

Transcript of Garnett H. Kelsoe, Ph.D.

Date: February 5, 2026
Case: Merck Sharp & Dohme LLC -v- Halozyme Inc. (PTAB)

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Halozyme EX2302
Merck v. Halozyme
PGR2025-00006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,
v.
HALOZYME INC.,
Patent Owner.

Case Nos. PGR2025-00003; 00004; 00006; 00009

U.S. Patent Nos. 11,952,600; 12,018,298; 12,152,262; 12,123,035

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ZOOM VIDEO DEPOSITION

Taken on behalf of the Patent Owner Halozyme Inc.

GARNETT H. KELSOE, Ph.D.

Chapel Hill, North Carolina

February 5, 2026

9:09 a.m.

Job No.: 619072

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I N D E X

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PAGE

GARNETT H. KELSOE, Ph.D.

Examination By Mr. Powers 7

E X H I B I T S

NUMBER	DESCRIPTION	PAGE
Exhibit 2215	MF59 Adjuvant enhances lDiversity and Affinity of Mediated Immune Response to Pandemic Influenza Vaccines	85

P R E V I O U S L Y M A R K E D E X H I B I T S

NUMBER	PAGE
Exhibit 1001	38
Exhibit 1170	63
Exhibit 2114	113
Exhibit 2116	109

P R O C E E D I N G S

CONCIERGE HARRISON: Thank you to everyone for attending this proceeding remotely, which we anticipate will run smoothly. 09:07:56 09:08:02 09:08:04 09:08:07

Please remember to speak slowly and do your best not to talk over one another. Please be aware that we are recording this proceeding for backup purposes. Any off-the-record discussions should be had away from the computer. Please remember to mute your mic for those conversations. 09:08:09 09:08:11 09:08:13 09:08:13 09:08:14 09:08:16 09:08:19

Please have your video enabled to help the reporter identify who's speaking. If you are unable to connect with video and are connecting via phone, please identify yourself each time before speaking. 09:08:20 09:08:23 09:08:23 09:08:25 09:08:28

I apologize in advance for any technical-related interruptions. 09:08:28 09:08:31

Thank you. 09:08:37

THE VIDEOGRAPHER: Stand by for video read-on. 09:08:38 09:08:38

Here begins Media Number 1 in the videotaped deposition of Dr. Garnett Kelsoe in the matter of Merck Sharp & Dohme, LLC vs. Halozyme, Inc., in the United States Patent and Trademark Office for the Patent Trial and Appeal Board. Case Number PGR2025-00003, 00004, 00006, 00009. 09:08:38 09:08:45 09:08:49 09:08:55 09:08:57 09:08:59 09:09:04

Today's date is February 5, 2026. The time on the video monitor is 9:09 a.m. The remote videographer today is Richard Kuritz representing Planet Depos. 09:09:15 09:09:19 09:09:23 09:09:29

Would counsel please voice identify themselves and state whom they represent. 09:09:31 09:09:34

MR. POWERS: Sure. I'm Ralph Powers, III, from Sterne, Kessler, Goldstein & Fox, on behalf of patent owner Halozyme. With me in the room is Tyler Liu, also with Sterne Kessler, and Nancy Zhang from Quinn Emanuel. Joining us on the line today, Eldora Ellison from Sterne Kessler, Aubrey Haddach and Josh Mack from Halozyme. 09:09:37 09:09:39 09:09:39 09:09:43 09:09:43 09:09:48 09:09:51 09:09:54

MS. WANG: And this is Sue Wang from 09:09:56

the law firm of Sidley Austin, here on behalf of petitioner, Merck Sharp & Dohme, LLC. With me today are Chelsea Himes and Amit Bhatla, both also from the Sidley Austin law firm. Also here for the witness, Dr. Garnett Kelsoe. 09:09:58 09:10:00 09:10:03 09:10:06 09:10:09 09:10:11

THE VIDEOGRAPHER: The court reporter today is Audra Smith representing Planet Depos. 09:10:15 09:10:16 09:10:17

GARNETT H. KELSOE, Ph.D., 09:10:18

having declared under penalty of perjury to tell the truth, the whole truth and nothing but the truth, was examined and testified as follows: 09:10:18 09:10:18 09:10:18

EXAMINATION 09:10:18

BY MR. POWERS: 09:10:31

Q Good morning, Dr. Kelsoe. 09:10:31

A Good morning. 09:10:37

I'm actually -- I'm terribly sorry. I was told to instruct the following: That there were errors in the declaration. 09:10:37 09:10:39 09:10:43

Q Okay. 09:10:52

A And -- 09:10:53

Q So you have some documents prepared in front of you? 09:10:54 09:10:55

A Yes. 09:10:58

Q Is that right? 09:10:58

A Yep. 09:10:58

Q Okay. So let's talk about what those are. So I see you have a binder in front of you? 09:10:58 09:11:00

A Yes, this is my declaration. 09:11:02

Q Okay. I see several documents in that binder. Can you tell me what those are, please? 09:11:03 09:11:05

A Yes. It's the declaration and the patent. 09:11:07 09:11:12

Q When you say "declaration," there -- 09:11:13

A Kelsoe Declaration. 09:11:18

(Overlapping speakers.) 09:11:18

Q -- there are four declarations involved in today's proceedings? 09:11:18 09:11:21

A Yes. 09:11:22

Q And we're going to go over ground rules, but one of the things we have to be mindful of today is to not talk over each other just so that there's a clear record. 09:11:22 09:11:24 09:11:26 09:11:28

A Very good. 09:11:30

Q So let me try that question again 09:11:31

because I think we were talking over each other a 09:11:32

little bit. 09:11:34

A May I ask one favor of you? I'm 09:11:34

terribly sorry. I'm hard of hearing. If you 09:11:38

could speak up, it would be helpful. 09:11:40

Q Yes, sir, I will do that. 09:11:42

A Thank you. 09:11:43

Q If you have trouble understanding my 09:11:43

question for any reason throughout today, feel 09:11:45

free to ask me to repeat it. 09:11:47

A Yes. 09:11:49

Q Okay. So I see that there are some 09:11:49

documents in front of you. You said, I think, 09:11:50

there are some declarations in front of you. What 09:11:57

are those declarations? 09:11:59

A These are my declarations in response 09:12:01

to the patent claims, what I understand to be the 09:12:04

several patents that have been made by Halozyme. 09:12:09

Q Are those the four declarations that 09:12:15

you submitted in relation to the four PGR 09:12:16

proceedings we're here to talk about today? 09:12:20

A Yes, sir, they are. 09:12:22

Q Okay. And so I think we have the 09:12:25

exhibit numbers for those. And if you look at the 09:12:27

bottom right corner of each of those documents, 09:12:29

maybe you could say what the exhibit numbers are 09:12:32

there in front of you. 09:12:34

A The Exhibit 1134. 09:12:36

Q What case is that for? 09:12:42

A I'm terribly sorry? 09:12:43

Q No problem. What PGR number is that 09:12:45

for? 09:12:47

A I don't know what a PGR number is, I'm 09:12:48

sorry. 09:12:50

Q Do you know what a PGR is? 09:12:50

A No. 09:12:52

Q Okay. 09:12:52

A I'm an immunologist. 09:12:52

Q No problem. If you look at the face 09:12:55

page of that document, the one that you just are 09:12:57

on. 09:12:59

A Yes. Ah, yes. 09:13:03

Q Should have a PGR number on it. 09:13:03
A I beg your pardon. Yes. 09:13:05
Q No problem. We'll get through it. 09:13:07
What PGR number is there? 09:13:08
A This is PGR2025-00003. 09:13:08
Q Okay. And what exhibit number is that? 09:13:14
A The exhibit number is 1134. 09:13:16
Q And that's your declaration? 09:13:20
A This is my declaration. 09:13:21
Q Okay. If you go to the signature page of that declaration. 09:13:22
A Yes. 09:13:43
Q Is that your signature on that page? 09:13:44
A That is my signature. 09:13:45
Q Did you sign that document? 09:13:46
A I did. 09:13:47
Q Okay. And what's the date on that? 09:13:48
A 20 January 2026. 09:13:51
Q Okay. Is that when you put in this declaration? 09:13:53
A Yes. 09:13:55
Q Signed this declaration? 09:13:55

Okay. And now we've got the first one down. There's some others, right? 09:13:57 09:13:59

A That is correct. 09:14:01

Q All right. Let's do the same thing for each of the others. 09:14:02 09:14:03

A Yes. Second is case number PGR2025-00004. Again, Exhibit 1134. 09:14:06 09:14:08

Q Okay. And your signature page? 09:14:23

A Signed by me on January 20, 2026. 09:14:37

Q Okay. Very good. Let's move to the next one. 09:14:39 09:14:42

A PGR2025-00006, Exhibit 1134. My signature of 20, 2026, January 2026. 09:14:49 09:15:09

Q Okay. And the next one? 09:15:13

A PGR number PGR2025-00009, Exhibit 1134. And pardon me, my signature of 20 January 2026. 09:15:15 09:15:44

Q Are there any other documents -- so we've gone through the four declarations that you submitted in association with each of these PGRs we're here to talk about today. Are there any other documents in front of you that you brought into the room? 09:15:51 09:15:53 09:15:55 09:15:58 09:16:00 09:16:02

A I have a list of errata, an errata list. 09:16:07 09:16:10

Q Okay. Is that the list that counsel presented me? 09:16:10 09:16:12

A Yes. 09:16:18

Q Okay. And let's talk about what that errata list contains. 09:16:18 09:16:21

A It is an exchange of exhibit numbers in the paragraph 125, Exhibit 1194, was listed to a paper, Chowpongpang, et al., 2004, and that is now numbered Exhibit 1150, referring to exactly the same reference. 09:16:25 09:16:33 09:16:39 09:16:44 09:16:49

Q So is it true that the reference was labeled Exhibit 1194 but it should have been 1150? 09:16:50 09:16:53

A That is correct. 09:16:58

Q Okay. Who discovered that error? 09:17:00

A The Merck Sharp Dohme counsel did. 09:17:08

Q Okay. And when did Merck Sharp Dohme counsel alert you to the error? 09:17:11 09:17:12

A I was told this yesterday. 09:17:16

Q Okay. Any other errors that you found in your declaration? 09:17:19 09:17:21

A It's the second error in Appendix A, which is the same renumbering of Chowpongpang, et al. 09:17:26 09:17:30 09:17:35

Q Right. So this transposition of the exhibit number was in two places; is that right? 09:17:35 09:17:38

A That is correct. 09:17:40

Q Any other errors that you found in your declarations? 09:17:40 09:17:42

A None to my knowledge. 09:17:42

Q Did you review declarations in preparation for today's meeting? 09:17:44 09:17:46

A I certainly did. 09:17:48

Q Okay. Have you ever been deposed before? 09:17:48 09:17:52

A Yes. 09:17:52

Q When was that? 09:17:53

A The most recent was several years ago, five or seven years ago. 09:17:56 09:17:58

Q Any other times? 09:18:01

A I've been deposed twice. 09:18:03

Q Were those related to patent cases? 09:18:06

A Yes, they were. 09:18:09

Q What was the name of the first case you were deposed in? 09:18:10 09:18:12

A The first -- I don't remember the name of the first case. The first case I was a consultant for a firm called Fish & Neave, and it had to do with a dispute between a particular molecule that might have had therapeutic benefit, CD154, a costimulatory molecule. 09:18:13 09:18:14 09:18:20 09:18:25 09:18:29 09:18:34

Q Do you remember if you were on the side of the patent owner or the patent challenger? 09:18:39 09:18:41

A I don't remember. 09:18:44

Q And do you remember the name of the litigants in that case? 09:18:46 09:18:57

A I don't -- my recollection is the litigants were two large biotech firms. I actually -- my area of expertise was the two individual research groups. One identified the human form of CD154 and the other the mouse form of CD154. 09:19:06 09:19:09 09:19:12 09:19:18 09:19:22 09:19:25

So the dispute was between the -- who -- my understanding was, if you knew one, did you know both. That was -- I don't know how else 09:19:27 09:19:32 09:19:36

to say it, but that was sort of what -- yeah. 09:19:39

Q Do you remember the gist of your 09:19:43

opinion in that case? 09:19:44

A My opinion was that there were 09:19:46

significant differences between the two 09:19:52

species-specific CD154s, and knowledge of one did 09:19:53

not guarantee knowledge of the other. 09:19:57

Q Was that called a "patent interference 09:20:00

proceeding"? 09:20:05

A I have no idea. 09:20:07

Q Do you remember if it was a District 09:20:08

Court proceeding? 09:20:09

A No. I was deposed, and later I 09:20:16

accompanied the lawyers from Fish & Neave to the 09:20:21

International Patent Office in Munich, and -- but 09:20:25

I wasn't called to speak there, so I don't have -- 09:20:28

I don't really know. 09:20:31

Q Was that a case proceeding in the 09:20:32

United States, or was that a case proceeding 09:20:34

abroad? 09:20:36

A My understanding is the original 09:20:37

deposition had to do with United States, and then 09:20:40

the later deposition had to do with international patent. I don't really know. 09:20:43 09:20:47

Q You're -- sorry. Were you finished? 09:20:50

A Yes. 09:20:53

Q Okay. Were you deposed only once as part of that case? 09:20:53 09:20:57

A That is correct. 09:20:58

Q Did you ever testify at trial as part of that case? 09:20:59 09:21:01

A I've never testified at trial. 09:21:02

Q Okay. And you said you'd been deposed twice before, right? 09:21:04 09:21:06

A Yes. 09:21:07

Q So that was the first time. 09:21:07

A Yes. 09:21:08

Q What was the second? What was the second time or the other time? 09:21:08 09:21:09

A The second time was -- I was contacted by lawyers from Morrison Foerster and was -- and I actually don't remember the -- I don't remember the case very well. It was. It had to do with a protein of potential therapeutic utility, but I 09:21:11 09:21:21 09:21:29 09:21:35 09:21:49

think there was a question of whether or not how the protein was discovered was somehow relevant to this, but I just don't remember my testimony. 09:21:53 09:21:57 09:22:02

Q Okay. And when was that time? When was that? 09:22:04 09:22:07

A That was the most recent, and that was five, seven, eight years ago. 09:22:07 09:22:09

Q Okay. Somewhere between five and eight? 09:22:12 09:22:14

A Actually, here at Duke. 09:22:14

Q Here in this hotel? 09:22:17

A Yes. 09:22:18

Q I see. 09:22:18

Did you testify at trial as part of that case? 09:22:19 09:22:23

A No, I did not. 09:22:24

Q So you've been deposed twice before but never testified at trial, right? 09:22:25 09:22:28

A That is correct. 09:22:30

Q Okay. So you've done this before, but I'll go over some ground rules with you. So I'll ask questions. Your counsel may object, but you 09:22:30 09:22:33 09:22:36

need to answer my question unless the instruction is not to answer the question. Is that clear? 09:22:42 09:22:44

A That is clear. 09:22:46

Q All right. And as we alluded to earlier, as you can see, this is all being taken down by a court reporter, so it's important we don't talk over each other. So I'll do my best not to interrupt you, and I ask that you not interrupt me. Is that fair? 09:22:47 09:22:50 09:22:54 09:22:56 09:22:59 09:23:01

A Yes. 09:23:03

Q Okay. If at any point you need a break today, just let me know. I'll be happy to take a break. I might just try to finish up a few more questions, and I also ask that if I have a question pending, you answer that before we take a break. Is that fair? 09:23:04 09:23:08 09:23:11 09:23:14 09:23:16 09:23:18

A Yes. 09:23:20

Q Okay. Great. 09:23:20

Any reason you can't give truthful testimony today? 09:23:20 09:23:24

A No. 09:23:25

Q Besides the documents that we went over 09:23:28

previously, is there anything else that you brought to the deposition today? 09:23:30 09:23:32

A I have only this in my possession. 09:23:39

Q The four declarations? 09:23:41

A The four declarations, yes. 09:23:42

Q And the errata sheet? 09:23:42

A Yes, yes. 09:23:44

Q No other papers are in front of you? 09:23:44

A No, sir. 09:23:47

Q Okay. What did you do to prepare for today's deposition? 09:23:47 09:23:49

A I reviewed my declaration and I was -- I met with the Merck Sharp & Dohme attorneys yesterday, and they helped me prepare for this. 09:23:54 09:24:01 09:24:05

Q Okay. About how long did you meet with counsel? 09:24:10 09:24:12

A Yesterday? 09:24:14

Q Yes, sir. 09:24:15

A 9:00 until 5:00. 09:24:15

Q Okay. Did you meet with counsel in preparation for today's deposition prior to that -- prior to yesterday's meeting? 09:24:18 09:24:20 09:24:22

A We've had Zoom meetings from time to time over the last several months. 09:24:25 09:24:28

