Transcript of Dr. Sheldon Park

Date: August 7, 2025
Case: Merck Sharp & Dohme LLC -v- Halozyme Inc. (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3

4 MERCK SHARP & DOHME LLC,

5 Petitioner,

6 v.

7 HALOZYME INC.,

8 Patent Owner.

9 Case Nos. PGR2025-00003;

10 PGR2025-00004; PGR2025-00006;

11 PGR2025-00009

12 U.S. Patent No. 12,123,035

13

14 Videotaped Deposition of

15 DR. SHELDON PARK

16 Buffalo, New York

17 Thursday, August 7, 2025

18 8:45 a.m. EST

19

20 Job No.: 594918

21 Pages: 1 - 234

22 Reported By: Kadi A. Harmon

1 Deposition of DR. SHELDON PARK, held at
2 the offices of:
3
4 Hyatt Regency Buffalo
5 Two Fountain Plaza
6 Buffalo, NY 14202
7
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9
10 Pursuant to notice, before Kadi A. Harmon,
11 Court Reporter and Notary Public in and for the
12 State of New York.
13
14
15
16
17
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19
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21
22

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2
3 ALSO PRESENT:
4
5 Charlotte Forrest, Videographer
6 Raechel Meyerowich, Technician
7 Mark Stewart, Merck
8 Eric Majcherzak, Merck
9 Aubrey Hoddach, Halozyme
10 Joshua Mack, Halozyme
11 Dr. Michael Hecht
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C O N T E N T S

EXAMINATION OF DR. SHELDON PARK PAGE
By Attorney Martin 9

E X H I B I T S

(Attached to the Transcript.)

PARK DEPOSITION EXHIBIT PAGE
Exhibit 2068 Errata 27

PREVIOUSLY MARKED EXHIBITS

(Retained by Counsel.)

EXHIBIT PAGE
Exhibit 1004 PGR2025-00003 18
US Patent No. 11,952,600
Exhibit 1004 PGR2025-00004 18
US Patent No. 1,218,298
Exhibit 1004 PGR2025-00006 18
US Patent No. 12,152,262
Exhibit 1004 PGR2025-00009 19
US Patent No. 12,123,035
Exhibit 1054 BLAST Sequences 81
Exhibit 1057 Clustal Omega Alignment 81

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

2 THE VIDEOGRAPHER: Here begins Media 08:44:30

3 Number 1 in the videotaped deposition of 08:44:38

4 Dr. Sheldon Park, in the matter of Merck Sharp & 08:44:40

5 Dohme, LLC versus Halozyme Inc., in the United 08:44:45

6 States Patent and Trademark Office, before the 08:44:48

7 Patent Trial and Appeal Board; Case Numbers 08:44:50

8 PGR2025-00003, PGR2025-00004, PGR2025-00006, and 08:44:54

9 PGR2025-00009. 08:45:08

10 Today's date is Thursday, August 7th, 08:45:13

11 2025. The time on the video monitor is 8:45 a.m., 08:45:18

12 Eastern time. 08:45:22

13 The videographer today is Charlotte 08:45:22

14 Forrest representing Planet Depos. This video 08:45:25

15 deposition is taking place at Two Fountain Plaza, 08:45:25

16 Buffalo, New York, 14202. 08:45:31

17 Would Counsel please voice-identify 08:45:33

18 themselves and state whom they represent? 08:45:34

19 ATTORNEY MARTIN: Lauren Martin from Quinn 08:45:36

20 Emanuel on behalf of Patent Owner, and with me I 08:45:39

21 have Elliot Choi, also from Quinn Emanuel, and 08:45:42

22 Trey Powers, from Sterne Kessler. 08:45:50

1 ATTORNEY KUSHAN: Jeff Kushan from Sidney 08:45:50
2 Austin on behalf of Petitioner, Merck. With me is 08:45:55
3 Christine Engen. 08:45:55
4 Also, remotely we have attendees Kalen 08:45:56
5 Sullivan and Chelsea Himes from Sidney Austin, and 08:46:02
6 I believe Mark Stewart from Merck and Eric 08:46:05
7 Majcherzak from Merck, and you'll have to get a 08:46:12
8 spelling on the last one. 08:46:15
9 I think that's it for us. 08:46:17
10 Do you want to announce your remote 08:46:18
11 participants? 08:46:22
12 ATTORNEY MARTIN: Yeah. Can someone 08:46:22
13 announce the remote participants? 08:46:23
14 ATTORNEY ELLISON: I can do it. 08:46:32
15 This is Eldora Ellison from Sterne, 08:46:37
16 Kessler, Goldstein & Fox on behalf of Halozyme. 08:46:38
17 And it looks like we're joined by Zach Summers 08:46:39
18 from Quinn Emanuel, Aubrey Hoddach from Halozyme, 08:46:40
19 Josh -- Joshua Mack from Halozyme, and I think 08:46:44
20 that's it. Thank you. 08:46:48
21 ATTORNEY MARTIN: Thank you. 08:46:50
22 THE VIDEOGRAPHER: All right. Thank you, 08:46:50

1 Counsel. 08:46:52
2 The Court Reporter today is Kadi Harmon 08:46:52
3 representing Planet Depos. The witness will now 08:46:55
4 be sworn. 08:46:58
5 THE COURT REPORTER: Okay. Would you
6 raise your right hand, please?
7 THE WITNESS: Yes.
8 THE COURT REPORTER: Do you swear or
9 affirm that the testimony you provide today will
10 be the truth, the whole truth and nothing but the
11 truth? 08:47:13
12 THE WITNESS: I do. 08:47:13
13 THE COURT REPORTER: Thank you. 08:47:16
14 E X A M I N A T I O N 08:47:17
15 BY ATTORNEY MARTIN:
16 Q Good morning, Dr. Park. 08:47:18
17 A Good morning. 08:47:19
18 Q Can you please state your full name and 08:47:19
19 address for the record? 08:47:22
20 A Sheldon Park, at 4 Fawn Meadows Court, 08:47:22
21 Amherst, New York, 14068. 08:47:26
22 Q Where are you employed, Dr. Park? 08:47:28

1 A I am employed at the University at 08:47:30
2 Buffalo. 08:47:33
3 Q And how long have you been at the 08:47:33
4 University of Buffalo? 08:47:36
5 A I have been there since year 2006. 08:47:37
6 Q And what's your position at University of 08:47:40
7 Buffalo? 08:47:43
8 A I'm currently an associate professor of 08:47:44
9 chemical and biological engineering. 08:47:49
10 Q Do you have any interest in the outcome of 08:47:53
11 this litigation? 08:47:55
12 A No. I do not. 08:47:55
13 Q When were you first contacted about this 08:47:57
14 case? 08:47:59
15 A I was first contacted back in July 2024. 08:48:03
16 Q And do you recall who contacted you? 08:48:06
17 A Mr. Jeff Kushan contacted me. 08:48:09
18 Q Have you ever been deposed before? 08:48:14
19 A No. This is the first time. 08:48:16
20 Q So Dr. Park, if at any time during the 08:48:18
21 deposition you would like clarification on one of 08:48:26
22 my questions, please ask me for clarification, and 08:48:30

1 not your counsel. 08:48:33
2 A I will. 08:48:34
3 Q Thank you. 08:48:35
4 Dr. Park, do you understand that you 08:48:36
5 cannot discuss the substance of this deposition 08:48:40
6 with anyone until the deposition is over, 08:48:42
7 including during breaks? 08:48:46
8 A I understand that. 08:48:47
9 Q Thank you. 08:48:48
10 Your counsel may object to some of my 08:48:49
11 questions during the course of the deposition, but 08:49:00
12 you have to answer every question unless you're 08:49:02
13 instructed not to answer by your counsel. 08:49:05
14 Do you understand? 08:49:08
15 A Yes. I understand. 08:49:08
16 Q And if at any time you need to take a 08:49:09
17 break, just let me know and we can take a break. 08:49:13
18 But I do ask that if a question is pending, you'll 08:49:16
19 answer the question and then we can take a break. 08:49:19
20 A I understand. 08:49:22
21 Q All right. Have you collaborated with 08:49:22
22 Merck before in your -- in your career? 08:49:32

1 A No. I have not. 08:49:34
2 Q Has Merck funded any of your research? 08:49:35
3 A No. 08:49:43
4 Q Have you ever had any -- any type of the 08:49:44
5 relationship with Merck, other than this 08:49:55
6 litigation? 08:49:57
7 A No. 08:49:58
8 Q Do you know Dr. Michael Hecht? 08:49:58
9 A I don't know him personally. I know of 08:50:06
10 his name from his publication. I read his work. 08:50:10
11 That is the extent of my familiarity with 08:50:15
12 Dr. Hecht. 08:50:19
13 Q Have you ever collaborated with Dr. Hecht? 08:50:19
14 A He wrote a chapter for me in a book that I 08:50:23
15 was editing. 08:50:30
16 (Reporter clarification.) 08:50:32
17 Q Any other collaboration? 08:50:32
18 A No. 08:50:35
19 Q Did you speak with him about his book 08:50:36
20 chapter, or did you correspond with him about his 08:50:39
21 book chapter? 08:50:43
22 A I emailed him, invited him to contribute a 08:50:44

1 chapter, and he was nice enough to do that. 08:50:47
2 Q Why did you ask him to contribute the 08:50:47
3 chapter? 08:50:49
4 A Because he was an authority in the field. 08:50:50
5 Q Have you ever heard of the company 08:51:01
6 Alteogen? 08:51:05
7 A What company? 08:51:06
8 Q Alteogen. 08:51:08
9 A No, never. 08:51:10
10 Q Do you have any experience with 08:51:11
11 hyaluronidases? 08:51:27
12 A No. 08:51:28
13 Q Do you have experience with enzymes 08:51:29
14 generally? 08:51:34
15 A No. 08:51:34
16 Q Do you know how many human hyaluronidases 08:51:35
17 there are? 08:51:42
18 A Yes. I believe there are five versions of 08:51:45
19 hyaluronidases. 08:51:49
20 Q Do you know what they're called? 08:51:50
21 A Hyaluronidase 1 through 4, and PH20. 08:51:52
22 Q Do you know which ones cleave hyaluronic 08:51:58

1 acid? 08:52:04
2 A HYAL1 and 2, and PH20 are believed to be 08:52:04
3 hyaluronidases. HYAL4, I think is a -- got 08:52:10
4 something related, the name of which just escapes 08:52:20
5 me. And then Hyaluronidase 3, I don't think it 08:52:25
6 has a known activity. 08:52:34
7 (Reporter clarification.) 08:52:38
8 A Known enzymatic activity. 08:52:38
9 Q Have you done any work with PH20? 08:52:45
10 A No. 08:52:49
11 Q What's the function of PH20? 08:52:50
12 ATTORNEY KUSHAN: Objection. Form. 08:52:57
13 A PH20, based on my reading, is an enzyme 08:53:01
14 that cleaves hyaluronic acid. 08:53:06
15 (Reporter clarification.) 08:53:18
16 Q Do you know specifically how PH20 cleaves 08:53:18
17 hyaluronic acid, what the mechanism of action is? 08:53:26
18 A I read papers on that, so I have some 08:53:29
19 knowledge of it. 08:53:33
20 Q And did you read those papers in 08:53:34
21 connection with your work on this case? 08:53:38
22 A I did. 08:53:39

1 Q So outside of your work on this case, do 08:53:40
2 you have any -- strike that. 08:53:45
3 Before you started working on this case, 08:53:50
4 had you ever had any experience with PH20? 08:53:56
5 A No. 08:53:58
6 Q Before you started working on this case, 08:53:59
7 had you ever -- had you had any experience with 08:54:03
8 hyaluronidases? 08:54:08
9 A No. 08:54:09
10 Q Did you know how many human hyaluronidases 08:54:10
11 there were before you started working on this 08:54:14
12 case? 08:54:16
13 A No. 08:54:17
14 Q Did you know which human hyaluronidases 08:54:17
15 cleave hyaluronic acid before you started working 08:54:21
16 on this case? 08:54:26
17 A No. 08:54:27
18 Q So is it fair to say that all of your 08:54:27
19 hyaluronidase-related knowledge was learned in 08:54:31
20 connection with this case? 08:54:36
21 ATTORNEY KUSHAN: Objection to form. 08:54:37
22 A Much of what I know about hyaluronidase 08:54:43

1 comes from the reading that I initiated in 08:54:46
2 relation to this case. 08:54:52
3 Q Before you started working on this case, 08:55:05
4 had you examined any structures of hyaluronidase 08:55:08
5 proteins? 08:55:14
6 A No. 08:55:16
7 Q Before you started working on this case, 08:55:16
8 had you performed any sequence assignment analysis 08:55:19
9 for hyaluronidases? 08:55:26
10 A No. 08:55:26
11 Q Have you performed any structural analysis 08:55:30
12 on any other carbohydrate active enzyme? 08:55:39
13 ATTORNEY KUSHAN: Objection to foundation. 08:55:46
14 A Any carbohydrate enzymes? 08:55:47
15 Q Uh-huh. 08:55:52
16 A Yes. I was working on a project, 08:56:02
17 NIH-funded project. 08:55:58
18 Q And what enzyme was that? 08:55:59
19 A It was ST3GAL1. 08:56:14
20 (Reporter clarification.) 08:56:24
21 Q And what work did you do with ST3GAL1? 08:56:24
22 A It's an enzyme that transfers hyaluronic 08:56:26

1 acid to a glycan we were engineering. My -- my 08:56:30
2 collaborator and I were working on engineering 08:56:35
3 that enzyme into a glycan binding protein. 08:56:39
4 Q And did you succeed in transforming the 08:56:48
5 enzyme into a glycan binding protein? 08:56:54
6 A Yes. We did. 08:56:58
7 Q How did you do that? 08:56:59
8 A Combination of rational engineering and 08:57:01
9 directed evolution. 08:57:05
10 (Reporter clarification.) 08:57:15
11 Q And when -- when did you do that work? 08:57:15
12 A The work was funded around 2020. The 08:57:19
13 money might have started coming in 2021. I forget 08:57:27
14 the exact time. And for the last four or five 08:57:33
15 years, we've worked on it. 08:57:36
16 Q Have you done any work with any other -- 08:57:46
17 sorry. Strike that. 08:57:51
18 Have you done any work with glycoside 08:57:52
19 hydrolase enzymes? 08:57:58
20 ATTORNEY KUSHAN: Objection. Form. 08:58:01
21 A I have not worked with any other glycoside 08:58:03
22 hydrolase enzyme. 08:58:09

1 ATTORNEY MARTIN: I'm going to introduce 08:58:11
2 the declaration -- your four declarations for the 08:58:13
3 four PGRs that we're talking about. 08:58:17
4 These have been -- these are of record in 08:58:22
5 the cases, so the first one is Exhibit 1004 to 08:58:27
6 PGR2025-00003, regarding US Patent Number 08:58:35
7 11,952,600. 08:58:44
8 THE WITNESS: Okay.
9 (Previously marked Exhibit 1004 introduced
10 and retained by counsel.) 08:58:54
11 ATTORNEY MARTIN: All right. The second 08:58:54
12 one is Exhibit 1004 for PGR2025-00004, regarding 08:58:55
13 US Patent Number 1,218,298. 08:59:03
14 THE WITNESS: Okay. 08:59:10
15 (Previously marked Exhibit 1004 introduced
16 and retained by counsel.)
17 ATTORNEY MARTIN: The third is 08:59:11
18 Exhibit 1004 for PGR2025-00006, regarding US 08:59:12
19 Patent Number 12,152,262. 08:59:23
20 (Previously marked Exhibit 1004 introduced
21 and retained by counsel.) 08:59:27
22 ATTORNEY MARTIN: And then the fourth is 08:59:27

1 Exhibit 1004 for PGR2025-00009, regarding US 08:59:29
2 Patent Number 12,123,035. 08:59:39
3 (Previously marked Exhibit 1004 introduced
4 and retained by counsel.)
5 BY ATTORNEY MARTIN:
6 Q Dr. Park, are these four the declarations 08:59:45
7 that you submitted in support of each of the four 08:59:48
8 PGRs? 08:59:52
9 A Yes. They are the four declarations I 09:01:16
10 submitted. 09:01:19
11 Q And you signed each of those four 09:01:20
12 declarations, correct? 09:01:23
13 A I did sign them. 09:01:24
14 Q So you have -- you have papers with you. 09:01:26
15 Can you explain what that is? 09:01:33
16 A Oh, yeah. Absolutely. 09:01:34
17 I wanted to identify some minor errors -- 09:01:36
18 Q Okay.
19 A -- that came in. 09:01:39
20 Q Uh-huh.
21 A Should I give them to you first, or read 09:01:44
22 them to you? They're minor. 09:01:47

1 First one, which appears in 09:01:50
2 Paragraph 145(b) of the proceeding ending in 3, it 09:01:57
3 reads, somewhere in there, 134 rows. It should be 09:02:08
4 95 rows. 09:02:15
5 The reason that this error came in is 09:02:17
6 because initially the analysis was performed with 09:02:21
7 the sequences that were available by the end of 09:02:26
8 year 2012, December 2012. Afterwards, the 09:02:28
9 sequences were revised to end in December of 2011, 09:02:39
10 one year prior. As a result, the number of 09:02:49
11 sequences that were included in the sample was 09:02:54
12 reduced from 134 to 95. So that's what the first 09:02:58
13 errata indicates. 09:03:08
14 Q Okay. So to be clear, if you're on 09:03:08
15 Page 80 of the declaration for proceeding ending 09:03:11
16 in 3 -- 09:03:17
17 A Uh-huh. 09:03:19
18 Q -- it says -- there's a sentence that says 09:03:19
19 there were 134 rows, and you're saying that the 09:03:27
20 number 134 should instead read 95? 09:03:32
21 A That is correct. 09:03:34
22 Q Thank you. Okay. 09:03:35

1 A And the corresponding errors in the other 09:03:39
2 proceedings are, in the proceeding ending in 4, 09:03:42
3 Paragraph 151(b); proceeding ending in 006, 09:03:46
4 Paragraph 147(b); and the final proceeding ending 09:03:53
5 in 9, Paragraph 127(b), the substance of the error 09:03:57
6 is the same. 09:04:02
7 Q So in each of those cases, the -- there 09:04:02
8 were 134 rows should read there were 95 rows? 09:04:05
9 A That is correct. 09:04:07
10 Q Okay. 09:04:08
11 A The next error is a typo, which is in 09:04:10
12 paragraph -- they're all in the same paragraph of 09:04:18
13 all four proceedings, Paragraph 97. 09:04:25
14 It reads, currently: Position 374 in 09:04:30
15 PH20. 09:04:37
16 It should read: Position 372 in PH20. 09:04:38
17 That's a typographical error. 09:04:43
18 Paragraph 42 should read, instead of 09:04:47
19 isoforms of PH20, the correct terminology should 09:04:53
20 have been: Homologs of PH20. 09:05:00
21 (Reporter clarification.)
22 A Paragraph 12 -- 09:05:05

1 Q Sorry, what? Paragraph 42? 09:05:05
2 A 42. Yeah. 09:05:11
3 The last sentence of Paragraph 42 says: 09:05:23
4 At least four isoforms of PH20. 09:05:28
5 Q Oh, okay. Okay.
6 A Should read: Homologs of PH20. 09:05:31
7 Q Thank you. 09:05:36
8 A And Paragraph 12, that's the ending of 09:05:37
9 Paragraph 12. I believe just prior to the 09:05:43
10 parentheses should read, instead of structure, 09:05:48
11 structure relationship, should simply read: 09:05:53
12 Structure. 09:05:59
13 Q As well as with techniques and tools used 09:05:59
14 to analyze protein structure? 09:06:04
15 A That is correct.
16 Q Period.
17 A Period.
18 Q Or, actually, it's: Protein structure, 09:06:10
19 parentheses. 09:06:10
20 A That's correct. 09:06:11
21 Q Got it. 09:06:11
22 A There are errors unique to some of the 09:06:12

1 proceedings. 09:06:36
2 Proceeding ending in 03, Paragraph 109, it 09:06:16
3 lists a few amino acids in that paragraph. 09:06:23
4 109, yes. In the parentheses, it should 09:06:44
5 say: E31, P32 and D34, which is currently 09:06:51
6 missing. And L317, N321, E324. 09:06:57
7 Paragraph 100 in the same document also 09:07:06
8 lists several -- Paragraph 100, I think it should 09:07:20
9 have been in Paragraph 100. I don't see that. I 09:07:42
10 think the paragraph number is not correct. 09:07:49
11 Maybe I can -- I think that it should be 09:07:55
12 around -- let me see -- 109. So let me go there 09:08:00
13 and maybe I can find it. In fact, it's 09:08:04
14 Paragraph 110. 09:08:08
15 Q Oh, okay.
16 A Yeah. Not 100. 09:08:09
17 Q Okay. 09:08:11
18 A Yeah. In the -- in there, there's a 09:08:12
19 parentheses that ends in M323. M323 should not be 09:08:15
20 there. 09:08:24
21 Q Okay.
22 A So it ends in L319. 09:08:24

1 Okay. Appendix C in the same document, 09:08:30
2 Row Number 4, Column J, says: K320 has 9 09:08:39
3 neighbors. 09:08:45
4 It should read: K320 has 8 neighbors. 09:08:45
5 Moving on to the next document, proceeding 09:08:53
6 ending in 4, 004, Paragraph 134, typographical 09:08:57
7 error of 34. 09:09:07
8 It says: Glutamate at position 34. 09:09:12
9 It should say: Glutamate at position 31. 09:09:17
10 Oh, yes. Yes. Halfway through glutamate 09:09:32
11 at position 31.
12 (Reporter clarification.)
13 A Moving on to the next one. 09:09:53
14 Appendix C was cut off. It's a table of 09:09:54
15 evaluation. And in an Excel spreadsheet, it 09:09:59
16 should have been a wrap around, but the column got 09:10:04
17 cut off, so some of the words got left out. So 09:10:08
18 Appendix C -- yeah. 09:10:13
19 Okay. In this table, the column -- Row 09:10:28
20 Number 4, Column 1 -- I'm sorry -- Column I, not 09:10:34
21 Column 1, the comments column. 09:10:38
22 It should say: Hydrophobic contacts

1 to F64.
2 So that was left out. 09:10:45
3 Q Sorry. For which row? 09:10:45
4 A It says Row Number 4. 09:10:48
5 Q Number 4.
6 A Column I. The comments column, it says: 09:10:50
7 Hydrophobic contacts to --
8 (Reporter clarification.)
9 A Hydrophobic contacts to F64. 09:11:00
10 Appendix -- the same appendix, Row 09:11:05
11 Number 5 this time, the same column: Potential 09:11:08
12 charge repulsion. 09:11:13
13 Row Number 8: Hydrophobic contacts to 09:11:18
14 F64. 09:11:26
15 Row Number 10: Increased hydrophobic 09:11:26
16 contacts, hydrophobic exposed. 09:11:31
17 Row Number 11: Increased hydrophobic 09:11:36
18 contacts.
19 And finally, Row Number 13: Increased 09:11:39
20 hydrophobic contacts, Ncap. 09:11:45
21 So those are the minor errors I 09:11:49
22 identified. I wanted to bring them to your 09:11:54

1 attention. 09:11:56
2 Q Okay. Thank you. 09:11:57
3 Is that all the -- did we get all of them? 09:11:59
4 A Absolute yes.
5 Q Okay. Thank you. 09:12:01
6 ATTORNEY KUSHAN: Those are just copies. 09:12:01
7 Can I get one? 09:12:04
8 THE WITNESS: Okay. Absolutely. 09:12:05
9 ATTORNEY KUSHAN: Do you want to introduce 09:12:06
10 this as an exhibit? It's up to you. 09:12:08
11 ATTORNEY MARTIN: Yeah. Actually, that's 09:12:09
12 probably a good idea. 09:12:15
13 So Park Exhibit 1 will be the Errata. 09:12:17
14 ATTORNEY KUSHAN: Do you happen to know,
15 Trey, what the last exhibit... 09:12:23
16 ATTORNEY POWERS: 2037 [sic]. 09:12:23
17 ATTORNEY KUSHAN: So why don't we -- do 09:12:25
18 you want to do a --
19 ATTORNEY POWERS: Start at 2037. 09:12:29
20 ATTORNEY MARTIN: Okay. So 2037. 09:12:29
21 ATTORNEY KUSHAN: So this will be 2037. 09:12:30
22 ATTORNEY POWERS: Yeah.

1 (Park Deposition Exhibit 2068 marked for
2 identification and attached to the transcript.)
3 ATTORNEY KUSHAN: Can you just --
4 THE WITNESS: Oh, okay. Yeah. 09:13:18
5 BY ATTORNEY MARTIN: 09:13:18
6 Q So Dr. Park, can you turn to the exhibit 09:13:20
7 list for -- 09:13:23
8 A Exhibit list. 09:13:23
9 Q Well, I guess let's use the --
10 A Sure. 09:13:23
11 Q -- the one ending in 3. 09:13:24
12 So each of your declarations has an 09:13:28
13 exhibit list, correct? 09:13:31
14 A I believe so. Should I check? 09:13:32
15 I believe that they are the same. I see 09:13:46
16 exhibit list here. There we go, assuming they are 09:13:49
17 the same. 09:14:02
18 Yes. I see an exhibit list there too. 09:14:02
19 Q Okay. So there's an exhibit list in each 09:14:05
20 of the four declarations, correct? 09:14:08
21 A That is correct. 09:14:09
22 Q All right. And just as an example, you 09:14:10

1 can look at the exhibit list for PGR 3, and that's 09:14:13
2 on page -- starts on Page 99 of Exhibit 1004. 09:14:18
3 A Exhibit 1004?
4 Q Yes. 09:14:32
5 A 1004.
6 Q So that's the exhibit list? 09:14:34
7 A Yes. Yes. The declaration you mean. 09:14:35
8 Got it.
9 (Reporter clarification.) 09:14:40
10 Q So the exhibit list on -- you're at the 09:14:40
11 exhibit list on Page 99 of the declaration on 09:14:44
12 PGR 3? 09:14:46
13 A That is correct. I am. 09:14:47
14 Q All right. And Dr. Park, you listed all 09:14:49
15 of the materials you considered forming your 09:14:56
16 opinions in that declaration on your exhibit list, 09:14:59
17 correct? 09:15:03
18 ATTORNEY KUSHAN: Objection. 09:15:04
19 A Yes. 09:15:07
20 ATTORNEY KUSHAN: Sorry. 09:15:08
21 Objection. Foundation. 09:15:11
22 Go ahead.

1 A Yes. I included the references that I 09:15:12
2 read in preparation for this declaration. 09:15:13
3 Q Did you include all of the materials that 09:15:17
4 you considered in forming your opinions on your 09:15:19
5 exhibit list? 09:15:22
6 A I did. 09:15:27
7 Q Now your declaration in matter PGR 3, if 09:15:28
8 you go to the cover page for that declaration, you 09:15:47
9 see it says: Case Number PGR 2025-3, and then 09:15:51
10 under that, there's a patent number, US Patent 09:15:56
11 Number 11,952,600. 09:16:17
12 Do you see that? 09:16:05
13 A I see the patent number, yes. 09:16:05
14 Q Are you familiar with the '600 patent? 09:16:08
15 A No. I'm not familiar with this patent. 09:16:11
16 Q Have you ever seen the '600 patent? 09:16:13
17 A No. I have not seen this patent. 09:16:19
18 Q Did you consider the '600 patent in 09:16:21
19 forming your opinions for this matter? 09:16:25
20 A No. I did not. 09:16:27
21 Q Did -- as part of your analysis in this 09:16:33
22 case, did you go and look up the '600 patent? 09:16:35

1 A No. I did not look up the patent '600. 09:16:39
2 Q Have you ever read a patent? 09:16:43
3 A I read a patent that's listed in the 09:16:47
4 exhibit list for the first time. 09:16:51
5 Q And that patent is the '429 patent; is 09:16:54
6 that right? Exhibit 1005, US Patent Number 09:17:01
7 7,767,429? 09:17:09
8 A That's correct. '429 patent. 09:17:09
9 Q Is the '429 patent the first patent you 09:17:12
10 ever read? 09:17:15
11 A That is the first patent that I've ever 09:17:15
12 read. Yeah. 09:17:18
13 Q Okay. 09:17:19
14 A Except for my own patent, come to think of 09:17:31
15 it. 09:17:35
16 Q Uh-huh.
17 A It was so long ago I forgot about it. The 09:17:36
18 patent was prepared by the lawyers, and I think I 09:17:39
19 read -- I wouldn't say I read the final patent, 09:17:44
20 but whatever was prepared at some point along the 09:17:50
21 process, I was involved in drafting that patent, 09:17:55
22 so you could say that might count as a patent. 09:18:04

1 Q Do you know if it issued as a patent? 09:18:10
2 A Say it again? 09:18:15
3 Q Do you know if your patent issued? 09:18:16
4 A Oh. It was issued, yes. 09:18:18
5 Q All right. But you don't know if you've 09:18:19
6 seen the issued patent? 09:18:20
7 A I have seen it, but I haven't read it. 09:18:20
8 Q Okay.
9 A It was good enough to know that I was 09:18:23
10 granted a patent. 09:18:26
11 Q Understood. 09:18:27
12 All right. So is it fair to say that the 09:18:28
13 only issued patent that you've ever read is the 09:18:32
14 '429 patent? 09:18:35
15 A That is correct, yes. 09:18:37
16 Q Did you -- do you know what's claimed in 09:18:50
17 the '600 patent? 09:18:57
18 A I understand it's about a mutation in a 09:19:03
19 protein, which I assume is PH20. But that's about 09:19:09
20 it. 09:19:15
21 Q Have you ever seen the patent claims for 09:19:15
22 the '600 patent? 09:19:19

1 A No. I have not. 09:19:20
2 Q Do you know what's disclosed in the 09:19:21
3 specification for the '600 patent? 09:19:25
4 A No. 09:19:27
5 Q Do you know -- do you have any idea of 09:19:28
6 anything that's disclosed in the '600 patent? 09:19:31
7 A No. 09:19:35
8 Q When you read the '429 patent, did you 09:19:35
9 read the claims? 09:19:46
10 A Can I get a copy of the '429 patent to see 09:19:50
11 where the claim is listed? 09:19:54
12 Q Sure. 09:19:57
13 So while we wait for the '429 patent, you 09:20:36
14 cited everything that you considered in forming 09:21:03
15 your opinions in your declaration, correct? 09:21:05
16 A I cited all the references that I felt 09:21:10
17 relevant to the declaration, yes. 09:21:15
18 Q And if something was, in your opinion, 09:21:16
19 relevant to your analysis, then you would have 09:21:19
20 cited -- cited it in the declaration, correct? 09:21:22
21 A I would have cited any relevant 09:21:25
22 references. 09:21:30

1 Q So if there's a reference that's not cited 09:21:30
2 in your declaration, is it fair to assume that 09:21:33
3 that reference is not relevant to your analysis? 09:21:36
4 ATTORNEY KUSHAN: Objection. Form. 09:21:38
5 A I would have felt that that reference was 09:21:40
6 not directly relevant to my declaration. 09:21:44
7 Q All right. And so just quickly looking at 09:21:50
8 the other -- your other three declarations, so the 09:21:53
9 declaration for matter 4, do you see on the cover 09:21:59
10 page, it references US Patent Number 12,018,298? 09:22:05
11 So do you understand that your declaration 09:22:11
12 in PGR matter 4 was submitted with respect to the 09:22:16
13 proceeding concerning the '298 patent? 09:22:20
14 A That seems reasonable. 09:22:24
15 Q Have you ever seen the '298 patent? 09:22:26
16 A No. I have not. 09:22:31
17 Q Did you consider the '298 patent in 09:22:32
18 forming your opinions in PGR matter 4? 09:22:40
19 A No. I have not. 09:22:42
20 Q Do you know what's claimed in the '298 09:22:43
21 patent? 09:22:48
22 A I believe it's a mutation on a protein, 09:22:48

