

James J. Moon, Ph.D.
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1 A. I have not done calculations to variations
2 of modified PH20.

3 But it's my opinion that all the modified
4 PH20 polypeptides that meet the definition as
5 outlined in Paragraph 14 would generate polyclonal
6 antibodies.

7 Q. And it's your opinion that if that set of
8 modified PH20 polypeptides includes 1049 different
9 polypeptide sequences, every one of those
10 polypeptide sequences, when administered to a
11 mammal, will induce antibodies that binds to the
12 wild-type PH20.

13 Is that your testimony?

14 DR. KHANDURI: Objection; form.

15 A. Once again, I have not calculated the
16 number of potential mutations and variations of
17 modified PH20.

18 But it's my opinion that all the allowed
19 modifications to PH20, as outlined in 14, would
20 result in polyclonal antibodies generated in female
21 mammals against any of the modified PH20
22 polypeptides, would bind to the wild-type PH20
23 polypeptide in vivo.

24 DR. KHANDURI: Counsel, it's
25 been about an hour. Can we take a break

1 soon?

2 MR. KUSHAN: Would you like to
3 take a break?

4 WITNESS: Yes.

5 MR. KUSHAN: Okay. We'll take a
6 break.

7 VIDEOGRAPHER: Off the record at
8 10:52 a.m.

9 (Whereupon, a recess was taken.)

10 VIDEOGRAPHER: We are going back
11 on the record at 11:18 a.m.

12 BY MR. KUSHAN:

13 Q. So, Dr. Moon, did you speak to anybody
14 over the break?

15 A. Yes. I talked briefly with my counsel
16 during the break.

17 Q. What did you talk about?

18 A. We continued to talk about lifespan
19 extension, yeah. Nothing related to the cases.

20 Q. All right. So do you remember earlier, at
21 the beginning of the deposition today, I told you
22 that, in the deposition, I ask you a question and
23 you have to answer the question I put to you.

24 Do you understand that?

25 A. Yes, I understand that.

1 Q. All right. And you understand that over
2 the last session of questions and answers, there was
3 a disconnect between the questions I put to you and
4 the answers you were providing to me. You were not
5 answering my questions.

6 Do you appreciate that?

7 DR. KHANDURI: Objection; form,
8 foundation.

9 A. I think I answered your question during
10 the last session.

11 Q. So do you recall I asked you one question
12 about the methodology someone might use in
13 evaluating a mutated poly- -- PH20 polypeptide, and
14 your understanding of my question seemed to be,
15 would I -- how do I find the best version of a PH20
16 polypeptide to use as a vaccine? And that's a
17 disconnect.

18 So I'd like you to please listen carefully
19 to the question that I present to you and answer the
20 question that I present to you directly.

21 If you don't understand the question I've
22 presented to you, tell me you don't understand it,
23 and I'll try to give you a better question.

24 If we go through the day today and you
25 cannot answer the question that I'm asking you, we

1 may need to have another deposition.

2 So I wanted you to understand that you
3 have to -- we're entitled to ask you questions, and
4 we're entitled to get your answers to my questions
5 that I've put to you.

6 Do you understand that?

7 DR. KHANDURI: Objection; form.

8 A. I understand that.

9 Q. Great. Could you go to your declaration
10 and go to Page 12 and look at Paragraph 22.

11 A. This is Case -0004?

12 Q. -0003.

13 A. -3?

14 Q. Yes. Do you have the -0003?

15 A. I used to have. Wait.

16 Q. Did you put those back?

17 A. Yeah.

18 MR. KUSHAN: Could you go look
19 and see if there's a -000- --

20 DR. KHANDURI: Oh. You want me
21 to take....

22 MR. BHATLA: -- -03 is down
23 there.

24 COURT REPORTER: I'm sorry.

25 MR. BHATLA: Six.

1 WITNESS: Thank you.

2 MR. KUSHAN: It's always
3 important to have the same document.

4 WITNESS: Yeah.

5 DR. KHANDURI: Counsel, could
6 you give all four declarations to the
7 witness, please.

8 (Exhibits handed to the witness.)

9 DR. KHANDURI: Thank you.

10 BY MR. KUSHAN:

11 Q. All right. So go to Page 12,
12 Paragraph 22.

13 A. Yes. I'm looking at Paragraph 22.

14 Q. All right. Do you see there's a figure
15 above Paragraph 22?

16 A. Yes, I see the figure.

17 Q. Okay. And it's illustrating different --
18 different antibodies, each binding to a distinct
19 epitope on the antigen, as it's depicted in the
20 picture -- figure. Right?

21 A. The figures are showing monoclonal
22 antibodies, the antigen with the different epitopes,
23 and polyclonal antibodies.

24 Q. Okay. So when you immunize a subject with
25 an antigen, you'll produce B cells that each

1 individually produce one antibody. Right?

2 A. Each B cell produces one type of
3 monoclonal antibody.

4 Q. Okay. And using the illustration you have
5 on Page 12, different B cells will be the source of
6 each of the different antibodies binding to a
7 different epitope on the antigen. Right?

8 DR. KHANDURI: Objection; form.

9 A. Yes. In general, B cells produce
10 monoclonal antibodies to each epitope. And when you
11 have a collection of B cells, they would cover
12 polyclonal antibodies.

13 Q. Okay. So if I have immunized a mammal
14 with an antigen and there's polyclonal antibody
15 response to that immunization, it creates a
16 repertoire of B cells that produce, each of them, a
17 different antibody that collectively make up the
18 antibodies in the polyclonal antisera.

19 Is that a fair statement?

20 DR. KHANDURI: Objection; form.

21 A. After vaccination, each B cell will
22 produce monoclonal antibody, and collection of the
23 B cells will produce polyclonal antibodies with a
24 diverse repertoire.

25 Q. Okay. Now, if you go to Paragraph 42 of

1 your declaration. This is on Page 24.

2 Do you see, in the middle -- in the second
3 sentence, you state:

4 ...POSAs would have
5 expected that each of these
6 polypeptides would present
7 numerous epitopes to the host's
8 immune system when administered
9 as a vaccine to a human female.

10 And that's referencing the set of modified
11 PH20 polypeptides -- well, sorry, the set -- that's
12 referring to the set of wild-type polypeptides that
13 are in SEQ ID 3 and 32-66. Right?

14 (Witness reading.)

15 A. I see the sentence in Paragraph 42.

16 Q. And you understand -- and your testimony
17 there is that a POSA would have expected that the
18 different polypeptides in that set would each
19 present numerous epitopes to the host's immune
20 system when that polypeptide was administered as a
21 vaccine to a human female. Right?

22 A. In Paragraph 42:

23 PH20 polypeptide with
24 amino acid sequence of any of
25 Sequence ID No. 3 and 32 and --

1 to 66 are at least 430 amino
2 acids long. Thus, POSA would
3 have expected that each of
4 these polypeptides would
5 present numerous epitopes to
6 the host's immune system when
7 administered as a vaccine to a
8 human female.

9 Q. Okay. So when a mammal is immunized with
10 one of those PH20 polypeptides, will antibodies to
11 every one of the epitopes on the modified PH20
12 polypeptide be produced during that polyclonal
13 antibody response?

14 DR. KHANDURI: Objection; form.

15 A. As I mentioned earlier, modified PH20
16 polypeptides will generate polyclonal antibody
17 responses.

18 And every one of modified PH20 would be
19 expected to generate polyclonal antibody responses.

20 Q. And my question was: Would the
21 immunization with the PH20 polypeptide cause the
22 mammal to produce antibodies to every epitope on the
23 PH20 polypeptide?

24 Do you understand my question?

25 A. I understand your question.

1 Q. Could you answer my question now?

2 A. When you perform immunizations with
3 polypeptides with multiple epitopes, as in PH20, you
4 expect to get polyclonal antibody responses to
5 multiple epitopes within that polypeptide.

6 There may be some epitopes that may not
7 generate antibody response. But, collectively, the
8 polypeptide has numerous multi-epitopes. Therefore,
9 a POSA would expect to get polyclonal antibody
10 responses covering a multitude of epitopes.

11 Q. What types of epitopes on the PH20 would
12 not induce production of antibodies against them?

13 DR. KHANDURI: Objection; form.

14 A. In general, when there are multiple
15 epitopes present in an antigen, they will generate
16 polyclonal antibodies against the multiple epitopes.

17 There may be some epitopes that do not
18 generate antibody response, but the majority of
19 epitopes found within the polypeptide will generate
20 antibody responses.

21 And we are focused on the mixture of
22 antibodies within the polyclonal repertoire. So you
23 anticipate generating polyclonal antibodies covering
24 the majority of epitopes found within that
25 polypeptide.

1 Q. Okay. And my question, again, is focused
2 on -- not the majority of the epitopes being bound
3 by the antibodies in the polyclonal.

4 I'm speaking to the -- what you
5 acknowledge, there are some epitopes that may not
6 induce production of an antibody against those
7 epitopes. I'm asking you about those epitopes.

8 And then, my specific question is: What
9 might cause the immune system to not produce
10 antibodies against those epitopes?

11 Do you understand my question?

12 A. Yes, I understand your question. Yeah.

13 Q. So please answer my question.

14 A. In general, there are multiple epitopes
15 present within polypeptide.

16 And when you vaccinate individual, they
17 will generate polyclonal antibodies covering a
18 multitude of epitopes within the polypeptide.

19 And there are many research tools
20 available that a POSA would use to generate
21 polyclonal antibody responses to even broader number
22 of epitopes present within that polypeptide
23 structures.

24 Q. So that answer does not an- -- that does
25 not answer the question I asked.

1 I was asking you about the epitopes on the
2 PH20 polypeptide that may not induce production of
3 an antibody response against those particular
4 epitopes.

5 And I'm asking you: What are the reasons
6 why the immune system might not produce antibodies
7 against certain of those epitopes on the PH20
8 polypeptide?

9 DR. KHANDURI: Objection; form.

10 A. There are some epitopes that could
11 generate high antibody response with high affinity.
12 There are some epitopes that could generate lower
13 affinity response.

14 But, collectively, these are still
15 polyclonal antibodies that are binding to multitude
16 of epitopes available in polypeptides.

17 Q. So is one of the reasons why the immune
18 system may not produce, in the polyclonal response,
19 antibodies to certain epitopes that the antibodies
20 don't form with sufficient affinity to the epitope?

21 DR. KHANDURI: Objection; form.

22 A. There may be certain epitopes that
23 generate lower affinity antibody response.

24 But, collectively, when you look at large
25 complex antigens, such as PH20, they present

1 multiple epitopes.

2 And, collectively, there are whole
3 polyclonal repertoires that will allow binding to
4 PH20.

5 Q. Dr. Moon, I want to make sure you
6 understand: I wasn't asking you about the majority
7 of the epitopes. I wasn't asking about the
8 collective response. My questions are pretty
9 narrow.

10 I'm only asking about the epitopes that do
11 not induce formation of antibodies within the
12 polyclonal antibody response.

13 So one reason may be that the antibodies
14 that are -- the B cells produced have insufficient
15 affinity.

16 That's one reason. Is that right?

17 DR. KHANDURI: Objection; form.

18 A. Once again, there may be some epitopes
19 that generate low affinity response.

20 But, collectively, there are multiple
21 epitopes in PH20 that would allow generation of
22 polyclonal antibodies.

23 Q. Dr. Moon --

24 MR. KUSHAN: All right. I'm
25 going to move to strike.

1 Q. The last answer just illustrates that I
2 didn't -- I explicitly asked you to focus on not the
3 collective response, but the particular epitopes
4 that are not inducing a response.

5 And I just want you to focus on the
6 questions I'm presenting and answer those, if you
7 could.

8 If you can't answer the question, you can
9 tell me that, but I need you to answer the question
10 that I'm presenting to you.

11 So are there any other reasons why the
12 immune system will not produce an antibody to an
13 epitope on the PH20 protein when the PH20 protein is
14 used in a vaccine?

15 DR. KHANDURI: Objection; form.

16 A. I gave you my response, that there may be
17 some epitopes that generates low affinity antibody
18 response.

19 Q. Have you ever heard of the concept of
20 "immune tolerance"?

21 A. Yes.

22 Q. What is immune tolerance in the context of
23 the polyclonal antibody response?

24 A. In Paragraph 32, I stated:

25 The "immune system is

1 trained not to respond to self
2 molecules (in order to avoid
3 autoimmunity)." However, under
4 certain conditions, an antibody
5 response against self-antigens
6 is desired to counter
7 overexpression of the
8 self-antigen in a disease (such
9 as, TNF-alpha overexpression
10 causing chronic inflammation in
11 cachexia, Crohn's disease, and
12 rheumatoid arthritis).

13 And:

14 By December 2021 [sic], a
15 POSA would have known of
16 techniques to elicit a
17 polyclonal antibody response
18 against a self-antigen.

19 Q. Dr. Moon, is it your understanding that
20 the human PH20 protein is a self-antigen in humans?

21 A. I understand PH20 is a sperm-associated
22 protein.

23 Q. Dr. Moon, my question was: Do you
24 understand that the PH20 -- human PH20 protein is a
25 self-antigen in humans?

1 Can you answer that question.

2 DR. KHANDURI: Objection; form.

3 A. I understand PH20 is a sperm-associated
4 protein.

5 As for whether it's expressed in females,
6 I do not know.

7 Q. Did you investigate whether the human PH20
8 protein is expressed in females before you prepared
9 your opinions?

10 A. I understand PH20 is a sperm-associated
11 protein.

12 I do not know whether PH20 is expressed in
13 females.

14 But my opinions stay the same, that
15 modified PH20 will generate polyclonal antibody
16 responses.

17 Q. Do you know if the PH20 protein is on the
18 Y chromosome of human males?

19 That's -- sorry.

20 Do you know if the PH20 gene is on the
21 Y chromosome in humans?

22 A. I do not know that.

23 Q. Do you know what chromosome the human PH20
24 gene is located on in humans?

25 A. I do not know that.

1 MR. KUSHAN: I'm going to mark
2 as Exhibit 1119 a paper in the journal
3 "Matrix Biology," Vol. 20, Pages 499 to
4 508, 2001; the first author Csoka,
5 C-s-o-k-a.

6 (Whereupon, Exhibit 1119 was marked for
7 identification.)

8 Q. If you could, Dr. Moon, review the first
9 portion of the abstract of this paper.

10 And once -- and I'm going to ask you, as
11 you read that: Does this give you information about
12 where -- what chromosomes the genes of the PH20 --
13 encodes the PH20 protein are located on?

14 (Witness reading.)

15 Q. Dr. Moon, have you determined if this
16 information in Exhibit 1119 identifies the
17 chromosome on which the PH20 gene is located?

18 DR. KHANDURI: Objection; form.

19 A. This is first time I'm seeing this
20 document, so I'd like to finish reading it.

21 Q. So you're incapable of reading the
22 sentence and understanding in the abstract:

23 Three genes (HYAL1, HYAL2
24 and HYAL3) are clustered on
25 chromosome 3p21.3, and another

1 two genes (HYAL4 and
2 PH-20/SPAM1) and one expressed
3 pseudogene (HYALP1) are
4 similarly clustered on
5 chromosome 7q31.3.

6 DR. KHANDURI: Objection; form.

7 Q. That information is insufficient to tell
8 you what gene -- or what chromosome the PH20 gene is
9 located on in the human?

10 DR. KHANDURI: Objection; form.

11 A. I see that sentence in the abstract.

12 Q. Do you have reason --

13 A. But before I can give my opinions, I'd
14 like to read the paper.

15 Q. So you have not previously investigated
16 whether the PH20 gene is expressed in human females.
17 Right?

18 DR. KHANDURI: Objection; form.

19 A. Once again, I have not seen this document
20 before. So I do not know whether PH20 is expressed
21 in females or not.

22 Q. All right. Let's move on.

23 So, before, we were speaking of the
24 polyclonal antibody response to the PH20 protein and
25 whether antibodies will form in that polyclonal

1 response against every epitope on the PH20 protein.

2 Is it true that in a polyclonal antibody
3 response, some epitopes will induce a stronger
4 immune response than other epitopes on the protein?

5 DR. KHANDURI: Objection; form.

6 A. In a protein antigen, there are multiple
7 epitopes. And a complex antigen, including PH20,
8 would also have multiple epitopes that may have
9 higher -- that may generate high antibody affinity
10 monoclonals or lower affinity monoclonals.

11 But, collectively, a complex antigen like
12 PH20 will generate polyclonal antibodies.

13 Q. In the -- in that response, the epitopes
14 that induced the stronger responses, do those have a
15 term that's used in connection with those epitopes
16 in immunology?

17 A. Immunol- -- in immunological terms, people
18 generally refer to them as immunodominant epitopes.

19 Q. "Immunodominant epitopes." Okay.

20 If you immunize a mammal with a mutated
21 form of PH20, are the epitopes associated with the
22 locations of mutations in the PH20 protein typically
23 the immunodominant epitopes?

24 DR. KHANDURI: Objection; form.

25 A. Could you repeat the question?

1 Q. Sure. If you're immunizing a mammal with
2 a mutated form of the PH20 protein, is it true that
3 the epitopes that are associated with the sites of
4 mutation on the structure of the PH20 protein are
5 the immunodominant epitopes in a polyclonal
6 response?

7 A. So there are multiple epitopes in a large
8 complex protein like PH20. And when you introduce
9 mutations, as specified in Paragraph 14, that will
10 generate polyclonal antibody responses.

11 There may be some epitopes that are
12 immunodominant. There may be epitopes that are less
13 immunodominant.

14 But, collectively, you still get
15 polyclonal antibodies that will bind to wild-type
16 PH20.

17 Q. Dr. Moon, that didn't answer my question.

18 I was asking you whether the sites of the
19 mutations on the modified PH20 polypeptide are the
20 locations where the -- those epitopes associated
21 with those modified structures are typically the
22 immunodominant epitopes in a polyclonal antibody
23 response.

24 Can you answer that question.

25 DR. KHANDURI: Objection; form.

1 A. Once again, when you immunize someone with
2 a large, complex antigen like PH20, there are
3 multiple epitopes that are present.

4 And there are epitopes that may generate
5 high affinity antibodies. There are epitopes that
6 may generate a bit lower affinity antibodies.

7 But, collectively, the polyclonal
8 antibodies will cover multiple epitopes.

9 So even if you make mutations that are
10 less immunodominant, they would still generate
11 antibody responses covering multiple epitopes within
12 PH20.

13 Q. Dr. Moon, that's the second time I asked
14 you the question, and you've still not answered my
15 question.

16 So my question is asking whether the sites
17 of the mutations of the modified PH20 create
18 epitopes that are immunodominant epitopes in a
19 polyclonal antibody response.

20 Are you able to answer that question,
21 please?

22 DR. KHANDURI: Objection; form.

23 A. As I responded before, there are multiple
24 epitopes in PH20.

25 There are epitopes that are -- that may

1 generate high affinity. There are epitopes that are
2 less immunodominant and generate less affinities.

3 But, collectively, these mutated, modified
4 PH20 would contain multiple epitopes. And even if
5 the mutations are less immunodominant, the modified
6 PH20 would generate polyclonal antibodies that cover
7 multiple epitopes in multi- -- in wild-type PH20.

8 Q. So that is the third time I've asked you
9 the question, and you've still not answered the
10 question I presented to you.

11 I want you to just tell me: Are you able
12 to answer the question whether epitopes associated
13 with the modifications made to a modified PH20
14 polypeptide are usually the immunodominant epitopes
15 on a modified PH20 polypeptide when it's used as the
16 immunogen in a polyclonal antibody response?

17 Can you answer that question.

18 DR. KHANDURI: Objection; form.

19 A. I think I answered your question already.

20 It's my opinion that there are multiple
21 epitopes present in PH20.

22 And even if you make mutations in
23 immunodominant epitope or less immunodominant
24 epitope, the resulting polypeptide will generate
25 polyclonal antibody responses.

1 Q. And that -- for the fourth time, that is
2 not my question.

3 I'm asking you: So -- do you understand
4 that I'm asking you about an epitope that is
5 associated with the mutation made to the PH20
6 polypeptide?

7 Do you understand that is part of my
8 question being put to you?

9 A. Yes, I understand that.

10 Q. Okay. So I'm asking whether that epitope
11 associated with a muta- -- with the mutation in the
12 PH20 protein is typically an immunodominant epitope
13 when you use the PH20 as an immunogen to raise a
14 polyclonal antibody response.

15 Do you understand the question?

16 A. Yes.

17 Q. Okay. Please answer that question.

18 DR. KHANDURI: Objection; form.

19 A. I'll give you the same answer: Regardless
20 of whether mutated position reside within --

21 Q. I'm going to interrupt you, because
22 that -- you've -- you just told me you're going to
23 give me the same answer, and I've told you before
24 that's not responding to my question.

25 My question is asking you whether you know

1 that a site of a mutation that gives rise to an
2 epitope -- so this is the epitope associated with
3 the site of the mutation in the PH20 polypeptide --
4 is that epitope associated with the mutation,
5 typically an immunodominant epitope, if you use the
6 protein, the PH20 protein, as the immunogen?

7 Can you answer that question.

8 DR. KHANDURI: Objection; form.

9 Counsel, this is the second time
10 you have interrupted the witness. He's
11 answering the question the best he can.
12 Please let him complete his answer.

13 Q. So go ahead. Can you answer my question.

14 A. So going back to Paragraph 14 --

15 Q. Okay.

16 MR. KUSHAN: I'm going to --

17 Counsel, I'm going to -- I'm
18 going to ask the witness again to answer
19 the question I put to him. And ask him --

20 Q. Are you able to answer the question
21 whether the -- an epitope associated with the site
22 of a mutation on the PH20 protein is typically an
23 immunodominant epitope when the modified PH20 is
24 used as an immunogen to raise a polyclonal antibody
25 response?

1 Do you understand my question to you?

2 DR. KHANDURI: Objection; form.

3 Please, Counsel, for the third
4 time, do not interrupt the witness. Let
5 him complete his answer.

6 MR. KUSHAN: We're going to
7 recall the witness if he refuses to answer
8 questions. I just want to put you on
9 notice.

10 DR. KHANDURI: He is answering
11 the question --

12 MR. KUSHAN: No, he's not.

13 DR. KHANDURI: -- the best he
14 can.

15 MR. KUSHAN: So I'm going to
16 excuse the witness. We're going to go on
17 the record.

18 Can you step out of the room,
19 please.

20 WITNESS: Sure.

21 MR. KUSHAN: Thank you,
22 Dr. Moon.

23 (Witness leaves the conference room.)

24 MR. KUSHAN: We're going to ask
25 for another deposition of this witness if

1 he refuses to answer the questions we're
2 putting to him.

3 You can tell me he's answering
4 the question, but you know absolutely that
5 every single answer he gives me is
6 ignoring the question I'm putting to him.

7 He's refusing to answer
8 literally every question I'm asking.

9 So I'm putting you on notice
10 that this is not an acceptable behavior
11 for a witness in a deposition.

12 And we will reserve our right to
13 recall the witness for an additional
14 deposition if he refuses to -- continues
15 to refuse to answer our questions.

16 DR. KHANDURI: We disagree.

17 He's answering the question the
18 way you are presenting him.

19 Ask clearer questions, and
20 hopefully you'll get the answer that
21 you're hoping for.

22 He's answering that -- he's
23 answering the best he can.

24 MR. KUSHAN: He's refusing to
25 answer.

1 DR. KHANDURI: We disagree.

2 MR. KUSHAN: Recall your
3 witness.

4 DR. KHANDURI: Are you ready?

5 MR. KUSHAN: Yeah.

6 (Pause.)

7 BY MR. KUSHAN:

8 Q. Dr. Moon, when you were retrieved, did
9 your counsel give you any instructions?

10 A. No.

11 Q. Any -- did she say anything to you?

12 A. No.

13 Q. All right. So if I introduce a mutation
14 into the PH20 polypeptide, an amino acid
15 substitution, or a series of them, I can alter the
16 structure of the protein. Is that correct?

17 A. I assume, depending on where you introduce
18 mutations, you could alter the structure of the
19 resulting protein.

20 Q. And that structure may be a structure not
21 present in the wild-type PH20 protein. Correct?

22 DR. KHANDURI: Objection; form.

23 A. Depending on where you introduce
24 mutations, the resulting structure may be similar
25 or -- similar to PH20 or not. Yes.

1 Q. So in the scenario where the structure is
2 not similar to the corresponding structure, in the
3 wild-type protein, can that structure, that modified
4 structure, become an epitope recognized by an
5 antibody if you use that modified PH20 protein as an
6 immunogen?

7 A. Could you repeat the question?

8 Q. So in the scenario where the structure
9 that has been introduced with the mutation is not a
10 structure found in the wild-type protein, could that
11 modified structure become an epitope recognized by
12 an antibody if you used the modified PH20 protein as
13 the immunogen?

14 DR. KHANDURI: Objection; form.

15 A. Yes. If you introduce any mutation and
16 the resulting structures are different from
17 wild-type PH20, that can be used to generate
18 antibody responses.

19 Q. And the epitope, the new epitope that
20 we've been discussing, the one that's associated
21 with the modified structure, could that epitope be
22 an immunodominant epitope?

23 DR. KHANDURI: Objection; form.

24 A. The mutations could be an immunodominant
25 epitope or not, as I mentioned before. And that

1 doesn't matter whether it generates polyclonal
2 antibody responses or not.

3 Q. Do you know whether changed structures on
4 a modified PH20 polypeptide are typically
5 immunodominant relative to the native structure or
6 structures on the PH20 polypeptide?

7 DR. KHANDURI: Objection; form.

8 A. When you introduce a mutation to a
9 protein, regardless of where the mutation occurs, a
10 POSA would find ways to generate polyclonal antibody
11 responses.

12 Q. So my question was whether the changed
13 structures associated with the mutation tend to be
14 immunodominant epitopes on the immunogen.

15 Can you answer that question.

16 A. Could you repeat the question again?

17 Q. Sure. Is it typical that the changed
18 structure on a protein like PH20 that is associated
19 with the mutation -- those changed structures, do
20 they tend to be immunodominant epitopes when you use
21 the mutated protein as an immunogen compared to the
22 wild-type structure?

23 DR. KHANDURI: Objection; form.

24 A. When you introduce mutations to a protein,
25 in general, and if that results in changes in the

1 structure, that mutated protein will generate
2 polyclonal antibody responses.

3 Q. Right. And I'm asking if the responses --
4 well, I'm asking you if the changed structure is
5 an -- typically an immunodominant epitope in that
6 response.

7 DR. KHANDURI: Objection; form.

8 A. If the mutation results in protein
9 structures that are distinct from the wild-type
10 protein, regardless of where the mutation occurs,
11 whether it's an immunodominant or less
12 immunodominant epitope, that will result in
13 polyclonal antibody responses.