Q In preparation for today's deposition, did you meet with counsel -- 09:24:32 09:24:34

A Oh. 09:24:36

Q -- other than yesterday? 09:24:36

A No. 09:24:38

Q Okay. About how long did you spend reading your declarations in preparation for today's deposition? 09:24:38 09:24:41 09:24:43

A The two times -- I've read the declaration twice, one prior to the signatures to -- and corrections there. The declaration's approximately 100 pages long. It takes me about three and a half hours to read that carefully. And so three and a half hours previously and three and a half hours yesterday. 09:24:47 09:24:51 09:24:55 09:24:59 09:25:02 09:25:05 09:25:08

Q As part of your preparation for today's deposition, did you look at any other documents beyond your declaration? 09:25:14 09:25:16 09:25:19

A I have refreshed my memory of the papers that I cite and the declaration as evidence 09:25:24 09:25:28

for my opinion. 09:25:31

Q Any documents that you didn't cite in your declaration that you reviewed as part of your preparation for today's deposition? 09:25:36 09:25:38 09:25:40

A No. 09:25:44

Q Now, there are four declarations that we're going to be talking about today, and is it fair to say that those are highly similar declarations? 09:25:44 09:25:46 09:25:49 09:25:53

A I would say they're highly similar, yes, sir. 09:25:53 09:25:55

Q And if there are any differences in any of the declarations that would affect any answer to a question today, will you let me know? 09:25:55 09:25:57 09:26:00

A I shall. 09:26:02

Q Otherwise, is it fair that we consider the questions answered for all four of the declarations? 09:26:03 09:26:05 09:26:08

A That is correct. 09:26:08

Q Okay. Did you talk to anyone besides counsel regarding the substance of your deposition today? 09:26:14 09:26:16 09:26:18

A I did not. 09:26:18

Q Do you intend to offer any new opinions today that are not contained in your declarations? 09:26:36 09:26:39

A No. 09:26:41

Q And if I refer to "this case" in any of my questions today, you'll understand me to mean collectively the four PGR proceedings we're here to talk about. Is that fair? 09:26:42 09:26:47 09:26:50 09:26:53

A I so understand. 09:26:55

Q Okay. When were you first approached to provide a declaration in this case? 09:27:01 09:27:03

A It was sometime in October of 2025. 09:27:08

Q Okay. And who approached you? 09:27:11

A Ms. Wang and Jeff Kushan. 09:27:14

Q Kushan. 09:27:22

A Kushan, thank you. 09:27:23

Q And when did you start working on your declarations in this case? 09:27:25 09:27:28

A The process for making my declaration was to review -- I was told to review the portions of the -- I guess the patent claim -- I don't know the appropriate term -- that dealt with 09:27:34 09:27:36 09:27:44 09:27:46

immunocontraceptives and to read the declarations of Dr. Moon and Dr. Sharer -- Cherr. And then that was the initial -- my initial, I guess, beginning of this. 09:27:58 09:28:01 09:28:06 09:28:12

Q Do you remember when that was? 09:28:13

A It would have been in mid-October. I don't remember exactly. 09:28:15 09:28:18

Q How long did you spend preparing your declaration? 09:28:19 09:28:23

A In toto? 09:28:24

Q Yes, sir. 09:28:26

A Oh, probably 60 or 70 hours. 09:28:27

Q And besides counsel, did you speak with anyone in order to create your declarations? 09:28:33 09:28:35

A No, I did not. 09:28:38

Q Did you speak with anyone at Merck? 09:28:39

A Oh. No, I did not. 09:28:41

Q Have you ever heard of Dr. Michael Hecht? 09:28:45 09:28:47

A Could you repeat the question? 09:28:49

Q Sure. 09:28:51

Have you ever heard of Dr. Michael 09:28:51

Hecht? 09:28:52

A I have not. Let me rephrase that. I never met or interacted with Dr. Hecht. I don't know who he is. 09:28:55 09:29:01 09:29:04

Q Have you ever heard of him? 09:29:06

A I can't recall. 09:29:08

Q Are you aware that he provided a declaration in this case? 09:29:11 09:29:12

A No. 09:29:14

Q Have you ever heard of Dr. Sheldon Park? 09:29:17 09:29:20

A No. 09:29:21

Q Are you aware that he provided a declaration in these cases? 09:29:21 09:29:23

A I am not. 09:29:25

Q Have you ever heard of Dr. James Naismith? 09:29:28 09:29:31

A I know the name. I don't -- I've never met Dr. Naismith. 09:29:35 09:29:37

Q How do you know the name? 09:29:38

A He's a distinguished structural biologist. 09:29:40 09:29:44

Q Are you aware that he provided a declaration in this case? 09:29:45 09:29:47

A No. 09:29:53

Q Did you speak with anyone at all besides counsel regarding your declaration in this case? 09:29:57 09:29:59 09:30:02

A No. 09:30:04

Q Have you ever interacted with Dr. Naismith? 09:30:09 09:30:11

A No. 09:30:12

Q You don't describe yourself professionally as a reproductive biologist, right? 09:30:23 09:30:25

A I am not. 09:30:29

Q You're not an expert in reproductive biology, correct? 09:30:30 09:30:32

A I'm not an expert in reproductive biology. 09:30:32 09:30:34

Q You have no expertise in ovarian function, right? 09:30:34 09:30:37

A I do not. 09:30:37

Q You have no expertise in ovulation, right? 09:30:38 09:30:41

A No. 09:30:41
Q No, you don't have expertise? 09:30:46
A No, I don't have expertise. 09:30:47
Q You don't have expertise in the female 09:30:49
reproductive tract, right? 09:30:51
A No, I do not. 09:30:53
Q You don't have expertise in female 09:30:55
reproductive hormones, correct? 09:30:57
A I do not. 09:31:00
Q You have no expertise in 09:31:00
spermatogenesis, correct? 09:31:01
A Beyond my master's thesis of 09:31:05
spermatogenesis in cestodes, no. 09:31:07
Q What is a cestode? 09:31:11
A Cestode's a tapeworm. 09:31:12
Q You have no expertise in 09:31:14
spermatogenesis in mammals, correct? 09:31:15
A I do not. 09:31:19
Q You have no expertise in sperm function 09:31:19
in mammals, correct? 09:31:20
A At what level do you mean "no 09:31:22
knowledge"? 09:31:23

Q Oh, I didn't say "no knowledge." I said "no expertise." 09:31:24 09:31:26

A No expertise. I do not have expertise. 09:31:28

Q And you're not an expert in male reproductive hormones, correct? 09:31:30 09:31:32

A I am not. 09:31:34

Q You're not an expert in mammalian sperm physiology, correct? 09:31:35 09:31:38

A I am not. 09:31:39

Q You're not an expert in acrosome biology, correct? 09:31:40 09:31:44

A I am not. 09:31:45

Q Before being retained in this case, had you heard of PH20? 09:31:46 09:31:47

A I have not. 09:31:50

Q So the first time you heard of PH20 was after you were retained in this case; is that correct? 09:31:51 09:31:53 09:31:55

A That is correct. 09:31:55

Q And that would have been sometime in October 2025, right? 09:31:56 09:31:57

A Yes. 09:31:59

Q The first time you heard of PH20 was in October of 2025, right? 09:32:00 09:32:02

A That is correct. 09:32:05

Q You're not an expert in mammalian fertilization, correct? 09:32:06 09:32:09

A No, I am not. 09:32:10

Q Do you understand that fertilization is a sequence of time-ordered biological events? 09:32:11 09:32:13

A In a general way, yes. 09:32:17

Q Is it your understanding that those events must occur in a specific order? 09:32:21 09:32:22

A In a general way, yes. 09:32:25

Q You're not an expert in those -- in the sequence of those molecular events required for mammalian fertilization, correct? 09:32:28 09:32:30 09:32:35

A I am not. 09:32:37

Q If you were interested in designing an immunocontraceptive, you would have to rely on a reproductive physiologist or reproductive biologist to understand the details of the science, right? 09:32:38 09:32:47 09:32:48 09:32:52 09:32:54

MS. WANG: Objection to form. 09:32:55

A Could you repeat the question? I want to make sure I understood it correctly. 09:32:57 09:32:59

BY MR. POWERS: 09:33:02

Q If you were interested in designing an immunocontraceptive, you would have to rely on a reproductive physiologist or reproductive biologist to understand the details of the science involved, right? 09:33:02 09:33:06 09:33:08 09:33:10 09:33:13

MS. WANG: Same objection. 09:33:16

A If I were -- I'm repeating because I'm trying to work my way through the question. I beg your pardon. 09:33:26 09:33:29 09:33:31

Yes. To determine -- to determine the target of the immunocontraceptive, I would certainly, since that lies outside of my field of expertise, I would rely on a reproductive biologist, yes. 09:33:31 09:33:40 09:33:41 09:33:43 09:33:49

BY MR. POWERS: 09:33:50

Q You don't describe yourself as an expert in fertility or infertility, correct? 09:33:50 09:33:52

A That is correct. 09:33:55

Q And you don't describe yourself as an 09:33:56

expert in contraception, correct? 09:33:57

A That is correct. 09:34:00

Q You've not authored a peer-reviewed paper about mammalian reproductive biology, correct? 09:34:01 09:34:04 09:34:04

A I have not. 09:34:07

Q You've not authored a review article on mammalian fertilization or sperm function, correct? 09:34:08 09:34:10 09:34:12

A I have not. 09:34:13

Q You've not conducted fertility studies in mammals, right? 09:34:14 09:34:16

A I have not. 09:34:17

Q You've not designed experiments to study sperm-egg interaction in mammals, correct? 09:34:19 09:34:21

A I have not. 09:34:25

Q Do you know what an acrosome reaction assay is? 09:34:26 09:34:29

A No. Not precisely. 09:34:30

Q So I bet it's fair to say you've never performed an acrosome reaction? 09:34:33 09:34:35

A It is fair to say that, yes. 09:34:38

Q Do you know what a sperm motility assay is? 09:34:40 09:34:42

A Only in general terms. 09:34:42

Q Have you ever -- 09:34:43

A Performed -- 09:34:44

Q Have you ever performed one? 09:34:44

A I have never performed a sperm motility assay. 09:34:46 09:34:48

Q Do you know what a sperm penetration assay is? 09:34:49 09:34:50

A I do not. 09:34:51

Q Have you ever performed one? 09:34:53

A I have not. 09:34:55

Q Do you know what a sperm capacitation assay is? 09:34:55 09:34:58

A I do not. 09:34:58

Q Have you ever performed one? 09:34:59

A I have not. 09:35:00

Q Do you know what a Huhner test is? 09:35:02

A I beg your pardon. Could you repeat, please? 09:35:05 09:35:07

Q Sure. A Huhner test? 09:35:08

A I do not. 09:35:09

Q Have you ever performed a Huhner test? 09:35:10

A I have not. 09:35:13

Q In any of the work that you've done as a scientist, have you ever measured fertilization outcomes? 09:35:23 09:35:25 09:35:27

A I have not. 09:35:28

Q You're not an expert in hyaluronidases, correct? 09:35:31 09:35:33

A I am not. 09:35:35

Q And you've never published a paper on PH20, right? 09:35:38 09:35:40

A I have never published a paper on PH20. 09:35:41

Q Let's look at your declaration. If we go to paragraph 8 of your declaration. You can use the one from the 003 case. 09:36:00 09:36:06 09:36:08

You say you relied on your "familiarity with scientific literature in my field and further reviewed a number of publications in developing my analysis." 09:36:17 09:36:19 09:36:23 09:36:27

What is your field that you referred to in that statement? 09:36:27 09:36:29

A I am an expert in antibody responses and antibody maturation. 09:36:30 09:36:34

Q You're an immunologist? 09:36:37

A I'm an immunologist. 09:36:38

Q In that statement we just read, you seem to imply that you relied on publications outside of your field. Is that fair? 09:36:40 09:36:41 09:36:43

MS. WANG: Objection to form. 09:36:45

A I relied on the publications describing the effects of PH20 vaccination in various species, yes, and that's literature I would not normally read. 09:36:47 09:36:51 09:36:56 09:36:59

BY MR. POWERS: 09:36:59

Q Because that literature is outside of your field; is that correct? 09:36:59 09:37:01

A That literature is outside my field. 09:37:02

Q In paragraph 9 of your declaration, you say: I have been asked by counsel to provide my opinions from the perspective of a person having ordinary skill in the art before December 30, 2011. I have also been asked -- 09:37:06 09:37:09 09:37:11 09:37:14 09:37:19

THE VIDEOGRAPHER: We lost you guys for 09:37:21

a second. I believe your guys' connection is unstable. 09:37:23 09:37:25

(Off-the-record discussion.) 09:38:01

THE VIDEOGRAPHER: We're back on the record. The time is 9:38 a.m. 11:46:27 09:38:05

BY MR. POWERS: 09:38:06

Q I'll repeat that question for you. 09:38:09

A Thank you. 09:38:11

Q Paragraph 9 of your declaration -- Exhibit 1134 -- you say: I have been asked by counsel to provide my opinions from the perspective of a person of having ordinary skill in the art before December 30, 2011. I have also been asked to consider that perspective as of December 28, 2012. 09:38:15 09:38:17 09:38:22 09:38:25 09:38:28 09:38:33 09:38:35

Do you see that? 09:38:37

A Yes. 09:38:38

Q And you provide two dates there, right? 09:38:40

A (Nonverbal response.) 09:38:43

Q Need a verbal answer. 09:38:45

A Oh, yes. I'm sorry. Yes. 09:38:46

Q Oh, that's one of the ground rules I 09:38:48

should have said. 09:38:50

A I beg your pardon. 09:38:51

Q This is being transcribed, so a verbal 09:38:52

answer is needed. 09:38:56

So you provide two dates there. Why 09:38:59

did you consider the perspective of a person of 09:39:01

ordinary skill in the arts before December 30, 09:39:03

2011? 09:39:07

A I was instructed by Merck Sharp & Dohme 09:39:08

counsel. 09:39:12

Q Do you know why that date might be 09:39:12

relevant? 09:39:16

A I don't. 09:39:16

Q What about December 28, 2012? 09:39:16

A Same answer. I was instructed, and I 09:39:18

don't have any relevant reason to understand why. 09:39:22

Q Okay. So you don't know why you 09:39:25

considered two different dates in forming the 09:39:30

opinions that you express in your declaration? 09:39:32

A I do not. 09:39:34

Q In your view, there was no development 09:39:39

between December 30, 2011, and December 28, 2012, 09:39:41

that alters any of your opinions, correct? 09:39:44

A Yes. That's my opinion, that there was 09:39:49

no -- that was there was no increase in knowledge 09:39:52

that would significantly alter my opinions. That 09:39:55

is correct. 09:39:58

Q There was no advance in the art that 09:39:58

you considered that might have changed any of your 09:40:02

opinions; is that right? 09:40:06

A In the art relevant to PH20 antibody 09:40:08

responses, no. 09:40:13

Q Do you have any experience using 09:40:15

techniques and tools to analyze protein structure? 09:40:17

A I have some limited expertise. 09:40:21

Q Have you ever done sequence searching 09:40:23

and sequence alignments at the protein level? 09:40:26

A Yes. 09:40:29

Q Have you ever used protein modeling 09:40:30

software? 09:40:33

A I have not. We use AlphaFold 3, but I 09:40:34

do that through a colleague who is an expert as a 09:40:38

bioengineer. 09:40:41

Q So you're not an expert in AlphaFold 3? 09:40:42

A In predicting, no, I am not. 09:40:46

Q Did you review -- you say, I believe, in your declaration that you reviewed the '600 patent; is that right? 09:41:10 09:41:13 09:41:16

A Yes. 09:41:17

Q You understand that modified PH20 polypeptides are recited in the claims of the '600 patent, right? 09:41:20 09:41:23 09:41:26

A That's my understanding. Yes, that's what I understood. 09:41:27 09:41:28

Q I'm going to hand you what's previously been marked Exhibit 1001. 09:41:37 09:41:38

(Previously marked Exhibit Number 1001 was identified.) 09:41:53 09:41:53

BY MR. POWERS: 09:41:53

Q Do you recognize this document, Doctor? 09:41:53

A Yes. 09:41:56

Q What is this document? 09:41:56

A This is one of the patents that I was told to inspect. 09:41:57 09:41:58

Q Which patent? Go to the second page, you might see a number. 09:42:00 09:42:04

A Yes. This is the 6 -- the so-called 11,952,600 patent. 09:42:06 09:42:14

Q We can call that the '600 patent today? Is that okay? 09:42:17 09:42:19

A That's fine. Thank you. 09:42:20

Q It's a lot easier to say. 09:42:20

And you reviewed the patent as part of your work in this case, right? 09:42:22 09:42:26

A I did. 09:42:28

Q Do you see that the patent has column numbers, if you look through the patent? 09:42:39 09:42:42

