Transcript of Dr. Sheldon Park, Volume 2

Date: August 21, 2025
Case: Merck Sharp & Dohme LLC -v- Halozyme Inc. (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

Halozyme EX2078
Merck v. Halozyme
PGR2025-00024

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2 _____

3 BEFORE THE PATENT TRIAL AND APPEAL BOARD

4 _____

5 MERCK SHARP & DOHME LLC,

6 Petitioner,

7 v.

8 HALOZYME INC.,

9 Patent Owner.

10 _____

11 Case Nos. PGR2025-00003;
PGR2025-00004; PGR2025-00006;
12 PGR2025-00009
U.S. Patent No. 12,123,035

13 _____

14 Videotaped Deposition of

15 DR. SHELDON PARK

16 Volume 2

17 Buffalo, New York

18 Thursday, August 21, 2025
10:38 a.m. EST

19

20 Job No.: 597231

21 Pages: 235 - 362

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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17 Crystal Alexander, Technician
18 Mark Stewart, Merck
19 Eric Majcherzak, Merck
20 Aubrey Hoddach, Halozyme
21 Joshua Mack, Halozyme
22

C O N T E N T S

EXAMINATION OF DR. SHELDON PARK PAGE
By Attorney Martin 242

E X H I B I T S

(Attached to the Transcript.)

PARK DEPOSITION EXHIBIT PAGE
Exhibit 2069 Mutational Analysis Table, 2024-11-7, Native Excel File 244
Exhibit 2070 Mutational Analysis Table, 2024-11-7, PDF File 360

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

2 THE VIDEOGRAPHER: Here begins this Media 10:38:04

3 Number 1 in the videotaped deposition of 10:38:08

4 Dr. Sheldon Park, in the matter of Merck Sharp & 10:38:11

5 Dohme LLC versus Halozyme Inc., in the court -- 10:38:13

6 I'm sorry -- in the United States Patent and 10:38:16

7 Trademark Office; Case Number PGR2025-0003, 0004, 10:38:19

8 0006 and 0009. 10:38:27

9 Today is August 21st, 2025, and the time 10:38:30

10 on the monitor is 10:38 a.m. My name is David 10:38:36

11 Hernandez. I am the videographer, and I am 10:38:41

12 representing Planet Depos. This video deposition 10:38:43

13 is taking place at Hyatt Regency, Buffalo, New 10:38:46

14 York, Zip Code 14202. 10:38:52

15 Would Counsel please voice-identify 10:38:53

16 themselves and state whom they represent? 10:38:57

17 ATTORNEY MARTIN: Lauren Martin from Quinn 10:38:59

18 Emanuel on behalf of Halozyme, and with me I have 10:39:03

19 Trey Powers from Sterne Kessler, also on behalf of 10:39:04

20 Halozyme. 10:39:10

21 ATTORNEY KUSHAN: Jeff Kushan for Merck, 10:39:11

22 and with me in the room is Christine Engen. 10:39:16

1 And then they're -- we're going to have an 10:39:18
2 announcement of the people that are participating 10:39:21
3 remotely by the remote technician. 10:39:25
4 THE AV TECHNICIAN: Yes. 10:39:25
5 Remotely, on behalf of Merck, we have 10:39:25
6 Chelsea Himes, Eric Majcherzak, Kalen Sullivan, 10:39:29
7 Mark Stewart and Rachel B. Zinng. 10:39:32
8 And on behalf Halozyme, we have Audrey 10:39:36
9 Haddach, Eldora Ellison, Joshua Mack and Zach 10:39:40
10 Summers. 10:39:45
11 THE VIDEOGRAPHER: The Court Reporter 10:39:47
12 today is Kadi Harmon representing Planet Depos. 10:39:48
13 The witness will be sworn. 10:39:51
14 THE COURT REPORTER: Okay. Would you
15 raise your right hand, please?
16 Do you swear or affirm that the testimony
17 you provide today will be the truth, the whole
18 truth and nothing but the truth? 10:40:04
19 THE WITNESS: Yes I do. 10:40:04
20 THE COURT REPORTER: Thank you. 10:40:06
21 ATTORNEY MARTIN: Good morning, Dr. Park. 10:40:09
22 THE WITNESS: Good morning. 10:40:11

1 ATTORNEY KUSHAN: Good morning. 10:40:11
2 Before we begin, I just want to confirm on 10:40:13
3 the record that we've -- the parties have agreed 10:40:15
4 that the scope of this second deposition is going 10:40:16
5 to be limited to -- if I can read this 10:40:19
6 correctly -- the subject matter of the deposition 10:40:21
7 will be limited to topics reasonably related to 10:40:23
8 the newly-produced spreadsheet, which is the one 10:40:27
9 which we produced at the deposition of Dr. Park 10:40:29
10 that took place two weeks ago. 10:40:32
11 ATTORNEY MARTIN: So to be clear, the 10:40:34
12 newly produced spreadsheet, as we understand it, 10:40:36
13 is the one that we have on the screen, the 10:40:38
14 2024-11-7? 10:40:44
15 ATTORNEY KUSHAN: Correct. 10:40:45
16 ATTORNEY MARTIN: Okay. Just making sure 10:40:46
17 we're all on the same page about what the
18 spreadsheet is. 10:40:48
19 ATTORNEY KUSHAN: All right. Thank you. 10:40:48
20 ATTORNEY MARTIN: Yup. 10:40:50
21 E X A M I N A T I O N 10:40:52
22 BY ATTORNEY MARTIN:

1 Q Good morning, Dr. Park. 10:40:53
2 A Good morning. 10:40:54
3 Q So at the -- oh actually, so just to, 10:40:55
4 again, go over the -- the ground rules here, if 10:41:04
5 you require a clarification on any issue, please 10:41:09
6 ask me as opposed to your Counsel. Is that okay? 10:41:14
7 A Yes. 10:41:16
8 Q What did you do to prepare for this 10:41:17
9 deposition? 10:41:20
10 A I studied the spreadsheet in question, and 10:41:22
11 read the declarations again. 10:41:26
12 Q About how much time do you think you spent 10:41:28
13 preparing for this deposition? 10:41:31
14 A For this particular deposition, four or 10:41:33
15 five hours. 10:41:37
16 Q All right. Did you meet with anyone to 10:41:38
17 prepare for this deposition? 10:41:42
18 A I met with counsel. 10:41:46
19 Q Did you meet with anyone else? 10:41:49
20 A No. 10:41:51
21 Q About how long would you say you met with 10:41:52
22 counsel? 10:41:55

1 A About three hours I think. 10:41:59
2 Q And when did you meet with counsel? 10:42:01
3 A Yesterday. 10:42:04
4 Q Have you spoken with Dr. Hecht since 10:42:07
5 the -- your last deposition? 10:42:11
6 A No. 10:42:13
7 Q Have you emailed with Dr. Hecht since your 10:42:14
8 last deposition? 10:42:20
9 A No. 10:42:21
10 ATTORNEY MARTIN: So I would like to mark 10:42:24
11 as Exhibit 2069 the spreadsheet entitled: 10:42:26
12 Mutational Analysis Table, 2024-11-7. 10:42:34
13 (Park Deposition Exhibit 2069 marked for
14 identification and attached to the transcript.) 10:42:46
15 Q And it should be on your screen, Dr. Park. 10:42:46
16 A Yes. 10:42:50
17 Q Dr. Park, did you -- 10:42:52
18 ATTORNEY KUSHAN: Sorry. Sorry. 10:42:53
19 ATTORNEY MARTIN: Huh?
20 ATTORNEY KUSHAN: Are you introducing a 10:42:54
21 paper copy for the deposition today? 10:42:56
22 ATTORNEY MARTIN: I have a paper copy 10:43:03

1 printed, but I'm really hoping to just use the 10:43:06
2 electronic copy. 10:43:09
3 ATTORNEY KUSHAN: Okay. Do you -- I'm 10:43:10
4 just wondering about the record, because obviously 10:43:15
5 when we go in, you'll have a -- are you going to 10:43:18
6 make a PDF of -- I'm just trying to make sure the 10:43:21
7 logistics of this exhibit are clear, because 10:43:23
8 you're working off the native file, correct? 10:43:25
9 ATTORNEY MARTIN: Yeah. Why don't we -- 10:43:27
10 ATTORNEY KUSHAN: Do you want to take a 10:43:29
11 break and sort this out very quickly, or do you 10:43:30
12 want to just sort this out at the next break? 10:43:33
13 ATTORNEY MARTIN: Let's just go, and then 10:43:33
14 we can sort it out at the next break. 10:43:35
15 ATTORNEY KUSHAN: All right. 10:43:35
16 BY ATTORNEY MARTIN: 10:43:38
17 Q Okay. So Dr. Park, do you recognize the 10:43:39
18 spreadsheet, the mutational analysis spreadsheet, 10:43:45
19 that is Exhibit 2069? 10:43:51
20 A Yes. I do. 10:44:22
21 Q And what is this spreadsheet? 10:44:22
22 A This spreadsheet is a compilation of the 10:44:31

1 amino acid substitutions that I see among multiple 10:44:42
2 sequence alined homologs of PH20, along with 10:44:49
3 the -- my evaluation of various substitutions. 10:44:59
4 Q Did you prepare this spreadsheet? 10:45:02
5 A I did. 10:45:05
6 Q Did anyone assist you in preparing the 10:45:12
7 spreadsheet that is Exhibit 2069? 10:45:16
8 A Counsel helped with the formatting of the 10:45:28
9 spreadsheet, for instance adding the mature PH20 10:45:31
10 sequence numbers, as opposed to the full-length 10:45:40
11 number, for instance. But all substantive inputs 10:45:44
12 were made by me. 10:45:51
13 Q So you physically typed everything into 10:45:52
14 the spreadsheet? 10:45:55
15 A I did. Not by hand. I wrote a script 10:45:58
16 that generated the data, which I was able to copy 10:46:06
17 and paste into the spreadsheet. Yes. 10:46:10
18 Q And is this the spreadsheet that you 10:46:17
19 described at your prior deposition that you 10:46:23
20 prepared and performed in your analysis in this 10:46:25
21 case? 10:46:31
22 A Yes. This is the spreadsheet I was 10:46:31

1 referring to. 10:46:33
2 Q And you provided the spreadsheet to 10:46:34
3 counsel? 10:46:39
4 A Yes. I provided it to counsel and updated 10:46:41
5 them with changes over time. 10:46:46
6 Q When you say you updated them with changes 10:46:52
7 over time, can you explain what you mean by that? 10:46:56
8 A Sure. 10:46:58
9 Initially the spreadsheet was created, or 10:47:00
10 it was unpopulated. None of the scores were in, 10:47:08
11 or very few of them might have been in. 10:47:12
12 It took time to perform the analysis -- 10:47:16
13 many hours, many days -- and we met periodically 10:47:20
14 during which meetings I gave them the updated 10:47:26
15 sheet and told them this is what I've done so far, 10:47:30
16 and this is what my plan is going forward. 10:47:35
17 Q So is Exhibit 2069 the final spreadsheet 10:47:41
18 that includes your entire analysis? 10:47:47
19 A This is the final sheet. 10:47:49
20 Q And so this final sheet includes five 10:47:54
21 worksheets, correct? 10:48:01
22 A There are five worksheets in there. Yes. 10:48:04

1 Q Do you recall when you sent this final 10:48:17
2 spreadsheet to counsel? 10:48:20
3 A I think it was November 7th, 2024, because 10:48:27
4 the file was labeled as 11-7-24, and I think we 10:48:32
5 must have met at that time. But I don't recall 10:48:39
6 for sure. I would have to look through my emails 10:48:43
7 to confirm. But around that time. 10:48:48
8 Q And when you sent -- strike that. 10:48:53
9 So can you confirm that this document that 10:48:56
10 we've marked as Exhibit 2069 is, in fact, the 10:49:00
11 final spreadsheet that you sent to counsel? 10:49:05
12 A Yes. I am sure this is the final sheet. 10:49:11
13 Q Okay. When you were performing your 10:49:14
14 analysis, at any point did you include additional 10:49:21
15 worksheets that are not shown here? 10:49:24
16 ATTORNEY KUSHAN: Objection. Foundation. 10:49:27
17 A Did I include additional worksheets 10:49:33
18 besides those five sheets that we see here? 10:49:36
19 Q Correct. 10:49:40
20 A No. This was the only working copy that I 10:49:42
21 prepared at the beginning, and it was updated over 10:49:46
22 time, but I did not create other sheets besides 10:49:50

1 these. 10:49:54
2 Q Did you delete anything from this 10:49:54
3 spreadsheet as you updated it over time? 10:49:57
4 A No. I don't think so. 10:50:03
5 Q Are there any other documents that you 10:50:07
6 generated as part of your analysis that you 10:50:10
7 provided to counsel besides this spreadsheet? 10:50:13
8 ATTORNEY KUSHAN: I'm going to -- the 10:50:16
9 scope of that question may implicate work product, 10:50:23
10 so I'm going to direct the witness to not answer 10:50:27
11 that question. If you want to rephrase it. 10:50:31
12 Q Are you going to follow Counsel's 10:50:34
13 instruction? 10:50:39
14 A I will. 10:50:37
15 Q Are there any other documents that you 10:50:39
16 generated that you relied on in providing your 10:50:41
17 opinions in this case that you provided to counsel 10:50:45
18 besides this spreadsheet? 10:50:48
19 A No. 10:50:58
20 Q You've mentioned earlier that you wrote a 10:51:04
21 script that generated the data that you then 10:51:07
22 copied and pasted into the spreadsheet, right? 10:51:14

1 A That is correct. 10:51:18
2 Q And was that script included in the 10:51:18
3 declaration that you provided in this case? 10:51:21
4 A No. I don't think so. It's a routine 10:51:27
5 script that took information from the -- the 10:51:32
6 content of Appendix D, if I'm not mistaken, which 10:51:38
7 lists all the -- the probabilities for all the 10:51:43
8 substitutions, and I put them in a format that was 10:51:47
9 suited for a spreadsheet. 10:51:51
10 Q Okay. 10:51:54
11 A That's all I did. 10:51:55
12 Q Okay. Did anyone else who is not -- 10:51:56
13 sorry. Strike that. 10:52:07
14 Did anyone else besides counsel, anyone 10:52:08
15 who's not a lawyer, assist you in creating this 10:52:11
16 spreadsheet? 10:52:14
17 A No. 10:52:16
18 Q Was it your idea to generate this 10:52:24
19 spreadsheet? 10:52:31
20 A Yes. It was. 10:52:36
21 Q And why did you decide to generate the 10:52:40
22 spreadsheet? 10:52:44

1 A I needed a systematic way of keeping track 10:52:46
2 of what substitutions were being evaluated, and a 10:52:50
3 spreadsheet seemed like a good idea. 10:52:55
4 Q And did you decide what information was 10:53:05
5 included in the spreadsheet? 10:53:07
6 A Yes. Initially that information was 10:53:10
7 decided by -- by myself, which comprised of 10:53:14
8 residue number, wild-type identity and 10:53:19
9 substitutions, a subset of what we see in this 10:53:23
10 spreadsheet. And later on, additional information 10:53:32
11 was added, for instance, the mature PH20 residue 10:53:36
12 number, as well as the HYAL1, corresponding HYAL1 10:53:43
13 residue identity, and residue number was added for 10:53:51
14 convenience for counsel.
15 (Reporter clarification.) 10:54:03
16 Q And why was the HYAL1 residue information 10:54:03
17 included? 10:54:07
18 A It facilitates comparison with the 10:54:12
19 literature. Studies were done on HYAL1, 10:54:16
20 mutational studies for instance, and those papers 10:54:21
21 referred to certain residues by their residue 10:54:24
22 number and identity. It's easier to look up that 10:54:28

1 information if they're on the same spreadsheet. 10:54:37
2 Q Did you consider adding in a column for 10:54:47
3 the bee venom residues? 10:54:50
4 A I did not consider that. I thought HYAL1 10:54:58
5 structure was sufficient, and since that was a 10:55:03
6 structure that was used to build the homology 10:55:09
7 model of PH20, I decided that HYAL1 was the more 10:55:16
8 relevant information than bee venom hyaluronidase. 10:55:23
9 Q Are there -- when you do an alignment for 10:55:31
10 HYAL1 and PH20, are there any gaps in the 10:55:35
11 sequence? 10:55:38
12 A Alignment between HYAL1 and PH20? 10:55:38
13 Q Yes. 10:55:45
14 A Or the entire multiple sequence alignment? 10:55:46
15 Q HYAL1 and PH20. Because that's what you 10:55:47
16 have in the spreadsheet. 10:55:51
17 ATTORNEY KUSHAN: Objection. Foundation. 10:55:52
18 A Yes. There are insertions and deletions: 10:55:53
19 Three insertions, each of which has an additional 10:55:58
20 residue; and three deletions, each of which, 10:56:03
21 again, deletes one residue between the two. 10:56:08
22 Q And did you account for the insertions and 10:56:12

1 deletions, and the locations of insertions and 10:56:17
2 deletions, on the variant tab in the spreadsheet? 10:56:18
3 ATTORNEY KUSHAN: Objection. Form. 10:56:21
4 A The mapping of the residue numbers is 10:56:25
5 based on structural alignment. I overlaid HYAL1 10:56:31
6 structure with PH20 model structure, and based on 10:56:36
7 what residues are near what residues, I created a 10:56:40
8 mapping between the two proteins, and that mapping 10:56:45
9 is what appears in the spreadsheet. 10:56:49
10 Q Okay. Do you know if Dr. Hecht received a 10:56:52
11 copy of the spreadsheet? 10:57:06
12 A I do not know. 10:57:10
13 Q Do you know if Dr. Hecht reviewed the 10:57:12
14 spreadsheet? 10:57:17
15 A I do not know that either. 10:57:18
16 Q Do you know whether Dr. Hecht -- 10:57:20
17 A I'll revise that. 10:57:27
18 Q Uh-huh. 10:57:29
19 A During the meetings with Dr. Hecht, Zoom 10:57:29
20 meetings, I think he referred to certain 10:57:34
21 substitutions in positions, at various positions. 10:57:36
22 That makes me think that he must have that 10:57:42