1 again probably PH20. Other than that, I'm not 09:22:55
2 familiar with the content of that patent. 09:22:58
3 Q Do you know what's disclosed in the '298 09:23:01
4 patent? 09:23:05
5 A No. I don't. 09:23:05
6 Q And then PGR -- your declaration in PGR 09:23:12
7 matter 6, on the cover page, lists US Patent 09:23:18
8 Number 12,152,262. 09:23:24
9 So do you understand that your declaration 09:23:27
10 in PGR matter 6 was submitted proceeding 09:23:30
11 concerning the '262 patent? 09:23:35
12 A It appears that way. 09:23:38
13 Q Have you ever seen the '262 patent? 09:23:39
14 A I have not seen that patent, '262. 09:23:44
15 Q Do you know what's claimed in the '262 09:23:47
16 patent? 09:23:50
17 A Again, I'm assuming it's a mutation on a 09:23:54
18 protein, PH20 perhaps. That's the extent of my 09:23:58
19 assumption. 09:24:03
20 Q So you don't know for sure. You're 09:24:04
21 just -- you're assuming that there's a mutation on 09:24:07
22 PH20 that's claimed? 09:24:11

1 A I do not know that for sure. I've never 09:24:12
2 seen the patent, so I don't know what's claimed in 09:24:17
3 it. 09:24:21
4 Q Did you ask for the patent when you were 09:24:21
5 performing your analysis? 09:24:24
6 A No. I did not. 09:24:28
7 Q Did you think that the patent was relevant 09:24:29
8 to your analysis? 09:24:31
9 A No. I didn't think so. 09:24:34
10 Q So you don't know what's disclosed in the 09:24:38
11 '262 patent? 09:24:41
12 A I don't know what's disclosed in that 09:24:42
13 patent. 09:24:44
14 Q All right. And then finally, your 09:24:50
15 declaration in PGR matter 9 lists US Patent Number 09:24:52
16 12,123,035. 09:25:02
17 So do you understand that your declaration 09:25:05
18 in PGR matter 9 was submitted with respect to the 09:25:07
19 '035 patent? 09:25:12
20 A That's my reading of it. 09:25:17
21 Q Have you ever seen the '035 patent? 09:25:18
22 A No. I have not seen the patent '035. 09:25:23

1 Q Do you know what's claimed in the '035 09:25:27
2 patent? 09:25:30
3 A Perhaps a mutation on PH20. 09:25:31
4 Q But you don't know for sure? 09:25:35
5 A I don't know it for sure. 09:25:37
6 Q And do you know what's disclosed in the 09:25:38
7 '035 patent? 09:25:42
8 A No. I don't know what's disclosed in that 09:25:42
9 patent. 09:25:46
10 Q All right. Dr. Park, do you know what a 09:25:47
11 patent claim is? 09:26:13
12 A Only in a lay term. 09:26:15
13 Q And what's your lay understanding of what 09:26:18
14 a patent claim is? 09:26:20
15 A You make a discovery, and you take 09:26:22
16 ownership of that discovery, and the government 09:26:26
17 gives you some authority, claims, for that 09:26:31
18 discovery over other people. 09:26:37
19 Q Do you know what a -- what the terms -- 09:26:42
20 strike that. 09:26:46
21 Have you ever interpreted a patent claim? 09:26:47
22 A No. I have not. 09:27:01

1 Q Okay. Do you understand that trial has 09:27:02
2 been instituted in the four PGRs that we're 09:27:14
3 talking about today? 09:27:17
4 A No. 09:27:20
5 Q Okay. Have you seen the institution 09:27:21
6 decision for any of those -- any of these PGRs? 09:27:24
7 A What do you mean by institution decision? 09:27:28
8 Q It's a decision that was issued by the 09:27:31
9 Patent -- by the PTAB? 09:27:35
10 A By the patent? 09:27:38
11 Q By the Patent Office? 09:27:40
12 A By the Patent Office. 09:27:42
13 What did they issue? 09:27:44
14 Q It's called an institution decision. 09:27:46
15 A And what does the -- what does the 09:27:49
16 decision say? 09:27:51
17 Q I'm just asking if you've seen it. 09:27:51
18 A Oh, no. I've -- I have not seen it. 09:27:54
19 Q Okay. All right. 09:27:56
20 Okay. So Dr. Park, in your work, have you 09:28:22
21 attempted to predict the impact of substitutions 09:28:26
22 on protein function? 09:28:32

1 ATTORNEY KUSHAN: Objection. Form. 09:28:34
2 A In what work are you referring to? 09:28:35
3 Q Your work outside of this case. Just 09:28:37
4 your -- in your career. 09:28:40
5 A In my career? 09:28:42
6 Q Uh-huh. 09:28:44
7 A Yes. 09:28:44
8 Q Can you estimate how many -- for how many 09:28:47
9 proteins you've done this type of analysis, where 09:28:55
10 you're trying to impact -- predict the impact of 09:29:01
11 substitutions on protein function? 09:29:05
12 ATTORNEY KUSHAN: Objection. Form. 09:29:07
13 A The total number of proteins that I have 09:29:11
14 ever worked on? Is that what you're asking? 09:29:14
15 Q Yes. 09:29:17
16 A In my career? 09:29:18
17 Q Yes. 09:29:24
18 A I would say 10. 09:29:27
19 Q And what types of proteins were those 09:29:32
20 proteins that you worked on? 09:29:42
21 What was the function? 09:29:45
22 ATTORNEY KUSHAN: Objection. Form. 09:29:47

1 A They vary. They include binders, small 09:29:49
2 molecule binders, antibody, small proteins that 09:29:57
3 bind other proteins. 09:30:05
4 Q Anything else? 09:30:10
5 A Protein that binds DNA. Protein that 09:30:13
6 binds carbohydrate. I think that's it. 09:30:19
7 Q And what kind of work have you done on 09:30:35
8 antibodies? 09:30:38
9 A I use directed evolution to engineer an 09:30:43
10 antibody that binds an antigen in a pH dependant 09:30:49
11 manner. 09:30:57
12 Q When you say you used directed evolution, 09:31:02
13 do you mean that you screened a library of 09:31:07
14 antibodies to identify antibodies that had the 09:31:12
15 desired pH dependant binding profile? 09:31:15
16 ATTORNEY KUSHAN: Objection. Foundation. 09:31:17
17 A That is exactly what I did. 09:31:20
18 Q Okay. How did you generate -- or, sorry. 09:31:45
19 Strike that. 09:31:49
20 Did you generate the library of antibodies 09:31:49
21 that you screened? 09:31:51
22 A How did I generate the library? 09:31:51

1 Q Well, did you generate the library? 09:31:53
2 ATTORNEY KUSHAN: Objection. Foundation. 09:31:56
3 A We constructed the library ourselves. 09:32:00
4 Q And how -- 09:32:03
5 A My students and I. 09:32:05
6 Q And how did you construct the library? 09:32:07
7 What -- I'll ask a better question. 09:32:14
8 What -- strike that. 09:32:15
9 Did you introduce specific mutations into 09:32:25
10 sequences when you generated the library, or was 09:32:43
11 it just a random library of antibodies? 09:32:46
12 ATTORNEY KUSHAN: Objection. Form. 09:32:51
13 Objection to foundation. 09:32:52
14 A It was a combination of both. 09:32:53
15 Q Okay. In the analysis that you performed 09:33:34
16 in these matters, you used several different 09:33:37
17 computational tools, correct? 09:33:43
18 A I used tools that involved computation in 09:33:46
19 the back -- background, yes. 09:33:52
20 Q And you -- specifically, you used PyMol, 09:33:54
21 SWISS-MODEL, Clustal Omega and BLAST; is that 09:33:58
22 right? 09:34:05

1 A Those were the four major tools and web 09:34:05
2 services I used. 09:34:12
3 Q Are there any other computational tools 09:34:13
4 that you used in your analysis for these PGRs? 09:34:17
5 A No. 09:34:20
6 Q And were all four of these tools known in 09:34:21
7 2011? 09:34:25
8 A They were well-known, and widely used. 09:34:29
9 Q In your work in the 2011 time frame, were 09:34:33
10 you using programs like PyMol, SWISS-MODEL, 09:34:49
11 Clustal Omega and BLAST? 09:35:02
12 A I was using them actively, yes. 09:35:03
13 Q Were there other computational tools that 09:35:08
14 were in use in the 2011 time frame that are 09:35:15
15 similar to PyMol, SWISS-MODEL, Clustal Omega and 09:35:20
16 BLAST? 09:35:25
17 ATTORNEY KUSHAN: Objection. Form. 09:35:26
18 And objection. Foundation. 09:35:28
19 A Are there alternative tools? 09:35:31
20 Q Yes. 09:35:34
21 A For some of them, there were alternative 09:35:35
22 tools. 09:35:44

1 Q And what are some examples of alternative 09:35:45
2 tools that were available in 2011? 09:35:48
3 A For instance, PyMol, which is a molecular 09:35:55
4 viewer. There was software, and even today there 09:36:00
5 is that software, that was written out of use in 09:36:05
6 San Francisco, Chimera, which does very similar 09:36:10
7 work as PyMol. 09:36:17
8 Q What about Coot? Was that available? 09:36:19
9 A Coot is a much more advanced tool used in 09:36:24
10 molecular modeling, determining X-ray crystal 09:36:31
11 structure. It's a more niche application compared 09:36:40
12 to PyMol or Chimera. 09:36:43
13 Q But in 2011, Chimera, PyMol and Coot were 09:36:43
14 all available? 09:36:56
15 A Yes. 09:36:56
16 Q And SWISS-MODEL is a -- strike that. 09:36:56
17 Were there alternatives to SWISS-MODEL 09:37:04
18 that were available in 2011? 09:37:09
19 A Yes. There were alternatives. 09:37:13
20 Q What were those? 09:37:16
21 A MODELLER, for instance. Perhaps Rosetta. 09:37:19
22 (Reporter clarification.) 09:37:33

1 Q Any others? 09:37:33
2 A There might have been. I don't remember. 09:37:35
3 Q In your work in 2011, were you using 09:37:38
4 structure prediction programs like SWISS-MODEL? 09:37:44
5 ATTORNEY KUSHAN: Objection. Form. 09:37:50
6 A Prior to 2011, I had used SWISS-MODEL. 09:37:55
7 Not in the year of 2011. 09:38:01
8 Q Okay. In that time frame, had you used 09:38:03
9 MODELLER? 09:38:10
10 A No. I did not use MODELLER. 09:38:12
11 Q And what about Rosetta? Did you use 09:38:15
12 Rosetta in that time frame? 09:38:18
13 A No. 09:38:21
14 Q How does SWISS-MODEL compare with MODELLER 09:38:23
15 and Rosetta? 09:38:30
16 ATTORNEY KUSHAN: Objection. Form. 09:38:31
17 A SWISS-MODEL is a web service, as opposed 09:38:33
18 to Rosetta and MODELLER that you need to run at 09:38:38
19 the command line. So one would have to be much 09:38:42
20 more sophisticated to be able to use them. 09:38:45
21 And they also required licensing 09:38:48
22 sometimes. Even if it's an academic licensing, 09:38:50

1 you would have to sign a form. So there was a lot 09:38:54
2 more involved in launching those programs, and not 09:38:57
3 many people had the -- the resources or the 09:39:01
4 capability to do it. 09:39:03
5 Q So is that why you used SWISS-MODEL as 09:39:05
6 opposed to MODELLER or Rosetta? 09:39:16
7 A That is correct. 09:39:17
8 Q And in the 2011 time frame, in your work 09:39:18
9 were you using PyMol? 09:39:22
10 A Yes. I was. 09:39:25
11 Q Did you use Chimera or Coot in that time 09:39:26
12 frame? 09:39:39
13 A I used Chimera sometimes, but in the end 09:39:39
14 we decided to go with PyMol because it was easier 09:39:46
15 to work with. 09:39:51
16 Q And do you have any experience with Coot? 09:39:59
17 A I have never used Coot. 09:40:03
18 Q Have you ever solved a protein crystal 09:40:13
19 structure? 09:40:17
20 A I solved a crystal structure in 09:40:21
21 collaboration with a crystallographer. 09:40:27
22 Q So -- 09:40:33

A Two structures. 09:40:33
Q Two structures?
A To be precise. 09:40:35
Q So and what was your involvement in 09:40:36
solving those structures? 09:40:40
A I made the protein, purify the protein, 09:40:41
and provide the protein to the crystallographer so 09:40:47
that they could crystalize and determine the 09:40:54
structure. And at the end, I interpreted the 09:40:58
structure and wrote the paper. 09:41:01
Q But you didn't actually -- you interpreted 09:41:03
the -- you interpreted the model once the 09:41:10
structure was solved; is that right? 09:41:12
ATTORNEY KUSHAN: Objection. Foundation. 09:41:14
A Once the structure has been determined by 09:41:16
the crystallographer, I interpreted it, compared 09:41:21
with the prediction, and ultimately wrote the 09:41:27
paper, which got published, as me as the leading 09:41:34
author. 09:41:43
(Reporter clarification.) 09:41:45
Q And what proteins were those when you were 09:41:45
involved in solving the structure? 09:41:49

1 A One is FK-506 binding protein. The second 09:41:52
2 is monomeric streptavidin. 09:42:00
3 Q And the papers that you wrote in 09:42:08
4 connection with those -- sorry. Strike that. 09:42:11
5 The papers that were published in 09:42:14
6 connection with that work, are those on your CV? 09:42:18
7 A Yes. They are. 09:42:22
8 ATTORNEY MARTIN: So we've probably been 09:42:27
9 going for an hour. Do you want to take a short 09:42:30
10 break? 09:42:34
11 THE WITNESS: Sounds great. 09:42:35
12 THE VIDEOGRAPHER: We are going off the 09:42:38
13 record. The time is 9:42 a.m. 09:42:40
14 (Recess from 9:42 a.m. until 9:54 a.m.) 09:42:44
15 THE VIDEOGRAPHER: We are back on the 09:54:23
16 record. The time is 9:54 a.m. 09:54:24
17 BY ATTORNEY MARTIN: 09:54:28
18 Q Welcome back, Dr. Park. 09:54:29
19 So in the 2011 time frame, had you used 09:54:31
20 the SWISS-MODEL program to predict protein 09:54:36
21 structure? 09:54:41
22 ATTORNEY KUSHAN: Objection. Form. 09:54:41

1 A Predict a protein structure? I used 09:54:45
2 SWISS-MODEL to model a protein. Predict might be 09:54:50
3 a little over -- an overstatement. 09:54:57
4 Q Okay. Let me ask a more clear question 09:54:59
5 then. 09:55:03
6 So in the 2011 time frame, had you used 09:55:04
7 the SWISS-MODEL program to model a protein 09:55:08
8 structure? 09:55:12
9 A Yes. I have. 09:55:12
10 Q Okay. So can you turn in your declaration 09:55:13
11 for the matter 3 case? 09:55:30
12 A Which one? 09:55:32
13 Q The one that you have opened right there. 09:55:33
14 A Yes. 09:55:37
15 Q So Paragraph 12, which is on Page 3. 09:55:37
16 A Yes. 09:55:53
17 Q And you said: Counsel for Merck provided 09:55:54
18 the following description of a person of ordinary 09:55:58
19 skill of the art in the 2011 time frame for you to 09:56:04
20 evaluate; is that right? 09:56:10
21 A Yes. 09:56:12
22 Q And your -- the definition that you 09:56:12

1 provided: A person of ordinary skill in the art 09:56:14
2 in the 2011 time frame would have had an 09:56:17
3 undergraduate degree, a Ph.D., and postdoctoral 09:56:20
4 experience in scientific fields relevant to the 09:56:24
5 study of protein structure and function, e.g., 09:56:27
6 chemistry, biochemistry, biology, biophysics. 09:56:28
7 From training and experience, the person would 09:56:33
8 have been familiar with factors influencing 09:56:34
9 protein structure, folding inactivity, production 09:56:36
10 of modified proteins, using recombinant DNA 09:56:41
11 techniques, and use of biological assays to 09:56:44
12 characterize protein function, as well as 09:56:49
13 techniques and tools used to analyze protein 09:56:49
14 structure, i.e., sequence searching and 09:56:52
15 alignments, protein modeling software, et cetera; 09:56:55
16 is that right? 09:56:59
17 A That's correct. That was the description 09:57:00
18 provided by counsel. 09:57:03
19 Q Okay. And so throughout this deposition, 09:57:05
20 I'm going to use the term POSA to refer to person 09:57:08
21 of ordinary skill in the art. 09:57:15
22 A Okay. 09:57:17

1 Q Okay. In the 2011 time frame, were you a 09:57:17
2 person of ordinary skill in the art? 09:57:22
3 Did you meet this definition? 09:57:26
4 A In the year 2011, I was a POSA, yes. 09:57:29
5 Q And so in the 2011 time frame, a POSA 09:57:33
6 could have used the SWISS-MODEL program to model a 09:57:42
7 protein structure; is that right? 09:57:46
8 A That is correct. 09:57:47
9 Q And in the 2011 time frame, a POSA also 09:57:47
10 could have used MODELLER and Rosetta to model a 09:57:50
11 protein structure; is that right? 09:57:57
12 A If we say a POSA is a person of ordinary 09:57:59
13 skill, I do not think it would be reasonable to 09:58:05
14 expect a POSA to be able to use other software 09:58:10
15 that I mentioned earlier, including MODELLER or 09:58:14
16 Rosetta. 09:58:18
17 Q And is that because you would have to get 09:58:19
18 a license to use those programs, and the POSA 09:58:21
19 wouldn't necessarily have a license? 09:58:26
20 A No. The learning curve would have been 09:58:28
21 very steep. 09:58:32
22 Q Oh. Okay. They're just more 09:58:32

1 technically -- 09:58:34
2 A Highly more -- 09:58:36
3 Q Okay.
4 A -- advanced. 09:58:38
5 Q Okay. So in your view, the POSA could 09:58:38
6 have used SWISS-MODEL, but not necessarily 09:58:41
7 MODELLER or Rosetta? 09:58:45
8 A That is correct. 09:58:48
9 Q Okay. Thanks. 09:58:49
10 All right. And then in the 2011 time 09:58:51
11 frame, had you used Clustal Omega for sequence 09:59:12
12 alignments? 09:59:17
13 A I did. 09:59:17
14 Q And the skilled person, or POSA, in 2011 09:59:17
15 could have used Clustal Omega to perform a 09:59:25
16 sequence alignment, correct? 09:59:28
17 A That's correct. 09:59:28
18 Q Were there other programs that the POSA 09:59:29
19 could have used in the 2011 time frame to run 09:59:34
20 sequence alignments? 09:59:38
21 A There were other sequence alignment 09:59:41
22 programs out there, but most of them were esoteric 09:59:46

1 in a way, not well-known. A person who 09:59:55
2 specializes in bioinformatics might know the 10:00:00
3 advantages of using different programs. But a 10:00:05
4 POSA would not be in a position to compare and 10:00:10
5 contrast different programs to see if there is a 10:00:14
6 benefit in using other program. And as such, they 10:00:18
7 would have used something like Clustal Omega as 10:00:24
8 opposed to other algorithms. 10:00:28
9 Q Okay. And would the skilled person have 10:00:30
10 been able to use BLAST to identify homologous 10:00:41
11 sequences in the 2011 time frame? 10:00:46
12 A A POSA would have been able to use BLAST 10:00:50
13 to find homologous sequences, yes. 10:00:55
14 Q Were there any other tools that a POSA 10:01:00
15 could have used in the 2011 time frame to identify 10:01:05
16 homologous sequences for alignment besides BLAST? 10:01:10
17 A I haven't used any other program besides 10:01:14
18 BLAST personally. I would think that there might 10:01:19
19 have been, but I'm not aware of any particular one 10:01:23
20 that would be equally versatile as BLAST, and an 10:01:26
21 ordinary person, a person of ordinary skill, would 10:01:36
22 have chosen BLAST as a search tool as opposed to 10:01:40

1 any other tools out there. 10:01:46
2 Q How many times in your career would you 10:01:49
3 say you've used SWISS-MODEL to generate a homology 10:02:14
4 model of a protein? 10:02:22
5 A How many times? That's a very difficult 10:02:24
6 estimate. 10:02:30
7 Q Okay. 10:02:30
8 A It's almost like asking how many times 10:02:33
9 have you gone to the bathroom in your lifetime. I 10:02:39
10 would say many. I don't know exactly how many. 10:02:43
11 Q Okay. So you used -- you've used 10:02:45
12 SWISS-MODEL frequently in your work to generate 10:02:51
13 homology models; is that right? 10:02:54
14 ATTORNEY KUSHAN: Objection. Form. 10:02:54
15 A At times, yes. 10:02:55
16 Q Okay. What's the purpose of generating -- 10:02:57
17 well, actually strike that. 10:03:03
18 Like me make sure I'm using the right 10:03:05
19 terminology here. 10:03:09
20 So the model that you generate using 10:03:10
21 SWISS-MODEL, would you refer to that as a model, 10:03:14
22 or a homology model, or is there some other term? 10:03:15

1 A You can use either one. 10:03:24
2 Q Uh-huh.
3 A Unless the structure of the protein is 10:03:26
4 known, any time you have a model, it's going to be 10:03:28
5 a constructed model as opposed to an experimental 10:03:32
6 structure. So in this particular case, we're 10:03:38
7 talking about homology model. 10:03:41
8 Can one generate a model any other way? I 10:03:44
9 don't know. So homology model/model, I think 10:03:50
10 either one would work here. 10:03:54
11 Q Okay. 10:03:56
12 A And when you say model, I would understand 10:03:57
13 that to mean homology model going forward. 10:04:01
14 Q Okay. Thank you. 10:04:04
15 So what's the purpose of generating a 10:04:05
16 homology model for a protein structure? 10:04:08
17 A It allows you to look at the molecule, as 10:04:18
18 opposed to imagining it in your head. 10:04:22
19 Q And it's useful to be able to look at the 10:04:27
20 molecule, right? 10:04:31
21 A Absolutely. 10:04:32
22 Q And you can use homology modeling to 10:04:38

1 predict the impact of substitutions in a protein? 10:04:42
2 ATTORNEY KUSHAN: Objection to foundation. 10:04:46
3 Also to form. 10:04:48
4 A A homology model can help you to evaluate 10:04:49
5 the impact of a substitution. Yes. 10:04:54
6 Q So can you turn in your declaration for 10:05:03
7 the -- the one that you have open for matter 3 -- 10:05:08
8 turn to Paragraph 20? 10:05:12
9 A Okay. 10:05:26
10 Q And in the first sentence, you say that: 10:05:27
11 Proteins often can tolerate a single amino acid 10:05:32
12 substitution in non-essential regions of the 10:05:35
13 protein structure; is that right? 10:05:38
14 A That's the sentence, yes. 10:05:42
15 Q What is -- what do you mean when you say 10:05:44
16 non-essential regions of the protein structure? 10:05:50
17 A A non-essential region of the protein 10:05:58
18 structure is the part of the protein that is not 10:06:04
19 critical to the folding of the protein. 10:06:09
20 (Reporter clarification.) 10:06:34
21 Q How can you tell whether a region of a 10:06:34
22 protein is essential to the folding of the 10:06:42

1 protein? 10:06:45
2 A You can tell by looking at a bunch of 10:06:46
3 sequences that are related, homologous that is, to 10:06:50
4 one protein, and -- and have high sequence 10:06:58
5 similarity so that they all fold to the same 10:07:02
6 structure, and by comparing those sequences, you 10:07:07
7 can identify the amino acids that are important 10:07:12
8 for folding and the amino acids that are less 10:07:16
9 important for folding. 10:07:19
10 Q So wait. I'm going to unpack that. 10:07:22
11 So first -- and again, just to make sure 10:07:28
12 that we're aligned on terminology -- so you used 10:07:31
13 the word homologous. Can you explain what you 10:07:37
14 mean when you say homologous? 10:07:42
15 A Absolutely. Homologous or homology refers 10:07:43
16 to two or more genes in proteins that have a 10:07:51
17 common ancestor. Two proteins that have 10:07:55
18 originated from a common ancestral gene would have 10:08:01
19 homology, and therefore be homologous. 10:08:08
20 Q Can you use the term homology to refer 10:08:12
21 to -- strike that. 10:08:30
22 Does the term homology, as you're using 10:08:31

1 it, does that only refer to naturally occurring 10:08:35
2 proteins? 10:08:42
3 A Yes. That's how the word should be used, 10:08:42
4 and is used in practice. 10:08:46
5 Q Okay. And then you also talked about a 10:08:50
6 high sequence similarity. So what do you consider 10:09:00
7 to be a high sequence similarity? 10:09:04
8 A It's a spectrum. Similarity is something 10:09:13
9 that can be measured based on the sequence. You 10:09:17
10 can count the number of amino acids that are 10:09:23
11 identical between two sequences, plus the pairs of 10:09:26
12 amino acids, matching pairs, that are supposed to 10:09:32
13 be similar in some chemical aspects. That 10:09:38
14 definition can vary. Then you can count the 10:09:43
15 number of those positions and divide by the whole 10:09:46
16 length of the protein. That will give you a 10:09:49
17 number, which would be the similarity of that 10:09:51
18 protein, of those two proteins. 10:09:54
19 And now, getting back to high sequence 10:09:57
20 similarity. It's not a black and white thing. 10:10:00
21 It's more of a convention, perhaps used by 10:10:07
22 practitioners in the field to indicate that two 10:10:11

1 proteins have sequences that are fully similar, 10:10:15
2 and therefore have a similarity percentage above a 10:10:21
3 certain number. 10:10:27
4 That number is not set in stone, 10:10:31
5 unfortunately. However, practitioners would feel 10:10:34
6 comfortable saying that, say, 50 percent would be 10:10:38
7 a reasonable number to define high similarity. 10:10:42
8 Q Okay. And so if two sequences have, let's 10:10:48
9 say, 60 percent sequence similarity, and before -- 10:10:52
10 strike that. 10:10:57
11 Before we get there, I want to distinguish 10:10:57
12 between similarity and identity, right? 10:11:01
13 So when you say high sequence similarity, 10:11:04
14 you mean not necessarily identical, not 10:11:08
15 necessarily identity, but that allows for some 10:11:11
16 conservative substitutions or conservative 10:11:14
17 changes; is that right? 10:11:18
18 ATTORNEY KUSHAN: Objection. Form. 10:11:19
19 Also objection to foundation. 10:11:20
20 A Identity is a subset of similarity, yes. 10:11:24
21 And to go from identity to similarity, you do 10:11:28
22 allow some slight changes. What's debatable is 10:11:32

1 exactly what should be counted as an allowed 10:11:38
2 substitution. 10:11:42
3 Q Uh-huh.
4 A That -- I don't know the exact definition 10:11:43
5 of that. But accounting for those substitutions, 10:11:46
6 you would have a slightly higher number for 10:11:51
7 similarity, as opposed to identity. 10:11:54
8 Both terms are used. One doesn't stick to 10:11:57
9 one or the other religiously, but use the term 10:12:04
10 with the expectation that the reader or the 10:12:11
11 listener would understand what you mean by that. 10:12:15
12 Q Okay. So if a protein, or two proteins 10:12:19
13 have sequence -- strike that. Let me start over. 10:12:25
14 You have two sequences that are, let's 10:12:26
15 say, 60 percent similar. Would you consider those 10:12:36
16 two sequences to be -- to have high sequence 10:12:42
17 similarity? 10:12:46
18 ATTORNEY KUSHAN: Objection to foundation. 10:12:47
19 Objection as to form. 10:12:48
20 A Assuming certain conditions are met, I 10:12:53
21 would say that they are similar. 10:12:58
22 Q What conditions? 10:13:00

1 A The similarity has to extend over a 10:13:03
2 reasonable extent of the protein. In other words, 10:13:08
3 you can't have similarity within the first 50 10:13:12
4 amino acids out of 500 amino acids and call that 10:13:17
5 similar. Because the similarity would -- so you 10:13:23
6 have to factor that in, how much of -- of the 10:13:29
7 protein -- 10:13:34
8 Q So --
9 A -- would match. 10:13:37
10 Q Okay. So if the -- the sequence alignment 10:13:37
11 for the entire protein had, let's say, 60 percent 10:13:42
12 similarity, would you consider those two sequences 10:13:46
13 to be highly similar? 10:13:51
14 ATTORNEY KUSHAN: Objection. Foundation. 10:13:54
15 Objection as to form. 10:13:55
16 A If you're comparing just the sequence and 10:13:56
17 limit your discussion and interpretation to the 10:14:01
18 similarity alone? Yes. I would think that they 10:14:04
19 are similar. 10:14:09
20 Q Okay. So you mentioned that if you have a 10:14:16
21 bunch of sequences, a bunch of homologous 10:14:58
22 sequences that have a high sequence similarity so 10:15:05

1 that they all fold to the same structure, you can 10:15:09
2 compare those sequences and identify the amino 10:15:12
3 acids that are important for folding. 10:15:15
4 How -- and my question is: If you have a 10:15:18
5 bunch of sequences that are homologous, and have 10:15:22
6 high sequence similarity, how do you know that 10:15:26
7 they all fold to the same structure? 10:15:30
8 A That's the standard that the industry goes 10:15:36
9 by. If you ask a practitioner in the field: I 10:15:40
10 have two proteins that are homologous and have 10:15:50
11 high sequence similarity, would I expect them to 10:15:53
12 fold to the same structure, of course I would say 10:15:58
13 yes. 10:16:01
14 Q And why is that? 10:16:01
15 A It's a matter of protein evolution. 10:16:15
16 Protein structures, if one compares the folding 10:16:19
17 structure to an entire space of -- conformational 10:16:28
18 space that can be adopted by the polypeptide, it's 10:16:34
19 a very small fraction. 10:16:41
20 Now, if you have homologous proteins, 10:16:43
21 meaning they came from the same ancestor, and they 10:16:46
22 have maintained similar sequence similarity, they 10:16:51

1 would be obligated to explore that very small 10:16:56
2 sliver of the conformational space. They would 10:17:03
3 not be able to go and randomly find another island 10:17:08
4 of stability in that conformational space that can 10:17:13
5 be occupied by that particular sequence. So that 10:17:17
6 restricts what the protein can do. 10:17:19
7 So this is the foundation behind the 10:17:23
8 assumption that homologous highly similar 10:17:28
9 sequences would adopt the same conformational 10:17:33
10 three-dimensional structure. 10:17:38
11 Q So you said at the beginning of your 10:17:46
12 answer: If one compares folding structure to the 10:17:49
13 entire space of conformational space that can be 10:17:53
14 adopted by the polypeptides, it's a very small 10:18:06
15 fraction. 10:18:00
16 Can you explain what you mean by that, and 10:18:01
17 why that's the case? 10:18:03
18 A Conformational space, you can think of it 10:18:08
19 as the ensemble of all the shapes that a given 10:18:12
20 polypeptide can assume. It could be a folding 10:18:18
21 structure. It could be DNA structure, some random 10:18:23
22 structures. 10:18:28

1 The folding structure that one sees in a 10:18:29
2 crystal structure or model structure, that's just 10:18:34
3 a small fraction compared to whatever else, 10:18:38
4 whatever other shapes this -- this particular 10:18:42
5 polypeptide may assume. 10:18:46
6 Why is it a small fraction? Because 10:18:48
7 folding structure will be defined by a combination 10:18:52
8 of dihedral angles. And in a folded protein, you 10:18:55
9 would have pretty well-defined values of dihedral 10:19:03
10 angles, both main chain and side chains. The 10:19:04
11 entire conformational space would encompass all 10:19:09
12 the available values of all the dihedral angles. 10:19:15
13 Therefore, the folding structure would correspond 10:19:20
14 to a very small fraction of that entire ensemble.
15 (Reporter clarification.) 10:19:38
16 Q Okay. So the actual folded structure for 10:19:45
17 a given sequence corresponds to a very small 10:19:59
18 fraction of the potential conformational space 10:20:10
19 that that -- that could be occupied by -- that 10:20:14
20 could be occupied by folded protein structures? 10:20:17
21 ATTORNEY KUSHAN: Objection. Form. 10:20:17
22 Objection. Foundation. 10:21:54

1 A Could you repeat that question, please? 10:20:20
2 Q The actual folded structure for a given 10:20:23
3 sequence corresponds to a very small fraction of 10:21:46
4 the conformational space that -- that could be 10:20:28
5 occupied by that sequence? 10:20:35
6 ATTORNEY KUSHAN: Objection. Form. 10:20:37
7 And objection to foundation. 10:20:39
8 A Not by that sequence. 10:20:41
9 Q Uh-huh.
10 A A polypeptide of that length. 10:20:43
11 Q Oh, okay. 10:20:47
12 A Or if you do not constrain the protein to 10:20:48
13 adopt a structure and do something in nature, and 10:20:58
14 you consider all theoretical possibilities that 10:21:02
15 can be adopted -- it doesn't mean that it will 10:21:07
16 be -- it can be adopted by a polypeptide of that 10:21:12
17 length, that space would be much, much bigger 10:21:14
18 compared to the folded space, folded conformation. 10:21:19
19 Q Okay. All right. 10:21:26
20 And then going back to your previous 10:21:57
21 answer where you said that you compare the 10:22:00
22 sequences and identify the amino acids that are 10:22:03