A I'm not an expert, but -- I don't actually. 09:42:49 09:42:55

Q If you look at the top of the pages in sort of the body of the patent -- 09:42:55 09:42:58

A Okay. 09:42:59

Q -- the column numbers. 09:42:59

It might be easier if we use page numbers. 09:43:02 09:43:04

A That would be helpful for a nonexpert. 09:43:05

Q Those are all in the document as well at the bottom right corner. If you go to 09:43:08 09:43:10

page 182. Actually, the very last page. 09:43:13

A Oh, this. 09:43:21

Q The end of the document. 09:43:21

A Oh, yes. 09:43:28

Q And did you previously review the claims of this patent? 09:43:29 09:43:31

A Only those claims related to the use of PH20 variants as an immunocontraceptive. 09:43:33 09:43:37

Q Did you review claim 1 of this patent? 09:43:40

A If that -- I don't remember what claim 1 is, but if I -- whatever claim I reviewed only dealt with the contraceptive function of the potential contraceptive function of PH20 immunogen. 09:43:46 09:43:47 09:43:52 09:43:57 09:44:00

Q Can you take your time and tell me which claim that is in the '600 patent? Which claim that you reviewed? 09:44:01 09:44:04 09:44:10

A What is this? 09:44:38

(Sotto voce reading.) 09:45:38

Q I'll withdraw the question. 09:45:41

A Yes. 09:45:43

Q So you told me that you reviewed the 09:45:43

'600 patent and you reviewed at least some of the claims. Is that fair? 09:45:46 09:45:48

A Yes. 09:45:49

MS. WANG: Objection to form. 09:45:50

BY MR. POWERS: 09:45:51

Q And I'd like you to review claim 1 of the '600 patent and tell me if claim 1 requires the modified PH20 polypeptides to contain any hyaluronidase activity? 09:45:51 09:45:56 09:46:00 09:46:04

MS. WANG: Objection to form and scope. 09:46:08

A It does not. It simply claims 95 percent identity. 09:46:09 09:46:33

Q There's no -- 09:46:35

(Stenographer requested clarification.) 09:46:35

A It does not. It claims 95 percent identity. 09:46:35 09:46:35

BY MR. POWERS: 09:46:36

Q There's no activity requirement in the claim, right? 09:46:36 09:46:38

MS. WANG: Objection to form and scope. 09:46:39

A That is the claim, that's correct. 09:46:42

BY MR. POWERS: 09:46:44

Q Okay. Let's see the next patent, please. Doctor, I'm going to hand you what's been previously marked Exhibit 1001, the 0004 case, we're going to just do the same exercise with respect to claim 1. 09:46:44 09:46:53 09:47:02 09:47:12 09:47:17

A Uh-huh. 09:47:20

Q Is it your understanding that the specification between -- among all the patents at issue today is the same? 09:47:24 09:47:25 09:47:29

A Yes, that is correct. 09:47:29

Q The claims differ, right? 09:47:34

A Modestly so, but yes. 09:47:35

Q And so I'd like you to read claim 1. First of all, do you recognize this document in front of you? 09:47:39 09:47:48 09:47:50

A I do. 09:47:50

Q And what is this document? 09:47:50

A This is either a patent or a patent application. I don't know the difference. This is the -- one of the patents to the '298 patent of the utility of PH20. 09:47:51 09:47:53 09:48:03 09:48:05

Q Right. It's the '298 patent we can 09:48:07

call it today? 09:48:09

A Yes, sir. 09:48:10

Q Okay. And if you look at claim 1 -- 09:48:11

first of all, you reviewed the claims of the '298 patent, right? 09:48:14 09:48:16

A That is correct. 09:48:17

Q And if you look at claim 1 of the '298 patent, can I tell me if that claim requires any hyaluronidase activity? 09:48:19 09:48:22 09:48:31

MS. WANG: Objection to form and scope. 09:48:35

A No. Claim 1 simply establishes a series of polypeptides that -- I beg your pardon -- have 95 percent sequence identity to the parental PH20 -- modified PH20 polypeptide. 09:48:47 09:48:52 09:48:56 09:49:01

BY MR. POWERS: 09:49:08

Q So it claims a structure, correct? 09:49:08

MS. WANG: Objection to form and scope. 09:49:15

A Could you repeat that, please? 09:49:17

BY MR. POWERS: 09:49:18

Q The claim claims a structure? 09:49:18

A It does not claim a structure. It claims amino acid sequence. 09:49:20 09:49:23

Q A sequence, I see. 09:49:25

But there's no requirement for any 09:49:27

hyaluronidase activity, right? 09:49:37

A No. 09:49:38

MS. WANG: Objection to form and scope. 09:49:39

A I do not see that in claim 1. 09:49:41

BY MR. POWERS: 09:49:43

Q Okay. I'm going to hand you the next 09:49:43

patent. 09:49:46

A Thank you. 09:49:58

Q And this has been previously marked 09:49:58

Exhibit 1001 in the 0006 case. 09:50:00

A Uh-huh. 09:50:08

MR. POWERS: I'm getting a message to 09:50:14

go off the record to fix a technical issue 09:50:15

with the video. 09:50:17

THE WITNESS: All right. 09:50:20

THE STENOGRAPHER: Okay. Off the 09:50:20

record at 9:50 a.m. 09:50:21

(Whereupon, a brief recess was taken.) 10:07:49

THE VIDEOGRAPHER: We are back on the 10:10:59

record. The time is 10:11. 10:11:08

BY MR. POWERS: 10:11:10

Q Welcome back, Dr. Kelsoe. 10:11:10

A Thank you. 10:11:13

Q Sorry about that technical interruption. Did you speak to counsel during the break? 10:11:14 10:11:15 10:11:18

A I did. 10:11:20

Q Did you speak about the substance of your testimony today? 10:11:21 10:11:23

A I did not. 10:11:24

Q What did you speak about? 10:11:25

A How nice this room looks. 10:11:29

Q I agree. It's nice. 10:11:32

I think before we left I had just handed you a document that is marked Exhibit 1001 in the 0006 case. Do you have that document in front of you still? 10:11:33 10:11:38 10:11:43 10:11:49

A 1001. Yes. This is the patent. This '262, and this is '298, and this is -- 10:11:51 10:12:06

Q It should be the '600 there. 10:12:18

A '600. 10:12:20

Q Yes. If we go back to '262, that's the 10:12:21

document that I want to ask you about. 10:12:24

A I beg your pardon. 10:12:26

Q Now, that's the third of -- 10:12:30

A '298. 10:12:30

Q -- the four patents. 10:12:30

A Yes. I'm sorry. '262. 10:12:33

Q Okay. And you reviewed this patent in association with preparation of your declarations, right? 10:12:34 10:12:36 10:12:39

A In the aspects that were relevant to my testimony, yes. 10:12:40 10:12:43

Q And you say in your declaration that you reviewed the claims of the patent, too, right? 10:12:45 10:12:49

MS. WANG: Objection to form. 10:12:57

A Could you direct me to where in my declaration I say that I've reviewed the claims? 10:13:01 10:13:05

BY MR. POWERS: 10:13:09

Q If you go to paragraph 15 of your declaration. 10:13:09 10:13:11

A Okay. 10:13:12

Yes. 10:13:19

Q And so you reviewed the claims of the 10:13:20

patent, right? 10:13:22

MS. WANG: Objection to form. 10:13:23

A I looked -- well, I mean, I think 10:13:31

paragraph 15 is pretty clear. I looked at the -- 10:13:33

my understanding is, is that I have commented on 10:13:44

and my declaration states that I was focusing on 10:13:50

the utility of the variant PH20 polypeptides as a 10:13:54

successful immunogen. 10:14:01

BY MR. POWERS: 10:14:04

Q Would you take a look at claim 1 of the 10:14:04

'262 patent for me, please? 10:14:07

A Make sure I'm going to the right one 10:14:15

here. 10:14:16

Q As we did with the previous claims that 10:14:16

we talked about today, can you confirm that 10:14:19

claim 1 does not require the modified PH20 10:14:23

polypeptide to contain any hyaluronidase activity? 10:14:27

MS. WANG: Objection to form, scope. 10:14:31

A My reading says that's not stated. 10:14:33

It's just a series of amino acid sequence 10:14:35

variability. 10:14:40

BY MR. POWERS: 10:14:40

Q So you don't read claim 1 to require any hyaluronidase activity, right? 10:14:40 10:14:44

MS. WANG: Objection to form, scope. 10:14:45

A To the best of my understanding, no. 10:14:47

BY MR. POWERS: 10:14:49

Q Can you set that aside? Let's look at the fourth patent. 10:14:49 10:14:52

A Thank you. 10:14:54

BY MR. POWERS: 10:15:12

Q I just handed you what's been previously marked Exhibit 1001 in the 00009 PGR. 10:15:12 10:15:14

Do you have the document in front of you? 10:15:19 10:15:22

A Yes, I do. 10:15:23

Q And have you seen this document before? 10:15:23

A Yes. 10:15:27

Q What is this document? 10:15:27

A This is the patent regarding the PH20 polypeptide. 10:15:29 10:15:39

Q It's the '035 patent, right? 10:15:39

A Yes. 10:15:42

Q And you reviewed this document before 10:15:43

signing your declaration? 10:15:45

A Those sections relative to what my testimony is about, yes. 10:15:46 10:15:51

Q And if you look at the claims of this patent -- so back to the end of the patent on the second-to-last page. 10:15:52 10:15:55 10:15:58

A Uh-huh. 10:15:59

Q It's going to start. I'm going to ask you the same question about claim 1 of this patent. Take a moment to review that claim, and please let me know if there's any requirement for the recited modified PH20 polypeptides to contain hyaluronidase activity? 10:15:59 10:16:04 10:16:08 10:16:10 10:16:13 10:16:17

MS. WANG: Objection to form, scope. 10:16:20

A There is none. 10:16:22

BY MR. POWERS: 10:16:22

Q So there's no requirement for hyaluronidase activity in claim 1 of the '035 patent, right? 10:16:22 10:16:26 10:16:28

MS. WANG: Objection to form. 10:16:29

A My understanding, claim 1 does not address whether or not hyaluronidase activity is 10:16:30 10:16:32

present. 10:16:37

BY MR. POWERS: 10:16:42

Q Thank you. You can set that aside. 10:16:42

Dr. Kelsoe, what's a monoclonal antibody? 10:16:44 10:16:54

A Monoclonal antibody is the product of the single B cell that is traditionally generated by fusion of an active B cell with a myeloma line or, more usually now, an antibody that is made as recombinant protein and expressed in a cell line. 10:16:55 10:16:59 10:17:03 10:17:15 10:17:19

Q Monoclonal antibodies have been widely used in biomedical research for decades, right? 10:17:23 10:17:27

A That's correct. 10:17:30

Q What are monoclonal antibodies useful for? 10:17:31 10:17:36

MS. WANG: Objection to form. 10:17:36

A Monoclonal antibodies have a lot of use. The biggest use, from my perspective, is they got a Nobel Prize for two of my friends. But they're useful in diagnostics. They're useful in therapeutics. 10:17:39 10:17:41 10:17:43 10:17:49 10:17:52

BY MR. POWERS: 10:17:53

Q When was that Nobel Prize awarded? 10:17:53

A It must have been in the 1990s. I don't remember when. 10:17:57 10:18:00

Q What was the breakthrough that led to that Nobel Prize? 10:18:01 10:18:03

A Georges K hler trying to see if he could get antibodies produced by fusion between these two cells in Cesar Milstein's lab. 10:18:06 10:18:09 10:18:12

Q A hybridoma in a B cell? 10:18:14

A Yes. 10:18:17

Q And obviously it worked? 10:18:17

A Worked very well, yes. 10:18:18

Q And that research was conducted when? 10:18:20

A Cambridge University. 10:18:25

Q Oh, I'm sorry, when? When was that research? 10:18:26 10:18:27

A When? That would have been -- for me it's a long time ago. In the late 1970s, early 1980s, yes. 10:18:27 10:18:32 10:18:35

Q And you mentioned earlier that monoclonal antibodies are useful for diagnostics. Can you elaborate on that a little bit? 10:18:37 10:18:41 10:18:44

MS. WANG: Objection to form. 10:18:47

A Yes. Monoclonal antibodies are used, for example, in histology for labeling tissue sections for antigens associated with tumors. They are useful in diagnosis of particular kinds of pathogens. They're useful for the identification of cell products appropriated in appropriate places. 10:18:47 10:18:51 10:18:56 10:19:01 10:19:05 10:19:08 10:19:15

BY MR. POWERS: 10:19:15

Q You mentioned also that monoclonal antibodies are useful as therapeutic agents? 10:19:15 10:19:18

A That is correct. 10:19:21

Q Can you elaborate on that a little bit more? 10:19:22 10:19:23

MS. WANG: Objection to form. 10:19:25

A All right. The passive administration of monoclonal antibodies have been used most, I guess, interestingly as a therapeutic for snakebite. The snakebite venoms can be neutralized by monoclonal antibodies, decreasing the damage done by the -- by the toxins, by the venom toxins. 10:19:26 10:19:30 10:19:35 10:19:43 10:19:49 10:19:52 10:19:54

BY MR. POWERS: 10:19:56

Q Are there any other uses, therapeutic uses for monoclonal antibodies? 10:19:56 10:19:58

A Oh, there are many. But most famously and most recently the costimulatory molecules PDL1 CTLA4 -- 10:20:00 10:20:03 10:20:11

(Stenographer requested clarification.) 10:20:11

A PDL1. Antibodies for PDL1, antibodies for CTLA4. These antibodies are significant in terms of reordering the immune status of people with either chronic infection or with tumors. 11:46:27 10:20:16 10:20:21 10:20:26

BY MR. POWERS: 10:20:28

Q Are monoclonal antibodies useful as research tools? 10:20:31 10:20:34

A They are highly useful. 10:20:35

Q What kind of research tools can be used with monoclonal antibodies? 10:20:36 10:20:38

A What kind of research? 10:20:41

Q Yes. 10:20:42

A Just about everything except physics. 10:20:43

Q Well, are monoclonal antibodies used frequently by molecular biologists in their 10:20:48 10:20:51

research? 10:20:54

A Molecular biologists do, yes, use 10:20:56

monoclonal antibodies. 10:20:59

Q What kind of assays are these 10:21:01

monoclonal antibodies useful for? 10:21:03

MS. WANG: Objection to form. 10:21:05

A I don't quite -- the question is rather 10:21:06

broad, so could you -- could you be specific? 10:21:08

BY MR. POWERS: 10:21:11

Q Well, do monoclonal antibodies have 10:21:11

broad use in research? 10:21:13

MS. WANG: Objection to form. 10:21:15

A Yes, they do. 10:21:16

BY MR. POWERS: 10:21:17

Q Can you give me some specific examples 10:21:17

of how monoclonal antibodies are useful as 10:21:20

research tools? 10:21:23

A Yes. Monoclonal antibodies are 10:21:24

routinely used, for example, in transplantation to 10:21:25

identify the specific -- the specific MAC types of 10:21:31

the transplantee and the donor. 10:21:39

Monoclonal antibodies, as I mentioned, 10:21:41

are used in pathology regularly to diagnose and to understand pathologic conditions. 10:21:43 10:21:47

Immunologists use monoclonal antibodies routinely to measure other antibodies, for example, the presence and location of antigen, or to type the kinds of lymphocytes that are recovered from secondary lymphoid tissues. 10:21:50 10:21:54 10:21:56 10:22:00 10:22:04

Q Is it fair to say that monoclonal antibodies are useful to bind proteins? 10:22:08 10:22:09

A The great majority of useful monoclonal antibodies are probably directed towards protein. 10:22:14 10:22:17

Q And that can be also -- yeah -- to detect proteins? 10:22:20 10:22:22

A And to detect protein, yes. 10:22:24

Q Can monoclonal antibodies be useful to neutralize biological targets? 10:22:28 10:22:30

A Yes. Monoclonal antibodies are used, at least experimentally, as protective agents against certain infections. 10:22:34 10:22:36 10:22:44

Monoclonal antibodies, as I've already said, are useful for snake venom and are administered in such a way. 10:22:47 10:22:50 10:22:54

Q Are monoclonal antibodies useful for immunoassays? 10:22:56 10:22:59

A Monoclonal antibodies are critical in immunoassays, yes. 10:23:02 10:23:03

Q Are they useful for western blots? 10:23:05

A Some antibodies are useful for western blots. Some antibodies are not, monoclonal or otherwise. 10:23:10 10:23:13 10:23:15

Q Right. How -- in, let's say, December 11, 2012, how did one go about generating monoclonal antibodies? 10:23:16 10:23:26 10:23:31