1 information. Whether that is the entire 10:57:45
2 spreadsheet or not, that I'm not sure. 10:57:49
3 Q Can you explain what you mean by that? 10:57:54
4 A Yes. He was able to follow my narration 10:57:58
5 when I say: I see these substitutions with this 10:58:03
6 percentage. And his response, or lack of 10:58:08
7 response, made me think that he must be looking at 10:58:17
8 the same information on his end, versus he wasn't 10:58:24
9 puzzled by what I was saying, which makes me think 10:58:31
10 he must be looking at the same thing -- thing, at 10:58:36
11 his end. 10:58:39
12 Q Okay. 10:58:40
13 A Whether that is the entire spreadsheet, or 10:58:41
14 just that portion of the spreadsheet, that I don't 10:58:44
15 know. 10:58:51
16 Q So in your analysis in the spreadsheet, 10:58:51
17 you consider more residues on PH20 than you 10:58:54
18 expressly address in the declarations you've 10:58:59
19 submitted; is that right? 10:59:02
20 A That is -- that is correct. I analyze 10:59:07
21 many more positions and substitutions than 10:59:11
22 included in the final declarations. 10:59:15

1 Q Do you know whether Dr. Hecht is aware of 10:59:16
2 the fact that you analyzed more positions and 10:59:19
3 substitutions than those that were included in the 10:59:24
4 final declarations? 10:59:27
5 A I believe so. I think I said it during 10:59:31
6 the meeting. I think I described to him exactly 10:59:36
7 what I was doing, which starts with sequence 10:59:39
8 alignment, finding substitutions above a certain 10:59:45
9 threshold -- 10 percent, 5 percent -- and that was 10:59:53
10 followed by a systematic analysis of each 10:59:58
11 substitution based on some certain criteria. This 11:00:03
12 was all described to him, so he must understand 11:00:06
13 that I was analyzing other positions as well. 11:00:10
14 Q Okay. And in your conversations with 11:00:17
15 Dr. Hecht, did you discuss other -- your analysis 11:00:20
16 of other positions and substitutions that were not 11:00:26
17 included in your final declaration? 11:00:31
18 ATTORNEY KUSHAN: Objection. Foundation. 11:00:32
19 A Our discussions were limited to the 11:00:33
20 positions that were in the declarations. 11:00:37
21 Q So you didn't discuss any positions that 11:00:44
22 were not in the declarations? 11:00:48

1 A No. I don't think so. 11:00:49
2 Q So in the spreadsheet, let's start with 11:01:12
3 the -- the tab that's labeled: Conserved. 11:01:19
4 And Dr. Park, can you just explain what is 11:01:34
5 in each column as you go across from A through 11:01:38
6 Column I? 11:01:43
7 A Uh-huh. Starting with the Column A, 11:01:44
8 hyaluronidase 1 residue number, this is the 11:02:03
9 number -- the residue number or the number of the 11:02:06
10 residue corresponding to the PH20 residue listed 11:02:10
11 in C and D, the full-length residue number and 11:02:21
12 mature residue number, and PH20 residue identity 11:02:26
13 in Column E. 11:02:30
14 So the first five columns are just the 11:02:33
15 mapping that I described earlier. So that's 11:02:40
16 pretty straightforward. And then based on 11:02:42
17 structural overlay, to make sure that I'm looking 11:02:45
18 at the corresponding residues. That's followed by 11:02:48
19 residue percentage, which is the percentage of 11:02:52
20 that residue, wild-type PH20 residue, that appears 11:02:56
21 in the multiple sequence alignment. 11:03:07
22 That's followed by the number of -- the 11:03:09

1 neighbor, neighbors, which is a metric that I 11:03:12
2 computed using PyMol by selecting each residue and 11:03:16
3 identifying the residues that are within certain 11:03:24
4 distance cut-off, in this case, 5 angstrom, and 11:03:28
5 counting how many residues there are in that 11:03:31
6 sphere. That's a useful metric to see whether an 11:03:37
7 amino acid is buried or solvent exposed. It's a 11:03:41
8 commonly used metric in the literature. 11:03:47
9 And the Column H is another metric that's 11:03:48
10 often used as well, which is fractional solvent 11:03:50
11 accessible surface area, fractional surface area, 11:03:56
12 or FSASA, which is the area of surface solvent 11:03:58
13 exposed area of that residue in this structure, 11:04:05
14 divided by the maximum surface area available to 11:04:09
15 that residue, if that residue were in an isolated 11:04:14
16 environment, usually in the context of a 11:04:20
17 tripeptide. Glycine, followed by that particular 11:04:23
18 residue, followed by another glycine. This is 11:04:32
19 what's commonly used.
20 That gives it the maximum surface area 11:04:35
21 available. By dividing those two numbers, you get 11:04:38
22 a fractional surface area, which is a useful way 11:04:43

1 to think about how buried a given residue is. So 11:04:48
2 that's Column H. 11:04:49
3 And Column I, which is comments, something 11:04:50
4 that I wrote down to keep track of my thinking in 11:04:54
5 a way. It's not comprehensive in any regard, but 11:05:02
6 as I was looking at the residues in the structure, 11:05:07
7 if anything jumped out, I would write it down in 11:05:11
8 that column. Or, if I remember the literature 11:05:16
9 example where that residue was examined, I might 11:05:20
10 say something to that effect. So that's Column I: 11:05:25
11 Comments. 11:05:30
12 Q Okay.
13 A So that is the entire scope. 11:05:31
14 Q And just, to make sure that I understand 11:05:33
15 in terms of the -- how you're mapping the HYAL1 11:05:37
16 residues with the PH20 residues, so am I 11:05:43
17 understanding correctly that, for example, in the 11:05:46
18 PH20 model, at PH20 residue number 49, right, you 11:05:48
19 have the PH20 residue you list as F. 11:05:55
20 So you've aligned the PH20 model with the 11:06:00
21 HYAL1 model, and you would see that in that same 11:06:04
22 position, there is also an F for HYAL1, and then 11:06:08

1 you would look at the number, or the position of 11:06:10
2 HYAL1 for that F, and you would find that it's 11:06:13
3 number 32? 11:06:15
4 A That is correct. Yes. 11:06:15
5 Q Okay. And then you also mentioned for the 11:06:17
6 neighbors column that the number of neighbors at a 11:06:23
7 particular position can give you a sense of 11:06:28
8 whether that residue is buried versus solvent 11:06:31
9 exposed; is that right? 11:06:38
10 A Yes. 11:06:38
11 Q Is there a cutoff that's known in the art 11:06:39
12 in the terms of what -- how many neighbors would 11:06:40
13 constitute buried versus solvent exposed? 11:06:45
14 ATTORNEY KUSHAN: Objection. Form. 11:06:51
15 A No. There is no hard cutoff. And in 11:06:52
16 other words, there's no hard cutoff in terms of 11:06:58
17 the number of neighbors; and furthermore, the 11:07:01
18 cutoff distance, to define the neighbor also 11:07:05
19 varies greatly. So this methodology of looking at 11:07:09
20 how many residues are nearby is a common practice. 11:07:16
21 How it's practiced really varies. 11:07:24
22 Q And how many residues, or how many 11:07:28

1 neighbors, would you consider to indicate that a 11:07:32
2 residue is buried? 11:07:36
3 ATTORNEY KUSHAN: Objection. Foundation. 11:07:38
4 Also objection to form. 11:07:41
5 A It is really a spectrum. 11:07:43
6 (Reporter clarification.)
7 A I would say at the upper end of 10 or more 11:07:52
8 would seem like a buried residue. A number that's 11:07:58
9 in the lower end of the spectrum, say 5 or fewer, 11:08:02
10 would seem like a solvent exposed residue. In 11:08:15
11 between, it could really be one or the other 11:08:21
12 depending on the circumstance. 11:08:22
13 Q So can we look at HYAL1 position 75, which 11:08:34
14 is the tyrosine? 11:08:43
15 A Uh-huh. 11:08:45
16 Q And your comments for that tyrosine are 11:08:45
17 the bottom of the substrate binding pocket; is 11:08:55
18 that right? 11:09:00
19 A Yes. That's my comment. 11:09:00
20 Q Can you explain what that comment means? 11:09:02
21 A This is an example of the thoughts that 11:09:05
22 kind of came to my head as I was looking at the 11:09:11

1 structure, and here I took the trouble of writing 11:09:14
2 down that this particular residue is located at 11:09:21
3 the bottom of the binding pocket of the enzyme 11:09:26
4 where it may be important for catalysis. 11:09:30
5 Q When you say the bottom of the substrate 11:09:34
6 binding pocket, what do you mean by bottom? 11:09:37
7 A Right. This enzyme has a very deep 11:09:39
8 groove, so at the bottom of the binding pocket 11:09:45
9 would be the bottom of that groove. 11:09:49
10 Q And then -- 11:09:55
11 A But I have to say -- excuse me. 11:09:56
12 Q Yeah. 11:09:58
13 A That my comments are not very systematic 11:09:59
14 or thorough. A lot of the times I don't feel the 11:10:03
15 urge to write down anything, so then I would just 11:10:08
16 skip to the next residue. 11:10:12
17 Q And what was the purpose of noting that -- 11:10:22
18 that tyrosine position 75 is at the bottom of the 11:10:26
19 substrate binding pocket? 11:10:31
20 A Right. It doesn't serve a lot of purpose. 11:10:39
21 Just because I wasn't going about it very 11:10:43
22 systematically. I think I started writing it down 11:10:46

1 at the beginning, and quickly got bored with that 11:10:51
2 practice and then stopped writing anything. So 11:10:55
3 there wasn't a whole lot of point there. 11:11:00
4 Q Okay. And in 2011, it was known that the 11:11:03
5 active site for HYAL1 and PH20 is a -- is a 11:11:12
6 groove; is that right? 11:11:17
7 ATTORNEY KUSHAN: Objection. Foundation. 11:11:18
8 A Yes. The structure of HYAL1 and the 11:11:21
9 structure of bee venom hyaluronidase had already 11:11:48
10 been solved. People knew what the enzyme looked 11:11:32
11 like and where the substrate would bind, and the 11:11:38
12 binding pocket was well understood. 11:11:41
13 Q So your comment -- and this comment 11:11:53
14 appears repeatedly in the conserved tab -- for 11:11:56
15 glycine at position 94 is left-handed alpha helix. 11:12:03
16 Can you explain what that means? 11:12:11
17 A Yes. Glycine, being the only amino acid 11:12:14
18 that is asymmetric, because it has two hydrogens 11:12:24
19 attached to C-alpha, as opposed to all other 19 11:12:34
20 amino acids where it has 1 hydrogen and heavy 11:12:39
21 atoms. It behaves differently, and one of the 11:12:41
22 things that a glycine can do that no other amino 11:12:45

1 acid can do easily is that it can adopt a main 11:12:51
2 chain conformation that corresponds to left-handed 11:12:56
3 alpha helical conformation. 11:13:04
4 (Reporter clarification.) 11:13:10
5 A And therefore, if a position requires such 11:13:10
6 a conformation, the options available at that 11:13:15
7 position are very limited, namely to glycine, and 11:13:19
8 that could explain why this glycine is conserved 11:13:26
9 at this position. So I was noting the fact that 11:13:32
10 it was interesting that glycine is conserved at 11:13:34
11 this position, and why that may be. 11:13:38
12 And I would look at the conformation, the 11:13:40
13 main chain conformation of that residue, and it 11:13:48
14 turns out those residues marked as left-handed 11:13:50
15 alpha helix are indeed appeared in the left-handed 11:13:56
16 alpha helical portion of the Ramachandran plot. 11:14:01
17 (Reporter clarification.) 11:14:16
18 A That was that. 11:14:16
19 Q Okay.
20 A Yes. 11:14:17
21 Q But those glycines are not necessarily 11:14:17
22 actually part of a left-handed alpha helix in the 11:14:22

1 structure, correct? 11:14:25
2 ATTORNEY KUSHAN: Objection. Foundation. 11:14:26
3 A That would be the case. I don't remember 11:14:29
4 seeing any left-handed alpha helix in the 11:14:33
5 structure, so a left-handed alpha helix does not 11:14:40
6 exist in the protein. However, a particular 11:14:45
7 residue can adopt that particular conformation, as 11:14:49
8 these glycines seem to be doing. 11:14:51
9 Q So am I understanding correctly that for 11:15:03
10 those glycines for which you identified 11:15:07
11 left-handed alpha helix, the phy psi angles for 11:15:11
12 the background of those glycines are in the
13 left-handed alpha helix portion the Ramachandran 11:15:13
14 plot? 11:15:19
15 A That's what I observed. 11:15:20
16 Q And I think you said that glycine is an 11:15:29
17 asymmetric amino acid, in that... 11:15:34
18 A Oh. I meant to say symmetric. 11:15:59
19 Q Okay.
20 A I apologize. 11:16:02
21 Q Okay.
22 A Yes. Because everything else is 11:16:04

1 asymmetric, and this one is symmetric. 11:16:07
2 Q Okay. Okay. That would -- that clarifies 11:16:09
3 it. 11:16:11
4 A Yes. 11:16:11
5 Q So glycine is symmetric; whereas the other 11:16:12
6 ones are asymmetric? 11:16:13
7 A That is correct. 11:16:13
8 Q And glycine is symmetric because it has 11:16:14
9 two hydrogens attached to the C-alpha, as opposed 11:16:15
10 to one hydrogen and an R group? 11:16:18
11 A That's correct. 11:16:22
12 Q Okay. All right.
13 A That's precisely what I meant to say. 11:16:23
14 Q Okay. Okay. And then, so for example, 11:16:26
15 for position 129, aspartate 129 in the HYAL1 11:16:42
16 structure, you have catalytic as your comment. 11:16:52
17 What does that mean?
18 (Reporter clarification.) 11:17:03
19 A These residues, D129 of HYAL1 and E131 of 11:17:03
20 HYAL1, they are known to be involved in a 11:17:12
21 catalysis and that's been shown by others through 11:17:18
22 mutagenesis mutational studies. And I confirmed 11:17:23

1 the location of those residues with respect to the 11:17:30
2 bound substrate and noted that, yeah indeed, yes 11:17:33
3 indeed, those residues seem to be important for 11:17:40
4 catalysis. In other words -- in other words, I 11:17:44
5 was confirming, based on my own observation, what 11:17:48
6 others have reported. 11:17:53
7 Q And how could you confirm -- how did you 11:17:54
8 confirm based on your own observation that those 11:17:59
9 residues were involved in the catalysis? 11:18:02
10 A Visualizing -- by visualizing what was 11:18:06
11 reported in the paper, and how those side chains 11:18:11
12 are positioned with respect to the substrate, I 11:18:15
13 could convince myself that these residues must be 11:18:18
14 formed from catalysis. 11:18:23
15 Q Did you evaluate whether there were 11:18:28
16 non-covalent interactions between the D129 and 11:18:30
17 E131 in the substrate? 11:18:36
18 A They seem to be in a position where they 11:18:47
19 would be involved in catalysis, because their 11:18:51
20 carboxyl ends are exactly where they should be in 11:18:57
21 order to perform acid-based catalysis. So based 11:19:04
22 on the positioning of those carboxyl groups, I was 11:19:09

1 able to convince myself that, indeed, those 11:19:13
2 residues must be important for catalysis. 11:19:16
3 Q Okay. And is that -- did you perform a 11:19:19
4 similar analysis for tyrosine 202 in the HYAL1 11:19:28
5 structure? 11:19:44
6 (Reporter clarification.) 11:19:46
7 A Similar analysis, yes, in that I viewed 11:19:46
8 the structure and confirmed that this tyrosine 11:19:51
9 with its hydroxyl group was in a position where it 11:19:58
10 was involved in the potential chemical reaction 11:20:06
11 that was described in the paper. 11:20:10
12 (Reporter clarification.) 11:20:31
13 Q And so on the conserved tab in the 11:20:31
14 spreadsheet, there are 68 -- 68 positions, right? 11:20:35
15 A That is correct. 11:20:41
16 Q And those 68 positions are the 68 amino 11:20:42
17 acids that you categorized as, or classified as 11:20:45
18 essential in your declaration; is that right? 11:20:50
19 A Yes. These are the 68 essential residues 11:20:55
20 I reported in one -- in there somewhere. 11:20:59
21 Q Yes. 11:21:05
22 And you identified these residues through 11:21:05

1 your multiple sequence alignment, right? 11:21:08
2 A That is correct. 11:21:13
3 Q Okay. So now let's go to the variant tab. 11:21:24
4 So Dr. Park, the variant tab includes the 11:21:52
5 positions on -- I guess, strike that. 11:22:00
6 Let me start again. 11:22:08
7 So just starting with the HYAL1, right, 11:22:08
8 the variant tab includes residues for HYAL1 11:22:11
9 starting at position 22, and then if you scroll 11:22:17
10 all the way down, it ends at position 421? 11:22:20
11 A That's correct. 11:22:24
12 Q And for the mature PH20 residue, it starts 11:22:25
13 at position 4 and ends at position 403? 11:22:32
14 A That is right. 11:22:38
15 Q And you did not include the conserved 11:22:40
16 residues or the essential residues in the variant 11:22:45
17 tab, right? 11:22:51
18 A That's right. Those essential residues 11:22:52
19 were taken out of the list and put into a 11:22:54
20 different tab that we just went over. 11:22:57
21 Q Okay. So is it fair to say that the 11:23:00
22 variant tab includes the positions that you 11:23:03