1 important for folding, you're talking about amino 10:22:06
2 acids that are important for folding are the ones 10:22:10
3 that are conserved in the alignment, right? 10:22:13
4 A Yeah. Amino acids that are conserved in 10:22:18
5 the alignment are the residues that are important 10:22:22
6 for folding. Yes. 10:22:26
7 Q Okay. How many sequences do you need to 10:22:28
8 have in your alignment to know that you've
9 identified residues that are important for 10:22:40
10 folding? 10:22:34
11 ATTORNEY KUSHAN: Objection. Foundation. 10:22:34
12 A The more sequences, the better. Since 10:22:44
13 you're trying to get a statistical sense of what 10:22:48
14 amino acids are conserved, a larger sample would 10:22:56
15 be better.
16 There's no cut-off. You can do it with 10:22:59
17 smaller set. And the difference is with a smaller 10:23:02
18 set, it may look as if more residues are conserved 10:23:10
19 just because you are starting with a smaller set, 10:23:15
20 and you see less variation. 10:23:20
21 As you increase the sample size, you may 10:23:22
22 observe some of those positions that begin to 10:23:28

1 vary. But the sample size can be small I suppose. 10:23:27
2 There's no hard cut-off. 10:23:36
3 Q Okay. So we started this discussion by 10:23:57
4 looking at Paragraph 20, and I asked about what 10:24:01
5 are -- what you meant by non-essential regions of 10:24:07
6 the protein structure, and am I understanding 10:24:13
7 correctly that the non-essential regions of the 10:24:17
8 protein structure are identified based on a 10:24:20
9 sequence alignment, and specifically they are the 10:24:23
10 residues in the sequence alignment that are not 10:24:25
11 conserved? 10:24:30
12 A The positions, the residues, in a multiple 10:24:33
13 sequence alignment that are not conserved are 10:24:39
14 labeled as non-essential regions in this 10:24:48
15 declaration, and they may vary. And the fact that 10:24:54
16 they do vary among homologous high sequence 10:25:06
17 similarity sequences suggests that they may be 10:25:14
18 non-essential, although it's a quote/unquote 10:25:18
19 non-essential. 10:25:24
20 Q Uh-huh. So what do you mean when you say 10:25:24
21 quote/unquote non-essential? 10:25:26
22 A Meaning that it doesn't mean that 10:25:28

1 anything -- they're not anything goes residues. 10:25:32
2 You can't just randomly choose mutations at those 10:25:36
3 positions. They are still important, but they may 10:25:39
4 be qualitatively different than the residues that 10:25:43
5 are strictly conserved, or conserved to a very 10:25:46
6 high degree. 10:25:52
7 (Reporter clarification.) 10:25:54
8 Q So when you use the term non-essential, 10:25:54
9 non-essential region in -- in this declaration, 10:25:59
10 are you referring to positions in the sequence 10:26:01
11 that can potentially tolerate substitution, as 10:26:03
12 opposed to those that cannot tolerate 10:26:08
13 substitution? 10:26:11
14 A It -- it starts -- it starts with the -- 10:26:16
15 with the definition of what non-essential residues 10:26:25
16 are. So these are definitions, meaning the 10:26:30
17 positions in the multiple sequence alignment where 10:26:34
18 we see variation, we label them as non-essential. 10:26:37
19 Whether they tolerate substitutions or not comes 10:26:42
20 later. 10:26:44
21 Q Okay. But why did you label them 10:26:45
22 non-essential? 10:26:48

1 A We label them as non-essential in the 10:26:51
2 sense that they are varied among homologous 10:26:54
3 sequences that bode the same structure, which 10:27:01
4 means those residues may allow variation. So in 10:27:07
5 that sense, they're not critical. The identity of 10:27:12
6 those amino acids are not critical to adopt this 10:27:20
7 common fold shared by all homologous proteins in 10:27:21
8 that group. 10:27:29
9 Q Did you use the term non-essential in your 10:27:30
10 work in 2011 to identify non-conserved residues in 10:27:35
11 sequence alignments? 10:27:41
12 ATTORNEY KUSHAN: Objection. Foundation. 10:27:42
13 A No. I did not use the term non-essential 10:27:47
14 when I used it for my purpose. 10:27:51
15 Q Have you ever used the phrase 10:27:53
16 non-essential region of a protein structure, 10:27:57
17 outside of your work in this case? 10:28:01
18 A No. 10:28:05
19 Q So why did you use the term non-essential 10:28:07
20 region to refer to non-conserved positions in 10:28:10
21 sequence alignment for this case? 10:28:21
22 A The task that I was given was to identify 10:28:25

1 non-essential positions in PH20 and identify 10:28:30
2 substitutions at those positions. So my task came 10:28:39
3 down to two things: One to identify what those 10:28:43
4 non-essential positions may be; and second, 10:28:48
5 evaluate various substitutions at those positions 10:28:50
6 to see if there are substitutions at non-essential 10:28:57
7 positions that would be tolerated. 10:29:04
8 And that is motivated by patent '427, 10:29:06
9 which I believe is quoted in Paragraph 32. We use 10:29:16
10 the term non-essential because that's what is in 10:29:26
11 the patent, and I was trying to see -- I was 10:29:31
12 tasked to identify the substitutions at 10:29:41
13 non-essential positions as described in the patent 10:29:48
14 to see where they are and what they may be. 10:29:50
15 Q Okay. 10:29:54
16 A That's why I went about defining 10:29:54
17 non-essential positions, whereas previously I did 10:29:58
18 not do that in my other studies. 10:30:01
19 Q So in your opinion, would a POSA who sees 10:30:05
20 the term non-essential position, would they 10:30:18
21 understand that to mean a position in the sequence 10:30:21
22 alignment that is not conserved? 10:30:25

1 A The other way around. If they see 10:30:32
2 positions in a sequence alignment that is not 10:30:35
3 conserved, they would think it's non-essential. 10:30:40
4 Q Oh.
5 A They wouldn't go, start with non-essential 10:30:43
6 and say: Oh, aha. It's sort of backwards. 10:30:45
7 If they were to identify -- if they were 10:30:48
8 tasked to identify non-essential positions, that 10:30:54
9 is how they would go about doing that. 10:30:57
10 Q Okay. So if the POSA was tasked with 10:31:00
11 identifying non-essential regions in a protein 10:31:04
12 sequence, they would perform an alignment and 10:31:07
13 identify non-conserved -- non-conserved residues? 10:31:09
14 A Yes. Since non-essential means opposite 10:31:16
15 of essential; therefore, if you identify 10:31:20
16 essential, you would have identified 10:31:25
17 non-essential. 10:31:27
18 Q Okay. And the essential residues are 10:31:28
19 those that are conserved in the alignment, right? 10:31:32
20 A That would be a reasonable interpretation. 10:31:35
21 Q Okay. So let me make sure I got this 10:31:37
22 right. So a POSA tasked with identifying 10:31:41

1 essential residues in a protein sequence would 10:31:44
2 perform an alignment of homologous sequences and 10:31:48
3 identify those that are conserved, and that way 10:31:51
4 identify the essential residues. And then those 10:31:55
5 that are left, which are not conserved, are the 10:31:56
6 non-essential residues; is that right? 10:32:00
7 A That would be the correct logic, yes. 10:32:04
8 Q Thank you. 10:32:06
9 And I believe you mentioned the '427 10:32:07
10 patent, but it's '429 patent, right? 10:32:11
11 A Oh. Oh, I'm sorry. '429 patent, yes. 10:32:13
12 Q Okay. Thank you. 10:32:17
13 So let's turn to Paragraph 32 -- are we 10:33:01
14 already there -- in your declaration in matter 3? 10:33:05
15 And so the -- you have a block quote in 10:33:09
16 Paragraph 32 from the '429 patent, right? 10:33:13
17 A Yes. 10:33:17
18 Q And the second sentence of that block 10:33:17
19 quote says: Those of skill in this art recognize 10:33:32
20 that in general, single amino acid substitutions 10:33:35
21 in non-essential regions of a polypeptide do not 10:33:37
22 substantially alter biological activity; is that 10:33:41

1 right? 10:33:46
2 A That's correct. 10:33:46
3 Q So in the 2011 time frame, a POSA would 10:33:50
4 understand that if they performed a sequence 10:33:57
5 alignment of homologous sequences and identified 10:34:00
6 the non-conserved residues thereby giving them the 10:34:04
7 non-essential regions, that substitutions in those 10:34:14
8 non-essential positions would not substantially 10:34:18
9 alter biological activity; is that right? 10:34:20
10 ATTORNEY KUSHAN: Objection. Form. 10:34:24
11 A POSA in 2011 would have done that multiple 10:34:26
12 sequence alignment to identify non-essential 10:34:32
13 regions, and reasonably expect that the amino 10:34:35
14 acids found at those positions may be introduced 10:34:42
15 without substantially altering biological 10:34:48
16 activity, yes. 10:34:54
17 Q And how would -- what would the POSA 10:34:54
18 understand the phrase "substantially alter 10:34:57
19 biological activity" to mean? 10:34:59
20 A POSA would expect that sentence to mean 10:35:10
21 without loss of structure or function. 10:35:14
22 Q So loss of function, that means no -- that 10:35:18

1 means that -- sorry. Strike that. 10:35:21
2 When you say loss of function, do you mean 10:35:22
3 that you've eliminated the function? 10:35:26
4 ATTORNEY KUSHAN: Objection. Foundation. 10:35:29
5 Also objection as to form. 10:35:31
6 A It says: Substantially alter biological 10:35:34
7 activity. 10:36:09
8 A substantial drop in the enzyme activity 10:35:41
9 would be considered a substantial alteration. 10:35:46
10 Therefore, those need to be guarded against. 10:35:50
11 Q Uh-huh.
12 A However, the way the sentence is written, 10:35:53
13 single amino acid substitutions may be introduced 10:35:57
14 without altering the biological activity 10:36:00
15 substantially. 10:36:07
16 Q If two highly similar polypeptides fold in 10:36:31
17 the same way, could a POSA predict that they will 10:36:39
18 function in the same way? 10:36:48
19 ATTORNEY KUSHAN: Objection. Form. 10:36:49
20 Also objection as to foundation. 10:36:50
21 A If two polypeptides, proteins, fold the 10:36:56
22 same way, can I -- can a person, POSA, expect them 10:37:00

1 to have the same activity? No. 10:37:04
2 Q Okay. Why is that? 10:37:07
3 A Because enzyme relating activity is a very 10:37:13
4 subtle thing. Things can happen in the active 10:37:18
5 site, which doesn't really alter the shape of the 10:37:21
6 molecule, but can change the -- the function of 10:37:27
7 the enzyme somewhat. 10:37:30
8 For instance, hyaluronidase 4 -- I 10:37:32
9 remember hyaluronidase, yes. It hydrolyzes it 10:37:40
10 from carbohydrate then PH20, which hydrolyzes 10:37:44
11 hyaluronic acid. And maybe because of differences 10:37:44
12 in the active site, for instance. 10:37:49
13 Q Uh-huh.
14 A So they may look the same, but they may 10:37:52
15 act on different substrates, therefore, different 10:37:56
16 activities. So a POSA would understand that kind 10:38:00
17 of thing happens all the time. 10:38:02
18 Q Okay. Okay. So when you did your 10:38:06
19 homology sequence alignment for -- for PH20, did 10:38:13
20 you understand that all of the -- all of the 10:38:24
21 hyaluronidases that you included in your alignment 10:38:28
22 have -- I'm sorry. Strike that. 10:38:33

1 Your sequence alignment for PH20 includes, 10:38:34
2 for example, HYAL4, right? 10:38:39
3 A Yes. 10:38:48
4 Q And HYAL4 does not cleave HA, right? 10:38:49
5 A Not very well. 10:38:49
6 Q So why did you include HYAL4 in your 10:38:50
7 alignment for PH20 if they have different 10:39:00
8 functions? 10:39:02
9 A Because the question that we were 10:39:02
10 addressing was the -- the sequence structure 10:39:05
11 relationship in this family of proteins, and you 10:39:09
12 can learn by looking at all the sequences that 10:39:15
13 fold to the same structure, which include all 10:39:20
14 homologous sequences of PH20, regardless of how 10:39:26
15 they're labeled, or what their specific enzyme 10:39:30
16 activities may be, irrespective of their subtle 10:39:36
17 differences in substrate specificity or the 10:39:44
18 activity, enzymatic activity, doesn't change the 10:39:46
19 fact that yeah, they fold to the same structure; 10:39:51
20 therefore, the sequence -- all the sequences have 10:39:54
21 they share, common sequence in amino acid 10:39:57
22 restrictions and freedom, which can be beneficial 10:40:03

1 in our study. Therefore, it's important that we 10:40:09
2 include all the sequences, not just a subset of 10:40:13
3 highly similar sequences, for instance, by 10:40:18
4 limiting the analysis to PH20. 10:40:23
5 Q Okay. So you included hyaluronidases in 10:40:27
6 your alignment because you expect the homologous 10:40:32
7 hyaluronidases to all adopt the same fold, to all 10:40:41
8 fold in the same way, and as a result, that way 10:40:44
9 you're able to identify which residues are 10:40:47
10 essential for folding, as opposed to those which 10:40:53
11 are not; is that right? 10:40:54
12 A That is correct. 10:40:55
13 Q Okay.
14 A That is a fundamental assumption -- 10:40:56
15 Q Okay. 10:41:01
16 A -- in this discipline.
17 Q And so why would you expect all of the 10:41:02
18 hyaluronidases to fold the same way? 10:41:03
19 ATTORNEY KUSHAN: Objection. Foundation. 10:41:07
20 A In part for the reasons that I described 10:41:15
21 earlier. They are related sequences, and the 10:41:19
22 conformational space that can be explored by 10:41:23

1 related sequences will be clustered together into 10:41:28
2 a very small fraction of the old conformational 10:41:33
3 space that may be theoretically available to a 10:41:38
4 polypeptide of that size. 10:41:44
5 Now, if they do not fold, two 10:41:46
6 possibilities: One, they may fold to a completely 10:41:48
7 different structure, which is not possible, not 10:41:52
8 possible because they all came from the same 10:41:55
9 ancestral gene. That means they started in some 10:41:57
10 space, there would be no mechanism for them to go 10:42:02
11 to the next island, which may be light years away, 10:42:08
12 say.
13 Q Uh-huh.
14 A The other is they may not fold at all. If 10:42:12
15 that were the case, you wouldn't have those 10:42:16
16 concerned residues. Mutation would happen over 10:42:20
17 time that would eliminate those conserved 10:42:24
18 residues. 10:42:30
19 Evolution introduces mutations constantly 10:42:30
20 at some rate. And over time, once a protein loses 10:42:37
21 its benefit to the organism because it stopped 10:42:42
22 folding, then those sequences would very quickly 10:42:47

1 mutate away, drift away in the sequence space. 10:42:53
2 They would look very, very different than what 10:42:58
3 they started with. 10:43:01
4 So the fact that they do have conserved 10:43:03
5 residues guarantee that they're doing something, 10:43:06
6 even when you don't know what they are doing, 10:43:10
7 which I believe is the case with HYAL3, which has 10:43:18
8 unknown function. But they may do something. 10:43:18
9 They must be doing something. Otherwise, would 10:43:20
10 have gotten rid of over time. So this is the 10:43:22
11 reason that they would fold to the same structure. 10:43:29
12 Q Okay. So when you -- when you did your 10:43:33
13 alignment for PH20, did you include all of the 10:43:36
14 hyaluronidase sequences that were available in 10:43:40
15 2011, or did you use some other cut-off? 10:43:45
16 A Yes. I used the sequences that were 10:43:52
17 available as of the end of year 2011. 10:43:55
18 Q Okay. Can you explain how exactly you ran 10:44:01
19 your -- strike that. 10:44:06
20 You used BLAST to create the -- or, to 10:44:09
21 identify the sequences that would be in the 10:44:10
22 alignment; is that right? 10:44:14

1 A I used BLAST to identify sequences that 10:44:15
2 are similar to the seed sequence, or the target 10:44:19
3 sequence, PH20 human. 10:44:25
4 (Reporter clarification.) 10:44:38
5 Q And how exactly did you use BLAST? 10:44:38
6 Did you set any parameters? 10:44:42
7 Can you just walk me through what you did 10:44:44
8 in BLAST? 10:44:47
9 A BLAST is a web service. You enter the 10:44:47
10 target sequence, in this case, human PH20, a 10:44:54
11 protein sequence, and you hit -- run a button. 10:44:59
12 In my case, I did one thing that changed 10:45:10
13 the default setting from the number return 10:45:14
14 sequences expected was changed from 100, which is 10:45:20
15 the default value, to the maximum that was allowed 10:45:27
16 through the web service, which is 5,000. Because 10:45:30
17 I wanted to see all the sequences that were 10:45:35
18 available, not just the top 100. 10:45:38
19 Q Okay. Okay. And so then you then 10:45:41
20 whittled that down by -- by removing the sequences 10:45:51
21 that were only available after 2011 at the end? 10:45:56
22 A Only the sequences -- 10:45:59

1 ATTORNEY KUSHAN: Sorry. 10:46:02
2 Objection. Foundation. 10:46:02
3 Go ahead. 10:46:03
4 A Only the sequences that were available up 10:46:04
5 to the end of year 2011; that is correct. 10:46:07
6 Q Okay. And then you removed -- sorry. 10:46:45
7 So you obtained the 95 sequences after you 10:46:49
8 filtered out those available after December 29th, 10:46:54
9 2011, and then you removed 7 isoforms, leaving you 10:46:55
10 with 88 sequences; is that right? 10:46:57
11 A That is correct. 10:46:59
12 Q Can you explain what 7 isoforms are, and 10:47:00
13 why you removed them? 10:47:05
14 A Isoforms are different manifestations of 10:47:09
15 the same gene, resulting from alternative 10:47:14
16 splicing. They come from the same gene, but after 10:47:20
17 MRNA synthesize, they undergo splicing event. And 10:47:26
18 depending on where the splicing occurs, you get 10:47:28
19 slightly different forms. 10:47:33
20 Since they essentially come from the same 10:47:35
21 gene, having both of them represented in the final 10:47:37
22 set would introduce a bias. I wanted to eliminate 10:47:40

1 those redundancies by identifying isoforms and 10:47:45
2 ensuring that only one is represented in the final 10:47:49
3 set. 10:47:53
4 ATTORNEY MARTIN: Okay. So let's 10:48:06
5 introduce Exhibit 1054 and Exhibit 1057. 10:48:07
6 ATTORNEY KUSHAN: Lauren, do you want to 10:48:17
7 take a break? 10:48:19
8 We've been going for an hour and twenty, 10:48:20
9 or something. It's up to you. 10:48:23
10 ATTORNEY MARTIN: Yeah. That's fine. 10:48:26
11 THE WITNESS: Okay. Yeah. That would be 10:48:27
12 great. Yes. Yes. 10:48:29
13 THE VIDEOGRAPHER: We are going off the 10:48:30
14 record. The time is 10:48 a.m. 10:48:32
15 (Recess from 10:48 a.m. until 11:04 a.m.) 10:48:36
16 THE VIDEOGRAPHER: We are back on the 11:04:07
17 record. The time is 11:04 a.m. 11:04:11
18 ATTORNEY KUSHAN: We -- Brian Goldberg, 11:04:15
19 can you just announce yourself? 11:04:20
20 ATTORNEY GOLDBERG: Yes. Hi. This is 11:04:21
21 Brian Goldberg from Dechert LLP, and with me is 11:04:23
22 Dr. Michael Hecht, just listening in. 11:04:26

1 ATTORNEY MARTIN: All right. So welcome 11:04:48
2 back, Dr. Park. 11:04:49
3 Right before we left, we were introducing 11:04:51
4 Exhibits 1054 and 1057. 11:04:55
5 (Previously marked Exhibit 1054 introduced
6 and retained by counsel.) 11:05:35
7 (Previously marked Exhibit 1057 introduced 11:05:35
8 and retained by counsel.)
9 BY ATTORNEY MARTIN:
10 Q Did you prepare -- 11:05:35
11 A Yes.
12 Q -- 1054 and 1057? 11:05:37
13 A I did prepare both documents, yes. 11:05:38
14 Q Can you explain what Exhibit 1054 is? 11:05:41
15 A This is the header portion of the BLAST 11:06:06
16 result that has been filtered based on the 11:06:12
17 publication date of the individual sequences to 11:06:19
18 correspond to pre-2011 set. 11:06:24
19 Q Okay. And so Exhibit 1054 includes the 88 11:06:25
20 sequences that you used in your sequence 11:06:29
21 alignment; is that right? 11:06:33
22 A 1054 is a -- is a set of 95 sequences. 11:06:36

1 Q Oh. It's the 95? Okay. 11:06:41
2 A That's correct. 11:06:46
3 Q Okay. So Exhibit 1054 is the set of 95 11:06:51
4 sequences that you obtained from BLAST, and then 11:06:57
5 you removed this 7 isoforms to arrive at the 88 11:07:01
6 sequences in your alignment; is that right? 11:07:02
7 A That is correct. 11:07:05
8 Q Okay. And so in Exhibit 1054, the first 11:07:18
9 sequence listed is: Hyaluronidase PH20 isoform 2 11:07:29
10 Homo sapiens; is that right? 11:07:36
11 A That is correct. 11:07:41
12 Q Is that the sequence that you entered into 11:07:45
13 BLAST? 11:07:49
14 A That is the sequence that was entered to 11:07:52
15 do a BLAST search. Yes. 11:07:57
16 Q And so Exhibit 1054 identifies the protein 11:08:06
17 in question, hyaluronidase PH20 versus -- 11:08:19
18 actually, strike that. 11:08:28
19 So in Exhibit 1054, you can see which all 11:08:29
20 of the proteins that are included in the 11:08:33
21 alignment, and they include hyaluronidase PH20; 11:08:36
22 sperm adhesion molecule 1 precursor; 11:08:43

1 hyaluronidase-5-like; sperm adhesion molecule 1; 11:08:47
2 hyaluronidase-4; LOW-QUALITY PROTEIN 11:08:52
3 hyaluronidase-4; hyaluronoglucosaminidase -- I 11:09:03
4 really butchered that -- 6. 11:09:03
5 This one is just hyaluronidase; 11:09:08
6 hyaluronidase-2; hyaluronidase PH20-like; 11:09:12
7 hyaluronidase-1; hyaluronidase PH20 precursor. 11:09:19
8 Let's see. Hyaluronidase-2 precursor; 11:09:27
9 hyaluronoglucosaminidase 6 precursor; 11:09:44
10 hyaluronidase-like; hyaluronidase-4-like; 11:09:53
11 hyaluronidase-3 precursor. 11:09:59
12 I think I've got them; is that right? 11:10:01
13 ATTORNEY KUSHAN: Objection. Foundation. 11:10:04
14 A I wasn't sure what you were doing. Are 11:10:06
15 you reading the entire table, or are you selecting 11:10:10
16 some of them for some reasons? 11:10:14
17 Q I'm trying to filter as I go through and 11:10:16
18 just read out -- 11:10:20
19 A Filter based on what? 11:10:21
20 Q The first row or the first column. 11:10:23
21 A Yes. But what are you filtering for? 11:10:27
22 Q So I'm not reading hyaluronidase-4 eight 11:10:31

1 times. I'm just saying hyaluronidase -- 11:10:35
2 A Oh. I see what you're saying. Okay. 11:10:35
3 Q Yeah. 11:10:36
4 A So you're just saying that there are
5 different hyaluronidases here?
6 Q Yes. 11:10:36
7 A Okay. Yes. 11:10:37
8 Q Okay.
9 A I agree with that. 11:10:38
10 Q Okay. And then several columns over, is 11:10:41
11 there -- is that a percent identity or a percent 11:10:46
12 similarity that's given? 11:10:49
13 ATTORNEY KUSHAN: Objection. Foundation. 11:11:01
14 A I have to look back to the original file, 11:11:04
15 but my recollection says identity. 11:11:07
16 Q Okay. And so that field would give the 11:11:10
17 percent identity to the sequence that you entered, 11:11:14
18 which is the -- the first sequence, the 11:11:19
19 hyaluronidase PH20 isoform 2? 11:11:21
20 ATTORNEY KUSHAN: I'm sorry, Counsel. 11:11:23
21 Which -- which column are you referring to in the 11:11:28
22 exhibit? Maybe go from the far right, heading off 11:11:31

1 from the far right? 11:11:35
2 ATTORNEY MARTIN: Oh. From the far right. 11:11:35
3 Five. Right, so -- 11:11:38
4 THE WITNESS: In fact, yes. I do 11:11:39
5 apologize. There seems to be different numbers. 11:11:41
6 I do get confused. One of them does have a 11:11:47
7 percentage sign, but I'm not sure what the heading 11:11:51
8 of that is.
9 So perhaps I take back whatever I said 11:11:56
10 earlier, whether it was identity. I'll -- I'll 11:11:58
11 have to look at the original file with the 11:12:00
12 explanation of what each column means. 11:12:04
13 BY ATTORNEY MARTIN: 11:12:05
14 Q Okay. So you don't know if that's 11:12:05
15 identity or similarity? 11:12:07
16 A That I don't know right at this moment. 11:12:09
17 Yes. 11:12:12
18 Q Do you think it's either identity or 11:12:12
19 similarity, or is there another option? 11:12:15
20 A It makes me think that the one that says 11:12:17
21 percentage is not the identity or similarity. The 11:12:21
22 reason I say that is because I know the set of 88 11:12:24

1 or 95 sequences have sequences with similarity 11:12:29
2 down to about 40 percent. Land that column 11:12:34
3 doesn't seem to go down to 40 percent, so that 11:12:37
4 makes me think it's a coverage. Coverage. 11:12:43
5 Q Oh. I see. 11:12:46
6 A The identity I think may be the third from 11:12:47
7 the last column. 11:14:32
8 Q Okay. Okay. I got it. 11:12:51
9 Okay. So the column with the percentage
10 sign is potentially coverage? 11:12:52
11 A Coverage. 11:12:52
12 Q Meaning what portion of the -- what 11:12:53
13 portion of the -- is it the starting sequence 11:12:59
14 is... 11:13:03
15 A I believe so. 11:13:04
16 Q What percentage of the starting sequence 11:13:05
17 is being aligned with the test sequence? 11:13:08
18 A That's right. 11:13:12
19 Q Okay. Okay. And then -- and then the 11:13:13
20 column that's three columns in from the far right, 11:13:14
21 that number is potentially percent identity or 11:13:20
22 similarity? 11:13:24

1 A Identity or similarity. I want to say 11:13:24
2 identity. 11:13:27
3 Q Okay. 11:13:27
4 A Because I believe the similarities are -- 11:13:28
5 most of them were 50 percent and higher, and 11:13:32
6 identity here goes down to around 40 percent or 11:13:36
7 just below. I think the lowest percentage that I 11:13:41
8 remember was about 36 percent. So that seems to 11:13:45
9 match that value. That column seems to be the 11:13:49
10 identity. 11:13:53
11 Q Okay. And do you consider all of the 11:13:54
12 sequences in this BLAST result to be -- to have a 11:13:59
13 high sequence similarity, high degree of sequence 11:14:05
14 similarity? 11:14:11
15 A Yes. I do. 11:14:12
16 Q And do you consider that all of the 95 11:14:14
17 sequences in this BLAST result to be homologous 11:14:17
18 sequences? 11:14:20
19 A Yes. From the label of the individual 11:14:33
20 entries, they do suggest that they're homologous 11:14:36
21 proteins. 11:14:46
22 (Reporter clarification.) 11:14:49

1 THE VIDEOGRAPHER: Dr. Park, can you move 11:14:49
2 your microphone up just a bit? 11:14:52
3 THE WITNESS: Sure. 11:14:57
4 THE VIDEOGRAPHER: Thank you. 11:14:58
5 BY ATTORNEY MARTIN: 11:15:09
6 Q When you say the label of the individual 11:15:21
7 entry, what are you referring to? 11:15:23
8 A I mean the names that were given to the 11:15:29
9 individual sequences. The first column that you 11:15:34
10 were reading. 11:15:37
11 Q In other words, the hyaluronidases? 11:15:37
12 A That is correct. 11:15:41
13 Q Okay. The fact that they are all 11:15:42
14 hyaluronidases suggests that they are homologous 11:15:44
15 proteins? 11:15:49
16 ATTORNEY KUSHAN: Objection. Foundation. 11:15:50
17 A No. 11:15:51
18 Q Okay. 11:15:53
19 A If it's just a -- if I'm just focusing on 11:15:53
20 the name, I would find other hyaluronidase enzymes 11:15:57
21 out there that are not homologous to PH20. But in 11:16:01
22 this set, the combination of the sequence identity 11:16:07

1 and the names do indicate that I'm looking at 11:16:11
2 homologous proteins. 11:16:14
3 Q Okay. Okay. And when you say the 11:16:16
4 combination of the sequence identity, so is it the 11:16:18
5 sequence identity that is between 30 -- 36, 37 and 11:16:23
6 100, that combination, plus the name hyaluronidase 11:16:32
7 indicates that they're homologous? 11:17:45
8 ATTORNEY KUSHAN: Objection. Form. 11:16:42
9 Also objection to foundation. 11:16:43
10 A Yes. That would be the case. 11:16:44
11 BLAST doesn't know what it's returning. 11:16:47
12 It will return any sequence that looks similar to 11:16:50
13 the target sequence, and it will give you the 11:16:54
14 identity percentage. 11:16:57
15 So theoretically, one shouldn't be able to 11:16:59
16 tell whether they're homologous or not. But 11:17:03
17 combining that sequence identity with the names of 11:17:06
18 the enzymes would convince you that they are 11:17:10
19 homologous proteins. And the coverage. Identity 11:17:14
20 plus coverage and the names. 11:17:17
21 Q Okay. Sequence identity plus sequence 11:17:19
22 coverage plus the name indicates that they're 11:17:25

1 homologous? 11:17:29
2 A Yes. 11:17:31
3 Q Is there a range for sequence coverage 11:17:32
4 that you look for to determine whether two 11:17:35
5 proteins are homologous? 11:17:38
6 A No. Homologous proteins can have a wide 11:17:47
7 range of sequence identity. There's high sequence 11:17:52
8 similarity identity. There is a slightly lower 11:17:57
9 range of percentage, sometimes referred to as the 11:18:01
10 twilight zone, or you can have even lower 11:18:07
11 percentage, which may be detected using some very 11:18:12
12 sophisticated algorithms to establish some sort of 11:18:20
13 relationship, but at a very, very low percentage. 11:18:24
14 This is outside the realm of BLAST. BLAST would 11:18:27
15 not return those sequences. 11:18:32
16 Q Okay. What do you mean when you said the 11:18:33
17 twilight zone? 11:18:37
18 A Twilight zone refers to a range of 11:18:39
19 sequence identity, somewhere between 20 to 35 11:18:44
20 percent, which is sort of a grey area in a way, in 11:18:51
21 terms of interpreting sequence comparison. 11:18:54
22 Some sequences are very easy to interpret 11:18:58

1 because they are similar. Once a sequence 11:19:01
2 identity drops below a certain number, it gets to 11:19:09
3 be difficult. And even making the assumption that 11:19:12
4 they would fold to the same structure can be 11:19:16
5 questionable, and that would correspond to the 11:23:54
6 twilight zone that I mentioned, or the midnight 11:19:53
7 zone, that's even lower. So these are terms that 11:19:29
8 people use to refer to different levels of 11:19:34
9 sequence activity. 11:19:38
10 Q Do you know why they -- why it's called 11:19:39
11 twilight zone? 11:19:42
12 A Because you can't really see very well. 11:19:44
13 Q Okay. Got it. 11:19:49
14 And then midnight zone because you can't 11:19:58
15 really see? 11:20:01
16 A Too dark. Yeah. Pretty dark down there. 11:20:01
17 Q Okay. Got it. 11:20:02
18 So for the 95 sequences that are in 11:20:05
19 Exhibit 1054, you expect them to all fold the same 11:20:09
20 way? 11:20:14
21 A I do. 11:20:15
22 Q Would you expect that you could generate a 11:20:16