MS. WANG: Objection to form. 10:23:33

A At that time, the great majority of monoclonal antibodies were made by the immunization of an animal. At the time, rabbit serum, hamster, and mouse were the predominant three animals. The activated B cells were removed, and under conditions that allows membrane fusion, fused with myeloma cell line. 10:23:36 10:23:38 10:23:40 10:23:44 10:23:47 10:23:53 10:23:57

There's a selection step. The myeloma cell line carries a drug marker that allows the fused cells to survive. And one then screens the 10:24:01 10:24:02 10:24:07

clones that grow out for antigen specificity isotype, that sort of thing. 10:24:14 10:24:18

BY MR. POWERS: 10:24:21

Q That was a process that led to the Nobel Prize that you talked about, right? 10:24:21 10:24:23

A That is correct. 10:24:26

Q And that research was published in the '70s and '80s? 10:24:26 10:24:28

A Yes. That's the -- well -- by the time of the 1980s, hybridoma technology was a new and growing thing, yes. 10:24:30 10:24:33 10:24:40

Q So by 2011, 2012, generating a monoclonal antibody was considered routine laboratory work, right? 10:24:42 10:24:46 10:24:50

MS. WANG: Objection to form. 10:24:52

A I mean, it would -- there would be nothing novel. It may not be routine, but there would be nothing novel in making a monoclonal antibody in 2011. 10:24:53 10:24:54 10:24:57 10:25:01

BY MR. POWERS: 10:25:03

Q A person of ordinary skill in the art would know how to generate monoclonal antibodies 10:25:03 10:25:04

in 2012? 10:25:07

A In principle, yes. 10:25:08

Q There were commercially available services that generated monoclonal antibodies by 2012, right? 10:25:09 10:25:10 10:25:15

A That is correct. 10:25:16

Q Would you agree that monoclonal antibodies, in their creation, was a mature and established technology by December 2011? 10:25:16 10:25:18 10:25:20

MS. WANG: Objection to form. 10:25:23

A In 2011, was it a -- yes, I do, yes. 10:25:28

BY MR. POWERS: 10:25:30

Q You're familiar with the AIRE pathway, right? The AIRE -- 10:25:30 10:25:46

A AIRE, yes, uh-huh, I am familiar. 10:25:50

Q And that refers to an autoimmune regulator; is that right? 10:25:52 10:25:56

A That is correct. 10:25:57

Q And AIRE is expressed in medullary thymic epithelial cells, right? 10:25:58 10:26:01

A That is correct. May I -- 10:26:06

Q Yes. 10:26:08

A -- extend? 10:26:08
Q Please. 10:26:08
A It's expressed in several tissues, but its importance in T cell -- 10:26:09 10:26:12
Q Tolerance? 10:26:14
A -- maturation and tolerance occurs solely in the thymus. 10:26:15 10:26:18
Q Okay. You referred to it just a second ago, but AIRE's role is to promote thymic expression of certain peripheral tissue antigens, correct? 10:26:21 10:26:23 10:26:25 10:26:30
A That is correct. 10:26:30
Q And that thymic expression enables central T-cell tolerance if the protein is expressed in the medullar thymic epithelial cells, correct? 10:26:31 10:26:34 10:26:37 10:26:45
A Yes. Although, AIRE doesn't always express the entire protein, but probably only individual exons. 10:26:45 10:26:47 10:26:50
Q Okay. 10:26:52
A So one gets short products rather than the entire protein. 10:26:52 10:26:55

Q But the protein has to be expressed in order to be tolerized by AIRE? 10:26:57 10:26:59

A That is correct. 10:27:01

Q Some part of the -- 10:27:02

A Some fraction of it, yes. 10:27:04

Q Do you agree that not all tissue-specific antigens are regulated by AIRE? 10:27:08 10:27:09

A I don't know that they're not regulated by AIRE. There are 33,000-some-odd proteins in the average animal, and to say that exhaustively it has been excluded, I -- that, I don't know. 10:27:17 10:27:18 10:27:22 10:27:27

We do know from the papers referenced that many protein fragments that are not normally expressed are expressed later in life, postadolescence, are expressed in the thymus. But exhaustively I do not know that every, every protein is expressed there. 10:27:30 10:27:37 10:27:42 10:27:45 10:27:50 10:27:52

Q So certain proteins are probably not expressed by AIRE, right? 10:27:57 10:28:00

MS. WANG: Objection to form. 10:28:01

A I cannot agree with that. I don't -- I simply don't know whether they are or they are 10:28:02 10:28:03

not. 10:28:05

BY MR. POWERS: 10:28:06

Q I see. 10:28:06

You don't know one way or the other whether a protein is expressed by AIRE or not? 10:28:06 10:28:08

A I do know that many proteins are. I do not know that a specific protein is. 10:28:10 10:28:13

Q I see. 10:28:14

You don't cite any study in your declaration showing that PH20 is expressed by AIRE? 10:28:15 10:28:18 10:28:20

A I do not. 10:28:21

Q And in your declaration, you don't cite any data showing that PH20 is expressed in the thymus, right? 10:28:23 10:28:25 10:28:28

A I do not. 10:28:29

Q Demonstrating AIRE mediation requires evidence of thymic expression; don't you agree? 10:28:33 10:28:35

MS. WANG: Objection to form. 10:28:38

A Could you repeat? I'm sorry. Couldn't hear that. 10:28:39 10:28:41

BY MR. POWERS: 10:28:41

Q Sure. 10:28:41

Demonstrating AIRE-mediated tolerance 10:28:42

requires evidence of thymic expression, correct? 10:28:45

MS. WANG: Objection to form. 10:28:51

A No. Simply because we know that T 10:28:56

cells are tolerant to many, many, many peripheral 10:28:58

antigens without identifying them individually in 10:29:04

the thymus. There are potential exceptions. And 10:29:06

those T cells should not be tolerant, or we would 10:29:12

not have T regulatory cells for them. Two 10:29:16

different pathways. 10:29:20

That's all I can say. You would not 10:29:21

have to demonstrate it. What you would want to 10:29:26

show is that peripheral T cells in, for example, a 10:29:31

preadolescent, pre -- before sperm is produced, 10:29:37

those T cells -- if those T cells were tolerant to 10:29:42

a cell pathogen, then one would presume that the 10:29:44

associated antigens were at least, in part, 10:29:48

expressed in the thymus. 10:29:50

BY MR. POWERS: 10:29:53

Q I see. But sitting here today, you 10:29:53

have no data that indicate that any fragment of 10:29:54

PH20 or PH20 as a whole is expressed in thymus, right? 10:29:58 10:30:01

A I do not. 10:30:02

Q Dr. Kelsoe, I'm going to hand you what's previously been marked as Exhibit 1170. 10:30:30 10:30:32

A Thank you. 10:30:36

(Previously marked Exhibit Number 1170 was identified.) 10:30:36 10:30:36

BY MR. POWERS: 10:30:37

Q Now, you cite 1170 in your declaration, right? 10:30:37 10:30:49

A Yes. 10:30:50

Q What is 1170? 10:30:52

A 1170 is the standard textbook for immunology, Janeway's Immunobiology. 10:30:56 10:30:59

Q I think I remember it from undergrad. 10:31:04

Let's go to page 313. To be clear, that's 313, based on Janeway's numbers, which are on the top. 10:31:07 10:31:19 10:31:22

A Ah, okay. 10:31:22

Q -- in a moment. 10:31:22

A Okay. They're irregularly -- actually, 10:31:22

I can't find the Janeway numbers, so could you give me the -- 10:31:22 10:31:37

Q Yes, just a moment. 10:31:43

A Thank you. 10:31:49

Q Happy to. 10:31:49

A 128, 127. 10:31:49

Q It's page 110. 10:31:50

A Yes. 10:32:04

Q Get into the exhibit number now. 10:32:06

A Yes. 10:32:06

Q If you go to the second full paragraph of that page, it states: It is unlikely that all possible self-antigens -- I'm sorry. I'll start over. 10:32:06 10:32:14 10:32:20 10:32:23

It is unlikely that all possible self-proteins are expressed in the thymus. Thus, negative selection of the thymus may not remove all T cells reactive to self-antigens that appear exclusively in other tissues or are expressed at different stages of development. 10:32:23 10:32:25 10:32:30 10:32:32 10:32:36 10:32:39

Do you see that? 10:32:41

A Yes, I do. 10:32:41

Q So this reference that you cited is saying that not all self-proteins are expressed in the thymus, right? 10:32:44 10:32:46 10:32:48

MS. WANG: Objection to form. 10:32:50

A They say that it is unlikely that not all protein -- not all possible 33,000 polypeptides are expressed on the thymus; that is correct. 10:32:51 10:32:52 10:32:59 10:33:02

BY MR. POWERS: 10:33:02

Q And, therefore, the AIRE pathway would not apply to antigens that appear in other tissues, are express -- or are expressed at different stages of development, right? 10:33:02 10:33:04 10:33:06 10:33:07

MS. WANG: Objection to form. 10:33:10

A Well, so it goes on to say that later there are other peripheral regulatory mechanisms, T regulatory cells that minimize any loss of the thymus. But, yes, it's perfectly -- it's unlikely that every polypeptide is expressed in the thymus, and I'm sure that's what my declaration states. 10:33:10 10:33:19 10:33:21 10:33:26 10:33:31 10:33:34

BY MR. POWERS: 10:33:37

Q But you're aware, sitting here today, 10:33:37

of no evidence showing expression of PH20 in the thymus, right? 10:33:41 10:33:43

A Well, the evidence that there is -- no. I'm sorry. Yes. There is no evidence of -- direct evidence of PH20 expression in the thymus; that is correct. 10:33:51 10:33:56 10:34:00 10:34:03

Q Okay. You can set this document aside. 10:34:03

A Okay. 10:34:06

Q You are familiar with vaccine adjuvants, right? 10:34:07 10:34:11

A Yes, I am. 10:34:12

Q What's the role of adjuvant in vaccine formulation? 10:34:12 10:34:15

MS. WANG: Objection to form. 10:34:16

A An adjuvant is an analog of an inflammatory response, normally mediated by either pathogen structures called PAMPs or self-structures, damaged structures called DAMPs. Because it activates the innate immune response, it amplifies, generally, immune responses. 10:34:17 10:34:21 10:34:24 10:34:29 10:34:33 10:34:37

BY MR. POWERS: 10:34:42

Q So just to put it in simple plain 10:34:42

English, what does an adjuvant do in a vaccine? 10:34:44

A An adjuvant increases the amount of the response -- the size of the -- the magnitude of the response. 10:34:51 10:34:54 10:34:56

Q Would you agree that adjuvants were widely used before 2012? 10:34:58 10:34:59

A Yes. 10:35:01

Q Would you agree that adjuvants are capable of breaking tolerance? 10:35:04 10:35:06

A Not all adjuvants are easily capable of breaking tolerance. The most inflammatory adjuvants are, the famously complete Freund's is very good at this. 10:35:10 10:35:14 10:35:17 10:35:27

(Stenographer requested clarification.) 10:35:27

A A complete Freund's adjuvant. 10:21:57

But any adjuvant does promote the capacity to break tolerance, yes. 10:35:28 10:35:35

BY MR. POWERS: 10:35:39

Q Before December 2012, 2011, antigens -- sorry. Strike that. 10:35:39 10:35:44

Before December 2011, 2012, adjuvants were known that were capable of breaking 10:35:45 10:35:51

tolerance, right? 10:35:55

A That is correct. 10:35:56

Q PH20 is a sperm-specific protein, correct? 10:36:13

A Yes, it is. 10:36:15

Q Females do not produce sperm, correct? 10:36:17

A They do not. 10:36:20

Q Therefore, PH20 is not expressed in females, correct? 10:36:23

MS. WANG: Objection to form. 10:36:26

A The mature form of the protein cannot be expressed in females. That is correct. 10:36:29

BY MR. POWERS: 10:36:32

Q There's no form of PH20 that's expressed in females, correct? 10:36:33

A Only if AIRE does not activate expression of PH20 in the thymus. 10:36:40

Q Which you have no data for, right? 10:36:45

A Which I do not have data for. 10:36:47

Q Okay. Let's go back to your declaration, paragraph 90. 10:36:48

A 9-0? 10:36:52

Q Yes, sir. 10:37:09

A Yes. 10:37:17

Q I see -- Okay. So had you heard of DEFB126 before reading Dr. Cherr's declaration? 10:37:21 10:37:27

A I don't know what you said. 10:37:32

Q No problem. 10:37:33

Had you heard of DEFB126 before reading Dr. Cherr's declaration? 10:37:34 10:37:40

A I have not. 10:37:42

Q Would you agree with me that sperm is coated with a glycol protein called DEFB126? 10:37:43 10:37:46

A I have no knowledge of that. I would have to review Dr. Cherr's statements. 10:37:53 10:37:55

Q Do you understand that DEFB126 is linked to negatively charged oligosaccharides that facilitate sperm movement and cloak sperm from immune surveillance of the female reproductive tract? 10:38:00 10:38:03 10:38:07 10:38:10 10:38:13

A Again, I would have to review Dr. Cherr's statement in this. 10:38:14 10:38:15

Q Do you have any understanding that because sperm is coated by DEFB126, it's not 10:38:22 10:38:24

considered a foreign invading cell? 10:38:27

A Well, I will say that -- I can't answer 10:38:32

it because I have no real knowledge of the 10:38:50

particular agent in mind. On the other hand, 10:38:52

there are a large number of women -- fortunately, 10:38:59

the antisperm antibodies in many women are not 10:39:02

functionally contraceptive -- some are, some are 10:39:09

not. And so somehow these individuals became 10:39:13

sensitized to sperm. 10:39:15

Q Do you agree that antibody binding to 10:39:21

sperm is a significant cause of infertility in 10:39:25

women? 10:39:28

MS. WANG: Objection to form. 10:39:29

A I'm told that there are -- I don't know 10:39:32

what the frequencies are because I'm not a 10:39:33

reproductive biologist, but I know that there is 10:39:37

an association. I think it's only an association 10:39:38

between women with antibodies to sperm and reduced 10:39:42

fertility, yes. 10:39:49

BY MR. POWERS: 10:39:52

Q Do you agree that a larger protein is 10:39:52

going to have more epitopes than a smaller protein 10:40:22

as a general matter? 10:40:25

MS. WANG: Objection to form. 10:40:27

A In the general sense, yes. 10:40:29

BY MR. POWERS: 10:40:33

Q In 2011, would a person of ordinary skill in the art have appreciated that? 10:40:33

A Yes, they would. 10:40:38

Q If you go to paragraph 34 of your declaration. 10:40:53

A Could you repeat the page number again, please? 10:40:57

Q Yes, sir. 34. 10:40:59

A 34. 10:41:01

Q Paragraph 34. 10:41:02

A Oh. All right. 10:41:05

Yes. 10:41:19

Q Okay. And that chart is from Janeway, right? 10:41:19

A That is correct. 10:41:22

Q Thank you. 10:41:23

Second row down under Parameter, Janeway mentions Dose. 10:41:23

10:41:24

10:41:38

Do you see that? 10:41:40

A Yes. 10:41:41

Q What do you understand dosage -- strike that. 10:41:44

What do you understand "dose" to mean here? 10:41:46

A Dose is the amount of antigen provided as the immune stimulus. 10:41:51

Q And just to back up, this is a chart that is entitled "Factors that influence the immunogenicity of proteins," right? 10:41:57

A Yes. 10:42:03

Q Reproduced from Janeway, correct? 10:42:07

A I'm terribly sorry? 10:42:07

Q Yeah, no problem. 10:42:11

Reproduced from the Janeway reference? 10:42:12

A That is correct. 10:42:12

Q Exhibit 1170. And you've put it in your declaration here, correct? 10:42:15

A Yes. 10:42:16

Q And under Dose, you said that -- dose is the amount of antigen provided as the immune 10:42:19 10:42:21 10:42:22 10:42:34

stimulus, right? 10:42:37

A Yes. 10:42:38

Q By December 2011, a person of ordinary skill in the art would have been able to optimize the dose given to improve immunogenicity of an antigen, correct? 10:42:42 10:42:45 10:42:48 10:42:52

MS. WANG: Objection to form. 10:42:53

A Experiments exactly establishing the sort of a normal distribution for antigen quantity and response were performed well before that, yes. 10:42:54 10:42:58 10:43:05

BY MR. POWERS: 10:43:09

Q One way to improve the immunogenicity of a vaccine is to give more antigen, correct? 10:43:09 10:43:12

A To a certain point, then it becomes worse. 10:43:15 10:43:18

Q Right. But a person of ordinary skill in the art would have understood that in 2011, right? 10:43:18 10:43:19 10:43:23

