amino acid modification, such as at least one 14:55:16
9 amino acid replacement as described herein, in its 14:55:19
10 sequence of amino acids compared to a reference 14:55:23
11 unmodified PH20 polypeptide. A modified PH20 14:55:26
12 polypeptide can have up to 150 amino acids 14:55:31
13 replacements" -- emphasized -- "so long as the 14:55:36
14 resulting modified PH20 polypeptide exhibits 14:55:38
15 hyaluronidase activity." 14:55:41
16 Q Well, that didn't answer the question. 14:55:43
17 So the specification uses the term 14:55:45
18 modified PH20 polypeptide to refer to both active 14:55:47
19 and inactive PH20 polypeptides; yes, no, or I 14:55:51
20 don't know? 14:56:00
21 MR. KUSHAN: Objection as to form. 14:56:00
22 A I think we'd have to look at it. We'd 14:56:09

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 Objection as to form. 16:18:05
2 A I would say enough properties so that 16:18:14
3 someone of -- skilled in the art knows what it is 16:18:18
4 and how it's used. 16:18:21
5 And in the case of a -- of macromolecules 16:18:29
6 like this, you know, you'd want to sequence; you'd 16:18:34
7 want to know something about its secondary 16:18:37
8 structure, its tertiary structure, its activity, 16:18:39
9 its solubility, you know, its protein properties. 16:18:45
10 Q So in order to -- in order to invent, for 16:18:47
11 example, a PH20 polypeptide, would you have to 16:18:51
12 disclose a crystal structure? 16:18:56
13 A Have to what? 16:18:57
14 Q Disclose a crystal structure of PH20? 16:18:58
15 A Of a -- of a mutant? What -- 16:19:03
16 Q Of PH20 in general? 16:19:04
17 MR. KUSHAN: Objection. Foundation. 16:19:06
18 A You would have to know enough about it so 16:19:23
19 that one could understand what it is that's 16:19:27
20 approaching with such and such activity with such 16:19:29
21 and such uses. Whether you needed a crystal 16:19:32
22 structure or not, my assumption is that would have 16:19:40

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
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
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

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

one that was only 4 percent active. But for 16:41:03
academic studies, you might. 16:41:07
But if I were, you know, getting back to 16:41:08
these patents, I would say that 4 percent is not 16:41:12
something you'd want to pursue. 16:41:15
Q But if it's something that you might want 16:41:19
to pursue for academic studies, then, it has the 16:41:21
potential utility. Isn't that right? 16:41:25
MR. KUSHAN: Objection. Foundation. 16:41:27
A I -- okay. Let me restate that. For 16:41:30
academic studies, yes. If it's something that a 16:41:35
company sells for use in an academic lab as a 16:41:37
reagent, that's a use. That's not what I was 16:41:41
meaning. What I was meaning is in terms of basic 16:41:44
research and understanding and something that's 16:41:47
interesting, but I would say -- so let's be clear 16:41:49
about that. 16:41:51
So something of low activity -- if you 16:41:51
have a polymer such as hyaluronic acid, and you 16:41:54
want to degrade it in a laboratory, some company 16:41:59
might sell you a hyaluronidase that's only 5 16:42:02
percent as active as the natural one. And that 16:42:05

1 would be perfectly adequate. You would purchase 16:42:09
2 it and use it perhaps. 16:42:09
3 That's a different example of -- when I 16:42:11
4 say it's of academic interest, then I'm saying, 16:42:12
5 oh, it's intellectually interesting as I try and 16:42:18
6 tease apart which amino acids are doing what. I 16:42:20
7 might want this data for intellectual interests,
8 but I'm not using it for something. 16:42:25
9 Q So if a company were to sell, as a 16:42:28
10 reagent, the hyaluronidase that's only 5 percent 16:42:32
11 as active -- 16:42:35
12 A You say 5 percent, did you say? 16:42:35
13 Q Yes, 5 percent is active as wild-type, 16:42:37
14 that would still be a use; right? That would 16:42:40
15 still have utility? 16:42:42
16 A If a company were selling that as a 16:42:43
17 laboratory reagent. Is that what you're saying? 16:42:45
18 Q Yes. 16:42:48
19 A I would say that's a low-activity protein, 16:42:48
20 but it's not inactive. And that would be used. 16:42:51
21 That's why before I was so uncomfortable with 16:42:55
22 fixating on 40 percent. 16:42:56