1 determined were non-essential in the structure? 11:23:06
2 A That is correct. These are the 11:23:14
3 non-essential residues that I referred to in the 11:23:16
4 declaration. 11:23:20
5 Q And the alternate residue column, my 11:23:30
6 understanding -- do I understand correctly that 11:23:39
7 the alternate residue column provides those 11:23:42
8 residues that appear at that position in the 11:23:46
9 multiple sequence alignment? 11:23:50
10 A That's correct. Minus the wild-type, yes. 11:23:54
11 Q Yes. Okay. So for example, the first 11:23:58
12 entry on here, which is position 22 in HYAL1, so 11:24:02
13 F22 in HYAL1 and R4 in mature PH20, right, and the 11:24:11
14 alternative residues are T, A, Q, S, K, G, 11:24:18
15 correct? 11:24:26
16 A Those are listed. Yes. 11:24:26
17 Q So in the sequence alignment, the residue 11:24:29
18 at that position is R for PH20, and F for HYAL1, 11:24:34
19 and then the other letters that are listed in the 11:24:38
20 alternative residue column are the other 11:24:43
21 alternatives at that position? 11:24:47
22 A In this example, at this position, those 11:24:55

1 alternate residues are some of the residues that 11:25:02
2 appear in that position as part of the multiple 11:25:06
3 sequence alignment. Later on I realized that some 11:25:12
4 of the residues -- some residues were left out. 11:25:16
5 Exactly how that happened, I'm not sure. 11:25:21
6 But here we see T, A, Q, S, K, G. There 11:25:24
7 were additional residues of low percentages that 11:25:31
8 were somehow not included. But these residues do 11:25:39
9 represent part of the residues or substitutions 11:25:46
10 that we see at this position in the multiple 11:25:53
11 sequence alignment. 11:25:56
12 Q Okay. So the alternative residues include 11:25:57
13 some, but not all, of the residues that appear in 11:26:01
14 that position in the multiple sequence alignment? 11:26:04
15 ATTORNEY KUSHAN: Objection. Foundation. 11:26:07
16 A For this position, that is the case. Not 11:26:09
17 all positions have missing substitutions, but at 11:26:14
18 this position, I notice that there were some 11:26:18
19 missing residues. The missing residues can be 11:26:59
20 seen in Appendix D, which lists the raw data, and 11:26:26
21 they were, as I mentioned earlier, reformatted by 11:26:33
22 a script to a form that was more suited for a 11:26:40

1 spreadsheet, and you can get the full list from 11:26:51
2 that Appendix D. 11:26:54
3 Q Okay. Oh. So actually, just to 11:26:56
4 clarify -- and this is going to apply to both the 11:27:22
5 conserved and the variant tabs -- when you say 11:27:25
6 number of neighbors, is that in the PH20? 11:27:32
7 Is that for the PH20 model or in the HYAL1 11:27:35
8 structure? 11:27:38
9 A In the PH20 model. 11:27:38
10 Q Okay. And the FSASA, that's also 11:27:39
11 calculated for the PH20 model? 11:27:44
12 A That's correct. 11:27:46
13 Q Okay. And in the conserved tab, when you 11:27:47
14 talked about the -- the phy psi angles and the 11:27:58
15 left-handed alpha helix for those glycines, was 11:28:08
16 that with respect to the PH20 model? 11:28:10
17 A I wrote the comments based on PH20. I 11:28:22
18 suspect that it also applies to HYAL1. 11:28:29
19 Q Okay. 11:28:34
20 A I don't know that for sure, but given that 11:28:35
21 these glycines are conserved at these positions, I 11:28:38
22 would expect the reason for that is the 11:28:40

1 left-handed helical conformation in both cases. 11:28:41
2 Q Okay. So going back to the variant tab, 11:28:47
3 can you explain how you selected the residues that 11:29:05
4 you analyzed to determine whether you would, you 11:29:10
5 know, give it a rating 1, 2, or 3? 11:29:14
6 A How did I select the positions to 11:29:24
7 evaluate? 11:29:26
8 Q Yes. 11:29:26
9 A Having obtained the list of substitutions 11:29:34
10 available at each position and rank order them 11:29:40
11 based on percentage, I started looking at all the 11:29:45
12 substitutions that were above a certain threshold, 11:29:49
13 and that threshold was 10 percent initially, and I 11:29:54
14 started evaluating each substitution, thinking 11:30:00
15 that 10 percent and up represents a reasonable 11:30:05
16 frequency. And if a given residue appears with 11:30:13
17 such a high frequency, it may be worth examining. 11:30:19
18 And I looked at each substitution in the 11:30:24
19 context of PH20, and scored the mutation, and 11:30:29
20 proceeded on to the next one. I did that for the 11:30:35
21 entire set that's listed in variant, in the 11:30:41
22 variant tab, after which I thought I could expand 11:30:46

1 the search a bit more, and decided to include 11:30:53
2 additional substitutions that had frequencies down 11:30:58
3 to 5 percent. 11:31:02
4 Anything above 5 percent would ensure that 11:31:04
5 I'm not looking at conserved positions, because 11:31:08
6 conserved positions were defined or marked as 11:31:12
7 such, as having 95 percent frequency or higher. 11:31:18
8 Therefore, by looking at 6 percent and 5 percent, 11:31:24
9 and higher percentage, for substitution, I make 11:31:28
10 sure that I'm only looking at non-essential 11:31:36
11 positions. So I searched down to 5 percent,
12 expanded the search and evaluation down to 5 11:31:39
13 percent, which gave me more substitutions to 11:31:40
14 examine, and that's how I ended up with the list 11:31:47
15 that I have here. 11:31:51
16 Q So are you saying that when you were 11:31:54
17 trying to identify whether a residue was essential 11:32:00
18 or not, you started with a 90 percent cutoff, and 11:32:03
19 then you increased that cutoff to 95 percent 11:32:06
20 cutoff? 11:32:10
21 ATTORNEY KUSHAN: Objection. Foundation. 11:32:12
22 A No. That decision -- 11:32:14

1 Q Okay. 11:32:14
2 A -- to include or define conserved or 11:32:15
3 essential versus non-essential, that had already 11:32:19
4 been set at 95 percent. When I started looking at 11:32:23
5 the substitutions, I arbitrarily imposed a minimum 11:32:28
6 threshold at 10 percent, which it gave me a 11:32:36
7 certain number of substitutions to look at. At a 11:32:42
8 later time, I relaxed the condition somewhat so 11:32:47
9 that I could look at more substitutions, and that 11:32:52
10 went down to 5 percent. 11:32:57
11 Q Okay. But so for example, if you look in 11:32:59
12 the chart, the first entry, the F22 R4, for 11:33:02
13 example, you didn't assign any rating to the 11:33:09
14 substitutions in that position, but the residue 11:33:14
15 percent is above 10, right? 11:33:19
16 So like, T appears 15.9 percent of the 11:33:22
17 time. A appears 11.36 percent of the time. But 11:33:26
18 you didn't evaluate those. So I'm trying to 11:33:31
19 square that with what you just said in terms of 11:33:35
20 evaluating every substitution that appears, you 11:33:38
21 know, more than 5 percent of the time. 11:33:41
22 Can you explain that? 11:33:45

1 A The intention was to look at every 11:33:48
2 substitutions that appear at 5 percent or higher. 11:33:52
3 I didn't adhere to that religiously. 11:33:57
4 The first position at 4 arginine, that 11:34:02
5 is -- at a position where residue is exposed to 11:34:16
6 the solvent, ultimately I didn't think that it 11:34:25
7 added really much value, whether I evaluated that 11:34:31
8 residue or not. So I think that this position 11:34:37
9 was -- was not looked at -- right. Yeah. Okay. 11:34:42
10 The first few residues. So it's not just 11:34:55
11 the first position, but also the one after that -- 11:34:59
12 A, P -- both of which also have residues or 11:35:04
13 substitutions that are above 5 percent, I didn't 11:35:12
14 think that it was worth looking at them, given 11:35:16
15 that they are at the interminus, which is poorly 11:35:19
16 defined anyway. I think that that was perhaps the 11:35:25
17 reasoning behind that. 11:35:38
18 I may have also looked at the residue 11:35:42
19 specific quality factor to see whether these 11:35:46
20 positions are modeled with high accuracy or not, 11:35:51
21 which I can obtain from SWISS-MODEL. Given that 11:35:56
22 this position is not conserved at all, look 11:36:02

1 between HYAL1 and PH20, and perhaps a low quality 11:36:07
2 estimate, I may have decided that I can skip those 11:36:14
3 positions and -- and look at other residues only. 11:36:18
4 At this point I think that that's all I remember. 11:36:31
5 (Reporter clarification.) 11:37:01
6 A I became more consistent after that 11:37:01
7 though. 11:37:05
8 Q Okay. Okay. So did you perform any 11:37:06
9 analysis as to what potential substitutions would 11:37:24
10 be tolerated at positions 4 through 6 in the 11:37:28
11 mature PH20 sequence? 11:37:36
12 A I don't think so. No. 11:37:44
13 Q Okay. So then the first residue that you 11:37:48
14 analyze in the spreadsheet is V8 mature PH20 11:37:54
15 position 8; is that right? 11:38:03
16 A That is correct. Yes. 11:38:04
17 Q And for that position, you considered 2 11:38:05
18 substitutions, right, the first one is V to I, and 11:38:19
19 the second one is V to L; is that right? 11:38:25
20 A Yes. V to I, and V to L. Yes. 11:38:29
21 Q And you scored them both 2? 11:38:33
22 A I gave them a score of 2 each. 11:38:37

1 Q And for the V to I mutation, your note is 11:38:44
2 gain increased hydrophobic contacts; is that 11:38:49
3 right? 11:38:59
4 A That's what I wrote. Yes. 11:38:59
5 Q Can you explain what that means? 11:39:01
6 A Based on this very brief comment, which it 11:39:12
7 probably doesn't do justice to describe the 11:39:25
8 substitution fully, which would require looking at 11:39:28
9 the model and so on, which we're not doing here. 11:39:32
10 Based on the comment alone, it makes me 11:39:36
11 think that I was noting that as a result of 11:39:39
12 putting in a slightly larger residue, isoleucine, 11:39:42
13 I was able to see increased contact between the 11:39:50
14 terminal methyl group of isoleucine with its 11:39:54
15 neighbors, which might have contributed to 11:39:59
16 additional hydrophobic contacts, and therefore 11:40:04
17 perhaps an increase in stability. It was hard to 11:40:08
18 know for sure. Therefore, I wrote gain, but not 11:40:13
19 to the extent that it would deserve a score of 3. 11:40:19
20 Q Okay. And for the neighbors, you have -- 11:40:24
21 you identified neighbors for the -- the wild-type 11:40:29
22 as 6, and then for both substitutions as 6. 11:40:34

1 Did you go back through and redetermine 11:40:39
2 the number of neighbors for each substitution? 11:40:42
3 ATTORNEY KUSHAN: Objection. Foundation. 11:40:45
4 A If I'm not mistaken, and actually I -- 11:40:50
5 I'm 90 percent sure that I did not go back and 11:40:55
6 count the number of residues for each 11:41:00
7 substitution. So the number of neighbors that you 11:41:04
8 see for each substitution still corresponds to the 11:41:06
9 wild-type. 11:41:17
10 Q Okay. And do you know why for some of the 11:41:18
11 error cells in the neighbor column that are left 11:41:39
12 blank when you don't have any -- fill in the 11:41:43
13 number of neighbors, but in the FSASA column, you 11:41:46
14 have a dash to indicate that there's no FSASA. 11:41:54
15 So do you know why you left some cells 11:42:01
16 blank and put a dash in others? 11:42:04
17 ATTORNEY KUSHAN: Objection. Form. 11:42:07
18 A I don't know why that may be the case, but 11:42:25
19 I want to say that may happen because I might have 11:42:34
20 noticed some residues missing, for instance, as I 11:42:40
21 mentioned in the earlier case for arginine 4. I 11:42:44
22 might have noticed some substitutions were left 11:42:57

1 out unless I put them in at a later time, and that 11:42:59
2 particular column did not get updated. 11:43:03
3 Q Okay. 11:43:09
4 A It's a result of working off a -- an 11:43:09
5 existing sheet and trying to update it, rather 11:43:13
6 than creating a whole new sheet, which would be 11:43:17
7 more consistent. 11:43:22
8 Q Uh-huh. 11:43:23
9 A Might have been more consistent. 11:43:24
10 ATTORNEY MARTIN: Okay. So we might have 11:43:30
11 been going for over an hour. 11:43:32
12 Do you want to take a short break? 11:43:34
13 THE WITNESS: Okay. Great. 11:43:37
14 ATTORNEY KUSHAN: Very good. 11:43:38
15 THE VIDEOGRAPHER: We are going off the 11:43:38
16 record. The time is 11:43 a.m. 11:43:40
17 (Recess from 11:43 a.m. until 11:58 a.m.) 11:43:46
18 THE VIDEOGRAPHER: We are going back on 11:59:22
19 the record. The time is 11:59 a.m. 11:59:24
20 BY ATTORNEY MARTIN: 11:59:28
21 Q Welcome back, Dr. Park. 11:59:29
22 Did you discuss the substance of your 11:59:31

1 testimony during the break? 11:59:33
2 A No. I did not. 11:59:34
3 Q So before the break, we were discussing 11:59:35
4 the variant tab on Exhibit 2069? 11:59:39
5 A Uh-huh. 11:59:44
6 Q So this tab has 2,815 rows; is that right? 11:59:44
7 A There are 2,815 rows. Yes. 12:00:05
8 Q And is it fair to say that for every 12:00:15
9 single substitution that you analyzed, you gave it 12:00:26
10 a score of either 1, 2 or 3? 12:00:30
11 A Yes. My scores were limited to 1, 2, 12:00:33
12 or 3. 12:00:38
13 Q And so in order to determine the total 12:00:38
14 number of substitutions that you analyzed, that 12:00:41
15 can be determined by identifying all of the 12:00:49
16 residues for which you have assigned a score of 1, 12:00:51
17 2 or 3? 12:00:55
18 A That is correct. You can look at the 12:01:01
19 Column H, and wherever you see a score that 12:01:04
20 represents a substitution that I evaluated, you 12:01:12
21 can count those rows to know how many 12:01:15
22 substitutions I have evaluated. 12:01:20

1 Q And if you do that, you get 100 -- I'm 12:01:22
2 sorry. Strike that. 12:01:24
3 If you do that, you get 832 substitutions, 12:01:24
4 right? 12:01:29
5 A I believe it was 836, but it could be 832. 12:01:32
6 Q Okay. Could you use the Count A function 12:01:39
7 in Excel to determine the cells in Column H that 12:02:01
8 have values in them, and then tabulate the number 12:02:06
9 of substitutions that you considered that way? 12:02:13
10 A I suppose so. I'm not very familiar with 12:02:16
11 functions in Excel. Count would -- could be 12:02:21
12 one -- one way to do it. But there are different 12:02:26
13 ways of doing it, I suppose. 12:02:29
14 Q Okay. And for those substitutions that 12:02:31
15 you scored a 1, you determined that those 12:02:39
16 substitutions were likely to be not tolerated, 12:02:42
17 correct? 12:02:48
18 A Yeah. For the substitutions that I 12:02:50
19 scored 1, I saw perhaps more unfavorable 12:02:53
20 interactions resulting from the substitutions than 12:03:05
21 favorable interactions, which then led me to 12:03:09
22 conclude a score of 1. 12:03:13

1 Q And you -- out of the, we'll say, 830-some 12:03:14
2 substitutions that you considered, you ranked 83 12:03:22
3 of them a 1; is that right? 12:03:25
4 A That sounds about right. I believe it was 12:03:31
5 about 10 percent. 12:03:34
6 Q So about 10 percent of the substitutions 12:03:35
7 that you considered, you determined would be 12:03:37
8 likely -- would be likely not tolerated? 12:03:41
9 ATTORNEY KUSHAN: Objection. Foundation. 12:03:44
10 A Based on my evaluation, 10 percent of the 12:03:52
11 substitutions that I have evaluated, my prediction 12:03:55
12 was that they would not be tolerated. 12:04:02
13 Q And the other 90 percent, you predicted 12:04:05
14 that they would be tolerated, right? 12:04:10
15 ATTORNEY KUSHAN: Objection. Foundation. 12:04:16
16 A Again, among the substitutions that I have 12:04:17
17 evaluated, I expect about 90 percent of them to be 12:04:21
18 tolerated. 12:04:27
19 Q Now, the 830-some substitutions that you 12:04:32
20 considered, those are about a third of the 12:04:44
21 potential substitutions that are listed on the 12:04:47
22 variant tab, right? 12:04:49

1 A About a third, maybe a little less than a 12:04:53
2 third. A little less than a third, but around 12:04:59
3 there. Yes. 12:05:04
4 Q Okay. And so you considered around a 12:05:05
5 third-ish of the potential substitutions on the 12:05:08
6 variant tab, and concluded that 90 percent of them 12:05:15
7 were likely to be tolerated, right? 12:05:18
8 ATTORNEY KUSHAN: Objection form. 12:05:21
9 Also, objection as to foundation. 12:05:22
10 A Among the substitutions that I have 12:05:29
11 evaluated, which corresponds to high frequency 12:05:34
12 substitutions, I saw approximately 90 percent of 12:05:39
13 them would be tolerated. I expect those numbers 12:05:42
14 to be different if I had evaluated all 2,815 12:05:47
15 substitutions, which would also include lower 12:05:52
16 percentage substitutions, and therefore may be 12:05:56
17 more likely to be not tolerated than the ones that 12:06:01
18 I have evaluated. 12:06:07
19 Q Okay. So for those positions that aren't 12:06:10
20 substituted quite so frequently, it may be the 12:06:20
21 case that substitutions are less tolerated -- less 12:06:22
22 tolerated at that -- at those positions? 12:06:27