A Yes. 10:43:23

Q Is frequency of dose or serial dosing another way a person of ordinary skill in the art would have known how to improve immunogenicity of 10:43:37 10:43:40 10:43:44

an antigen? 10:43:49

MS. WANG: Objection to form. 10:43:50

A At the time, 2011, it was clear that 10:43:51

after a first injection, a first administration of 10:43:56

antigen, a second administration -- generally 10:44:00

there was a time limit. It had to be greater than 10:44:04

a couple of weeks. A second -- a second dose of 10:44:08

antigen, the response was larger, was greater, was 10:44:13

higher in magnitude, yes. 10:44:16

BY MR. POWERS: 10:44:19

Q And these are so-called "booster 10:44:19

doses," right? 10:44:21

A That is correct. 10:44:23

Q Next row down in Janeway is "Route." 10:44:38

Do you see that? 10:44:41

A Yes, I do. 10:44:42

Q What do you understand route to mean 10:44:44

here? 10:44:47

A This basically refers to the way or the 10:44:48

method of introduction of antigen. Subcutaneous 10:44:54

is beneath the skin, intraperitoneal is into the 10:44:58

peritoneal cavity, intravenous is directly into 10:45:02

the blood, and intragastric would be via the stomach, so-called enteral exposure of antigen. 10:45:06 10:45:11

Q Do you agree that in December 2011 -- by December 2011, a person of ordinary skill in the art could choose different routes of administration to maximize the immunogenicity of an antigen? 10:45:15 10:45:17 10:45:21 10:45:23 10:45:26

A They could use different routes of administration to maximize the response. The immunogenicity of the antigen is a factor of the antigen, not of the route, yes. 10:45:30 10:45:33 10:45:37 10:45:40

Q Does immunogenicity of the antigen correlate with response? 10:45:42 10:45:44

A Yes, to a large degree. 10:45:49

Q Now, one known way of administering an antigen is through the mucosal route, right? 10:45:50 10:45:54

A The enteral pathway shown here, yes. Intragastric. 10:45:57 10:45:59

Q Intragastric is one example of a mucosal route? 10:46:03 10:46:05

A Yes. 10:46:07

Q But there are other mucosal routes 10:46:07

known, correct? 10:46:10

A There are. There are the nasopharynx 10:46:12

route for lungs. There are sublingual routes, 10:46:17

which become intragastric, and there's suppository 10:46:24

routes that are directly into the intestine. 10:46:28

Q Those routes were known as of 2011? 10:46:37

A Yes, they were. 10:46:40

Q A few more rows down, I see adjuvants 10:46:47

on this chart. 10:46:50

A Yes. 10:46:51

Q Actually, before we get there, do you 10:46:54

have any -- do you remember if in the '600 10:47:00

patents, and the other patents in the proceeding, 10:47:05

they disclosed that administration to mucosa is 10:47:07

contemplated? 10:47:09

A Yes, I do. In reference to the Moon 10:47:11

declaration, the Cherr declaration especially, but 10:47:16

also in the -- in the part that describes the 10:47:19

potential for the PH20 as a contraceptive vaccine. 10:47:23

Q And the patents articulate a mucosal 10:47:30

route is contemplated, correct? 10:47:32

MS. WANG: Objection. 10:47:37

A I don't remember. 10:47:38

BY MR. POWERS: 10:47:38

Q If we go to the '600 patents in front of you there. If we look at column 169. Up at the top of the pages, there are column numbers. And then we go to -- down on column 169, line 7 to 11. 10:47:38 10:47:40 10:47:53 10:47:55 10:48:08

There it says: Topical administration is contemplated for transdermal delivery and also for administration into the eyes or mucosa -- 10:48:08 10:48:16 10:48:19

A Yes. 10:48:22

Q -- or for inhalation therapies. 10:48:22

A Uh-huh. 10:48:25

Q Nasal solutions of active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered. 10:48:25 10:48:28 10:48:30 10:48:34

Do you see that? 10:48:34

A Yes. 10:48:35

Q So the patent does talk about mucosal administration, correct? 10:48:35 10:48:37

A Yes, it does. 10:48:37

MS. WANG: Objection to form. 10:48:38

BY MR. POWERS: 10:48:38

Q Let's see. 10:48:38

A Excuse me. But I read this not to be immunization at all but simply a pathway for exposure. 10:48:39 10:49:07 10:49:10

Q Okay. If we go to -- now, you say that an effective therapeutic response depends on antibody concentration and binding strength. 10:49:11 10:49:17 10:49:26

A Yes. 10:49:29

Q And binding strength is affinity and avidity, correct? 10:49:31 10:49:33

A That is correct. 10:49:35

Q The relationship between antibody titer and binding affinity was well understood before 2012, correct? 10:49:36 10:49:38 10:49:41

MS. WANG: Objection to form. 10:49:43

A There's no relationship between quantity and affinity. Affinity is an intrinsic property of the antibody combining side. Quantity is how many antibodies are present. But they are independently -- they segregate independently. 10:49:46 10:49:47 10:49:52 10:49:56 10:49:58

BY MR. POWERS: 10:50:01

Q Do you agree that increasing antibody titers can offset concerns about moderate binding affinity in eliciting an effective biological response? 10:50:01 10:50:08 10:50:11 10:50:15

A I do not. 10:50:16

Q Do you agree that the greater concentration of the antibody, the less need there is for high binding affinity? 10:50:19 10:50:20 10:50:22

A In what context are you asking the question? As a therapeutic agent? 10:50:27 10:50:29

Q In a general context. 10:50:33

A So as you -- I'm sure you know, the affinity is simply the equilibrium constant of the antigen binding to and falling off of the antibody. And if you have more antibody, the equilibrium constant stays the same because the equilibrium constant is measured by the concentration of the ligand. 10:50:39 10:50:41 10:50:45 10:50:48 10:50:54 10:50:59 10:51:02

So the answer is no. That's why I wanted to make sure I understood the context of what you're saying. 10:51:04 10:51:08 10:51:11

Q You didn't testify in your declaration that antibodies must reach a particular affinity or avidity to elicit an effective therapeutic response, correct? 10:51:15 10:51:16 10:51:19 10:51:23

A I did not state a threshold. I did not. 10:51:24 10:51:26

Q You agree that it was known -- well, do you agree that it was known by 2012 that adjuvants can be used not only to raise titers but influence how well antibodies bind to antigen? 10:51:30 10:51:40 10:51:42 10:51:47

A Actually, I can't agree with that. The magnitude of the response is increased. Whether or not there is affinity maturation, the increase in binding strength is proportional to a different part of the response, a so-called germinal center response. 10:51:51 10:51:55 10:51:58 10:52:02 10:52:06 10:52:11

(Stenographer requested clarification.) 10:52:11

BY MR. POWERS: 10:52:11

Q Can adjuvants increase a germinal center response? 10:52:13 10:52:16

A No. 10:52:17

Q Can adjuvants promote B-cell maturation 10:52:18

in clonal expansion? 10:52:23

A So that is an issue of great debate. 10:52:30

Mostly people believe now that adjuvants work by 10:52:33

increased recruitment of unstimulated cells to 10:52:38

become stimulated. Broadening, if you will, the 10:52:42

base of the response so that it's bigger. 10:52:45

I don't think there is any evidence 10:52:49

that it accentuates the process of selection in 10:52:52

germinal centers. 10:52:58

Q Does -- is there evidence that 10:53:02

adjuvants increase somatic hypermutation in B-cell 10:53:04

maturation? 10:53:14

A None whatsoever. 10:53:18

Q You're not aware of any evidence that 10:53:18

suggests that B-cell maturation and somatic 10:53:20

hypermutation is increased by adjuvants; is that 10:53:22

correct? 10:53:25

A Only the magnitude of the response. 10:53:26

Never the rate of -- the rate of somatic 10:53:29

hypermutation is determined by a different 10:53:31

process. 10:53:37

Q All right. Let's take a break. 10:53:37

A Thank you. 10:53:39

THE VIDEOGRAPHER: We're going off the record. The time is 10:53. 10:53:41 10:53:42

(Whereupon, a brief recess was taken.) 10:53:44

THE VIDEOGRAPHER: We are back on the record. The time is 11:18. 11:18:32 11:18:33

BY MR. POWERS: 11:18:36

Q Dr. Kelsoe, what is affinity maturation? 11:18:36 11:18:39

A Affinity maturation is the general process of antibodies acquiring higher and higher affinity for their antigen ligand through a process of somatic evolution in a germinal center. 11:18:40 11:18:42 11:18:49 11:18:52

Q And was it known that adjuvants can increase affinity maturation as of 2011? 11:19:00 11:19:06

A Adjuvants increase the magnitude of the response. They cannot intrinsically increase the affinity maturation. 11:19:09 11:19:12 11:19:16

Q Can adjuvants help generate broadly neutralized antibodies? 11:19:17 11:19:19

A Almost all immunogens use -- let me rephrase what I'm trying to say. 11:19:22 11:19:26

Adjuvants are routinely used and are instead of soluble proteins to elicit the germinal center response and to make high affinity antibodies. 11:19:27 11:19:29 11:19:34 11:19:38

Q Those high affinity antibodies include broadly neutralized antibodies, correct? 11:19:40 11:19:42

MS. WANG: Objection to form. 11:19:45

A Broadly neutralizing antibodies are a subset of high affinity antibodies, yes. 11:19:46 11:19:49

BY MR. POWERS: 11:19:52

Q So we agree that somatic evolution happens in a germinal center, right? 11:19:52 11:20:02

A Yes, we do. 11:20:04

Q And adjuvants, you said, are routinely used to elicit a germinal center response, correct? 11:20:07 11:20:11 11:20:15

A No. Adjuvants are used to initiate -- to initiate the immune response and to magnify the size of that initiation. The TB collaboration that leads up to the germinal center reaction is not much impacted by adjuvant. 11:20:19 11:20:22 11:20:27 11:20:30 11:20:34

In fact, if I can expand on that. 11:20:40

Immunization with soluble proteins does not lead generally to very good antibody responses. In fact, sometimes it leads to tolerance. So adjuvants are routinely used to elicit all sorts of antibody responses in animals and humans. 11:20:47 11:20:50 11:20:53 11:20:56 11:20:59

Q As part of their use in vaccines, though, do you agree that adjuvants can promote antibody affinity maturation? 11:21:03 11:21:06 11:21:09

MS. WANG: Objection to form. 11:21:13

A No. They promote -- the magnitude of the response and the affinity maturation is determined by the interaction of T and B cells within the germinal center. 11:21:14 11:21:20 11:21:22 11:21:26

BY MR. POWERS: 11:21:27

Q Is it your position that adjuvants do not impact the interaction of T and B cells within the germinal center to promote antibody affinity maturation? 11:21:27 11:21:30 11:21:34 11:21:37

A They do not. 11:21:38

Q Do you agree that adjuvants can be used not only to raise titers but influence how well antibodies bind to antigen? 11:21:48 11:21:50 11:21:54

MS. WANG: Objection to form. 11:21:56

A That question is simply rephrasing of the question you just asked me, and the answer is no. Adjuvants may increase the diversity of B cells responding to an antigen, but they don't change the somatic evolution within the germinal center. 11:21:57 11:21:59 11:22:04 11:22:08 11:22:11 11:22:14

BY MR. POWERS: 11:22:15

Q Are you familiar with the journal Science Translational Medicine? 11:22:15 11:22:20

A I am. 11:22:22

Q Is that a peer-reviewed journal? 11:22:23

A It is. 11:22:24

Q Is it considered a good journal? 11:22:25

A It is. 11:22:26

Q I'd like to introduce a new exhibit. This will get number 2215. 11:22:27 11:22:27

(Exhibit Number 2215 was identified as of this date.) 11:22:27 09:30:46

A Thank you. 09:22:20

BY MR. POWERS: 09:22:20

Q Dr. Kelsoe, you've been handed what's 09:22:20

been marked 2215. Have you seen this document before? 11:23:09 11:23:13

A I have not. 11:23:13

Q This is a publication from Science Translational Medicine, right? 11:23:17 11:23:18

A Yes. 11:23:21

Q And it's dated June 1, 2011, right? 11:23:21

A Yes. 11:23:24

Q Do you agree that a person of ordinary skill in the art, as of December 2011, would have known of this reference? 11:23:25 11:23:26 11:23:29

A Yes. 11:23:31

Q The first author on this reference is? Surender Khurana, right? 11:23:32 11:23:36

A Yes. 11:23:39

Q Are you familiar with that person? 11:23:44

A No. 11:23:45

Q The senior author is Hana Golding. Do you see that? 11:23:45 11:23:48

A Yes. 11:23:49

Q Are you familiar with that person? 11:23:49

A I am not. 11:23:50

Q The first and senior author -- the first and senior authors are out of the FDA, Food and Drug Administration, in Bethesda, Maryland, correct? 11:24:06 11:24:09 11:24:12 11:24:16

A Yes. Jon Yewdell is at the NIAID. I know Jon Yewdell well. And Rino Rappuoli is Novartis, and I know of Rino Rappuoli. 11:24:25 11:24:28 11:24:33

Q You referred to Jon Yewdell? 11:24:36

A Yes. 11:24:38

Q Do you respect him as a scientist? 11:24:38

A He's a good scientist. 11:24:41

Q And he's one of the authors on this paper, correct? 11:24:43 11:24:45

A Yes, he is. 11:24:46

Q Let's look at the abstract of this paper. It discusses MF59; do you see that? 11:24:53 11:24:54

A Yes, I do. 11:25:03

Q MF59 is an adjuvant, correct? 11:25:04

A That is correct. 11:25:06

Q About two-thirds of the way down in the abstract, it says: Moreover, MF59 also improved antibody affinity maturation after each sequential 11:25:10 11:25:12 11:25:17

vaccination against avian H5N1 in adults. 11:25:20

Correct? 11:25:26

A Yes. 11:25:26

Q So here the authors report that an adjuvant is improving antibody affinity maturation, correct? 11:25:27 11:25:29 11:25:32

MS. WANG: Objection to form. 11:25:33

A I need to read the paper to see what the comparison is to. 11:25:34 11:25:37

BY MR. POWERS: 11:25:39

Q Take your time. 11:25:39

A Thank you. 11:25:40

Yes. 11:25:59

Q Okay. 11:26:01

A So the comparator here is unimmunized -- unadjuvanted hemagglutinin vaccine. That's the standard vaccine form that is given to humans against influenza. As I told you recently, the role of adjuvant is significantly greater in magnifying the size of the immune response as compared to unadjuvanted -- unadjuvanted antigens, which you can all see -- also see here. The 11:26:01 11:26:03 11:26:09 11:26:13 11:26:18 11:26:24 11:26:28 11:26:32

oil-and-water vaccine is simply another form of slow-release and inflammatory signal. 11:26:38 11:26:43

So the comparison here now is not against two different kinds of adjuvant or it's compared to a suboptimal point of immunization with an adjuvanted immunization. 11:26:45 11:26:52 11:26:55 11:26:59

Q Well, none of my questions before were about comparing two different types of adjuvant. I asked you before if an adjuvant could improve antibody affinity maturation, and these authors, you would agree, indicate that MF59 improved antibody affinity maturation, correct? 11:27:01 11:27:03 11:27:06 11:27:10 11:27:13 11:27:19

MS. WANG: Objection to form. 11:27:21

A So improvement -- yes. So improvement by definition requires a comparator. 11:27:22 11:27:25

Q Uh-huh. 11:27:28

A So when I say that an adjuvant does not change the rate of affinity maturation, I'm precisely correct in that: Adjuvants don't change the interaction of B cells in germinal centers. The initial -- what the adjuvant has done in this particular case is it increases the size of the 11:27:28 11:27:33 11:27:36 11:27:41 11:27:44 11:27:47

response, the number and the diversity, which you'll notice that it says "enhances diversity" as a part of the title. It increases the diversity of B cells recruited to the immune response and to the germinal center. 11:27:50 11:27:53 11:27:57 11:28:01 11:28:07

BY MR. POWERS: 11:28:08

Q Uh-huh. 11:28:08

A But it doesn't change the somatic evolution, per se, going in the germinal center. 11:28:09 11:28:13

Q You agree, though, that the authors wrote "MF59 also improved antibody affinity maturation," correct? 11:28:17 11:28:19 11:28:23

A That is the title of the paper. 11:28:25

Q You can set that aside. 11:28:29

What are neutralizing antibodies? 11:28:31

A Neutralizing antibodies are antibodies that block, for example, the increase site of a virus into their target cell or an antibody that blocks the toxin activity of a specific pathogenetic toxin. 11:28:36 11:28:39 11:28:42 11:28:48 11:28:51

Q And why are neutralizing antibodies important? 11:28:53 11:28:56

A Neutralizing antibodies in the case of pathogens prevent infection or, in the case of a toxin, prevent the effect of the toxin on organ systems. 11:28:56 11:28:59 11:29:05 11:29:09

Q By 2012, adjuvants were known that could break peripheral tolerance, correct? 11:29:13 11:29:15

A Adjuvants were known capable of breaking peripheral tolerance; that is correct. 11:29:20 11:29:22