1 model of any of the sequences in Exhibit 1054 11:20:29
2 using the SWISS-MODEL? 11:20:33
3 ATTORNEY KUSHAN: Objection. Foundation. 11:20:41
4 A Generate a homology model of the sequences 11:20:42
5 in this list? 11:20:46
6 Q Yes. 11:20:47
7 A Using SWISS-MODEL? 11:20:47
8 Q Yes. 11:20:50
9 A That depends on the sequence identity 11:20:55
10 between the individual sequences and the model, 11:21:01
11 which is from HYAL1. In the case of PH20, the 11:21:05
12 identity is sufficiently high. 41 percent, 45 11:21:15
13 percent, somewhere around there. 11:21:17
14 For other sequences, once you do the 11:21:19
15 comparison with HYAL1, I don't know what that 11:21:24
16 sequence percentage is. The percentage that's 11:21:30
17 listed here is an identity to PH20 doesn't 11:21:30
18 guarantee that they would similarly have high 11:21:33
19 percent -- percentage identity with respect to 11:21:37
20 HYAL1, and that would determine whether a reliable 11:21:40
21 homology model can be generated for these entries. 11:21:47
22 Q Okay. I understand. 11:21:53

1 So you said 45-ish percent sequence 11:21:54
2 identity for PH -- between PH20 and HYAL1, that's 11:22:00
3 sufficiently high to use SWISS-MODEL to generate a 11:22:01
4 homology model; is that right? 11:22:07
5 ATTORNEY KUSHAN: Objection. Foundation. 11:22:09
6 A That will give you a structure model that 11:22:11
7 is overall reliable and can be used for subsequent 11:22:19
8 studies, yes. 11:22:25
9 Q Is there a minimum amount of sequence 11:22:30
10 identity that you need to satisfy in order to use 11:22:33
11 SWISS-MODEL to generate a homology model? 11:22:37
12 ATTORNEY KUSHAN: Objection. Foundation. 11:22:44
13 A This is another one of those questions 11:22:46
14 where one doesn't have a solid number, except a 11:22:50
15 number that's commonly used and understood. A 30 11:22:54
16 percent identity between two proteins that are 11:23:00
17 homologous would be assumed to fold the same 11:23:07
18 structure. 11:23:10
19 Q Okay. 11:23:11
20 A So if it's 31 percent, I don't know. But 11:23:12
21 if it's 45 percent, that seems like a pretty safe 11:23:16
22 place to be. 11:23:21

1 Q Okay. Got it. 11:23:22
2 And so the 30 percent identity between two 11:23:26
3 proteins that are homologous, they would be 11:23:31
4 assumed to fold the same structure? Is that 30 11:23:35
5 percent number, is that well-known in the field? 11:23:38
6 ATTORNEY KUSHAN: Objection. Foundation. 11:23:42
7 A If you ask a POSA to put a number on that, 11:23:43
8 I think they would name 30 percent. 11:23:48
9 Q Okay. And was that the case in 2011? 11:23:51
10 A The understanding of 30 percent being sort 11:23:57
11 of the cut-off has been around for a long, long 11:24:01
12 time, including 2011, yes. 11:24:05
13 Q Okay. Would you consider proteins that 11:24:08
14 have more than 40 percent sequence identity to be 11:24:33
15 highly homologous? 11:24:37
16 ATTORNEY KUSHAN: Objection. Form. 11:24:39
17 A No. Those are unrelated issues. 11:24:43
18 Similarity is a similarity. Homology -- 11:24:47
19 homologous -- homologous proteins. 11:24:52
20 Q Oh, okay. 11:24:54
21 A You know, homology and homologous proteins 11:24:55
22 are -- that's a separate issue. They tend to go 11:25:00

1 hand in hand, but there's no direct correlation 11:25:04
2 between the two. 11:25:08
3 Q Okay. I understand. 11:25:10
4 Because you could have proteins that are 11:25:11
5 more similar in sequence that are completely
6 evolutionarily unrelated, so those would not be 11:25:15
7 homologous proteins; is that what you're saying? 11:25:17
8 A Yes. Although that might be difficult 11:25:20
9 to -- to -- I don't know. It may be difficult to 11:25:24
10 imagine. I don't know. 11:25:32
11 Q Okay. 11:25:33
12 A But again, those two are separate issues. 11:25:34
13 They should not be mixed. 11:25:38
14 Q Okay. Understood. 11:25:40
15 Okay. All right. So then looking at 11:25:47
16 10 -- Exhibit 1057. 11:25:48
17 A 57. Yes. 11:25:57
18 Q So Exhibit 1057 is the alignment that you 11:25:57
19 generated using Clustal Omega, right? 11:26:03
20 A This is the alignment that was produced by 11:26:04
21 Clustal Omega, yes. 11:26:09
22 Q And you generated the alignment -- you 11:26:11

1 used Clustal Omega to generate the alignment, 11:26:12
2 right? 11:26:15
3 A That's how I generated the sequence 11:26:16
4 alignment, yes. 11:26:20
5 Q And I believe I asked earlier about other 11:26:24
6 programs that could have been used for sequence 11:26:28
7 alignments, and I believe you said that a POSA in 11:26:31
8 2011 would have used Clustal Omega. 11:26:35
9 Is that the case just for multiple 11:26:38
10 sequence alignments? 11:26:41
11 A Clustal Omega is -- it's an algorithm 11:26:44
12 that's designed to align multiple sequences. 11:26:50
13 Q If a POSA wanted to do a pairwise 11:26:54
14 alignment, what would they have used in 2011? 11:26:58
15 A They would have used BLAST. 11:27:02
16 Q Okay. 11:27:04
17 A BLAST does have a feature that allows you 11:27:05
18 to submit two sequences and do pairwise alignment. 11:27:10
19 Q Okay. And you can match the sequences 11:27:16
20 that are in Exhibit 1057 with the sequences that 11:27:30
21 are in Exhibit 1054 based on the designation? 11:27:35
22 I'm not sure what the right term for that 11:27:42

1 is, but in the left-hand most column on 1057; is 11:27:46
2 that right? 11:27:50
3 A The accession numbers are -- 11:27:50
4 Q Accession numbers. Thank you. 11:27:54
5 A Yes.
6 Q Okay. So yeah. You use the accession 11:27:56
7 number -- you can use the accession numbers in 11:27:57
8 Exhibit 1057, which are in the left-hand most 11:28:02
9 column to match the sequences in Exhibit 1057 with 11:28:05
10 the sequences in 1054; is that right? 11:28:09
11 A Yes. 11:28:09
12 Q So the first -- the sequence at the very 11:28:15
13 top in Exhibit 1057 has accession number 11:28:19
14 NP003108.2, and that sequence in Exhibit 1054, 11:28:29
15 that's the third sequence on the list. 11:28:33
16 It's PH20 isoform number 1; is that right? 11:28:39
17 A That is correct. Yes. 11:28:42
18 Q Do you know why you used the isoform 11:28:43
19 number 1 as your lead sequence in the alignment in 11:28:49
20 1057, as opposed to the isoform 2 that you entered 11:28:52
21 into BLAST in Exhibit 1054? 11:28:57
22 A Yeah. That's a byproduct of the 11:29:04

1 processing steps that I took in order to reduce 11:29:11
2 the set of 95 sequences to 88 by illuminating 11:29:15
3 redundancy. 11:29:22
4 At the time I assumed that the longest 11:29:25
5 sequence might be what we want. Given that two -- 11:29:29
6 given two sequences that are from the same gene, I 11:29:35
7 decided to go with the longest isoform. That was 11:29:42
8 the logic in the script that I developed in order 11:29:46
9 to identify redundancy and filter it down to 88. 11:29:49
10 It turned out that isoform 1 has 511 amino 11:29:57
11 acids; whereas isoform 2 has 9 -- 509 amino acids. 11:30:04
12 So the program picked isoform 1 as opposed to 11:30:10
13 isoform 2 as the sequence to keep in the final 88. 11:30:15
14 They are different in the final 14 amino 11:30:20
15 acids of isoform 2. They are identical up to 495, 11:30:25
16 but afterwards they deviate. And for that reason, 11:30:32
17 isoform 1 ended up being included in the final 11:30:43
18 set. And because I didn't -- yeah. So that was 11:30:49
19 that. 11:30:50
20 Q Okay. Okay. So you selected the longest 11:30:50
21 isoform, which is isoform 1, which has the 511 11:30:56
22 amino acids as the lead sequence in your 11:31:01

1 alignment? 11:31:02
2 A That's correct. Yes. 11:31:02
3 Q Okay. All right.
4 A 511, minus the ones that didn't match to 11:31:05
5 isoform 2. In other words, the sequences that 11:31:09
6 were used in the multiple sequence alignment are 11:31:13
7 the portions of the sequences that were matched by 11:31:17
8 BLAST. 11:31:22
9 Q Okay. 11:31:24
10 A So comparing isoform 2 and 1, that 11:31:25
11 alignment went up to 495. So only the first 495 11:31:29
12 amino acids of isoform 1 was used in the final 11:31:36
13 multiple sequence alignment, which incidentally is 11:31:42
14 exactly the same as isoform 2. 11:31:46
15 Q Okay. I understand. 11:31:49
16 A So despite the fact that it has a 11:31:49
17 different accession number, the results would have 11:31:52
18 been identical. But I used... 11:31:57
19 Q Okay. Okay. I see. Okay. I understand. 11:31:58
20 All right. So let's turn in your 11:32:39
21 declaration to Paragraph 30. 11:32:40
22 A Okay. 11:33:07

1 Q All right. So in Paragraph 30, you say: 11:33:10
2 Using the alignment identified 68 largely 11:33:13
3 invariant residues that a skilled artisan would 11:33:17
4 have deemed essential residues in PH20 based on 11:33:23
5 the sequence alignment, and then you have the 11:33:29
6 table, right? 11:33:28
7 A Yes. 11:33:29
8 Q Can you explain what you mean by the term 11:33:31
9 invariant in that sentence? 11:33:36
10 A By invariant, I mean that once the 11:33:45
11 sequences have been aligned by Clustal Omega, 11:33:49
12 there are certain positions where the identity of 11:33:55
13 the amino acid does not change at all, or it 11:33:58
14 changes only ever so slightly. 11:34:02
15 Q And the cut-off that you used to identify 11:34:09
16 invariant residues is 95 percent; is that right? 11:34:12
17 A I used 95 percent as the cut-off, yes. 11:34:21
18 Q And how did you arrive at the 95 percent 11:34:25
19 number? 11:34:29
20 A Well, there are two ways to think about 11:34:37
21 it. I wanted to ensure that the preference of the 11:34:43
22 wild-type amino acid at that position is 11:34:50

1 statistically significant compared to other amino 11:34:55
2 acids that may occur at that position. And 95 11:35:01
3 percent seemed pretty convincing. 11:35:02
4 (Reporter clarification.) 11:35:11
5 A That would be a simple explanation. 11:35:11
6 Q Had you used a 95 percent cut-off in your 11:35:17
7 work before to identify invariant residues? 11:35:21
8 ATTORNEY KUSHAN: Objection. Form. 11:35:27
9 A Never had the occasion to having to 11:35:31
10 identify invariant residues before. So no, I have 11:35:36
11 not used 95 percent per se. 11:35:44
12 Q So in your work, when you perform sequence 11:35:46
13 alignments, you never identified invariant 11:35:50
14 residues in those alignments? 11:35:56
15 ATTORNEY KUSHAN: Objection. Foundation. 11:36:01
16 A I do identify. However, the focus of my 11:36:02
17 past studies have not been on invariant residues. 11:36:07
18 Therefore, having to put a number on where the 11:36:20
19 cut-off needs to be has never occurred. 11:36:24
20 Q So are you saying that in your work, when 11:36:28
21 you would perform a sequence alignment like this, 11:36:32
22 you would identify residues that were conserved, 11:36:35

1 but you never had to go through the exercise of 11:36:40
2 categorizing residues, as invariant versus not 11:36:43
3 invariant, and so that's why you haven't -- you 11:36:50
4 didn't use a cut-off? 11:36:52
5 ATTORNEY KUSHAN: Objection. Form. 11:36:53
6 A Right. My goals were different and did 11:36:54
7 not require having to identify invariant residues 11:36:58
8 and having to put a number on the conservation. 11:37:05
9 Q So in your work in 2011, did you perform 11:37:10
10 BLAST searches and then form sequence alignments 11:37:15
11 of homologous proteins, like you did here? 11:37:19
12 ATTORNEY KUSHAN: Objection. Foundation. 11:37:22
13 A Are you referring to my independent work? 11:37:23
14 Q Yes. 11:37:27
15 A That might have happened in 2011? 11:37:28
16 Q Yes. 11:37:31
17 A Which, by the way, I haven't done any in 11:37:31
18 2011, I don't think. 11:37:35
19 But prior to that, perhaps? 11:37:36
20 Q Uh-huh. Yeah. In your independent work. 11:37:39
21 A Yeah. What about it? 11:37:40
22 Q Had you used BLAST to identify homologous 11:37:42

1 sequences and then perform the multiple sequence 11:37:46
2 alignment? 11:37:50
3 A That I have, yes. 11:37:53
4 Q Okay. And why did you do that? What was 11:37:54
5 the goal? 11:37:57
6 A The goal was to identify what other amino 11:37:58
7 acids we might try at various positions in the 11:38:02
8 protein that we're working with. 11:38:06
9 Q So you were -- you performed this 11:38:10
10 alignment to identify potential candidates for 11:38:13
11 substitution in the protein that you were working 11:38:17
12 with? 11:38:21
13 A That is correct. 11:38:21
14 Q Okay. Did you already -- did you know 11:38:22
15 what residues were essential for function in that 11:38:30
16 protein? 11:38:34
17 ATTORNEY KUSHAN: Objection. Foundation. 11:38:35
18 A Essential residues weren't of interest to 11:38:39
19 us. It was actually a non-essential residue, a 11:38:43
20 residue that actually varied quite a bit from one 11:38:47
21 protein to another that we were interested in. We 11:38:52
22 wanted to see whether we could introduce a 11:38:56

1 mutation at that variable position in order to 11:39:02
2 improve the function of that protein that we were 11:39:05
3 working with. 11:39:06
4 Q And why were you focussed on that one 11:39:06
5 specific position? 11:39:10
6 A There have been a lot of studies on this 11:39:12
7 protein. This is a well-known protein. And the 11:39:15
8 amino acids important for function were also well 11:39:22
9 known, so we paid our attention to those positions 11:39:27
10 more than amino acids. 11:39:32
11 Q Okay. What protein? 11:39:37
12 A Streptavidin. 11:39:39
13 Q So you were trying to improve the function 11:39:58
14 in streptavidin by introducing mutations at a 11:40:02
15 particular position; is that right? 11:40:08
16 A That is correct. 11:40:08
17 Q And how did you arrive at the particular 11:40:09
18 position that you wanted to change in 11:40:13
19 streptavidin? 11:40:17
20 A That position was known to be important. 11:40:17
21 Q Was it known to be important through 11:40:24
22 studies in the literature? 11:40:29

1 A Yes. 11:40:28
2 Q When you say important, what do you mean? 11:40:39
3 A The residue at that position seems to be 11:40:45
4 involved in ligand binding. 11:40:52
5 (Reporter clarification.) 11:41:03
6 Q And were you able to improve streptavidin 11:41:03
7 activity by introducing mutations at that 11:41:13
8 position? 11:41:12
9 A Yes. It did improve. 11:41:14
10 Q Did you do the work in your lab that 11:41:23
11 identified that position as important in ligand 11:41:25
12 binding? 11:41:32
13 A Did we do the work in the lab? 11:41:33
14 Repeat that question, please. 11:41:37
15 Q Let me try to ask a different question. 11:41:38
16 How do you know that that position was -- 11:41:42
17 that that position was important in ligand 11:41:47
18 binding? 11:41:49
19 A As I said, previous studies by other labs 11:41:50
20 have identified that position to be involved in 11:41:56
21 ligand binding. 11:42:02
22 Q Was that position that you were trying to 11:42:32

1 change in streptavidin, was that position 11:42:36
2 essential to the protein folding? 11:42:39
3 A No. I don't think so. 11:42:46
4 Q Okay. In your -- in your work, in terms 11:42:51
5 of introducing substitutions into proteins, have 11:42:59
6 you ever tried introducing substitutions into a 11:43:04
7 position that is essential for protein folding? 11:43:06
8 ATTORNEY KUSHAN: Objection. Form. 11:43:10
9 A No. I have never tried to introduce a 11:43:14
10 mutation at a position that is known to be 11:43:17
11 important for folding. 11:43:21
12 Q Would you expect that if you tried to 11:43:22
13 introduce a mutation into a position known to be 11:43:25
14 important for folding, that the -- that the 11:43:28
15 protein would not be able to fold correctly? 11:43:29
16 A I would expect that; therefore, I would 11:43:36
17 not try that. 11:43:39
18 Q Is it fair to say that a person skilled in 11:43:49
19 the art would expect that if you introduced 11:43:54
20 positions into residues that are important for 11:43:58
21 folding, the resulting protein will not be 11:44:02
22 properly folded? 11:44:06

1 ATTORNEY KUSHAN: Objection. Foundation. 11:44:08
2 A I think you may have garbled up words 11:44:12
3 there. 11:44:17
4 Q That's possible. Let me try to ask that 11:44:17
5 better. 11:44:20
6 A Okay. 11:44:20
7 Q So okay. So would persons skilled in the 11:44:20
8 art understand that if you try to introduce a 11:44:28
9 substitution into a position known to be important 11:44:32
10 for folding, the protein would not be able to fold 11:44:36
11 correctly? 11:44:39
12 ATTORNEY KUSHAN: Objection. Foundation. 11:44:40
13 Objection as to form. 11:44:41
14 A That really depends on the nature of the 11:44:43
15 conservation. Some amino acids and residues are 11:44:49
16 important for reasons other than folding itself. 11:44:55
17 If it's an enzyme, for instance, the residue may 11:45:00
18 be important for catalysis.
19 (Reporter clarification.) 11:45:15
20 A And mutating those residues would abrogate 11:45:15
21 enzyme function; however, it would have minimal 11:45:23
22 impact on the folding of the protein. 11:45:27

1 So knowing what the conservation is for 11:45:27
2 would be relevant to calibrate one's expectation. 11:45:32
3 Q Okay. So along those lines, the skilled 11:45:37
4 person would expect that if you make a 11:45:43
5 substitution in a residue that's essential for 11:45:46
6 catalysis, the skilled person would expect that 11:45:51
7 you're going to inactivate the protein; is that 11:45:53
8 right? 11:45:57
9 ATTORNEY KUSHAN: Objection. Foundation. 11:45:57
10 Objection as to form. 11:45:58
11 A Introducing a mutation at a position that 11:46:01
12 is catalytically important often abrogates the 11:46:06
13 enzyme function. That would be the expectation. 11:46:14
14 Q So let's turn to Appendix D-1. 11:46:26
15 A D-1?
16 Q D-1, yeah. Which starts on Page 126. 11:46:41
17 Okay. You have it. 11:46:44
18 A I'm on that. 11:46:44
19 Q Can you explain what you have -- what 11:46:46
20 you've set forth in exhibit -- or, Appendix D-1, 11:47:11
21 Appendix D, Part 1, rather? 11:46:57
22 A D, Part 1. Yes. 11:46:59

1 This is the output of the analysis of the 11:47:06
2 multiple sequence alignment from Clustal Omega 11:47:14
3 that we saw earlier in Exhibit 1057. I developed 11:47:18
4 a script that took this as an input, and for each 11:47:27
5 amino acid in PH20 -- that's the top line -- I 11:47:33
6 would give it a residue number -- that's 11:47:46
7 wild-type 1, wild-type 2 -- corresponding to the 11:47:51
8 first amino acid, second amino acid, of PH20. And 11:47:54
9 for that position, from the alignment, I counted 11:48:00
10 the appearance of various amino acids and computed 11:48:05
11 the actual number, as well as the percentage, 11:48:10
12 which is divided by -- which is obtained by 11:48:16
13 dividing that number by 88. 11:48:20
14 So for the first position, you have 11:48:24
15 methionine, M, wild-type position number 1, 11:48:33
16 methionine. If you look at the alignment, you see 11:48:34
17 some sequences that have methionine at the 11:48:38
18 beginning. But then there are a lot of sequences 11:48:41
19 that don't have any matching residue. The absence 11:48:45
20 of a matching residue is indicated by dashes. 11:48:48
21 So there are a lot of dashes. So the dash 11:48:51
22 appears 72 times. Methionine appears 16 times, 11:48:53

1 divided by 88, will give you 18.18. So the top 11:48:59
2 line says: Methionine appears 18.18 percentage, 11:49:00
3 but the most frequent residue, in this case a 11:49:05
4 dash, appears 81.81 percentage. 11:49:15
5 Then you will do that for every position 11:49:18
6 of PH20, all the way down to the last amino acid, 11:49:21
7 which I believe is 495 -- yeah, 495 -- for the 11:49:28
8 reasons that I explained earlier. 11:49:35
9 Q Okay. And the sequence that you used 11:49:37
10 includes the 35 amino acid signal peptide, right? 11:49:40
11 A It does include the 35 signal sequence at 11:49:45
12 the beginning, yes. 11:49:50
13 Q Okay. So we start with position -- let's 11:49:51
14 see. Actually, let's just do -- so you refer to 11:49:57
15 position 320, or in the full length sequence it's 11:50:05
16 position 355, right? 11:50:09
17 A The full length sequence number would be 11:50:11
18 355. That is correct. 11:50:15
19 Q So in Appendix D-1, the residue in 11:50:16
20 question is residue 355? 11:50:22
21 A That is correct. 11:50:24
22 Q And that's on Page 146? 11:50:26

1 A Okay. 11:50:31
2 Q Okay. So it says: Wild-type 355 is D, 11:50:34
3 right? 11:50:40
4 Did you get it? 11:50:42
5 A I thought I did. 11:50:43
6 Q Wild-type residue position 355 is D, 11:50:45
7 right? 11:50:50
8 A Yes. 11:50:51
9 Q And if I'm understanding this correctly, 11:50:51
10 then D appears 10.22 percent of the time? 11:50:54
11 A Yes. 10.22 percent of the time, out of 11:50:59
12 the 88 sequences. 11:51:02
13 Q Okay. And the most common residue at that 11:51:03
14 position is K, right? 11:51:07
15 A That is correct. 11:51:09
16 Q And K appears 57.95 percent of the time? 11:51:10
17 A That's right. It appears 51 times out of 11:51:15
18 88, corresponding to 57.95 percent. Yes. 11:51:20
19 Q Okay. So why does it say, like, res394? 11:51:24
20 A Okay. One, you can ignore that number. 11:51:29
21 Q Okay.
22 A It's just a bookkeeping number. 11:51:32

1 Q Okay. 11:51:36
2 A Including all the dashes in the alignment. 11:51:37
3 Yeah. So I didn't know what I was using this 11:51:41
4 output for, ultimately when I was developing the 11:51:44
5 algorithm. So I just kept track of all the 11:51:48
6 positions. Because of the dashes, the wild-type 11:51:52
7 number actually corresponds to the amino acid 11:51:58
8 number in PH20. 11:52:02
9 Q Uh-huh.
10 A But res394, that's just a position in this 11:52:03
11 particular format. 11:52:09
12 Q Oh, okay. Okay. Got it. Thanks. 11:52:10
13 Okay. So in -- at the position 355, in 11:52:14
14 your alignment then all of the residues that 11:52:21
15 appear there, which are K, D, H, R, N, Q, S, G, E, 11:52:30
16 those are all of the amino acids that appear at 11:52:38
17 position 355 in the alignment; is that right? 11:53:10
18 A Yeah. The position corresponding to 11:52:44
19 wild-type residue in PH20, 355, yes. 11:52:50
20 Q Yes. Okay. 11:53:04
21 All right. So can you turn to 11:54:06
22 Paragraph 31? 11:54:07

1 A Okay. 11:54:18
2 Q So -- oh, actually. Sorry. 11:54:19
3 So we've talked about Paragraph 30, which 11:54:29
4 is where you have the 95 percent cut-off, right, 11:54:32
5 the essential residues? 11:54:38
6 A Yes. 11:54:40
7 Q Okay. And then you have a chart on 11:54:40
8 Page 14, and that gives all of the essential 11:54:42
9 residues; is that right? 11:54:47
10 A Page 14 lists essential residues, yes. 11:54:50
11 Q Okay. And so you have the residue number, 11:54:53
12 which is the -- the position in the wild-type 11:54:58
13 sequence that includes the signal sequence, right? 11:55:03
14 A Yes. Residue number -- yes. 11:55:11
15 Q Okay. And then the mature residue number 11:55:15
16 is the position in the sequence that does not 11:55:18
17 include the signal sequence? In other words, you 11:55:21
18 just subtract 35 from the residue number? 11:55:23
19 A That's correct. 11:55:27
20 Q Okay. And then the PH20 residue, and then 11:55:28
21 you have residue percent. So is the residue 11:55:34
22 percent the frequency with which the PH20 residue 11:55:40

1 occurs in the alignment of that position? 11:55:44
2 A That is correct. The residue percentage 11:55:47
3 corresponds to the wile type residue of PH20. 11:55:50
4 Q Okay. So for example, the first entry in 11:55:57
5 your chart is mature residue position 14, and it's 11:56:00
6 PH20 residue F, and the residue appears 95.5 11:56:09
7 percent of the time. So is it the case then 11:56:16
8 that -- am I understanding this correctly, that in 11:56:18
9 the alignment at mature residue position 14, 95.5 11:56:20
10 percent of the time there is an F? 11:56:26
11 A That is correct. 11:56:27
12 Q Okay. So then -- and there are 68 11:56:37
13 residues that you identified as essential, right? 11:56:44
14 A There are 68 residues in this table 11:56:49
15 labeled essential, yes. 11:56:53
16 Q And those 68 residues are the residues 11:56:56
17 that the skilled person would understand to be 11:57:01
18 essential to protein folding? 11:57:05
19 ATTORNEY KUSHAN: Objection. Foundation. 11:57:06
20 A Essential, not necessarily for folding. 11:57:11
21 Again, some residues may be conserved for other 11:57:16
22 reasons besides folding a cell. For this class of 11:57:22

1 proteins, that really comes down to the catalatic 11:57:26
2 residue. So catalatically important residues also
3 be conserved, and therefore included in this list. 11:57:32
4 Q So -- okay. So is the 68 residue list 11:57:35
5 then, does that include residues that are 11:57:40
6 essential for folding and/or catalytic activity? 11:57:41
7 ATTORNEY KUSHAN: Objection. Foundation. 11:57:47
8 A One would think that. 11:57:48
9 Q Okay. All right. 11:57:50
10 So now let's go to Paragraph 31 on the 11:57:53
11 next page. 11:57:56
12 So the second and third -- I'm looking at 11:58:07
13 the second and third sentence in Paragraph 31. 11:58:13
14 A I did get it. 11:58:17
15 Q Nice. Okay. 11:58:18
16 The second and third sentence in 11:58:21
17 Paragraph 31: The existence of evolutionary 11:58:24
18 segregation at these positions indicates that the 11:58:30
19 homologous proteins have tolerated different amino 11:58:32
20 acids at those positions. 11:58:34
21 And so am I understanding correctly that 11:58:35
22 because the positions that you've labeled as 11:58:46

1 non-essential, because there's variation in the 11:58:48
2 amino acid at that position in the sequence, for 11:58:52
3 homologous proteins, that would indicate to a POSA 11:58:56
4 that the POSA could potentially introduce 11:59:00
5 substitutions at those positions? 11:59:05
6 A Because there is variation among naturally 11:59:13
7 occurring homologous proteins, a POSA would be 11:59:17
8 justified in thinking that a mutation may be made 11:59:22
9 at those positions without damaging the enzyme. 11:59:28
10 Q Okay. And then you say: Amino acids at 11:59:33
11 these positions in the different hyaluronidase 11:59:36
12 proteins would be considered non-essential 11:59:38
13 residues because the proteins presumably still 11:59:41
14 exhibit hyaluronidase activity when they are 11:59:43
15 mutated; is that right? 11:59:51
16 A They are considered non-essential, given 11:59:53
17 that there is variation. In other words, the 11:59:57
18 wild-type residue identity is not strictly 12:00:01
19 required, and that makes it non-essential from 12:00:06
20 that sense. 12:00:09
21 Again, it doesn't mean that it's anything 12:00:12
22 goes. One has to be careful. But from that 12:00:15

1 definition, yes. 12:00:19
2 Q But there are -- there are proteins in the 12:00:24
3 alignment that don't exhibit hyaluronidase 12:00:28
4 activity, right? 12:00:32
5 A That is correct. Yes. HYAL3, as I 12:00:33
6 mentioned earlier, doesn't seem to have known 12:00:38
7 activity. It must still be folded, and must be 12:00:41
8 doing something. Otherwise, there's no reason to 12:00:44
9 keep those amino acids where they are. It's so 12:00:48
10 easy to mutate them away. 12:00:49
11 In fact, hyaluronidase 6 in human is 12:00:51
12 supposed to be a pseudo gene, but it has diversed 12:00:53
13 so much you can't even find it, actually. It's 12:01:00
14 not easy to find.
15 The same fate would have happened to
16 hyaluronidase 3. The fact that it's around and 12:01:05
17 has all those conserved residues suggests that it 12:01:07
18 must be doing something. And in order to do be 12:01:11
19 doing something for a protein, it has to be 12:01:14
20 folded. 12:01:18
21 So one can deduce based on those 12:01:18
22 observations that -- yeah. So they are doing 12:01:23

1 something. They might not have strictly the 12:01:24
2 hyaluronidase activity. However, what's important 12:01:28
3 is that they do have a structure that is 12:01:31
4 sufficient to support activity. 12:01:35
5 That's what one would take away from this 12:01:40
6 multiple sequence alignment. Not a strict reading 12:01:45
7 that these enzymes exist because in the group, 12:01:47
8 they exhibit hyaluronidase activity, which we know 12:01:50
9 to be not true, with 3 and 4, for instance. 12:01:54
10 Q Okay. So the person of ordinary skill in 12:02:09
11 the art would understand that amino acids at those 12:02:12
12 non-essential positions and the different 12:02:30
13 hyaluronidase proteins -- actually, strike that. 12:02:23
14 It's going to be garbled. 12:02:24
15 I mean, the skilled person would 12:02:24
16 understand that the non-essential residues are 12:02:27
17 potentially amenable to change because different 12:02:35
18 amino acids are allowed at those positions and the 12:02:40
19 resulting proteins are folded and exhibit whatever 12:02:45
20 activity it is that they do? 12:02:48
21 A That was a long sentence. If you could 12:02:55
22 repeat some part of that sentence? 12:03:00

1 Q Uh-huh. 12:03:02
2 So the amino acids at the -- at the 12:03:06
3 positions that you termed non-essential would be 12:03:09
4 considered non-essential because the protein -- 12:03:13
5 the resulting protein is still folded and exhibits 12:03:15
6 some activity? 12:03:21
7 A They must have activity. Some activity, a 12:03:27
8 lot of activity, that's hard to say. But they 12:03:30
9 must have activity, and you still see a variation 12:03:35
10 in those individual sequences. Coupling those two 12:03:41
11 things was -- would lead one to believe that you 12:03:47
12 can have variation at these positions without 12:03:53
13 compromising the activity of the protein, which in 12:03:57
14 turn assumes that the protein would be folded. 12:04:02
15 ATTORNEY MARTIN: So it's 12:05. Is now a 12:04:13
16 good time to break for lunch? 12:04:17
17 ATTORNEY KUSHAN: Sure. 12:04:22
18 THE WITNESS: Okay. 12:04:23
19 THE VIDEOGRAPHER: We are going off the 12:04:23
20 record. The time is 12:04 p.m. 12:04:27
21 (Recess from 12:04 p.m. until 1:06 p.m.) 12:04:32
22 THE VIDEOGRAPHER: We are back on the 13:06:31