1 ATTORNEY KUSHAN: Objection to foundation. 12:06:28
2 A That would be my expectation. 12:06:30
3 Q Now, we were talking about around a third 12:06:57
4 of the substitutions. But to be clear, you 12:07:01
5 considered 329 positions in your analysis, right? 12:07:06
6 A 397 minus 68. 300 -- is it 397 minus 68, 12:07:16
7 329? Is that what you said, that 329? 12:07:31
8 Q Yes. 12:07:35
9 A Okay. Fine. Yes. Positions. Yes. 12:07:35
10 Q Okay. So can we look, for example, at -- 12:07:37
11 in the variant tab, at position 47 -- position 417 12:08:21
12 in HYAL1, 399, in -- you have it on the screen. 12:08:27
13 399. Yeah. 12:08:32
14 A Uh-huh. 12:08:33
15 Q For the mature PH20. And for this 12:08:34
16 position, you -- you assigned the mutation to R 12:08:41
17 at 2, the mutation to S at 1, the mutation to Q 12:08:50
18 at 2, and the mutation to K at 2; is that right? 12:08:57
19 A I see that. Yes. 12:09:01
20 Q And so for the mutations to R and S, in 12:09:03
21 your comments you've noted for both, you say loss. 12:09:07
22 But for R, you score that a 2 versus for S you 12:09:12

1 scored it a 1. 12:09:16
2 Can you explain how -- can you explain how 12:09:18
3 you arrived at the score of a 1 for S versus 2 12:09:25
4 for R, when you've noted that both are potentially 12:09:28
5 a loss? 12:09:36
6 A Yes. This represents a -- a limitation in 12:09:36
7 the comment, the way the comment column is used. 12:09:41
8 I do not elaborate on my thinking beyond writing 12:09:46
9 down a few words to remind myself what was going 12:09:51
10 on. To fully understand and appreciate the 12:09:55
11 difference, one really has to look at the 12:10:00
12 structure. And viewing at the structure, it would 12:10:03
13 be clearer why one residue would be scored a 2, 12:10:07
14 and another residue would be scored a 1, even 12:10:13
15 though both of them result in some loss of 12:10:17
16 contacts. 12:10:21
17 It's a matter of degree, which is 12:10:22
18 difficult to capture with just a few words. I 12:10:25
19 would have to write a whole paragraph, which I did 12:10:31
20 not do, for every substitution for lack of time. 12:10:36
21 And that Column I, the comments column, is taken 12:10:42
22 in that spirit. As a quick note to myself, 12:10:46

1 perhaps more so than to other people who are 12:10:50
2 viewing it at a later time, that there was a 12:10:54
3 thinking behind it that was based on Van der Waals 12:10:59
4 contacts or hydrophobic contacts, and this is what 12:11:06
5 led me to the score that we see in Column H. But 12:11:10
6 again, it doesn't paint the full picture, so one 12:11:15
7 has to take it in that spirit. 12:11:20
8 Q As a general matter, how did you determine 12:11:23
9 that a loss would be significant enough to score 12:11:27
10 it as a 1 versus a 2? 12:11:30
11 A So that is the art that I was trying to 12:11:38
12 refine by applying it to many different 12:11:42
13 substitutions at many different positions. It's 12:11:49
14 hard to know where the line has to be drawn when 12:11:53
15 you're doing it for the first time. And for that 12:11:56
16 reason, I felt that it was important that I look 12:12:00
17 at many different substitutions, and perhaps look 12:12:04
18 at them multiple times, to see if I am comfortable 12:12:12
19 with that evaluation. 12:12:15
20 In the end, it comes down to what would 12:12:16
21 another person of my experience and knowledge 12:12:19
22 would say about this position and this 12:12:24

1 substitution, namely, the POSA. What would a POSA 12:12:29
2 say for that substitution, and do I feel 12:12:33
3 comfortable with that score. And that's the 12:12:39
4 mindset that I have to get to, and that was the 12:12:43
5 goal in evaluating all these other positions so 12:12:48
6 that I could settle on to a system that, as vague 12:12:53
7 as it may be, lives in my mind, makes sense, and 12:13:00
8 somehow convince myself that this is how a POSA 12:13:07
9 would look at that substitution. 12:13:11
10 Q So in your mind, in your system, how would 12:13:17
11 a POSA distinguish between a loss that's a 2 12:13:21
12 versus a loss that's a 1? 12:13:25
13 A That's like asking the judges on American 12:13:30
14 Idol why would you say yes or no. You can point 12:13:34
15 things out, and say: I like this aspect. I like 12:13:40
16 that aspect. I don't like this. 12:13:44
17 But what's important is that the judges 12:13:50
18 have similar set of experience so they can 12:13:53
19 understand what they're looking at, even when 12:13:56
20 description or quantification becomes very 12:14:01
21 difficult. So it's a gray area that an 12:14:05
22 experienced person might understand that may be 12:14:12

1 difficult for somebody else who doesn't have a 12:14:18
2 similar training. 12:14:27
3 Q So are you saying that whether a loss was 12:14:29
4 scored as a 1 or a 2 was a subjective 12:14:33
5 determination? 12:14:37
6 ATTORNEY KUSHAN: Objection. Foundation. 12:14:38
7 A Given that this is a score given by a 12:14:43
8 human evaluator, namely myself, to a degree it is 12:14:47
9 subjective. But my goal was to be as objective as 12:14:55
10 possible, given that constraint. 12:15:00
11 Can I give a score and feel comfortable 12:15:04
12 that this is consistent with how such a 12:15:11
13 substitution should be judged by others who have 12:15:15
14 similar background as myself? That is the 12:15:21
15 criteria that I was aiming for, and I feel that I 12:15:28
16 have reached that through the iterative exercise. 12:15:33
17 Q So as you performed your analysis, the 12:15:53
18 framework that you used changed over time; is that 12:15:56
19 right? 12:15:59
20 ATTORNEY KUSHAN: Objection. Foundation. 12:15:59
21 Also objection as to form. 12:16:02
22 A What do you mean by the framework? 12:16:03

1 Q The different criteria that you were using 12:16:06
2 when you evaluated each substitution. 12:16:11
3 A Sometimes it's that. Other times it's 12:16:18
4 catching something that I overlooked the first 12:16:24
5 time. Those would also happen. I remember one 12:16:27
6 example where I scored a substitution in a certain 12:16:33
7 way, and later on went back and said perhaps I 12:16:39
8 shouldn't be doing that. 12:16:45
9 And this was a residue that was in the 12:16:47
10 binding pocket and I -- initially, I gave it a 12:16:49
11 score of 1 thinking that that residue is likely to 12:16:55
12 be involved in catalysis, although there was no 12:17:01
13 literature evidence for that. Based on the 12:17:06
14 structure, I predicted that residue might be 12:17:09
15 important for catalysis, and as a result, any 12:17:15
16 substitution at that position would be 12:17:19
17 detrimental. So I gave it a score of 1. 12:17:22
18 However, upon coming back to that residue 12:17:25
19 at a later time, I noticed that I was making too 12:17:29
20 many assumptions about what that residue was 12:17:33
21 doing. Other than its position, there was really 12:17:36
22 no evidence that that residue was, indeed, 12:17:40

1 involved in catalysis. 12:17:43
2 My thinking was if I had put in a 12:17:46
3 substrate in the binding pocket, some portion of 12:17:50
4 the substrate might be near that residue, and that 12:17:54
5 residue might be involved in that interaction. So 12:17:58
6 there were layers of assumption that went in, 12:18:01
7 which led me to judge any substitution at that 12:18:06
8 position as bad. But I realized that that's not 12:18:12
9 how I should be doing it. I should really look at 12:18:18
10 the structure as is and work with what's available 12:18:22
11 to me, rather than build my evaluation upon 12:18:25
12 assumptions and assumptions. 12:18:33
13 So framework has changed in that regard. 12:18:36
14 But I felt much more confident about how -- how I 12:18:42
15 was judging different substitutions, having 12:18:49
16 completed two cycles of evaluation. So if there 12:18:52
17 were any subsequent changes, I think those were 12:18:58
18 much more subtle than initially. 12:19:02
19 Q And you said that determining whether 12:19:06
20 something would be a loss versus -- I'm sorry. 12:19:10
21 Strike that. 12:19:12
22 You said that determining whether 12:19:12

1 something would be not tolerated and scored a 1 12:19:13
2 versus tolerated and scored a 2 was -- is an art, 12:19:18
3 but you were -- in realty, you were considering 12:19:22
4 the change in potential interactions and the 12:19:28
5 position of the residue in the structure when you 12:19:31
6 made the substitution, right? 12:19:33
7 ATTORNEY KUSHAN: Objection. Form. 12:19:35
8 Objection. Foundation. 12:19:37
9 A Please repeat that question. It was not 12:19:40
10 clear to me. 12:19:43
11 Q Yeah. So when you're determining whether 12:19:43
12 a given substitution would be tolerated versus not 12:19:46
13 tolerated, you were examining quantitative 12:19:50
14 criteria, in terms of the positioning of the 12:19:58
15 residue and the interactions, right? 12:20:01
16 A I wouldn't say quantitative. It's hard to 12:20:05
17 put a number on different contributions. This is 12:20:12
18 at the core of the dilemma. 12:20:16
19 When I have two interactions, how do I sum 12:20:20
20 them up, especially when there's a conflict? When 12:20:23
21 one is good and the other one is not, which one 12:20:30
22 wins? Does it come out as a net positive 12:20:35

1 interaction, or is it a net negative interaction? 12:20:39
2 Unfortunately, I don't have a number that 12:20:44
3 I can add. So it's not a quantitative evaluation, 12:20:46
4 although I try to compare two quantities. Each 12:20:53
5 quantity comes without any definite number, so I 12:20:58
6 have to evaluate the sum of the interactions in 12:21:04
7 some qualitative way, but being mindful of how 12:21:10
8 important each aspect of the interaction may be. 12:21:18
9 Q And in the end, your conclusion was based 12:21:31
10 on how you viewed what you thought a skilled 12:21:34
11 person would conclude with the information 12:21:38
12 available to you? 12:21:41
13 A That is the guideline. The -- when 12:21:46
14 there's an overwhelming evidence for one type of 12:21:51
15 interaction, then it's a much easier and more 12:21:55
16 straightforward decision than in another case 12:22:00
17 where you may have an abundance of conflicting 12:22:04
18 interactions. So some substitutions are much more 12:22:11
19 difficult and challenging to evaluate than others. 12:22:16
20 That's just a fact of life. 12:22:22
21 Q So in 2011, when evaluating a protein 12:22:39
22 structure, a POSA would have considered the number 12:22:42

1 of neighbors; is that right? 12:22:45
2 ATTORNEY KUSHAN: Objection. Foundation. 12:22:49
3 A That could be one of the things that they 12:22:54
4 would look at. Looking at the number of neighbors 12:22:57
5 or counting the number of neighbors is a common 12:23:03
6 practice to see how solvent exposed a given 12:23:08
7 residue is. Since a residue that's on the surface 12:23:14
8 has fewer neighbors, it would result in a smaller 12:23:18
9 set of interactions that would constrain the 12:23:29
10 choice at that position. 12:23:34
11 Another position that has a lot of 12:23:37
12 neighbors tends to be buried, and it says 12:23:39
13 something about that position as well. So it is 12:23:46
14 one of the metrics, along with the fractional 12:23:49
15 accessible surface area. 12:23:53
16 I computed them because they are commonly 12:23:57
17 used for comparative structural analysis. Then I 12:24:01
18 incorporated them in my thinking. They don't have 12:24:06
19 very strong predictive power, unfortunately. I do 12:24:16
20 not rely on them much, other than as a quick 12:24:20
21 guide -- quick summary of what their position is 12:24:28
22 like. 12:24:34

1 Q So for a given substitution, you looked at 12:24:35
2 the structure and evaluated whether that residue 12:24:40
3 was buried or not buried as part of your analysis, 12:24:43
4 right? 12:24:48
5 ATTORNEY KUSHAN: Objection. Foundation. 12:24:48
6 A Looking at whether a position is buried or 12:24:50
7 not is an essential thing that went into my 12:24:55
8 analysis. I do not rely on the number of 12:25:02
9 neighbors exclusively as a way of extracting that 12:25:05
10 information. That information is better gotten by 12:25:10
11 looking at the structure. 12:25:13
12 The number is there as a way of quickly 12:25:14
13 summarizing what that position is like. I can 12:25:23
14 look at these numbers after the fact and do a 12:25:27
15 forensic analysis of all the positions that I've 12:26:12
16 looked at, what are they like? I can gain a quick 12:25:33
17 understanding of that distribution because the 12:25:38
18 number can be plotted. 12:25:45
19 They're a poor representation of the 12:25:50
20 structural complexity at each position. It 12:25:54
21 doesn't capture all the things that are going on 12:25:56
22 there. But as a quick summary of what that 12:26:01

1 residue was like, it has a place in the analysis. 12:26:05
2 Q Would you say that the potential 12:26:25
3 substitutions that you considered are the ones 12:26:28
4 that are most likely to be tolerated? 12:26:30
5 ATTORNEY KUSHAN: Objection. Foundation. 12:26:34
6 Objection to form. 12:26:36
7 A Can I hear that question again, please? 12:26:37
8 Q So before, when I pointed out that you 12:26:45
9 looked at around a third-ish of the substitutions 12:26:49
10 that are in variant -- in the variant tab, and you 12:26:54
11 noted that you -- the ones that you identified 12:26:57
12 were the ones that were -- or, the ones that you 12:26:59
13 analyzed appeared with the most frequency, would 12:27:03
14 you say that that -- that that subset that you 12:27:09
15 analyzed are the ones that are most likely to be 12:27:13
16 tolerated -- 12:27:17
17 ATTORNEY MARTIN: Objection. 12:27:17
18 Q -- because they appeared with the most 12:27:19
19 frequency? 12:27:21
20 ATTORNEY KUSHAN: Objection to form. 12:27:21
21 Objection. Objection as to foundation. 12:27:23
22 A I did not have any preconceived notion of 12:27:24

1 whether that would be the case. For those who do 12:27:29
2 consensus engineering or consensus-based 12:27:33
3 engineering, that's what they often do. They 12:27:39
4 would generate a multiple sequence alignment and 12:27:44
5 make a mutant that contains all the most 12:27:48
6 frequently appearing residues at each position. 12:27:51
7 So there's a thinking that the residues 12:27:54
8 that have a higher frequency are better in some 12:27:56
9 sense. I'm aware of that fact. However, in my 12:28:00
10 analysis, that didn't play a role. Because when I 12:28:11
11 evaluated individual substitutions, I was mostly 12:28:14
12 guided by what that residue, or what that 12:28:19
13 substitution was doing at that position, and my 12:28:26
14 evaluation was based on what I saw in the 12:28:29
15 structure, not so much based on the frequency. 12:28:32
16 Q Okay. So for the roughly two-thirds that 12:28:35
17 you didn't evaluate, can you say one way or the 12:28:39
18 other whether you think they would be tolerated? 12:28:42
19 A What about the two-thirds that I haven't 12:28:46
20 evaluated? What was the question again? 12:28:50
21 Q Can you say one way or the other whether 12:28:51
22 you think that they would be tolerated? 12:28:55

1 A Oh. It's hard to speculate. I would have 12:28:59
2 to look at them. The prevailing notion may say 12:29:01
3 that less frequent amino acids are likely to be 12:29:09
4 less tolerated, that I think one has to look at 12:29:15
5 them. I cannot say. 12:29:21
6 Q Okay. So there's a heat map on the 12:29:22
7 variant tab, right? 12:29:38
8 A Yes. At the very top. 12:29:39
9 Q Did you generate the heat map? 12:29:41
10 A I generated that heat map. Yes. 12:29:43
11 Q Can you explain how you generated the heat 12:29:45
12 map? 12:29:48
13 A Yes. There are different ways of doing 12:29:50
14 it. I wrote a script, which took the information 12:29:54
15 on Columns E, F and H, and those are the wild-type 12:30:00
16 residue, mutant or substitution residue, plus the 12:30:14
17 evaluation column of H. 12:30:22
18 Wherever there was an evaluation, which we 12:30:24
19 agreed was around 830 or so, I listed the 12:30:28
20 wild-type and mutant combination, and tabulated 12:30:32
21 them on a 20x20 matrix, counted the number of 12:30:39
22 incidences where that pair appeared, and plotted 12:30:47

1 that as a heat map. 12:30:54
2 Q But there are -- so there are some 12:31:11
3 potential alternative residues that aren't in -- 12:31:14
4 that aren't included on the variant tab, right, so 12:31:19
5 those are not included in the heat map; is that 12:31:24
6 right? 12:31:29
7 A That is correct. These only represent the 12:31:29
8 ones that I have evaluated. 12:31:32
9 Q Just to be clear, so is the heat map all 12:31:34
10 of the alternative residues that are in Column F 12:31:38
11 on the variant tab, or is it just those that you 12:31:43
12 actually looked at and determined and gave us -- 12:31:47
13 and, you know, scored? 12:31:50
14 A It's a letter. 12:31:50
15 Q All right.
16 A Just the substitutions that I have 12:31:51
17 evaluated. 12:31:53
18 Q Oh, okay. So the heat map is just the 12:31:53
19 substitutions that you scored? 12:31:56
20 A That is correct. 12:31:58
21 Q And what does the 0 to 14 signify? What's 12:31:58
22 that range signify? 12:32:07

1 A That is the number of instances for that 12:32:08
2 particular combination. 12:32:11
3 Q Okay. And as we had said before, around 12:32:13
4 90 percent of the substitutions that you scored 12:32:24
5 were predicted to be likely tolerated, right? 12:32:27
6 A That is correct. Yes. 12:32:31
7 Q So about 90 percent of the substitutions 12:32:33
8 in the heat map are likely to be tolerated? 12:32:36
9 ATTORNEY KUSHAN: Objection. Foundation. 12:32:40
10 A That is the math. 12:32:43
11 Q Okay. 12:32:44
12 A Yes. There are 830 or so counts in this 12:32:45
13 heat map, 90 percent of which were scored either 2 12:32:51
14 or 3. 12:32:57
15 Q Okay. And I just want to make sure that 12:32:57
16 the ones that were -- that the substitutions that 12:33:01
17 were scored 1 are still shown in the heat map? 12:33:03
18 A That is true. 12:33:09
19 Q Okay. 12:33:19
20 A That is correct. 12:33:10
21 Q Okay. Have you prepared heat maps like 12:33:12
22 this in your work outside of this case? 12:33:16