Q And before 2012, 2011 adjuvants were known that could induce broadly neutralizing antibodies, right? 11:29:24 11:29:27 11:29:30

A That is correct. 11:29:31

Q And that's even to self-proteins, correct? 11:29:32 11:29:35

A I'm not sure I know an example of a broad -- a so-called "broadly neutralizing antibody" to a self-protein. 11:29:35 11:29:38 11:29:41

Q But you do agree that adjuvants could break peripheral tolerance, correct? 11:29:46 11:29:48

MS. WANG: Objection to form. 11:29:53

A As a matter of course, the adjuvants are capable of doing so. Routinely they do not; 11:29:54 11:29:55

otherwise, we would break tolerance every time we got our annual flu shots or MMR shots or any other standard childhood vaccination. So they only break tolerance when, one, the ligand is a self-antigen, and, two, the inflammation that it induces is sufficient to overcome the regulatory factors that prevent that. 11:30:00 11:30:03 11:30:11 11:30:15 11:30:17 11:30:20 11:30:23

BY MR. POWERS: 11:30:26

Q Skilled artisans knew of adjuvants that could break tolerance? 11:30:26 11:30:28

A Yes, they did. 11:30:30

Q B cells generate antibody diversity through site-specific recombination, correct? 11:30:30 11:30:59

A In what context do you mean site-dependent recombination? 11:31:10 11:31:12

Q Site-specific recombination called V(D)J joining? 11:31:14 11:31:18

A Yes. Yes. B-cell receptors are generated during the development of B cells by this V(D)J recombination process. 11:31:19 11:31:22 11:31:25

Q And would you agree that creates a diverse B cell repertoire? 11:31:27 11:31:29

A It certainly does. 11:31:32

Q That repertoire is capable of recognizing a wide variety of protein antigens, correct? 11:31:33 11:31:35 11:31:38

A That is correct. 11:31:38

Q After antigen exposure, B cells undergo antigen-driven somatic hypermutation, correct? 11:31:39 11:31:43

A B cells alone cannot -- cannot drive somatic hypermutation. They need a special T cell and special environment for that to happen, yes. 11:31:46 11:31:50 11:31:54

Q That's the helper T cell, correct? 11:31:56

A That is the T follicular helper cell, yes. 11:31:58 11:31:59

Q Special helper T cell? 11:32:01

A Yes. 11:32:02

Q Okay. And so that special helper T cell in the follicular environment drives B-cell hyper -- somatic hypermutation, correct? 11:32:03 11:32:04 11:32:09

A No. It activates the B cell. The B cell is entered into a differentiated state in which a particular enzyme, activation-induced cytidine deaminase, is deregulated during one 11:32:12 11:32:15 11:32:20 11:32:24

phase of the B cell -- it's a follicular phase in the germinal center. The T cells are required to maintain this state, but the B cells entered the state after the initial -- so -- I'm going to rephrase it. 11:32:28 11:32:33 11:32:37 11:32:40 11:32:43

When AICDA is expressed, the B cells are not in contact with T cells; they do so independently. 11:32:44 11:32:48 11:32:51

Q I see. 11:32:51

But I think the answer to my question is, yes, that the helper T cells promote B cell somatic hypermutation, right? 11:32:54 11:33:03 11:33:09

MS. WANG: Objection to form. 11:33:14

A Well, my answer to your question is they are necessary for B cells' mutation, but they do not promote it. 11:33:14 11:33:16 11:33:20

BY MR. POWERS: 11:33:21

Q I see. 11:33:21

And somatic hypermutation is the process by which point mutations are introduced into antibody variable regions, right? 11:33:21 11:33:31 11:33:34

A That is correct. 11:33:36

Q Those mutations can increase antibody affinity for a target antigen, correct? 11:33:37 11:33:41

A They both increase and decrease, yes. 11:33:43

Q Right. 11:33:45

The increased binders are selected? 11:33:46

A That is correct. 11:33:48

Q So the immune system has an evolutionary mechanism to select for increased binding affinity to a target antigen? 11:33:49 11:33:51 11:33:54

A That is correct. 11:33:57

Q And B cells with improved affinity in their antibodies are selected for survival and expansion, correct? 11:34:07 11:34:10 11:34:13

A B cells that are selected -- if I may be precise, there are two outcomes for selected B cells, and that is either to leave the germinal center and differentiate into a memory cell or an antibody-secreting cell or to return to the portion of the germinal center in which additional mutations are accrued. And then to return for a second round or a third round or a fourth round of selection, yes. 11:34:18 11:34:22 11:34:25 11:34:29 11:34:31 11:34:36 11:34:38 11:34:42 11:34:46

Q I see. So those B cells can undergo multiple rounds of selection to continuously select for better binders to the antigen? 11:34:46 11:34:48 11:34:51

A That is correct. 11:34:54

MS. WANG: Objection to form. 11:34:55

BY MR. POWERS: 11:34:56

Q And this process is referred to as affinity maturation, correct? 11:34:56 11:34:59

A That is correct. 11:35:01

Q An affinity maturation ideally results in antibodies that binds effectively to a particular antigen, correct? 11:35:04 11:35:06 11:35:09

A That is correct. 11:35:11

Q Successful B cell activation leads to clonal expansion, correct? 11:35:14 11:35:17

A Depends on what kind of antigen. What kind of antigen do you have in mind? 11:35:21 11:35:23

I'll rephrase. I'll reexplain. 11:35:27

Contact with the so-called T-independent antigen drives clonal proliferation independently of the B cell and its differentiation into an antibody-secreting set. 11:35:30 11:35:32 11:35:36 11:35:39

Response to a T-dependent antigen activates the B cell, requires the survival signal from a matched T helper cell, and then those cells transit back to the follicle to create the germinal center, in which that process is repeated as we just described -- 11:35:43 11:35:46 11:35:51 11:35:55 11:35:59 11:36:02

Q I see. 11:36:03

A -- over and over. 11:36:04

Q Can you give me an example of a T-independent antigen? 11:36:05 11:36:07

A Polysaccharide of -- pneumoniae polysaccharide. 11:36:08 11:36:11

Q What makes an antigen T cell independent? 11:36:12 11:36:15

A The product is capable of stimulating an alternative pathway of survival and activation usually through toll-like receptor ligands. 11:36:17 11:36:20 11:36:25

(Stenographer requested clarification.) 11:36:33

BY MR. POWERS: 11:36:33

Q Can you give me an example of a T-dependent antigen? 11:36:35 11:36:37

A The influenza hemagglutinin. 11:36:39

Q What makes an antigen T cell dependent? 11:36:46
A The T cell -- the hemagglutinin is 11:36:49
capable of activating the B cell, but not 11:36:53
providing the so-called second survival and 11:36:56
proliferation signal that is dependent on the T 11:36:59
cell. 11:37:03
Q I see. So the second survival signal 11:37:11
in the first case comes from some interaction with 11:37:14
the toll-like receptor? 11:37:16
A It can be. So, for example, the 11:37:18
interaction with -- there are receptors for a 11:37:21
T-independent antigen called Flagellin. 11:37:25
Flagellin, a bacterial product, not only is it 11:37:28
recognized by the B cell-cell antigen receptor, 11:37:32
but it also interacts directly with toll-like 11:37:34
receptors. 11:37:37
Q In a T cell dependent antigen, the 11:37:41
second survival signal comes from the T cell, 11:37:44
correct? 11:37:46
A That is correct. 11:37:46
Q Just going back to the B cell-cell 11:38:10
somatic hypermutation we were talking about 11:38:12

earlier, was that phenomenon well known in the literature prior to 2012? 11:38:16 11:38:21

A Yes. 11:38:23

MS. WANG: Objection to form. 11:38:24

BY MR. POWERS: 11:38:36

Q Sorry? 11:38:36

A Yes. Originally published in '91 or '96 in Cell and in Nature. 11:38:37 11:38:42

Q I see. So it had been out there for a while? 11:38:45 11:38:47

A Yes. 11:38:47

Q The female genital tract is considered mucosal tissue, right? 11:38:52 11:38:55

A Yes. 11:38:57

Q You agree that mucosal tissues have immune characteristics that differ from systemic tissues? 11:38:58 11:39:00 11:39:03

A Yes. 11:39:05

Q One of those differences is the predominance of mucosal antibodies, correct? 11:39:06 11:39:08

A The way I interpret it, that's sort of a circular -- a circular statement. There are 11:39:19 11:39:20

antibodies on the surface, the mucosal surface of mucosa. That's for sure. Some are produced locally and some are systemic and transported there. 11:39:25 11:39:29 11:39:33 11:39:36

Q Right. So you would agree that mucosal surfaces have distinct set of antibodies compared to systemic tissues, right? 11:39:39 11:39:41 11:39:44

MS. WANG: Objection to form. 11:39:46

A Yes. In the sense that mucosal surfaces are not inside, they're outside of us, and so much like the interior of our mouth, they're exposed to different antigens routinely, whereas your lymph nodes generally are not, yes. 11:39:50 11:39:52 11:39:55 11:39:58 11:40:01

BY MR. POWERS: 11:40:05

Q One of those mucosal antibody isotypes is IgA, correct? 11:40:05 11:40:10

A That is correct. 11:40:12

Q Generating antibodies at mucosal sites often requires mucosal immune activation, correct? 11:40:16 11:40:20

A It depends on the species. So there's a receptor called the neonatal Fc receptor, which is abundant in humans, for example, and in 11:40:25 11:40:29 11:40:36

rabbits. 11:40:39

The neonatal receptor is responsible 11:40:40

for two things: One, transport of maternal IgG 11:40:43

into the fetus early on. It's not all -- not all 11:40:48

animals. For example, mice get their maternal IgG 11:40:54

by milk suckling, and it's transported into the 11:40:58

blood from the lumen of the gut backwards into the 11:41:02

blood. Humans and rabbits give it directly from 11:41:05

the placenta. 11:41:11

So the amount of -- the amount of -- 11:41:12

the immunoglobulin is produced locally in both 11:41:17

ways is what I'm trying to say. I'm sorry, yeah. 11:41:20

Q Locally in both ways. What do you mean 11:41:23

by that? 11:41:25

A I'm sorry, that was -- that was 11:41:26

terribly confusing. 11:41:26

There are local patches of lymphoid 11:41:28

tissues along the guts of all vertebrates. We 11:41:34

often think of Peyer's patches as -- as guts. 11:41:39

These are essentially fixed lymph nodes that are 11:41:44

closely approximated to the internal lining of the 11:41:48

mucosa. They contain standard germinal centers 11:41:54

that persist chronically because of the bacterial antigens that are chronically stimulating -- the gut is not a sterile place. 11:41:58 11:42:01 11:42:04

These secrete antibodies. They also secrete IgG. And that antibody is transported by two different mechanisms into the lumen of the gut. 11:42:07 11:42:09 11:42:13 11:42:16

The same thing occurs in systemic immunization. It's just that there's no -- generally for us there's no chronic stimulation because there's no chronic exposure to outside antigen with lymph nodes or spleen. 11:42:17 11:42:21 11:42:24 11:42:27 11:42:31

Q These lymphoid tissues that exist in the mucosal lining, are they able to host B cell-cell maturation? 11:42:34 11:42:36 11:42:43

A B cell-cell maturation in the sense of activation by antigen differentiation, yes, they do. 11:42:48 11:42:50 11:42:53

Q And is it your understanding that those lymphoid tissues exist in the reproductive tract of the female? 11:42:54 11:42:57 11:43:02

A My understanding is that they do. 11:43:03

Q Are you unsure about that? 11:43:08

A I don't know -- all mucosal surfaces 11:43:10

that I know, the nasopharynx, the gut, all have 11:43:12

these lymphoid patches. I do not know 11:43:15

specifically that the female reproductive tract 11:43:18

does. 11:43:21

Q You didn't consider as part of your 11:43:21

opinion whether or not the female reproductive 11:43:23

tract does host such lymphoid tissues, correct? 11:43:25

A No. That was not relevant to my 11:43:28

declaration. 11:43:30

Q Do you agree that mucosal vaccines can 11:43:34

preferentially stimulate mucosal immune response? 11:43:37

A They are designed to do so, yes. 11:43:41

Q That was the intent -- that would be 11:43:42

the intent of giving a mucosal vaccine, correct? 11:43:44

A That is correct. 11:43:47

Q You agree that intranasal vaccination 11:43:50

is a form of mucosal vaccine delivery, right? 11:43:53

A They are. 11:43:56

Q Do you agree that intranasal 11:43:57

vaccination can be efficient at inducing 11:43:59

antigen-specific antibody responses? 11:44:02

A They can be, yes. 11:44:04

MS. WANG: Objection to form. 11:44:06

BY MR. POWERS: 11:44:08

Q And same question but with regard to the female genital tract. So do you understand that intranasal vaccination can be efficient at inducing antigen-specific antibody responses in the female reproductive tract? 11:44:08 11:44:10 11:44:14 11:44:18 11:44:21

MS. WANG: Objection to form. 11:44:23

A I don't know. 11:44:26

BY MR. POWERS: 11:44:28

Q You don't know whether or not that was reported in the prior art? 11:44:28 11:44:30

A I know it was discussed in the prior art. It was claimed that this might be a way to increase antibody titers. I know -- yes, that's the extent that I know. 11:44:32 11:44:34 11:44:39 11:44:44

Q You didn't consider such references in offering your opinions in your declaration; is that correct? 11:44:48 11:44:51 11:44:53

MS. WANG: Objection to form. 11:44:54

A I didn't consider it to be relevant to my declaration. 11:44:54 11:44:58

BY MR. POWERS: 11:45:00

Q There were studies that showed that intranasal administration of antigen elicited a stronger AGG -- sorry. Try that again. 11:45:00 11:45:02 11:45:05

There were studies that showed that intranasal administration of an antigen elicited stronger IgA responses than for IgG, right? 11:45:08 11:45:10 11:45:15

A That would be expected, yes. 11:45:18

Q What's the importance of an IgA response in mucosal tissue? 11:45:26 11:45:28

MS. WANG: Objection to form. 11:45:30

A The -- so the response is that in the mucosal lymphoid aggregates, the mucosal tissues, the T follicular helper cells that are resident there, and the T helper cells that are resident there, are specialized to promote class switch to IgA. 11:45:39 11:45:41 11:45:46 11:45:50 11:45:52 11:46:04

(Stenographer requested clarification.) 11:46:04

A And that's based on the cytokine profile that they do. And that specialization is 11:46:27 11:46:11

not seen in parental lymphoid sites to a great deal. So they're biased to producing IgA. They also produce IgG and they produce IgM. 11:46:14 11:46:21 11:46:28

BY MR. POWERS: 11:46:31

Q I see. 11:46:31

So IgA is the predominant isotype produced in mucosal lining; is that right? 11:46:32 11:46:39

A It is the prominent -- it is the predominant resident B cell-cell population, yes, plasmacyte population. 11:46:41 11:46:43 11:46:46

Q But IgA and IgM exist as well, right? 11:46:50

A And IgG, yes. 11:46:52

Q And IgG. 11:46:54

A Yes. 11:46:55

Q I see. That's what I meant. 11:46:56

So just evolutionarily, though, what is the role of IgA in the mucosal lining? 11:46:59 11:47:02

MS. WANG: Objection to form. 11:47:08

A Yeah. So the imputed role of IgA is there's a special joining piece that allows it to be secreted across the mucosal barrier into the luminal contents, and we presume that -- we know 11:47:11 11:47:13 11:47:17 11:47:21

that antigen is taken into these local germinal centers from the luminal contents, activates the B cells, they proliferate, they mutate, they class switch, and the antibodies, as those cells leave the germinal centers, some significant population of them stay locally, and the antibodies that they secrete Crete with the so-called secretory piece are transmitted into the lumen of the gut. So they're -- in that sense, they are a local producer of mucosal antibodies. 11:47:30 11:47:34 11:47:36 11:47:39 11:47:41 11:47:43 11:47:46 11:47:49 11:47:54 11:47:56

BY MR. POWERS: 11:48:00

Q And those -- so IgA exists as a dimer, correct? 11:48:00 11:48:05

A In its native form, it is -- it's an IgG-like dimeric -- what am I trying to say -- identical symmetrical molecule. It can be joined together by the so-called J chain, and that makes it a four-valent antibody. 11:48:07 11:48:13 11:48:22 11:48:26 11:48:29