1 record. The time is 1:06 p.m. 13:06:35
2 BY ATTORNEY MARTIN: 13:06:38
3 Q Welcome back, Dr. Park. 13:06:40
4 Did you discuss the substance of your 13:06:42
5 deposition with anyone during the break? 13:06:44
6 A No. I did not. 13:06:47
7 ATTORNEY MARTIN: Okay. So can I ask, is 13:06:48
8 Dr. Hecht still on the Zoom? 13:06:51
9 ATTORNEY KUSHAN: I don't know. 13:06:55
10 Brian, are you on the Zoom? 13:06:58
11 ATTORNEY GOLDBERG: Sorry. I was just 13:07:02
12 unmuting. 13:07:05
13 Yes. Dr. Hecht and I are on the Zoom. 13:07:06
14 ATTORNEY MARTIN: Okay. So we object to 13:07:09
15 Dr. Hecht listening in to this deposition because 13:07:11
16 we believe it's improper witness coaching. 13:07:15
17 And so we're going to ask Dr. Hecht to 13:07:20
18 stop listening to the deposition. 13:07:21
19 ATTORNEY KUSHAN: How is this witness 13:07:21
20 coaching? 13:07:24
21 ATTORNEY MARTIN: Because he's listening 13:07:26
22 to the deposition, presumably to prepare for his

1 own deposition. 13:07:27
2 ATTORNEY KUSHAN: He can review the 13:07:27
3 deposition transcript, too. 13:07:29
4 ATTORNEY MARTIN: But it's different to 13:07:29
5 listen in to the deposition of another expert in 13:07:32
6 the same case and then -- 13:07:33
7 ATTORNEY KUSHAN: How? 13:07:33
8 ATTORNEY MARTIN: -- see how depositions 13:07:33
9 go so that you can understand, you know, what to 13:07:35
10 do for your deposition. 13:07:37
11 ATTORNEY KUSHAN: Look, I've been in 13:07:38
12 depositions where an expert who is not being 13:07:40
13 deposed is attending, and never been the basis for 13:07:43
14 objection. 13:10:06
15 ATTORNEY MARTIN: I have never had a 13:07:48
16 deposition where another -- an expert for the same 13:07:50
17 side is listening to -- who has not yet been 13:07:53
18 deposed is listening to another expert be deposed 13:07:55
19 before him. I have never had that, ever. 13:08:00
20 ATTORNEY KUSHAN: Well, you can object. I 13:08:03
21 don't know how long he's going to be on. You 13:08:08
22 know, he can remove himself. If you want to 13:08:10

1 consult with this -- with me on this, we can do 13:08:11
2 that on the next break. 13:08:15
3 ATTORNEY MARTIN: Okay. So our objection 13:08:15
4 is noted on the record, and understand that you're 13:08:17
5 not willing to remove Dr. Hecht from the 13:08:20
6 deposition. 13:08:23
7 ATTORNEY KUSHAN: Correct. 13:08:23
8 ATTORNEY MARTIN: All right. And to be 13:08:24
9 clear, the objection is witness coaching under 13:08:29
10 FRE-615. 13:08:37
11 BY ATTORNEY MARTIN: 13:08:49
12 Q Okay. So at the beginning -- at the very 13:08:50
13 beginning of this deposition, Dr. Park, you 13:08:54
14 gave -- you gave me a chart that had the 13:08:58
15 corrections to your declarations, right? 13:09:01
16 A Yeah. 13:09:03
17 Q So when did -- when did those corrections 13:09:04
18 first come to your attention? 13:09:06
19 A I noticed these errors while I was reading 13:09:21
20 the declarations in preparation for today's 13:09:27
21 deposition. 13:09:30
22 Q Okay. And when did that -- when did that 13:09:30

1 happen? 13:09:37
2 A The past three weeks, I would say. 13:09:41
3 Q Okay. And when was the chart prepared? 13:09:44
4 A This chart? 13:09:49
5 Q Yes. 13:09:50
6 A This was given to me this morning. 13:09:56
7 Q Got it. 13:09:59
8 Dr. Park, what did -- what did you do to 13:10:15
9 prepare for this deposition? 13:10:17
10 A To prepare for this deposition, I read the 13:10:22
11 declarations over. I read the articles over. I 13:10:29
12 went over the data to make sure that I was 13:10:34
13 familiar with the content of each file that was 13:10:38
14 being submitted. 13:10:42
15 Q When you said the data, you mean the data 13:10:47
16 in the appendices, or the exhibits to your 13:10:50
17 declaration? 13:10:54
18 A That's correct. 13:10:54
19 Q Okay. Did --
20 A I wanted to know what was exactly in that 13:10:55
21 file. I think I knew what it was, but wanted to 13:10:59
22 go over that one more time. 13:11:02

1 Q Did you meet with anyone to prepare for 13:11:03
2 this deposition? 13:11:06
3 A I met with counsel. 13:11:10
4 Q Was there anyone present who was not a 13:11:12
5 lawyer? 13:11:15
6 A No. 13:11:20
7 Q Okay. Have you had any communications 13:11:21
8 with Dr. Hecht regarding this case? 13:11:32
9 A We had Zoom meetings together. 13:11:40
10 Q About how many Zoom meetings? 13:11:43
11 A I want to say maybe four. I know it was 13:11:51
12 less than seven for sure, because I elaborated on 13:11:59
13 some of the positions, and there were seven of 13:12:06
14 them. 13:12:12
15 At some of the meetings, I discussed more 13:12:12
16 than one position, so it was definitely less than 13:12:15
17 seven. I don't remember exactly how many I 13:12:19
18 discussed at which days. My feeling is doubling 13:12:21
19 up -- doubling up on some of the days. It might 13:12:27
20 have been four meetings, say. 13:12:30
21 Q And approximately when did those meetings 13:12:33
22 take place? 13:12:37

1 A I think it was toward the end of last year 13:12:44
2 and beginning of this year. 13:12:48
3 Q Approximately how long were those 13:12:54
4 meetings? 13:12:57
5 A Those Zoom meetings lasted an hour and a 13:13:02
6 half to two hours each. 13:13:07
7 Q Did you -- did you ask to speak to 13:13:16
8 Dr. Hecht, or did he ask to speak to you, do you 13:13:20
9 know? 13:13:26
10 A During the Zoom meeting you mean? 13:13:26
11 Q Did you initiate -- in order to initiate 13:13:29
12 the meeting, did you request to speak with 13:13:31
13 Dr. Hecht? 13:13:37
14 A To initiate the meeting? 13:13:37
15 Q Yes. 13:13:40
16 A No. Those meetings were set up by 13:13:40
17 Mr. Kushan. 13:13:47
18 Q Okay. Got it. 13:13:48
19 Was any -- was anyone else present -- 13:13:49
20 strike that. 13:13:51
21 Was counsel present during the meetings 13:13:51
22 with Dr. Hecht? 13:13:54

1 A Yes. 13:13:55
2 Q Okay. Did you communicate with Dr. Hecht 13:13:57
3 about the substance of your declarations after you 13:14:23
4 signed them? 13:14:30
5 A After I signed them? I'm afraid I can't 13:14:28
6 tell which happened first, signing or the 13:14:39
7 discussion. 13:14:42
8 Q Okay. So let's turn -- did you -- did you 13:14:43
9 read Dr. Hecht's declarations? 13:15:43
10 A No. 13:15:45
11 Q Do you know what Dr. Hecht opined on in 13:15:45
12 connection with these PGRs? 13:15:51
13 A Pardon? 13:15:53
14 Q Do you know what the substance of 13:15:54
15 Dr. Hecht's testimony is? 13:15:56
16 A No. 13:15:58
17 Q Did you ask doctor -- or, sorry. Strike 13:15:58
18 that. 13:16:00
19 So let's turn to Paragraph 85. 13:16:00
20 ATTORNEY KUSHAN: I'm sorry, Counsel. 13:16:35
21 Before you proceed, we're going to have 13:16:36
22 Dr. Hecht leave this Zoom. We, of course, 13:16:39

1 disagree with your objection, but as of respect of 13:16:43
2 your request, we're going to honor your request 13:16:47
3 and have him leave. 13:16:51
4 ATTORNEY MARTIN: Thank you. 13:16:52
5 BY ATTORNEY MARTIN: 13:17:07
6 Q Okay. So in this section -- so, yeah. 13:17:09
7 Are you in Paragraph 85? 13:17:28
8 A I am in Paragraph 85. I wanted to see 13:17:30
9 where Paragraph 85 comes in, in the overall scheme 13:17:34
10 of things as I'm flipping through here. 13:17:39
11 Okay. I'll listen to your question first. 13:17:43
12 Q Okay. So the second sentence in 13:17:48
13 Paragraph 85, you say: I balanced the type of 13:17:52
14 impact of the substitutions based on the magnitude 13:17:55
15 of each interaction may have on the protein 13:18:00
16 structure. 13:18:03
17 Can you explain what you mean by the 13:18:04
18 impact of the substitutions, like, what -- what 13:18:06
19 you mean by impact, I guess? 13:18:09
20 A When a substitution is made, changes 13:19:00
21 happen. Some are favorable changes. Others are 13:19:04
22 unfavorable changes, and those changes are listed 13:19:09

1 in the paragraphs before this. There are many of 13:19:14
2 them. 13:19:17
3 Q Uh-huh. 13:19:18
4 A I was just looking through them. Many of 13:19:21
5 them are enumerated. I am factoring all of those 13:19:24
6 positive and negative changes trying to come up 13:19:32
7 with an estimate of where the net effects falls. 13:19:37
8 (Reporter clarification.) 13:19:44
9 Q Okay. So is it fair to say that you're 13:19:44
10 analyzing all the potential effects of a 13:19:50
11 substitution, and then trying to arrive at the 13:19:54
12 overall net effect? 13:19:58
13 A That would be a correct summary, yes. 13:19:59
14 Q Okay. And when you reference the 13:20:04
15 magnitude of each interaction, what do you mean -- 13:20:06
16 what do you mean by magnitude? 13:20:10
17 A It's more of a perception. When there are 13:20:19
18 two conflicting changes, I need to decide whether 13:20:25
19 there are of equivalent magnitude, meaning is one 13:20:30
20 as positive as the other one is negative, or is 13:20:36
21 one factor more significant than the other. And 13:20:41
22 if so, what would be the sum of all those number 13:20:44

1 of interactions. 13:20:51
2 So without putting a number on the 13:20:54
3 magnitude, which obviously cannot be done, based 13:20:58
4 on visual inspection, I try to apply my experience 13:21:03
5 and my viewpoint as a POSA, to determine whether 13:21:09
6 the net change would be in favor of the protein 13:21:22
7 structure and stability and function, or the other 13:21:27
8 way around, whether it would negatively impact the 13:21:31
9 structure and function. 13:21:34
10 Q And so based on that assessment, you used 13:21:45
11 a scoring system of -- using the numbers 1, 2 13:21:54
12 and 3, right? 13:21:58
13 A I did use a system of 1, 2 and 3. Yes. 13:21:58
14 Q Had you used that scoring system before in 13:22:01
15 your work, outside of this case? 13:22:05
16 A Maybe implicitly, but not in those terms. 13:22:11
17 Q So is it fair to say that in your work 13:22:17
18 outside of this case, you had perhaps looked at 13:22:22
19 potential substitution and determine whether you 13:22:25
20 would expect it to improve the stability or have a 13:22:29
21 neutral effect or have a negative effect, but you 13:22:33
22 wouldn't necessarily give it a 1, 2 or 3 rating? 13:22:37

1 ATTORNEY KUSHAN: Objection. Form. 13:22:41
2 A That is correct. I never had the need to 13:22:45
3 put a number on what I see. 13:22:49
4 Q And why did you need to put a number on 13:22:55
5 what you see in your analysis in this case? 13:22:58
6 A In order to put those substitutions in 2/3 13:23:08
7 bins so that I can say whether a mutation would be 13:23:12
8 likely to be tolerated or not tolerated. I had to 13:23:20
9 make that qualitative decision for the purpose of 13:23:27
10 this declaration, and that required me to classify 13:23:34
11 the substitutions in different bins. There could 13:23:37
12 have been two, yes or no. But as I was looking 13:23:42
13 through the substitutions, some stood out and I 13:23:45
14 felt comfortable classifying some of them as a 13:23:48
15 favorable mutation, not just acceptable mutual 13:23:55
16 mutations. 13:24:22
17 Q So did you arrive at the 1, 2, 3 scoring 13:24:02
18 system as you were doing your analysis in this 13:24:06
19 case? 13:24:11
20 A Yes. I developed the system 1, 2 and 3 as 13:24:11
21 I was looking at the substitutions. 13:24:16
22 Q Okay. So is it fair to say that a score 13:24:39

1 of 3 would be expected to be a favorable 13:24:42
2 substitution; is that right? 13:24:47
3 A That's how the system is set up, yes. 13:24:50
4 Q Okay. 13:24:53
5 A By classification. System is set up, so 13:24:53
6 that 3 indicates a favorable substitution. 13:24:58
7 Q And then is 2, is that a neutral 13:25:01
8 substitution? 13:25:05
9 A Neutral plus/minus delta. In other words, 13:25:06
10 I -- if there's a change in stability in either 13:25:14
11 direction, I thought it would be minor change, not 13:25:18
12 really worthy of separate classification, but 13:25:22
13 something equivalent to wild-type. 13:25:30
14 Q Okay. And 1, is that a disfavored 13:25:35
15 substitution, or unfavorable substitution? 13:25:43
16 A 1 corresponds to substitutions for which I 13:25:47
17 had real reservation. Something about the 13:25:51
18 substitution, say, worried me, then I would put 13:25:56
19 that substitution in the category of 1. 13:25:59
20 Q And when you say it worried you, does 13:26:01
21 that -- does that mean that you would expect it to 13:26:05
22 potentially have a detrimental impact on protein 13:26:08

1 structure or function? 13:26:19
2 A Yes. That's what I mean. 13:26:19
3 Q Okay. And for a neutral change, would you 13:26:21
4 expect that change to not have a meaningful effect 13:26:24
5 on protein structure and function? 13:26:28
6 A That's correct. There may be a change, 13:26:32
7 but I didn't think the change would be meaningful 13:26:35
8 enough. 13:26:38
9 Q So for those residues where you scored the 13:26:39
10 mutation as a 2, you would expect those changes 13:26:43
11 not to meaningfully impact the protein structure 13:26:48
12 and function? 13:26:54
13 A That would be the correct way to interpret 13:26:55
14 a score of 2. 13:26:57
15 Q And for a score of 3, you would expect 13:26:59
16 that the substitution potentially would improve 13:27:02
17 function, or would have no effect on function? 13:27:08
18 ATTORNEY KUSHAN: Objection. Foundation. 13:27:11
19 A Score of 3 is a substitution that I can 13:27:15
20 get excited about. Yes. So those are 13:27:20
21 substitutions I had high hopes for. 13:27:26
22 Q And when you say you have high hopes for 13:27:31

1 them, what would you expect to see with those 13:27:34
2 substitutions? 13:27:38
3 A I would expect those substitutions to 13:27:39
4 improve the stability and perhaps function of the 13:27:41
5 enzyme. 13:27:45
6 Q How could you tell if a mutation improves 13:27:46
7 the stability of an enzyme? 13:27:51
8 A There are a number of things one needs to 13:27:55
9 consider when entertaining a substitution. If the 13:27:59
10 individual factors are favorable, then I would 13:28:06
11 expect the net effect of the substitution would be 13:28:11
12 overall favorable. And if I see several such 13:28:15
13 effects, combined with an absence of any 13:28:21
14 noticeable negative effect, I would think that 13:28:27
15 that substitution would improve the protein, not 13:28:32
16 necessarily the enzyme, but a protein in terms of 13:28:37
17 stability. 13:28:40
18 Q Okay. So you mentioned that in your work 13:28:41
19 outside of this case you would analyze potential 13:29:09
20 substitution and determine whether it would be 13:29:12
21 favorable, unfavorable or neutral. Was that the 13:29:14
22 case in the 2011 time frame? 13:29:18

1 A Again, in 2011, I don't think I was doing 13:29:24
2 that particularly. But if you're referring to 13:29:29
3 time before then, I was looking at various 13:29:32
4 substitutions. Most of the time, I wouldn't care 13:29:36
5 for substitutions that are 2 or 1. Neutral 13:29:40
6 substitutions are not that interesting from my 13:29:44
7 perspective.
8 My ultimate goal as an academic person is 13:29:46
9 to publish. You need to have an exciting 13:29:50
10 discovery to publish. A neutral substitution does 13:29:53
11 not constitute an exciting discovery that deserves 13:29:59
12 a publication. As such, I wouldn't care much 13:30:02
13 about substitutions that are 2, much less 1. It 13:30:06
14 would have to be 3, and plus. 13:30:09
15 So those are the substitutions that I 13:30:11
16 would care mostly about. There were many 13:30:14
17 substitutions that would be in the groups of 2's 13:30:19
18 and 1's. I wouldn't care much about them. 13:30:21
19 Q So if you were looking to make a 13:30:40
20 substitution into a -- into a protein, you 13:30:43
21 wouldn't be looking for a substitution that would 13:30:47
22 have no effect. You would be looking for a 13:30:50

1 substitution that would have an improved effect, 13:30:55
2 or at least some difference in effect; is that 13:30:56
3 right? 13:30:58
4 ATTORNEY KUSHAN: Objection. Foundation. 13:30:58
5 Also objection as to form. 13:31:00
6 A We're talking about a different situation, 13:31:03
7 different scenario. My goal as an independent 13:31:08
8 researcher would not necessarily be aligned with 13:31:12
9 the goals of this particular declaration. My 13:31:16
10 objective is quite different. 13:31:20
11 As you said, I would be interested in 13:31:23
12 improving the enzyme, not necessarily finding a 13:31:25
13 substitution that would be neutral and doesn't 13:31:30
14 really change the protein per se. That is not 13:31:34
15 really the mandate for this work. 13:31:40
16 As I understand it, I was instructed to go 13:31:47
17 find substitutions that would be tolerated at 13:31:49
18 non-essential positions in this enzyme, and that's 13:31:54
19 what I did. 13:31:57
20 Q Okay. And when you say tolerated, you 13:31:58
21 mean substitutions that were neutral or 13:32:17
22 beneficial; is that right? 13:32:05

1 ATTORNEY KUSHAN: Objection. Foundation. 13:32:07
2 A I define the word tolerate in the 13:32:08
3 declaration. 13:32:14
4 Q Uh-huh.
5 A It's in the terminology used in the 13:32:19
6 declaration, Page 5 I believe. 13:32:22
7 Q Oh. It's actually in Paragraph 20. 13:32:33
8 A Oh, is it. Okay. The following, yes. 13:32:35
9 I use the word tolerate -- it should be in 13:32:40
10 quotation -- here to mean that the presence of a 13:32:44
11 single amino acid at a particular position of the 13:32:47
12 protein's amino acid sequence does not materially 13:32:50
13 alter the local structure around that position in 13:32:55
14 the protein, and thus does not meaningfully alter 13:32:55
15 the biological activity of the protein.
16 In terms of ranking, that would correspond 13:32:59
17 to 2 and 3 of the classification. 13:33:02
18 Q Okay. So going back to -- let's see. 13:33:08
19 So do you -- would you expect that 13:33:29
20 mutations that you've scored as 2 or 3, would you 13:33:42
21 expect those to impact protein function? 13:33:47
22 A Hard to say. I have not considered that 13:33:59

1 aspect much. I was mostly concerned with the 13:34:03
2 compatibility of the substitution in terms of the 13:34:09
3 structure, whether the substitution would be 13:34:18
4 tolerated by the structure of the PH20. 13:34:20
5 If those substitutions are within the 13:34:24
6 active site, which I can roughly guess based on 13:34:28
7 the shape of the molecule. However, precisely 13:34:32
8 what residues are involved in catalysis is not 13:34:37
9 well known, so that would at best, an educated 13:34:42
10 guess. If I see a position that is close to where 13:34:45
11 I would expect the ligand or the substrate would 13:34:49
12 be, then I would try to include that in the 13:34:53
13 consideration. But I was mostly interested in the 13:34:59
14 compatibility of the substitution with the 13:35:04
15 structure of the enzyme more than anything else. 13:35:08
16 Q Okay. So did you -- did you evaluate 13:35:11
17 whether you would expect the change to impact the 13:35:16
18 function of the protein? 13:35:19
19 A I did not address that question directly. 13:35:23
20 However, when it was apparent to me that the 13:35:27
21 substrate would be near that particular position, 13:35:36
22 I tried to model that as much as possible. 13:35:39

1 However, the substrate bound structure of the 13:35:45
2 enzyme is not known. Therefore, those 13:35:49
3 considerations may not be very accurate. 13:35:55
4 Fortunately, there weren't that many positions, 13:36:00
5 because the active site residues are fewer than 13:36:04
6 the rest of the protein. 13:36:14
7 In other words, there are more amino acids 13:36:16
8 away from the active site than at the active site. 13:36:19
9 So a fraction of the residues might be in the 13:36:25
10 active site, and I would, if I can, fold that into 13:36:28
11 the consideration, but not actively. If I get 13:36:33
12 the -- the role of the enzymatic function 13:36:38
13 incorrect, I do not worry about that aspect much. 13:36:43
14 Q So you say in Paragraph 20, in the context 13:37:04
15 of your definition of tolerate, that the -- it 13:37:38
16 doesn't materially alter the local structure, and 13:37:25
17 thus does not meaningfully alter the biological 13:37:28
18 activity of the protein, right? 13:37:35
19 ATTORNEY KUSHAN: Objection. Foundation. 13:37:39
20 A Does not meaningfully alter the biological 13:37:42
21 activity in the way of structural preservations. 13:37:48
22 In other words, a substitution that doesn't 13:37:55

1 change the structure of a protein, it would not 13:37:59
2 affect the activity of the enzyme unless, of 13:38:05
3 course that residue happens to be involved in 13:38:09
4 catalysis. 13:38:16
5 Some of them are known. We know from 13:38:18
6 other publications that there are catalytic 13:38:22
7 residues. If you mutate them, you would lose the 13:38:26
8 activity 100 percent, and those positions are also 13:38:31
9 unlikely to be structurally important. 13:38:34
10 Based on the structure, one can surmise 13:38:38
11 that some of those substitutions are important for 13:38:44
12 catalyst, but not necessarily for the folding of 13:38:51
13 the protein. So here, what is meant is it doesn't 13:38:56
14 affect the biological activity because the 13:39:32
15 structure will be maintained upon substitution. 13:39:07
16 Q So you expect that after the substitution 13:39:10
17 is made, that the -- the protein structure -- the 13:39:15
18 protein will maintain the same structure, and so 13:39:20
19 therefore it will also maintain the same function; 13:39:23
20 is that right? 13:39:26
21 ATTORNEY KUSHAN: Objection. Foundation. 13:39:26
22 Also objection as to form. 13:39:28

A Given that the structure of the protein is 13:39:34
critical for its activity, if you introduce a 13:39:38
substitution that leaves a structure untouched, it 13:39:44
would be reasonable to think that the biological 13:39:50
activity would remain the same. 13:39:54
Q And so is it your opinion that a person of 13:40:04
ordinary skill in the art would expect that if you 13:40:08
leave a structure untouched that the biological 13:40:12
activity would remain the same? 13:40:16
ATTORNEY KUSHAN: Objection. Foundation. 13:40:19
Also objection as to form. 13:40:23
A To a degree that would be true, as long 13:40:26
as, as I said earlier, the mutation does not 13:40:37
affect known catalytically important residues. In 13:40:45
this case, you can keep the structure the same and 13:40:51
you would lose activity. So all bets are off in 13:40:55
those cases. 13:40:58
Q Okay. When you look at the model, the 13:40:59
structural model, are you able to identify 13:41:04
residues that are important for protein folding? 13:41:09
A From the structure alone, no. That would 13:41:17
be hard. 13:41:22

1 Q In connection with the -- are you able to 13:41:28
2 use the structure in connection with the alignment 13:41:31
3 to identify residues that important for protein 13:41:34
4 folding? 13:41:37
5 A I think the alignment can help you 13:41:40
6 greatly. It will help you identify a significant 13:41:45
7 number of residues that are important for folding. 13:41:50
8 Q I'm just trying to understand what is it 13:41:55
9 about a residue that makes it important for 13:41:58
10 protein folding? 13:42:01
11 ATTORNEY KUSHAN: Objection to form. 13:42:03
12 A That's the essence of protein folding. If 13:42:09
13 I knew the answer, it would be great. I don't 13:42:14
14 think anybody does, unfortunately. 13:42:18
15 Q Okay. So when you designed the scoring 13:42:20
16 system that you used in this declaration, you were 13:42:56
17 approaching the issue from the perspective of a 13:43:01
18 POSA; is that right? 13:43:05
19 A Yes. 13:43:07
20 Q Okay. 13:43:12
21 Okay. So can we turn to Appendix C? 13:43:35
22 A I am at Appendix C. 13:43:59

1 Q Okay. So Appendix C has your analysis for 13:44:02
2 position 320; is that right? 13:44:12
3 A That is correct. 13:44:18
4 Q And is it correct that the alternate -- 13:44:21
5 strike that. 13:44:29
6 So for position 320, the alternative 13:44:29
7 residues that you considered are those alternative 13:44:36
8 residues that appear at position 320 in the 13:44:40
9 alignment; is that right? 13:44:43
10 ATTORNEY KUSHAN: Objection. 13:44:46
11 A Yes. 13:44:47
12 ATTORNEY KUSHAN: Objection to foundation. 13:44:48
13 Go ahead. 13:44:51
14 Q So the only residues that you consider as 13:44:51
15 alternative residues are those that appear in the 13:44:54
16 alignment at that position, right? 13:44:58
17 ATTORNEY KUSHAN: Objection. Foundation. 13:45:00
18 A I only consider the residues that appeared 13:45:04
19 in the multiple sequence alignment for 13:45:07
20 consideration at this position, yes. 13:45:10
21 Q Why did you only consider the residues 13:45:12
22 that appear in the multiple sequence alignment at 13:45:15

1 that position? 13:45:18
2 A That goes back to the assumption that was 13:45:25
3 stated earlier in the declaration, that the 13:45:28
4 residues that appear among homologous sequences 13:45:31
5 have been tested by evolution and proven to be 13:45:40
6 compatible with the structure. Therefore, looking 13:45:44
7 at those possibilities would make sense. 13:45:48
8 And so that is in the Paragraph 31, I 13:46:07
9 think, which is the one that you referred to 13:46:09
10 earlier. Maybe... 13:46:11
11 The existence of evolutionary variation at 13:46:29
12 these positions indicates that the homologous 13:46:31
13 proteins have tolerated different amino acids at 13:46:38
14 those positions, including 320. Those proteins 13:46:42
15 presumably exhibit hyaluronidase activity when 13:46:44
16 they are mutated. 13:46:54
17 So in other words, the homologous 13:46:56
18 sequences that are part of the multiple sequence 13:46:57
19 alignment, they are -- they have explored other 13:46:59
20 possible substitutions at various non-essential 13:47:04
21 positions, including 320, and somehow they have 13:47:08
22 survived. They continue to exhibit activities, if 13:47:15

1 necessary, or at a minimum, managed to stay 13:47:20
2 folded, which, as we discussed earlier, is 13:47:26
3 supported by the fact that conserved residues are 13:47:30
4 conserved, and they're conserved for a reason. 13:47:37
5 Without a reason, there is no reason for them to 13:47:42
6 be conserved. 13:47:46
7 So that is the evidence that they would 13:47:51
8 fold to the same structure. So that's the reason 13:47:51
9 for testing these residues, as opposed to other
10 residues that are not listed in the -- 13:47:55
11 Q Okay. 13:48:00
12 A -- in the multiple sequence alignment. 13:48:01
13 Q A POSA would understand that they could 13:48:07
14 also -- that they could, for example, at 13:48:10
15 position 320, that the aspartic acid could be 13:48:15
16 mutated to one of the other -- another amino acid
17 that's not listed here; is that right?
18 (Reporter clarification.) 13:48:33
19 A Could you repeat the question? What a 13:48:33
20 POSA might assume again? 13:48:36
21 Q Oh. A POSA would understand that if they 13:48:36
22 were looking to substitution position 320 -- 13:48:39

1 A Yes. 13:48:42
2 Q -- they could change position 320 13:48:42
3 theoretically to any of the other 19 amino acids, 13:48:46
4 right? 13:48:49
5 A Not if they have any hope of finding an 13:48:53
6 acceptable mutant. If they're looking for an 13:48:59
7 acceptable substitution, a POSA who's familiar 13:49:03
8 with the literature wouldn't just try any amino 13:49:07
9 acid. There has to be a foundation for what they 13:49:10
10 try, and this would give them the foundation. The 13:49:14
11 other substitutions wouldn't make any sense, so 13:49:18
12 they wouldn't try. Yeah. That's not what a POSA 13:49:22
13 would do. 13:49:27
14 Q So a POSA wouldn't just make random 13:49:34
15 changes and kind of hope for the best? 13:49:37
16 ATTORNEY KUSHAN: Objection. Foundation. 13:49:39
17 Also objection as to form. 13:49:42
18 A Not a POSA. A person off the street, yes. 13:49:43
19 But a person who is supposed to be 13:49:48
20 educated in the field and understand the factors 13:49:51
21 that contribute to protein folding, stability, no. 13:49:55
22 They wouldn't randomly try a substitution. No. 13:50:01

1 They wouldn't. 13:50:07
2 Q So in exhibit -- I'm sorry -- Appendix C, 13:50:38
3 the far right of Appendix C in your chart, you 13:50:43
4 have factors, hydrophobicity, secondary structure 13:50:49
5 and interactions, and there's the Number 1, for 13:50:51
6 some of them, but not all of them. 13:50:55
7 Can you just explain how you -- what this 13:50:57
8 means -- what that means? 13:50:59
9 A First of all, 1 is meant to be a check. 13:51:03
10 So you can understand 1 as a substitute for a 13:51:10
11 check. 13:51:16
12 (Reporter clarification.) 13:51:16
13 A Checkmark. I was doing this in Excel 13:51:16
14 spreadsheet, and it's easier to enter 1, as 13:51:24
15 opposed to a checkmark. 13:51:27
16 The three columns, which have the labels 13:51:28
17 of: Hydrophobicity, secondary structure, and then 13:51:33
18 I forget what the third one says. 13:51:36
19 Q Interactions. 13:51:38
20 A Interactions -- are the three main 13:51:39
21 categories of interactions, attributes that I 13:51:41
22 should consider during a substitution, and they 13:51:46

1 correspond to the intrinsic properties of that 13:51:51
2 amino acid, which is supposed to be the first 13:51:56
3 column. 13:51:59
4 I labeled it as hydrophobicity, but it 13:52:00
5 should really be hydrophobicity/hydrophilicity, 13:52:07
6 lots of other things that one might think of, 13:52:07
7 that's -- that belongs to that amino acid. 13:52:10
8 The second column is the secondary 13:52:13
9 structure, meaning the compatibility of this amino 13:52:17
10 acid with the underlying secondary structure of 13:52:21
11 that protein.
12 And the third column is the interaction, 13:52:21
13 meaning the interaction of the wild-type and 13:52:25
14 mutant residue with its neighbors. 13:52:29
15 So these are the three aspects that I 13:52:32
16 consider as a personal note, as I was scoring 13:52:34
17 different substitutions. It is important to note 13:52:38
18 that I considered all three for every 13:52:42
19 substitution, but sometimes I'd make a checkmark 13:52:47
20 as an -- as an indication to myself, oh, pay 13:52:50
21 attention to that, what just sort of jumped out, 13:52:54
22 that kind of a thing. 13:52:58

1 Q So does the check mean, for example, for 13:52:59
2 secondary -- you have a check for R, for secondary 13:53:03
3 structure, does that mean that the R gene at that 13:53:07
4 position is compatible with the secondary 13:53:13
5 structure; is that what that means? 13:53:17
6 A One shouldn't look at it as a 13:53:18
7 compatibility, but rather secondary structure is 13:53:23
8 an aspect that I considered and it jumped out as 13:53:27
9 one of the factors that would affect the final 13:53:32
10 decision. 13:53:37
11 Q Okay. I'm just trying to understand if 13:53:38
12 the check is good -- a good thing or a bad thing, 13:53:40
13 or just a note to yourself? 13:53:42
14 A Just a note. 13:53:44
15 Q Just a note. 13:53:45
16 A Yes.
17 Q Okay. Got it. Okay. 13:53:45
18 And so when you said the hydrophobicity 13:53:47
19 should really be the properties of the amino acid, 13:53:50
20 is that looking to see if the two amino acids are 13:53:53
21 comparable in terms of, like, size and chemistry, 13:53:56
22 or is that something else? 13:54:00