14 Q. Right. And I'm asking if responses -- I'm
15 asking you if the changed structure is an --
16 typically an immunodominant epitope in that
17 response.

18 DR. KHANDURI: Objection; form.

19 A. If the mutation results in protein
20 structures that are distinct from the wild-type
21 protein, regardless of where the mutation occurs,
22 whether it's an immunodominant or less
23 immunodominant epitope, that will result in
24 polyclonal antibody responses.

25 Q. Right. And that does not answer my

1 question, again.

2 I'm asking whether the changed structure
3 typically is an immunodominant epitope.

4 DR. KHANDURI: Objection; form.

5 A. Could you repeat the question again?

6 Q. Yes. So we were referring to the changed
7 structure on the protein.

8 A. Right.

9 Q. You're with me. Right?

10 A. Right.

11 Q. Okay. I'm asking if that changed
12 structure is typically an immunodominant epitope.

13 DR. KHANDURI: Objection; form.

14 A. If a mutation introduced the protein
15 results and changed the structure, in general, that
16 changed structure will trigger more antibody
17 responses.

18 Q. So it would be an immunodominant epitope?

19 DR. KHANDURI: Objection; form.

20 A. There are multiple epitopes within a given
21 protein.

22 And to say a specific domain is an
23 immunodominant epitope, you will need to test other
24 epitopes and compare.

25 Q. So you --

1 A. I --

2 Q. Are you finished?

3 A. Yes. Yes.

4 Q. So you would have to test each mutated
5 PH20 protein to know what kind of repertoire the
6 body would produce in the polyclonal antibody
7 response.

8 Is that fair?

9 DR. KHANDURI: Objection; form,
10 foundation.

11 A. As I mentioned, each of the modified PH20
12 will generate polyclonal antibody responses.

13 Q. But you would not know what antibodies are
14 in the polyclonal antibody repertoire unless you
15 tested it, the mutated protein?

16 DR. KHANDURI: Objection; form.

17 A. Mutated protein will generate polyclonal
18 antibody responses that are binding to multiple
19 epitopes within the target protein.

20 Q. So you don't know one way or another --
21 sorry.

22 So I asked you:

23 Would you have to test
24 each mutated PH20 protein to
25 know what kind of repertoire of

1 antibodies in the body --

2 Sorry.

3 You would have to test
4 each mutated PH20 protein to
5 know what kind of repertoire
6 the body would produce in the
7 polyclonal antibody response.

8 Is that fair?

9 And your answer was:

10 As I mentioned, each of
11 the modified PH20 polypeptides
12 would generate a polyclonal
13 antibody response.

14 So I was asking whether you would need to
15 test the particular modified PH20 polypeptide to
16 understand what the particular antibody repertoire
17 was in the polyclonal response. And you gave me a
18 general answer.

19 I'm just wondering -- or, can you answer
20 the question I put to you.

21 DR. KHANDURI: Objection; form.

22 A. If your scientific question is whether
23 each antibody binds to specific domains in the
24 target protein -- and there are ways to test them.

25 But what I'm saying is: All modified

1 version of PH20 will generate polyclonal antibodies
2 that will bind to wild-type PH20.

3 Q. Dr. Moon, are you familiar with vaccines
4 against the human papillomavirus?

5 A. In general, I'm familiar with vaccine
6 efforts against papillomavirus.

7 Q. Okay. And there's an FDA-approved vaccine
8 available for the HPV virus. Right?

9 A. Yes. There's an FDA-approved vaccine
10 product against HPV.

11 Q. Do you know what it's called?

12 A. I believe it's called Gardasil.

13 Q. Have you studied the Gardasil vaccine or
14 its behavior as a vaccine previously in your
15 professional work?

16 DR. KHANDURI: Objection; form.

17 A. I have not studied Gardasil vaccine
18 specifically in the past.

19 Q. Do you know how Gardasil is administered
20 to patients?

21 A. It's my understanding that it's
22 administered parenterally.

23 Q. Where does the virus associated with HPV
24 manifest itself in the human body?

25 A. It's my understanding that HPV infection

1 can occur in many parts in the body, including
2 reproductive tract.

3 Q. Does that include the reproductive tract
4 in females?

5 A. Yes. I understand HPV infection can occur
6 in female reproductive tract.

7 MR. KUSHAN: I'm going to
8 introduce an exhibit, which is 1120.

9 (Whereupon, Exhibit 1120 was marked for
10 identification.)

11 DR. KHANDURI: You can drop it.
12 Thank you.

13 WITNESS: Thank you.

14 BY MR. KUSHAN:

15 Q. This is a paper in PL- -- the journal
16 "PLOS," first author Huo, H-u-o, Vol. 7, Issue 3.
17 Page e33736 is the first page. March of 2012.

18 This paper is reporting on a comparison of
19 administration of HPV antigens to human subjects by
20 a sublingual route and by an intramuscular route.

21 Dr. Moon, a sublingual route is a mucosal
22 administration route. Right?

23 A. Sublingual route is considered a mucosal
24 route.

25 Q. Okay. And an intramuscular is an

1 intra- -- is a systemic exposure of the antigen.

2 Right?

3 A. Intramuscular is considered a systemic
4 exposure.

5 Q. All right. Could you go to Page e33736.

6 And do you see there's a figure, Figure 2,
7 on the top half of this page.

8 And I'll just walk you through this. On
9 the -- in Panel -- are you there?

10 A. Figure 2?

11 Q. Figure 2, yeah.

12 A. Yes, I'm looking at Figure 2.

13 Q. And it's Figure 2.

14 And Panel A is showing responses of
15 subjects immunized intramuscularly.

16 And Panel B is showing responses of
17 subjects immunized sublingually.

18 And it's showing the frequency -- all
19 these bars are showing the frequency of antibody
20 secreting cells in the assay.

21 Is this kind of data something that you
22 are familiar with, generally, in your work?

23 DR. KHANDURI: Objection; form.

24 A. Yes. In my lab, we study similar results
25 in vaccine studies.

1 Q. And so, the responses being shown are over
2 a 20-day period with different -- with the vaccine,
3 with different -- different formulation of the
4 HPV16 VLP.

5 And, just generally, does the response
6 seen with the intramuscular administration appear to
7 be at or above the level of the response observed
8 with the sublingual administration of the vaccines?

9 DR. KHANDURI: Objection; scope.

10 (Witness reading.)

11 A. In general, the data points associated
12 with the intramuscular in Panel A seem to be higher
13 than what's shown in Panel B with the sublingual
14 route.

15 Q. Look at the paragraph on the right column,
16 at the bottom of the page, that starts, "One of the
17 potential translational advantages...."

18 Do you see that paragraph?

19 A. Yes, I see that paragraph.

20 Q. And there's a statement in there. It
21 says:

22 ...while intramuscular
23 immunization was capable of
24 inducing measurable virus
25 neutralizing activity in

1 cervical and/or vaginal
2 secretions in 3/6 subjects
3 (concomitant with high serum
4 neutralizing titers suggesting
5 transudation of serum IgG)....

6 Do you know what "transudation of serum
7 IgG" is referring to?

8 A. I assume it refers to translocation from
9 serum to cervical and/or vaginal sites, in this
10 sentence.

11 Q. Okay. So that's one way antibodies in the
12 circulation that result from a systemic immunization
13 can get into the mucosal compartment within the
14 reproductive tract of human females. Right?

15 DR. KHANDURI: Objection; form,
16 scope.

17 A. In general, serum IgG can translocate to
18 reproductive tract.

19 Q. If you could go to the next page, and
20 there's a figure there, Figure 3.

21 And again, it's comparing the effects of
22 immunization by the intramuscular route -- those are
23 the three graphs on the left side -- and sublingual
24 immunization on the right side.

25 And in this graph, "A" refers to the

1 response in the serum of the antibodies.

2 In the "B" segment, that's labeled as
3 being antibody in the cervical secretions.

4 And in "C," it's antibody in vaginal
5 secretions.

6 Do you see that?

7 A. I see that -- I see that in Figure
8 Caption 3.

9 Q. Okay. And look at the scales of the plots
10 on the left side, associated with intramuscular
11 administration, as compared to the scales of the
12 sublingual administration.

13 Do the responses of the Ig [sic] measured
14 in serum cervical secretions and vaginal
15 secretions -- are those higher than the levels
16 observed for sublingual administration in those
17 three locations?

18 DR. KHANDURI: Objection; form,
19 scope.

20 A. I see that, in general, in Figure 3, the
21 values shown on the left column is higher than the
22 values shown on the right column.

23 Q. So do you see any impediments of systemic
24 administration of the immunogen in this HPV vaccine
25 at creating sufficient levels of IgG in the female

1 reproductive tract?

2 DR. KHANDURI: Objection;

3 form -- objection; form.

4 A. This is first time I see this document.

5 But I see, in the case of this particular
6 immunogen, Gardasil, the figures in 3 show
7 intramuscular immunization has high antibody titers
8 compared with the sublingual.

9 Q. There's high antibody titers in the female
10 reproductive tract. Right?

11 A. In this particular data set, they show
12 higher antibody IgG responses in serum, cervical,
13 and vaginal sites for intramuscular sites, in
14 this -- in this particular assay.

15 Q. Have you -- are you familiar with the term
16 "transcytosis"?

17 A. Yes. In general, I'm familiar with the
18 term "transcytosis."

19 Q. What is "transcytosis"?

20 A. That usually refers to a cell that's
21 binding to a protein or target agent and shuttling
22 it to the other side of the cell body.

23 Q. Is transcytosis a mechanism that can
24 transport immun- -- immunoglobulin G in the
25 circulatory system into the human female

1 reproductive tract?

2 DR. KHANDURI: Objection; form.

3 A. In general, transcytosis can be used to
4 shuttle antibodies from one site to another across
5 the cell membrane.

6 Q. Do you know how that occurs?

7 A. I'm generally familiar with the process of
8 transcytosis.

9 Q. How does that -- how does transcytosis
10 move immunoglobulin from the circulatory system into
11 the human female reproductive tract?

12 A. Once again, I'm generally familiar with
13 the term "transcytosis."

14 And antibodies can bind to Fc receptors on
15 cell membrane, resulting in transcytosis.

16 MR. KUSHAN: Okay. I'm going to
17 introduce Exhibit 1121. This is a paper
18 published in "PNAS," Vol. 108, No. 11,
19 Pages 4388 to 4393, March 15, 2011. First
20 author is Li.

21 (Whereupon, Exhibit 1121 was marked for
22 identification.)

23 Q. And if you want to look at -- just look at
24 the abstract of this paper.

25 Is this referring -- this is referring to

1 the role of FcRn in mediating transcytosis of IgG.

2 Just read the abstract and then let me
3 know if that's generally what this paper is
4 addressing.

5 DR. KHANDURI: Objection; scope.

6 (Witness reading.)

7 A. Okay. I read the abstract.

8 Q. So you see, in the middle of the abstract,
9 about halfway down, it says:

10 Furthermore, endosomal
11 acidification appears to be a
12 prerequisite for FcRn-mediated
13 IgG transcytosis; IgG
14 transcytosis was demonstrated
15 in vivo by translocation of
16 systemically administered IgG
17 into the genital lumen in
18 wild-type but not FcRn-KO -- or
19 knockout -- mice.

20 Is that point consistent with the
21 explanation you provided a bit ago about how
22 transcytosis works using the FcRn receptor?

23 DR. KHANDURI: Objection; form,
24 scope.

25 A. I see that sentence in the abstract. This

1 is first time I'm seeing this document.

2 But, in general, FcRn is involved in IgG
3 transcytosis.

4 Q. Okay.

5 DR. KHANDURI: Counsel, is this
6 a good time to take a break?

7 MR. KUSHAN: I was just thinking
8 that.

9 DR. KHANDURI: Okay.

10 MR. KUSHAN: Would this be a
11 good time for you, Dr. Moon, for lunch?

12 WITNESS: Yes.

13 MR. KUSHAN: Okay. Why don't we
14 break for lunch.

15 DR. KHANDURI: Half an hour?

16 MR. KUSHAN: That's fine.

17 VIDEOGRAPHER: Going off the
18 record at 12:28 p.m.

19 (Whereupon, a recess was taken for lunch
20 at 12:28 p.m.)

21 - - -

22

23

24

25

1 A F T E R N O O N S E S S I O N

2 (Time noted: 1:13 p.m.)

3 VIDEOGRAPHER: We are going back
4 on the record at 1:13 p.m.

5 BY MR. KUSHAN:

6 Q. Dr. Moon, did you speak with anybody over
7 the break, lunch break?

8 A. I spoke with counsel about the lunch menu.
9 Other than that, we didn't discuss any cases.

10 Q. If you could turn to Page 19 of your
11 declaration, Paragraph 32. I think we discussed
12 this a bit earlier today.

13 A. So Case No. -003?

14 Q. Yeah, we'll go with -0003.

15 A. Page 19?

16 Q. 19. Paragraph 32.

17 A. Okay.

18 Q. So this is where you're discussing immune
19 tolerance. Correct?

20 A. In this paragraph, I discuss self
21 molecules and how to generate immune responses.

22 Q. In the normal functioning of the immune
23 system, immune tolerance functions to prevent the
24 immune system from mounting immune responses against
25 the host's own proteins. Right?

1 A. As I wrote in Paragraph 32:

2 The "immune system is
3 trained not to respond to self
4 molecules...."

5 Q. And is it fair to say that the immune
6 tolerance mechanisms in the body function to prevent
7 the survival and activation of B cells that would
8 produce antibodies against self-antigens?

9 DR. KHANDURI: Objection; form.

10 A. Could you repeat the question.

11 Q. Is it fair to say that the immune
12 tolerance mechanisms in the body function to prevent
13 the survival and activation of B cells that produce
14 antibodies that bind to self-antigens?

15 DR. KHANDURI: Objection; form.

16 A. So, in general, the immune system is
17 trained not to respond to self molecules, as I
18 stated in Paragraph 32.

19 Q. And my question was: There are mechanisms
20 in the immune system that implement immune
21 tolerance. Right?

22 DR. KHANDURI: Objection; form.

23 A. There are mechanisms in place related to
24 immune tolerance.

25 Q. And some of those mechanisms function to

1 remove B cells that produce antibodies that bind to
2 self-antigens. Right?

3 A. There are mechanisms that can remove
4 T cells responding to self-antigens.

5 Q. And these immune tolerance mechanisms are
6 both in central and peripheral tolerance immune
7 systems. Right?

8 DR. KHANDURI: Objection; form.

9 A. There are multiple mechanisms in place.
10 And central and peripheral tolerance are
11 involved in immune tolerance.

12 Q. Immune tolerance mechanisms operate both
13 in the mucosal and systemic immune responses.
14 Right?

15 A. Both the mucosal and cell compartments are
16 involved in immune tolerance.

17 Q. Would you agree that immune tolerance
18 mechanisms can alter the populations of both
19 long-lived plasma cells and memory B cells?

20 DR. KHANDURI: Objection; form.

21 A. There are mechanisms involved in
22 regulation of long-lived plasma and memory B cells.

23 Q. So is it fair to say that immune tolerance
24 mechanisms can influence the antibodies that are
25 within the antibody repertoire produced by a

1 polyclonal response to the PH20 protein?

2 DR. KHANDURI: Objection; form.

3 A. There are mechanisms involved in self
4 tolerance to self-proteins, but I do not know
5 whether PH20 is a self-protein or not in females.

6 Q. But, just generally -- not just for PH20,
7 but just generally, if someone is attempting to
8 vaccinate somebody with a self-protein and there are
9 not efforts made to overcome immune tolerance, the
10 body will not produce antibodies to the
11 self-protein.

12 Is that how self- -- is that how immune
13 tolerance works?

14 DR. KHANDURI: Objection; form.

15 A. In general, there are mechanisms in place
16 to control and modulate induction of antibodies to
17 self molecules.

18 But as I stated in Paragraph 32, under
19 certain conditions, an antibody response to
20 self-antigen can be induced and sometimes desired.

21 And there are multiple ways that a POSA
22 could have used to induce polyclonal antibody
23 responses against the multitude of antigens,
24 including a self-antigen.

25 Q. If I administered a self-protein to a

1 human in saline -- without adjuvants, without other
2 things in the composition -- would you expect the
3 human immune system to produce a polyclonal antibody
4 response against that self-protein?

5 DR. KHANDURI: Objection; form.

6 A. So, in general, there are mechanisms in
7 place to limit induction of antibody responses to
8 self molecules.

9 But as I mentioned, there are multiple
10 ways that a POSA could have used to induce
11 polyclonal antibody responses to protein antigens,
12 including a self-antigen.

13 Q. And to be clear, if they -- if the POSA
14 did not use those additional ways to overcome immune
15 tolerance, the human body would not mount a
16 polyclonal antibody response to that self-antigen.
17 Right?

18 A. In general, if you inject self-protein
19 into an individual, you don't expect to generate
20 antibody responses to the self-antigen.

21 Q. If I take a human prot- -- a human
22 self-protein that is found in other animals in
23 the -- well, sorry. Let me try that one again.

24 So if I have two species, and they have --
25 they both make the same protein, but they're

1 different species' versions of each protein -- in
2 that hypothetical -- kind of like PH20. There's a
3 human PH20. There's a mouse PH20. There are other
4 species of PH20.

5 If the two proteins, like the two PH20s,
6 mouse and human, have common epitopes in their
7 native wild-type form, would you expect antibodies
8 in the mouse to form against that common epitope if
9 you inject the human protein into the mouse?

10 DR. KHANDURI: Objection --

11 Q. Do you understand my question?

12 DR. KHANDURI: Objection; form.

13 A. If you inject proteins from different
14 species with 100% sequence identity, a POSA would
15 think injection of unmodified protein in saline
16 would not generate strong antibody responses.

17 But in most cases, proteins in different
18 species have less than 100% sequence identity. So
19 in those cases, you expect to get antibody
20 responses.

21 Q. If there is an epitope shared between the
22 human and mouse species of the native protein, would
23 the antibody -- antibodies in the mouse not be
24 produced against that epitope, which is shared
25 between the two species as a self epitope?

1 DR. KHANDURI: Objection; form.

2 A. Could you repeat the question?

3 Q. Of course. It's a complicated question,
4 so let me break it up for you.

5 So there could be, on two species of a
6 protein, a common epitope found on both species of
7 protein. Right?

8 A. Okay.

9 Q. And in each mammal, they could have an
10 antibody form -- or an antibody could recognize that
11 epitope as a self epitope. Right? Theoretically?

12 DR. KHANDURI: Objection; form.

13 A. So as long as there is a single epitope
14 mutation in those two proteins, a POSA would expect
15 to see generation of antibody responses.

16 Q. So if you mutate the common epitope shared
17 by the two proteins, that will induce production of
18 antibodies when you take one species' protein and
19 inject it in the other mammal?

20 DR. KHANDURI: Objection; form.

21 A. Oh, that's not what I stated.

22 Q. Okay.

23 A. I stated that as long as there is a single
24 epitope mutation anywhere within the protein --

25 Q. So --

1 A. -- that may -- that single mutation would
2 allow induction of antibodies to "multi" epitopes.

3 Q. So that would override immune tolerance
4 against the shared epitope between the two species?

5 DR. KHANDURI: Objection; form.

6 A. Once again, there's -- as long as there is
7 one single epitope, a single amino acid mutation in
8 the proteins, anywhere in the protein, that will
9 result in antibody responses spreading to multiple
10 epitopes found in the protein.

11 Q. So T cells and -- where do T cells and
12 B cells originate?

13 A. T cells are known to generate in --
14 T cells and B cells are known to generate in bone
15 marrow.

16 Q. And are both T cells and B cells trained
17 by the immune system?

18 DR. KHANDURI: Objection; form.

19 A. Both T cells and B cells are trained and
20 interact with immune systems.

21 Q. Does that training occur before T cells
22 and B cells migrate into the mucosal immune system?

23 A. Generally, T cells and B cells can be
24 trained in different parts of the body, including
25 bone marrow, thymus, spleen, and potentially mucosal

1 tissues, too.

2 Q. So you would expect immune tolerance to
3 function in mucosal -- in mucosal environment as
4 well. Right?

5 DR. KHANDURI: Objection; form.

6 A. There are mechanisms in place to maintain
7 immune tolerance in various tissues, including
8 mucosal compartments.

9 Q. Would you agree, in general, that most
10 proteins are poorly immunogenic or nonimmunogenic
11 when administered by themselves?

12 DR. KHANDURI: Objection; form.

13 A. Could you repeat the question?

14 Q. Sure. Would you agree with the statement
15 that most proteins are poorly immunogenic or
16 nonimmunogenic when administered by themselves?

17 A. I think this depends on the protein.

18 If you are injecting self-antigen protein,
19 without any modification, by itself, it may not
20 generate strong antibody responses, due to
21 mechanisms of immune tolerance.

22 But as long as there is a single epitope
23 mutation, of course I would find good ways to induce
24 antibody responses.

25 Q. Do you commonly try to overcome immune

1 tolerance using an adjuvant when you administer the
2 protein?

3 A. Yes. Adjuvants are used to induce
4 antibody responses with protein antigens.

5 Q. Can adjuvants have varying degrees of
6 impact on the magnitude of the immune response
7 against a protein?

8 DR. KHANDURI: Objection; form.

9 A. In general, adjuvants are used to induce
10 higher antibody titers, together with protein
11 antigens.

12 Q. Can you use, in a vaccine in a human, a
13 highly potent adjuvant?

14 DR. KHANDURI: Objection; form.

15 Q. And to be clear, something that would
16 overcome immune tolerance to the injected protein.

17 DR. KHANDURI: Objection; form.

18 A. There are strong adjuvants that are well
19 reported in the literature.

20 Q. Are there any risks of using a strong
21 adjuvant in a vaccine for a human?

22 A. There are adjuvants that are known to
23 cause injection inflammation.

24 So, in those cases, researchers have to be
25 cautious on selection of adjuvants.

1 Q. Can you induce autoimmunity to a
2 self-protein that is other than the one being
3 injected, if you use a powerful adjuvant, in a
4 human?

5 DR. KHANDURI: Objection; form.

6 A. When you use a very strong adjuvant, there
7 is concern of potential side effects, including
8 inflammation and induction of antibodies to other
9 proteins.

10 Q. So does that limit the choices for
11 adjuvants that could be used in human vaccines?

12 A. There are many choices of adjuvants that
13 are in development. And many, but not all, can be
14 used in humans.

15 Q. Could you go to Paragraph 23 of your
16 declaration on Page 12.

17 A. Paragraph 22?

18 Q. 23.

19 A. 23? Okay.

20 Q. You make a reference at the bottom of that
21 paragraph to epitopes that are linear?

22 A. Yes, I mentioned linear epitopes here.

23 Q. What do you mean by "linear" epitope?

24 A. What I mean by "linear" is that these are
25 contiguous amino acid sequences within the antigen.

1 Q. And those are -- there's another kind of
2 epitope called "conformational" epitope. Right?

3 A. Yes. Conformational epitope is another
4 kind of epitope in an antigen.

5 Q. And what's the difference between a linear
6 epitope and a conformational epitope?

7 A. Linear epitopes refer to contiguous domain
8 of antigen that -- that will induce antibody
9 responses.

10 Configuration -- configurational epitopes
11 refer to epitopes that are formed by
12 three-dimensional structure of the antigen inducing
13 antibody responses.

14 Q. Will conformational epitopes in a protein
15 be preserved in a protein that has been denatured?

16 A. Some conformational epitopes in a protein
17 can still be maintained after denaturization.

18 Q. Would you say the majority of the
19 conformational epitopes will be maintained in a
20 denatured protein?

21 DR. KHANDURI: Objection; form.

22 A. I think it depends on the method of
23 denaturization. There are some techniques that will
24 disrupt more conformational epitopes compared with
25 others.

1 Q. Is it fair to say that the -- a disruption
2 of the structure of the protein can destroy
3 conformational epitopes?

4 A. If you denature a protein, you could
5 disrupt conformational epitopes of a certain region.

6 And once again, depending on the
7 techniques of denaturization, the extent to have
8 disruption in conformational epitopes may be
9 different.

10 Q. So the number of antibodies that might
11 form to a denatured PH20 protein may be different
12 than the number of antibodies that would form to the
13 undenatured wild-type PH20 protein?

14 DR. KHANDURI: Objection; form.

15 A. Once again, depending on the method of
16 denaturization, number of epitopes in one form of
17 antigen versus other may be different, the number of
18 configuration of epitopes.

19 Q. If you could look at Paragraph 22 of your
20 declaration, also on Page 12.

21 No. I'm sorry. Hold on one second.

22 This always happens in depositions, where
23 your pages become disordered. Just bear with me.

24 (Pause.)

25 Q. All right. If I could have you do this:

1 Go to Page 25 and look at Paragraph 44.

2 A. Okay. I'm looking at Paragraph 44.

3 Q. Okay. Do you see, about five or six lines
4 down, there's -- you say:

5 ...or the modified PH20
6 polypeptide underwent a
7 conformational change (e.g.,
8 due to intentional
9 denaturation)....

10 Do you see that?

11 A. Yes, I see that.

12 Q. I see that word -- those two words being
13 used together at several places in your declaration,
14 "intentional denaturation."

15 What do you mean by the words "intentional
16 denaturation," as you're using it in your
17 declaration?

18 A. In vaccine studies, researchers could
19 intentionally denature a given protein for vaccine
20 applications as well.

21 So researchers could use undisrupted
22 antigen or antigen that is intentionally disrupted
23 or intentionally denatured to generate antibody
24 responses.

25 And as I mentioned, there are many

1 techniques available to achieve denaturization of a
2 protein.

3 Q. Can mutations into -- introduced into the
4 amino acid sequence of a protein cause denaturation
5 of the protein?

6 A. I would assume some amino acid
7 modifications to a protein can result in unfolding
8 or denaturization of the antigen.

9 Q. And if those amino acid mutations caused
10 unfolding or denaturation of the protein, would the
11 denatured or unfolded protein have a different
12 number of epitopes on it compared to the wild-type
13 protein?

14 DR. KHANDURI: Objection; form.

15 A. As I mentioned in Paragraph 44, even if
16 you intentionally denature a protein, the vast
17 majority of the epitopes would be still present for
18 induction of antibody responses.

19 Q. Are the majority of epitopes on a protein
20 like PH20 linear epitopes or conformational
21 epitopes?

22 A. In general, large complex proteins like
23 PH20 have both conformational and linear epitopes.

24 Q. Do you know whether there are more
25 conformational epitopes than linear epitopes, or

1 vice versa, on the PH20 protein?