Q Quadrivalent; is that correct? 11:48:33

A It would be quadrivalent in that case, yes. 11:48:35 11:48:37

Q Does the quadrivalency of the IgA dimer 11:48:40

assist with binding to antigen? 11:48:45

A The quadrivalency increases the 11:48:50

apparent binding strength, the so-called avidity, 11:48:53

which is the sum of binding of the individual 11:48:57

combining sites, which is affinity, yes. 11:49:00

Q And does the quadrivalency help 11:49:02

agglutinate antigen as well? 11:49:07

MS. WANG: Objection to form. 11:49:10

A Multivalents antibodies, IgM, IgA, are 11:49:11

efficient agglutinators, yes. 11:49:15

MR. POWERS: It's 11:50. Would you 11:49:18

like to take a break for lunch? 11:49:30

THE WITNESS: I would be happy with 11:49:31

that. 11:49:32

MR. POWERS: Okay. Me too. Thank you. 11:49:32

THE WITNESS: Thank you. 11:49:35

THE VIDEOGRAPHER: We're going off the 11:49:36

record. Time is 11:49. 11:49:36

(Whereupon, a recess was taken.) 11:51:25

THE VIDEOGRAPHER: Okay. We're back on 12:42:57

the record. The time is 1:04 p.m. 01:04:30

BY MR. POWERS: 01:04:34

Q Welcome back, Dr. Kelsoe. 01:04:35
A Thank you. 01:04:37
Q During the lunch break or at any break so far today, have you spoken with counsel about the substance of your testimony? 01:04:37 01:04:40 01:04:42
A I have not. 01:04:43
Q Dr. Kelsoe, by 2012, it was well known that antisperm antibodies could impair fertility through multiple mechanisms, correct? 01:04:47 01:04:50 01:04:55
A To my knowledge, no. I'm not an expert on the antisperm antibody and fertility. I know the association, but I don't know the mechanism. 01:04:59 01:05:02 01:05:06
Q I'm going to hand you a document that's been previously marked in this case as Exhibit 2116. 01:05:23 01:05:24 01:05:27
(Previously marked Exhibit Number 2116 was identified.) 01:05:33 01:05:33
BY MR. POWERS: 01:05:33
Q Here it is. 01:05:33
Could you pass this to Madam Court Reporter? Thank you. 01:05:33 01:05:34
Do you recognize this document, Doctor? 01:05:39

A Yes. 01:05:41
Q What is this document? 01:05:41
A This is a review paper on antisperm 01:05:43
antibodies and fertility. 01:05:48
Q You didn't cite this document in your 01:05:51
declaration, did you? 01:05:53
A I don't think so, no. 01:05:54
Q Dr. Cherr did cite it in his 01:05:55
declaration, though, correct? 01:05:57
A I'm sorry, was that a question? 01:06:05
Q It was. 01:06:07
Dr. Cherr cited this document in his 01:06:07
declaration, right? 01:06:10
A All right. Yes. 01:06:10
Q Now, if you look at page 174 in this 01:06:15
document? 01:06:21
A Yes. 01:06:31
Q Just to back up, is it your 01:06:32
understanding that this is a review article? 01:06:33
A Yes. 01:06:35
Q Exhibit 2116 is a review article, 01:06:36
right? 01:06:39

A (Nonverbal response.) 01:06:40
Did I say yes? 01:06:43
Q You need to -- 01:06:44
A I'm sorry. Yes. 01:06:44
Q I just asked a slightly different and 01:06:45
better question. So 2116 is a review article, 01:06:47
right? 01:06:52
A 2116, "Antisperm antibodies and 01:06:52
conception" is a review article. 01:06:57
Q Thank you. 01:06:59
And on page 174, in the first paragraph 01:06:59
on the left side, about the middle of that 01:07:12
paragraph, the sentence starts "Jager, et al." 01:07:15
Do you see that? 01:07:22
A The middle of the paper Jager... 01:07:23
Q One, two, three, four, five, six, 01:07:28
seven -- eight lines down in that paragraph. 01:07:30
A One, two, three, four, five, six, 01:07:33
seven, eight... 01:07:35
Yes, Jager, et al., I beg your pardon. 01:07:37
Uh-huh. 01:07:39
Q Yes. It says: Jager, et al. reported 01:07:40

that IgG can also induce a shaking phenomenon but suggested that the fragment crystallizable (Fc) region of the IgG molecule may be impairing the motility of the antibody-bound sperm in the cervical mucus. 01:07:42 01:07:47 01:07:51 01:07:54 01:07:57

A Yes. 01:07:59

Q Is that correct? 01:07:59

A That is correct. 01:07:59

Q Okay. So antibodies were thought to impair the motility of the antibody-bound sperm in the cervical mucus, correct? 01:08:00 01:08:04 01:08:07

A That is the claim, yes. 01:08:08

Q Do you agree that antisperm antibodies can inhibit sperm motility? 01:08:16 01:08:17

MS. WANG: Objection to form. 01:08:23

A I have no direct knowledge of that. 01:08:24

BY MR. POWERS: 01:08:25

Q Do you agree that antisperm antibodies can induce sperm agglutination? 01:08:25 01:08:27

MS. WANG: Objection to form. 01:08:32

A In vitro, that's an assay I know that has been used, yes. 01:08:33 01:08:36

BY MR. POWERS: 01:08:37

Q So antibodies that bind sperm can cause agglutination? 01:08:37 01:08:43

A Ex vivo, that's for sure. 01:08:44

Q Do you have any knowledge of whether that can happen in vivo? 01:08:47 01:08:48

A I do not. 01:08:51

Q You don't know one way or the other? 01:08:51

A I do know that it's -- ex vivo is an actual test that's been performed by various laboratories. I do not know whether it occurs in vivo. 01:08:52 01:08:55 01:08:58 01:09:01

Q Okay. Are you aware of the Frayne reference? 01:09:02 01:09:21

A A frame reference? 01:09:24

Q I'm going to hand you -- 01:09:26

A Okay, thank you. 01:09:26

Q -- Exhibit 2114. 01:09:26

(Previously marked Exhibit Number 2114 was identified.) 01:09:28 01:09:28

A Very good, thank you. 01:09:29

Yes. This is another review, yes. 01:09:43

BY MR. POWERS: 01:09:44

Q Another review -- what's the title? So you've seen this document before? 01:09:44 01:09:46

A I don't think so, no. 01:09:47

Q You actually cited this document in your declaration. 01:09:51 01:09:53

A Then it's slipped my memory, then, because there's been dozens of those, yes. 01:09:54 01:09:56

Q No problem. 01:09:59

So what's the title of this document? 01:10:00

A "The potential use of sperm antigens as targets for immunocontraception; past, present, and future." 01:10:03 01:10:06 01:10:12

Q If you go to page 3 of that document. 01:10:14

A Yes. 01:10:21

Q In the first full paragraph of that -- of text on that page, it says: However, the detrimental effect of such antibodies on fertility is primarily caused by their ability to trap or agglutinate sperm in semen and cervical mucous rather than specifically inhibiting -- rather than by specifically inhibiting gamete interactions. 01:10:22 01:10:28 01:10:33 01:10:37 01:10:40 01:10:44 01:10:46

Correct? 01:10:51

A I'm trying to find this. This is on page 3? 01:10:51 01:10:53

Q Page 3 of the document. 01:10:54

A One, two -- oh, I'm sorry. I was on the wrong page. Beg your pardon. 01:10:57 01:10:58

And the paragraph is the center -- 01:11:00

Q The first full paragraph on page 3, and I'd like to direct you to the text at the bottom of that paragraph starting with "However." 01:11:07 01:11:09 01:11:11

A Hmm. Yes. "However, the detrimental effects of such antibodies on fertility is primarily caused by their ability to trap or agglutinate sperm in semen and cervical..." 01:11:14 01:11:18 01:11:20 01:11:23

That's what the sentence says. 01:11:29

Q And this article was published in 1999, correct? 01:11:30 01:11:34

A That is correct. 01:11:34

Q So a person of ordinary skill in the art in 2011 or 2012 would have known of this article, correct? 01:11:34 01:11:36 01:11:40

A Yes. 01:11:40

Q And so would you agree with me that it was reported in the literature that antibodies can agglutinate sperm in vivo? 01:11:42 01:11:44 01:11:48

A Is that what this actually says? 01:11:52

That is the claim of this review, absolutely. 01:12:39 01:12:44

Q Do you agree that interference with sperm capacitation was another recognized mechanism? 01:12:51 01:12:52 01:12:55

A From my reading -- I'm not intimately familiar with that, but from my reading that was proposed as a second possibility, yes. 01:12:57 01:13:01 01:13:02

Q A mechanism of infertility? 01:13:04

A Yes. 01:13:07

Q And interference with the acrosome reaction was also a known mechanism of interference with fertility, correct? 01:13:09 01:13:10 01:13:14

A I think in terms of in vitro fertility studies, acrosome inhibition, the penetrating part of the sperm, that was shown to inhibit in vitro fertilization. 01:13:17 01:13:22 01:13:24 01:13:28

Q And do you agree that antisperm 01:13:35

antibodies were known to simulate complement-mediated sperm lysis? 01:13:38 01:13:40

A No. I do not know that. 01:13:44

Q Okay. I'm going to direct you back to Exhibit 2116. 01:13:56 01:13:58

A Yes. 01:14:01

Q The Chamley reference -- 01:14:02

A Yes. 01:14:05

Q -- which was cited by Dr. Cherr? 01:14:05

A Uh-huh. 01:14:07

Q On page 174 of that reference -- 01:14:13

A Yes. 01:14:16

Q Forgive me. 175 on that reference, on the left column, in the left column. 01:14:16 01:14:37

A Uh-huh. 01:14:39

Q Eight lines down, there's a sentence that starts with "D'Cruz, et al." 01:14:39 01:14:44

A Yes. 01:14:48

Q It says: D'Cruz, et al. have also demonstrated that sperm-bound ASA obtained from the ejaculates of men with ASA are capable of activating complement. 01:14:52 01:14:55 01:14:58 01:15:02

A Uh-huh. 01:15:04
Q Do you see that statement? 01:15:05
A Yes, I do. 01:15:06
Q So isn't it true that antisperm 01:15:07
antibodies were known to simulate 01:15:09
complement-mediated sperm lysis? 01:15:11
A These were all in vitro assays, and so 01:15:14
in vitro, yes. Evidently that's been reported. 01:15:18
Q Do you have any knowledge of whether or 01:15:23
not such results were found in vivo? 01:15:24
A Not to my knowledge. I do not have 01:15:31
that knowledge. 01:15:33
Q PH20 is a sperm-associated protein, 01:15:33
correct? 01:15:36
A That is correct. 01:15:39
Q And PH20 is expressed on the surface of 01:15:39
sperm, correct? 01:15:42
A That is correct. 01:15:44
Q PH20 is localized on the sperm 01:15:47
acrosome, correct? 01:15:49
A I thought it was in the posterior head, 01:15:53
which is below the acrosome. That's where the 01:15:55

PH20 antibody binds anyway. 01:16:00

Q Okay. Do you know where on the sperm 01:16:02

PH20 binds and -- or sorry -- PH20 is localized? 01:16:05

A My understanding from the Primakoff 01:16:11

paper in which the original antibodies -- the 01:16:15

sperm antibodies were described, all the PH 01:16:20

antibodies -- PH20 is the relevant one -- bind on 01:16:24

the posterior head. 01:16:28

Q Anywhere else where you know, one way 01:16:30

or the other, whether PH20 is localized in the 01:16:33

sperm? 01:16:36

A Only by those antibodies. I just know 01:16:37

from the immunofluorescence image that they 01:16:41

provided as a result. 01:16:45

Q But you do understand that PH20 is a 01:16:47

surface protein on sperm -- 01:16:50

A I do. 01:16:53

Q -- correct? 01:16:53

A person of ordinary skill in the art 01:16:57

would expect that an antibody bound to PH20 on 01:17:00

sperm would be an antisperm antibody, correct? 01:17:03

A By definition, yes. 01:17:06

MS. WANG: Objection to form. 01:17:08

BY MR. POWERS: 01:17:08

Q And once bound an antibody bound to PH20 could impair motility like other sperm antibodies, correct? 01:17:08 01:17:12 01:17:17

MS. WANG: Objection to form. 01:17:20

A So -- despite my old master's thesis, I am not an expert on sperm motility. 01:17:22 01:17:26

Basically, the binding of PH20 antibodies that were described by Primakoff originally show bindings on the head, not on the tail, and I would have guessed that antisperm antibodies that bind to the tail would more likely inhibit motility than those that bind to its head. 01:17:32 01:17:36 01:17:38 01:17:41 01:17:45 01:17:49

BY MR. POWERS: 01:17:52

Q But you don't know one way or the other sitting here today? 01:17:52 01:17:55

A Beyond what I just explained, I do not know. 01:17:56 01:17:57

Q Do you know if an antibody bound to PH20 on sperm could cause sperm agglutination? 01:18:01 01:18:05

A If the sperm were in close enough 01:18:12

approximation and the antibody could span the distance between the two, yes. 01:18:14 01:18:17

Q It could cause agglutination? 01:18:20

A Under the ideal conditions, absolutely. 01:18:22

Q Do you know if an antibody bound to PH20 on sperm could produce sperm penetration through cervical mucus? 01:18:26 01:18:28 01:18:30

A I have no firsthand knowledge of this at all. It would surprise me. But these are tiny molecules. You know, these are less than a few angstroms long. Why this would delay the antibody migrating through cervical mucus, I just -- perhaps it could, but I find it -- these are molecules. 01:18:37 01:18:39 01:18:48 01:18:51 01:18:55 01:18:59 01:19:06

Q This isn't really your field, correct? 01:19:06

MS. WANG: Objection to form. 01:19:10

A This is not my field, that is correct. 01:19:11

BY MR. POWERS: 01:19:13

Q Do you know if an anti-PH20 antibody could interfere with capacitation of sperm? 01:19:13 01:19:17

A From my reading, my understanding is that the binding that has been studied is post 01:19:24 01:19:27

capacitation, so I don't know. I mean, I simply don't know whether it could or not. 01:19:30 01:19:35

Q You don't know one way or the other? 01:19:37

A I do not. 01:19:38

Q Do you know if an anti-PH20 antibody binding to sperm could interfere with the acrosome reaction? 01:19:39 01:19:41 01:19:46

A The acrosome is at the apex of the head. The antibodies are at the posterior head. I would assume not. Given the fact that -- no, that's it. I don't know. Yeah. 01:19:48 01:19:51 01:19:53 01:20:00

Q You don't know one way or the other? 01:20:02

A Only from sort of general biological principles. 01:20:04 01:20:07

Q Do you know if an anti-PH20 antibody bound to sperm could activate complement and promote sperm lysis? 01:20:09 01:20:13 01:20:18

A The antibody, in theory, if complement is available, could promote sperm lysis, depending on, of course, the isotype and the density of antibody on the sperm. 01:20:21 01:20:25 01:20:29 01:20:32

Q So, yes, it's a possibility, right? 01:20:34

A It is a possibility. 01:20:35

MS. WANG: Objection to form. 01:20:36

BY MR. POWERS: 01:20:36

Q Do you know what the zona pellucida is? 01:20:36

A In general terms. I know it's the region that surrounds the ovum prior to fertilization. 01:20:43 01:20:46 01:20:50

Q Do you know what the zona pellucida is made of? 01:20:51 01:20:53

A Hyaluronans, my understanding is. Mucous, sort of. 01:20:54 01:20:57

Q Do you know if an anti-PH20 antibody bound to sperm could interfere with the sperm's penetration of the zona pellucida? 01:21:01 01:21:03 01:21:06

A My understanding from the readings is that it slows -- ex vivo, it slows penetration of the zona pellucida. 01:21:10 01:21:11 01:21:14

Q But you're not an expert in the biology of the zona pellucida? 01:21:17 01:21:19

A I'm certainly not. 01:21:21

Q Do you still have your declarations in front of you? 01:21:55 01:21:56

A Yes. 01:22:01

Q Would you go to paragraph 63 of your declaration? In that paragraph you talk about ZP3, right? 01:22:01 01:22:03 01:22:15

A Let me just read the paragraph to make sure I'm with you on this. 01:22:17 01:22:18

Q Sure. 01:22:19

A Yes. I've read the paragraph now. 01:22:35

Q In that paragraph you talk about ZP3, correct? 01:22:40 01:22:43

A mZP3, yes. 01:22:45

Q ZP3 is an ovarian antigen, correct? 01:22:51

A I certainly don't know. As an immunologist, I simply took that as an immunogen. A sperm associated or -- of a -- not a sperm associated -- a fertilization associated immunogen. 01:22:56 01:22:59 01:23:04 01:23:07 01:23:10

Q Do you know what ZP stands for in mZP3? 01:23:11

A Zona pellucida, I suppose. 01:23:15

Q Yeah. So applying that logic, would you agree that ZP3 is an ovarian antigen? 01:23:17 01:23:19

A It surrounds the ovum, yes. 01:23:23

Q So ZP3 is expressed by female ovarian tissue, right? 01:23:27 01:23:33

A Uh-huh. 01:23:34

Q So it's a self-antigen in females, correct? 01:23:34 01:23:36

A It would be, yes. 01:23:37

Q Do you agree that this group that you referred to in this paragraph was able to raise antibodies against ZP3 even though it was a self-antigen in females? 01:23:42 01:23:45 01:23:47 01:23:50