1 ATTORNEY KUSHAN: Objection. Foundation. 13:54:04
2 A All of them. 13:54:05
3 Q Okay. 13:54:06
4 A All of them. It could be a hydrophilic 13:54:06
5 amino acid being substituted with a hydrophilic 13:54:15
6 amino acid. Well, I took that into consideration. 13:54:18
7 Checkmark. 13:54:21
8 Q Okay. 13:54:22
9 A That's what it means. 13:54:23
10 Q Okay. Can you explain the FSASA? 13:54:24
11 A Oh. The FSASA. 13:54:48
12 (Reporter clarification.) 13:54:50
13 A I call it accessible surface area -- 13:54:50
14 Q Uh-huh. Okay.
15 A -- as a way of quantifying how much a 13:54:54
16 given amino acid is exposed to the solvent. So 13:54:57
17 that pulls information regarding the -- the 13:55:05
18 neighbor, the environment where this residue 13:55:09
19 appears. If that residue is solvent exposed, then 13:55:11
20 this accessible surface area, fraction of 13:55:16
21 accessible surface area, would approach 1, because 13:55:20
22 the measured value at that position in this 13:55:23

1 protein is nearly as great as the maximum solvent 13:55:27
2 accessible surface area for that amino acid. 13:55:35
3 Q So in order to calculate the fractional 13:55:38
4 solvent accessible surface area, are you 13:55:46
5 determining the solvent accessible surface area in 13:55:49
6 the PyMol for that residue, and then dividing by 13:55:52
7 the maximum solvent accessible surface area for 13:55:57
8 that residue? 13:56:07
9 A That is correct, yes. 13:56:09
10 Q Okay. So the wild-type had -- the 13:56:29
11 wild-type, you have a fractional solvent 13:56:33
12 accessible surface area of .17. 13:56:39
13 Would you consider that to be varied? 13:56:42
14 ATTORNEY KUSHAN: Objection. Foundation. 13:56:45
15 A It is somewhat varied for that amino acid, 13:56:49
16 aspartic acid. 13:56:54
17 The important quantity to bear in mind is 13:56:58
18 not just the number that's listed here, but a 13:57:01
19 comparison of that number to the typical value for 13:57:04
20 that amino acid. For instance, the aspartic acid 13:57:10
21 has a much higher median fractional accessible 13:57:19
22 surface area, which I think is listed further down 13:57:22

1 in appendix -- which is page -- this is 13:57:25
2 Appendix E. This is an output from PyMol. 13:57:41
3 As I consider wild-type on each 13:57:47
4 substitution, I would look at the numbers that are 13:57:49
5 reported back to me, and I get this information 13:57:56
6 because it's written into the script that I 13:58:00
7 developed. 13:58:05
8 And this one says, on Page 192: For 13:58:05
9 aspartic acid at 355, position 355, the relative 13:58:13
10 area, or relative solvent accessible surface area, 13:58:20
11 0.17, whereas the mean is 0.388. 13:58:23
12 So on average, this amino acid is much 13:58:30
13 more solvent exposed, but at this position, it has 13:58:33
14 much smaller solvent accessible surface area. So 13:58:39
15 it gives you an idea of what kind of position 13:58:41
16 we're looking at, because not every position is 13:58:45
17 equal. 13:58:49
18 Q Can you turn to Page 178, Appendix D, 13:58:57
19 Part 5, solvent accessible surface area? 13:59:04
20 A Page 178? 13:59:10
21 Q Yeah. 13:59:15
22 A Okay. Sure. 13:59:15

1 Q Yeah. The chart is on 179. 13:59:16
2 A Sure. Sure.
3 Q Can you just explain the chart that's on 13:59:22
4 Page 179? 13:59:26
5 A Uh-huh. 13:59:27
6 So this is the normalizing factor, 13:59:28
7 normalization factor, that you mentioned earlier. 13:59:31
8 You measure the surface area of that amino acid 13:59:34
9 at position 320 in the structure, and divide that 13:59:38
10 number by something else. And that something else 13:59:43
11 is the maximum area possible for that amino acid, 13:59:48
12 which has been published. 13:59:53
13 Q Oh, okay. So am I understanding right 13:59:55
14 that the max solvent accessible surface area and 13:59:58
15 the median solvent accessible surface area have --
16 are published values from the Lins paper, and then 14:00:05
17 you've calculated the median solvent accessible 14:00:09
18 surface area fraction based on those numbers, and 14:00:16
19 that's in the third column? 14:00:18
20 A That is correct. Yes. 14:00:21
21 Q Okay. Got it. 14:00:23
22 Okay. So going back to Appendix C, 14:00:40

1 Page 125, so for N, you just have neutral in the 14:00:53
2 comments. What does -- and also for E, you have 14:01:11
3 neutral in the comment, and that's it. 14:01:17
4 Can you explain what that means? 14:01:20
5 A Yes. I consider that substitution to be 14:01:22
6 so unremarkable that there was nothing to say 14:01:29
7 about it. Oftentimes, D to N substitution is done 14:01:33
8 because they are similar in size, both 14:01:40
9 hydrophilic, and often no substitutions are made. 14:01:46
10 When I make that substitution in the 14:01:50
11 structure, I don't see a great deal of change one 14:01:53
12 way or another. Not -- nothing much. As a 14:01:57
13 result, I just give it a score of 2 with very 14:02:01
14 little comment. Nonetheless, I do consider all 14:02:08
15 three factors listed in the last three columns, 14:02:14
16 which includes intrinsic properties of the 14:02:18
17 individual amino acids, compatibility with the 14:02:22
18 secondary structure, and how that residue 14:02:25
19 wild-type and mutant might interact with its 14:02:31
20 neighbors. 14:02:34
21 So these are done, but in this case its so 14:02:35
22 automatic and it's so quick, really nothing stood 14:02:39

1 out, so I didn't really felt the urge to mark it 14:02:43
2 in anyway, other than noting that it's a very 14:02:46
3 neutral substitution with a score of 2. 14:02:51
4 Q Okay. So you analyzed eight different 14:02:55
5 potential alternative residues, right, for 14:03:06
6 position 320? 14:03:11
7 A There are eight alternative potential 14:03:12
8 substitutions at this position, yes. 14:03:18
9 Q And you conclude that all but one -- so 14:03:19
10 seven of them -- would be tolerated, right? 14:03:24
11 A Yes. Seven substitutions are listed here 14:03:27
12 with a score of 2 or 3, would be tolerated at this 14:03:31
13 position of 320. 14:03:37
14 Q And you would expect that one glycine 14:03:38
15 would be not tolerated, right? 14:03:43
16 A I had a strong feeling that it would not 14:03:45
17 be tolerated. 14:03:49
18 Q So what do you expect would happen if you 14:03:53
19 put glycine in position 320? 14:03:59
20 Do you think the protein wouldn't fold? 14:04:03
21 A It may fold. Its stability may be 14:04:06
22 significantly lower than that of wild-type, thus 14:04:12

1 resulting in a substantial loss of activity. 14:04:19
2 Q Okay. So you would expect that if you put 14:04:22
3 glycine in position 320, you would have a 14:04:26
4 substantial loss in activity? 14:04:31
5 A That is my expectation, yes. 14:04:32
6 Q But for the other seven amino acids that 14:04:32
7 you considered, you would expect the activity to 14:04:35
8 be comparable or better than wild-type; is that 14:04:36
9 right? 14:04:40
10 A That's correct. 14:04:40
11 ATTORNEY MARTIN: All right. We've been 14:04:45
12 going for another hour. 14:04:48
13 Want to take another short break? 14:04:51
14 THE WITNESS: That would be great. 14:04:54
15 Thank you. 14:04:56
16 THE VIDEOGRAPHER: We are going off the 14:04:56
17 record. The time is 2:04 p.m. 14:04:58
18 (Recess from 2:05 p.m. until 2:15 p.m.) 14:05:03
19 THE VIDEOGRAPHER: We are back on the 14:15:26
20 record. The time is 2:15 p.m. 14:15:29
21 BY ATTORNEY MARTIN: 14:15:32
22 Q Welcome back, Dr. Park. 14:15:33

1 Did you discuss the substance of your 14:15:36
2 deposition during the break with anyone? 14:15:39
3 A No. 14:15:41
4 Q So the principles that we've been talking 14:15:42
5 about in terms of -- in terms of protein structure 14:15:46
6 and function in your analysis, that all applies to 14:15:52
7 the 2011 time frame, right? 14:16:03
8 ATTORNEY KUSHAN: Objection. Form. 14:16:06
9 A Obviously the principles are timeless, but 14:16:08
10 the analysis was based on the sample that was 14:16:12
11 gathered with the time frame of 2011 in mind. 14:16:16
12 Q Okay. And the analysis that you performed 14:16:20
13 was done from the perspective of the skilled 14:16:23
14 person in 2011, right? 14:16:31
15 (Reporter clarification.) 14:16:34
16 A Yes. It was. 14:16:34
17 Q Okay. All right. If you have -- if you 14:16:35
18 had homologous proteins that were 90 percent 14:16:45
19 identical in sequence, would you expect that those 14:16:52
20 proteins share the same structure and function? 14:16:55
21 ATTORNEY KUSHAN: Objection. Foundation. 14:16:58
22 A Two proteins that are homologous and have 14:17:05

1 a sequence identity/similarity, 90 percent, do I 14:17:11
2 expect them to adopt the same structure? If these 14:17:18
3 are naturally occurring sequences, yes. 14:17:23
4 Q Would you expect them to have the same 14:17:32
5 function? 14:17:35
6 A No. They may have subtly or dramatically 14:17:38
7 different functions, depending on what's going on 14:17:48
8 at the active site. 14:17:51
9 Q Okay. 14:17:53
10 A Although that may be less likely once you 14:17:53
11 have 90 percent. Was that the percentage you 14:17:57
12 mentioned? 14:17:59
13 Q Yes. 90 percent. 14:18:00
14 A 90 percent? Yes. Chances are they would 14:18:02
15 have very similar functions. 14:18:05
16 Q Okay. And I believe you mentioned earlier 14:18:27
17 this morning that you had done work with 14:18:29
18 antibodies? 14:18:32
19 A Yes. 14:18:33
20 Q Do you know whether changes in the 14:18:33
21 framework region of an antibody can impact 14:18:35
22 binding? 14:18:40

1 ATTORNEY KUSHAN: Objection. Foundation. 14:18:41
2 A Yes. It can. 14:18:44
3 Q Is it possible to make changes in the 14:18:49
4 framework region of an antibody that will 14:18:51
5 eliminate the ability of the antibody to bind the 14:19:12
6 antigen? 14:19:02
7 A It can, too. 14:19:03
8 Q Let's go to Paragraph 88 in your 14:19:08
9 declaration. 14:19:20
10 All right. So Paragraph 88 is under the 14:19:37
11 header that reads: Analysis of published results 14:19:40
12 for mutations of hyaluronidase proteins; is that 14:19:45
13 right? 14:19:49
14 A That is correct. 14:19:49
15 Q And in Paragraph 88, you say: In my 14:19:51
16 evaluation of single amino acid substitutions, I 14:19:53
17 considered biochemical and structural data 14:19:57
18 reported in the scientific literature before 14:20:00
19 December of 2011, particularly those reported in 14:20:00
20 Chao, Zhang, Stern and Arming; is that right? 14:20:08
21 A That's correct. 14:20:15
22 Q Why did you consider biochemical and 14:20:16

1 structural data as part of your analysis? 14:20:21
2 A Structural data as reported in, say, Chao 14:20:42
3 paper is very useful in terms of developing our 14:20:59
4 own model for evaluation of individual 14:20:52
5 substitutions. 14:20:55
6 Biochemical data reported in other papers, 14:20:55
7 they're useful because they report the 14:21:01
8 consequences of introducing the mutations at 14:21:05
9 various places in the protein. Some conserved, 14:21:10
10 some less conserved. So they are useful. 14:21:15
11 Q So why are -- why is it that biochemical 14:21:20
12 data that reports the consequences of introducing 14:21:24
13 substitutions into a protein, why is that useful? 14:21:31
14 ATTORNEY KUSHAN: Objection. Foundation. 14:21:34
15 Also objection as to form. 14:21:36
16 A They are useful because they help you 14:21:39
17 identify what amino acids are important, and in 14:21:42
18 some cases, it can even be used to deduce whether 14:21:46
19 a protein would fold. 14:21:53
20 For instance, if you introduce a mutation 14:21:57
21 and you get very little protein expressed in the 14:22:00
22 same expression system, that may be because the 14:22:05

1 protein has unfolded, and as a result is no longer 14:22:08
2 soluble. So this would be the standard way of 14:22:13
3 interpreting mutational effects. 14:22:18
4 Q And are mutation data for both 14:22:25
5 conservative and non-conservative changes useful? 14:22:31
6 ATTORNEY KUSHAN: Objection. Foundation. 14:22:36
7 A They are useful because they say different 14:22:45
8 things. 14:22:48
9 Q Can you explain that? 14:22:48
10 A If you introduce mutation at a conserved 14:22:52
11 position and you lose activity, function, 14:22:58
12 expression, then it confirms that those conserved 14:23:00
13 residues are important. 14:23:04
14 If you introduce a mutation at a 14:23:06
15 non-conserved position and nothing happens, the 14:23:09
16 protein maintains the same activity, then you know 14:23:12
17 those mutations are interchangeable to a degree 14:23:17
18 and they would tolerate substitutions. 14:23:21
19 So they hold different information, all of 14:23:24
20 which can be useful, and some, in some ways 14:23:27
21 support our findings. 14:23:32
22 Q Okay. How did you identify the Chao, 14:23:45

1 Zhang, Stern and Arming references? 14:23:50
2 A I did a public search with some keywords. 14:23:57
3 I don't remember exactly what. Hyaluronidase 14:24:04
4 would be a good starting point, or PH20. 14:24:11
5 Sometimes I would look up bibliography references 14:24:13
6 at the end of a paper and move backwards in time 14:24:21
7 and find earlier examples. 14:25:11
8 Q Okay. Can you turn to Paragraph 91? 14:25:11
9 A Yes. I'm at Paragraph 91. 14:25:20
10 Q So in Paragraph 91, you state: Chao 14:25:22
11 identified the residues in the active site of 14:25:24
12 HYAL1 that are involved in catalysis as Asp129, 14:25:29
13 Glu131, and Tyr202, which correspond to Asp146, 14:25:33
14 Glu148, and Tyrosine 219 in PH20. It also 14:25:41
15 identified a number of other residues in a cleft 14:25:47
16 where the ligand binds.
17 And I'm not going to read them out. 14:25:49
18 So the question is: Do you understand -- 14:25:55
19 sorry. Strike that. 14:26:03
20 Is it correct that Aspartic Acid 146, 14:26:04
21 Glutamate 148, and Tyrosine 219 in PH20 are 14:26:12
22 involved in catalysis based on the Chao paper? 14:26:18

1 ATTORNEY KUSHAN: Objection. Foundation. 14:26:21
2 A Yes. I would think so. 14:26:25
3 Q Okay. And do you know if the residues 14:26:29
4 that are listed -- listed in the cleft, those 14:26:36
5 are -- are those the HYAL1 residue numbers, or 14:26:40
6 you're not sure? 14:26:47
7 A I'm pretty sure there are -- those are 14:26:48
8 HYAL1 residues. 14:26:51
9 Q Okay. So you'd have to go and convert to 14:26:52
10 figure out what the residues are in PH20? 14:26:56
11 A Yes. There is a table at the end that -- 14:27:01
12 Q Oh, okay. 14:27:05
13 A -- in those amino acids to PH20 residues. 14:27:07
14 Q Okay.
15 A It's on paragraph -- Page 170 -- it goes 14:27:07
16 on for a while. 168. It's Appendix D, Part 4. 14:27:14
17 Q Appendix D, Part 4.
18 A Page 7 -- starting at Page 167. 14:27:20
19 Q Oh. I got it.
20 A It allows the mapping of PH20 to HYAL1. 14:27:23
21 Q Okay. Great. 14:27:28
22 Okay. And so would you expect that in 14:27:55

1 PH20 those residues -- the PH20 version of those 14:27:59
2 residues are also in the cleft where the ligand 14:28:00
3 binds? 14:28:04
4 A Yes. 14:28:05
5 Q Okay. And so if you turn to -- can you 14:28:10
6 please turn to Paragraph 95? 14:28:37
7 A Yes. I'm at Paragraph 95. 14:28:54
8 Q So in Paragraph 95, you reference the 14:28:56
9 testing in Zhang of single mutant HYAL1 proteins; 14:29:00
10 is that right? 14:29:06
11 A These are mutational results from single 14:29:11
12 point mutations, yes. 14:29:14
13 Q And in the -- the Zhang paper, am I 14:29:18
14 understanding correctly that the mutations at the 14:29:23
15 D129N, E131Q, Y202F, Y247F, and R265L mutations, 14:29:30
16 have little or no activity? 14:29:47
17 A The figure shows that, yes. 14:29:54
18 Q Okay. 14:29:58
19 Okay. And so then the -- the results from 14:30:16
20 Zhang, from the mutagenesis in Zhang, those are 14:30:20
21 shown in a table in Paragraph 99 in your 14:30:26
22 declaration, right? 14:30:30

1 A Paragraph 99? All right. Okay. 14:30:31
2 Q So just the -- in Paragraph 99, you've 14:30:43
3 reproduced the chart from the Zhang paper that has 14:30:49
4 the results of the mutagenesis testing? 14:30:52
5 A That is correct. 14:30:58
6 Q Do you know what the distinction is 14:31:03
7 between catalytic mutants, substrate binding 14:31:05
8 mutants, and punitive structural mutants? 14:31:10
9 ATTORNEY KUSHAN: Objection. Foundation. 14:31:17
10 A My reading of that table with those three 14:31:27
11 classifications would be catalytic mutants are 14:31:31
12 mutants where catalytic residues or residues that 14:31:37
13 are directly involved in catalysis have been 14:31:39
14 mutated. 14:31:42
15 Substrate binding mutants are the 14:31:42
16 mutations where an amino acid involved in 14:31:45
17 substrate recognition and binding has been 14:31:48
18 mutated. 14:31:52
19 And punitive structural mutants would be 14:31:52
20 mutations that affect the enzyme in some other 14:32:01
21 ways. 14:32:03
22 Q Okay. And then can you turn to 14:32:03

1 Paragraph 101? 14:32:29
2 So and in Paragraph 101, you list the 14:32:38
3 results from Arming, where Arming identified five 14:32:43
4 single mutations that greatly reduced PH20 14:32:48
5 activity, right? 14:32:52
6 A Yes. 14:32:53
7 Q And then, as well as four conserved 14:32:53
8 cysteine residues that formed disulfide bonds, and 14:32:58
9 that PH20 truncated at position 341 exhibited no 14:33:02
10 activity, right? 14:33:07
11 A That's correct. 14:33:07
12 Q So how is the Arming data, how did you use 14:33:08
13 that in your analysis? 14:33:12
14 A I use these biochemical data to confirm 14:33:23
15 the finding from the multiple sequence alignment, 14:33:27
16 which suggested conservation of certain positions, 14:33:32
17 and they track the biochemical data, in that if 14:33:37
18 you mutate those residues, you lose activity. 14:33:40
19 Q So the biochemical data, consistent with 14:33:48
20 the multiple sequence alignment, and confirmed 14:33:53
21 that certain residues are essential for activity; 14:33:54
22 is that right? 14:33:58

1 A Yes. 14:33:58
2 ATTORNEY KUSHAN: Objection. Foundation. 14:33:58
3 And also objection as to form. 14:34:00
4 A Yes. That's how the biochemical data 14:34:02
5 would be useful to our analysis. 14:34:07
6 Q So would you expect based on the 14:34:16
7 biochemical data, for example in Arming, that if 14:34:18
8 you change position 113, that you're likely to 14:34:25
9 reduce PH20 activity? 14:34:33
10 ATTORNEY KUSHAN: Objection. Foundation. 14:34:41
11 Also objection as to form. 14:34:43
12 A These note that -- these note that 14:34:44
13 glutamine 113 is not wild-type. This is the 14:34:49
14 mutant -- 14:34:52
15 Q Oh, oh. Sorry. 14:34:53
16 A Yes. 14:34:55
17 Q Okay. So if you change position 113 to 14:34:55
18 glutamine -- 14:35:01
19 A That is correct. 14:35:01
20 Q -- then you will -- okay. 14:35:02
21 A That is correct. 14:35:03
22 Q Okay. Thank you. 14:35:04

1 A Yes. 14:35:05
2 Q Would you expect based on the Arming 14:35:06
3 results that if you change the four conserved 14:35:13
4 cysteine residues that you would reduce PH20 14:35:20
5 activity? 14:35:24
6 ATTORNEY KUSHAN: Objection. Foundation. 14:35:24
7 Also objection as to form. 14:35:26
8 (Reporter clarification.) 14:35:42
9 A Yes. I would totally expect mutating any 14:35:42
10 of the conserved cysteine residues involved in 14:35:46
11 that sulfuric bond would result in total loss of 14:35:51
12 protein activity. 14:35:56
13 Q All right. So let's turn to 14:36:09
14 Paragraph 102. 14:36:11
15 So in Paragraphs 102 and 103, you describe 14:36:28
16 your unbiased scoring system, right? 14:36:33
17 A That's correct. 14:36:44
18 Q And you said that it's necessary for you 14:36:45
19 to evaluate a lot of different types of 14:36:49
20 substitutions, and through that process you 14:36:52
21 developed a consistent methodology; is that right? 14:37:00
22 A That's correct. 14:37:05

1 Q So why was it necessary to evaluate a lot 14:37:06
2 of different types of substitutions? 14:37:08
3 A It gives you a breadth in your analysis. 14:37:17
4 It tells you how to deal with different types of 14:37:23
5 substitutions. Some conserved, some not 14:37:27
6 conserved, small to large, large to small, all 14:37:31
7 kinds of differences. You want to be familiar 14:37:35
8 with different types of substitutions that can 14:37:37
9 happen so that you can develop a more consistent 14:37:40
10 methodology that can be applied to all 14:37:46
11 substitutions in your data set. 14:37:54
12 Q So when you say -- so did, as part of your 14:37:58
13 analysis, did you evaluate a lot of different 14:38:06
14 types of substitutions? 14:38:10
15 A I did. I mapped the types of 14:38:14
16 substitutions by tabulating different combinations 14:38:18
17 of from and to amino acids, and it was pretty well 14:38:25
18 populated in that distribution. 14:38:33
19 Q How many different types of substitutions 14:38:36
20 did you consider? 14:38:39
21 A I haven't counted, so out of the 20 by 20 14:38:43
22 minus 20, 380 types of substitutions that can 14:38:52

1 exist, a pretty significant fraction of them were 14:38:59
2 found to exist in this PH20 data set. 14:39:05
3 (Reporter clarification.) 14:39:14
4 Q And what are you referring to when you 14:39:14
5 talk about the PH20 data set? 14:39:18
6 A That's the multiple sequence on 14:39:22
7 alignment -- 14:39:26
8 Q Okay. 14:39:26
9 A -- data set that I am speaking of. 14:39:27
10 Q Okay. Did you consider substitutions at 14:39:30
11 every position in PH20? 14:39:35
12 A I considered as many substitutions as 14:39:38
13 possible. There were approximately 3,000 14:39:42
14 substitutions suggested by the multiple sequence 14:39:49
15 alignment. That was too many for me to consider. 14:39:52
16 I considered about one quarter of them. 14:39:57
17 Q Okay. And have you provided -- when you 14:40:01
18 say you considered them, can you explain what you 14:40:05
19 did for each one of those? 14:40:09
20 A Absolutely. For each substitution that 14:40:11
21 was suggested by the sequence alignment, starting 14:40:18
22 from those substitutions involving amino acids 14:40:23

1 that appear with decent frequency, which I started 14:40:27
2 with 10 percent, but ultimately went down to 5 14:40:35
3 percent. 14:40:39
4 So in the end, any substitutions to an 14:40:39
5 amino acid that occur with a frequency 5 or 14:40:42
6 greater percentage, I considered the wild-type 14:40:45
7 residue in the context of the modeled PH20 14:40:50
8 structure, as well as the individual substitutions 14:40:55
9 listed in the multiple sequence alignment. And 14:40:59
10 for each substitution, I scored the substitution 14:41:03
11 on a scale of 1 to 3, using the metric that was 14:41:09
12 demonstrated in Appendix C earlier. 14:41:16
13 Q And did you record -- did you record the 14:41:20
14 results of that analysis for every substitution 14:41:24
15 that you analyzed? 14:41:27
16 A Yes. I created a spreadsheet and provided 14:41:29
17 that to counsel. 14:41:35
18 Q You provided a spreadsheet with your 14:41:36
19 analysis for every single residue that you 14:41:40
20 considered to counsel? 14:41:44
21 A Yes. I did. 14:41:44
22 Q So you said that when you went through the 14:41:45

1 analysis, you would revisit the scores for each 14:42:10
2 position multiple times to make sure that the way 14:42:12
3 you assigned scores was consistent. 14:42:13
4 Can you explain what you mean by that? 14:42:17
5 A Yes. I would look at a substitution, give 14:42:20
6 it a score, move on to the next position, consider 14:42:28
7 substitutions at the next position, finish them, 14:42:31
8 move on to the next position, consider 14:42:36
9 substitutions. 14:42:38
10 I finished this exercise all the way to 14:42:39
11 the end of the structure, and just to be 14:42:42
12 consistent, I went back to the beginning, and 14:42:46
13 repeated that exercise to either confirm what I 14:42:49
14 had found the first time around, or I might have 14:42:54
15 decided, perhaps I was a bit too harsh here, and I 14:42:58
16 would update the score a little bit. This I did 14:43:05
17 twice for the whole set. 14:43:09
18 Q So you looked at every single substitution 14:43:10
19 twice? 14:43:15
20 A Every single substitution which amounted 14:43:16
21 to roughly one quarter of the complete set of 14:43:21
22 possible substitutions, which as I said was 14:43:26

1 about 3,000 substitutions. 14:43:29
2 Q Okay. And did your analysis in total for 14:43:47
3 all of those positions, did you rely on that 14:43:35
4 analysis in forming the opinions that you set 14:43:39
5 forth in your declaration? 14:43:42
6 A That analysis was the backbone of the 14:43:48
7 current declaration. 14:43:52
8 Q And was it important for you to consider 14:43:54
9 every single position and substitution that you 14:43:56
10 considered in order to validate your scoring 14:44:00
11 system? 14:44:04
12 ATTORNEY KUSHAN: Objection to form. 14:44:05
13 A Was it necessary? Maybe not. I suppose I 14:44:09
14 could have done less work. I wanted to be 14:44:17
15 thorough about my analysis and be as rigorous as 14:44:22
16 possible. If I had looked at only 10 14:44:31
17 substitutions, it's hard to know that I am doing 14:44:34
18 it objectively. 14:44:37
19 It's only through repetition that I 14:44:38
20 developed confidence in my scoring system and can 14:44:42
21 vouch that I am being objective when evaluating 14:44:49
22 the substitution. So for that reason I thought it 14:44:51

1 was important that I do a bit of a blind study in 14:44:52
2 a way, look at the substitutions without paying 14:44:54
3 attention to, you know, why they may be important. 14:44:59
4 Look at it as cleanly as possible and 14:45:03
5 score it and see if I can come back at a later 14:45:07
6 time and arrive at the same score. This was the 14:45:11
7 objective. And for that I thought it was 14:45:17
8 important that I start with a very large set, or 14:45:21
9 set a goal for a larger set as what's practical. 14:45:24
10 Q Okay. And do you know, did you change the 14:45:27
11 score when you went back and revisited some of the 14:45:31
12 substitutions? 14:45:34
13 A Yes. I wasn't surprised that this 14:45:35
14 happened. It's not unlike looking at students' 14:45:39
15 exams. You start grading them, and once you get 14:45:43
16 to the end of it and you realize that maybe I was 14:45:48
17 a bit too harsh on this question. Let me go back 14:45:53
18 and try to do a slightly different job. 14:45:56
19 I found that a fraction of the 14:46:01
20 substitutions which I had previously scored could 14:46:03
21 have been interpreted differently, and I updated 14:46:07
22 them. In the process, I think it helped really to 14:46:13

1 refine my methodology, became more consistent, 14:46:19
2 which then led to more confidence in how I was 14:46:25
3 evaluating individual substitutions. 14:46:32
4 Q So did you rely on the -- the spreadsheet 14:47:08
5 that you provided to counsel for your analysis for 14:47:10
6 each of the declarations that you submitted? 14:47:13
7 ATTORNEY KUSHAN: Objection to form. 14:47:18
8 A The -- the complete set of analysis, which 14:47:19
9 was recorded in a spreadsheet, formed the 14:47:26
10 foundation for these four sets of declarations. 14:47:29
11 ATTORNEY MARTIN: Okay. So counsel, we 14:47:33
12 would like to request the spreadsheet, since it 14:47:48
13 was the foundation for all four declarations. 14:47:53
14 ATTORNEY KUSHAN: Okay. Do you want to 14:47:57
15 have a conversation on the break about that? 14:47:58
16 ATTORNEY MARTIN: Sure. 14:48:00
17 BY ATTORNEY MARTIN: 14:48:07
18 Q So you've mentioned that when you went 14:48:08
19 back and did your analysis again, the second 14:48:11
20 analysis, you noticed that you were too harsh for 14:48:15
21 some of the substitutions. 14:48:20
22 Can you just explain what you meant by 14:48:21

1 that? 14:48:24
2 A Being too harsh was an example. I 14:48:24
3 wouldn't say that the correction was always in one 14:48:30
4 direction. It might have gone both directions, 1 14:48:32
5 going to 2, 2 going into 3, vice-versa. So they 14:48:36
6 did move around. 14:48:40
7 So based on the follow-up examination, 14:48:42
8 where I either noticed other interactions which I 14:48:44
9 had missed earlier, or I have seen similar 14:48:49
10 interactions elsewhere, which then led me to one 14:48:55
11 score, which I then felt should be applied 14:49:02
12 similarly at a different position. 14:49:06
13 So that influenced my thinking, and hence 14:49:10
14 the final score. And the score got updated in 14:49:15
15 some of the cases, but it wasn't always 14:49:21
16 improvement. Sometimes it could have been the 14:49:27
17 other way around. 14:49:30
18 Q So in the 2011 time frame, if a POSA is 14:49:39
19 trying to determine the impact of a potential 14:49:42
20 substitution, would they have done the similar 14:49:45
21 analysis where they look at -- where they look at 14:49:49
22 the substitution and determine if it's potentially 14:49:54

1 going to favorable, neutral or unfavorable? 14:49:58
2 A In the year 2011, to consider a mutation, 14:50:02
3 it would have been very common and expected for a 14:50:08
4 POSA to generate a model and consider the 14:50:15
5 substitution in that structural context. 14:50:27
6 Q So you said that you looked at about -- I 14:50:41
7 think you said you looked at about a quarter of 14:50:44
8 the 3,000 and some; is that right? 14:50:51
9 A About a quarter, yes. 820 or 830. 14:50:51
10 (Reporter clarification.) 14:51:03
11 A I don't know exactly. Somewhere around 14:51:03
12 there, slightly over 800 substitutions. 14:51:05
13 Q How did you pick those 800-some -- how did 14:51:05
14 you pick the ones that you looked at? 14:51:12
15 A I started with substitutions that appeared 14:51:15
16 with high frequency. Ultimately I looked at all 14:51:19
17 substitutions that involved amino acids that 14:51:26
18 appeared with a frequency of 5 or greater 14:51:30
19 percentage. So I started at the top. After doing 14:51:59
20 10 percent, I think I had about 450. 14:51:37
21 I said: Okay. 450's not bad but I can do 14:51:40
22 better. So let's do additional 5 percent. That 14:51:44