2 A. I do not know, for the case of specific
3 PH20, whether there are more configurational or
4 linear epitopes.

5 Q. Did you investigate the epitopes that are
6 present on the human PH20 protein as part of your
7 preparation of your declaration -- of your
8 declaration here?

9 DR. KHANDURI: Objection; form.

10 A. PH20 is a large, complex protein.

11 So, in general, those complex proteins
12 have multiple epitopes, including linear and
13 configurational epitopes.

14 As for the number of epitopes on PH20, I
15 didn't look into number of epitopes.

16 But I understand there are multiple
17 epitopes that can serve as both configurational and
18 linear epitopes.

19 Q. If you intentionally denature a protein
20 antigen like PH20, can you refold the protein by
21 removing or changing the conditions in which it's
22 found?

23 DR. KHANDURI: Objection; form.

24 A. I think it -- I think it depends on the
25 method of denaturization, whether you can refold

1 disrupted protein or not.

2 Q. Have you personally refolded proteins that
3 have been denatured?

4 A. I have not personally refolded proteins
5 that were denatured.

6 But I examined literature. I worked in a
7 multidisciplinary research lab that worked on
8 protein antigens.

9 Q. Can a denatured modified PH20 protein form
10 aggregates?

11 DR. KHANDURI: Objection; form.

12 A. In general, denatured proteins could or
13 could not result in aggregation.

14 Q. Can mutations introduced into the PH20
15 protein induce the protein to form aggregates?

16 DR. KHANDURI: Objection; form.

17 A. In general, mutations in any given protein
18 could result in protein aggregation.

19 Q. Do aggregated proteins present different
20 epitopes relative to the native, properly folded
21 protein; for example, in PH20?

22 DR. KHANDURI: Exam- -- excuse
23 me. Objection; form.

24 A. Once again, large proteins have multiple
25 epitopes. And that will be the same for PH20.

1 Q. Do you know how protein aggregates form?

2 A. In general, when hydrophobic domains are
3 exposed to external surface, that can result in
4 protein aggregation.

5 Q. And those can -- those hydrophobic
6 portions that get exposed can form complexes between
7 multiple molecules of the protein in a random way.
8 Right?

9 A. There may be some proteins that aggregate,
10 resulting in some changes.

11 But, in general, even after protein
12 aggregation, the aggregated proteins will still
13 present epitopes that will induce polyclonal
14 antibody responses to the parent protein.

15 Q. Can an aggregated protein present new
16 epitopes not originally present on the wild-type
17 protein?

18 A. In some cases, aggregated proteins could
19 present some new configurational epitopes.

20 Q. Could you look at Paragraph 44 again.

21 A. Okay.

22 Q. Do you see, in the first sentence, you
23 state:

24 Moreover, given the high
25 degree of amino acid sequence

1 identity (at least 95%) between
2 the administered modified PH20
3 polypeptides and the wild-type
4 human PH [sic] polypeptide
5 (SEQ ID 7), even if some
6 epitopes on the modified PH20
7 polypeptide were changed or
8 disrupted....

9 And then you continue on.

10 When you were forming your opinions, did
11 you consider the modified PH20 polypeptides that you
12 were addressing to be those that were 95% sequence
13 identity with SEQ ID 7?

14 DR. KHANDURI: Objection; form.
15 (Witness reading.)

16 A. I understand the modified PH20
17 polypeptides have the definitions given in
18 Paragraph 14.

19 Q. So you're referring to proteins that have
20 95% sequence identity that are admin- -- sorry.

21 You're speaking of proteins being
22 administered, which are the modified PH20
23 polypeptides.

24 And you're saying those, in this sentence,
25 are those with 95% sequence identity with the

1 wild-type PH20 polypeptide SEQ ID 7. Right?

2 DR. KHANDURI: Objection; form.

3 A. I understand polypeptides shown in
4 Sequence No. 3 and 32-66 are truncated version of
5 PH20 found in human sperm, which is indicated by
6 Sequence ID No. 7.

7 And I understand there's a high degree of
8 amino acid sequence identity, at least 95%, between
9 modified PH20 polypeptides and wild-type human PH20
10 polypeptide, as shown in ID No. 7.

11 But, by extension, because Sequence ID
12 No. 3 and 32-66 are truncated version of Sequence ID
13 No. 7, there would be also high degree of amino acid
14 sequence identity between modified PH20 and PH20
15 shown in Sequence 3 and 32-66.

16 Q. But in Paragraph 44 in your declaration,
17 you're referring to modified PH20 polypeptides that
18 have 95% sequence identity to SEQ ID 7. Right?

19 (Witness reading.)

20 A. I understand there is a high degree of
21 sequence identity between modified PH20 and
22 wild-type human PH20 polypeptide sequence shown in
23 7, as well as truncated version of wild-type human
24 PH20 shown in Sequence No. 3 and 32-66.

25 And by that extension, a POSA would think

1 the vast majority of the epitopes on the modified
2 PH20 polypeptides to be the same or similar to those
3 on the wild-type human PH20 polypeptide shown in
4 Sequence No. 7, as well as the truncated version,
5 Sequence No. 3, and 20, 32-66.

6 Q. So just to be clear, what you're
7 addressing in Paragraph 44 is the set of modified
8 PH20 polypeptides that are 95% identical to
9 SEQ ID 7.

10 And you also believe that polypeptides
11 that are 95% sequence identity with SEQ ID 3 and
12 32-66 also would induce antibodies that bind to the
13 wild-type PH20.

14 Is that what you're saying?

15 DR. KHANDURI: Objection; form.

16 A. Could you repeat the question.

17 Q. So --

18 A. Yeah.

19 Q. -- what's -- so what's written in
20 Paragraph 44 is addressing modified PH20
21 polypeptides that are 95% sequence identity -- or
22 have 95% sequence identity with SEQ ID 7. Right?

23 (Witness reading.)

24 A. There is a high degree of amino acid
25 sequence identity between modified PH20 and

1 wild-type human PH20 shown in Sequence No. 7, but --
2 in addition, not "but" -- in addition, there's high
3 degree of sequence identity between modified PH20
4 and wild-type PH20 polypeptide shown in Sequence
5 No. 3 and 32-66.

6 Q. Okay. Do you know if SEQ ID 7 is a
7 soluble form of human PH20?

8 A. I do not know whether it's a soluble form.

9 Q. Did you investigate how many of the
10 modified PH20 polypeptides that you described in
11 Paragraph 14 will become denatured because of the
12 changes to the protein?

13 DR. KHANDURI: Objection; form.

14 A. I do not know how many of the modified
15 PH20, as described in Paragraph 14, are in soluble
16 form.

17 Q. Did you investigate how many of the
18 modified PH20 polypeptides you defined in
19 Paragraph 14 that will become aggregated?

20 A. I do not know how many of those variants
21 described in Paragraph 14 will result in protein
22 aggregation.

23 Q. Did you investigate how many of the
24 modified PH20 polypeptides in the set defined in
25 Paragraph 14 will become misfolded because of the

1 mutations made to them?

2 DR. KHANDURI: Objection; form.

3 A. I do not know how many of the modified
4 PH20 will result in disruption or misfolding.

5 Q. But it's your testimony that regardless of
6 that uncertainty, every single modified PH20
7 polypeptide within the definition in Paragraph 4 --
8 14 will cause production of polyclonal antibodies in
9 a human that bind to the wild-type PH20 on sperm?

10 DR. KHANDURI: Objection; form.

11 A. It's my opinion that modified PH20
12 polypeptide, as defined in Paragraph 14, will result
13 in polyclonal antibodies that will bind to wild-type
14 human PH20 polypeptide in vivo.

15 Q. So if you look in Paragraph 45, please.
16 And just....

17 If you can look, there's -- you say
18 "irrespective of," and then you list three
19 conditions:

20 ...the location of an
21 amino acid difference on any of
22 the admin- -- on any of the
23 administered modified PH20
24 polypeptides relative to the
25 wild-type, whether any of the

1 administered PH20 polypeptides
2 are enzymatically active, or
3 whether the administered
4 modified PH20 polypeptide has a
5 conformational change (such as
6 due to intentional
7 denaturation)....

8 So you're saying, regardless of those
9 three things happening when you make mutations to
10 the PH20 protein, you believe administering any of
11 the PH20 polypeptides within the scope of what you
12 say in Paragraph 14 will raise antibodies that bind
13 to the wild-type PH20 on human sperm?

14 DR. KHANDURI: Objection; form.

15 A. It is my opinion that a POSA would have
16 expected the polyclonal antibodies generated against
17 the administered modified PH20 polypeptides,
18 regardless of the three conditions I listed in
19 Paragraph 45, will result in antibodies that bind to
20 wild-type PH20 polypeptide.

21 Q. Do you also personally believe that to be
22 true?

23 DR. KHANDURI: Objection; form.

24 A. This is my personal opinion that I stated
25 in the declaration.

1 Q. And just to be clear, I'm just confirming
2 that you're not telling -- you're not just saying
3 your opinion is that the POSA would believe it.

4 I just -- I'm asking: You personally
5 believe it, regardless of whether a POSA believes
6 it?

7 A. I personally believe this as well.

8 Q. Did you evaluate any structural models of
9 the PH20 protein in forming your opinions in your
10 declarations?

11 DR. KHANDURI: Objection; form.

12 A. As I mentioned, modified PH20 will have
13 multiple epitopes. And even after denaturation, the
14 modified PH20 will have multiple epitopes that will
15 generate polyclonal antibody responses.

16 Therefore, the structure of modified PH20
17 does not play a major role in forming my opinions.

18 A POSA would have used modified PH20 as --
19 without further modification.

20 What I mean by is that a POSA would have
21 used a denatured or nondenatured modified PH20 to
22 generate polyclonal antibody responses.

23 Q. Does it matter to you how many, or the
24 locations of amino acid modifications, are in the
25 modified PH20 in -- as to the ability of the

1 modified PH20 to create antibodies and a polyclonal
2 response against the wild-type protein?

3 DR. KHANDURI: Objection; form.

4 A. As I mentioned in Paragraph 14, as long as
5 there is single epitope amino acid modification, a
6 modified PH20, all the variations of that would
7 result in polyclonal antibody responses.

8 Q. So your opinion is: As long as the PH20
9 in that -- sorry.

10 As you just said -- strike that.

11 So you just stated that as long as there
12 is the one amino acid substitution in the modified
13 PH20 being used.

14 Are you assuming that the modified PH20
15 that's being administered in your example to the
16 human has only one amino acid substitution in it?

17 DR. KHANDURI: Objection; form.

18 A. Regardless of number of mutations, as long
19 as it meets the definition stated in Paragraph 14,
20 it's my -- it's my opinion that modified PH20
21 injected into human females will result in
22 polyclonal antibody responses.

23 Q. So just to be clear, are you saying that
24 your opinions are based on a modified PH20
25 polypeptide that has only the one identified change

1 at position 320 in it?

2 DR. KHANDURI: Objection; form.

3 A. My opinion stays the same, whether
4 modified PH20 has only one modification at
5 position 320 or many modifications, so that up to
6 95% is identical to the Sequence ID No. 3 and 32-66.

7 All these variants would be expected to
8 generate polyclonal antibody responses.

9 Q. Is it your opinion that any sequence --
10 any contiguous sequence of amino acids within the
11 PH20 protein sequence can be a linear epitope?

12 DR. KHANDURI: Objection; form.

13 A. Any potential linear contiguous sequences
14 in a given protein could be a linear epitope.

15 And, same thing can be generally said to
16 PH20 as well.

17 Q. So anywhere in the -- so if I pick any
18 stretch of contiguous amino acids within the PH20,
19 the native PH20 polypeptide sequence, any stretch of
20 amino acids will be a linear epitope, as we've --

21 DR. KHANDURI: Object --

22 Q. -- been using that term in the -- in your
23 declarations?

24 DR. KHANDURI: Objection; form.

25 A. There are multiple linear and

1 configurational epitopes in any given protein.

2 Q. I'm just trying to clarify.

3 Are there a smaller number of linear
4 epitopes on the modified -- or in the native PH20
5 polypeptide than as many as you can derive from just
6 picking any stretch of the amino acid sequence?

7 That's a bad question. Let me try it
8 again.

9 In order to be a B cell epitope, does the
10 linear sequence have to be bound by a B cell?

11 DR. KHANDURI: Objection; form.

12 A. In general, B cells need to bind to their
13 target epitope to generate antibody responses.

14 Q. So not every -- not any sequence within
15 the PH20 sequence will provide that as a place where
16 a B cell can bind. Right?

17 DR. KHANDURI: Objection; form.

18 A. So again, there are multiple epitopes in a
19 complex protein. There are multiple linear epitopes
20 that B cells can bind to.

21 Q. Let me try a better question.

22 Do you agree that in order for antibodies
23 specific to a linear epitope on PH20 to be produced,
24 the B cells must recognize the linear epitope
25 through their BCR?

1 DR. KHANDURI: Objection; form.

2 A. In general, BCR on B cells need to bind to
3 an epitope to generate antibody responses.

4 Q. Do you know how many linear B-cell
5 epitopes are on the PH20 wild-type protein sequence?

6 DR. KHANDURI: Objection; form.

7 A. I don't know how many B-cell epitopes
8 there are in wild-type PH20, but I understand there
9 are many potential epitopes.

10 Q. In December of 2012, could a person of
11 ordinary skill have determined how many B-cell
12 epitopes are present on the wild-type PH20 sequence?

13 I'm sorry.

14 In December 2012, could a person of
15 ordinary skill have determined how many linear
16 B-cell epitopes are present on the wild-type PH20
17 sequence?

18 A. All the linear epitopes within a given
19 protein could serve as a B-cell epitope.

20 Q. Could linear sequences of amino acids
21 buried within the protein interior function as a
22 linear B-cell epitope on the human PH20 protein?

23 DR. KHANDURI: Objection; form.

24 A. Even if you have linear epitopes buried in
25 3D structure of a protein, if you denature the

1 protein and expose the linear epitope, that will
2 serve as a linear B-cell epitope.

3 Q. Will the antibody that forms against that
4 buried linear epitope bind to the native wild-type
5 PH20 on sperm?

6 DR. KHANDURI: Objection; form.

7 A. Could you repeat the question?

8 Q. Yes. You gave me an example of forming an
9 antibody to a linear B-cell epitope on the interior
10 of the protein where you used the denatured form of
11 the protein.

12 And my question is whether that antibody
13 that binds to the linear B-cell epitope that is on
14 the denatured form, but in the folded protein, is on
15 the interior of the protein -- I'm asking if that
16 antibody will bind to the native PH20 protein on
17 sperm.

18 A. So once you denature a protein and expose
19 internal linear epitopes, that can generate antibody
20 responses to that epitope. And that can trigger
21 subsequent immune responses to other domains found
22 in that antigen, resulting in polyclonal antibody
23 responses to multiple other epitopes.

24 So if you were to use modified PH20 and
25 denature it, it will generate antibody responses

1 that will trigger subsequent polyclonal antibodies
2 that bind to wild-type PH20 bound -- found in sperm.

3 Q. But the antibody that binds to the linear
4 B-cell epitope that's ordinarily in a buried site
5 will not bind to the native structure found on --
6 PH20 found on sperm. Right?

7 DR. KHANDURI: Objection; form.

8 A. As I mentioned, when you denature a
9 protein, that can result in internal domains to be
10 exposed, resulting in B-cell responses, then that
11 will trigger other B-cell activations that result in
12 polyclonal antibodies against the multiple epitopes.

13 Q. All right. Let's take --

14 A. And I can see the similar conditions can
15 occur in the case of a modified PH20.

16 Q. But I'm trying to just -- let's take the
17 other antibodies that might also form off the table
18 for a minute.

19 I'm just asking about the antibody that
20 you referred to that formed to the linear B-cell
21 epitope on the interior of the protein that was made
22 with the denatured PH20.

23 That antibody will not bind to the folded
24 PH20 protein on sperm. Right?

25 DR. KHANDURI: Objection; form.

1 A. I do not know enough about biology or PH20
2 in sperm to answer that particular hypothetical
3 question.

4 DR. KHANDURI: Counsel, can we
5 take a break soon?

6 MR. KUSHAN: I have just one or
7 two more questions, then we can take a
8 break.

9 Q. Do you -- so did you investigate whether
10 PH20 on sperm, after it enters the reproductive
11 tract until it fertilizes the egg, undergoes any
12 kind of structural change?

13 DR. KHANDURI: Objection; form.

14 A. I just know PH20 is a sperm-associated
15 protein.

16 Q. So you don't know whether the protein
17 itself undergoes structural changes to its sequence
18 between the time it enters the reproductive tract
19 until it fertilizes the egg?

20 A. I did not study the structure of PH20 in
21 human female reproductive tract.

22 But it's my opinion that regardless of the
23 sequence variance within modified PH20, those would
24 serve as antigens that will generate polyclonal
25 antibodies that will bind to wild-type PH20

1 associated with sperm.

2 MR. KUSHAN: Do you want to take
3 a break?

4 WITNESS: Sure.

5 MR. KUSHAN: Okay.

6 VIDEOGRAPHER: Off the record at
7 2:21 p.m.

8 (Whereupon, a recess was taken.)

9 VIDEOGRAPHER: We are going back
10 on the record at 2:54 p.m.

11 BY MR. KUSHAN:

12 Q. Dr. Moon, did you speak with counsel
13 during the break?

14 A. No, I did not.

15 Q. To prepare your declarations in this
16 case -- I just want to confirm a couple of your
17 answers from before.

18 One question I asked you is whether you
19 had looked at a PH20 homology model as part of the
20 work that you did to prepare your declarations.

21 Did you look at a PH20 homology model?

22 DR. KHANDURI: Objection; form.

23 A. Could you clarify the question?

24 Q. Right. So, you know, proteins exist in
25 three dimensions. Right?

1 A. Proteins exist in three-dimensional
2 structure.

3 Q. And so, if you did a X-ray crystallography
4 study of the protein, you could get information that
5 is used to create a three-dimensional image of the
6 protein. Right?

7 DR. KHANDURI: Objection; form.

8 A. You can study 3D structure of a protein
9 using crystallography.

10 Q. Right. And you can use SWISS-MODEL to
11 also create a model of a protein structure using its
12 amino acid sequence. Right?

13 DR. KHANDURI: Objection; form.

14 A. That's another method of looking at
15 protein structure.

16 Q. So all I'm asking is: Did you look at one
17 of those PH20 structural models in the course of
18 preparing your opinions in this case?

19 DR. KHANDURI: Objection; form.

20 A. I did not need to look into structure of
21 PH20 to arrive at my opinion that I stated in the
22 declaration that modified PH20 will generate
23 polyclonal antibody responses that will bind to
24 wild-type human PH20 polypeptide.

25 Q. So, Dr. Moon, my question wasn't whether

1 you had an opinion about this, but my question was
2 just a question about whether you did something.

3 And I asked -- and it's very simple: Did
4 you look at a PH20 homology model in the course of
5 preparing your opinions in this case?

6 DR. KHANDURI: Objection; form.

7 A. I used the UniProt to look at sequence
8 identity between modified PH20 polypeptides and
9 other sequences listed in my declaration.

10 Q. But you --

11 A. I did not use crystallography or
12 SWISS-MODEL to examine PH20 during preparation of
13 this declaration.

14 Q. And you didn't view a PH20 model --
15 sorry.

16 You did not view a structural model of
17 PH20 in forming your opinions in the declaration.
18 Is that right?

19 DR. KHANDURI: Objection; form.

20 (Witness reading.)

21 A. I did not use SWISS-MODEL or
22 crystallography model to study PH20 in order to form
23 my opinion that modified PH20 polypeptide will
24 generate polyclonal antibodies that will bind to
25 wild-type human PH20.

1 Q. So at the very beginning of the deposition
2 today, you explained that in your -- some of the
3 work that you did during your postdoc phase, that
4 you investigated the location of linear epitopes.

5 Do you remember that explanation you gave
6 us?

7 A. I remember our exchange.

8 Q. And that involves making fragments of the
9 protein that you were trying to locate the linear
10 epitopes in. Right?

11 DR. KHANDURI: Objection; form.

12 A. In the postdoctoral training time, I used
13 fragmented proteins for vaccine applications.

14 Q. So in February -- I'm sorry.

15 In December of 2012, a POSA could have
16 used other techniques to locate linear B-cell
17 epitopes on the surface of the human PH20 protein.
18 Right?

19 DR. KHANDURI: Objection; form.

20 A. There are tools available to study
21 epitopes in any given protein.

22 Q. Are those computational tools?

23 A. Those tools would include the
24 computational tools.

25 Q. So a person of skill in the art could have

1 used computational tools in 2012 to locate the
2 positions of linear B-cell epitopes on the PH20
3 protein that are on the surface of the protein.
4 Right?

5 DR. KHANDURI: Objection; form.

6 A. Computational tools can be used to study
7 structure of a protein, including PH20.

8 Q. And also to find the locations of the
9 B-cell epitopes on the surface of the protein.
10 Right?

11 A. Computational tools can be used to study
12 structure of a protein, as well as epitopes in a
13 given protein.

14 Q. And the location of the epitopes as well.
15 Right?

16 A. Computational tools can be used to study
17 structure of a protein and potential epitopes.

18 But as I mentioned in my declaration,
19 modified PH20 polypeptide will degenerate
20 polypeptides that will bind to wild-type human PH20.

21 And I did not need to examine
22 computational models to arrive at this opinion.

23 Q. As part of your work in this case forming
24 opinions about linear epitopes that give rise to
25 B cells -- sorry. Try that one again.

1 As part of your work in this case, did you
2 look for any reports of investigations into the
3 locations of B-cell epitopes on the human PH20
4 protein?

5 DR. KHANDURI: Objection; form.

6 A. PH20, I understand, is a large protein
7 with multiple epitopes. And modified PH20 also has
8 multiple epitopes that will induce polyclonal
9 antibody responses.

10 And I didn't need to use computational
11 tools to arrive at my opinion that modified PH20
12 polypeptides will induce polyclonal antibodies
13 against the wild-type human PH20.

14 Q. So, Dr. Moon, my question is much simpler,
15 and you don't need to repeat what you already have
16 said many times today.

17 I'm just asking about what you did to
18 prepare these declarations. And one thing -- I'm
19 asking a very specific thing.

20 Did you look for information published in
21 the literature that describe the location of B-cell
22 epitopes on the human PH20 protein?

23 DR. KHANDURI: Objection; form.

24 A. I did not look into published epitopes
25 within PH20.

1 Q. Okay.

2 A. But I understand there are multiple
3 epitopes in PH20 that can serve as epitopes for
4 generating polyclonal antibody responses.

5 MR. KUSHAN: We're going to mark
6 Exhibit 1122.

7 (Whereupon, Exhibit 1122 was marked for
8 identification.)

9 MR. KUSHAN: Sorry.

10 DR. KHANDURI: Thank you.

11 MR. KUSHAN: This is a paper
12 published in the "AAPS Journal,"
13 Vol. 24 -- numbered 110, starting at
14 Page 109, published in 2022, first author
15 Marie Printz.

16 BY MR. KUSHAN:

17 Q. Dr. Moon, could you look down at the left
18 corner of the paper and tell me what affiliation --
19 what company affiliation Marie Printz has?

20 A. I see Halozyme Therapeutics as an author
21 affiliation for Dr. Marie Printz.

22 Q. Halozyme owns the patents that are the
23 subject of these proceedings. Right?

24 A. I understand Halozyme is the owner of the
25 patent that I -- the case, -0003.

1 Q. Look in the abstract, and do you see that
2 the authors reported that they had identified -- or
3 they stated:

4 FIFTEEN EPITOPES IN THE
5 rHuPH20 --
6 THAT'S THE RECOMBINANT HUMAN PH20.
7 -- SEQUENCE HAD THE
8 POTENTIAL TO CROSS-REACT WITH
9 B CELLS.

10 Do you see that?

11 (No audible response.)

12 Q. It's about four lines from the bottom of
13 the paragraph, left column.

14 A. I see the sentence:

15 FIFTEEN EPITOPES IN THE
16 rHuPH20 SEQUENCE HAD THE
17 POTENTIAL TO CROSS-REACT TO
18 B CELLS.

19 But this is the first time I'm seeing this
20 document.

21 Q. Okay. Could you turn to Page 110. I just
22 want to focus you on -- in the left column of
23 Page 110, under the heading "B Cell Epitope
24 Prediction."

25 A. Which page, please?

1 Q. Page 110. The page number is in the top
2 right corner.

3 A. They're all 110.

4 Q. Oh, wait. That's right.

5 There it is, Page 5 of 15.

6 Do you see that?

7 A. Okay.

8 Q. And in the left column, they're talking
9 about B Cell Epitope Prediction and B Cell Epitope
10 Mapping.

11 And about halfway down the paragraph of
12 the B Cell Epitope Prediction paragraph, in the
13 middle of the page, it says:

14 Potential antigenic
15 epitopes for rHuPH20 were
16 identified by employing a model
17 of the 3D crystal structure of
18 recombinant human PH20, which
19 was based on the crystal
20 structure of HYAL1....

21 Do you see that?

22 (Witness reading.)

23 A. Yes, I see that sentence.

24 Q. And that's performing an inspection of a
25 PH20 homology model that we were talking about a

1 couple minutes ago. Right?

2 DR. KHANDURI: Objection; form.

3 (Witness reading.)

4 A. I see here that they used a model of the
5 3D crystal structure of rHuPH20.

6 Q. And do you see that the crystal structure
7 model was based on the crystal structure of the
8 HYAL1 protein?

9 That's the clause -- that's the part of
10 the sentence after that parenthetical. The part
11 that says "which was based on the crystal structure
12 of HYAL1."

13 DR. KHANDURI: Objection; form,
14 relevance.

15 A. I see the sentence. It reads, "which was
16 based on the crystal structure of HYAL1 using amino
17 acids 2-403 of rHuPH20."

18 Q. Okay. And then, in the next sentence,
19 they said:

20 Potential epitopes were
21 identified on the basis of
22 structure and solvent
23 accessibility....

24 In February of 20- -- I'm sorry.

25 In December of 2012, could a POSA have

1 performed these steps of inspecting the PH20 model
2 in evaluating structure and solvent accessibility of
3 the protein to identify linear B-cell epitopes?

4 DR. KHANDURI: Objection; form,
5 scope.

6 (Witness reading.)

7 Q. Dr. Moon, I want to make sure you
8 understood -- I'm just asking a simpler question:
9 In December of 2012, could a person of skill in the
10 art have used a PH20 homology model and inspected
11 the structure and solvent accessibility of the
12 protein to identify linear B-cell epitopes on the
13 human PH20 protein?