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

A I know why. I'm looking for words to best 16:48:03
explain it. If you break something, it no longer 16:48:09
performs its function or its function is 16:48:27
diminished. If you break it simultaneously in 16:48:29
five places, then its function is more 16:48:33
dramatically diminished. 16:48:36
If you break a bone in your leg, you can 16:48:44
maybe hobble along. If you break five bones, you 16:48:47
won't. Sorry for the negative graphic, but yeah. 16:48:50
Q All right. So let's mark Exhibit 1013. 16:48:57
(Exhibit 1013 was introduced for
identification.)
Q Dr. Hecht, do you recognize Exhibit 1013? 16:49:23
A The Frost paper. 16:49:26
Q Yes. Do you recognize -- sorry, strike 16:49:27
that. 16:50:22
You relied on Exhibit 1013 in forming your 16:50:23
opinions in this case? 16:50:26
A I looked, yeah. I looked at the Frost 16:50:27
paper. That was part of my thinking about this 16:50:29
project, yeah. 16:50:31
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

A Yeah. I think that's a misuse of the word 17:27:27
structure, but it's often described that way. I 17:27:29
think the word structure, to my mind, connotes 17:27:31
three dimensions. 17:27:36
Q Do proteins have a chemical formula? 17:27:49
A Do proteins what? 17:28:07
Q Have a chemical formula? 17:28:08
A You can write a chemical formula. Sure. 17:28:10
It's not very interesting but you could add up all 17:28:13
the atoms and count how many carbons are there, 17:28:16
how many oxygens are there and so on. So you 17:28:19
could do that. 17:28:21
It's -- as I said, it's not very 17:28:22
interesting because, as I said, you could have 17:28:25
many different sequences with the same chemical 17:28:29
formula, same number of carbons and hydrogens and 17:28:31
nitrogens and oxygens and so on, but they're 17:28:35
completely different entities even though they 17:28:38
have the same formula. 17:28:39
People who do mass spectrometry are, you 17:28:45
know, might be concerned with the formula because 17:28:47
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 17:48:32
4 at single amino acid substitutions, where one 17:48:38
5 amino acid has replaced -- it has been replaced in 17:48:42
6 the context of an otherwise wild-type protein. 17:48:45
7 Q So are you saying that, in general, 17:48:51
8 knowledge about the tolerance of every single 17:48:56
9 position in PH20 is, in fact, useless? 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 17:49:05
13 useful. 17:49:07
14 Q And it's useful because it gives you 17:49:08
15 information about the extent to which each 17:49:09
16 position tolerates change and the extent -- and 17:49:12
17 the types of changes that each position may 17:49:17
18 tolerate? 17:49:20
19 MR. KUSHAN: Objection. Foundation. Also 17:49:20
20 objection as to form. 17:49:22
21 A It provides some insight about the 17:49:26
22 tolerance to substitution in the context of an 17:49:29

otherwise wild-type protein. 17:49:34

Q So you would agree that there are some 17:49:38

positions in the protein -- and, actually, just to 17:49:41

make sure that we're on the same page here, let's 17:49:45

look at your inactives table, which, again, starts 17:49:48

at page 142. 17:49:55

A Okay. 17:50:03

Q And the grayed-out positions -- and the 17:50:03

grayed-out, yeah, positions in your inactives 17:50:06

table, those are positions in which every single 17:50:09

substitution tested was active? 17:50:12

And if you would like to double-check that 17:50:14

for -- please go ahead, like, for example, 17:50:17

position 24. 17:50:19

A So in the example, position 24, let's go 17:50:21

back. That's what it looks like. Again, I'm 17:50:24

not -- you know, unless we go and test every 17:50:27

single one -- I don't want to commit to it, but 17:50:30

position 24, what you said -- 17:50:33

Q Yeah.

A -- is consistent. 17:50:34

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 18:07:45
4 percent? 18:07:50
5 A Confidence means -- well, it depends on 18:07:52
6 the parameter. Confidence in a structure -- am I 18:08:16
7 confident that it's correct plus or minus two 18:08:19
8 angstroms? Or am I confident that it's correct 18:08:22
9 plus or minus two-tenths of an angstrom? If the 18:08:25
10 issue is activity, am I confident that it's still 18:08:29
11 as active as the original, or am I confident that 18:08:32
12 it has more than one one-thousandth of the 18:08:35
13 activity? 18:08:39
14 It's not -- again, it's not binary; it's 18:08:39
15 not black and white. But the point is that as you 18:08:42
16 make -- as you attempt to make many 18:08:45
17 simultaneous -- as you attempt to make many 18:08:48
18 simultaneous mutations, the data that you had that 18:08:54
19 made you comfortable to make one mutation would 18:08:58
20 make you way less comfortable to make an abundance 18:09:02
21 of mutations because of issues like cooperativity 18:09:05
22 and because of issues that the structure is 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