1 added another 400. 14:51:50
2 Q Okay. Got it. 14:51:53
3 Okay. So can you turn to Paragraph 149? 14:52:32
4 A I'm at Paragraph 149. 14:52:57
5 Q So starting on Paragraph 149 is how you -- 14:52:58
6 is where you explain how you generated the 14:53:01
7 homology model using the SWISS-MODEL, right? 14:53:03
8 A That's correct. 14:53:08
9 Q So can you just explain kind of 14:53:08
10 step-by-step how you went about generating the 14:53:12
11 homology model using the SWISS-MODEL? 14:53:16
12 A Okay. SWISS-MODEL is a web service which 14:53:46
13 makes it very convenient for somebody who's not an 14:53:52
14 expert or a specialist in structural 14:53:55
15 bioinformatics to use the structure of a known 14:54:00
16 homologous protein as the starting point to 14:54:05
17 generate a model for a protein of interest, such 14:54:09
18 as PH20. 14:54:14
19 You visit the website, enter PH20 14:54:15
20 sequence. The website will take the sequence, 14:54:19
21 compare the sequence with the structures in their 14:54:22
22 database. And based on the matching, it will give 14:54:27

1 you a list of potential templates that you can use 14:54:31
2 with a QME score -- that's quality of model 14:54:36
3 estimate -- QME score. The higher the better. So 14:54:43
4 it gives you idea of which template you might want 14:54:45
5 to use. 14:54:48
6 At that point, you have a choice of 14:54:49
7 choosing one or more template, and submit the job. 14:54:51
8 And the job runs in the background, at the end of 14:54:55
9 which you will be notified and then you'll be able 14:55:00
10 to download the homology model of your protein. 14:55:02
11 That's it. 14:55:08
12 Q Okay. So you entered -- so you went to 14:55:09
13 the SWISS-MODEL website and you entered the 14:55:15
14 sequence for PH20, and then you asked the program 14:55:17
15 to identify potential templates; is that right? 14:55:22
16 A That is correct. 14:55:27
17 ATTORNEY KUSHAN: Or, sorry. 14:55:28
18 Objection to form. 14:55:31
19 Q And so then it give you potential 14:55:32
20 templates and then you selected the HYAL1 as the 14:55:35
21 template; is that right? 14:55:37
22 A Yes. 14:55:38

1 Q Okay. So you selected HYAL1 as the 14:55:43
2 template to use for the homology model? 14:55:48
3 ATTORNEY KUSHAN: Objection to form. 14:55:55
4 A I used the HYAL1 structure as the template 14:55:56
5 for my homology model, yes. 14:56:01
6 Q Why did you use HYAL1 as the template? 14:56:03
7 A That was really the only template that was 14:56:07
8 viable. When I read the service, only two 14:56:11
9 structures came back as actually: HYAL1 14:56:15
10 structure, and another structure that had nothing 14:56:20
11 to do with this protein. 14:56:25
12 Q Okay. 14:56:27
13 A Apparently there was some similarly over a 14:56:27
14 span of, perhaps 50 amino acids, which is not even 14:56:32
15 a protein. So it was pretty clear that I don't 14:56:36
16 have a whole lot of options, other than HYAL1. So 14:56:41
17 you pick that, and the rest is automated. 14:56:47
18 Q Okay. And so on Page 84, you have the 14:56:50
19 SWISS-MODEL result; is that right? 14:57:10
20 A Yes. This is the result of homology 14:57:19
21 modeling. Yes. 14:57:29
22 (Reporter clarification.) 14:57:30

1 Q And can you explain what the GMQE is? 14:57:30
2 A Yes. G -- GMQE stands for global model 14:57:39
3 quality estimate. It give you an idea of how good 14:57:44
4 the template is so that you can choose the right 14:57:48
5 template among several that are returned 14:57:56
6 initially, so that way you don't waste your time 14:58:00
7 modeling it against a template that's not even 14:58:05
8 appropriate. 14:58:10
9 So higher the better. Here it's 0.69. 14:58:15
10 The second template that came back I think had
11 a 0.1 or something.
12 Q Okay.
13 A So pretty clear cut. 14:58:16
14 Q Is 0.69, is that a -- is that a good 14:58:26
15 value, in your experience? 14:58:24
16 A I don't know actually. I think 0.69 is a 14:58:27
17 reasonable score based on the publication. I 14:58:44
18 don't have a lot of experience working with a 14:58:36
19 template that has lower QM -- GMQE value, so I 14:58:39
20 can't quite say. 14:58:43
21 Q Okay. 14:58:53
22 A But what's comforting is that we know 14:58:53

1 HYAL1 and PH20 are pretty similar based on the 14:58:58
2 sequence alignment. So if that high sequence 14:59:03
3 identity translates into 0.69, I think it's 14:59:04
4 reasonable to assume that that is an acceptable 14:59:09
5 value. 14:59:12
6 Q And the sequence identity is given as 14:59:12
7 40.24 percent; is that right? 14:59:18
8 A Yes. That's what this website says. 14:59:20
9 Q And then there's also a QMEAN DisCo 14:59:26
10 Global. Can you explain what that is? 14:59:35
11 A QMEAN DisCo Local stands for qualitative 14:59:39
12 model energy analysis, distance correlation local, 14:59:44
13 meaning individual analysis. 14:59:47
14 Q And the value is given as .75 plus or 14:59:49
15 minus .05. 14:59:58
16 What does that mean? 14:59:59
17 ATTORNEY KUSHAN: Objection. Foundation. 15:00:02
18 A In this graph, 0.75 I think is the average 15:00:04
19 or mean, and anything above that is colored blue. 15:00:09
20 Anything below that is colored red. 15:00:16
21 The critical number is 0.6, according to 15:00:19
22 publication. It says 0.6 and up, you would have 15:00:22

1 some confidence in that modeling structure at that 15:00:30
2 residue position, and sometimes it falls below 15:00:34
3 because the sequence identity might be low in that 15:00:38
4 region. 15:00:49
5 (Reporter clarification.) 15:00:59
6 Q Okay. And so when you did your analysis, 15:00:59
7 did you -- at the positions that you looked at, 15:01:04
8 did you consider what the -- what the value was at 15:01:06
9 that -- at that position for the QMEAN DisCo? 15:01:11
10 A Yes. 15:01:16
11 Q Okay.
12 A I checked it and it was about .6. I 15:01:17
13 forget the exact value, but -- 15:01:29
14 Q Okay.
15 A -- above that threshold. 15:01:25
16 Q Okay. 15:01:27
17 Okay. And so then you have -- on Page 86, 15:01:39
18 you have: The relative QMEAN assessment for the 15:01:52
19 entire protein and the local QMEAN quality 15:02:03
20 assessment; is that right? 15:02:06
21 A That is correct. 15:02:07
22 Q Can you explain the graph on the left on 15:02:08

1 Page 86? 15:02:14
2 A QMEAN 4, or quality model energy analysis, 15:02:19
3 is a statistical energy comprised of four 15:02:26
4 independent terms, including torsion energy, 15:02:32
5 solvent interaction, secondary structure and 15:02:38
6 atomic interaction. Those four terms are added up 15:02:41
7 some way to give a total score of QMEAN 4. 15:02:47
8 And what's plotted on this graph is a Z 15:02:54
9 score, which indicates the multiples of the 15:03:02
10 standard deviation for our structure compared to 15:03:05
11 the average energy expected for a protein of that 15:03:14
12 size. 15:03:19
13 Q And so what does this graph tell you about 15:03:37
14 the model that you generated? 15:03:40
15 A The graph tells you that the model is 15:03:43
16 reasonable. 15:03:47
17 Q Okay. And what about the graph on the 15:03:53
18 right? 15:03:57
19 A The graph on the right is the -- the local 15:04:00
20 quality estimate, which is the expanded view of 15:04:06
21 the earlier tiny graph where 0.6 is the number to 15:04:11
22 watch out for. And the position where the local 15:04:19

1 quality estimate is about .6 is a place where one 15:04:24
2 can trust the model and carry on with the 15:04:28
3 analysis. 15:04:32
4 Q Okay. 15:04:32
5 (Reporter clarification.) 15:04:47
6 Q And you also, above those graphs at the 15:04:47
7 very top of Page 86, you mention that the whole 15:04:56
8 protein had an overall QMEAN score of minus 2.83, 15:05:02
9 which is the -- which is below the threshold of 15:05:08
10 minus 4, indicative of acceptable quality.
11 So what is the QMEAN score of minus 2.83? 15:05:17
12 A Right. So QMEAN stands for qualitative 15:05:21
13 model energy analysis. That's the aggregate sum 15:05:25
14 of the four terms that I mentioned earlier -- 15:05:30
15 torsion energy, solvent exposure, blah, blah -- 15:05:33
16 and minus 2.83 corresponds to the multiple of the 15:05:35
17 standard deviation from the average energy 15:05:44
18 expected for a protein of that size. So that is 15:05:46
19 what's shown on the left of the figure. 15:05:51
20 The star is our model, and what this graph 15:05:53
21 says is that that star is minus 2.83 standard 15:05:57
22 deviation away from the median, or median or 15:06:06

1 average, of the energy at that protein size, for 15:06:11
2 that protein size, which is the X axis. 15:06:17
3 Q Oh, okay. Okay. Got it. Okay. Thanks. 15:06:21
4 So in Paragraph 153, you refer to B factor 15:06:49
5 scores? 15:06:58
6 (Reporter clarification.) 15:07:00
7 Q And you equate a local QMEAN reliability 15:07:00
8 to a B factor score? 15:07:06
9 A Yes. 15:07:09
10 Q Is that right? 15:07:09
11 A Yes. 15:07:10
12 Q Okay. And so the graph on the right, in 15:07:12
13 the local quality estimate graph on the right on 15:07:19
14 Page 86, is that a graph of B factor scores? 15:07:23
15 A That is correct. 15:07:28
16 Q Okay.
17 A The values shown on the right side of that 15:07:30
18 graph is recorded in the B factor column of the 15:07:34
19 PDB file. You can extract that value. 15:07:45
20 (Reporter clarification.) 15:07:48
21 Q Okay. So the PDB file that you download 15:07:48
22 from SWISS-MODEL, in the B factor column, it has 15:07:54

1 the numbers that are -- for each atom, right? 15:07:54
2 A Residue. 15:07:56
3 Q For each residue? 15:07:58
4 A Yes.
5 Q That provides the local QMEAN reliability? 15:08:00
6 A That's correct, yes. So you can extract 15:08:02
7 that information from that B factor column. 15:08:05
8 ATTORNEY MARTIN: Okay. Okay. Got it. 15:08:34
9 All right. We've probably been going for 15:08:34
10 another an hour. 15:08:39
11 Do you want to take another break? 15:08:40
12 THE WITNESS: Yes, yes, yes. 15:08:43
13 ATTORNEY KUSHAN: Why don't we stay on the 15:08:44
14 record for a minute, and let Dr. Park step out. 15:08:46
15 THE WITNESS: Okay.
16 ATTORNEY KUSHAN: So we can discuss an
17 issue you raised. 15:08:51
18 THE VIDEOGRAPHER: Do you want to stay on 15:08:51
19 the video record as well? 15:08:53
20 ATTORNEY KUSHAN: You can take the video 15:08:56
21 off. 15:08:57
22 THE VIDEOGRAPHER: We are going off the 15:09:00

1 video record. The time is 3:08 p.m. 15:09:02
2 ATTORNEY KUSHAN: So we're willing to 15:09:06
3 entertain a request to produce the spreadsheet 15:09:10
4 that he referred to. I want to make clear that, 15:09:14
5 you know, you've had these declarations since 15:09:19
6 November/December. 15:09:20
7 You filed Patent Owner response, 15:09:21
8 preliminary responses. We filed replies. And 15:09:24
9 what we pointed out in our replies was that you 15:09:27
10 were misreading paragraphs of the declaration. 15:09:27
11 We pointed you to Paragraphs 102 and 103 15:09:30
12 in our replies to the Board, and what we said was 15:09:34
13 your characterization that we had directed him to 15:09:38
14 specific residues to consider only, was false. We 15:09:41
15 made it very clear, and we also pointed out this 15:09:44
16 additional explanation in the declaration, that he 15:09:48
17 had -- he's telling you he evaluated lots of 15:09:51
18 positions. That's what he just confirmed in his 15:09:54
19 testimony. 15:09:59
20 So I want to make it clear, you had a 15:09:59
21 chance to ask for this many months ago, and we 15:10:02
22 don't expect that you should, you know, seek to 15:10:05

1 get an additional deposition of him or anything 15:10:08
2 like that, claiming prejudice, because you've had 15:10:11
3 the opportunity, you've had the knowledge, you've 15:10:14
4 had our position about him doing more work than 15:10:14
5 what was limited to each individual declaration as 15:10:15
6 specific position. 15:10:18
7 So we're happy -- like I said, we can work 15:10:19
8 to produce this spreadsheet. We can add it in as 15:10:23
9 an exhibit if you want, and we can provide it to 15:10:28
10 you. 15:10:30
11 ATTORNEY MARTIN: So a couple of things. 15:10:31
12 There's no way from his declaration that 15:10:32
13 one could extract that he looked at 820 to 830 15:10:35
14 different substitutions, and gave you a 15:10:41
15 spreadsheet with the data. It's not clear from 15:10:44
16 this declaration at all how many positions he 15:10:47
17 looked at, and then how many substitutions he 15:10:50
18 looked at in each position. 15:10:53
19 He could have looked at 10, right? He 15:10:55
20 could have looked at, you know, 10 different 15:10:58
21 positions of like, a handful of different 15:11:01
22 substitutions, maybe, like, 10 at each position. 15:11:03

1 That's very different from what he just said, 15:11:04
2 which is 100 and -- 820 to 830. 15:11:07
3 There are like -- this is purely 15:11:09
4 qualitative. There -- there is no way for us to 15:11:12
5 know, based on the declaration, what he did. And 15:11:15
6 so there's no -- there's no way -- there is no 15:11:17
7 possible way that we could have predicted that he 15:11:21
8 gave you a spreadsheet with 820 to 830 15:11:25
9 substitutions in it, and then asked for it and 15:11:27
10 then considered it. We just did not have that 15:11:29
11 level of information. 15:11:32
12 You guys are you ones who -- hold on. I 15:11:33
13 listened to you go on for a very long time, so let 15:11:35
14 me -- 15:11:39
15 ATTORNEY KUSHAN: Go ahead. 15:11:40
16 ATTORNEY MARTIN: -- say my piece and 15:11:42
17 then, you know, you can respond. 15:11:44
18 You know, you guys had the opportunity to 15:11:45
19 make clear what he did or didn't do. You had the 15:11:47
20 opportunity to frame what he did and didn't do. 15:11:51
21 And that's what you did in your declaration. We 15:11:55
22 read it. Literally, we read it, and we understood 15:11:55

1 the best that we could. And if it's the case that 15:11:57
2 he considered 800 and some positions, you should 15:12:00
3 have told us that, right, as opposed to trying to 15:12:04
4 put it on us to somehow psychically extrapolate 15:12:06
5 out of this declaration what it was that he did, 15:12:09
6 and put the onus on us to go and ask you. 15:12:11
7 And also, I mean, you guys have been 15:12:15
8 serially filing PGRs over time, right, where you 15:12:16
9 come up with new tables with new positions. Like 15:12:20
10 when you filed the fist one, how could we possibly 15:12:25
11 know what positions he looked at. We get no 15:12:30
12 information or positions he looked at because 15:12:34
13 you're filing more PGRs, but there was no way that 15:12:35
14 we could have known that at the very beginning. 15:12:36
15 It's just totally unreasonable. 15:12:39
16 So it's really -- like, it's really, 15:12:41
17 really not clear from anything that you guys 15:12:42
18 have -- maybe it's clear for you because you know 15:12:44
19 that there's a spreadsheet. It was not clear from 15:12:46
20 our perspective that there was this spreadsheet 15:12:47
21 that we should have known to ask about. We just 15:12:49
22 didn't know. 15:12:52

1 And so in terms of asking for another 15:12:53
2 deposition, I haven't seen the spreadsheet, right? 15:12:54
3 We need to see the spreadsheet, and then we can go 15:12:57
4 from there. But as an initial matter, we would 15:13:00
5 like the spreadsheet. 15:13:03
6 ATTORNEY KUSHAN: So I'll be very brief. 15:13:04
7 The point I made was that when you read 15:13:06
8 Paragraphs 102 and 103, and you see him explain 15:13:09
9 that he did a lot of different types of -- 15:13:13
10 evaluated a lot of different types of 15:13:15
11 substitutions. He conducted an analysis that did 15:13:17
12 not focus on any particular position. 15:13:20
13 And the natural thing would have been
14 to -- if you had a question or you thought this 15:13:24
15 was relevant information, would be to drop an 15:13:27
16 email to me saying: Hey, you appear to be relying 15:13:27
17 on additional information that you haven't 15:13:31
18 included in the record. 15:13:33
19 ATTORNEY POWERS: Jeff, that's why we have 15:13:34
20 a deposition. 15:13:36
21 ATTORNEY KUSHAN: What? 15:13:37
22 ATTORNEY POWERS: That's why we have a 15:13:38

1 deposition, so we can ask him these questions. 15:13:39
2 ATTORNEY KUSHAN: No. You chose to tell a 15:13:40
3 narrative where you said we, you know, you've 15:13:41
4 invented -- you've basically ignored these 15:13:43
5 passages, and misquoted and mischaracterized the 15:13:47
6 scope of work he was asked to do.
7 And then you went to the Board, and you 15:13:52
8 said: Deny these institutions because they 15:13:55
9 directed him to review only position 320. So it 15:13:56
10 was advancing that narrative you were going for. 15:13:58
11 I have done this in many, many cases, 15:14:00
12 where if we have an expert do analytical work, the 15:14:03
13 other side can read the explanation that work has 15:14:08
14 been done, and if you feel there's an incomplete 15:14:09
15 record or you need more information about what he 15:14:13
16 did, we would have responded, and we would have, 15:14:16
17 you know, we could have provided or explained what 15:14:17
18 additional information existed. That's my point. 15:14:19
19 And the Board obviously wants us to 15:14:22
20 cooperate and not bring things to them that are, 15:14:23
21 you know, going to waste their time. So that's 15:14:26
22 why in a normal setting, you can contact opposing 15:14:28

1 counsel and ask questions.
2 Is there more evidence? Is there more 15:14:32
3 work product of this expert? And we would have 15:14:37
4 then had this conversation three months ago, and 15:14:40
5 then maybe you wouldn't have filed, you know, all 15:14:41
6 those arguments. 15:14:41
7 But the point of it is, you could have 15:14:42
8 gotten -- you could have explored -- 15:14:45
9 ATTORNEY POWERS: Well, you withheld them. 15:14:45
10 ATTORNEY KUSHAN: We didn't withhold the 15:14:48
11 document.
12 ATTORNEY POWERS: Certainly seems like it. 15:14:49
13 ATTORNEY KUSHAN: We made clear -- you can 15:14:49
14 read the -- look, we've told you he didn't limit 15:14:51
15 his analysis. We've told you that evaluated lots 15:14:54
16 of positions, and we would have, you know, 15:14:57
17 responded if you had contacted us about this. 15:14:59
18 So bottom line, we are going to go back 15:15:02
19 and we will work to get this over to you as 15:15:06
20 rapidly as we can. I think the question that you 15:15:10
21 guys should think about is, you know, why did -- 15:15:12
22 why did you wait? 15:15:15

1 And that's my point. So I'm happy to -- 15:15:16
2 ATTORNEY MARTIN: Yeah. We -- you've said 15:15:20
3 your piece. I've said my piece. Trey has said 15:15:21
4 his piece. 15:15:24
5 We didn't wait, right? Like, you guys had 15:15:25
6 the burden under the rules to provide the 15:15:28
7 information that your expert is relying on that 15:15:29
8 forms the backbone of the declarations that he 15:15:32
9 submitted. So you should have given us the 15:15:34
10 spreadsheet. 15:15:36
11 You can give us the spreadsheet now. 15:15:37
12 You're going to give us the spreadsheet, so... 15:15:37
13 ATTORNEY KUSHAN: Do you want it, like, 15:15:39
14 right now? 15:15:41
15 ATTORNEY MARTIN: We can move forward. 15:15:42
16 As soon as possible would be great. 15:15:43
17 ATTORNEY KUSHAN: I don't think we can 15:15:46
18 create -- I don't think we can turn it into paper 15:15:52
19 now, so that's the point. 15:15:55
20 ATTORNEY MARTIN: I mean, I would hope 15:15:56
21 that you would give it in, like, an electronic 15:15:57
22 format. I mean, if you hand me like -- if you 15:15:59

1 hand me something that's this big, you know, a 15:16:01
2 foot-tall stack of paper with 800 and some rows, 15:16:05
3 I'm going to be a little unhappy, so please just
4 give me a PDF, or... 15:16:09
5 ATTORNEY KUSHAN: You'll get -- yeah. 15:16:12
6 You'll get an electronic version. 15:16:13
7 ATTORNEY MARTIN: Okay. Thank you.
8 ATTORNEY KUSHAN: All right. So we'll... 15:16:16
9 ATTORNEY MARTIN: Want to take a break? 15:16:18
10 ATTORNEY KUSHAN: Yeah. 15:16:20
11 ATTORNEY MARTIN: Okay. 15:16:21
12 ATTORNEY KUSHAN: Now we can go off the 15:16:22
13 record. 15:16:24
14 (Recess from 3:16 p.m. until 3:34 p.m.) 15:16:27
15 THE VIDEOGRAPHER: We are back on the 15:34:51
16 record. The time is 3:34 p.m. 15:35:03
17 BY ATTORNEY MARTIN: 15:35:10
18 Q All right. Okay. Can you turn -- 15:35:11
19 Dr. Park, can you turn to Paragraph 161? 15:35:25
20 A I'm at Paragraph 161. 15:35:34
21 Q Okay. Oh, actually. Let's look at 160. 15:35:37
22 A 160. 15:35:47

1 Q So you said that protein structure models 15:35:50
2 generated by SWISS-MODEL, similar tools in 2011 15:35:55
3 would have been reliable for evaluating single 15:36:01
4 amino acid substitutions that are in regions of 15:36:04
5 PH20 where there is a sufficiently reliable local 15:36:04
6 QMEAN score, right? 15:36:06
7 A Yes. That is correct. 15:36:09
8 Q And then you say: This is possible 15:36:10
9 because only one residue is being changed and the 15:36:17
10 remainder of the protein is still based on the 15:36:20
11 reliable experimentally determined structure, 15:36:24
12 right? 15:36:28
13 A Correct. 15:36:28
14 Q So when you say only one residue is being 15:36:29
15 changed, are you referring to the fact that you're 15:36:33
16 using the mutagenesis feature in PyMol to change 15:36:41
17 one amino acid in the protein? 15:36:41
18 ATTORNEY KUSHAN: Objection. Foundation. 15:36:45
19 A Introducing a mutation in PyMol is for 15:36:46
20 convenience only. You can see it in realtime in a 15:36:51
21 matter of seconds. I do it so I can see the 15:36:55
22 mutation quickly. However, if I want to generate 15:37:00

1 a more reliable model, I would generate a mutant 15:37:04
2 sequence of PH20, resubmit it to SWISS-MODEL, and 15:37:10
3 generate PyMol's model again. So I do this in 15:37:15
4 parallel. 15:37:17
5 Q Okay. And is that because PyMol does 15:37:18
6 not -- does not do an energy minimization when it 15:37:21
7 does the mutagenesis? 15:37:26
8 ATTORNEY KUSHAN: Objection. Foundation. 15:37:29
9 A It does not do minimization, energy 15:37:31
10 minimization. That's part of the answer. But 15:37:34
11 it's also because when you introduce a mutation 15:37:39
12 using PyMol, you're using PH20 as the template for 15:37:43
13 generating mutant structure. It would be more 15:37:50
14 fair if that mutant structure were generated using 15:37:54
15 HYAL1 structure as the template, just so that you 15:37:58
16 can treat wild-type and mutant the same way. 15:38:03
17 Q Okay. So hypothetically, you could take 15:38:06
18 the PH20 sequence and introduce two substitutions, 15:38:10
19 and then put that sequence -- put the two 15:38:15
20 substitutions into SWISS-MODEL and generate a 15:38:19
21 homology model using HYAL1 as the template, right? 15:38:27
22 ATTORNEY KUSHAN: Objection. Form. 15:38:28

1 A Yes. If you submit a sequence containing 15:38:29
2 two substitutions through SWISS-MODEL, it will 15:38:32
3 generate a homology model corresponding to that 15:38:34
4 mutant structure. That is true. 15:38:39
5 Unfortunately, that's not the end of the 15:38:45
6 story. Because modeling is not just a matter of 15:38:47
7 generating a PDB file. It also involves the -- 15:38:53
8 the subsequent aspect, which involves an expert 15:38:58
9 looking at the structure and making sense of it, 15:39:02
10 and that's where the problem occurs. 15:39:05
11 Q And what's the problem? 15:39:08
12 A The problem is when you're looking at one 15:39:11
13 substitution, there are only so many interactions 15:39:15
14 that a single amino acid can make, and those are 15:39:21
15 relatively straightforward to discern for an 15:39:29
16 expert. They look at the substitution. They can 15:39:35
17 estimate the three properties that I mentioned: 15:39:42
18 The intrinsic property of the amino acid, 15:39:45
19 secondary structure compatibility and 15:39:47
20 interactions. Those are relatively 15:39:48
21 straightforward, relatively speaking. 15:39:52
22 Once you start introducing the mutations, 15:39:55

1 more than one mutation, and if those mutations 15:40:01
2 happen to be -- to say, one, if they're close, or 15:40:11
3 if they're far away. 15:40:14
4 If they're far away, you can treat them -- 15:40:15
5 treat them as independent mutations so you can 15:40:19
6 evaluate them one at a time. That's fine. 15:40:23
7 However, if those substitutions happen to be very 15:40:25
8 close to each other, what happens is now suddenly 15:40:29
9 you have to deal with many more possible changes 15:40:33
10 in the interactions, because the individual 15:40:36
11 substitutions would now alter their interactions 15:40:40
12 with their neighbor, and there would be 15:40:45
13 interactions between them as well. 15:40:47
14 So now that results in both positive and 15:40:50
15 negative interactions, all of which need to be 15:40:53
16 tracked and estimated. Unfortunately, a person 15:40:56
17 viewing the structure would not be able to 15:41:02
18 differentiate many of these subtle changes, 15:41:05
19 especially if there are multiple mutations nearby. 15:41:11
20 Q Okay. So let's say you have your PH20 15:41:16
21 structure, and you introduce two substitutions 15:41:21
22 that are far apart in the structure. 15:41:25

1 Am I understanding correctly that you 15:41:29
2 could -- you could evaluate those -- you could 15:41:31
3 evaluate those substitutions using the model, the 15:41:34
4 homology model that you generate, because they're 15:41:39
5 far away from each other and so you're not going 15:41:43
6 to have this neighbor effect? 15:41:46
7 ATTORNEY KUSHAN: Objection. Foundation. 15:41:48
8 Objection as to form. 15:41:49
9 A One can make an approximation and say 15:41:50
10 because they are spatially far apart from each 15:41:54
11 other, their interactions would be minimal. 15:42:01
12 Therefore, they can be treated independently, yes. 15:42:01
13 (Reporter clarification.) 15:42:08
14 Q And so when you say they can be treated 15:42:08
15 independently, you mean that you can go and look 15:42:11
16 in the structure at -- at the effect of the 15:42:13
17 substitution at each position independently and 15:42:17
18 see how that substitution is impacting the local 15:42:20
19 environment, and it would be two different 15:42:28
20 analyses because they're far apart in the protein; 15:42:33
21 is that right? 15:42:37
22 A Yes. That would be the case. 15:42:37

1 Q Okay. 15:42:39
2 A That would be an approximation, but I 15:42:39
3 would think it would be a reasonable 15:42:43
4 approximation. Distant residues are known to be
5 coupled in some cases, but they're not very 15:42:47
6 common. 15:42:49
7 So if you introduce a mutation that are 15:42:50
8 far apart from each other, then each mutation can 15:42:52
9 be treated independently and evaluated 15:42:57
10 independently, and one may be able to estimate the 15:42:59
11 combined effect of the two or more mutations, if 15:43:06
12 necessary, and include whether the mutant would be 15:43:11
13 better or worse than wild-type. 15:43:17
14 (Reporter clarification.) 15:43:26
15 Q Okay. So then if you have two 15:43:26
16 substitutions that are close together, am I 15:43:30
17 understanding correctly that if you make two 15:43:33
18 substitutions that are close together, then they 15:43:36
19 could interact with each other, and if you're 15:43:41
20 going through and identifying and cataloging every 15:43:44
21 single interaction that -- every single 15:43:47
22 interaction at a particular position, when you 15:43:50

1 then make a change, let's say right next to that 15:43:54
2 position, you then have to go through and catalog 15:43:58
3 every single one of the interactions at the second 15:44:01
4 substitution, and so then it becomes difficult to 15:44:02
5 tease out the effects of the combination, as 15:44:06
6 opposed to just making the single substitution? 15:44:11
7 ATTORNEY KUSHAN: Objection to form. 15:44:15
8 Also objection to foundation. 15:44:16
9 A It does come down to the number game. As 15:44:20
10 you introduce more and more mutations, the number 15:44:25
11 of possible favorable and unfavorable interactions 15:44:28
12 increases exponentially, and can quickly overwhelm 15:44:35
13 a person's ability to evaluate them. 15:44:43
14 And many of the combinations may be very 15:44:47
15 nuanced. In other words, the differences between 15:44:53
16 different conformations and different combinations 15:44:58
17 of mutations would be very nuanced, to be able 15:45:02
18 to -- for a person to be able to -- to say whether 15:45:08
19 one would be better than another set of mutants, 15:45:10
20 mutations. 15:45:16
21 Q Okay. So let's say you're mutating two 15:45:17
22 residues that are right next to each other in the 15:45:23

1 protein. Okay? Just the two. I'm trying to 15:45:26
2 understand why it is that -- why it is that that 15:45:30
3 creates an issue when you're doing your 15:45:38
4 comparison? 15:45:41
5 So you have your PH20 sequence and you 15:45:44
6 mutate two residues right next to each other, and
7 you compare that model with the wild-type PH20 15:45:48
8 model. So what is it about the fact that the 15:45:53
9 residues are right next to each other that is 15:45:58
10 making the analysis difficult? 15:46:01
11 ATTORNEY KUSHAN: Objection. Form. 15:46:03
12 A Yeah. Again, the problem is not the 15:46:06
13 generation of the model, per se. But here I'm 15:46:11
14 using the word modeling, not only to indicate the 15:46:14
15 mechanics of going through the SWISS-MODEL portal 15:46:19
16 downloading PBD, which can be done regardless of 15:46:22
17 what you put in, but the subsequent step -- the 15:46:26
18 human intervention portion of the modeling, which 15:46:32
19 involves interpretation of the mutations, becomes 15:46:36
20 very quickly intractable. 15:46:40
21 And the reason for that is because of 15:46:45
22 the -- the very large number of changes that occur 15:46:49

1 following multiple simultaneous mutations. They 15:46:54
2 can't be broken down. In other words, the number 15:47:02
3 of interactions they need to keep track of does 15:47:05
4 not grow linearly, as you would expect if those 15:47:05
5 sites are independent, but they would grow 15:47:12
6 exponentially. 15:47:15
7 Q Okay. So you agree that technically you 15:47:16
8 can introduce multiple mutations into a 15:47:21
9 sequence -- into a sequence, and then you could 15:47:27
10 submit that sequence for PH20 into SWISS-MODEL, 15:47:30
11 and you download a PBD file with the resulting 15:47:33
12 homology model, right? 15:47:38
13 A Well, I don't -- 15:47:40
14 ATTORNEY KUSHAN: Sorry. 15:47:40
15 Objection. Foundation. 15:47:41
16 A I don't argue that you can do it. If you 15:47:45
17 have many combinations, it might take a while. 15:47:53
18 But you can generate a PBD file, files. 15:47:56
19 Unfortunately, it doesn't really get you anywhere, 15:48:00
20 because SWISS-MODEL doesn't put a number on -- it 15:48:04
21 doesn't tell you anything about the energetics of 15:48:10
22 those substitutions. All it does is -- it's going 15:48:14