14 DR. KHANDURI: Objection; form,
15 scope, relevance.

16 (Witness reading.)

17 Q. Dr. Moon, my -- the answer to my question,
18 I don't believe, is in this paper. I'm asking -- I
19 want to make sure you understood my question.

20 Can you tell me what my question was?

21 DR. KHANDURI: Objection; form.

22 A. Could you repeat your question?

23 Q. Sure.

24 A. Yeah.

25 Q. I just want to know if a person of skill

1 in the art, a POSA, in December of 2012 could have
2 used a PH20 homology model, and by inspecting the
3 structure and solvent accessibility of the protein,
4 they could have identified the linear B-cell
5 epitopes on the surface of the human PH20 protein.

6 DR. KHANDURI: Objection; form,
7 scope, relevance.

8 (Witness reading.)

9 A. Can I spend more time to read this paper?

10 Q. I don't believe that's necessary. I just
11 want to know --

12 A. Okay.

13 Q. -- were -- you were a person of skill in
14 the art in 20- -- December 2012. Right?

15 A. Yes.

16 Q. If you look at that description, I'm
17 asking -- I'm only asking you: As a person skilled
18 in the art, could you have performed those steps
19 that are listed in the bottom half of the paragraph
20 under B-cell epitope prediction in February of
21 20- -- in December of 2012?

22 DR. KHANDURI: Objection; form,
23 scope, relevance.

24 A. I think I need to read the whole paper.

25 Q. So you're -- so do you know -- are you

1 aware of any reason why a POSA could not have
2 performed these steps of using a PH20 homology model
3 and looking at the structure and solvent
4 accessibility of the protein to identify the linear
5 B-cell epitopes on PH20, on its surface?

6 DR. KHANDURI: Objection; form,
7 scope, relevance.

8 A. This is the first time I'm looking at this
9 particular document, and I'd like to read it through
10 before answering your questions related to this
11 document.

12 Q. So I'm allowed to ask you questions about
13 what you believe. And my questions are focused on
14 the capabilities of a POSA in December of 2012 --
15 which you say you were, right? -- that -- you're
16 maintaining you're a person of skill in the art in
17 2012?

18 DR. KHANDURI: Objection; form.

19 A. I meet at least the qualifications of a
20 POSA.

21 Q. And so, I'm asking you if you could have
22 performed those steps that are described in that one
23 paragraph to identify the linear B-cell epitopes on
24 PH20. Yes or no, could you have done that?

25 DR. KHANDURI: Objection; form,

1 scope.

2 A. Yeah, I'll need to read the entire
3 document before --

4 Q. Why?

5 A. -- answering that.

6 DR. KHANDURI: Objection; form.

7 Q. Why do you need to read the other -- the
8 rest of the document to answer my question?

9 DR. KHANDURI: Objection; form,
10 scope.

11 Q. Let me help you.

12 Were -- was it possible to inspect a model
13 of the 3D crystal structure of PH20, based on the
14 crystal structure of HYAL1 in December of 2012 --

15 DR. KHANDURI: Objection; form,
16 scope.

17 Q. -- based on your knowledge and
18 understanding as a POSA in December of 2012?

19 DR. KHANDURI: Objection; form,
20 scope.

21 A. I'd like to read the document before --

22 Q. Dr. Park [sic] --

23 A. -- answering.

24 Q. -- let me ask -- I'm -- you're avoiding
25 answering the question.

1 MR. KUSHAN: It's not funny.

2 Okay? Just --

3 MS. ZHANG: You got his name
4 wrong.

5 MR. CHOI: His name's not
6 "Dr.~Park."

7 MR. KUSHAN: Sorry. I
8 apologize. I'll withdraw that.

9 Q. Dr. Moon, if you could just listen very
10 carefully. My question is asking whether you, as a
11 person skilled in the art, could have performed
12 these steps in December of 2012.

13 DR. KHANDURI: Objection; form,
14 scope.

15 A. I would like to read the entire document
16 before answering the question.

17 Q. So you're unable to answer that question
18 without reading the entire document. That's your
19 testimony?

20 DR. KHANDURI: Objection; form.

21 Q. About something you would know in December
22 of 2012.

23 DR. KHANDURI: Objection; form.

24 A. I would like to read the entire document
25 before answering specific questions.

1 Q. I'll take that as a you cannot answer my
2 question based on knowledge you had in December of
3 2012.

4 DR. KHANDURI: Objection; form.

5 Q. Is that fair?

6 DR. KHANDURI: Objection; form.

7 A. Once again, you're asking about a specific
8 experiment described in one paragraph out of
9 15 pages of document. And I'd like to read the
10 entire document before answering your question.

11 Q. So I'm not asking you about the results at
12 this point. What I'm asking you, if you're familiar
13 with the tools that were used and referenced in that
14 paragraph.

15 Do you know what a homology model is,
16 Dr. Moon?

17 DR. KHANDURI: Objection; form,
18 foundation.

19 (Witness reading.)

20 A. Where does it say "homology model"?

21 Q. It says that:

22 Potential antigenic
23 epitopes for recombinant human
24 PH20 were identified by
25 employing a model of the 3D

1 crystal structure of rHuPH20,
2 which was based on the crystal
3 structure of HYAL1 using amino
4 acids 2-403....

5 Do you understand that to be describing a
6 homology model that is based on the crystal
7 structure of HYAL1?

8 DR. KHANDURI: Objection; form,
9 scope.

10 A. It doesn't say "homology model" in the
11 document.

12 Q. So you don't recognize, from that
13 description, that they're referring to a PH20
14 homology model. Is that right?

15 DR. KHANDURI: Objection; form,
16 scope.

17 A. Before answering particular question about
18 this document, I would like to read the whole
19 document.

20 Q. All right. So I'm going to take your
21 answer -- you are refusing to answer my question or
22 you do not know the answer to my question. And I
23 will take that as your testimony.

24 DR. KHANDURI: Objection; form.

25 A. The document -- paragraph you mention

1 doesn't mention "homology model."

2 Q. Do you know what a homology model is and
3 how they're prepared?

4 A. So I would like to read the whole document
5 before I answer --

6 Q. No, no. My --

7 A. -- that question.

8 Q. Dr. Moon, my question was: Do you know
9 what a homology model based on a crystal structure
10 is?

11 DR. KHANDURI: Objection; form.

12 A. I would like to read the whole document
13 before answering any --

14 Q. Dr. -- Dr. Moon, I'm not asking -- this is
15 a question that's not based on this document. This
16 is a question based on your knowledge.

17 Do you know what a homology model is?

18 A. Are you referring to sequence alignment
19 models --

20 Q. No.

21 A. -- used in UniProt?

22 Q. No. I'm referring to a model that is
23 produced by SWISS-MODEL based on an amino acid
24 sequence and the structure -- the crystal structure
25 of HYAL1, which produces a model of the PH20

1 protein.

2 DR. KHANDURI: Objection; form,
3 scope.

4 Q. Do you know what that is?

5 A. Before answering specific questions, I
6 would like to read this whole document.

7 Q. Is it your testimony that in December of
8 2012, a POSA would not know what a homology model
9 is?

10 DR. KHANDURI: Objection; form.
11 (Witness reading.)

12 Q. Just to be clear, my question that's
13 pending right now is based on your personal
14 knowledge and not anything on a piece of paper in
15 front of you.

16 My question is: Do you know what a
17 homology model is, Dr. Moon?

18 DR. KHANDURI: Objection; form,
19 scope.

20 A. As I mentioned, as of 2012, I used many
21 different tools to analyze protein structure,
22 looking at sequence searching and alignments,
23 protein modeling software, and etc.

24 Q. So --

25 A. And I was in a part of multidisciplinary

1 team that examined protein modeling softwares to
2 design vaccine antigens.

3 Q. Have you ever used a software program
4 called PyMOL?

5 A. Could you repeat that?

6 Q. Have you ever used a software program
7 called PyMOL?

8 A. I have not used PyMOL --

9 Q. Have you used --

10 A. -- personally.

11 Q. Have you ever used any software program to
12 view a protein structural model?

13 DR. KHANDURI: Objection; form.

14 A. I was in a multidisciplinary research
15 group, as of 2012, to study protein structure using
16 modeling softwares.

17 But I have not personally used
18 three-dimensional structure models.

19 Q. All right. So if you could go to
20 Paragraph 36 of your declaration.

21 Sorry. Let's go back a couple of
22 paragraphs.

23 If you look at Paragraph 34 that's on
24 Page 20, and you're discussing in this paragraph and
25 two paragraphs that follow it:

1 ...polyclonal antibodies
2 generated against a polypeptide
3 antigen were known to
4 cross-react with another
5 polypeptide having as low as
6 ~46 – 49% sequence identity to
7 the stimulating polypeptide,
8 irrespective of whether the
9 polypeptides are from a
10 different animal species.

11 Do you see what --

12 A. Yes, I see that sentence.

13 Q. All right. And then, if you could go to
14 Paragraph 55, referring back to that Section VI:

15 ...polyclonal
16 antibodies --

17 This is what you state in Paragraph 55:

18 ...polyclonal --
19 polyclonal antibodies were
20 known to cross-react with a
21 polypeptide having as low as
22 ~46 – 49% sequence identity
23 with the polypeptide that
24 stimulated the polyclonal
25 antibody response.

1 A. Yes, I see that sentence.

2 Q. All right. So an antibody that binds to
3 two proteins, two different proteins, you're
4 referring to that as a cross-reactive antibody.
5 Right?

6 DR. KHANDURI: Objection; form.

7 A. "Cross-reactive antibody" generally refers
8 to antibodies that bind to two different proteins.

9 Q. So the one antibody is recognizing two --
10 the same antigenic determinant on two different
11 proteins.

12 Is that fair?

13 DR. KHANDURI: Objection; form.

14 A. "Cross-reactive antibody" generally refers
15 to antibodies that bind to two different proteins.

16 Q. And it's able to bind to two different
17 proteins because the same epitope is present on both
18 proteins. Right?

19 A. In general, cross-reactive antibodies bind
20 to similar or the same domains found within two
21 different proteins.

22 Q. Is it your opinion that any pair of
23 proteins that share 46% sequence identity will
24 induce production of cross-reactive antibodies that
25 bind to both proteins?

1 DR. KHANDURI: Objection; form.

2 A. I listed multiple examples where
3 polyclonal antibodies were known to cross-react with
4 other proteins in my declaration. And polyclonal
5 antibodies were known to cross-react to the
6 polypeptide having as low as about 46 to 49%
7 sequence identity with a polypeptide that stimulated
8 the polyclonal antibody response.

9 Q. So could you also ask -- answer my
10 question?

11 DR. KHANDURI: Objection; form.

12 A. Could you repeat your question?

13 Q. Yes. So you -- your answer to my last
14 question was explaining that you had found some
15 examples of proteins that induce production of
16 cross-reactive antibodies. Right?

17 A. There are examples that I listed in my
18 declaration.

19 Q. Right. And so, my question was actually
20 different. My question was: Is it your opinion
21 that any pair of two proteins that share 46%
22 sequence identity will induce production of
23 cross-reactive antibodies that bind to both
24 proteins?

25 That's my question. Could you please

1 answer that question.

2 DR. KHANDURI: Objection; form,
3 scope.

4 A. It is my opinion that proteins with a
5 sequence homology as low as about 46% sequence
6 identity will generate polyclonal antibodies that
7 cross-react with the other protein.

8 Q. So you list three examples of those types
9 of pairs of proteins that produced cross-reactive
10 antibodies in your declaration. Right?

11 DR. KHANDURI: Objection; form.

12 A. I listed three different examples where
13 antibodies generated cross-reactive polyclonal
14 antibody responses.

15 Q. How did you find the example of the
16 proteins that had 46% sequence identity?

17 DR. KHANDURI: Objection; form.

18 And I would caution Dr. Moon to
19 not divulge the substance of communication
20 with the counsel.

21 To the extent you can answer the
22 question without revealing the substance
23 of communications with counsel, you can do
24 so.

25 A. I searched the literature to find examples

1 where antibodies having various sequence identity
2 generates cross-reactive antibody responses.

3 Q. Did you find any other examples of two
4 proteins that had 46% sequence identity that induced
5 production of cross-reactive antibodies?

6 DR. KHANDURI: Dr. Moon, I will
7 caution you to not divulge the substance
8 of any --

9 MR. KUSHAN: Wait, wait, wait,
10 wait. He was describing his -- he said he
11 did a search, and I'm asking about his
12 search.

13 I'm not asking about his
14 conversations with you. So --

15 DR. KHANDURI: Yeah. Let me put
16 what I want to say on record. Okay?

17 MR. KUSHAN: I -- go ahead.

18 DR. KHANDURI: Dr. Moon, I will
19 caution you to not divulge the substance
20 of communication with counsel.

21 To the extent you can answer the
22 question without revealing the substance
23 of communications, you can do so.

24 BY MR. KUSHAN:

25 Q. And I'm clarifying: My question is about

1 what you did, Dr. Moon.

2 So based on your last answer, you said you
3 performed a search of the literature, looking for
4 examples of production of cross-reactive epitopes.
5 Right?

6 DR. KHANDURI: Objection; form.

7 A. I reviewed the literature where
8 cross-reactive antibody responses were generated.

9 Q. Dr. Moon, let me just clarify: Did you
10 perform a search of the literature to look for
11 examples of two proteins that share sequence
12 identity and produce cross-reactive antibodies?

13 DR. KHANDURI: Objection; form.

14 A. Could you repeat your question?

15 Q. Yeah, sure. I just want to know: Did you
16 do a literature search yourself to look for examples
17 of proteins from different sources that produced
18 cross-reactive antibodies?

19 DR. KHANDURI: Objection; form.

20 A. I did a literature search myself to look
21 for cases and examples where polyclonal antibodies
22 were generated.

23 Q. And you found three examples?

24 DR. KHANDURI: Objection; form.

25 A. I found at least three examples that I

1 listed in the declaration.

2 Q. Did you find any examples, other than the
3 one you list, where the sequence identity was
4 between 46 and 49% of the two proteins?

5 DR. KHANDURI: Objection; form.

6 A. There may be -- there may have been more
7 examples like this. But in my declaration, I put
8 one example where polypeptides having as low as 46
9 to 49 sequence identity generating polyclonal
10 cross-reactive antibody responses.

11 Q. Dr. Moon, did you find any other papers,
12 besides the three that you list in your declaration,
13 that reported results, from testing of two different
14 proteins, a capability to produce cross-reactive
15 epitopes that you did not include in your
16 declaration?

17 DR. KHANDURI: Objection; form.

18 A. There may have been other examples. But I
19 don't recall a specific example at the moment.

20 Q. Did you find any examples of two proteins
21 that had 90% sequence identity which failed to
22 produce cross-reactive antibodies?

23 (Witness reading.)

24 A. As I wrote in Paragraph 35, this is an
25 example where proteins with a 90% sequence identity

1 between mouse MOG domain and human MOG domain
2 generating polyclonal cross-reactive antibody
3 responses.

4 I also list another example in
5 Paragraph 36, where a protein with a sequence
6 homology -- sequence identity at 90%, 95%, or 98%
7 with a chicken, human, and rat type II collagen
8 inducing cross-reactive antibody responses --

9 Q. You did not --

10 A. -- in this --

11 Q. -- identify any examples other than these
12 three. Right?

13 DR. KHANDURI: Objection; form.

14 A. There may have been other examples like
15 this, but I don't recall the specific examples.

16 Q. Why did you not include them in your
17 declaration?

18 DR. KHANDURI: Objection; form.

19 (Witness reading.)

20 A. Once again, I may have seen other examples
21 in the literature. But I provided three concrete
22 examples in my declaration.

23 Q. Right. My question was trying to
24 understand why, if you saw other examples that
25 supported this idea that two proteins with 46%

1 sequence identity will induce production of
2 cross-reactive epitopes, why did you not include
3 those other examples in your declaration?

4 (Witness reading.)

5 A. Once again, I may have seen other
6 examples, other than those three cases, during my
7 search, but these three cases were sufficient to
8 help me form my opinions outlined in this
9 declaration.

10 Q. Are you speculating that there might have
11 been other examples that you could find, or are you
12 telling us under oath that you found other examples
13 besides these three and you chose not to discuss
14 them?

15 Which of those two situations are you
16 describing to us?

17 DR. KHANDURI: Objection; form.

18 A. Could you repeat the question?

19 Q. Yes. I'm trying to determine if you are
20 speculating if you -- there might be additional
21 examples that could be found, as opposed to you
22 found other examples of two proteins with 46% or
23 higher sequence identity producing cross-reactive
24 epitopes.

25 I'm trying to figure out: Which scenario

1 are we speaking of? You did -- you might find more,
2 or you did find more examples in your search?

3 DR. KHANDURI: Objection; form.

4 (Pause.)

5 A. So these three examples allowed me to form
6 opinions outlined in this declaration.

7 There may have been other examples. But I
8 don't recall the specific example at the moment,
9 sitting here today.

10 Q. And it's your opinion that any two
11 proteins that have at least 46% sequence identity
12 will induce production of cross-reactive epitopes
13 when you immunize a mammal with those two different
14 antigens?

15 DR. KHANDURI: Objection; form.

16 Q. Sorry. Let me strike that question.

17 (Pause.)

18 Q. Could you confirm that after performing
19 your literature search, you found no publications or
20 other information indicating that antibodies raised
21 against one species of PH20 induced production of
22 any antibody that bound to another species like
23 PH20?

24 DR. KHANDURI: Objection; form.

25 A. I didn't look into specific examples of

1 PH20 injected into animals to form my opinions that
2 proteins with a sequence identity greater than at
3 least 46% will generate cross-reactive polyclonal
4 antibody responses.

5 Modified -- based on these, modified PH20
6 would be expected to generate polyclonal antibody
7 responses that will bind to wild-type PH20.

8 Q. Are you aware of any examples of PH20
9 proteins from different species producing
10 cross-reactive antibodies through immunization of a
11 mammal?

12 A. Once again, I didn't look into specific
13 examples of PH20 generating antibody responses in
14 animals.

15 But reviewing the literature, I found at
16 least three examples, outlined here, showing that
17 protein with a sequence homology of at least 46%
18 would generate cross-reactive antibody responses.

19 And those three examples allowed me to
20 form the opinion that modified PH20 will generate
21 polyclonal antibody responses that will bind to
22 wild-type PH20 when injected in human females, as
23 well as in other --

24 Q. All right.

25 A. -- female mammals.

1 MR. KUSHAN: Why don't we take a
2 break?

3 VIDEOGRAPHER: We'll go off?

4 MR. KUSHAN: Yeah.

5 VIDEOGRAPHER: Off the record at
6 3:53 p.m.

7 (Whereupon, a recess was taken.)

8 VIDEOGRAPHER: We are going back
9 on the record at 4:27 p.m.

10 BY MR. KUSHAN:

11 Q. Dr. Moon, I'm going to hand you an exhibit
12 that's already been marked Exhibit EX2153.

13 (Whereupon, Halozyme Exhibit EX2153,
14 previously marked, was presented to the witness.)

15 DR. KHANDURI: Thank you.

16 Q. I believe this is the paper that you rely
17 on in Paragraph 34 of your declaration. Is that
18 right?

19 A. Exhibit 2153 is one of the exhibits that I
20 reviewed.

21 Q. So you relied on the information in
22 Exhibit 2153 to support your opinions in your
23 declaration. Right?

24 A. Exhibit 2153 is one of the exhibits that I
25 used to form my opinions.

1 Q. Okay. Now, this is a very simple
2 question: Did you find this paper, or was this
3 paper provided to you?

4 DR. KHANDURI: Dr. Moon, I will
5 caution you not to divulge the substance
6 of communication with counsel.

7 To the extent you can answer the
8 question without revealing the substance
9 of communications with the counsel, you
10 can do so.

11 MR. KUSHAN: Sorry. Are you
12 alleging there is a privilege basis
13 relating to my question?

14 DR. KHANDURI: Could be.

15 MR. KUSHAN: Could you step out,
16 Dr. Park -- I'm sorry. I'm so sorry.

17 Dr. Moon, could you please step
18 out of the room for one minute? And I
19 just have to talk to your counsel.

20 (Witness leaves the conference
21 room.)

22 MR. KUSHAN: I just want to
23 understand, get it on the record, why you
24 believe there could be an assertion of
25 privilege of work product relating to the

1 question I asked, which was: How did he
2 get this paper?

3 DR. KHANDURI: I'm just
4 cautioning the witness --

5 MR. KUSHAN: No --

6 DR. KHANDURI: -- do not divulge
7 the substance of communication. That's
8 all.

9 MR. KUSHAN: You're signaling to
10 the witness that there may be privilege.
11 And I want to understand the basis that
12 you have for privilege to that statement.

13 DR. KHANDURI: Yeah. I want to
14 make sure Dr. Moon understands the bounds
15 of the answer that he -- he should give in
16 response to your question. That's all.

17 MR. KUSHAN: So my question is
18 not very complicated. It's: Where did he
19 get the paper?

20 And there's no basis of --
21 there's no theory of privilege that would
22 suggest that is privileged.

23 DR. KHANDURI: I asserted my --
24 I stated my caution to Dr. Moon on record.
25 It's on record.

1 And I think we can move on.

2 MR. KUSHAN: I'm asking you to
3 not say it again, because you're coaching
4 your witness. And I'm just --

5 DR. KHANDURI: I'm not --

6 MR. KUSHAN: There's no --
7 there's no conceivable basis of privilege
8 in the source of the document that he's
9 using to support his opinions in this
10 proceeding. That's my point.

11 And by you saying -- cautioning
12 him not to reveal privilege, you're
13 coaching him. And I believe that's
14 improper, and I would just ask that you
15 not do that anymore.

16 DR. KHANDURI: I disagree. It's
17 fully appropriate, I think.

18 MR. KUSHAN: All right.

19 DR. KHANDURI: Let's just move
20 on.

21 MR. KUSHAN: But you've not
22 identified -- there's no theory you have
23 why his answer could be privileged.

24 DR. KHANDURI: I'm cautioning
25 the witness to be aware that his

1 answers -- in case his answers lead to
2 communications with counsel, he should be
3 aware of that. That's all.

4 MR. KUSHAN: Well, if you hear
5 him say that in his answer, you can
6 intervene.

7 DR. KHANDURI: So --

8 MR. KUSHAN: That's the proper
9 way.

10 DR. KHANDURI: -- let's just
11 move on --

12 MR. KUSHAN: That's the -- no.
13 That's the proper way to deal with it. If
14 you sense that he's going to start
15 revealing privileged communications, you
16 can interrupt the witness and instruct me
17 [sic] not to answer. Okay?

18 DR. KHANDURI: It would be too
19 late by then.

20 MR. KUSHAN: No. It's not.
21 You -- you can jump in. It's not --

22 DR. KHANDURI: It could be too
23 late by then. Let's just move on.

24 I've made my point.

25 MR. KUSHAN: Can you go get --

1 DR. KHANDURI: Yep.

2 MR. KUSHAN: -- your witness.

3 (Witness returns to the
4 conference room.)

5 DR. KHANDURI: Thank you.

6 BY MR. KUSHAN:

7 Q. Dr. Moon, do you recall the question I
8 asked you before the break? Or --

9 A. Could you --

10 Q. -- just before you left?

11 A. Could you repeat the question?

12 Q. Yes. The question is: Did you find
13 Exhibit 2153 yourself, or was Exhibit 2153 provided
14 to you?

15 DR. KHANDURI: Dr. Moon, the
16 same caution.

17 (Witness reading.)

18 A. I believe this is one of the papers I
19 found during the literature search.

20 Q. And do you have any recollection of
21 finding any other paper, besides this and the other
22 two papers that are cited in your declaration, that
23 showed that two different proteins with less than
24 90% sequence identity generated cross-reactive
25 antibodies?

1 DR. KHANDURI: Objection; form.

2 (Pause.)

3 Q. I'm going to read the question again to be
4 clear.

5 Do you have any recollection of -- other
6 than Exhibit 2153 and the other two papers cited in
7 your declaration, of a paper that you found in your
8 search that had less than 90% sequence identity --
9 sorry.

10 MR. KUSHAN: Yeah, (sotto voce)
11 we lost antibodies.

12 Q. Yeah. All right. So let's try it one
13 more time.

14 So, Dr. Moon, you performed a search for
15 literature that resulted in you finding, as you just
16 testified, Exhibit 2153. Right?

17 A. Yes. I did a literature search, and I
18 believe this is one of the papers I found during the
19 literature search.

20 MR. KUSHAN: And I'm going to
21 hand you Exhibit 2154.

22 (Whereupon, Halozyme Exhibit EX2154,
23 previously marked, was presented to the witness.)

24 DR. KHANDURI: Thanks.

25 Q. This is another one of the papers that is

1 cited in your declaration. And you addressed this
2 one in Paragraph 35. Right?

3 This is the same paper that you cited in
4 Paragraph 35. Right?

5 A. I cited this paper in Paragraph 35.

6 Q. And you relied on this paper to support
7 your opinion that two proteins with 90% sequence
8 identity or higher will generate cross-reactive --
9 cross-reactive antibodies. Correct?

10 (Pause.)

11 DR. KHANDURI: Objection; form.

12 A. I cited, in Paragraph 35, this paper,
13 2154, showed that two proteins with a sequence
14 identity of about 90% is generating cross-reactive
15 antibody responses.

16 Q. And so, you relied on the information in
17 Exhibit 2154 to support your opinions in your
18 declaration. Correct?

19 A. Exhibit 2154 is one of the documents that
20 I relied on to prepare my declaration.

21 And as outlined in Paragraph 35, this
22 exhibit showed that proteins with about 90% sequence
23 identity generates cross-reactive antibody
24 responses.

25 Q. Dr. Moon, did you find Exhibit 2154, or

1 was it provided to you?

2 (Witness reading.)

3 A. I believe this is one of the papers I
4 found during my literature search.

5 MR. KUSHAN: Okay. I'm going to
6 hand you another exhibit. This is
7 Exhibit 2155.

8 (Whereupon, Halozyme Exhibit EX2155,
9 previously marked, was presented to the witness.)

10 Q. And I believe this is the paper by
11 Trentham that is addressed in Paragraph 36 of your
12 declaration.

13 Did you rely on Exhibit 2155 to support
14 your opinions in your declaration?

15 (Witness reading.)

16 A. I relied on many papers to prepare my
17 declaration, and this is one of the papers that I
18 used.

19 Q. Dr. Moon, did you find Exhibit 2155, or
20 was Exhibit 2155 provided to you?

21 (Witness reading.)

22 A. I believe this is one of the papers that I
23 found during the literature search that allowed me
24 to form the opinions outlined in the declaration.