1 A No. 12:33:18
2 Q Why did you prepare this heat map? 12:33:20
3 A One of the things that I was aiming for as 12:33:26
4 I was going through the substitution analysis was 12:33:30
5 to develop a robust system, and I needed a way of 12:33:34
6 knowing how robust my system was, and that I 12:33:40
7 believed involved looking at many different kinds 12:33:48
8 of substitutions; and therefore, I wanted to keep 12:33:53
9 track of what sort of substitutions I was looking 12:34:00
10 at. 12:34:05
11 If the heat map shows a lot of empty 12:34:05
12 space, that would indicate that my coverage is 12:34:10
13 limited, so I wanted to make sure that the heat 12:34:14
14 map is well-populated, and that was also the 12:34:19
15 reason that I went from 10 percent to 5 percent in 12:34:25
16 terms of putting a limit on the substitutions. 12:34:28
17 I think at some point, I generated a heat 12:34:31
18 map and didn't -- I wasn't convinced that I had 12:34:34
19 enough statistics in there, and felt that I might 12:34:40
20 want to do more. 12:34:44
21 Q Okay. So you wanted to make sure that you 12:34:49
22 were evaluating substitutions across the spectrum 12:34:53

1 of -- of the 20 amino acids? 12:34:59
2 A That's correct. 12:35:00
3 Q So does this heat map show the -- the 12:35:14
4 frequency with which you evaluated a particular 12:35:28
5 type of substitution, for example, from lycine to 12:35:31
6 arginine? 12:35:42
7 A It give you the statistics. Yes. 12:35:43
8 The lycine to arginine substitution is one 12:35:45
9 of the bluest. Yeah. I would say it's one of the 12:35:49
10 darkest blue, which on the scale on the right side 12:35:54
11 would represent perhaps 14/15. So there were as 12:36:00
12 many as 14 or 15 substitutions that involved K to 12:36:07
13 R substitutions, and those were evaluated. Yes. 12:36:11
14 (Reporter clarification.) 12:36:17
15 Q Okay. And so you did not evaluate very 12:36:17
16 many substitutions involving histamines; is that 12:36:22
17 right? 12:36:29
18 ATTORNEY KUSHAN: Objection. Foundation. 12:36:29
19 A That seems to be the case. 12:36:30
20 Q And you also did not identify or evaluate 12:36:32
21 many substitutions involving tryptophan? 12:36:36
22 A That also seems to be the case. Not my 12:36:43

1 fault that PH20 doesn't have a lot of histamines 12:36:48
2 or tryptophan. 12:36:52
3 Q And it looks like you did not -- you did 12:36:57
4 not evaluate any substitutions for cystine? 12:37:01
5 A I believe that all cystines in PH20 are 12:37:04
6 strictly conserved; therefore, they were not part 12:37:05
7 of the non-essential positions, and -- and not 12:37:09
8 scored as a result. 12:37:11
9 Q Okay. As part of your analysis in scoring 12:37:12
10 a substitution a 1, 2 or a 3, did you evaluate the 12:38:02
11 secondary structure in which that residue appears? 12:38:07
12 A Absolutely all substitutions were 12:38:13
13 evaluated based on a combination of the intrinsic 12:38:15
14 properties of the amino acid, its compatibility 12:38:21
15 with the secondary structure, as well as its 12:38:25
16 potential interactions with neighbors. All three 12:38:28
17 types of interactions were considered in the 12:38:32
18 evaluation. 12:38:35
19 Q Why didn't you include a column for, or a 12:38:36
20 column identifying the secondary structure for 12:38:40
21 each residue in the variant tab? 12:38:43
22 ATTORNEY KUSHAN: Objection. Foundation. 12:38:53

1 A You're referring to the Columns L, M 12:38:59
2 and N? 12:39:03
3 Q Well, you didn't -- there's a column 12:39:06
4 entitled: Secondary structure. 12:39:08
5 And in that column, sometimes you have 12:39:10
6 a 1, but you don't actually go through and 12:39:13
7 identify what the secondary structure is. 12:39:16
8 A Right. The -- there are three columns 12:39:19
9 there, three factors: Hydrophobicity, secondary 12:39:23
10 structure, interactions, as I label them. 12:39:27
11 Although those are just shorthands 12:39:28
12 referring to amino acid properties, secondary 12:39:32
13 structure compatibility, tertiary interactions. 12:39:37
14 (Reporter clarification.) 12:39:45
15 A Of course every substitution was evaluated 12:39:45
16 according to all three. If I mark every single 12:39:46
17 one, you would have 1 everywhere, which doesn't 12:39:50
18 tell you anything. These are the interactions 12:39:55
19 that sort of jumped out as being significant, or 12:39:58
20 something that stood out when I considered that 12:40:04
21 particular substitution. 12:40:08
22 These markings should be considered as, 12:40:10

1 say, personal notes as I go along. That doesn't 12:40:17
2 mean that I only focused on hydrophobicity, 12:40:21
3 secondary structure, or tertiary interactions to 12:40:29
4 the exclusion of the ones that are not marked. 12:40:29
5 In any given case, one may stand out for 12:40:33
6 whatever reason, and I would mark that as a 12:40:38
7 reminder that this is one of the reasons that I 12:40:42
8 gave the score of such and such. 12:40:46
9 Q So if you go to the SASA tab at the 12:40:58
10 bottom? 12:41:03
11 A Yes. 12:41:03
12 Q So on the SASA tab, you do have a 12:41:04
13 secondary structure column, right? 12:41:08
14 A That is correct. 12:41:11
15 Q So why did you include the secondary 12:41:13
16 structure column on the SASA tab, but not on the 12:41:16
17 variant tab? 12:41:23
18 A When I do an evaluation, I look at the 12:41:30
19 structure, not the markings of secondary structure 12:41:32
20 that's provided by PyMol. PyMol -- this column of 12:41:38
21 secondary structure on SASA tab is from PyMol. 12:41:43
22 That's automatically generated. 12:41:49

1 When I do an evaluation, I don't look up 12:41:52
2 the secondary structure based on what PyMol says. 12:41:55
3 I can look at the structure perfectly well by 12:42:03
4 myself, so I don't need that information in the 12:42:09
5 variant tab because that's apparent from my visual 12:42:14
6 inspection. 12:42:18
7 Q Okay. And so -- so L means loop; is that 12:42:22
8 right?
9 (Reporter clarification.) 12:42:28
10 A Loop. Yes. Loop. 12:42:28
11 Q In the secondary structure column. 12:42:29
12 And H means helix; is that right? 12:42:34
13 A Helix. Yes. 12:42:36
14 Q And S means sheet? 12:42:38
15 A That is correct. 12:42:42
16 Q Okay. So going back to the variant tab in 12:43:30
17 your -- in the comments field, you will have 12:43:37
18 neutral: And then notes, loss: And then notes, 12:43:43
19 or gain: And then notes. 12:43:51
20 Can you just explain what you mean by 12:43:55
21 gain, loss and neutral? 12:43:58
22 A Right. A score of 2 is a very broad 12:44:00

1 range. When I set out to determine if a 12:44:04
2 substitution is tolerated or not tolerated, I, at 12:44:10
3 some level, had to decide what's considered not 12:44:19
4 tolerated. 12:44:23
5 Is it a 0 percent activity? Very few 12:44:24
6 things are a 0 percent activity. So it will be 12:44:29
7 some low percentage activity compared to 12:44:35
8 wild-type. That boundary remains to be decided. 12:44:40
9 In the middle, or at the top, there may be 12:44:43
10 some mutations that are pretty convincingly a good 12:44:47
11 substitution. There's a small fraction of 12:44:56
12 substitutions that fall into that category, and 12:45:00
13 they kind of jump out. You look at them and you 12:45:03
14 only see good things. The stars are lined up in a 12:45:07
15 way. 12:45:11
16 In the middle you see a lot of variation, 12:45:12
17 and those are all going to end up with a score 12:45:15
18 of 2. However, I felt the urge to comment that 12:45:19
19 they're not all equal. Some may still be slightly 12:45:27
20 a favorable substitution, although it doesn't 12:45:32
21 quite rise to the level of being given the honor 12:45:38
22 of 3. 12:45:42

1 I wanted to make a note of it because it's 12:45:44
2 only one time. Once I get past that substitution, 12:45:48
3 I will lose that information. I wanted to keep 12:45:52
4 track of what I was doing. So I wanted to make a 12:45:56
5 distinction between mutual substitutions, which I 12:46:00
6 really thought nothing much is going to happen 12:46:11
7 here. 12:46:12
8 There's a good -- is that the one I used? 12:46:13
9 There's a loss, and maybe good. These are sort of 12:46:13
10 in the upper range of the -- of the score 2. So I 12:46:16
11 wanted to make a note of that subtle difference, 12:46:23
12 although in the end, it didn't really matter 12:46:26
13 because all these substitutions ended up being 12:46:29
14 labeled as tolerated. But I wanted to -- given 12:46:36
15 the amount of effort that I put into evaluating 12:46:43
16 them, I wanted to keep a record of what I was 12:46:48
17 doing. So I tried to put in that information. 12:46:51
18 Settled on three keywords: Mutual, loss 12:46:57
19 and good, and I tried to elaborate a little bit by 12:47:03
20 adding some additional information if possible. 12:47:13
21 Q So let's go to the neighbor tab. 12:47:48
22 A Okay. 12:47:53

1 Q And there's a plot for FSASA versus number 12:47:53
2 of neighbors. Did you generate that plot? 12:48:05
3 A I generated that. 12:48:08
4 Q How did you generate that? 12:48:09
5 A I generate it from the Columns D and E, 12:48:11
6 just created a dot plot from those two columns. 12:48:16
7 Q Okay.
8 (Reporter clarification.) 12:48:24
9 Q And did you use this plot in your 12:48:24
10 analysis? 12:48:27
11 A No. This was to see if those two 12:48:31
12 parameters were correlated. Since they are 12:48:36
13 commonly used in the field to look at how buried a 12:48:42
14 given residue is, and I have already compiled the 12:48:47
15 two sets of information, I wanted to see if they 12:48:50
16 are correlated. If they are loosely correlated, 12:48:54
17 perhaps too loosely to be of much use, so I didn't 12:49:01
18 use it in my analysis. 12:49:06
19 Q It looks like there are some fractional 12:49:08
20 solvent accessible surface area values that are 12:49:16
21 above 1, or at least one that's above 1. 12:49:23
22 Can you explain that? 12:49:24

1 A Yeah. That's a funny data point. That, I 12:49:25
2 think, is a lycine somewhere that appears on a 12:49:29
3 loop in PH20. And it seems, based on PyMol 12:49:34
4 calculation, the accessible surface area for that 12:49:43
5 residue was even greater than what can be computed 12:49:48
6 in a random peptide consisting of glycine, 12:49:53
7 glycine, glycine. 12:50:05
8 Q Oh, okay. 12:50:07
9 A Yeah. So that ended up being greater than
10 100 percent.
11 Q Okay. Okay. And so for the number of 12:50:08
12 neighbors, the way that you define neighbors in 12:50:10
13 your analysis is shown in the box: Number of 12:50:14
14 neighbors on the neighbor tab; is that right? 12:50:16
15 A That is correct. 12:50:19
16 Q And so we already talked before about the 12:50:20
17 residues within 5 angstroms? 12:50:24
18 A That's right. 12:50:29
19 Q Is that fair to say that you select -- 12:50:30
20 that you considered as neighbors all residues that 12:50:31
21 had at least one atom within 5 angstroms of an 12:50:33
22 atom on the residue you were considering? 12:50:37

1 A On the residue that I'm considering, I 12:50:42
2 started out with the side chain atoms only. 12:50:46
3 Q Uh-huh. 12:50:50
4 A And from there, I would compare the 12:50:51
5 distance, and any atom, any residue, whose atom 12:50:53
6 may be 5 -- within 5 angstrom of any of the atoms 12:50:58
7 of the side chain of the residue I'm considering, 12:51:01
8 yes. It would be considered a neighbor in my 12:51:04
9 definition. 12:51:06
10 Q Okay. And that's -- that's the number 1 12:51:07
11 point, right, selected side chain atoms only? 12:51:09
12 So you -- 12:51:12
13 A That is correct. 12:51:12
14 Q Okay. So for the -- the residue that 12:51:13
15 you're considering, you focus only on the atoms in 12:51:15
16 the side chain, and then you select all atoms 12:51:21
17 within 5 angstroms of -- 12:51:22
18 A Of those side chain atoms. 12:51:22
19 Q Yes. 12:51:25
20 A That is correct. Yes. 12:51:26
21 Q Can you explain what you mean when you 12:51:27
22 say: Gly equals CA? 12:51:31

1 A Uh-huh. Since glycine doesn't have a side 12:51:36
2 chain, I used the C-alpha atom as the starting 12:51:41
3 point. 12:51:45
4 Q Okay. Okay. So you considered that side 12:51:45
5 chain, if you will, for the lycine to be the 12:51:47
6 C-alpha atom when you're doing that 5 angstrom 12:51:48
7 analysis? 12:51:53
8 A For all the other amino acids, C-alpha 12:51:53
9 atom was not included. 12:51:56
10 Q Okay. And why did you restrict your 12:51:57
11 neighbor analysis to only side chain atoms, as 12:52:05
12 opposed to main chain atoms? 12:52:09
13 A Because main chain atoms are shared by all 12:52:13
14 amino acids, regardless of what you're 12:52:16
15 substituting in. And I thought the information 12:52:20
16 would be more distilled and relevant if I limit my 12:52:22
17 view to side chain atoms only. 12:52:26
18 Q Do you think that that restricted your 12:52:31
19 analysis in any way, the fact that you limited the 12:52:35
20 neighbor cutoff to atoms in the side chain? 12:52:39
21 ATTORNEY KUSHAN: Objection. Foundation. 12:52:41
22 A No. That didn't affect my analysis 12:52:45

1 because the number of neighbors was not part of 12:52:49
2 the analysis. It was an information that I 12:52:53
3 generated because I could, and because it's often 12:52:56
4 done. 12:53:04
5 But ultimately my evaluation was based on 12:53:05
6 my viewing of the structure, and not on the strict 12:53:09
7 listing of the side of the neighbors. Therefore, 12:53:15
8 whether the neighbors are defined using the side 12:53:19
9 chain only, or main chain plus side chains, would 12:53:23
10 not matter so much. 12:53:29
11 ATTORNEY MARTIN: Okay. I think we've 12:53:31
12 probably gone for another hour, if you want to 12:53:34
13 take another break. 12:53:38
14 THE WITNESS: Oh, sure. Yes. 12:53:39
15 THE VIDEOGRAPHER: We are going off the 12:53:41
16 record. The time is 12:53 p.m. 12:53:42
17 (Recess from 12:53 p.m. until 1:50 p.m.) 12:53:48
18 THE VIDEOGRAPHER: We are going back on 13:50:35
19 record. The time is 1:50 p.m. 13:50:37
20 BY ATTORNEY MARTIN: 13:50:45
21 Q Welcome back, Dr. Park. 13:50:41
22 A Thank you.