1 to give you the best structure it can, given the 15:48:20
2 sequence. 15:48:24
3 It may be a horrendous combination of 15:48:24
4 mutations. SWISS-MODEL would not know the 15:48:30
5 difference between that and the best sequence. It 15:48:32
6 just gives you the best structure it can by going 15:48:35
7 through the set of routines that it's designed to 15:48:38
8 do, and you generate a PBD file. 15:48:44
9 And sure, you can download it. But what 15:48:49
10 do you do with it? The problem is you can't do 15:48:51
11 anything, and there's no methodology that will 15:48:55
12 allow you to compare two structures containing 15:49:01
13 substitutions that are near each other if it's a 15:49:06
14 large number. There's no proven and accepted 15:49:10
15 methodology that one can go through systemically 15:49:14
16 to evaluate and compare those sets of structures 15:49:17
17 and sequences, which I consider still part of the 15:49:23
18 modeling. 15:49:27
19 Q Uh-huh. 15:49:28
20 A Because modeling is not just generating 15:49:29
21 the PBD file, but also looking at it and making 15:49:32
22 sense of it. And you will -- one will run into a 15:49:36

1 combinatorial, combinatorially intractable 15:49:44
2 situation very quickly if mutations occur close to 15:49:48
3 each other. 15:49:53
4 Q And the combinatorially intractability is 15:49:54
5 because of all of the -- all of the new 15:50:00
6 interactions that are forming, and you can't keep 15:50:02
7 track of all of the new interactions that are 15:50:06
8 forming when you're making multiple changes close 15:50:09
9 together in the protein; is that right? 15:50:11
10 A That is true. Two parts: One, to share a 15:50:14
11 number of interactions that one needs to keep 15:50:20
12 track of increases very quickly, as I pointed out, 15:50:22
13 exponentially, and that will expose the 15:50:29
14 fundamental shortfalls, shortcomings of the energy 15:50:36
15 field that is used to evaluate different 15:50:39
16 substitutions. Those energy fields are 15:50:43
17 incomplete. Incomplete. 15:50:47
18 And I think I got it. 15:50:51
19 They are unfortunately incomplete. There 15:50:54
20 are many effects that are overlooked by the -- the 15:50:57
21 force field, and those errors would compound as 15:51:02
22 you begin to change more interactions, and now the 15:51:07

1 uncertainty that results from those shortcomings 15:51:12
2 in the force -- force field would essentially 15:51:18
3 prevent one to make a meaningful comparison 15:51:23
4 between structures. 15:51:28
5 Q So is the problem that you're -- is the 15:51:30
6 problem the comparison, that you're comparing the 15:51:31
7 wild-type structure with the structure that has, 15:51:35
8 let's say, two changes that are right next to each 15:51:37
9 other, and you're trying to account for, let's 15:51:40
10 take position 320 -- you're trying to account for 15:51:43
11 all of the interactions at position 320, and then 15:51:46
12 in the wild-type structure, and then if you make 15:51:53
13 two changes -- well actually, wait. 15:51:59
14 Let me start over. Let me try this a
15 different way. 15:52:04
16 All right. So you have your wild-type 15:52:04
17 PH20 model. Let's say you make your position, 15:52:08
18 your change at position 320, right? And you make 15:52:11
19 your SWISS-MODEL model at position 320. 15:52:13
20 Could you then make a change at 15:52:15
21 position 321, and then compare that model to the 15:52:18
22 model at position in which you changed 15:52:22

1 position 320? 15:52:26
2 A Both mutations, or just one mutation? 15:52:28
3 Q So the -- wait. You have your wild-type, 15:52:32
4 and you have your mutant 320, and then you have 15:52:41
5 your mutant 320 and 321. 15:52:42
6 A Okay. Single point mutant versus double 15:52:43
7 mutant? 15:52:47
8 Q Yes. Could you do that -- could you do 15:52:47
9 that comparison, I guess three-way comparison -- 15:52:50
10 ATTORNEY KUSHAN: Objection. 15:52:54
11 Q -- to evaluate the -- to model the 15:52:55
12 mutation at positions 320 and 321? 15:52:59
13 ATTORNEY KUSHAN: Objection. Foundation. 15:53:02
14 Objection to form. 15:53:03
15 A It depends on the types of mutations that 15:53:05
16 you would introduce. Some combinations are more 15:53:08
17 straightforward than others. If one mutation is 15:53:12
18 outright bad, then no matter what you do at the 15:53:16
19 other position, you may just kill the protein. So 15:53:21
20 that -- that's an easy combination. 15:53:25
21 There may be scenarios where it's not 15:53:28
22 clear what happens. And now if you increase it to 15:53:31

1 three and four and five positions which are all 15:53:38
2 simultaneously changing, and now all of a sudden, 15:53:44
3 a lot of things are changing. 15:53:48
4 So you have to -- one has to compare the 15:53:50
5 initial wild-type set of interactions with the 15:53:54
6 interactions that you see in a single point mutant 15:53:58
7 or a quintuple mutant, and a lot of things have 15:54:04
8 changed, and unfortunately the energy function 15:54:11
9 that is used and needed to evaluate these 15:54:16
10 different changes and interactions are not very 15:54:19
11 accurate. 15:54:23
12 And those errors would compound as you 15:54:25
13 begin to introduce more and more, and there are 15:54:28
14 other missing components to the force field which 15:54:33
15 may not have been very important initially, for a 15:54:38
16 single point mutant, will become very apparent as 15:54:42
17 you -- it would become more significant because 15:54:48
18 they individually introduce uncertainties, and 15:54:53
19 errors so that it becomes nearly impossible to 15:54:58
20 make any meaningful statement comparing one set of 15:55:03
21 five mutants versus another set of five mutants, 15:55:08
22 or a single mutant. That's the challenge. 15:55:15

1 Q So the challenge is that -- I'm trying to 15:55:16
2 understand if the challenge is that you have to 15:55:21
3 count all of the different interactions that have 15:55:23
4 changed, and that's just a lot of interactions 15:55:25
5 that have changed when you have, like, five 15:55:27
6 mutations right next to each other on a protein, 15:55:30
7 or if the problem is that you don't know if 15:55:33
8 those -- let's say you're making five changes, if 15:55:35
9 those replaced residues are in the correct 15:55:40
10 position in the model, because there's an issue 15:55:43
11 with the energetics that the computer program is 15:55:46
12 using to build the homology model. 15:55:51
13 I'm trying to understand if which one of 15:55:54
14 those two things it is that you're -- 15:55:56
15 A Oh, absolutely. 15:55:57
16 ATTORNEY KUSHAN: Objection. Foundation. 15:55:58
17 Objection to form. 15:56:00
18 A SWISS-MODEL does side chain modeling, 15:56:05
19 meaning after the backbone structure has been 15:56:12
20 determined, it would go through different rotamer 15:56:17
21 states and identify the set of rotamers that the 15:56:21
22 minimize the energy. 15:56:30

1 (Reporter clarification.) 15:56:32
2 A That it does pretty well, because it uses 15:56:32
3 an external algorithm actually, SCWRL, I think 15:56:36
4 that's called.
5 It's known to be pretty good at side chain 15:56:43
6 modeling. And it will find the best combination 15:56:48
7 of rotamers. So internally consistent. So 15:56:53
8 comparing one rotamer set for that quintuple 15:57:00
9 mutant to another rotamer set containing exactly
10 the same mutations, in other words, if you change 15:57:05
11 the confirmations of the five residues, SCWRL will 15:57:05
12 know how to do it. 15:57:12
13 So it will give you the best rotamer. 15:57:13
14 However, it doesn't give you a method of comparing 15:57:17
15 that mutant with another mutant containing 15:57:20
16 different amino acids at the same positions. That 15:57:26
17 requires different analysis, post-model 15:57:29
18 generation. You generate the model, and then 15:57:33
19 comes the analysis. How does one analyze that? 15:57:38
20 For a single point mutant, visual 15:57:42
21 inspection is often sufficient. That has been 15:57:43
22 known to be very successful. And that's also 15:57:48

1 proven by publication. People have done that. 15:57:52
2 For multiple point mutations, it becomes 15:57:56
3 very difficult for a human to juggle many 15:58:00
4 different possible interactions. 15:58:07
5 But that's only the problem. As I said,
6 there are two parts to it: One is the sheer 15:58:09
7 number of conformations, or combinatorial 15:58:10
8 interactions that we -- we need to keep track of. 15:58:16
9 But even if we were to do that diligently 15:58:19
10 and somehow tabulate all 5,000 interactions that 15:58:25
11 have changed, it still doesn't give you the answer 15:58:26
12 because the force field, energy field, that is 15:58:31
13 needed to estimate the energies for those 15:58:34
14 individual interactions is not there. It's 15:58:38
15 incomplete. 15:58:43
16 And that is a struggle that the whole 15:58:43
17 community has to deal with, and was not a solved 15:58:47
18 problem back in 2011. I don't think it's a solved 15:58:59
19 problem as of today. 15:58:56
20 Q Okay. Okay. So I think that what I'm 15:58:58
21 struggling with is that PH20 is -- PH20 is 40 15:59:07
22 percent-ish identical to HYAL1, the template 15:59:17

1 structure, right? 15:59:26
2 A Yes. 15:59:26
3 Q Okay.
4 A It is. 15:59:27
5 Q Human PH20. Let's say Rhesus monkey PH20 15:59:27
6 is, I don't know, like 37 percent -- I'm just 15:59:37
7 making up a number -- 37 percent identical to 15:59:42
8 HYAL1, right? 15:59:46
9 Presumably there's more than one change, 15:59:47
10 one difference between Rhesus monkey PH20 and 15:59:52
11 human PH20 that presumably you could still 15:59:53
12 generate a Rhesus monkey model using SWISS-MODEL 15:59:54
13 for Rhesus monkey PH20, the same way you could for 15:59:58
14 human PH20. 16:00:01
15 And if based on what you're saying about 16:00:02
16 the multiple mutation issue, I don't understand 16:00:04
17 why it's okay to use SWISS-MODEL to generate a 16:00:09
18 human PH20 model, and that's okay, but somehow 16:00:13
19 there's no force field and you're going to get 16:00:20
20 gibberish if you try to generate a model for
21 Rhesus monkey PH20, despite the fact that the 16:00:24
22 Rhesus monkey PH20 and the human PH20 have 16:00:27

1 multiple differences in their sequences? 16:00:31
2 That's -- that's what I'm not 16:00:33
3 understanding. Because the template sequence that 16:00:35
4 you're using has more than one change, right, to 16:00:38
5 PH20? The HYAL1 sequence is more than one amino 16:00:42
6 acid off of PH20, and you're still able to use 16:00:47
7 that as a template, so -- 16:00:50
8 A Absolutely. No problem with the Rhesus 16:00:51
9 monkey. It can generate a model. 16:00:55
10 Q Okay. 16:00:56
11 A What you cannot do is compare the Rhesus 16:00:57
12 monkey PH20, compare that to human PH20. 16:01:00
13 Q Okay. Okay. It's the comparison that 16:01:01
14 we're talking about? 16:01:04
15 A It's the comparison that you cannot do. 16:01:05
16 Q Okay.
17 A That's what -- that's what comes down to 16:01:08
18 the mutant analysis. 16:01:10
19 Q Okay. 16:01:11
20 A If you introduce the mutation in PH20, the 16:01:12
21 model will not tell you how to compare the two 16:01:16
22 structures. 16:01:22

1 Q Okay. All right. I am now following. 16:01:18
2 Thank you for that. 16:01:24
3 A I'm sorry for that very long-winded and 16:01:24
4 somewhat confusing answer. 16:01:30
5 Q No. I'm now following. Thank you. 16:01:30
6 All right. So let's turn to 16:03:00
7 Paragraph 107. 16:03:02
8 A Okay. I'm at Paragraph 107. 16:03:22
9 Q So you say: I visualized position 320 -- 16:03:41
10 (Reporter clarification.)
11 Q Paragraph 107: I visualized position 320 16:03:52
12 within the PH20 model using PyMol. First, I 16:03:52
13 confirmed that position 320 was not near the 16:03:58
14 active site, right? 16:04:01
15 A That's correct. 16:04:02
16 Q How did you confirm that position 320 was 16:04:04
17 not near the active site? 16:04:07
18 A I built a model of PH20 with the substrate 16:04:15
19 in the binding pocket, and that substrate was
20 imported from the bee venom hyaluronidase. And 16:04:26
21 through superposition and transferring of the 16:04:27
22 glycan, I could see where the substrate would sit 16:04:31

1 in the binding pocket, and 320 was not near that 16:04:35
2 binding pocket. 16:04:40
3 Q When you say not near, I'm just trying to 16:04:41
4 understand what that means. Is that a 16:04:44
5 quantitative or qualitative? 16:04:46
6 A Sure. I don't have an exact number in 16:04:49
7 terms of the distance in angstroms, but it was 16:04:52
8 sufficiently far away from where the bound 16:04:56
9 substrate is, which led me to believe that it's 16:05:00
10 unlikely that this residue 320, regardless of what 16:05:05
11 that amino acids is, I didn't think that that 16:05:10
12 would be in a position to interact with a 16:05:14
13 substrate in any significant way. 16:05:16
14 Q And why is that evaluation as to whether 16:05:19
15 position 320 is near the active site, why is that 16:05:23
16 important in your analysis? 16:05:28
17 A When you start mutating residues in the 16:05:33
18 binding pocket, now you have to worry about the 16:05:37
19 impact of the substitution on catalysis directly, 16:05:41
20 in addition to its potential impact on the 16:05:47
21 structure. I wanted to isolate those two effects 16:05:53
22 and consider only the structural aspect, not the 16:05:56

1 functional aspect. 16:06:02
2 Q Okay. 16:06:05
3 ATTORNEY KUSHAN: Can we take a one-minute 16:06:08
4 break so I can let Christine in? 16:06:11
5 ATTORNEY MARTIN: Oh, yeah. 16:06:14
6 THE VIDEOGRAPHER: We are going off the 16:06:16
7 record. The time is 4:06 p.m. 16:06:18
8 (Recess from 4:06 p.m. until 4:08 p.m.) 16:06:22
9 THE VIDEOGRAPHER: We are back on the 16:08:48
10 record. The time is 4:08 p.m. 16:08:50
11 BY ATTORNEY MARTIN: 16:08:59
12 Q Okay. Dr. Park, can you please turn to 16:09:00
13 Paragraph 52? 16:09:05
14 A Paragraph 52? I am at Paragraph 52. 16:09:26
15 Q So in Paragraph 52, you say that the Yue 16:09:39
16 paper also pointed out that there was a better 16:09:44
17 correlation between substitutions and 16:09:47
18 destabilizing changes when the nature of an 16:09:50
19 interaction was combined with this location. 16:09:54
20 Do you agree that the location of a 16:09:58
21 residue is an important factor to consider when 16:10:04
22 evaluating the impact of a substitution? 16:10:08

1 Actually, strike that. 16:10:30
2 If you turn to Paragraph 53 -- 16:10:33
3 A Okay.
4 Q -- in the last sentence, it looks like you
5 address this.
6 You say: The location of the amino acid 16:10:36
7 being changed within the protein structure is an 16:10:37
8 important consideration in assessing whether a 16:10:39
9 single amino acid substitution will be tolerated 16:10:42
10 or not, right? 16:10:50
11 A That's correct. 16:10:50
12 Q So do you agree that the location of the 16:10:50
13 amino acid is an important consideration when 16:10:54
14 you're evaluating substitutions? 16:10:56
15 A Was the question: Is the location an 16:10:57
16 important consideration? 16:10:59
17 Q Yes. Yes. 16:10:59
18 A The location of the substitution is an 16:11:05
19 important consideration, yes. 16:11:08
20 Q So why -- why is the location of an amino 16:11:09
21 acid an important consideration? 16:11:11
22 A There are many factors that go in. It's 16:11:20

1 listed in that Paragraph 52 as well, where it 16:11:24
2 says, for example: Proteins are more consistently 16:11:30
3 destabilized by a single amino acid change that 16:11:37
4 introduced a large side chain that caused a steric 16:11:41
5 clash within a buried position of the protein. 16:11:43
6 (Reporter clarification.) 16:11:55
7 A That's because in a buried position, many 16:11:55
8 structural constraints of what can go in, in terms 16:11:57
9 of size, the shape, in addition to the 16:12:02
10 hydrophobicity/hydrophilicity. 16:12:05
11 So the constraints are different whether a 16:12:09
12 position is buried as opposed to, say, solvent 16:12:16
13 exposed. In a solvent exposed position, there's a 16:12:23
14 lot of freedom. You still need to satisfy some 16:12:26
15 constraints, but having done that, there's a lot 16:12:32
16 of freedom in terms of choosing an amino acid, 16:12:38
17 just because there are fewer structural 16:12:43
18 constraints. 16:12:48
19 Q What are -- what do you mean when you say 16:12:49
20 structural constraints? 16:12:51
21 A Structural constraints that I refer to 16:12:53
22 include the ones that I mentioned earlier, say, 16:12:58

1 the volume or the shape. The amino acids at a 16:13:01
2 buried position will force the choice of amino 16:13:11
3 acid to be introduced to be a certain way. It not 16:13:17
4 only has to fit into that space, but it also needs 16:13:22
5 to have the right shape. 16:13:27
6 Those constraints are not as prominent at 16:13:30
7 a solvent exposed position. The amino acid will 16:13:35
8 have to satisfy some constraint, for instance, 16:13:42
9 based on hydrophilicity/hydrophobicity. 16:13:46
10 (Reporter clarification.) 16:13:57
11 A But beyond that, there is much liberty. 16:13:57
12 Q So as a -- is it correct that as a general 16:14:05
13 matter, a buried hydrophobic residue is going to 16:14:09
14 be less amenable to substitution than a solvent 16:14:16
15 exposed hydrophilic residue? 16:14:21
16 A It's always dangerous to generalize, but 16:14:26
17 in many cases, buried positions are harder to 16:14:30
18 mutate properly, compared to a solvent exposed 16:14:37
19 position. Yes. 16:14:41
20 Q Did you look -- did you identify where on 16:14:46
21 the structure -- strike that. 16:14:50
22 If you were to introduce a single amino 16:15:23

1 acid change that introduced a large side chain, 16:15:26
2 let's say a large charged side chain, into a 16:15:29
3 buried hydrophobic pocket in the protein, would 16:15:33
4 you expect that to cause problems for your 16:15:38
5 protein? 16:15:43
6 ATTORNEY KUSHAN: Objection. Foundation. 16:15:44
7 A That's a very complicated scenario, 16:15:48
8 introducing a large charged residue into a buried 16:15:54
9 position, was it? 16:15:58
10 Q Uh-huh. 16:15:59
11 A It's hard to imagine a scenario where that 16:16:00
12 would happen. The large side chain would have to 16:16:05
13 be the right size to fit into it, first of all. 16:16:09
14 And having a charge that's buried is a no-no when 16:16:15
15 you're doing important engineering. This, I 16:16:22
16 think, would be one of the worst combination of 16:16:26
17 position versus amino acid choice. 16:16:31
18 Q Okay. 16:16:35
19 A Yes. So it would be a pretty bad mutation 16:16:35
20 in general. Now, can one think of a scenario 16:16:41
21 where this is not the case, well, anything is 16:16:45
22 possible. But I think in general, that would be 16:16:47

1 challenging. 16:16:51
2 Q Okay. Would you expect -- would you 16:16:52
3 expect to get a misfolded protein, or an inactive 16:16:54
4 protein, if you did something like that? 16:17:01
5 A In all likelihood, and very high 16:17:06
6 probability, I think the -- that substitution 16:17:10
7 would be highly destabilizing. 16:17:13
8 (Reporter clarification.) 16:17:19
9 Q So if you -- let's say you change 16:17:19
10 multiple -- multiple buried hydrophobic residues 16:17:24
11 to large charged residues all at the same time, 16:17:33
12 would you expect to get a functional protein, or 16:17:36
13 would you expect to get not -- an inactive 16:17:40
14 protein? 16:17:43
15 ATTORNEY KUSHAN: Objection. Foundation. 16:17:44
16 Objection as to form. 16:17:46
17 A We're talking about a very highly 16:17:48
18 coordinated and orchestrated mutation, which I 16:17:58
19 think would be extremely difficult to pull off. 16:18:03
20 Q So you would expect that it would not -- 16:18:04
21 you would not get a functional protein out of 16:18:06
22 that, right? 16:18:10

1 ATTORNEY KUSHAN: Objection. Form. 16:18:10
2 A If I were a betting man, I would not bet 16:18:11
3 in favor of that mutation. 16:18:15
4 Q Okay. And you don't need a SWISS-MODEL 16:18:25
5 homology model to predict that that's not going to 16:18:21
6 work, right? 16:18:24
7 ATTORNEY KUSHAN: Objection. Foundation. 16:18:26
8 A SWISS-MODEL can generate a model that one 16:18:31
9 can expect to see whether such combination might 16:18:36
10 be possible, and being able to see the model with 16:18:41
11 your own eye might be very helpful. 16:18:47
12 What I am objecting earlier is that the 16:18:53
13 likelihood of finding a pair of charge mutations, 16:18:55
14 I think that was the scenario? 16:19:01
15 Q For multiple -- multiple charge. 16:19:03
16 A Multiple charge, no less. 16:19:04
17 Q Uh-huh.
18 A To fit into hydrophobic pocket and somehow 16:19:06
19 make everybody happy and keep the protein 16:19:15
20 functional, would be a very difficult task, with 16:19:19
21 or without SWISS-MODEL. 16:19:23
22 (Reporter clarification.) 16:19:29

1 ATTORNEY KUSHAN: Can we just -- whoever 16:19:29
2 has joined, announce themselves? 16:19:33
3 THE VIDEOGRAPHER: It looks like 16:19:37
4 Mr. Goldberg signed in again. 16:19:39
5 ATTORNEY KUSHAN: Brian, can you hear us? 16:19:42
6 ATTORNEY GOLDBERG: I can. 16:19:45
7 ATTORNEY KUSHAN: Are you by yourself? 16:19:47
8 ATTORNEY GOLDBERG: Yes. 16:19:49
9 ATTORNEY KUSHAN: Okay. Just wanted to 16:19:50
10 make sure. 16:19:52
11 ATTORNEY MARTIN: Thank you. 16:19:53
12 ATTORNEY GOLDBERG: Yeah. 16:19:53
13 BY ATTORNEY MARTIN: 16:20:08
14 Q So you used a distance cut-off of 5 16:20:08
15 angstroms to identify neighbors in your analysis; 16:20:15
16 is that right? 16:20:17
17 A I did. 16:20:17
18 Q Why did you use 5 angstroms as the 16:20:18
19 cut-off? 16:20:22
20 A It's a number that's commonly used. 16:20:24
21 Q So is that a typical cut-off in the art to 16:20:30
22 identify neighbors for a particular residue? 16:20:33

A I would say so. 16:20:39
Q And was that the case in 2011? 16:20:41
A Yes. The cut-off hasn't changed. 16:20:46
Q Okay. Let's turn to Paragraph 70. 16:20:51
A I'm at Paragraph 70. 16:22:02
Q And in Paragraph 70, you say that: The 16:22:04
propensity of different amino acids to support 16:22:10
helix or beta sheet formation was generally known; 16:22:12
is that right? 16:22:13
A That's correct. 16:22:16
Q And was that generally known in 2011? 16:22:17
A Yes. 16:22:25
Q And you have a chart under Paragraph 70 16:22:25
that identifies good and poor alpha helix and beta 16:22:29
sheet formers, right? 16:22:38
(Reporter clarification.) 16:22:41
A Yes. There's a chart. 16:22:41
Q Did you prepare this chart? 16:22:43
A Yes. I did. 16:22:49
Q And was this chart created based on what 16:22:50
the skilled person would understand in 2011? 16:22:57
A Yes. 16:23:00

1 Q Okay. 16:23:05
2 A This would be regularly understood by a 16:23:06
3 POSA. 16:23:09
4 Q So we had talked about the various 16:24:07
5 interactions that you considered in your analysis 16:24:11
6 to determine whether a substitution would be 16:24:16
7 favorable or neutral or unfavorable, and you used 16:24:19
8 two publications -- the Wang publication and the 16:24:24
9 Yue publication -- for the -- to identify or list 16:24:29
10 those interactions; is that right? 16:24:33
11 ATTORNEY KUSHAN: Objection. Foundation. 16:24:38
12 A Yes. I used those two publications as a 16:24:40
13 demonstration that there were other precedents 16:24:46
14 doing similar things. 16:24:55
15 Q And how did you identify those two papers? 16:24:56
16 A I don't remember the exact steps I took, 16:24:59
17 but it must have been a combination of PubMed 16:25:09
18 search and Google search. 16:25:20
19 (Reporter clarification.) 16:25:28
20 Q And those papers evaluate SNPs, right, 16:25:28
21 single nucleotide polymorphisms; is that right? 16:25:38
22 A That's correct. 16:25:44

1 Q And in particular, they evaluate SNPs that 16:25:44
2 are known to cause disease, right? 16:25:50
3 A That's right. 16:25:52
4 Q And they try to identify the molecular 16:25:53
5 mechanism of action for why that particular SNP 16:25:57
6 causes disease? 16:25:58
7 A That's correct. 16:26:00
8 Q So is it fair to say that those two 16:26:01
9 papers, the Wang and the Yue paper, are evaluating 16:26:04
10 the relationship between structure and function in 16:26:07
11 terms of the impact on protein structure of a 16:26:11
12 particular mutation, and the function being a 16:26:18
13 destabilization and then the resulting disease? 16:26:23
14 ATTORNEY KUSHAN: Objection. Foundation. 16:26:27
15 A That's what they found in the paper. They 16:26:28
16 reported that 90 percent of the time, SNPs cause 16:26:32
17 instability in the protein, which is the -- the 16:26:38
18 direct cause of the disease. 16:26:41
19 Q So are those papers evaluating structure 16:26:41
20 function correlations for those various SNPs? 16:26:44
21 ATTORNEY KUSHAN: Objection. Foundation. 16:26:50
22 A Not structure function, but sequence 16:26:51

1 structure/stability. 16:26:53
2 ATTORNEY MARTIN: Okay. So we've been 16:26:55
3 going for a long time. Do you want to take a 16:27:03
4 quick break? 16:27:05
5 THE WITNESS: Sure. 16:27:09
6 ATTORNEY KUSHAN: Sure. 16:27:09
7 ATTORNEY MARTIN: See how much I have. 16:27:11
8 THE VIDEOGRAPHER: We are going off the 16:27:14
9 record. The time is 4:27 p.m. 16:27:23
10 (Recess from 4:27 p.m. until 4:50 p.m.) 16:27:30
11 THE VIDEOGRAPHER: We are back on the 16:50:24
12 record. The time is 4:50 p.m. 16:50:25
13 ATTORNEY MARTIN: All right. I just have 16:50:29
14 one more question, and then some things to read on 16:50:31
15 the record. 16:50:36
16 BY ATTORNEY MARTIN: 16:50:39
17 Q So -- so Dr. Park, you mentioned that you 16:50:40
18 had several conversations with Dr. Hecht in 16:50:41
19 connection with your analysis in this case. 16:50:45
20 So the question is: Did you rely on -- on 16:50:48
21 anything that you learned from Dr. Hecht in -- in 16:50:51
22 your analyses that are set forth in your 16:50:57

1 declarations? 16:51:02
2 A No. The conversation was more or less one 16:51:03
3 directional, me explaining to him what I had done, 16:51:11
4 and Dr. Hecht mostly agreeing with what I said. 16:51:14
5 ATTORNEY MARTIN: Okay. All right. So 16:51:24
6 let me just say what I'm going to say. 16:51:27
7 All right. So for the spreadsheet, we 16:51:30
8 object to the late production of the spreadsheet 16:51:34
9 under Rule 42.65. It's highly prejudicial that we 16:51:38
10 got the spreadsheet during the deposition, the 16:51:45
11 afternoon of the deposition. 16:51:49
12 And you know, it's very -- we appreciate 16:51:52
13 that you got us the spreadsheet, but at the same 16:51:55
14 time, right, I mean, it's a very small fonted, 16:52:00
15 large document with, like, 2,800 rows. 16:52:04
16 And it's in black and white, and there's a 16:52:08
17 figure that looks like it should be in color in 16:52:11
18 here, and we still don't have a color version of 16:52:15
19 it. 16:52:17
20 So it's obviously highly prejudicial that 16:52:18
21 we just got this now. We haven't been able to 16:52:21
22 talk to our experts about it. Obviously we can't 16:52:26

1 be expected to depose Dr. Park on it now, and so 16:52:29
2 we reserve the right to request a further 16:52:31
3 deposition and potentially other relief, so... 16:52:34
4 And we also object to the fact that 16:52:45
5 Dr. Hecht attended a portion of this deposition, 16:52:51
6 and we object to the potential -- we object to 16:52:53
7 Dr. Hecht reading the transcript from this 16:52:58
8 deposition because we think that it's witness 16:53:02
9 coaching. So we're going to put that on the 16:53:05
10 record as well. 16:53:08
11 And we object to, under Federal Rule of 16:53:11
12 Evidence 615 specifically, that Dr. Hecht listened 16:53:17
13 in on the deposition. We object to Dr. Hecht 16:53:22
14 reviewing the transcript under Federal Rule of 16:53:25
15 Evidence 615, and we object to the extent that 16:53:26
16 Dr. Hecht relies on any of today's testimony. 16:53:30
17 Okay. All right. So I think I'm done, 16:53:49
18 and pass the witness. 16:53:51
19 ATTORNEY KUSHAN: Can we have a 16:53:52
20 five-minute break, and then we can proceed? 16:53:58
21 Before we do that, we, of course, disagree 16:54:01
22 with the basis and propriety of the objections 16:54:04

1 you've raised about Dr. Hecht. 16:54:07
2 We also disagree with your arguments 16:54:09
3 regarding the late production -- or, supposedly 16:54:15
4 late production -- of this exhibit. And we are in 16:54:17
5 the process of emailing you the version of that 16:54:19
6 file with page numbers, which you should get 16:54:23
7 shortly. 16:54:27
8 But why don't we take our break? 16:54:28
9 THE VIDEOGRAPHER: We are going off the 16:54:32
10 record. The time is 4:54 p.m. 16:54:34
11 (Recess from 4:54 p.m. until 5:07 p.m.) 16:54:37
12 THE VIDEOGRAPHER: We are back on the 17:07:58
13 record. The time is 5:07 p.m. 17:08:01
14 ATTORNEY KUSHAN: Just before the break, 17:08:09
15 you made a number of comments, and my brief 17:08:12
16 response to that -- and we obviously can reserve 17:08:15
17 our ability to address other issues at a 17:08:18
18 subsequent point. 17:08:21
19 Promptly after you asked that Dr. Hecht 17:08:23
20 terminate his participation in this deposition, we 17:08:26
21 complied. And we don't think -- believe there's 17:08:26
22 any improper nature in his participation in the 17:08:30

1 deposition or, you know, watching it, and we don't 17:08:34
2 think there's been any prejudice as a consequence 17:08:39
3 of that. So we don't think there's any issue to 17:08:41
4 address in the future. 17:08:45
5 And that's -- at this point, we have no 17:08:48
6 questions for the witness, so we can end the 17:08:51
7 deposition. 17:08:53
8 ATTORNEY MARTIN: Okay. Great. 17:08:54
9 THE VIDEOGRAPHER: This marks the end of 17:08:55
10 the deposition of Dr. Sheldon Park. 17:08:59
11 We are going off the record at 5:08 p.m. 17:09:01
12 (The videotaped deposition of DR. SHELDON
13 PARK was concluded at 5:09 p.m.)
14
15
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18
19
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22

1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC
2
3 I, Kadi A. Harmon, Certified Reporter and
4 Notary Public within and for the State of New York
5 do hereby certify:
6
7 That Dr. Sheldon Park, the witness whose
8 deposition is hereinbefore set forth, was duly
9 sworn by me before the commencement of such
10 deposition and that such deposition was taken
11 before me and is a true record of the testimony
12 given by such witness.
13
14 I further certify that the adverse party,
15 Merck Sharp & Dohme, was represented by counsel at
16 the deposition.
17
18 I further certify that the deposition of
19 Dr. Sheldon Park, occurred at the offices of the
20 Hyatt Regency Buffalo on Thursday, the 7th day of
21 August, 2025, commencing at 8:45 a.m. to 5:09 p.m.
22

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 11th day of August, 2025.
10
11 My commission expires:
12 December 18, 2026
13
14
15 _____
16 NOTARY PUBLIC IN AND FOR THE
17 STATE OF NEW YORK
18
19
20
21
22

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