25 Q. And to be clear: As you sit here today,

1 you have no recollection of any other paper that
2 shows two proteins with a low 90% sequence identity
3 generating cross-reactive antibodies?

4 DR. KHANDURI: Objection; form.

5 A. Well, Exhibit 2153 shows proteins with --

6 MR. KUSHAN: I apologize. I'll
7 withdraw that question. That was
8 certainly imprecise.

9 Q. Other than the three papers that you cite
10 in your declaration, you cannot identify any other
11 paper, after you performed your search, that shows
12 two proteins with sequence identity of 46% to 90%
13 that generated cross-reactive antibodies.

14 DR. KHANDURI: Objection; form.

15 Q. Is that right?

16 DR. KHANDURI: Objection; form.

17 A. During my search, I may have found other
18 examples like these, but I don't recall the specific
19 reports at the moment.

20 Q. Can you -- do you recall what proteins --
21 what kind of proteins they were, if you remember a
22 paper?

23 (Witness reading.)

24 A. I may have seen other papers along these
25 line performed in mice, but I do not recall what

1 specific protein was used in those examples.

2 Q. If you could go to Exhibit 2153, which is
3 the heat shock protein paper.

4 Do you have that?

5 A. Yes, I have that.

6 Q. When you prepared your opinions in your
7 declaration, did you compare the proteins that were
8 discussed in Exhibit 2153 to PH20 proteins?

9 DR. KHANDURI: Objection; form.

10 A. Could you repeat the question?

11 (Pause.)

12 Q. Okay. My question was: When you formed
13 your opinions in your declaration about this topic
14 we've been discussing, did you compare the proteins
15 that were discussed in Exhibit 2153 in any way to
16 the PH20 proteins?

17 DR. KHANDURI: Objection; form.

18 A. Could you be more specific -- by
19 comparison?

20 Q. Sure. Did you -- did you see if they
21 were -- these proteins were enzymes like the PH20
22 proteins?

23 A. These studies are about use of proteins
24 for vaccine applications, how proteins of different
25 sequence identity are inducing cross-reactive

1 antibody responses.

2 Q. Were the heat shock proteins being used
3 as -- in a vaccine, or were they just being studied
4 because people had observed autoantibodies to be
5 produced against them?

6 DR. KHANDURI: Objection; form.

7 (Witness reading.)

8 A. In this particular report, the researchers
9 were studying heat shock protein in the setting of
10 infection with microbes.

11 And they are reporting mice can generate
12 antibody responses to heat shock protein.

13 Q. Dr. Moon, did you compare the length of
14 the protein sequences being discussed in the
15 Exhibit 23- -- 2153 paper to the length of the PH20
16 proteins as part of your analysis?

17 (Witness reading.)

18 A. I did not directly compare the length of
19 the heat shock protein to PH20 to arrive at my
20 opinions outlined in the declaration.

21 What this paper is showing is that, as
22 long as proteins have sequence identity as low as
23 46%, these antigens can generate cross-reactive
24 antibody responses.

25 And similar principles can be applied to

1 modify the PH20.

2 Q. And under the same reasoning, any two
3 proteins that have 46% sequence identity would also
4 generate cross-reactive antibodies. Correct?

5 DR. KHANDURI: Objection; form.

6 A. This paper clearly reported that proteins
7 with a sequence identity as low as 46% can generate
8 cross-reactive antibody responses.

9 Q. And I'm just exploring your reasoning why
10 that suggests that PH20 proteins with 46% sequence
11 identity to other proteins will generate
12 cross-reactive antibodies that bind to other PH20
13 proteins.

14 Why?

15 DR. KHANDURI: Objection; form.

16 A. Basically, these three papers, including
17 Exhibit 2153, are showing that when you use proteins
18 with sequence homology ranging from as low as 46% to
19 90% and higher, they are generating cross-reactive
20 antibody responses.

21 So the same principles could be expected
22 to work for modified PH20.

23 Q. Now, you're saying that because the two
24 proteins have 46% sequence identity or because
25 they're homologous proteins that have 46% sequence

1 identity?

2 DR. KHANDURI: Objection; form.

3 Q. I think, in your declarations, you just
4 refer to "sequence identity." Right?

5 (No audible response.)

6 Q. So if you look at Paragraph 34, you say:

7 ...polyclonal antibodies
8 generated against a polypeptide
9 antigen were known to
10 cross-react with another
11 polypeptide having as low as
12 ~46 – 49% sequence identity to
13 the stimulating polypeptide,
14 irrespective of whether the
15 polypeptides are from a
16 different animal species.

17 Right?

18 So that's sequence identity you're
19 referring to. Correct?

20 A. I'm referring to the sequence identity in
21 that statement.

22 Q. Right. And then, in the Oliver paper,
23 which is Exhibit 2154, you're referring to the
24 existence of 90% sequence identity between the mouse
25 and human MOG proteins. Right?

1 Again, it was the sequence identity that
2 you were pointing to to support your opinion that
3 the two proteins would generate cross-reactive
4 antibodies. Right?

5 A. In this exhibit, they used mouse MOG
6 protein and human MOG protein with a sequence
7 identity of about 90% to show cross-reactivity.

8 Q. And in Paragraph 36, regarding the
9 Exhibit 2155, which is the Trentham paper, again,
10 you're using sequence identities as a basis for your
11 opinion that the three proteins will generate
12 cross-reactive antibodies. Right?

13 A. This paper, 2155, showed that proteins
14 with a sequence identity 90%, 95%, or 98% generate
15 cross-reactive antibody responses.

16 Q. So again, your opinions are based on
17 sequence identity as the critical question above
18 46%?

19 DR. KHANDURI: Objection --
20 objection; form.

21 A. As I stated in Paragraph 37, based on
22 these reports:

23 ...POSA would have
24 expected that polyclonal
25 antibodies generated in a

1 subject against a polypeptide
2 would cross-react with
3 polypeptides having as low as
4 ~46 – 49% sequence identity....

5 Q. And that's true for any polypeptide that
6 meets that threshold of 46 to 49% sequence identity.
7 Right?

8 DR. KHANDURI: Objection; form.

9 A. (Reading):

10 ...POSA would have
11 expected that polyclonal
12 antibodies generated in a
13 subject against a polypeptide
14 would cross-react with
15 polypeptides having as low as
16 ~46 – 49% sequence identity....

17 Q. Okay. Now, we talked a bit earlier about
18 the alignments that you -- are in your declaration
19 in the appendix.

20 I just want to ask: Did you prepare the
21 alignments that are reported in Appendix B and
22 Appendix -- yeah.

23 So there are three alignments in
24 Appendix B. And did you prepare all these
25 alignments yourself?

1 (Witness reading.)

2 A. Yes, I recall I prepared the alignments
3 myself.

4 DR. KHANDURI: All right. Why
5 don't we take about a five-ish minute
6 break.

7 VIDEOGRAPHER: We're going off
8 the record --

9 DR. KHANDURI: Okay.

10 VIDEOGRAPHER: -- at 4:58 p.m.

11 (Whereupon, a recess was taken.)

12 VIDEOGRAPHER: We are going back
13 on the record at 5:13 p.m.

14 BY MR. KUSHAN:

15 Q. Dr. Moon, did you speak with anybody on
16 the break?

17 A. No.

18 MR. KUSHAN: Okay. I'm going to
19 mark as Exhibit 1123 an excerpt from a
20 textbook by Janeway -- Janeway's,
21 consisting of Chapters 8, 10, 12, 15, and
22 Appendix I.

23 (Whereupon, Exhibit 1123 was marked for
24 identification.)

25 Q. This is the 8th Edition of Janeway's

1 "Immunobiology," published in 2011 -- 2012, by
2 Garland Science.

3 Yes. There are portions of Chapters 8,
4 10, 12, 15, and Appendix I.

5 Dr. Park [sic], are you familiar with the
6 Janeway's Immunobiology textbook?

7 A. By the way, I'm Dr. Moon.

8 Q. I'm sorry. I'm so --

9 A. Yeah.

10 Q. I -- sorry. I've said that a couple times
11 today. I wanted to apologize.

12 A. Okay.

13 Q. Dr. Moon, can I just clarify: Have you
14 seen or are you familiar with this Immunobiology
15 textbook from Janeway's?

16 A. I may have read this a long time ago.

17 Q. Would this have been one of the textbooks
18 you might have used in the 2008 to 2012 time frame,
19 or earlier versions of it?

20 A. I don't --

21 DR. KHANDURI: Objection; form.

22 A. -- recall the exact text, but I may have
23 seen this long, long time ago.

24 Q. Okay. Could I ask that you go to the very
25 back, Page 721. And if you need to -- you can take

1 the paper -- the clip off.

2 I'm just going to ask you a couple
3 questions about the table that -- I'm sorry.

4 In the directory, it's --

5 A. What page?

6 Q. -- Page 719. It's Figure A.2.

7 A. So Figure A.2.

8 Figure A.2. Yeah, I'm looking at that.

9 Q. And this is a table that compiles "Factors
10 that influence the immunogenicity of proteins."

11 And I just want to go over some of these
12 characteristics and see if they are consistent with
13 your familiarity of this phenomenon of
14 immunogenicity of proteins. Okay?

15 (No audible response.)

16 Q. Do you agree, as it's being represented in
17 Figure A.2, that the size of a protein can influence
18 the immunogenicity of the protein?

19 (Witness reading.)

20 A. In general, size of antigen may affect
21 immunogenicity.

22 Q. Okay. And larger proteins are labeled
23 "increased immunogenicity."

24 Is that consistent with your experience?

25 (Witness reading.)

1 A. Could you repeat the question?

2 Q. Sure. Is it consistent with your
3 experiences in the field of immunology that larger
4 proteins are generally more immunogenic -- more --
5 more immunogenic than smaller proteins?

6 A. In general, larger proteins are more
7 immunogenic than smaller proteins.

8 Q. Okay. If you go a few rows down, there's
9 a row called "Form," and it has four boxes.

10 "Particulate" is described as being
11 increased immunogenicity compared to "soluble," as
12 to the -- I'm sorry -- yeah, particularly as
13 compared -- let me start over.

14 The table is describing proteins that are
15 in particulate form to be -- to have increased
16 immunogenicity relative to proteins that are
17 soluble. Is that right?

18 A. In general, particulate form of antigens
19 are known to be more immunogenic than soluble
20 proteins.

21 Q. And similarly, denatured forms of proteins
22 are known to be more immunogenic -- more immunogenic
23 than the native form of the protein. Correct?

24 A. In general, denatured proteins are more
25 immunogenic than native proteins.

1 Q. Okay. And the next row is describing
2 similarity to self-protein.

3 That's addressing the self-protein
4 questions we were discussing earlier today. Right?

5 A. I see that row, "Similarity to self
6 protein."

7 Q. And it's reporting that where a protein
8 has multiple differences relative to a self-protein,
9 that's increased immunogenic -- it has increased
10 immunogenicity. Correct?

11 A. It's been generally known that proteins
12 with multiple differences are more immunogenic.

13 Q. And proteins that have fewer differences
14 and are more similar to the native wild-type protein
15 have decreased immunogenicity. Right?

16 A. So this is a very general table that
17 describes immunogenicity of proteins.

18 The proteins with multiple differences are
19 known to be more immunogenic. A POSA would have
20 used proteins with fewer differences as an effective
21 antigen using different approaches that I outlined
22 in the declaration.

23 Q. And is it correct that these are
24 principles that someone who was a POSA in 2012 would
25 have been familiar with?

1 A. These are general concepts in immunology.

2 MR. KUSHAN: Okay. I have no
3 further questions.

4 DR. KHANDURI: We'll take --
5 we'll take a break.

6 Let's go off record.

7 VIDEOGRAPHER: Going off the
8 record at 5:23 p.m.

9 (Whereupon, a recess was taken.)

10 VIDEOGRAPHER: We are going back
11 on the record at 5:29 p.m.

12 DR. KHANDURI: Thank you,
13 Dr. Moon, for your time. We don't have
14 any questions for you. We invoke the
15 witness's right to read and sign.

16 MR. KUSHAN: Okay.

17 DR. KHANDURI: Thank you.

18 VIDEOGRAPHER: We are going off
19 the record --

20 DR. KHANDURI: We're off.

21 MR. KUSHAN: Yeah.

22 VIDEOGRAPHER: -- off the record
23 at 5:29 p.m.

24 (Whereupon the deposition concluded at
25 5:29 p.m.)

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DEPONENT'S SIGNATURE

Please be advised I have read the foregoing deposition, pages 1 through 201, inclusive. I hereby state there are:

(Check one)

_____ No corrections

_____ Corrections per attached

JAMES J. MOON, PH.D.

- (X) Reading and signing was requested.
- () Reading and signing was waived.
- () Reading and signing was not requested.

Should the signature of the witness not be affixed to the deposition, the witness shall not have availed himself of the opportunity to sign or the signature has been waived.

--oOo--

1	ERRATA SHEET		
2	NAME OF CASE: Merck Sharp & Dohme LLC v.		
3	Halozyme, Inc.		
4	DATE OF DEPOSITION: November 18, 2025		
5	NAME OF WITNESS: JAMES J. MOON, PH.D.		
6	Reason Codes:		
7	1: To clarify the record.		
8	2: To conform to the facts.		
9	3: To correct transcription error.		
10	Page _____	Line _____	Reason _____
11	From _____ to _____		
12	Page _____	Line _____	Reason _____
13	From _____ to _____		
14	Page _____	Line _____	Reason _____
15	From _____ to _____		
16	Page _____	Line _____	Reason _____
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19	From _____ to _____		
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22	Page _____	Line _____	Reason _____
23	From _____ to _____		
24	_____		
25	JAMES J. MOON, PH.D.	DATE	

1 DECLARATION UNDER PENALTY OF PERJURY

2 I am the witness in the foregoing
3 deposition.

4 I have read the foregoing deposition or
5 have had read to me the foregoing deposition, and
6 having made such changes and corrections as I
7 desired, I certify that the same is true in my own
8 knowledge.

9 I hereby declare under penalty of perjury
10 that the foregoing is true and correct.

11 In witness whereof, I hereby subscribe my
12 name this _____ day of _____, 2025.

13

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JAMES J. MOON, PH.D.

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CERTIFICATE

I, SUSAN ASHE, a Registered Merit Reporter and Notary Public, hereby certify that the foregoing is a true and accurate transcript of the deposition of said witness, who was first duly sworn by me on the date and place hereinbefore set forth.

I FURTHER CERTIFY that I am neither attorney nor counsel, nor related to or employed by any of the parties to the action in which this deposition was taken, and further that I am not a relative or employee of any attorney or counsel employed in this action, nor am I financially interested in this case.

Dated this 24th day of November 2025.



Susan Ashe, Notary Public
of the District of Columbia

My commission expires: May 14, 2028.

Exhibits	-0006 16:23	11 114:18	58:9,13,18 59:3,19,20 60:1 69:22 70:17 72:2 114:19 157:5 164:9 196:21 197:4
EX 1118 James J. Moon, Ph. D. 111825 6:10 27:19, 23	-0009 16:24	110 155:13 156:21,23 157:1,3	
EX 1119 James J. Moon, Ph. D. 111825 6:13 90:2,6, 16	-003 117:13	1118 27:19,23	16 21:19
EX 1120 James J. Moon, Ph. D. 111825 6:16 108:9	-004 54:8	1119 90:2,6,16	18 10:1,6 31:8 32:12
EX 1121 James J. Moon, Ph. D. 111825 6:21 114:17, 21	-006 54:15	1120 108:8,9	19 45:5 53:19 117:10,15,16
EX 1122 James J. Moon, Ph. D. 111825 7:4 155:6,7	-009 54:22	1121 114:17,21	1:13 117:2,4
EX 1123 James J. Moon, Ph. D. 111825 7:10 196:19, 23	-03 78:22	1122 155:6,7	2
-	-3 78:13	1123 196:19,23	2 109:6,10,11, 12,13
	0	11:18 76:11	2-403 158:17 165:4
	0003 17:21 18:1	12 78:10 79:11 80:5 127:16 129:20 196:21 197:4	20 62:15 67:16 68:1,22 69:22 90:3 137:5 168:24
	1	12:28 116:18,20	20- 158:24 160:14,21
	10 62:14,15 67:7 196:21 197:4	13 57:22	20-day 110:2
	100 14:6	14 21:1,19 49:23,25 54:6,8,15,22 59:16 62:19 63:5 68:8 71:10 72:15 73:5 74:22 75:5,19 93:9 97:14 135:18 138:11,15, 19,21,25 139:8,12 140:12 142:4,19	2000- 33:22 34:12
	100% 122:14,18	15 20:18 21:5, 19 57:7,23	2001 90:4
	100-ish 14:7		2008 25:8,10 26:2,14 27:13 197:18
--o0o-- 10:3	1001 19:6		2011 114:19 197:1
-000- 78:19	1049 56:3 74:20 75:8		2012 26:3 27:13
-0003 17:16 49:23 78:12,14 117:14 155:25	108 114:18		
-0004 16:6,23 78:11	109 155:14		

28:4,13 30:4,12 32:12,13,19 33:6,14,23, 24 34:1,4, 12,21 36:8, 14,17,19,20, 22 37:21,24 38:1 39:10, 13,17,20 40:23 41:12, 17 42:23,24 43:16,20,22 44:5,20,22, 24,25 45:3,7 46:10,22,23 48:12 49:14 67:15 68:23 69:21 70:18 71:20 72:3, 13 108:17 145:10,14 152:15 153:1 158:25 159:9 160:1,14,21 161:14,17 162:14,18 163:12,22 164:3 167:8, 20 168:15 197:1,18 200:24	2153 180:19,22,24 185:13 186:6,16 189:5 190:2, 8,15 191:15 192:17 2154 186:21 187:13,17, 19,25 193:23 2155 188:7,13,19, 20 194:9,13 22 66:22 78:10 79:12,13,15 127:17 129:19 23 57:22 127:15,18,19 23- 191:15 24 28:3 81:1 155:13 25 130:1 2:21 149:7 2:54 149:10	137:5,11 138:5 143:6 3/6 111:2 312 54:3 55:2 57:22 313 54:3,13 317 54:3,20 57:22 32 60:18 81:25 87:24 117:11,16 118:1,18 120:18 32-66 50:8 51:2,8 52:3 54:12, 19 55:2 66:3,15,19 81:13 136:4, 12,15,24 137:5,12 138:5 143:6 320 50:10 51:3,6 52:7,22,25 53:15,24 59:2 143:1,5 34 168:23 180:17 193:6 35 175:24 187:2,4,5, 12,21 36 168:20 176:5 188:11 194:8 37 194:21 3724 28:4	3746 28:4 3:53 180:6 3D 145:25 150:8 157:17 158:5 162:13 164:25 3p21.3 90:25
2013 43:15 2021 88:14 2022 155:14 2025 10:1,6 13:20 2025-0003 16:23 2074 15:19 2075 24:22,24 25:4	<hr/> 3 <hr/> 3 50:8 51:2,8 52:3 54:12, 19 55:1 57:22 66:2, 15,19 81:13, 25 108:16 111:20 112:8,20 113:6 136:4, 12,15,24	320 50:10 51:3,6 52:7,22,25 53:15,24 59:2 143:1,5 34 168:23 180:17 193:6 35 175:24 187:2,4,5, 12,21 36 168:20 176:5 188:11 194:8 37 194:21 3724 28:4	<hr/> 4 <hr/> 4 49:24 139:7 42 80:25 81:15, 22 430 52:4 65:18, 25 66:4 82:1 4388 114:19 4393 114:19 44 130:1,2 131:15 134:20 136:16 137:7,20 45 139:15 140:19 46 169:6,22 171:6 175:4, 8 193:12 195:4,6,16 46% 170:23 171:21 172:5,16 173:4 176:25 177:22 178:11

179:3,17 189:12 191:23 192:3,7,10, 18,24,25 194:18 49 175:9 49% 169:6,22 171:6 175:4 193:12 195:4,6,16 499 90:3 4:27 180:9 4:58 196:10	<hr/> 7 <hr/> 7 55:1 66:9, 10,19 108:16 135:5,13 136:1,6,10, 13,18,23 137:4,9,22 138:1,6 719 198:6 721 197:25 7q31.3 91:5	53:14,23 54:11,18 55:23 57:14 58:16 66:20 135:1,12,20, 25 136:8,18 137:8,11,21, 22 143:6 176:6 194:14 98% 176:6 194:14 9:37 45:18 9:55 45:21	accessibility 158:23 159:2,11 160:3 161:4 accommodates 66:22 achieve 131:1 acid 50:5,7,14, 19,25 51:1, 12,25 52:4, 20 53:2,7, 10,12,16,18, 22 54:10,11, 17,18,24,25 55:13,15,23 56:21 57:9 58:13,17,18 59:4,20 60:11,25 62:9,13,15 63:15 64:11 65:19 66:4 67:6,8 69:22 71:6,24 73:20 74:20 81:24 100:14 124:7 127:25 131:4,6,9 134:25 136:8,13 137:24 139:21 141:24 142:5,12,16 144:6 150:12 166:23 acidification 115:11 acids 53:9,19 63:3 82:2 143:10, 18,20 145:20 158:17 165:4 acknowledge 84:5
<hr/> 5 <hr/> 5 17:25 157:5 50 14:7 508 90:4 55 169:14,17 5:13 196:13 5:23 201:8 5:29 201:11,23,25	<hr/> 8 <hr/> 8 196:21 197:3 8:40 10:2,5 8th 196:25	<hr/> A <hr/> A.2 198:17 A.2. 198:6,7,8 a.m. 10:2,5 45:18,21 76:8,11 AAPS 155:12 ability 43:2 64:10 141:25 able 94:20 95:11 97:20 170:16 above 79:15 110:7 194:17 absolutely 99:4 abstract 90:9,22 91:11 114:24 115:2,7,8,25 156:1 acceptable 99:10	
<hr/> 6 <hr/> 6- 49:22 600- 49:22 66 82:1	<hr/> 9 <hr/> 90% 175:21,25 176:6 185:24 186:8 187:7, 14,22 189:2, 12 192:19 193:24 194:7,14 91 55:19 57:14 58:16 91% 54:25 55:22 95 55:19 95% 50:6,25 51:7 52:6,24		

across 114:4	admin- 135:20	aggregated 133:19	amino 50:5,7,14,
activation 118:7,13	139:22	134:12,15,18	18,25 51:1,
activations 147:11	administer 126:1	138:19	11,25 52:4,
active 140:2	administered 75:10 81:8,	aggregates 133:10,15	20 53:2,7,9,
activity 32:15,21	20 82:7	134:1	12,16,18,19,
110:25	107:19,22	aggregation 133:13,18	22 54:10,11,
added 60:24 61:13,	115:16	134:4,12	17,18,24,25
17 62:10	120:25	138:22	55:13,15,23
64:6	125:11,16	ago 13:20 115:21	56:21 57:8
adding 60:8,15,17	135:2,22	158:1	58:13,16,18
62:16	139:23	197:16,23	59:4,19,20
addition 20:25 57:21,	140:1,3,17	agree 74:5 119:17	60:11,25
22 58:12	142:15	125:9,14	62:8,13,14
61:3 138:2	administering 140:10	144:22	63:2,15
additional 52:20 57:23	administratio n	198:16	64:11 65:18
58:9,13 59:3	108:19,22	ahead 31:3 97:13	66:4 67:6,8
60:1 99:13	110:6,8	173:17	69:22 71:6,
121:14	112:11,12,	alignment 36:18 166:18	24 73:20
177:20	16,24	alignments 36:15 167:22	74:20 81:24
additions 57:8	Advanced 28:3	195:18,21,	82:1 100:14
address 20:23	advantages 110:17	23,25 196:2	124:7 127:25
addressed 187:1 188:11	affect 43:21 198:20	alleging 181:12	131:4,6,9
addressing 16:22 115:4	affiliation 155:18,19,21	allow 86:3,21	134:25
135:12	affinities 95:2	124:2	136:8,13
137:7,20	affinity 85:11,13,20,	allowed 18:19 51:16,	137:24
200:3	23 86:15,19	23 53:12	139:21
adjuvant 29:7 126:1,	87:17 92:9,	55:17 56:15	141:24
13,21 127:3,	10 94:5,6	67:1 68:17	142:5,12,16
6	95:1	75:18 161:12	143:10,18,20
adjuvants 121:1 126:3,	agent 113:21	178:5 179:19	144:6 145:20
5,9,18,22,25	agents 29:6	188:23	150:12
127:11,12	aggregate 134:9	allows 56:16 57:12	158:16 165:3
		alter 100:15,18	166:23
		119:18	Amit 10:24
			an- 84:24
			analysis 31:12 191:16
			analyze 35:23 167:21
			anchor 66:11
			and/or 111:1,9
			animal 44:1 169:10

193:16 animals 44:4 121:22 179:1,14 Ann 11:19 answer 12:15,16,23 14:24 17:21 42:11 49:10 70:13 72:11 74:19 76:23 77:19,25 83:1 84:13, 24,25 87:1, 6,8,9 89:1 93:17,24 94:20 95:12, 17 96:17,19, 23 97:7,12, 13,18,20 98:5,7 99:1, 5,7,15,20,25 102:15 103:25 106:9,18,19 148:2 159:17 162:8 163:17 164:1 165:21,22 166:5 171:9, 13 172:1,21 173:21 174:2 181:7 182:15 183:23 184:5,17 answered 68:19 77:9 94:14 95:9, 19 answering 69:11 70:12 77:5 97:11 98:10 99:3, 17,22,23 161:10 162:5,23,25 163:16,25	164:10 165:17 166:13 167:5 answers 17:18 77:2,4 78:4 149:17 184:1 anti- 41:21 antibodies 20:7 21:2,8 38:10,25 40:10,17,21 41:17,20 42:10,16,18, 21 43:1,5,9, 13 48:19 49:6 68:9,16 69:7 71:2,4 72:16 73:6 74:2,6,15 75:6,11,20 79:18,22,23 80:6,10,12, 18,23 82:10, 22 83:12,16, 22,23 84:3, 10,17 85:6, 15,19 86:11, 13,22 91:25 92:12 93:15 94:5,6,8 95:6 105:13 106:1 107:1 111:11 112:1 114:4,14 118:8,14 119:1,24 120:10,16 122:7,23 123:18 124:2 127:8 129:10,12 137:12 139:8,13 140:12,16,19 142:1 144:22 147:1,12,17	148:25 151:24 154:12 169:1,16,19 170:8,15,19, 24 171:3,5, 16,23 172:6, 10,13 173:1, 5 174:12,18, 21 175:22 178:20 179:10 185:25 186:11 187:9 189:3,13 192:4,12 193:7 194:4, 12,25 195:12 antibody 38:21 41:3, 13 43:21,25 44:4 48:24 62:3 64:23 65:7 71:7, 11,16 73:1 80:1,3,14, 17,22 82:13, 16,19 83:4, 7,9,18,20 84:6,21 85:3,11,23 86:12 87:12, 17,23 88:4, 17 89:15 91:24 92:2,9 93:10,22 94:11,19 95:16,25 96:14 97:24 101:5,12,18 102:2,10 103:2,13,24 104:16 105:6,12,14, 18 106:7,13, 16,23 109:19 112:3,4 113:7,9,12 119:25	120:19,22 121:3,7,11, 16,20 122:16,19,23 123:10,15 124:9 125:20,24 126:4,10 128:8,13 130:23 131:18 134:14 141:15,22 142:7,22 143:8 144:13 145:3 146:3, 9,12,16,19, 22,25 147:3, 19,23 150:23 154:9 155:4 169:25 170:2,4,7,9, 14 171:8 172:14 173:2 174:8 175:10 176:2,8 178:22 179:4,6,13, 18,21 187:15,23 191:1,12,24 192:8,20 194:15 anticipate 83:23 antigen 33:10,11 35:13 37:5 40:18 43:9, 14 49:1,7 62:3 72:21, 25 74:9,11 79:19,22,25 80:7,14 83:15 92:6, 7,11 94:2 109:1 127:25 128:4,8,12
---	--	--	---