A That's what their claim is, yes. 01:23:52

Q Do you agree that a mucosal antibody response isn't relevant for ovarian tissue? 01:23:54 01:23:57

A Could you repeat the question. 01:24:00

Q In this context or this -- where you're talking about this paper, is a mucosal antibody response relevant or is systemic antibody response? 01:24:02 01:24:05 01:24:08 01:24:12

A To my recollection, this was not a mucosal immunization. This was a systemic immunization. 01:24:13 01:24:15 01:24:17

Q So a mucosal antibody response isn't 01:24:19

relevant for this paper that you're talking about in this paragraph, right? 01:24:21 01:24:22

A Right. 01:24:23

MS. WANG: Objection to form. 01:24:24

A So what is relevant is the presence -- presumably is the presence of antibody. The mechanism is not shown, as I recall. It's simply there's a correlation. 01:24:25 01:24:29 01:24:31 01:24:35

So the question is, is can you get antibody into the fallopian tubes, the oviducts? Do you require an immune response that is mucosally associated, or can you have a systemic immune response? And systemic immune response, certainly in this case and in many other -- and in human vaccines can produce strong IgG responses in the mucosal surfaces. 01:24:37 01:24:43 01:24:47 01:24:52 01:24:57 01:25:01 01:25:03 01:25:10

So would a mucosal immunization be necessary in this case, the paper says it's not. Would it have been official? I can't speculate. 01:25:12 01:25:16 01:25:19

BY MR. POWERS: 01:25:24

Q Okay. Fair to say that the ovary is not subject to a mucosal immune response? 01:25:24 01:25:26

A The oviducts are connected to the outside like anything else. I would -- I don't know about the -- if there's any associated lymphoid tissue. I just don't know that. 01:25:31 01:25:34 01:25:38 01:25:44

Q Do you know where the ovum matures in a woman? 01:25:47 01:25:51

A Actually, no. Travels from the ovary through the fallopian tubes and it embeds somewhere in the plumbing going down, but I don't know for sure, no. 01:25:57 01:26:02 01:26:04 01:26:06

Q So you can't say one way or the other whether a mucosal immune response would be relevant to the paper that you address in paragraph 63 of your declaration? 01:26:08 01:26:10 01:26:14 01:26:18

MS. WANG: Objection to form. 01:26:21

BY MR. POWERS: 01:26:21

Q Right? 01:26:21

A I'm not sure that -- maybe I'm not -- the antifertilization state that's referenced here was achieved by systemic fertilization. 01:26:22 01:26:29 01:26:33

Q Right. 01:26:37

A If the antigen is an ovarian antigen, 01:26:37

then somehow the systemic antibody reached, presumably, prohibited fertilization. 01:26:40 01:26:43

Q And I'm trying to explore that with you. 01:26:51 01:26:53

A Okay. 01:26:53

Q Is that necessarily true if the oocyte matures in the ovary before it reaches any kind of mucosal secretion? 01:26:54 01:26:58 01:27:04

A I'm sorry. I understand the question now. 01:27:06 01:27:07

If the oocyte is prohibited from being released from the ovary, for example, I guess one would also see an anticonceptive state. 01:27:07 01:27:10 01:27:13

Q So simply by impairing the maturation of the oocyte to prevent it from releasing into the oviduct, you could see a decline in fertility, correct? 01:27:18 01:27:21 01:27:25 01:27:33

MS. WANG: Objection to form. 01:27:35

A Again, I'm not an expert. But that -- if one blocks sperm production, one sees a loss of fertility. If one block's ovum maturation and release, one would also see a loss of fertility. 01:27:36 01:27:38 01:27:44 01:27:47

BY MR. POWERS: 01:27:50

Q Another way of asking the question is, 01:27:50

the developing oocyte is not subject to the 01:27:52

mucosal compartment, right? 01:27:55

A Again, I don't know what is exposed to 01:27:59

the oviduct. I just don't know. 01:28:01

Q Do you agree that a useful 01:28:32

contraceptive doesn't require complete 01:28:34

infertility? 01:28:38

MS. WANG: Objection to form. 01:28:41

A I suppose that depends on what the 01:28:46

intent of the complete contraceptive activity is. 01:28:49

I would think in the case of, like, a human drug, 01:28:58

that 100 percent -- very high efficacy would be 01:29:04

required, 90-some-odd plus percent, much like 01:29:10

normal birth control, hormonal birth control. 01:29:14

If the immunization was used to reduce 01:29:17

wildlife populations, maybe 50 percent reduction 01:29:21

would be an ecological good thing. So I think it 01:29:26

depends on what the intent of the -- of the -- the 01:29:29

immune state is intended to address. 01:29:35

BY MR. POWERS: 01:29:36

Q So you can imagine a useful contraceptive that has efficacy as low as 50 percent? 01:29:36 01:29:38 01:29:42

MS. WANG: Objection to form. 01:29:44

BY MR. POWERS: 01:29:44

Q Is that right? 01:29:44

A That simply is a question relating to my prior answer. If you're controlling rabbit populations in Australia, maybe a 50 percent reduction would be ecologically beneficial. If you're trying to control human birth, for example, 50 percent reduction would probably not be useful. It certainly wouldn't -- it wouldn't match already standing mechanisms, hormonal mechanisms for contraception. 01:29:45 01:29:48 01:29:54 01:29:56 01:30:02 01:30:05 01:30:10 01:30:14 01:30:18

Q So it would depend on the use case? 01:30:19

A The intended use, I think so. 01:30:22

Q But at least some uses would be beneficial in a 50 percent reduction in fertility, right? 01:30:25 01:30:30 01:30:33

MS. WANG: Objection to form. 01:30:34

A 50 percent reduction would be good -- 01:30:35

or have a potential benefit only in those conditions. And I would imagine if you reduce the pigeon population of New York, a 50 percent reduction would be both beneficial and appreciated. If you reduce the fecundity of a married couple, a human married couple by 50 percent, that probably would not have any utility. 01:30:39 01:30:42 01:30:49 01:30:53 01:30:57 01:31:02 01:31:05 01:31:08

BY MR. POWERS: 01:31:11

Q Most contraceptives do not have 100 percent effectiveness, correct? 01:31:11 01:31:14

A I think hormonal contraceptives are -- and in my personal experience, greater than 99 percent effectiveness or something like that. Surgical resection vasectomies, 90-something percent positive. Tying the fallopian tubes are pretty close to 100 percent. I think those are all mechanisms of contraception. 01:31:20 01:31:23 01:31:28 01:31:32 01:31:37 01:31:44 01:31:46

Q So surgical interventions, you'd consider that contraception. 01:31:50 01:31:52

A It certainly stops conception. 01:31:54

Q Would it surprise you to know that the 01:32:00

real-world efficacy of birth control pills is only around 93 percent? 01:32:01 01:32:05

MS. WANG: Objection to form. 01:32:07

A It would surprise me. I'm obviously not an expert in reproductive biology, and I wonder, like all drug studies, how much of this is due to patient error in taking the drug versus the efficacy of the drug, per se. 01:32:13 01:32:16 01:32:19 01:32:22 01:32:25

BY MR. POWERS: 01:32:30

Q Do you agree that condoms don't have 100 percent effectiveness? 01:32:30 01:32:32

A I do. But that is condom use. As a physical barrier, it's 100 percent effective. 01:32:34 01:32:40

Q Are you aware of how effective condoms are with typical real-world use? 01:32:46 01:32:48

A No. 01:32:52

Q Would it surprise you that condoms are only around 87 percent effective with typical -- 01:32:53 01:32:54

A It would not surprise me. 01:32:58

Q Do you understand that contraceptives are sometimes used in combination? 01:33:00 01:33:02

MS. WANG: Objection to form. 01:33:09

BY MR. POWERS: 01:33:09

Q With one another? 01:33:09

Let me try that again. 01:33:12

A I mean, I'm not -- 01:33:13

Q Let me ask a different question. 01:33:14

A Yes, okay. 01:33:15

Q Do you understand that multiple modes of contraceptive devices or interventions are used in combination sometimes? 01:33:16 01:33:18 01:33:23

A I have no personal experience or professional experience to say yes or no. I just don't know. 01:33:26 01:33:27 01:33:33

Q You don't know one way or another? 01:33:33

A I mean, I'm thinking like -- I do not know one way or the other. 01:33:36 01:33:40

Q You've never heard of somebody using a condom in a spermicidal lubricant? 01:33:42 01:33:45

A You're absolutely correct. Only in the context of HIV transmission, but yes. 01:33:55 01:33:57

Q So is it fair to say that frequently multiple modes of contraception are used together? 01:34:00 01:34:03

MS. WANG: Objection to form. 01:34:07

A I don't know what the frequency is, but it's certainly frequent enough for me to know that this occurs. 01:34:10 01:34:12 01:34:14

BY MR. POWERS: 01:34:16

Q And you would agree that contraceptives have been and are still used today as tools for population control in animals, correct? 01:34:16 01:34:18 01:34:22

A Contraceptives? 01:34:25

Q Yes. 01:34:26

A Yes. 01:34:26

Q And you would agree that a method for population control in animals would not need to cause complete infertility to be useful -- 01:34:30 01:34:33 01:34:37

MS. WANG: Objection to form. 01:34:40

A That's my -- 01:34:40

(Stenographer requested clarification.) 01:34:40

Q You would agree that, as a method for population control, a contraceptive would not need to cause incomplete fertility to be useful, correct? 01:34:48 01:34:51 01:34:59 01:35:02

MS. WANG: Objection to form. 01:35:04

A I think that -- and, again, as I 01:35:04

described in the sense of ecological control for a species, a 50 percent reduction of the fecundity would have an important and valuable role. 01:35:07 01:35:12 01:35:18

BY MR. POWERS: 01:36:08

Q Do you agree that certain contraceptive methods are not designed to last for more than a few minutes? 01:36:08 01:36:10 01:36:12

MS. WANG: Objection to form. 01:36:13

A In my experience, condoms, for example, are employed for contraception on the order of minutes, yes. 01:36:26 01:36:28 01:36:32

Q Similar for spermicides? 01:36:35

A That would be my understanding. 01:36:40

Q What about the sponge method? 01:36:49

A I have no personal knowledge of the sponge method. 01:36:51 01:36:55

Q You have no expertise in the sponge method? 01:36:56 01:36:57

A I'm a male. We don't do that, but, no, I do not. 01:36:58 01:37:01

Q And what about spermicides? They're designed to only have efficacy for a few minutes, 01:37:06 01:37:09

correct? 01:37:11

A They should have a short half-life, 01:37:12

yes. 01:37:14

Q So you would agree that a persistent 01:37:14

response is not necessarily required for 01:37:16

contraception, right? 01:37:18

MS. WANG: Objection to form. 01:37:20

A Persistent... 01:37:21

Well, again, I think this gets to 01:37:22

intention. You just told me that condom use is 01:37:34

87 percent effective, whereas hormonal control is 01:37:41

93 percent effective. Both of those have the 01:37:46

potential of misuse, forgetting a pill or a 01:37:51

fracture of the condom or a loss of the condom. 01:37:55

But, yeah, if you think about 01:38:09

contraception, I think most people -- at least I 01:38:12

think about it as a family, someone who has a 01:38:13

family, is something that is lasting and not -- 01:38:16

relies at the last minute. 01:38:21

I couldn't imagine giving condoms to a 01:38:23

population of Australian rabbits and expecting any 01:38:27

sort of efficacy at all. 01:38:32

BY MR. POWERS: 01:38:34

Q That would be silly. 01:38:34

But you do agree that contraception 01:38:35

does not necessarily require a very long duration, 01:38:42

correct? 01:38:46

MS. WANG: Objection to form. 01:38:49

A In my understanding of contraception to 01:38:50

block, for example, the product of a single 01:38:53

coitus, it needs -- 01:39:02

(Stenographer requested clarification.) 01:39:07

A If the point was to only involve 01:25:38

contraception at that point, a relatively 01:39:13

short-acting contraceptive would be appropriate. 01:39:15

BY MR. POWERS: 01:39:20

Q Do you agree that condoms are a useful 01:39:20

contraception? 01:39:26

MS. WANG: Objection to form. 01:39:29

A I think that they have been used as a 01:39:29

useful contraceptive, at least in my world, in the 01:39:33

HIV world. They're more often used as 01:39:39

preventive-transmission block basically. 01:39:42

BY MR. POWERS: 01:39:48

Q And even at an 87 percent effective rate, they're considered useful, correct? 01:39:48 01:39:53

MS. WANG: Objection to form. 01:39:56

A They are considered useful given the consequences, for example, of HIV transmission, yes. 01:39:59 01:40:02 01:40:04

BY MR. POWERS: 01:40:08

Q As far as immunocontraception goes, you would agree that immunocontraception does not require lifelong antibodies, right? 01:40:08 01:40:21 01:40:23

MS. WANG: Objection to form. 01:40:25

A No. Putative contraceptive state and the one originally described by Primakoff was in guinea pigs, was reversible after a period of time. One could see how that would mean that the product would be a contraceptive and not a sterilizing product. 01:40:28 01:40:35 01:40:37 01:40:41 01:40:46 01:40:49

BY MR. POWERS: 01:40:53

Q Right. And you, therefore, might not want high titers of antibodies as part of your immune contraception at all times, right? 01:40:53 01:40:56 01:41:01

MS. WANG: Objection to form. 01:41:03

A The body takes care of that all by itself. There are very few antigens that have persistent antibody titers for periods of time longer than, let's say, five years. 01:41:03 01:41:09 01:41:12 01:41:16

BY MR. POWERS: 01:41:20

Q Do you agree that transient or even moderate antibody levels could be sufficient in an immunocontraceptive as long as they disrupt fertilization? 01:41:20 01:41:23 01:41:26 01:41:31

A Antibodies that -- 01:41:31

MS. WANG: Objection to form. 01:41:32

A -- effectively disrupt fertilization would be useful only if they persisted in sufficient amount for some period of time X, yes. 01:41:32 01:41:38 01:41:41

MR. POWERS: Let's take a little break. 01:41:47

THE VIDEOGRAPHER: We're going off the record. The time is 1:41 p.m. 01:41:52 01:41:53

(Whereupon, a brief recess was taken.) 01:56:23

THE VIDEOGRAPHER: We're back on the record. The time is 1:56 p.m. 01:56:34 01:56:35

BY MR. POWERS: 01:56:37

Q Dr. Kelsoe, during any of the breaks 01:56:37

today did you speak about the substance of your testimony with counsel? 01:56:39 01:56:41

A I did not. 01:56:42

MR. POWERS: Thank you very much. We have no further questions for you at this time. Pass the witness. 01:56:42 01:56:44 01:56:45

MS. WANG: Can you give us a few minutes? 01:56:50 01:56:51

THE VIDEOGRAPHER: Going off the record. The time is 1:56 p.m. 01:56:54 01:56:55

(Whereupon, a brief recess was taken.) 02:03:01

THE VIDEOGRAPHER: Back on the record. The time is 2:03 p.m. 02:03:01 02:03:41

MS. WANG: Thank you, Dr. Kelsoe. We have no questions. So the witness will read and sign. 02:03:46 02:03:47 02:03:50

THE VIDEOGRAPHER: This marks the end of the deposition of Dr. Garnett Kelsoe. We're going off the record at 2:04 p.m. 02:03:53 02:03:53 02:03:55

(Reserved signature.)

(The deposition concluded at 2:04 p.m.)

STATE OF NORTH CAROLINA)
COUNTY OF FORSYTH)

REPORTER'S CERTIFICATE

I, Audra Smith, Registered Professional Reporter in and for the above county and state, do hereby certify:

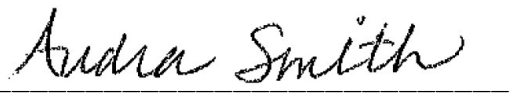
That GARNETT H. KELSOE, Ph.D., the witness whose deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition and that such deposition was taken before me and is a true record of the testimony given by such witness.

I further certify that the adverse party, the Petitioner MERCK SHARP & DOHME LLC, was represented by counsel at the deposition.

I further certify that the deposition of GARNETT H. KELSOE, Ph.D., occurred at Washington Duke Inn 3001 Cameron Blvd Durham, NC 27705 on Thursday, February 5, 2026, commencing at 9:09 AM to 2:04 PM.

I further certify that I am not related to any of the parties to this action by blood or marriage, I am not employed by or an attorney to any of the parties to this action, and that I am in no way interested, financially or otherwise, in the outcome of this matter.

IN WITNESS WHEREOF, I have hereto set my hand this 5th day of February, 2026.



Audra Smith, RPR, CRR, FCRR
Notary Number: 201329000033
Commission Expires: June 26, 2031

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