1 Q Did you discuss the substance of your 13:50:47
2 testimony at all during the break? 13:50:49
3 A No. I did not. 13:50:52
4 Q Do you still have the -- the spreadsheet 13:50:59
5 pulled up? 13:51:05
6 A Yes. It's still on the screen. 13:51:05
7 Q Okay. We were talking about the neighbor 13:51:07
8 tab? 13:51:41
9 A Neighbor tab. Yes. 13:51:41
10 Q So under the box that says: Number of 13:51:43
11 neighbors. 13:51:48
12 Then there's another box that says: 13:51:50
13 Rating; and then, average number of neighbors. 13:51:51
14 Can you explain what that means? 13:51:53
15 A It's another one of those things that I 13:51:58
16 looked at, just because the data was there. The 13:52:03
17 information was there. I wanted to see whether 13:52:07
18 there was any correlation between the ratings that 13:52:12
19 I gave, and the number of neighbors for that 13:52:17
20 position. 13:52:23
21 Yeah. I wanted to see -- this was after 13:52:28
22 the fact, after all the scores have been recorded. 13:52:31

1 I wanted to see, do I see any trend. So that's 13:52:38
2 what I observed. 13:52:43
3 Q Okay. And so when it says: Conserved, 13:52:45
4 does that refer to the residues that are in the -- 13:52:48
5 or, the positions that are in the conserved tab of 13:52:52
6 the spreadsheet? 13:52:57
7 A That is correct. Those 68 residues on the 13:52:57
8 conserved tab are the conserved in here. 13:53:01
9 Q And those 68 residues have an average 13:53:05
10 number of neighbors of 10.18; that's right -- is 13:53:09
11 that right? 13:53:13
12 A That is correct. 13:53:13
13 Q And then for those substitutions that you 13:53:14
14 gave a 1 rating, the average number of neighbors 13:53:18
15 was 8.63; is that right? 13:53:24
16 A That is correct. 13:53:28
17 Q Okay. So let's go back to the variant 13:53:54
18 tab. Is it fair to say that for all of the 13:53:58
19 positions that are included in the variant tab, 13:54:18
20 you considered at least one substitution for the 13:54:22
21 vast majority of those positions? 13:54:26
22 A For a large number of the residues in 13:54:30

1 variant, I have considered a substitution, one or 13:54:38
2 more substitutions. 13:54:47
3 Q So for a large number of -- of positions 13:54:47
4 in the variant tab, you have considered one or 13:54:50
5 more substitutions; is that right? 13:54:54
6 A I believe so. 13:54:57
7 Q Okay. And is it fair to say that you 13:55:04
8 considered every single position for which there 13:55:06
9 is an alternative residue that appears at least 10 13:55:11
10 percent of the time in the multiple sequence 13:55:17
11 alignment? 13:55:20
12 A For most of them, I have considered a 13:55:22
13 substitution. But as you pointed out, there were 13:55:25
14 some residues at the beginning that weren't 13:55:28
15 evaluated. 13:55:31
16 Q Uh-huh. 13:55:31
17 A Somehow I didn't think that they were 13:55:32
18 worth looking at. 13:55:36
19 Q But as a general matter, for the most 13:55:40
20 part, if there's an alternative residue that 13:55:44
21 appeared at least 10 percent of the time in the 13:55:48
22 multiple sequence alignment, you considered that 13:55:50

1 position in your analysis? 13:55:52
2 A I did. Yes. 13:55:56
3 ATTORNEY KUSHAN: I'm sorry. Let me have 13:55:57
4 time to object. 13:55:59
5 I'm going to object to foundation. 13:56:00
6 A If there's a residue that appears with 10 13:56:02
7 percent or higher, I, in general, considered that 13:56:05
8 substitution and evaluated that substitution. 13:56:10
9 That is my recollection. 13:56:16
10 Q So if you could scroll to -- so, strike 13:56:25
11 that. 13:56:35
12 I believe you testified that you started 13:56:35
13 by going through and analyzing every substitution 13:56:40
14 that appeared at least 10 percent of the time, and 13:56:46
15 then eventually you dropped the threshold down 13:56:48
16 to 5 percent of the time. 13:57:00
17 So you then considered all of the 13:57:03
18 substitutions that appeared at least 5 percent of 13:57:03
19 the time, for the most part; is that right? 13:57:06
20 A For the most part. Yes. 13:57:09
21 Q Okay. So can you turn to -- or, scroll in 13:57:11
22 the variant tab to position, HYAL1 position 57, 13:57:13

1 mature PH20 position 39? 13:57:16
2 And so for mature PH20 position 39, it's a 13:57:35
3 serine? 13:57:45
4 A I must be looking at the wrong residue. 13:57:45
5 What position was that again? 13:57:45
6 Q Oh. 57. HYAL1 position 57. 13:57:46
7 A 57?
8 Q Yeah. Mature PH20 position 39. 13:57:50
9 A 57. Aspartic acid, 57? 13:57:58
10 Q Yes. 13:58:02
11 A Serine 39? 13:58:03
12 Q Yes. 13:58:06
13 A Yes. 13:58:09
14 Q Okay. 13:58:09
15 A Okay. 13:58:10
16 Q And so the most frequent residue at that 13:58:10
17 position is the aspartate that's 40.9 percent of 13:58:11
18 the time, right? 13:58:14
19 A Yes. 13:58:15
20 Q And so you've considered the substitutions 13:58:15
21 D, Q and G for that position, right? 13:58:19
22 A That is correct, yes. 13:58:22

1 Q And the glycine appears 9.09 percent of 13:58:24
2 the time in the alignment? 13:58:29
3 A Yes. I believe so. 13:58:30
4 Q So glycine appears less than 10 percent of 13:58:32
5 the time, and you considered it in your analysis, 13:58:37
6 right? 13:58:39
7 ATTORNEY KUSHAN: Objection. Foundation. 13:58:42
8 A It appears that way. 13:58:47
9 Q But asparagine, right under glycine, 13:58:51
10 appears 7.95 percent of the time, but you did not 13:58:56
11 consider the asparagine substitution; is that 13:58:59
12 right? 13:59:02
13 A That seems to be the -- that seems to be 13:59:02
14 the case. Yes. 13:59:05
15 Q So can you explain why you considered 13:59:06
16 glycine, but not asparagine in that position? 13:59:10
17 A This was touched on earlier. I started 13:59:14
18 with 10 percent as the threshold, tried to 13:59:20
19 evaluate all of them as much possible. 13:59:24
20 Afterwards, I lowered the threshold to 5, and 13:59:27
21 again tried to evaluate as much -- as much as 13:59:32
22 possible. I did not adhere to that rule strictly. 13:59:34

1 In general, I tried to do most of them. 13:59:39
2 Sometimes I skipped them through oversight. I 13:59:43
3 would go down the list, and I feel like I did all 13:59:49
4 of them, and then I'd move on to the next 13:59:52
5 position, not realizing there are other residues 13:59:54
6 that I should have considered. So it could have 13:59:58
7 been that. 14:00:01
8 So it wasn't any conscientious decision to 14:00:02
9 evaluate one substitution and not the other. Any 14:00:07
10 omission is -- is random. 14:00:11
11 Q Is random; is that what you said? 14:00:13
12 A Yes. 14:00:15
13 Q Okay.
14 A It was left out randomly by mistake. 14:00:17
15 Q Are there residues that you -- for which 14:00:26
16 you considered substitutions that appear less 14:00:28
17 than 5 percent of the time? 14:00:32
18 A Are there residues that appear less than 5 14:00:34
19 percent of the time -- 14:00:37
20 Q That you --
21 A -- period? 14:00:38
22 Q That you considered in your analysis. 14:00:39

1 A Oh. Yes. I believe so. 14:00:41
2 Well, I see an example further down at 14:00:55
3 position 44, PH20, or HYAL1 position 62, proline. 14:00:58
4 I see one, 3.4 percent. 14:01:10
5 Perhaps a better example would be later on 14:01:18
6 at position 320 for which I wrote a detailed 14:01:21
7 description as part of the declaration. There 14:01:26
8 were other positions, other substitutions, that 14:01:30
9 had less than 5 percent, which were evaluated. 14:01:33
10 Q So why did you evaluate those 14:01:36
11 substitutions? 14:01:38
12 A By that time, I had already completed all 14:01:41
13 my analysis of all of positions, and provided a 14:01:45
14 spreadsheet to counsel, who then asked me to 14:01:49
15 elaborate on certain positions, including 320, 14:01:54
16 317, and so on. And since I'm being asked to 14:01:59
17 provide detailed description of the substitutions 14:02:06
18 and evaluation at those positions, I went back and 14:02:10
19 finished the analysis with all the substitutions 14:02:17
20 that were available at those positions. 14:02:20
21 Q So am I understanding correctly that you 14:02:24
22 completed your analysis and provided the 14:02:29

1 spreadsheet to counsel, and then you were asked to 14:02:31
2 go back and look at additional substitution at 14:02:34
3 certain, specific positions by counsel? 14:02:37
4 ATTORNEY KUSHAN: Objection. Foundation. 14:02:38
5 Objection as to form. 14:02:40
6 A I was asked about these positions that are 14:02:47
7 in the declaration, and I then proceeded to 14:02:49
8 analyze the rest. Since I'm being asked about 14:02:56
9 these positions, I wanted to make the study as 14:03:00
10 complete as possible, and thus concluded the 14:03:03
11 analysis with the other substitutions, which were 14:03:09
12 not included in the initial study. 14:03:13
13 Q Do you know for those positions which 14:03:17
14 substitutions were not included in the initial 14:03:21
15 study? 14:03:24
16 A Those would have been the ones that had a 14:03:28
17 frequency less than 5 percent. 14:03:31
18 Q Oh, okay. And for some of them, I mean 14:03:33
19 could it have been a frequency between 5 and 10 14:03:37
20 percent, since you didn't evaluate all of the 14:03:40
21 substitutions at the 5 to 10 -- in the 5 to 10 14:03:42
22 percent range? 14:03:49

1 A The substitutions that fell between 5 14:03:52
2 to 10 percent was included in the analysis at a 14:03:58
3 later time, and it wasn't meaning after the 10 14:04:03
4 percent, cutoff analysis. And then I went back 14:04:08
5 and decided to lower the threshold hold to 5 14:04:12
6 percent. It's the second stage of the analysis, 14:04:18
7 and that study wasn't done with 100 percent 14:04:20
8 coverage. There were some positions that were 14:04:26
9 left out. 14:04:28
10 I want to say that that omission was 14:04:28
11 small. I tried to cover as many as possible, but 14:04:34
12 given the time that was allowed to me, I think 14:04:43
13 some positions ended up being left out. But it's 14:04:49
14 a small percentage, and I would argue that most of 14:04:52
15 them were covered. Most of the substitutions 14:04:57
16 between 5 to 10 were included in the analysis by 14:05:00
17 the time I provided the spreadsheet to counsel. 14:05:05
18 Q When you say that -- you said the time 14:05:09
19 that was allowed to me. What do you mean by that? 14:05:28
20 A Well, at some point, I completed the 14:05:32
21 analysis down to 10 percent, and I looked at the 14:05:35
22 distribution of the substitutions, namely the heat 14:05:39

1 map, which I generated at times, and I wasn't 14:05:42
2 entirely satisfied with what I was seeing, thought 14:05:48
3 that I should perhaps include additional 14:05:55
4 substitutions, and went on to analyze more 14:05:59
5 substitutions, this time down to 5 percent. 14:06:07
6 And those residues ended up taking longer 14:06:10
7 than expected, actually. I think those residues
8 that fell between 5 to 10 percent were, in fact, 14:06:17
9 more challenging than the ones that had a 14:06:20
10 frequency above 10 percent, which were in ways, 14:06:23
11 more straightforward. 14:06:28
12 So I was going over the substitutions 14:06:30
13 within the range of 5 to 10 percent. It was 14:06:35
14 taking a while, and it was time for me to consult 14:06:38
15 with the lawyers. And by that time, I had not 14:06:46
16 completed all the evaluations. So there were some 14:06:51
17 positions -- positions and substitutions that 14:06:54
18 weren't included in that study. 14:06:57
19 Q Okay. So you didn't -- you didn't have 14:07:01
20 time to actually go through and look at all of the 14:07:03
21 substitutions that appear between 5 to 10 percent 14:07:07
22 of the time; is that right? 14:07:10

1 ATTORNEY KUSHAN: Objection. 14:07:11
2 Objection to foundation. 14:07:11
3 A That's what ended up happening. 14:07:13
4 Q Okay. There are some notes on the 14:07:16
5 spreadsheet where you say, for example, like: 14:09:02
6 Loss, crowded. 14:09:04
7 What do you mean by crowded? 14:09:05
8 ATTORNEY KUSHAN: Sorry. Could you direct 14:09:08
9 us to which -- where you're talking about? 14:09:11
10 THE WITNESS: Do you want to -- perhaps 14:09:15
11 you could point me to any specific example that I 14:09:16
12 can look at? 14:09:20
13 ATTORNEY MARTIN: Please don't coach your 14:09:20
14 witness -- 14:09:23
15 ATTORNEY KUSHAN: I'm not. I'm sorry. I 14:09:24
16 was asking you just to get oriented. 14:09:25
17 ATTORNEY MARTIN: Well, I wasn't asking 14:09:27
18 about a specific one. 14:09:27
19 BY ATTORNEY MARTIN:
20 Q I was asking what the word crowded means 14:09:28
21 when you write in your notes. 14:09:32
22 A Okay. If you -- generally speaking, loss, 14:09:32

1 crowded, refers to trying to put in a large 14:09:34
2 residue in a space that is not designed for that. 14:09:37
3 It results in overpacking, which is one of the 14:09:40
4 worst way of designing a substitution, because 14:09:44
5 that then results in repulsion, that can very 14:09:48
6 rapidly increase the energetics. 14:09:59
7 Q When you say increase the energetics, does 14:10:03
8 that mean that it would make it less energetically 14:10:04
9 favorable, and that's potentially less stable? 14:10:10
10 A That is correct. Yes. 14:10:10
11 So in general, when there's crowding, that 14:10:12
12 would result in loss of stability. I would 14:10:14
13 even -- I would either give such substitution a 14:10:17
14 score of 1, or at least remark it as 2, with a 14:10:22
15 comment of loss and crowding to indicate that this 14:10:28
16 is due to overpacking. 14:10:32
17 Q Okay. So you use two different -- you use 14:10:34
18 the word crowding, and you use the word 14:10:42
19 overpacking, and I just want to understand if 14:10:45
20 those are two different things or if they're the 14:10:48
21 same thing. 14:10:51
22 A They are the same. If there is 14:10:52

1 overpacking, it ends up being crowded. 14:10:55
2 Q Okay. And what does overpacking mean? 14:10:58
3 A Overpacking is a word sometimes used to 14:11:01
4 describe a situation where you are trying to put 14:11:06
5 in too many atoms in a space that's not designed 14:11:11
6 for that. The situation that I described earlier, 14:11:17
7 trying to put in a large residue containing more 14:11:21
8 atoms into a space that's not meant for that. 14:11:26
9 Q So can you turn to position HYAL1 14:11:30
10 position 34? 14:11:52
11 A 34? 14:11:56
12 Q Yes. 14:11:59
13 A Okay. 14:12:06
14 Q So position 34 is -- in HYAL1 is tyrosine, 14:12:06
15 and position 16 in mature PH20 is tryptophan; is 14:12:11
16 that right? 14:12:20
17 A That is correct, yes. 14:12:20
18 Q And so at this position, you evaluated 14:12:21
19 three different substitutions? You evaluated 14:12:24
20 valine, alanine and threonine; is that right? 14:12:29
21 (Reporter clarification.) 14:12:36
22 A That is correct. 14:12:36

1 Q And you scored each of them a 1; is that 14:12:36
2 right? 14:12:40
3 A Yes. I scored each of the three mutations 14:12:40
4 as 1. 14:12:45
5 Q And for each of the mutations, you have a 14:12:46
6 note about a cavity that's created; is that right? 14:12:52
7 A Yes. I elude to cavity creation. 14:12:56
8 Q What do you mean when you say cavity 14:13:00
9 creation? 14:13:03
10 A That's a scenario that's opposite of 14:13:07
11 overpacking/crowding. When you substitute a large 14:13:11
12 buried residue that makes ample Van der 14:13:17
13 Waals/hydrophobic contacts with neighbors, and you 14:13:25
14 substitute it with a smaller residue, now you lose 14:13:29
15 a lot of the contacts, and as a result -- and at
16 the same time, create a cavity, empty space, in 14:13:34
17 the protein, which is known to be destabilizing. 14:13:37
18 Q Are cavities always considered 14:13:40
19 destabilizing? 14:13:46
20 A Almost always cavities are considered 14:13:47
21 destabilizing. Sometimes they can be filled with 14:13:51
22 a solvent molecule to neutralize some of the -- 14:13:54

1 the loss. But in general, cavities are 14:14:02
2 destabilizing. 14:14:05
3 Q And why is that? 14:14:06
4 A Two things. 14:14:08
5 One, direct Van der Waals contacts 14:14:09
6 are lost.
7 (Reporter clarification.) 14:14:23
8 A Contacts are lost, and that's 14:14:23
9 energetically unfavorable. 14:14:27
10 And second, buried residues are 14:14:30
11 hydrophobic, and now you have lost hydrophobic 14:14:35
12 contacts. So those two combined would contribute 14:14:39
13 to a loss of stability. 14:14:43
14 Q Okay. So the tryptophan that's in PH20 14:14:46
15 occurs only 14.77 percent of the time in the 14:15:01
16 multiple sequence alignment, correct? 14:15:06
17 A Yes. It seems to appear 14.77 percent. 14:15:08
18 Q And the most frequent residue at that 14:15:12
19 position is valine, which is 30.68 percent; is 14:15:13
20 that right? 14:15:18
21 A That is correct. Yes. 14:15:18
22 Q But you scored valine, which is the 14:15:19

1 residue that occurs most often at that position, 14:15:22
2 a 1; is that right? 14:15:26
3 A That is correct. 14:15:27
4 Q So if valine at that position was really 14:15:33
5 problematic, would you expect valine to occur 30 14:15:38
6 percent of the time at that position? 14:15:44
7 ATTORNEY KUSHAN: Objection. Foundation. 14:15:45
8 Also as to form. 14:15:49
9 A This is the danger of relying on the 14:15:50
10 frequency alone. It doesn't consider the
11 structural context. Valine may be the most common 14:15:53
12 because it may have another residue that it 14:15:55
13 interacts with to compensate for its smaller size. 14:15:59
14 Perhaps those two or three or more residues work 14:16:03
15 together to create a stable core. 14:16:08
16 In the case of PH20, that may all be 14:16:13
17 facilitated by a single residue, tryptophan. So 14:16:17
18 if you substitute that tryptophan with a smaller 14:16:21
19 residue, you're introducing that mutation in the 14:16:24
20 wrong context, thus resulting in a loss of 14:16:28
21 stability. 14:16:34
22 So you can't go by the frequency alone. 14:16:35

1 Although that's sometimes used, one really has to 14:16:37
2 look at the structural context to really 14:16:43
3 understand that. 14:16:45
4 Q Okay. So can we now look at HYAL1 14:16:45
5 position 30? 14:18:10
6 A Okay. 14:18:14
7 Q And so HYAL1 position 30 is an arginine, 14:18:15
8 and at that position in PH20, there's a valine; is 14:18:22
9 that right? 14:18:28
10 A That is correct. Yes. 14:18:28
11 Q And the most frequent residue at that 14:18:29
12 position is arginine with 36.36 percent; and then 14:18:36
13 after that comes lycine at 26.13 percent, right? 14:18:41
14 A That is correct. 14:18:47
15 Q And you considered both the arginine and 14:18:48
16 the lycine mutations, meaning that you considered 14:18:52
17 changing the valine in PH20 to either an arginine 14:18:56
18 or a lycine, and you scored them both as 2, 14:18:58
19 correct? 14:19:01
20 A That is correct. Yes. 14:19:03
21 Q And for both -- in the comments for both 14:19:05
22 of those changes, you put loss, loss of 14:19:09