129:17	25:24 30:10	Ashe	assay
130:22 131:8	33:3,18	10:17	109:20
132:20	35:2,13	asked	113:14
146:22 169:3	37:12,16	20:5,22	asserted
193:9 198:20	44:12 72:18	21:1,6,17	182:23
200:21	130:20	31:9 42:8,9	assertion
antigenic	152:13	67:14,25	181:24
157:14	190:24	70:14 72:1	assessment
164:22	applied	74:1 77:11	65:14
170:10	30:17 56:25	84:25 87:2	associate
antigens	191:25	94:13 95:8	26:3,5 50:20
29:7,10	applies	105:22	associated
33:2,3,8,12,	32:2	149:18 151:3	92:21 93:3,
17 34:17	apply	182:1 185:8	20 95:12
35:2,24	17:22 30:23	asking	96:5,11
36:13 37:3,	31:9	35:3 39:14	97:2,4,21
6,16 38:11	appreciate	40:22 42:15	101:20
43:21 44:24	77:6	52:11 57:15,	102:13,18
85:25 108:19	approach	17,24 59:9,	107:23
120:23	49:6	23,24 60:23	110:11
121:11	approaches	61:9 68:18	112:10 149:1
126:4,11	46:15 200:21	69:14,19,23	assume
133:8 148:24	appropriate	70:1 71:13,	17:20 33:23
168:2 178:14	183:17	15,18,19	63:13 100:17
191:23	Arbor	72:20,21,22,	111:8 131:6
199:18	11:19	24 73:12,18	assuming
antisera	around	74:8 77:25	142:14
80:18	41:10	84:7 85:1,5	attempting
anybody	arrive	86:6,7,10	120:7
45:24 76:13	48:9 66:25	93:18 94:16	attended
117:6 196:15	150:21	96:3,4,10,25	27:5,11
anymore	153:22	99:8 103:3,	attending
183:15	154:11	4,14,15	11:7
apologize	191:19	104:2,11	Aubrey
163:8 189:6	art	106:14 141:4	11:8
197:11	31:15 45:2	146:15	audible
appearances	67:23 68:24	147:19	12:5,17 53:4
10:20	70:19 71:20	150:16	156:11 193:5
appears	72:1 152:25	154:17,19	198:15
115:11	159:10	159:8,18	Austin
appendix	160:1,14,18	160:17	10:23
195:19,21,	161:16	161:21	author
22,24 196:22	163:11	163:10	28:4 90:4
197:4	arthritis	164:7,11,12	108:16
application	88:12	166:14	114:20
25:22	article	173:11,13	155:14,20
applications	28:12,19,22	183:2	

authored 28:6,7	background 12:7 23:23	160:10	150:23
authors 156:2	bad 144:7	161:13	151:24
autoantibodies 191:4	bars 109:19	180:16	153:20
autoimmunity 88:3 127:1	based 35:5 47:10 49:5,17 51:5	181:24	170:8,15,16, 19,25 171:23
available 46:13 49:9 71:3 84:20 85:16 107:8 131:1 152:20	55:6 142:24 157:19 158:7,11,16 162:13,17 164:2 165:2, 6 166:9,15, 16,23 167:13 174:2 179:5 194:16,21	183:13	179:7,21 192:12
avoid 88:2	basically 35:14 48:3 64:21 192:16	185:18	binding 38:11,24 48:24 61:5 79:18 80:6 85:15 86:3 105:18 113:21
avoiding 162:24	basis 15:6 20:23 30:2 56:18 158:21 181:12 182:11,20 183:7 194:10	186:18	binds 75:11 106:23 146:13 147:3 170:2
aware 161:1 179:8 183:25 184:3	BCR 144:25 145:2	188:3,10,22	biochemistry 31:21,24 32:3,6
<hr/> B <hr/>			
B-CELL 145:4,7,11, 16,19,22 146:2,9,13 147:4,10,11, 20 152:16 153:2,9 154:3,21 159:3,12 160:4,20 161:5,23	bear 129:23	believes 141:5	bioengineering 24:1,3,6 29:25 32:1 44:9
back 40:23 45:20 58:22 59:24 72:23 76:10 78:16 97:14 117:3 149:9 168:21 169:14 180:8 196:12 197:25 201:10	beginning 76:21 152:1	Berkeley 24:1,3,6 26:21	biology 27:1 31:21, 24 32:3,6 90:3 148:1
	behalf 10:15,17 11:2	besides 52:22 58:9 175:12 177:13 185:21	biomaterials 26:22
	behavior 99:10 107:14	best 72:17,21,25 74:8,11 77:15 97:11 98:13 99:23	biomedical 25:24 30:18 44:11
	believe 28:20 30:4 45:1 55:7 107:12 137:10 140:10,21 141:3,5,7 159:18	Bhatla 10:24 78:22, 25	biomimetic 25:12,17
		biggest 33:4	biophysics 31:22,24 32:3,7
		bind 20:10 21:4 40:10 43:3, 13 64:10 68:11 75:22 93:15 107:2 114:14 118:14 119:1 137:12 139:9,13 140:12,19 144:12,16,20 145:2 146:4, 16 147:2,5, 23 148:25	bit 12:7 42:1 52:9 57:16 94:6 115:21 117:12 195:17
			blood

24:17,19,20 26:1	broader 84:21	carefully 17:7,9 77:18 163:10	156:23 157:9,12
body 105:6 106:1, 6 107:24 108:1 113:22 118:6,12 120:10 121:15 124:24	buried 145:21,24 146:4 147:4	case 44:13 46:4 54:8,15,22 57:2 58:20 65:23 66:16, 17 74:11 78:11 113:5 117:13 132:2 147:15 149:16 150:18 151:5 153:23 154:1 155:25 184:1	cells 24:17,18 47:22 79:25 80:5,9,11, 16,23 86:14 109:20 118:7,13 119:1,4,19, 22 124:11, 12,13,14,16, 19,21,22,23 144:12,20,24 145:2 153:25 156:9,18
bone 124:14,25	<hr/> C <hr/>		
boost 29:8,19	C-S-O-K-A 90:5	cases 55:5,12,24 57:11 76:19 117:9 122:17,19 126:24 134:18 174:21 177:6,7	central 119:6,10
bottom 18:2 49:24 110:16 127:20 156:12 160:19	C-TERMINUS 61:18 62:2, 25 65:9	caused 131:9	certain 85:7,19,22 88:4 120:19 129:5
bound 48:18 84:2 144:10 147:2 178:22	cachexia 88:11	causing 88:10	certainly 69:1 189:8
boundary 66:21	calculate 56:14	caution 14:22 172:18 173:7,19 181:5 182:24 185:16	cervical 111:1,9 112:3,14 113:12
bounds 182:14	calculated 51:15,22 52:15 75:15	cautioning 182:4 183:11,24	chance 21:22
boxes 199:9	calculation 51:21	cautious 126:25	change 53:18 69:25 70:22 73:14 130:7 140:5 142:25 148:12
break 12:22,24,25 45:10,23,25 46:7 75:25 76:3,6,14,16 116:6,14 117:7 123:4 148:5,8 149:3,13 180:2 185:8 196:6,16 201:5	calculations 51:18 56:6 66:25 75:1	cavity 21:8	changed 102:3,12,17, 19 103:4,15 104:2,6,11, 15,16 135:7
Brian 10:25	called 25:19 46:17 107:11,12 128:2 168:4, 7 199:9	cell 27:1 61:6 64:10 80:2, 21 113:20,22 114:5,15 119:15 144:9,10,16	changes 50:18 51:12 57:18,23 60:2 62:6 66:22 67:7, 16 68:1,4,22 69:2,22
briefly 76:15	candidate 72:18,21,25 74:9,11		
	candidates 68:25		
	capabilities 161:14		
	capability 175:14		
	capable 110:23		
	Caption 112:8		
	captured 51:25		
	career 39:7		

70:17 71:20	circulatory	collagen	comparing
72:2 73:21	113:25	176:7	111:21
102:25	114:10	collection	comparison
134:10	cite	43:8 80:11,	108:18
138:12	189:9	22	190:19
148:17	cited	collective	compartment
changing	14:16,19	86:8 87:3	111:13
132:21	18:12 19:3	collectively	compartments
Chapters	185:22 186:6	80:17 83:7	119:15 125:8
196:21 197:3	187:1,3,5,12	85:14,24	compiles
characteristi	clarify	86:2,20	198:9
cs	63:12 144:2	92:11 93:14	complete
198:12	149:23 174:9	94:7 95:3	97:12 98:5
characterize	197:13	column	complex
42:15,18	clarifying	110:15	85:25 92:7,
46:11	173:25	112:21,22	11 93:8 94:2
characterized	classes	156:13,22	131:22
41:13 42:21	27:7	157:8	132:10,11
43:5	clause	come	144:19
Chelsea	158:9	24:7,8 32:7	complexes
10:24	clean	common	134:6
chemistry	16:9	122:6,8	complicated
31:20,23	clear	123:6,16	123:3 182:18
32:2	35:17 39:14	commonly	component
Cherr	40:22 41:19	125:25	33:9
22:18,20,24,	121:13	communication	components
25	126:15 137:6	14:23 172:19	29:3
chicken	141:1 142:23	173:20 181:6	composition
176:7	167:12 186:4	182:7	121:2
Choi	188:25	communication	comprise
11:6 163:5	clearer	s	52:4
choices	99:19	15:1 172:23	comprising
127:10,12	clearly	173:23 181:9	50:4,24
choose	192:6	184:2,15	54:10,17,24
72:17,25	clip	company	computational
chose	198:1	155:19	48:12,21
177:13	closely	compare	49:2 64:18
chromosome	37:14	42:25 43:1	152:22,24
89:18,21,23	clustered	104:24	153:1,6,11,
90:17,25	90:24 91:4	190:7,14	16,22 154:10
91:5,8	coaching	191:13,18	computational
chromosomes	183:3,13	compared	ly
90:12	collaborated	43:6 102:21	49:5,17
chronic	40:5	112:11 113:8	computer
88:10	collaboration	128:24	63:22 64:1
circulation	35:15	131:12	65:21 72:5
111:12		199:11,13	

conceivable 183:7	131:20,23,25 140:5	contiguous 127:25 128:7 143:10,13,18	172:20,23 173:20 181:6,9,19 184:2
concept 87:19	connection 12:3 15:9	continue 135:9	counter 88:6
concepts 201:1	16:21 18:14 19:15 23:2 41:20 92:15	continued 76:18	couple 149:16 158:1 168:21 197:10 198:2
concern 21:14 127:7	consider 21:1 57:25 58:3 60:4 65:22 66:14 68:4 69:24 70:21 73:22 135:11	continues 99:14	course 17:14 42:6 53:6,11,21 65:22 123:3 125:23 150:17 151:4
concerns 19:25	considered 18:7 59:10, 14,22 60:7, 8,10,13 61:12 62:5, 7,16,24 63:2,7,16 66:7 69:1 73:20 108:23 109:3	control 120:16	courses 26:15,16,20, 22 27:1,6,8
concluded 201:24	consistent 115:20	conversation 13:2	coursework 27:3
concomitant 111:3	consisting 198:12,24 199:2	conversations 173:14	court 10:16,20 12:3 27:20 78:24
concrete 176:21	construct 64:14	copies 16:8,10,12	cover 80:11 94:8 95:6
conditions 88:4 120:19 132:21 139:19 140:18 147:14	constructed 63:9	corner 155:18 157:2	covered 28:20 52:19 53:17 55:8
conducted 70:11	contacted 13:17	correct 16:24 17:3 19:24 27:15 46:14 53:19 54:3 65:11 67:3 100:16, 21 117:19 187:9,18 192:4 193:19 199:23 200:10,23	courtesy 83:10,23 84:17 94:11
conference 98:23 181:20 185:4	contains 66:10	corresponding 101:2	create 34:19 72:4 94:17 142:1 150:5,11
configuration 128:10 129:18	contemplate 57:6,19	corner 155:18 157:2	creates 80:15
configuration al 128:10 132:3,13,17 134:19 144:1	contemplating 65:13	correct 16:24 17:3 19:24 27:15 46:14 53:19 54:3 65:11 67:3 100:16, 21 117:19 187:9,18 192:4 193:19 199:23 200:10,23	creating 112:25
confirm 23:7 24:23 71:25 149:16 178:18	context 87:22	corresponding 101:2	credit 27:7
confirming 141:1		counsel 10:19 12:13 13:3,17 14:17,23 15:1 16:7 20:5 21:17 23:3,6 41:25 46:1 57:1 69:15 70:4,6 74:1 75:24 76:15 79:5 97:9,17 98:3 100:9 116:5 117:8 148:4 149:12	
conformational 128:2,3,6, 14,16,19,24 129:3,5,8 130:7			

<p>critical 194:17</p> <p>Crohn's 88:11</p> <p>cross-react 156:8,17 169:4,20 171:3,5 172:7 193:10 195:2,14</p> <p>cross-reactive 170:4,7,14, 19,24 171:16,23 172:9,13 173:2,5 174:4,8,12, 18 175:10, 14,22 176:2, 8 177:2,23 178:12 179:3,10,18 185:24 187:8,9,14, 23 189:3,13 190:25 191:23 192:4,8,12, 19 194:3,12, 15</p> <p>cross-reactivity 194:7</p> <p>crystal 157:17,19 158:5,6,7, 11,16 162:13,14 165:1,2,6 166:9,24</p> <p>crystallography 150:3,9 151:11,22</p> <p>Csoka 90:4</p>	<p>CV 24:22,23 25:2</p> <p>cytokine 47:23,25</p> <hr/> <p style="text-align: center;">D</p> <hr/> <p>D.C. 10:13</p> <p>daily 15:4</p> <p>Darrell 26:4,6</p> <p>data 34:5 109:21 110:11 113:11</p> <p>date 13:19,23</p> <p>day 77:24</p> <p>deal 184:13</p> <p>December 30:4,12 32:13 33:6, 13,24 34:1, 12,21 36:8, 14,19,20,22 37:21 38:1 39:10,17 41:12 42:23, 24 43:15,22 45:3,7 46:10,22 48:12 67:14 68:23 69:21 70:18 72:3 88:14 145:10,14 152:15 158:25 159:9 160:1,14,21 161:14 162:14,18 163:12,21</p>	<p>164:2 167:7</p> <p>Dechert 10:25</p> <p>Decision 22:5</p> <p>Decisions 21:25</p> <p>declaration 14:16 15:6 16:1,3,5,8 17:16 18:1, 5,10,15,20, 24 20:14,16, 22 21:20,21 22:12,17 23:8,15 31:5,6 45:6 49:22 52:2 54:7 58:23, 25 59:12,18, 25 60:5,19 62:8 71:1 74:17 78:9 81:1 117:11 127:16 129:20 130:13,17 132:7,8 136:16 140:25 150:22 151:9,13,17 153:18 168:20 171:4,18 172:10 175:1,7,12, 16 176:17,22 177:3,9 178:6 180:17,23 185:22 186:7 187:1,18,20 188:12,14, 17,24 189:10 190:7,13 191:20 195:18</p>	<p>200:22</p> <p>declarations 14:20 15:12, 24 16:20,25 17:1,5,7,11, 13,19,22 18:16 19:10, 25 21:11,13 22:9,14 23:9,17 51:20 53:25 57:6 61:12 74:23 79:6 141:10 143:23 149:15,20 154:18 193:3</p> <p>decreased 200:15</p> <p>deeper 48:1</p> <p>defined 138:18,24 139:12</p> <p>defining 50:13</p> <p>definition 31:10 51:9, 16,23 52:1, 6,8,13,17 53:1,6,13,23 54:1 56:16, 18 58:13,15, 19 59:7,16 60:2,11 63:4 67:2 68:14, 17 71:10 72:14 73:5 75:4 139:7 142:19</p> <p>definitions 55:7 56:25 62:18 135:17</p> <p>degenerate 153:19</p> <p>degradation 48:8</p>
--	--	--	--

degree 23:25 24:2 31:16 44:9 134:25 136:7,13,20 137:24 138:3	199:21,24	160:16 165:13	12,14 24:7, 8,9 33:8 34:8 43:7 50:14,17 51:25 52:10, 11,16 55:9, 14,16,18,22, 24 56:11,17, 21 57:16 59:14,23 60:7 63:9 68:19 73:19 74:20 75:8 79:17,18,22 80:5,6,7,17 81:18 101:16 110:2,3 122:1,13,17 124:24 129:9,11,17 131:11 133:19 167:21 169:10 170:3,8,10, 15,16,21 171:20 172:12 174:17 175:13 178:13 179:9 185:23 190:24 193:16 200:21
degrees 29:23,25 31:23 126:5	denaturization 128:17,23 129:7,16 131:1,8 132:25	design 30:22 34:18 36:2 37:15 41:9 168:2	
deletion 53:9 60:10	depending 100:17,23 129:6,15	designed 33:1	
deletions 53:11,12 57:8	depends 125:17 128:22 132:24	designing 69:19	
deliver 29:2 33:2 37:5	depicted 79:19	desired 88:6 120:20	
delivered 29:6	deposed 11:20,21,23 12:9	destroy 129:2	
delivering 29:5	deposition 10:8 14:11, 13 15:10 17:15 73:11 76:21,22 78:1 98:25 99:11,14 152:1 201:24	determinant 170:10	
delivery 21:7 26:13	depositions 12:2 129:22	determine 38:13 39:23 177:19	
demonstrated 115:14	derive 144:5	determined 90:15 145:11,15	
denaturation 130:9,14,16 131:4,10 140:7 141:13	describe 28:9 66:3 154:21	develop 24:11 30:9, 19 32:22 37:15	
denature 129:4 130:19 131:16 132:19 145:25 146:18,25 147:8	described 19:19 48:22 59:7 138:10, 15,21 161:22 164:8 199:10	developed 29:2 33:1 34:15 37:2 43:6	
denatured 37:22,24 128:15,20 129:11 130:23 131:11 133:3,5,9,12 138:11 141:21 146:10,14 147:22	describes 200:17	developing 28:24 30:21 32:24	
	describing 165:5 173:10 177:16 199:14 200:1	development 26:13 28:21 30:3 38:6 48:16 127:13	
	description 14:11 51:5	devise 67:25 71:24 72:1	
		difference 128:5 139:21	
		differences 55:4 200:8, 12,13,18,20	
		different 17:19 19:11,	
			digest 40:9 digital 63:15 65:12 dimensions 149:25 directed 25:12 directly 77:20 191:18

directory 198:4	103:9,20	due 125:20 130:8 140:6	62:1 65:9
disagree 99:16 100:1 183:16	diverse 80:24	duly 11:11	Eldora 11:4
disciplinary 34:14	diversity 43:1		elicit 88:16
disconnect 71:18 73:9 77:3,17	divulge 14:22 172:19 173:7,19 181:5 182:6	<hr/> E <hr/>	ELISA 38:23,25 39:1,5 40:1, 3 41:2,5,11 46:13,18 47:13 49:9, 20
discrete 67:7	docking 48:23 49:6, 13,17	E-L-I-S-P-O-T 47:1	ELISPOT 47:1,13 49:20
discuss 38:14 117:9, 20 177:13	doctoral 26:18	e.g 130:7	ELISPOTS 46:17 47:4,9 49:9
discussed 14:17 23:5 47:8 60:19 117:11 190:8,15 191:14	document 79:3 90:20 91:19 113:4 116:1 156:20 161:9,11 162:3,8,21 163:15,18,24 164:9,10 165:11,18, 19,25 166:4, 12,15 167:6 183:8	e33736 108:17 109:5	Elliot 11:6
discussing 46:7 61:16 101:20 117:18 168:24 190:14 200:4	documents 18:6,8,11,13 21:24 22:4,7 187:19	earlier 20:25 21:18 76:20 82:15 117:12 195:17 197:19 200:4	Ellison 11:4
discussion 19:13	Dohme 10:9	early 13:20 70:10	Emanuel 11:7
disease 88:8,11	doing 28:16 35:18	Eastern 10:2,5	employing 157:16 164:25
diseases 24:10	domain 104:22 128:7 176:1	Edition 196:25	encodes 90:13
disordered 129:23	domains 47:22 48:25 106:23 134:2 146:21 147:9 170:20	education 27:2 30:11, 16	end 61:2,17
disrupt 128:24 129:5	Dr.~park. 163:6	educational 23:23	endosomal 115:10
disrupted 130:22 133:1 135:8	drop 108:11	effect 57:18 73:15	endothelial 24:17,18
disruption 129:1,8 139:4		effective 200:20	engineering 24:12 28:1, 18 30:1,18, 19
dissertation 25:11,15,16		effects 43:23,25 111:21 127:7	engineers 44:11
distinct 56:1 79:18		efficient 70:10 73:11	enters 148:10,18
		efforts 33:5 107:6 120:9	entire 162:2 163:15,18,24 164:10
		egg 148:11,19	
		either 15:22 61:2	

entitled 28:1 78:3,4	epitopes 38:2,11,13 39:12,21,25 40:4,7,15,17 41:1,8,10 43:6 46:8, 11,16,19 47:9,12 48:2,13,18, 20 64:10 79:22 81:7, 19 82:5,11 83:3,5,6,10, 11,15,16,17, 19,24 84:2, 5,7,10,14, 18,22 85:1, 4,7,10,12, 16,19,22 86:1,7,10, 18,21 87:3, 17 92:3,4,7, 8,13,15,18, 19,21,23 93:3,5,7,11, 12,20,22 94:3,4,5,8, 11,18,24,25 95:1,4,7,12, 14,21 102:14,20 104:20,24 105:19 122:6 124:2,10 127:21,22 128:7,10,11, 14,16,19,24 129:3,5,8, 16,18 131:12,17, 19,20,21,23, 25 132:4,5, 12,13,14,15, 17,18 133:20,25 134:13,16,19 135:6 137:1 141:13,14 144:1,4,18,	19 145:5,7, 9,12,16,18, 24 146:19,23 147:12 152:4,10,17, 21 153:2,9, 12,14,17,24 154:3,7,8, 22,24 155:3 156:4,15 157:15 158:20 159:3,12 160:5 161:5, 23 164:23 174:4 175:15 177:2,24 178:12 errors 17:10,12 estimate 14:1 evaluate 63:10 67:17 68:2,24 72:5 73:16 141:8 evaluated 58:25 evaluating 69:20 73:13 77:13 159:2 EX0---- 19:5 EX2153 180:12,13 EX2154 186:22 EX2155 188:8 exact 13:19,23 14:4 61:22 62:13 64:11 197:22 Exam- 133:22	examination 11:13 70:11 examine 151:12 153:21 examined 11:11 66:18 133:6 168:1 examples 33:16 60:3 63:10,16,23 171:2,15,17 172:8,12,25 173:3 174:4, 11,16,21,23, 25 175:2,7, 18,20 176:11,14, 15,20,22,24 177:3,6,11, 12,21,22 178:2,5,7,25 179:8,13,16, 19 189:18 190:1 excerpt 196:19 exchange 152:7 excuse 13:3 98:16 133:22 exhibit 15:12,15,19 19:5,7 24:22,24 25:4 27:18, 19,23 28:8,9 61:23 66:18 90:2,6,16 108:8,9 114:17,21 155:6,7 180:11,12, 13,19,22,24 185:13 186:6,16,21, 22 187:17,
--------------------------------	--	---	---

19,22,25	24 49:17	32:13,20	114:11
188:6,7,8,	expert	198:9	148:21
13,19,20	11:24 12:1	failed	179:25
189:5 190:2,	30:5,13	175:21	females
8,15 191:15	explain	fair	20:8 21:9
192:17	47:18 61:20	17:23 72:7	68:10 89:5,
193:23	explained	80:19 105:8	8,13 91:16,
194:5,9	152:2	106:8 118:5,	21 108:4
196:19,23	explaining	11 119:23	111:14 120:5
exhibits	171:14	129:1 164:5	142:21
14:16 15:5	explanation	170:12	179:22
18:17 19:5	32:12 115:21	fall	fertilizes
79:8 180:19,	152:5	13:24 59:21	148:11,19
24	explicitly	familiar	fewer
exist	33:25 87:2	32:13,20	200:13,20
149:24 150:1	exploring	107:3,5	field
existence	192:9	109:22	27:8 32:2
193:24	expose	113:15,17	199:3
expect	146:1,18	114:7,12	fields
53:21 69:6	exposed	164:12	31:18
74:14 83:4,9	134:3,6	197:5,14	Fifteen
121:2,19	147:10	200:25	156:4,15
122:7,19	exposure	familiarity	figure
123:14 125:2	109:1,4	198:13	71:20 79:14,
expectation	expressed	far	16,20 109:6,
71:8	89:5,8,12	69:25	10,11,12,13
expected	91:2,16,20	Fc	111:20
21:7 68:9,15	expressing	114:14	112:7,20
73:6 81:5,17	19:25	Fcrn	177:25
82:3,19	expression	115:1,22	198:6,7,8,17
140:16 143:7	36:23	116:2	figures
179:6 192:21	extension	Fcrn-ko	79:21 113:6
194:24	46:6 76:19	115:18	file
195:11	136:11,25	Fcrn-mediated	16:14
experience	extent	115:12	filed
31:17 198:24	14:24 129:7	FDA-APPROVED	17:22
experiences	172:21	107:7,9	find
35:4,5 199:3	173:21 181:7	February	47:24 48:2,
experiment	external	152:14	18,20 77:15
164:8	134:3	158:24	102:10
experimental		160:20	125:23 153:8
33:5 39:4		female	172:15,25
40:14,24		21:3 74:3,6,	173:3 175:2,
43:16		16 75:20	11,20 177:11
experiments	factored	81:9,21 82:8	178:1,2
37:22 40:25	57:3	108:6 112:25	181:2 185:12
47:7 48:10,	factors	113:9,25	187:25
	F		