about him in years, but, certainly, back when he 18:31:02
was -- yeah, he was -- he was a known -- yeah. 18:31:06
Q Okay. What about John Moult? Do you know 18:31:08
him? 18:31:15
A I know who he is, sure. 18:31:15
Q Is he a respected scientist? 18:31:17
A Yes. 18:31:18
Q Respected in the field? 18:31:19
A Sorry. Yes. Yeah. Sorry. I didn't hear 18:31:27
you. Yes. 18:31:29
Q Would you trust his work? 18:31:29
MR. KUSHAN: Objection. Foundation. 18:31:31
Objection as to form. 18:31:33
A It's a quirky question. I mean, with any 18:31:39
person, any author, any scientist, you don't want 18:31:47
to make a blanket statement like that. 18:31:51
But these were respected scientists, and I 18:31:54
would look at the work, and I would make my own 18:31:57
judgment. 18:32:02
Q What about Greg Petsko? 18:32:03
A He was on my thesis committee. I know who 18:32:07
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 18:41:01
2 contribution to function. 18:41:03
3 So the rational design approach has 18:41:04
4 limitations because it requires a great deal of 18:41:06
5 input to -- a great deal of very solid input as a 18:41:10
6 foundation for the rational design. 18:41:20
7 And he's highlighting that in many cases 18:41:22
8 that in-depth knowledge, that input, is 18:41:26
9 incomplete. And, therefore, the rational design 18:41:28
10 approach is challenging, irrespective of whether 18:41:30
11 we're talking about modified specificity in the 18:41:35
12 top line of this column or whether we're talking 18:41:37
13 about making mutations for the same specificity in 18:41:40
14 hyaluronidase. 18:41:44
15 Either way, rational design is -- is 18:41:44
16 challenged by whether -- by how much information 18:41:47
17 and how much understanding, you know, from the 18:41:49
18 structure, the physical chemistry, the 18:41:53
19 interactions by -- you know, your understanding is 18:41:55
20 incomplete, and so your rational design is 18:41:57
21 constrained by an incomplete understanding. 18:42:01
22 Q Okay. Let's mark Exhibit 1059. 18:42:03

1 (Exhibit 1059 was introduced for
2 identification.)
3 I'm not sure how you say his name, 18:42:24
4 Leisola? 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 18:42:32
9 answer that. 18:42:34
10 Q Okay. So in any event, Exhibit 1059 is a 18:42:35
11 paper that you considered in rendering your 18:42:38
12 opinion in this case; right? 18:42:39
13 A It's one of the ones listed in here, 18:42:40
14 right? 18:42:43
15 Q Yeah. 18:42:43
16 You cite it, for example, in Footnote 17 18:42:44
17 on page 21 in your declaration. 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 18:43:08
22 Exhibit 1059. 18:43:27

A Mm-hmm. 18:43:29
Q First full sentence: "At one end is an 18:43:30
approach commonly referred to as a rational 18:43:34
design, which aims to understand the principles of 18:43:37
protein structure and function well enough to 18:43:40
apply them in designing new properties or even 18:43:42
novel proteins using de novo design"; right? 18:43:45
A I see what you read, but I also want to 18:43:49
highlight the line before that, where they say 18:43:52
what I've been saying all day -- is that it's a 18:43:54
spec- -- is that it's a spectrum defined by two 18:43:57
extremes, right. It's a spectrum; it's not this 18:44:02
or that. It's a continuum. 18:44:05
Q So the continuum is what screening a 18:44:07
totally random library versus rationally selecting 18:44:09
the changes that you're going to make? I just 18:44:12
want to understand the continuum that you're 18:44:14
talking about. 18:44:17
MR. KUSHAN: Objection. Foundation. 18:44:18
A The continuum is at one extreme -- there 18:44:19
was a paper by Keith and Szostak -- Jack Szostak, 18:44:23
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

A Exactly. 18:58:48

So when Park went through the individual 18:58:49
amino acid substitutions that are on the last few 18:58:54
pages of each of my documents, it's a very, I 18:58:57
would say, erudite description of why this 18:59:05
mutation would likely be tolerated based on 18:59:09
sequence alignment, based on hydrogen bonds, based 18:59:12
on, you know, the model, the hydrogen bonds, the 18:59:17
accessible surface area, and all of that. 18:59:20

And so he's providing -- he's suggesting a 18:59:22
mutation and also providing an intellectual 18:59:26
underpinning for why that would work and thereby 18:59:31
guiding an expert in the field about what works 18:59:33
and what doesn't. 18:59:36

In contrast, the 5,000 or 6,000 things 18:59:39
listed in those tables are just lists with no 18:59:42
guidance about why something -- you know, you were 18:59:46
looking at before all these ones that failed to 18:59:49
work and all these ones that do work. There's no 18:59:51
guidance, right. There's nothing there. It 18:59:54
doesn't say whether, Oh, this works because, you 18:59:56
know, it's on the surface, whatever. 19:00:01

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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