1 hydrophobic contacts; is that right? 14:19:13
2 A Yes. Those are the comments. 14:19:17
3 Q So does that mean that you would consider 14:19:31
4 the arginine and the lycine substitutions to be 14:19:34
5 destabilizing at that position because you're 14:19:41
6 losing hydrophobic contacts, even though arginine 14:19:44
7 and lycine appear most often at that position? 14:19:49
8 A That is correct. Yes. Here we're looking 14:19:54
9 at a similar situation as in the earlier example, 14:19:58
10 where despite the higher frequency of occurrence, 14:20:02
11 some residues may not be the suitable amino acid 14:20:10
12 to put in that position because of its neighboring 14:20:13
13 amino acids. 14:20:18
14 Here, I don't know the details of it, but 14:20:19
15 based on my comment, it makes me think in the 14:20:21
16 neighborhood of this variant in PH20, there may be 14:20:27
17 an abundance of hydrophobic amino acids that may 14:20:31
18 not exist in HYAL1. Two proteins may have solved 14:20:36
19 that problem in different ways. 14:20:41
20 In the case of PH20, it does so by 14:20:44
21 clustering hydrophobic amino acids; whereas in 14:20:48
22 HYAL1, it approached it in a different way. If 14:20:51

1 you try to solve this particular problem by taking 14:20:54
2 parts of different solutions, then you don't get a 14:20:57
3 stable protein. You will destabilize the protein. 14:21:00
4 Q But at the end of the day, you still 14:21:06
5 scored both of those substitutions as a 2, which 14:21:09
6 would be tolerated; is that right? 14:21:13
7 A That is correct. This may not be apparent 14:21:15
8 from the sequence alone. However, in the 14:21:21
9 structure, I must have seen some conservation of 14:21:24
10 the interaction between valine and arginine that 14:21:29
11 warrants a higher score than 1. 14:21:33
12 For instance, arginine has carbons on 14:21:37
13 its -- in its side chain, just like valine does. 14:21:40
14 Its shape is different. Overall feature of the 14:21:45
15 amino acids is different. However, where it -- 14:21:50
16 the important contacts occur, those two residues 14:21:54
17 may conserve critical contacts. Therefore, 14:21:57
18 arginine may be tolerated to a degree, even though 14:22:01
19 it may not be the best solution, given that 14:22:06
20 position. 14:22:14
21 Q Okay. 14:22:14
22 ATTORNEY KUSHAN: The realtime on the 14:22:35

1 remote has stopped. 14:22:39
2 ATTORNEY MARTIN: Can we go off the 14:22:42
3 record? 14:22:43
4 ATTORNEY KUSHAN: Yes. 14:22:43
5 THE VIDEOGRAPHER: We are going off the 14:22:43
6 record. The time is 2:22 p.m. 14:22:45
7 (Recess from 2:22 p.m. until 2:24 p.m.) 14:22:46
8 THE VIDEOGRAPHER: We are going back on 14:24:26
9 the record. The time is 2:24 p.m. 14:24:27
10 BY ATTORNEY MARTIN: 14:24:30
11 Q Dr. Park, when you performed your analysis 14:24:40
12 on the conserved tab, you identified positions 14:24:42
13 that were known to be involved in the catalysis, 14:24:47
14 and then you also identified some positions that 14:24:52
15 were disclosed in the literature, for example, in 14:24:54
16 the Zhang paper and then in the Arming paper; is 14:25:01
17 that right? 14:25:04
18 ATTORNEY KUSHAN: Objection. Form. 14:25:04
19 A That's correct. I put some comments in, 14:25:05
20 although they're not comprehensive, as I mentioned 14:25:09
21 earlier. 14:25:12
22 Q So when you performed your analysis, did 14:25:13

1 you consider the mutagenesis data that was 14:25:15
2 disclosed in the literature regarding which 14:25:19
3 positions -- regarding the positions that were 14:25:22
4 known to be important for enzyme function? 14:25:27
5 A That was part of the intention. I wanted 14:25:33
6 to record some things that were disclosed in the 14:25:36
7 literature as a way of collecting all that 14:25:42
8 information at one place for easy reference. This 14:25:46
9 was especially important early on when I didn't 14:25:50
10 know much about the enzyme. I wanted to keep 14:25:54
11 track of what I was reading, so I started 14:25:57
12 recording some of it. But soon, it became not all 14:26:00
13 that relevant, so I stopped doing that. 14:26:04
14 Q Why do you say it became not that 14:26:08
15 relevant? 14:26:15
16 A Two things. One, this conserved tab is 14:26:15
17 only used to identify conserved/essential 14:26:21
18 positions, which we then quickly set aside as not 14:26:30
19 positions that we would explore any further. 14:26:37
20 And two, because by this time I had become 14:26:41
21 somewhat comfortable with the structure, I could 14:26:48
22 tell what was going on. I didn't have to consult 14:26:52

1 the literature all that much. So for those two 14:26:55
2 reasons, I became somewhat lax in terms of 14:26:59
3 note-taking. 14:27:04
4 Q Would you say that functional data 14:27:06
5 regarding a substitution, is that helpful in terms 14:27:11
6 of figuring out whether the substitution will be 14:27:16
7 tolerated? 14:27:20
8 ATTORNEY KUSHAN: Objection. Foundation. 14:27:22
9 A I'm not quite sure what you're asking. 14:27:24
10 ATTORNEY KUSHAN: Sorry. 14:27:28
11 THE WITNESS: Sorry. 14:27:29
12 ATTORNEY KUSHAN: You're asking, so this 14:27:30
13 last question was: Would you say that function 14:27:36
14 data regarding substitution is helpful in terms of 14:27:39
15 figuring whether the substitution will be 14:27:41
16 tolerated?
17 You're asking that generally? 14:27:43
18 ATTORNEY MARTIN: You're asking me a 14:27:48
19 question about my question? 14:27:50
20 ATTORNEY KUSHAN: I am. Because I'm 14:27:52
21 trying to figure out whether we're kind of 14:27:54
22 drifting outside the scope of the agreed-upon -- 14:27:54

1 ATTORNEY MARTIN: No. We're not. We're 14:27:56
2 talking about the spreadsheet. 14:27:58
3 ATTORNEY KUSHAN: Right. 14:28:01
4 ATTORNEY MARTIN: Right. 14:28:03
5 ATTORNEY KUSHAN: That's why -- 14:28:03
6 ATTORNEY MARTIN: Yeah.
7 ATTORNEY KUSHAN: -- I'm asking. So in 14:28:05
8 the context of the -- that's fine. 14:28:07
9 ATTORNEY MARTIN: In the context of the 14:28:08
10 analysis that Dr. Park performed. 14:28:10
11 ATTORNEY KUSHAN: All right. 14:28:12
12 ATTORNEY MARTIN: There's functional... 14:28:15
13 THE WITNESS: So if you wouldn't mind 14:28:15
14 repeating that question? 14:28:18
15 BY ATTORNEY MARTIN: 14:28:19
16 Q Okay. Is it -- so Dr. Park, in your 14:28:20
17 analysis, would it be helpful to know whether 14:28:23
18 there -- whether there is functional data showing 14:28:27
19 whether a particular mutation retained activity or 14:28:31
20 not? 14:28:38
21 A It depends on what mutations were studied. 14:28:41
22 If those mutations were on the conserved 14:28:47

1 positions here, they're interesting but not 14:28:53
2 directly relevant. If any of the non-essential 14:28:57
3 residues were mutated, I can use that to 14:29:00
4 crosscheck my findings, and hopefully they agree. 14:29:05
5 I don't recall whether I had such example. 14:29:10
6 I think most of the mutations done in the 14:29:13
7 literature were about conserved positions. So 14:29:20
8 again, those were interesting, helps me understand 14:29:24
9 the enzyme, but as far as this study is concerned, 14:29:28
10 they were indirectly relevant. 14:29:33
11 Q Okay. But if there were -- if there was 14:29:36
12 data for the residues that you considered in your 14:29:39
13 variant tab that showed whether those positions 14:29:43
14 retained functional activity, would that have been 14:29:48
15 helpful in your analysis in determining whether or 14:29:52
16 not -- in determining how you scored the potential 14:29:55
17 substitution? 14:29:58
18 ATTORNEY KUSHAN: Objection. Form. 14:29:59
19 A They would have given me confidence that I 14:30:04
20 was on the right track. For instance, here I'm 14:30:10
21 looking at HYAL position 35. It's valine, and
22 alanine in the case of PH20. I scored one, two, 14:30:15

1 three substitutions, each of which got a score 14:30:18
2 of 2, with some loss. 14:30:22
3 Now, if someone had done that particular 14:30:26
4 mutational study and observed that the mutant had, 14:30:29
5 say, 80 percent activity, I would say that's 14:30:33
6 great. That's exactly what I expected, and the 14:30:36
7 experimental study confirms it. So those studies 14:30:41
8 would have been very, very, useful. I don't think 14:30:46
9 there were many such studies though. 14:30:51
10 Q Okay. So if someone had done an 14:30:59
11 experimental study in which they tested for a 14:31:04
12 particular mutant that you evaluated, that would 14:31:08
13 have been -- that would have been very, very, 14:31:12
14 useful to your analysis; is that right? 14:31:13
15 ATTORNEY KUSHAN: Objection. Form. 14:31:16
16 Objection to foundation. 14:31:17
17 A I would have found it relevant and perhaps 14:31:18
18 useful, yes. 14:31:21
19 Q You said -- you used the term crosscheck 14:31:22
20 in one of your -- 14:31:28
21 A I'm sorry? 14:31:30
22 Q You used the term crosscheck. You said 14:31:30

1 you could crosscheck your analysis against the --
2 against functional data.
3 Can you just explain what you mean when 14:31:35
4 you say crosscheck? 14:31:38
5 A I'm just saying that confirmed my 14:31:38
6 evaluation. 14:31:41
7 Q Okay. 14:31:42
8 A That's what I meant. 14:31:42
9 Q Okay. And if you had functional data on 14:31:44
10 the various -- on some, strike that. 14:31:58
11 I'll start again. 14:32:01
12 If you had functional data for 14:32:01
13 substitutions that you considered in your 14:32:06
14 analysis, would you have been able to integrate 14:32:08
15 that data into your analysis to help -- to help, I 14:32:13
16 guess, iterate the framework that you were using 14:32:20
17 to score the various substitutions? 14:32:24
18 ATTORNEY KUSHAN: Objection. Form. 14:32:28
19 Objection. Foundation. 14:32:30
20 A It's hard to answer that question. 14:32:39
21 First of all, it doesn't have to be 14:32:44
22 particularly function. It could be stability. 14:32:46

1 The second, I wouldn't change my way of 14:32:51
2 analysis just because a single mutational study. 14:32:56
3 Hopefully it will confirm what I'm seeing. If it 14:33:00
4 disagrees with -- if the finding disagrees with 14:33:05
5 what I have predicted, I might think about it 14:33:10
6 somewhat. I might have concluded that perhaps 14:33:15
7 there are elements that are not included in the 14:33:19
8 analysis that was important there. 14:33:21
9 I wouldn't change my evaluation per se 14:33:24
10 because it's not clear to me how one would go 14:33:33
11 about changing it. The way I'm approaching it is 14:33:38
12 very standard. And for a person evaluating a 14:33:42
13 substitution, I don't think there's a lot of 14:33:47
14 leeway. There's not a whole lot of room in terms 14:33:51
15 of altering the approach as a result of some 14:33:58
16 mutational study input. 14:34:06
17 So again, it will be useful in the way of 14:34:10
18 confirming what I see. But if the result 14:34:16
19 disagrees with what I say or what I predict, I 14:34:19
20 don't think it would have resulted in much change. 14:34:26
21 Q Would it be helpful in terms of giving you 14:34:31
22 more confidence in your predictions, if it 14:34:37

1 confirmed your predictions? 14:34:41
2 A Absolutely, yes. Yes. If an experimental 14:34:43
3 finding confirms what I say, it would lend support 14:34:45
4 to my analysis. For sure. If it disagrees, it's 14:34:50
5 really hard to interpret that outcome. 14:34:57
6 Q And when you say it would be hard to 14:35:00
7 interpret that outcome, or you don't think it 14:35:31
8 would have resulted in much change if the result 14:35:34
9 disagreed with your analysis, is that because you 14:35:37
10 have a set -- a standard framework that you're 14:35:39
11 applying to each substitution and you don't know 14:35:42
12 how to change it based on functional data that 14:35:45
13 disagrees with your framework? 14:35:50
14 ATTORNEY KUSHAN: Objection. Foundation. 14:35:52
15 Objection to form. 14:35:53
16 A I think that would be the case. Yes. 14:35:57
17 It wouldn't be clear how the approach 14:36:01
18 would need to be changed in order to accommodate 14:36:06
19 those experimental findings. It's not like a 14:36:09
20 computational prediction where I can try a 14:36:16
21 different parameter or change the value of a 14:36:20
22 parameter and see if it fits better. That's not 14:36:22

1 how expert evaluation works. You look at it, take 14:36:28
2 all the factors into account and try to come up 14:36:32
3 with a prediction. 14:36:37
4 Now, if the prediction is not aligned with 14:36:40
5 an observation, clearly it suggests something. It 14:36:43
6 would not be very clear what it suggests, 14:36:51
7 unfortunately. But here, we're talking about a 14:36:55
8 hypothetical situation. I would need to know 14:37:05
9 exactly what data I'm dealing with in order to 14:37:08
10 give a more appropriate response. 14:37:12
11 Q What if you had data -- what if you had 14:37:14
12 data for every single position that you considered 14:37:18
13 in your analysis? Would that help you to refine 14:37:23
14 your framework? 14:37:26
15 ATTORNEY KUSHAN: Objection. Foundation. 14:37:27
16 A That also depends on what experimental 14:37:32
17 data we're talking about. Are we talking about 14:37:36
18 function, as you said earlier, or can it be 14:37:40
19 stability, thermal denaturation point, for 14:37:44
20 instance?
21 (Reporter clarification.)
22 A Or denaturation point, melting point? Or 14:37:52

1 is it the expression of the protein? 14:37:57
2 It could be any number of them, so I would 14:38:00
3 need to consider the experimental details to 14:38:04
4 provide any -- to give you any answer here. And 14:38:07
5 my response would depend on what that experimental 14:38:13
6 data exactly say. 14:38:19
7 Q So if you had data for every single 14:38:28
8 position that you considered in your analysis, 14:38:33
9 that potentially could help you to refine your 14:38:35
10 framework. It just depends on what type of data 14:38:38
11 it is that we're talking about? 14:38:41
12 A That would be one of the -- the 14:38:45
13 constraints. Hopefully it will be a consistent 14:38:46
14 study, that is one person did all the studies and 14:38:51
15 instead of 10 different groups doing 10 different 14:38:57
16 things, then we're in an even bigger mess. Now I 14:39:00
17 have to reconcile different experiments. 14:39:05
18 If the study is done in a very controlled 14:39:07
19 manner, looking at a parameter that is relevant, 14:39:11
20 in which case I think one can learn a lot from the 14:39:15
21 study. But it's only a very small set of 14:39:21
22 experiments that can be useful. Otherwise you 14:39:28

1 just end up with a lot of numbers, which are going 14:39:32
2 to be difficult to factor in. Again, interpreting 14:39:36
3 the data is going to be non-trivial. 14:39:41
4 Q So when you say a very small set of 14:39:52
5 experiments that can be useful, what small set of 14:39:55
6 experiments are you talking about? 14:40:09
7 A I think one set of experiments that can be 14:40:02
8 useful is, say, the stability measurement. If one 14:40:04
9 expressed every single mutant that's included in 14:40:07
10 this spreadsheet, expressed it, purified it, and 14:40:12
11 measured the melting temperature, and compared it 14:40:19
12 to wild-type, then we can try to correlate that 14:40:23
13 measurement with the prediction and see if they 14:40:28
14 are helpful. 14:40:34
15 I would say that that was the gist of the 14:40:36
16 study by Moult, which I cited in the declaration. 14:40:40
17 They did this kind of study using a set of 14:40:46
18 metrics similar to what I included in my 14:40:50
19 analysis -- looking at hydrophobicity, secondary 14:40:53
20 structure, and tertiary interaction -- and they 14:41:03
21 tried to interpret the consequences of various 14:41:06
22 single nucleotide polymorphism, which then 14:41:12

1 correlated with disease occurrences, and they 14:41:12
2 observed that 90 percent of the disease causing 14:41:17
3 mutations were due to loss of stability caused by 14:41:20
4 the mutation. So there's evidence that if you do 14:41:24
5 what I did here, you will be able to predict an 14:41:28
6 effect on the protein stability with high level of 14:41:41
7 confidence. 14:41:45
8 Q What if you have enzymatic activity data? 14:41:48
9 Is that -- is that helpful in determining -- is 14:41:55
10 that helpful in determining whether or not a 14:41:57
11 position is likely to be tolerated? 14:42:00
12 ATTORNEY KUSHAN: Objection. Foundation. 14:42:03
13 I'll also flag scope of the question. 14:42:11
14 (Reporter clarification.)
15 ATTORNEY KUSHAN: Foundation.
16 Objection to foundation, form, and also as
17 to the scope of this question. 14:42:17
18 A It's a related question, but not the same. 14:42:17
19 Q Uh-huh. 14:42:20
20 A Because you can create an unstable protein 14:42:21
21 and demonstrate that protein has exactly the same 14:42:26
22 enzymatic activity. In-vivo, however, it would 14:42:31