188:19	following	24 93:2,25	159:4,14,21
finding	20:18 31:10	94:22 95:18	160:6,22
185:21	follows	96:18 97:8	161:6,18,25
186:15	11:12	98:2 100:22	162:6,9,15,
fine	form	101:14,23	19 163:13,
16:11 116:16	15:6 18:20	102:7,23	20,23 164:4,
finish	19:21 20:4,	103:7,18	6,17 165:8,
12:23 90:20	24 21:16	104:4,13,19	15,24 166:11
finished	23:4 25:20	105:9,16	167:2,10,18
12:14 105:2	28:11 29:16	106:21	168:13
first	30:6 31:25	107:16	170:6,13
11:11 16:1	32:16 33:7	109:23	171:1,11
28:4 41:7	34:11,13,22	111:15	172:2,11,17
90:4,8,19	35:9,22	112:18 113:3	174:6,13,19,
108:16,17	36:9,25	114:2 115:23	24 175:5,17
113:4 114:19	37:10 38:4,	118:9,15,22	176:13,18
116:1 134:22	16 40:11	119:8,20	177:8,17
155:14	41:15,24	120:2,14	178:3,5,15,
156:19 161:8	42:20 43:4,	121:5 122:7,	24 179:1,20
five	11,17,19,20	8,12 123:1,	180:25 186:1
45:13 67:7	44:2,8 45:4	10,12,20	187:11
130:3	47:17,19	124:5,18	188:24
five-ish	48:7 49:4	125:5,12	189:4,14,16
196:5	50:22 51:14	126:8,14,17	190:9,17
focus	52:21 53:20	127:5 128:21	191:6 192:5,
24:13 25:14	54:4 55:11,	129:11,12,	15 193:2
26:10 71:23	20 56:5,8,	14,16 131:14	194:20 195:8
87:2,5	13,18,24	132:9,23	197:21
156:22	57:10 58:11	133:9,11,15,	199:9,15,18,
focused	59:5,13,17	16,23 134:1,	23
24:5 26:12	60:6 61:4,21	6 135:14	formal
28:17 37:4	62:11,23	136:2 137:15	27:7
83:21 84:1	63:11,17,24	138:7,8,13,	formation
161:13	64:8,17	16 139:2,10	26:1 86:11
focuses	65:4,16	140:14,23	formed
24:7	66:1,12,24	141:11	21:10 56:9
folded	67:9,19 68:6	142:3,17	57:5 63:7
133:20	69:4 70:3,23	143:2,12,24	66:17 128:11
146:14	71:14 72:8	144:11,17	147:20
147:23	73:24 74:24	145:1,6,23	190:12
folding	75:14 77:7	146:6,10,14	forming
32:14,21	78:7 80:8,20	147:7,17,25	15:14 18:14
follow	82:14 83:13	148:13	56:23 57:3
49:19 71:24	85:9,20,21	149:22	58:7 60:5
168:25	86:17 87:15	150:7,13,19	66:16 135:10
followed	89:2 90:18	151:6,19,22	141:9,17
73:13	91:6,10,18,	152:11,19	146:8 151:17
	25 92:5,21,	153:5 154:5,	153:23
		23 158:2,13	

forms 146:3 199:21	fragmented 40:21 48:9 152:13	general 14:11 29:1 47:20 80:9 83:14 84:14 102:25 104:15 106:18 107:5 110:11 111:17 112:20 113:17 114:3 116:2 118:16 120:15 121:6,18 125:9 126:9 131:22 132:11 133:12,17 134:2,11 144:12 145:2 170:19 198:20 199:6,18,24 200:16 201:1	95:1,2,6,24 101:17 102:10 103:1 105:12,17 106:12 107:1 117:21 121:19 122:16 124:13,14 125:20 130:23 141:15,22 143:8 144:13 145:3 146:19,25 148:24 150:22 151:24 172:6 179:3,6,18, 20 187:8 191:11,23 192:4,7,11 194:3,11,14
formulation 110:3	fragments 40:10,18 47:23,24 48:1,4 152:8	generally 12:23 28:15 92:18 109:22 110:5 114:7, 12 115:3 120:6,7 124:23 143:15 170:7,14 199:4 200:11	generated 20:8 21:2 68:10 75:20 140:16 169:2 172:13 174:8,22 185:24 189:13 193:8 194:25 195:12
forth 52:13	frame 27:16 197:18	generate 64:23 68:15 69:7 71:1,3, 7,10,16 72:15 73:6 74:2,6,15 75:5 82:16, 19 83:7,15, 18,19 84:17, 20 85:11,12, 23 86:19 89:15 92:9, 12 93:10 94:4,6,10	generates 72:25 87:17 102:1 173:2 187:23
found 83:19,24 101:10 121:22 123:6 124:10 132:22 136:5 146:21 147:2,5,6 170:20 171:14 174:23,25 177:12,21,22 178:19 179:15 185:19 186:7,18 188:4,23 189:17	framed 20:22		generating 83:23 155:4 175:9 176:2 179:13 187:14 189:3 192:19
foundation 54:5 55:21 62:12 74:25 77:8 105:10 164:18	frequency 109:18,19		generation 86:21 123:15
four 15:22,24 16:20 17:10, 22 19:9,11, 12,14,16,19, 20,25 20:1,2 21:11,13,14, 15,22 22:1,6 26:8 55:4,6, 12,24 57:5, 11 63:22 79:6 156:12 199:9	function 31:20 32:4 118:6,12,25 125:3 145:21		genes 90:12,23 91:1
four-year 26:7	functioning 117:22		
fourth 96:1	functions 117:23		
fragment 47:21	funny 163:1		
	future 73:16		
	<hr/> G <hr/>		
	Gardasil 107:12,13, 17,19 113:6		
	Garland 197:2		
	Gary 22:18		
	gave 87:16 106:17 146:8 152:5		
	gene 89:20,24 90:17 91:8, 16		

genital 115:17	188:5 196:7, 12,18 198:2	186:21 188:6	Himes 10:24
getting 28:14	201:7,10,18	handed 79:8	HIV 37:4,5,12,19
give 12:6,20 14:1,5,11 24:21 29:13 77:23 79:6 90:11 91:13 96:19,23 100:9 153:24 182:15	Goldberg 10:25 good 11:15 116:6, 11 125:23	happening 140:9 hard 42:3	Hold 129:21 homologous 192:25
given 19:18,22 51:19 57:1 104:20 130:19 133:17 134:24 135:17 143:14 144:1 145:18 152:21 153:13	GPI 66:11 grad 27:2 graph 111:25 graphs 111:23	heading 156:23 health 24:12 30:24 hear 184:4 heard 22:22 23:13, 19 87:19	homology 34:2,3 149:19,21 151:4 157:25 159:10 160:2 161:2 164:15,20 165:6,10,14 166:1,2,9,17 167:8,17 172:5 176:6 179:17 192:18
glycol 25:20	Great 78:9 greater 179:2	heat 190:3 191:2, 9,12,19 Hecht 22:11	hoping 99:21 host 26:23 host's 81:7,19 82:6 117:25
goes 18:3	Gregory 23:8 group 168:15	held 10:11 help 162:11 177:8 helper 61:6 64:10	hour 45:9 75:25 116:15 hours 14:2,3,4,6,7 houses 34:5 HPV 107:8,10,23, 25 108:5,19 112:24
going 15:17 17:15, 20 24:21 27:17 33:24 45:8,20 69:8 70:13,16 76:10 86:25 90:1,10 96:21,22 97:14,16,17, 18 98:6,15, 16,24 108:7 114:16 116:17 117:3 149:9 155:5 165:20 180:8,11 184:14 186:3,20	H <hr/> H-U-O 108:16 Haddach 11:8 half 26:8 109:7 116:15 160:19 halfway 115:9 157:11 Halozyme 10:10 11:3, 4,8 13:15 15:19 19:11 24:24 155:20,22,24 180:13 186:22 188:8 hand 180:11	hence 63:3 high 85:11 92:9 94:5 95:1 111:3 113:7, 9 134:24 136:7,13,20 137:24 138:2 higher 56:3 92:9 110:12 112:15,21 113:12 126:10 177:23 187:8 192:19 highly 126:13	host 26:23 host's 81:7,19 82:6 117:25 hour 45:9 75:25 116:15 hours 14:2,3,4,6,7 houses 34:5 HPV 107:8,10,23, 25 108:5,19 112:24 HPV16 110:4 human 20:8,11 21:8 24:12 30:5, 13,24 33:14, 19 68:10,12 74:3,6,16

81:9,21 82:8 88:20,24 89:7,18,23 91:9,16 107:4,24 108:19 111:14 113:25 114:11 121:1,3,15, 21 122:3,6, 9,22 126:12, 21 127:4,11 132:6 135:4 136:5,9,22, 23 137:3 138:1,7 139:9,14 140:13 142:16,21 145:22 148:21 150:24 151:25 152:17 153:20 154:3,13,22 156:6 157:18 159:13 160:5 164:23 176:1,7 179:22 193:25 194:6	HYAL3 90:24 HYAL4 91:1 HYALP1 91:3 hydrogels 25:12,17,18, 20,21,23,25 hydrophobic 134:2,5 hypothetical 122:2 148:2	identifies 90:16 identify 40:9,15,16 41:4 46:10 48:13 67:15 159:3,12 161:4,23 176:11 189:10 identifying 68:21 identities 194:10 identity 34:8 52:6,25 53:14,24 55:17 57:13 58:16 66:21 122:14,18 135:1,13,20, 25 136:8,14, 18,21 137:11,21, 22,25 138:3 151:8 169:6, 22 170:23 171:7,22 172:6,16 173:1,4 174:12 175:3,9,21, 25 176:6 177:1,23 178:11 179:2 185:24 186:8 187:8,14,23 189:2,12 190:25 191:22 192:3,7,11, 24 193:1,4, 12,18,20,24 194:1,7,14, 17 195:4,6, 16	Igg 111:5,7,17 112:25 113:12 115:1,13,16 116:2 ignoring 99:6 II 176:7 III 11:5 illustrates 87:1 illustrating 79:17 illustration 80:4 image 150:5 imagined 59:19 immobilized 43:10 immun- 113:24 immune 26:24 28:18 29:8,19 30:2,5,13 81:8,19 82:6 84:9 85:6,17 87:12,20,22, 25 92:4 117:18,21, 22,23,24 118:2,5,11, 16,20,24 119:5,6,11, 12,13,16,17, 23 120:9,12 121:3,14 124:3,17,20, 22 125:2,7, 21,25 126:6, 16 146:21
humans 29:13 30:10, 21 88:20,25 89:21,24 127:14	HYAL1 90:23 157:20 158:8,12,16 162:14 165:3,7 166:25	identities 194:10 identity 34:8 52:6,25 53:14,24 55:17 57:13 58:16 66:21 122:14,18 135:1,13,20, 25 136:8,14, 18,21 137:11,21, 22,25 138:3 151:8 169:6, 22 170:23 171:7,22 172:6,16 173:1,4 174:12 175:3,9,21, 25 176:6 177:1,23 178:11 179:2 185:24 186:8 187:8,14,23 189:2,12 190:25 191:22 192:3,7,11, 24 193:1,4, 12,18,20,24 194:1,7,14, 17 195:4,6, 16	Ig 112:13
Huo 108:16	HYAL2 90:23	I	
	ID 50:8 51:2,8 52:3 54:12, 19 55:1 66:2,3,8,10, 19 81:13,25 135:5,13 136:1,6,10, 11,12,18 137:9,11,22 138:6 143:6	idea 176:25	
	idea 176:25	identical 50:6,25 51:7 54:11,18,25 137:8 143:6	
	identical 50:6,25 51:7 54:11,18,25 137:8 143:6	identificatio	
	identificatio	n 27:24 46:8 90:7 108:10 114:22 155:8 196:24	
	identified 39:11,15,17, 20 41:8 142:25 156:2 157:16 158:21 160:4 164:24 183:22		

Immunity 28:2	immunogenicity 198:10,14, 18,21,23 199:11,16 200:10,15,17	17 54:13,20 55:2 108:3 152:23 175:15 176:16 177:2	85:2 86:11 92:3 120:22 121:10 123:17 125:23 126:3,9 127:1 128:8 133:15 134:13 137:12 154:8,12 170:24 171:15,22 177:1 178:12
immunization 42:17 43:24 80:15 82:21 110:23 111:12,22,24 113:7 179:10	immunogens 29:4,9	included 28:25 57:7	induced 43:17 92:14 120:20 173:4 178:21
immunizations 83:2	immunoglobulin 113:24 114:10	includes 75:8	inducing 47:25 87:4 110:24 128:12 176:8 190:25
immunize 79:24 92:20 94:1 178:13	immunological 92:17	including 26:23 29:7 33:2 35:12 38:23 49:9 66:19 92:7 108:1 120:24 121:12 124:24 125:7 127:7 132:12 153:7 192:16	induction 120:16 121:7 124:2 127:8 131:18
immunized 80:13 82:9 109:15,17	immunologists 46:19 47:20	incorporated 10:10 36:24 57:20 59:1,3 64:15 67:6 69:21	infection 107:25 108:5 191:10
immunizing 93:1	immunology 26:15,16,20 27:9,12 28:21 29:24 32:7 92:16 199:3 201:1	increased 198:23 199:11,15 200:9	infectious 29:18 33:16
Immunobiology 197:1,6,14	impact 26:23 73:21 126:6	incubate 47:22	inflammation 88:10 126:23 127:8
immunodominant 92:18,19,23 93:5,12,13, 22 94:10,18 95:2,5,14,23 96:12 97:5, 23 101:22,24 102:5,14,20 103:5,11,12, 16,22,23 104:3,12,18, 23	impediments 112:23	indicated 61:11 136:5	inflaming 32:20
immunogen 67:17 68:3 70:20 71:22 73:15 95:16 96:13 97:6, 24 101:6,13 102:14,21 112:24 113:6	implement 118:20	indicating 178:20	information 19:18,22 20:1 21:14 51:19 90:11, 16 91:7 150:4 154:20 178:20 180:21
immunogenic 125:10,15 199:4,5,7, 19,22,25 200:9,12,19	important 79:3	individual 22:10,18 23:8,10,18 43:24 51:13 73:20 84:16 121:19	
	imported 59:2	individually 66:15 80:1	
	imprecise 189:8	individuals 35:15	
	improper 183:14	induce 44:3 75:11 83:12 84:6	
	improve 24:12 29:3 30:2,24		
	incapable 90:21		
	include 50:9 51:2 52:19 53:9,		

187:16	intentionally	102:8,24	Jason
inject	130:19,22,23	108:8 114:17	10:14
121:18	131:16	introduced	Jeff
122:9,13	132:19	71:6 101:9	10:22
123:19	interact	104:14 131:3	job
injected	124:20	133:14	15:4 18:19
126:16 127:3	interacted	introducing	Josh
142:21	34:18 35:11	64:3	11:7
179:1,22	interacting	investigate	journal
injecting	40:20	89:7 132:5	90:2 108:15
125:18	interactions	138:9,17,23	155:12
injection	38:21,23	148:9	jump
122:15	interdiscipli	investigated	184:21
126:23	nary	33:13 43:23	
insert	32:1 44:10	44:14 91:15	
62:21	interested	152:4	<hr/> K <hr/>
inserted	47:14	investigation	Kess-
61:1,18,23	interior	48:6	13:16
62:1	145:21	investigation	Kessler
inserting	146:9,15	s	10:12 11:2,5
64:25 65:8,	147:21	154:2	Khanduri
17	internal	invoke	11:1,2 14:21
insertion	65:10 146:19	201:14	15:21 16:7,
62:24	147:9	involved	13 19:21
inside	interrupt	116:2	20:4,20,24
65:1	69:8 70:5	119:11,16,21	21:16 23:4
inspect	96:21 98:4	120:3	25:1 28:11
36:7 162:12	184:16	involves	29:16 30:6,
inspected	interrupted	48:3 152:8	14 31:25
159:10	97:10	irrespective	32:16 33:7
inspecting	intervene	139:18 169:8	34:11,13,22
159:1 160:2	184:6	193:14	35:9,22
inspection	intra-	Irvine	36:9,25
157:24	109:1	26:4,6	37:10 38:4,
Institution	intramuscular	Issue	16 40:11
21:25 22:5	108:20,25	108:16	41:15,24
instruct	109:3 110:6,		42:3,20
184:16	12,22 111:22	<hr/> J <hr/>	43:4,11,19
instructed	112:10	James	44:2,8 45:4,
12:16	113:7,13	10:8 11:10,	15 47:17,19
instructions	intramuscular	17 28:4	48:7 49:4
100:9	ly	Janeway	50:22 51:14
insufficient	109:15	196:20	52:21 53:20
86:14 91:7	introduce	Janeway's	54:4 55:11,
intentional	15:18 27:18	196:20,25	20 56:5,7,
130:8,14,15	93:8 100:13,	197:6,15	13,24 57:10
140:6	17,23 101:15		58:1,8,11

59:5,13 60:6	129:14	186:1,24	160:11,25
61:4,21	131:14	187:11	163:21
62:11,23	132:9,23	189:4,14,16	164:15
63:11,17,24	133:11,16,22	190:9,17	165:22
64:8,17	135:14 136:2	191:6 192:5,	166:2,8,17
65:4,16	137:15	15 193:2	167:4,8,16
66:1,12,24	138:13	194:19 195:8	174:15
67:9,19 68:6	139:2,10	196:4,9	knowledge
69:4,15	140:14,23	197:21	17:11,12
70:3,23	141:11	201:4,12,17,	162:17 164:2
71:14 72:8	142:3,17	20	166:16
73:24 74:24	143:2,12,21,	kind	167:14
75:14,24	24 144:11,17	29:12,14	known
77:7 78:7,20	145:1,6,23	63:8 105:5,	61:5 88:15
79:5,9 80:8,	146:6 147:7,	25 106:5	124:13,14
20 82:14	25 148:4,13	109:21 122:2	126:22
83:13 85:9,	149:22	128:1,4	169:3,20
21 86:17	150:7,13,19	148:12	171:3,5
87:15 89:2	151:6,19	189:21	193:9
90:18 91:6,	152:11,19	kinds	199:19,22
10,18 92:5,	153:5 154:5,	29:4 53:8	200:11,19
24 93:25	23 155:10	knockout	Kushan
94:22 95:18	158:2,13	115:19	10:22 11:14
96:18 97:8	159:4,14,21	know	15:17,23
98:2,10,13	160:6,22	12:9,19,22	16:11,15
99:16 100:1,	161:6,18,25	13:4,19,23	27:17,22
4,22 101:14,	162:6,9,15,	17:20 21:12	42:2 45:8,
23 102:7,23	19 163:13,	22:20,21	12,22 58:2
103:7,18	20,23 164:4,	23:11,12	69:17 70:6
104:4,13,19	6,17 165:8,	36:3 50:18	76:2,5,12
105:9,16	15,24 166:11	51:24 52:3,	78:18 79:2,
106:21	167:2,10,18	11 66:10,13	10 86:24
107:16	168:13	89:6,12,17,	90:1 97:16
108:11	170:6,13	20,22,23,25	98:6,12,15,
109:23 110:9	171:1,11	91:20 96:25	21,24 99:24
111:15	172:2,11,17	99:4 102:3	100:2,5,7
112:18 113:2	173:6,15,18	105:5,13,20,	108:7,14
114:2 115:5,	174:6,13,19,	25 106:5	114:16
23 116:5,9,	24 175:5,17	107:11,19	116:7,10,13,
15 118:9,15,	176:13,18	111:6 114:6	16 117:5
22 119:8,20	177:17	115:3 120:4	148:6 149:2,
120:2,14	178:3,15,24	131:24 132:2	5,11 155:5,
121:5	180:15	134:1 138:6,	9,11,16
122:10,12	181:4,14	8,14,20	163:1,7
123:1,12,20	182:3,6,13,	139:3 145:4,	173:9,17,24
124:5,18	23 183:5,16,	7 148:1,14,	180:1,4,10
125:5,12	19,24 184:7,	16 149:24	181:11,15,22
126:8,14,17	10,18,22	159:25	182:5,9,17
127:5 128:21	185:1,5,15		

183:2,6,18, 21 184:4,8, 12,20,25 185:2,6 186:10,20 188:5 189:6 196:14,18 201:2,16,21	191:13,15,18 level 110:7 levels 112:15,25 Levin 10:14 Li 114:20 life 46:6 lifespan 76:18 limit 121:7 127:10 limited 14:19 20:15 line 48:6 189:25 linear 39:11,12,18, 21,23,25 40:4,6,15, 17,19,20 41:1,8 46:8, 11,19 47:8, 12 48:2,13 127:21,22, 23,24 128:5, 7 131:20,23, 25 132:4,12, 18 143:11, 13,14,20,25 144:3,10,19, 23,24 145:4, 15,18,20,22, 24 146:1,2, 4,9,13,19 147:3,20 152:4,9,16 153:2,24 159:3,12 160:4 161:4, 23 lines 130:3 156:12	list 15:12,16 18:3,6,9,16, 23 19:4,8 45:6 139:18 172:8 175:3, 12 176:4 listed 15:6 18:9, 16,21 66:15, 18 140:18 151:9 160:19 171:2,17 172:12 175:1 listen 77:18 163:9 listing 63:15 literally 99:8 literature 14:15,18,19 15:8 21:10 41:7 47:11 126:19 133:6 154:21 172:25 174:3,7,10, 16,20 176:21 178:19 179:15 185:19 186:15,17,19 188:4,23 little 12:7 52:9 57:16 LLC 10:9 locate 152:9,16 153:1 located 89:24 90:13, 17 91:9 location 39:18,24 58:17 61:7,	25 139:20 152:4 153:14 154:21 locations 61:22 62:17, 21 65:6,18 92:22 93:20 112:17 141:24 153:8 154:3 long 51:5 52:4,5, 24 53:13,23 58:15 59:15 65:5,19 66:4,5 82:2 123:13,23 124:6 125:22 142:4,8,11, 18 191:22 197:16,23 long-lived 119:19,22 longer 66:9 look 19:4 31:6 32:11 60:18 78:10,18 85:24 110:15 112:9 114:23 129:19 130:1 132:15 134:20 139:15,17 149:21 150:16,20 151:4,7 154:2,20,24 155:17 156:1 160:16 168:23 174:10,16,20 178:25 179:12 193:6 looked 149:19
L			
lab 26:4 67:14 109:24 133:7 labeled 112:2 198:22 laboratory 24:16 26:6 language 50:19 52:19 53:17 large 85:24 93:7 94:2 131:22 132:10 133:24 154:6 larger 198:22 199:3,6 late 184:19,23 lead 184:1 learn 55:25 leaves 98:23 181:20 left 111:23 112:10,21 155:17 156:13,22 157:8 185:10 Legal 10:15,17 length 62:13 66:6			

looking 68:13 79:13 109:12 130:2 150:14 161:3,8 167:22 174:3 198:8	main 21:18	Mapping 157:10	measurable 110:24
lost 186:11	maintain 125:6	March 108:17 114:19	measured 112:13
lot 16:16	maintained 128:17,19	Marie 155:15,19,21	mechanism 113:23
louder 42:1	maintaining 161:16	mark 90:1 155:5 196:19	mechanisms 118:6,12,19, 23,25 119:3, 5,9,12,18, 21,24 120:3, 15 121:6 125:6,21
low 86:19 87:17 169:5,21 171:6 172:5 175:8 189:2 191:22 192:7,18 193:11 195:3,15	major 44:11 141:17	marked 15:20 24:25 27:23 90:6 108:9 114:21 155:7 180:12,14 186:23 188:9 196:23	mediating 115:1
lower 85:12,23 92:10 94:6	majority 83:18,24 84:2 86:6 128:18 131:17,19 137:1	marrow 124:15,25	medical 25:22 44:6
lumen 115:17	make 12:13 37:4 39:15 41:18 42:13 49:11 80:17 86:5 94:9 95:22 121:25 127:20 140:9 159:7,19 182:14	materials 15:11 18:4 28:3,24 32:24 33:1	meet 31:4 32:9 51:8,16 52:6,7,17 53:1,22 58:14,19 59:7,16 60:2 62:17 63:4 67:2 68:14 71:9 72:14 73:5 74:21 75:4 161:19
lunch 116:11,14,19 117:7,8	making 48:4 67:10 72:22 152:8	Matrix 90:3	meets 60:11 142:19 195:6
lymphocytes 46:20	males 89:18	matter 10:9 14:2 15:15 61:8 102:1 141:23	Melanie 23:16
<hr/> M <hr/>	mammal 41:14 42:16 43:24 75:11 80:13 82:9, 22 92:20 93:1 123:9, 19 178:13 179:11	matters 23:5 46:3	members 34:16 46:1
Mack 11:8	mammals 21:3 75:21 179:25	maximum 51:11,15,22 52:16 66:6 67:1	membrane 114:5,15
made 25:18 30:12 47:16 63:20 71:21 95:13 96:5 120:9 139:1 147:21 184:24	manifest 107:24	mean 35:23 46:12 59:14 70:25 127:23,24 130:15 141:20	memory 119:19,22
magnitude 126:6	map 38:2	meaning 41:22	mentally 67:10
		meaningful 55:10	mention 165:25 166:1
			mentioned 21:18,23 22:8,13