1 make a difference. Because a less stable protein 14:42:39
2 would not be around for very long in body. 14:42:42
3 Therefore, you would see a difference in what the 14:42:48
4 enzyme can do. 14:42:51
5 In the laboratory, it would get a biased 14:42:53
6 information, since you are ensuring that the 14:42:56
7 enzyme stays around and exhibit -- exhibits the 14:42:59
8 same level of activity, and that's not the same as 14:43:04
9 demonstrating that they are the same. So 14:43:08
10 functional study done under an artificial 14:43:11
11 situation can be misleading. 14:43:18
12 (Reporter clarification.) 14:43:27
13 Q But it's only -- strike that. 14:43:27
14 What if you don't care about stability? 14:43:29
15 What if you only care about enzyme function? 14:43:33
16 Then wouldn't the function -- functional 14:43:36
17 activity be helpful in determining whether or not 14:43:39
18 a mutation will be tolerated for the purposes of 14:43:42
19 function? 14:43:45
20 ATTORNEY KUSHAN: Objection. 14:43:45
21 I'm sorry.
22 Objection. Foundation. 14:43:47

1 Objection to form. 14:43:48
2 And also I'm going to object to this being 14:43:49
3 outside the scope of the agreed-upon scope of this 14:43:51
4 deposition. 14:43:55
5 A Okay. If you could repeat that question? 14:43:58
6 I can answer part of that question, but 14:44:01
7 there was a lot there. So perhaps you can repeat 14:44:08
8 that question? 14:44:10
9 Q If you don't care about the stability of 14:44:10
10 the protein, you only care about enzymatic 14:44:13
11 function, wouldn't functional activity, data on 14:44:17
12 functional activity, be helpful in determining 14:44:20
13 whether or not a mutation would be tolerated? 14:44:21
14 ATTORNEY KUSHAN: I'm going to object to 14:44:25
15 this question as being outside the scope of our 14:44:28
16 agreed-upon scope of this deposition. This is not 14:44:30
17 linked to the work he did. It's -- it's not. 14:44:31
18 ATTORNEY MARTIN: It's following off of 14:44:34
19 the question -- the answers that he has given. 14:44:37
20 ATTORNEY KUSHAN: No. That's another 14:44:39
21 hypothetical you presented, and it's -- it's not. 14:44:42
22 ATTORNEY MARTIN: Okay. Well, are you 14:44:43

1 going to instruct him not to answer? 14:44:44
2 ATTORNEY KUSHAN: I will -- yes. 14:44:45
3 ATTORNEY MARTIN: Are you going to --
4 ATTORNEY KUSHAN: I'm going to -- I'm 14:44:47
5 going to instruct you not to answer the last 14:44:48
6 question you were asked.
7 And if you want to present a question 14:44:50
8 that's linked to the work he did and the subject 14:44:51
9 of this deposition, go ahead. 14:44:54
10 ATTORNEY MARTIN: All right. 14:44:57
11 BY ATTORNEY MARTIN: 14:45:00
12 Q Okay. Dr. Park, when you -- are you 14:45:09
13 following your Counsel's instruction? 14:45:13
14 A Yes. I will. 14:45:16
15 Q Dr. Park, when you prepared your 14:45:17
16 spreadsheet and you were evaluating whether or not 14:45:21
17 a particular substitution was tolerated or not 14:45:23
18 tolerated, were you focused solely on protein 14:45:29
19 stability in making the determination as to 14:45:33
20 whether a mutation would be tolerated or not 14:45:36
21 tolerated? 14:45:42
22 A No. I considered both stability and 14:45:43

1 potential activity. If I see a residue that's 14:45:48
2 near the binding site, active site of the enzyme, 14:45:53
3 then I try to include that in the consideration as 14:45:59
4 much as possible. But if the position is away 14:46:05
5 from the active site, there wasn't much to 14:46:08
6 consider in terms of the function per se. 14:46:12
7 Therefore, the consideration came down to mostly 14:46:15
8 about the stability. 14:46:18
9 Q And so if you scored a protein as 1, does 14:46:20
10 that mean that you considered the mutation to 14:46:24
11 destroy the stability -- to destroy stability, 14:46:28
12 such that you would have an unstable protein? 14:46:34
13 ATTORNEY KUSHAN: Objection as to form. 14:46:37
14 A It could be that. If the position is 14:46:41
15 known to be far away from the active site, and if 14:46:47
16 I scored a given substitution a 1, then I must 14:46:51
17 have judged that substitution purely on stability. 14:47:02
18 Q So would you expect that -- strike that. 14:47:10
19 When you performed your analysis as 14:47:14
20 reflected in the spreadsheet, am I understanding 14:47:17
21 correctly that if a residue was far away from the 14:47:22
22 active site, you expected that changing that 14:47:25

1 residue would not impact activity of the protein? 14:47:28
2 ATTORNEY KUSHAN: Objection. Foundation. 14:47:31
3 Objection as to form. 14:47:33
4 A One can't really draw that conclusion. A 14:47:46
5 stability and activity are tightly coupled. I -- 14:47:50
6 I would expect a mutation, even if it's far away 14:47:59
7 from the active site, if it destabilizes the 14:48:04
8 protein sufficiently, it's going to lose activity. 14:48:09
9 Because it may result in deformation of the 14:48:13
10 active site through some long distance effect 14:48:19
11 that's maybe difficult to pinpoint, but it's not 14:48:24
12 unreasonable to think that some -- something like 14:48:28
13 that may happen. 14:48:30
14 Q Okay. So am I understanding correctly 14:48:35
15 that when you were determining whether a mutation 14:48:40
16 would be tolerated, if the position was far away 14:48:46
17 from the active site, you were focused on 14:48:52
18 stability. Because in that context, you would not 14:48:56
19 expect the position -- you would not expect the 14:49:00
20 substitution to directly involve the active site 14:49:03
21 or the catalytic reaction, and to the extent that 14:49:08
22 there was going to be impact on activity, it would 14:49:13

1 be because of a loss of stability? 14:49:16
2 ATTORNEY KUSHAN: Objection. Form. 14:49:18
3 Objection to foundation. 14:49:20
4 A Yes. That was the basis of my evaluation. 14:49:22
5 Q Okay. So if you have a residue that's 14:49:29
6 close to the active site and you're making a 14:49:34
7 substitution close to the active site, you 14:49:37
8 consider in your analysis whether that 14:49:41
9 substitution potentially could impact the active 14:49:44
10 site, and then also whether it potentially could 14:49:47
11 impact stability; is that right? 14:49:51
12 A That's correct. As you get closer to the 14:49:53
13 active site, the role of activity becomes more 14:49:56
14 pronounced. 14:50:00
15 Q Okay. And if you're far from the active 14:50:01
16 site, then is it fair to say that you would expect 14:50:04
17 that changes that do not impact stability of the 14:50:09
18 protein far -- and are far away from the active 14:50:13
19 site will not eliminate activity when you did your 14:50:16
20 analysis? 14:50:20
21 ATTORNEY KUSHAN: Objection. Form. 14:50:21
22 Objection to foundation. 14:50:23

1 A A substitution far away from the active 14:50:28
2 site that does not reduce the -- the stability of 14:50:33
3 the enzyme, would be considered tolerated, and 14:50:35
4 therefore would have been given a score of 2 or 3. 14:50:39
5 Q And you would expect -- and you expect 14:50:45
6 that -- sorry. Strike that. 14:50:48
7 As part of giving the residue a score of 2 14:50:51
8 and 3, you expect that the resulting protein will 14:51:08
9 still have enzymatic activity; is that right? 14:51:16
10 ATTORNEY KUSHAN: Objection. Form. 14:51:20
11 Objection as to foundation. 14:51:22
12 A That's correct. Yes. A mutation that's 14:51:25
13 given a score of 2 or 3 is expected to have 14:51:39
14 enzymatic activity. 14:51:36
15 ATTORNEY MARTIN: Okay. All right. 14:51:47
16 Can we go off the record? 14:51:48
17 ATTORNEY KUSHAN: Yes. 14:51:50
18 THE VIDEOGRAPHER: We are going off the 14:51:50
19 record. The time is 2:51 p.m. 14:51:52
20 (Recess from 2:51 p.m. until 3:07 p.m.) 14:51:55
21 THE VIDEOGRAPHER: We are going back on 15:07:26
22 the record. The time is 3:07 p.m. 15:07:28

1 BY ATTORNEY MARTIN: 15:07:32
2 Q Welcome back, Dr. Park. 15:07:33
3 A Thank you. 15:07:34
4 Q In scoring the -- in scoring the 15:07:37
5 substitutions that you considered as 1, 2 or 3, if 15:07:49
6 you had enzymatic functional data for each of the 15:07:56
7 substitutions that you considered, would that have 15:08:09
8 been helpful in your analysis? 15:08:10
9 ATTORNEY KUSHAN: Objection. Form. 15:08:12
10 A I would say that a chemical data like that 15:08:23
11 can be useful if they are done carefully enough to 15:08:28
12 tease apart the contributions to stability on the 15:08:42
13 one hand, and activity on the other. If those 15:08:45
14 effects can be teased out, they can be useful. 15:08:51
15 Other studies that are -- that only report 15:08:56
16 a change in activity can pose a challenge with 15:09:06
17 interpretation. So yes and no, depending on how 15:09:15
18 the study is done. 15:09:18
19 Q So why is it important to be able to tease 15:09:19
20 out contributions to stability and activity? 15:09:23
21 A Here, you are asking earlier if those 15:09:31
22 observations can be helpful in improving my 15:09:35

1 scoring methodology. It would help -- help to 15:09:39
2 know what aspects of my analysis is correct. 15:09:46
3 Q Oh. I see. 15:09:53
4 A That's why knowing what the contributions 15:09:55
5 are individually would be helpful. 15:09:58
6 Q Okay. And the scoring analysis that you 15:10:02
7 performed in the spreadsheet, that's an analysis 15:10:21
8 that -- that is the analysis that a POSA would 15:10:26
9 have done in the 2011/2012 time frame; is that 15:10:30
10 right? 15:10:35
11 A Yes. I believe so. 15:10:35
12 Q A protein that would not be stable 15:10:38
13 in-vivo? 15:11:06
14 A I'm sorry? 15:11:08
15 Q Strike that. Let me start again. 15:11:08
16 So when you performed your analysis in 15:11:11
17 your spreadsheet, did you consider the extent to 15:11:12
18 which the resulting protein would be stable 15:11:15
19 in-vivo? 15:11:18
20 ATTORNEY KUSHAN: Objection. Form. 15:11:19
21 A No. I did not. 15:11:23
22 Q I thought that you had testified before 15:11:44

1 the break about potential stability issues 15:11:47
2 in-vivo, and that was a potential issue with 15:11:53
3 in-vitro data. 15:11:59
4 Is that -- do you recall that testimony? 15:12:00
5 ATTORNEY KUSHAN: Objection. Foundation. 15:12:02
6 A Yes. 15:12:03
7 Q Was that -- did that answer, was that the 15:12:05
8 analysis that you were talking about? Did that 15:12:08
9 have anything to do with the analysis that you 15:12:11
10 performed in your spreadsheet? 15:12:14
11 ATTORNEY KUSHAN: Objection. Form and 15:12:15
12 foundation. 15:12:18
13 A No. My analysis was purely based on 15:12:18
14 biochemical stability and biochemical analysis. I 15:12:22
15 didn't consider in-vivo stability at all. 15:12:27
16 Q What's the difference between in-vivo 15:12:33
17 stability and biochemical stability? 15:12:39
18 A In-vivo stability includes half-life, for 15:12:41
19 instance, or potential for proteolytic degradation 15:12:52
20 by enzymes that may be there. 15:12:57
21 (Reporter clarification.) 15:13:02
22 A Other for an enzyme that may look very 15:13:02

1 similar in-vitro, may end up having very different 15:13:10
2 effect in-vivo. That is what's referred to as 15:13:17
3 in-vivo stability. 15:13:22
4 Q If a substitution -- strike that. 15:13:45
5 So for the substitutions that you scored 15:13:48
6 as 1, would you expect those substitutions to 15:13:53
7 result in a decrease in enzymatic activity, 15:13:56
8 because as a result of the decrease in biochemical 15:14:01
9 stability? 15:14:08
10 A I would expect so. An enzyme that is less 15:14:11
11 stable may unfold over time to a greater extent 15:14:17
12 than a more stable enzyme. Therefore, it would 15:14:22
13 lose activity, even though they may look the same 15:14:31
14 at the start. 15:14:35
15 Q And you've talked about stability testing 15:14:38
16 data. Would that be melting point testing data? 15:14:46
17 ATTORNEY KUSHAN: Objection. Foundation. 15:14:51
18 A It could be a melting point measurement, 15:14:55
19 or it could be enzymatic activity upon exposure to 15:14:59
20 high temperature, for instance, which may say 15:15:06
21 something about the unfolding of the enzyme. 15:15:10
22 Q Can you explain that? 15:15:12

1 A If a protein is less stable and you 15:15:15
2 elevate the temperature, then a greater fraction 15:15:19
3 of that protein would unfold, and therefore lose 15:15:23
4 activity. So activity would be an indirect read 15:15:30
5 out of the unfolding of the protein. A more 15:15:33
6 direct read out may involve, say, circular 15:15:34
7 dichroism spectroscopy.
8 (Reporter clarification.) 15:15:58
9 A So that would be a more direct biophysical 15:15:58
10 measurement of the unfolding of the protein. 15:16:07
11 Those are harder to perform. Therefore, one may 15:16:09
12 resort to an easier, indirect read out based on 15:16:13
13 enzymatic activity. 15:16:19
14 Q Okay. So am I understanding correctly 15:16:22
15 that, all else being equal, if you have a less 15:16:24
16 stable protein and you heat it, then you're going 15:16:25
17 to see a reduction in activity because the protein 15:16:28
18 is less stable at the higher temperature? 15:16:31
19 ATTORNEY KUSHAN: Objection. Foundation. 15:16:35
20 A At a higher temperature, you would see an 15:16:36
21 acceleration of the unfolding, and whatever 15:16:41
22 happens at room temperature would have -- would 15:16:44

1 happen more frequently or at an accelerated rate, 15:16:47
2 so you can see it in a more reasonable time. A 15:16:51
3 less stable protein, even a stable protein would 15:16:56
4 unfold even at room temperature over time. One 15:16:59
5 may have to wait a very long time to observe that. 15:17:05
6 By elevating the temperature, you accelerate the 15:17:09
7 process, and any difference between two proteins 15:17:13
8 would manifest itself on a shorter time scale, so 15:17:17
9 you would be able to tell. 15:17:20
10 ATTORNEY MARTIN: Okay. I don't have 15:18:21
11 anything else. 15:18:22
12 ATTORNEY KUSHAN: Okay. Can we take a 15:18:23
13 five-minute break? 15:18:25
14 ATTORNEY MARTIN: Uh-huh. 15:18:26
15 THE VIDEOGRAPHER: We are going off the 15:18:27
16 record. The time is 3:18 p.m. 15:18:28
17 (Recess from 3:18 p.m. until 3:25 p.m.) 15:18:32
18 THE VIDEOGRAPHER: We are going back on 15:25:43
19 the record. The time is 3:25 p.m. 15:25:45
20 ATTORNEY KUSHAN: We have no questions. 15:25:50
21 ATTORNEY MARTIN: Okay. Yeah. So I've 15:25:51
22 sent you guys the PDF of the spreadsheet that 15:25:52

1 we'll use as the exhibit to the deposition, 15:25:56
2 assuming that you're okay with it. Please -- 15:25:59
3 please let us know, once you -- once you actually 15:26:03
4 get it. 15:26:05
5 ATTORNEY KUSHAN: Once we get it. Yeah. 15:26:06
6 ATTORNEY MARTIN: And then we also -- so 15:26:09
7 based on the witness's -- based on Dr. Park's 15:26:12
8 testimony, it seems like Dr. Hecht may have had 15:26:19
9 access to the spreadsheet, or a part of the 15:26:20
10 spreadsheet, something along those lines, based on 15:26:23
11 their discussions.
12 And so if it's -- and we note that there 15:26:27
13 was no spreadsheet included as any exhibit or 15:26:28
14 appendix to Dr. Hecht's declaration, so in the 15:26:31
15 interest of avoiding an argument at Dr. Hecht's 15:26:35
16 deposition, if Dr. Hecht relied on the spreadsheet 15:26:41
17 or a part of the spreadsheet or whatever, please 15:26:45
18 send us whatever version of the spreadsheet it is 15:26:47
19 that Dr. Hecht has, so that we can review it and 15:26:50
20 ask him about it, as opposed to having to do this
21 exercise again. 15:26:58
22 ATTORNEY KUSHAN: Well, we'll circle back 15:26:58

1 with you on that question. 15:27:00
2 ATTORNEY MARTIN: Yeah. 15:27:02
3 ATTORNEY KUSHAN: All right.
4 ATTORNEY MARTIN: And also just to make
5 sure -- dotting all of the I's, crossing all the
6 T's -- if there's anything else that Dr. Hecht 15:27:03
7 relied on that wasn't in the materials that were 15:27:05
8 provided, please -- asking now, please send them 15:27:09
9 before the deposition. 15:27:13
10 ATTORNEY KUSHAN: All right. 15:27:15
11 ATTORNEY MARTIN: Okay.
12 ATTORNEY KUSHAN: We can go off the 15:27:16
13 record. 15:27:17
14 ATTORNEY MARTIN: All right. 15:27:18
15 THE VIDEOGRAPHER: This mark the end of 15:27:25
16 the deposition of Dr. Sheldon Park. 15:27:29
17 We are going off the record at 3:27 p.m.
18 (The videotaped deposition of DR. SHELDON
19 PARK was adjourned at 3:27 p.m.)
20 (Park Deposition Exhibit 2070 marked for
21 identification and attached to the transcript.)
22

CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

I, Kadi A. Harmon, Certified Reporter and Notary Public within and for the State of New York do hereby certify:

That Dr. Sheldon Park, the witness whose deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition and that such deposition was taken before me and is a true record of the testimony given by such witness.

I further certify that the adverse party, Merck Sharp & Dohme, was represented by counsel at the deposition.

I further certify that the deposition of Dr. Sheldon Park, occurred at the offices of the Hyatt Regency Buffalo on Thursday, the 21st day of August, 2025, commencing at 10:38 a.m. to 3:27 p.m.

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 25th 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

A

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