30:16 32:19	middle	64:18 167:23	17,21,24
48:15 49:8,	61:1 62:2,25	168:1,16	69:20 70:17,
14,15 60:23	64:25 81:2	models	19 71:1,4,6,
61:11 62:5	115:8 157:13	34:2,3,20	9,15,21
63:23 64:24	migrate	35:12 36:4	72:14 73:4,
65:5 68:8	124:22	141:8 150:17	17 74:2,5,
69:6 82:15	mind	153:22	14,18,21
101:25	16:10 30:23	166:19	75:2,3,8,17,
105:11	41:25 56:22	168:18	21 81:10
106:10 121:9	58:5 63:25	modification	82:11,15,18
127:22	64:6 67:18	50:9 51:2,6	89:15 93:19,
130:25	68:5 69:2,25	52:7,25	21 94:17
131:15	70:22 72:4	53:14,24	95:3,5,13,15
141:12 142:4	minute	54:13,20	97:23 101:3,
147:8 153:18	147:18	55:2,23 58:6	5,11,12,21
167:20	181:18 196:5	125:19	102:4 105:11
menu	minutes	141:19 142:5	106:11,15,25
117:8	45:13 158:1	143:4	130:5 133:9
Merck	misfolded	modifications	135:2,6,11,
10:9	138:25	51:7 52:18	16,22 136:9,
met	misfolding	53:8,12	14,17,21
14:16	139:4	55:13 58:17,	137:1,7,20,
method	MIT	18 59:20,21	25 138:3,10,
49:2 128:22	26:3,6,14	64:13 67:1,	14,18,24
129:15	mixture	11 68:13	139:3,6,11,
132:25	83:21	72:22 75:19	23 140:4,17
150:14	model	95:13 131:7	141:12,14,
methodology	33:11 34:9	141:24 143:5	16,18,21,25
71:23 73:22	38:3 64:14	modified	142:1,6,12,
77:12	149:19,21	20:9 21:4	14,20,24
methods	150:11	50:2,13,20,	143:4 144:4
48:21	151:4,14,16,	23 51:9,10,	146:24
mice	22 157:16,25	17 52:1,5,8,	147:15
115:19	158:4,7	13,17 53:1,	148:23
189:25	159:1,10	13,21,23	150:22
191:11	160:2 161:2	54:1,9,16,23	151:8,23
Michael	162:12	55:8,9 56:2,	153:19
22:11	164:15,20,25	10,17,22,25	154:7,11
Michigan	165:6,10,14	57:2,7,11	179:5,20
11:19	166:1,2,9,	58:6,14,15,	192:22
microbes	17,22,25	19 59:1,7,15	modify
191:10	167:8,17	60:3,8,11,14	50:16 192:1
microparticle	168:12	62:17,18	modulate
s	modeling	63:1,4 64:3,	120:16
28:2,18,23	36:2,5,12	13,19,21	MOG
29:2	38:8,20 40:6	65:6,10,19	176:1 193:25
	46:12 48:17	67:2,12,25	194:5,6
	49:6,16	68:2,11,14,	

molecules	188:19	93:7 94:3,8,	52:16 56:15
29:7 88:2	191:13	11,23 95:4,	57:12,21
117:21	196:15	7,20 104:20	75:16 92:22
118:4,17	197:7,13	105:18 119:9	93:9,19
120:17 121:8	201:13	120:21 121:9	94:9,17
134:7	morning	124:9	95:5,22
moment	11:15	132:12,16	100:18,24
175:19 178:8	mount	133:24 134:7	101:24
189:19	121:15	141:13,14	102:24
monoclonal	mounting	143:25	131:3,9
21:8 79:21	117:24	144:18,19	133:14,17
80:3,10,22	mouse	146:23	139:1 140:9
monoclonals	122:3,6,8,9,	147:12	142:18
92:10	22,23 176:1	154:7,8	
months	193:24 194:5	155:2 171:2	<hr/> N <hr/>
13:20	move	200:8,12,18	
Moon	86:25 91:22	multitude	N-TERMINUS
10:8 11:10,	114:10	83:10 84:18	62:1,25 65:9
17 14:21	183:1,19	85:15 120:23	name
16:7 28:5,6	184:11,23	muta-	10:14 11:15
45:23 57:15	mucosal	96:11	22:22,23
68:18 70:15	108:21,23	mutate	23:13,14,20,
71:12 73:8	111:13	123:16	21 163:3
76:13 86:5,	119:13,15	mutated	name's
23 88:19,23	124:22,25	37:11,13,15	163:5
90:8,15	125:3,8	43:17,20	named
93:17 94:13	multi	44:22,23,24	22:10,15,18
98:22 100:8	124:2	77:13 92:20	23:8
107:3 108:21	multi-	93:2 95:3	Nancy
116:11 117:6	95:7	96:20 102:21	11:6
149:12	multi-	103:1 105:4,	nano-
150:25	epitopes	15,17,24	28:2,18 29:2
154:14	83:8	106:4	nanoparticles
155:17	multidiscipli	mutation	28:23
159:7,17	nary	55:16 93:4	narrow
163:9 164:16	34:15,24	96:5,11	86:9
166:8,14	35:10,16	97:1,3,4,22	native
167:17	36:1,11	100:13	102:5 122:7,
172:18	37:1,15	101:9,15	22 133:20
173:6,18	38:5,18	102:8,9,13,	143:19 144:4
174:1,9	48:16 133:7	19 103:8,10,	146:4,16
175:11	167:25	19,21 104:14	147:5
180:11	168:14	123:14,24	199:23,25
181:4,17	multiple	124:1,7	200:14
182:14,24	83:3,5,14,16	125:23	necessary
185:7,15	84:14 86:1,	mutations	160:10
186:14	20 92:6,8	36:24 37:5,8	
187:25		51:16,23	

need	157:1	78:7 80:8,20	149:22
12:22 13:2	numbered	82:14 83:13	150:7,13,19
16:12 66:25	155:13	85:9,21	151:6,19
78:1 87:9	numerous	86:17 87:15	152:11,19
104:23	81:7,19 82:5	89:2 90:18	153:5 154:5,
106:14	83:8	91:6,10,18	23 158:2,13
144:12 145:2		92:5,24	159:4,14,21
150:20		93:25 94:22	160:6,22
153:21		95:18 96:18	161:6,18,25
154:10,15		97:8 98:2	162:6,9,15,
160:24		100:22	19 163:13,
162:2,7		101:14,23	20,23 164:4,
197:25		102:7,23	6,17 165:8,
neovasculariz		103:7,18	15,24 166:11
ation		104:4,13,19	167:2,10,18
25:13,17		105:9,16	168:13
neutralizing		106:21	170:6,13
110:25 111:4		107:16	171:1,11
never		109:23 110:9	172:2,11,17
22:24 23:19		111:15	174:6,13,19,
non-human		112:18	24 175:5,17
21:3		113:2,3	176:13,18
nondenatured		114:2 115:5,	177:17
141:21		23 118:9,15,	178:3,15,24
nonimmunogeni		22 119:8,20	186:1 187:11
c		120:2,14	189:4,14,16
125:10,16		121:5	190:9,17
normal		122:10,12	191:6 192:5,
117:22		123:1,12,20	15 193:2
noted		124:5,18	194:19,20
117:2		125:5,12	195:8 197:21
notice		126:8,14,17	objections
98:9 99:9		127:5 128:21	12:14
novel		129:14	observed
24:7		131:14	110:7 112:16
November		132:9,23	191:4
10:1,6		133:11,16,23	obtained
number		135:14 136:2	25:9 30:12
19:5,7		137:15	occur
51:11,15,22		138:13	108:1,5
52:16 56:1,		139:2,10	124:21
14,20 67:1		140:14,23	147:15
75:16 84:21		141:11	occurs
129:10,12,		142:3,17	102:9
16,17 131:12		143:2,12,24	103:10,21
132:14,15		144:11,17	114:6
142:18 144:3		145:1,6,23	offices
		146:6 147:7,	10:12
		25 148:13	

Okay 11:24 12:3, 13,16,20,21, 25 13:1,4,5 14:1,8 15:25 17:25 19:4 21:24 22:9 23:22 24:20 25:3,11,21 26:2 33:22 35:17 36:19 41:4,12 42:25 45:12 49:10 67:3 76:5 79:17, 24 80:4,13, 25 82:9 84:1 92:19 96:10, 17 97:15 104:11 107:7 108:25 111:11 112:9 114:16 115:7 116:4,9,13 117:17 123:8,22 127:19 130:2,3 134:21 138:6 149:5 155:1 156:21 157:7 158:18 160:12 163:2 173:16 181:1 184:17 188:5 190:12 195:17 196:9,18 197:12,24 198:14,22 199:8 200:1 201:2,16	38:5,17 47:24 52:15 65:17 67:10 75:15 86:18 90:10 91:19 94:1 114:12 124:6 129:6, 15 133:24 146:18 164:7 176:20 177:5 179:12 one 16:1,2,3,4 20:18 29:18, 21 33:5,10, 15 34:7 36:21 37:3 39:1 43:2,10 46:16 50:7 51:1 52:22 55:1,16 57:19,21 58:10 60:1 63:10 65:24 67:7 68:10, 19 71:5 74:11 75:9 77:11 80:1,2 82:10,11,18 85:17 86:13, 16 91:2 101:20 105:20 110:16 111:11 114:4 121:23 123:18 124:7 127:2 129:16,21 142:12,16,25 143:4 148:6 149:18 150:16 153:25 154:18 161:22 164:8 170:9 175:3, 8 178:21 180:19,24	181:18 185:18 186:12,18,25 187:2,19 188:3,17,22 197:17 ones 15:11 operate 119:12 opine 20:5 21:2,6 74:1 opined 20:13 opinion 15:7 56:19 74:4 75:3,7, 18 95:20 139:11 140:15,24 141:3 142:8, 20 143:3,9 148:22 150:21 151:1,23 153:22 154:11 170:22 171:20 172:4 178:10 179:20 187:7 194:2,11 opinions 15:14 18:15, 20,25 19:15, 24 20:15,23 21:11,13,20 56:9,23 57:4,5 58:7 59:17 60:5 63:7 66:16, 17 67:5 89:9,14 91:13 135:10 141:9,17 142:24 150:18	151:5,17 153:24 177:8 178:6 179:1 180:22,25 183:9 187:17 188:14,24 190:6,13 191:20 194:16 opposed 177:21 optimize 30:9 order 63:10 68:1, 24 88:2 144:9,22 151:22 ordinarily 147:4 ordinary 31:14 45:2 67:13 68:23 70:18 145:11,15 originally 134:16 originate 124:12 outlined 59:16 63:4 70:25 74:16 75:5,19 177:8 178:6 179:16 187:21 188:24 191:20 200:21 ovalbumin 33:11 overcome 120:9 121:14 125:25 126:16 overexpressio n
--	---	---	---

88:7,9 override 124:3 owned 19:11 owner 11:3 155:24 owns 155:22	pages 28:4 90:3 114:19 129:23 164:9 pair 170:22 171:21 pairs 172:9 pan-dr 61:5 Panel 109:9,14,16 110:12,13 paper 28:1,6,7 90:2,9 91:14 108:15,18 114:17,24 115:3 155:11,18 159:18 160:9,24 167:14 180:16 181:2,3 182:2,19 185:21 186:7 187:3,5,6,12 188:10 189:1,11,22 190:3 191:15,21 192:6 193:22 194:9,13 198:1 papers 15:3,10,13, 14 18:18,19, 22 19:2 175:11 185:18,22 186:6,18,25 188:3,16,17, 22 189:9,24 192:16	papillomaviru s 107:4,6 paragraph 20:18 21:1, 5,19 31:7,8 32:12 45:5 49:23,25 54:6,8,15,22 59:16 60:18 62:19 63:5 68:8 71:10 72:15 73:5 74:22 75:5 78:10 79:12, 13,15 80:25 81:15,22 87:24 93:9 97:14 110:15,18,19 117:11,16,20 118:1,18 120:18 127:15,17,21 129:19 130:1,2 131:15 134:20 135:18 136:16 137:7,20 138:11,15, 19,21,25 139:7,12,15 140:12,19 142:4,19 156:13 157:11,12 160:19 161:23 164:8,14 165:25 168:20,23,24 169:14,17 175:24 176:5 180:17 187:2,4,5, 12,21 188:11 193:6 194:8,	21 paragraphs 168:22,25 parameters 52:12 parent 134:14 parenterally 107:22 parenthetical 158:10 Park 22:15 162:22 181:16 197:5 part 15:3 18:18 30:8 65:13 96:7 132:6 149:19 153:23 154:1 158:9,10 167:25 191:16 particles 29:5 particular 24:13 30:18 47:15 55:15 57:6 58:5 61:23 64:5 69:20 85:3 87:3 106:15, 16 113:5,11, 14 148:2 161:9 165:17 191:8 particulate 199:10,15,18 parts 108:1 124:24 past 41:9 107:18 patent 11:3,24 12:1 155:25 patents 19:11,13,15,
<hr/> <p style="text-align: center;">P</p> <hr/>			
p.m. 116:18,20 117:2,4 149:7,10 180:6,9 196:10,13 201:8,11,23, 25 PADRE 60:9,16,20, 24 61:5,7, 14,17,23,25 62:2,9,14, 16,21,24 63:3 64:3,5, 9,15,19,22 65:2,5,8,14, 17 71:5 page 17:25 18:2,3 49:24 78:10 79:11 80:5 81:1 108:17 109:5,7 110:16 111:19 117:10,15 127:16 129:20 130:1 155:14 156:21,23,25 157:1,5,13 168:24 197:25 198:5,6			

17,19,23 20:2 21:14, 23 45:3 155:22 pathogen 29:19 pathogen- derived 33:17 pathogens 29:20,21 patients 107:20 Pause 100:6 129:24 178:4,17 186:2 187:10 190:11 pending 167:13 people 92:17 191:4 peptide 40:25 41:10 46:15,19 47:15 50:17 60:9 61:6 64:9 peptides 41:4 47:2,4, 6,9 percentage 55:17 Perfect 16:16 perform 35:14 41:11 44:21 48:23 49:16 74:12 83:2 174:10 performed 24:15 36:15, 17 37:22 39:3,5 40:3 43:22 44:15, 17,19 49:18 51:21 159:1	160:18 161:2,22 163:11 174:3 186:14 189:11,25 performing 157:24 178:18 period 27:13 28:10 33:6 37:17 39:7,8 110:2 peripheral 119:6,10 permitted 50:19 51:12 53:3 person 22:15,21 31:14 35:18 37:7 45:2 67:13,22 68:23 70:18 71:19,25 73:13 145:10,14 152:25 159:9,25 160:13,17 161:16 163:11 personal 35:4,5 140:24 167:13 personally 34:19,23 35:25 36:6, 10 37:7,13, 21 38:2 39:3,5 40:3 46:22 49:12, 16 56:14 133:2,4 140:21 141:4,7 168:10,17	Petitioner 10:23 Petsko 23:8,11,12 PGR2025-0003 16:2 PH 55:9 56:10 61:13 135:4 PH- 58:14 PH-20/SPAM1 91:2 Ph.d. 10:8 11:10 25:5,9 26:24 31:16 44:10 PH20 20:10,11 21:4 44:14, 15 50:2,13, 17,21,23 51:9,10,13, 17 52:1,5,8, 14,17 53:1, 13,22,23 54:1,9,16,23 55:8 56:2, 17,22,25 57:2,7,12,20 58:6,14,15, 19 59:1,7, 11,15 60:3, 8,12,14,17, 25 61:3 62:10,17,18, 22 63:1,3,4 64:4,7,13, 15,19,21 65:1,3,6,10, 14,19,23 66:7,9,11 67:2,8,11, 12,15 68:1, 2,11,12,14, 17,21,24 69:20 70:17, 19 71:1,4,6,	9,16,21 72:1,14 73:4,14,17, 22 74:2,5, 15,18,22 75:2,4,8,12, 17,19,21,22 77:13,15 81:11,23 82:10,11,15, 18,21,23 83:3,11 85:2,7,25 86:4,21 87:13 88:20, 21,24 89:3, 7,10,12,15, 17,20,23 90:12,13,17 91:8,16,20, 24 92:1,7, 12,21,22 93:2,4,8,16, 19 94:2,12, 17,24 95:4, 6,7,13,15,21 96:5,12,13 97:3,6,22,23 100:14,21,25 101:5,12,17 102:4,6,18 105:5,11,24 106:4,11,15 107:1,2 120:1,5,6 122:2,3,4 129:11,13 130:5 131:20,23 132:1,3,6, 10,14,20 133:9,14,21, 25 135:2,6, 11,16,22 136:1,5,9, 14,17,21,22, 24 137:2,3, 8,13,20,25 138:1,3,4,7,
---	--	---	--

10,15,18,24 139:4,6,9, 11,14,23 140:1,4,10, 11,13,17,20 141:9,12,14, 16,18,21,25 142:1,6,8, 13,14,20,24 143:4,11,16, 18,19 144:4, 15,23 145:5, 8,12,16,22 146:5,16,24 147:2,6,15, 22,24 148:1, 10,14,20,23, 25 149:19,21 150:17,21, 22,24 151:4, 8,12,14,17, 22,23,25 152:17 153:2,7,19, 20 154:3,6, 7,11,13,22, 25 155:3 156:6 157:18,25 159:1,10,13 160:2,5 161:2,5,24 162:13 164:24 165:13 166:25 178:21,23 179:1,5,7,8, 13,20,22 190:8,16,21 191:15,19 192:1,10,12, 22	phenomenon 198:13 phrase 50:2,20,23 55:8 physical 28:24 pick 49:22 143:17 picking 144:6 picture 79:20 pictured 63:25 64:3, 21 65:8,17 67:10 picturing 64:6 piece 167:14 PL- 108:15 place 118:23 119:9 120:15 121:7 125:6 144:15 places 130:13 plasma 119:19,22 play 141:17 please 10:19 12:19 17:19 27:22 69:15 70:4 77:18 79:7 84:13 94:21 96:17 97:12 98:3,19 139:15 156:25 171:25 181:17 PLOS 108:16	plots 112:9 PNAS 114:18 point 20:17 33:21 48:5 58:24 115:20 164:12 183:10 184:24 pointing 194:2 points 110:11 poly- 52:1 77:13 polyclonal 20:7 41:14, 17,21 42:10, 17,18,21 43:2,5,6,12, 17,21 64:23 68:9,16 69:7 71:2,3,7,11 72:16 73:6 74:2,6,15 75:5,20 79:23 80:12, 14,18,23 82:12,16,19 83:4,9,16, 22,23 84:3, 17,21 85:15, 18 86:3,12, 22 87:23 88:17 89:15 91:24,25 92:2,12 93:5,10,15, 22 94:7,19 95:6,16,25 96:14 97:24 102:1,10 103:2,13,24 105:6,12,14, 17 106:7,12, 17 107:1	120:1,22 121:3,11,16 134:13 139:8,13 140:16 141:15,22 142:1,7,22 143:8 146:22 147:1,12 148:24 150:23 151:24 154:8,12 155:4 169:1, 15,18,19,24 171:3,4,8 172:6,13 174:21 175:9 176:2 179:3, 6,21 193:7 194:24 195:11 polyethylene 25:20 polymer 25:19 polypeptide 20:12 21:5 42:11 44:14, 16 50:17 51:9,13 52:5,12 53:13 54:9, 16,23 56:1, 11 57:7,19, 20 58:6,19 59:1,8,11 60:17 61:8, 13 62:10 63:14 64:15 65:24 66:7, 23 67:8,15 68:1,2,4,12 69:21 70:17, 20 72:2 73:14,17 75:9,10,23 77:13,16
PH20S 122:5 phase 152:3			

81:20,23 82:12,21,23 83:5,8,19,25 84:15,18,22 85:2,8 93:19 95:14,15,24 96:6 97:3 100:14 102:4,6 106:15 130:6 135:4,7 136:1,10,22 137:3 138:4 139:7,12,14 140:4,20 142:25 143:19 144:5 150:24 151:23 153:19 169:2,5,7, 21,23 171:6, 7 193:8,11, 13 195:1,5, 13 polypeptides 20:10 21:4 50:3,4,14, 21,24 51:11, 17 52:2,14 54:1,10,17, 24 55:8,9 56:2,10,22 60:4 66:3 68:11,15,21, 25 74:5,19, 22 75:4,8,22 81:6,11,12, 18 82:4,10, 16 83:3 85:16 106:11 135:3,11,17, 23 136:3,9, 17 137:2,8, 10,21 138:10,18,24 139:24 140:1,11,17 151:8 153:20	154:12 169:9 175:8 193:15 195:3,15 poorly 125:10,15 populations 119:18 portion 90:9 portions 134:6 197:3 POSA 21:7 31:5,11 32:10 45:7 61:24 68:8, 15 69:6 71:3,9 72:13,18 73:2 74:5,14 81:17 82:2 83:9 84:20 88:15 102:10 120:21 121:10,13 122:14 123:14 136:25 140:15 141:3,5,18, 20 152:15 158:25 160:1 161:1,14,20 162:18 167:8 194:23 195:10 200:19,24 POSAS 81:4 pose 13:9 position 50:10 51:3,6 52:7,22,25 53:18,24 54:13,20 55:2,16 57:13 59:2 65:25 96:20	143:1,5 positioned 65:2 positions 53:5 54:2 55:24 57:22 153:2 possibilities 60:13 possible 60:1 62:6 67:12 69:2 73:14,19 162:12 post-doctoral 31:17 postdoc 26:7,9 152:3 postdoctoral 26:3,5,11, 12,17 27:4, 6,11 28:10, 16 29:1,11 30:8,17 33:9 37:18,20 39:6,8 152:12 potent 126:13 potential 25:23 30:10 51:6 64:12 68:13,25 75:16 110:17 127:7 143:13 145:9 153:17 156:8,17 157:14 158:20 164:22 potentially 124:25 powerful 127:3 Powers 11:5 16:19	Pratibha 11:1 13:17 prediction 156:24 157:9,12 160:20 preparation 132:7 151:12 prepare 14:10,13 67:5 149:15, 20 154:18 187:20 188:16 195:20,24 prepared 16:21 17:2, 4,8 21:11 22:10 89:8 166:3 190:6 196:2 preparing 15:10 19:15 150:18 151:5 prerequisite 115:12 present 77:19,20 81:6,19 82:5 83:15 84:15, 22 85:25 94:3 95:21 100:21 131:17 132:6 133:19 134:13,15, 16,19 145:12,16 170:17 presented 12:19 15:20 24:25 77:22 95:10 180:14 186:23 188:9 presenting 69:12 87:6, 10 99:18
---	--	---	---

preserved 128:15	24 17:2 19:10,16,20	professional 107:15	104:7,14,21 105:5,15,17,
pretty 86:8	20:3 21:15 22:1,6 23:2	program 24:4,6 168:3,6,11	19,24 106:4, 24 113:21 120:1
prevent 117:23 118:6,12	155:23	promote 26:1	121:11,25 122:1,9,15, 22 123:6,7, 18,24 124:8, 10 125:17,18 126:2,4,7, 10,16
preventive 24:9	process 12:10 69:24 70:16 73:16 114:7	proper 184:8,13	128:14,15, 16,20 129:2, 4,11,13 130:19 131:2,4,5,7, 10,11,13,16, 19 132:1,6, 10,19,20 133:1,8,9, 15,17,18,21 134:1,4,7, 11,14,15,17 138:12,21 140:10 141:9 142:2 143:11,14 144:1,19 145:5,19,21, 22,25 146:1, 10,11,14,15, 16,18 147:9, 21,24 148:15,16 150:4,6,8, 11,15 152:9, 17,21 153:3, 7,9,12,13,17 154:4,6,22 158:8 159:3, 12,13 160:3, 5 161:4 167:1,21,23 168:1,12,15 172:7 176:5 179:17 190:1,3 191:9,12,14,
previously 15:20 24:25 91:15 107:14 180:14 186:23 188:9	produce 33:5 37:13 79:25 80:1, 9,16,22,23 82:22 84:9 85:6,18 87:12 105:6 106:6 118:8, 13 119:1 120:10 121:3 174:12 175:14,22	properly 133:20	
primarily 33:15 35:3 38:19	produced 34:10 36:23 37:8 41:20 42:10,16 82:12 86:14 119:25 122:24 144:23 166:23 172:9 174:17 191:5	prot- 121:21	
principles 30:1,17 32:2,5,22 191:25 192:21 200:24	produces 80:2 166:25	protein 29:10,18 31:19 32:4, 14,21 33:2, 4,8,12,14, 19,20 34:2, 3,6,9,17,20 35:1,6,19, 23,24 36:1, 5,7,12,23 37:9 38:2,3, 7,8,13,22,25 39:11,13,18, 21,24 40:6, 9,18,20,21 41:16 42:12 43:3,13,18 46:11,12 47:5 48:5,9, 17 49:5,7,16 53:5 57:23 61:18 70:22 87:13 88:20, 22,24 89:4, 8,11,17 90:13 91:24 92:1,4,6,22 93:2,4,8 96:12 97:6, 22 100:16, 19,21 101:3, 5,10,12 102:9,18,21, 24 103:1,8, 10,19,21	
Printz 155:15,19,21	producing 177:23 179:9		
prior 33:13 34:4 47:10	product 107:10 181:25		
privilege 181:12,25 182:10,12,21 183:7,12	production 43:25 47:23, 25 83:12 84:6 85:2 123:17 139:8 170:24 171:15,22 173:5 174:4 177:1 178:12,21		
privileged 182:22 183:23 184:15			
procedures 73:12			
proceed 12:15			
proceeding 10:11 14:3 16:6 17:17, 21 18:1 49:23 183:10			
proceedings 12:4 16:21,			

19 194:6 198:17,18 199:23 200:6,7,14 protein-based 29:22 proteins 29:9,12,14, 17 32:25 34:8 36:16, 18 37:8,11, 14,23,24,25 47:21 48:9 117:25 122:5,13,17 123:14,17 124:8 125:10,15 127:9 131:22 132:11 133:2,4,12, 19,24 134:9, 12,18 135:19,21 149:24 150:1 152:13 170:3,8,11, 15,17,18,21, 23,25 171:4, 15,21,24 172:4,9,16 173:4 174:11,17 175:4,14,20, 25 176:25 177:22 178:11 179:2,9 185:23 187:7,13,22 189:2,5,12, 20,21 190:7, 8,14,16,21, 22,23,24 191:2,16,22 192:3,6,10, 11,13,17,24, 25 193:25	194:3,11,13 198:10,14,22 199:4,5,6,7, 14,16,20,21, 24,25 200:11,13, 17,18,20 provide 13:8 144:15 provided 19:10 31:12 49:10 74:19 115:21 176:21 181:3 185:13 188:1,20 providing 18:25 21:13 22:1,6 77:4 pseudogene 91:3 publications 178:19 published 28:3,13 114:18 154:20,24 155:12,14 197:1 purpose 30:20 purposes 31:11 put 27:21 61:2 76:23 77:3 78:5,16 96:8 97:19 98:8 106:20 173:15 175:7 putting 99:2,6,9 Pymol 35:7,20 36:3,7,11 168:4,7,8	<hr/> Q <hr/> qualifications 31:4 32:10 45:6 161:19 question 12:15,18,20, 23 14:25 20:16 22:3 39:16 40:12, 16 41:18,23 42:5,8,14 49:12 52:9 57:16 59:9, 24 60:22 61:10 62:4 63:12,18 67:21 68:19, 20 69:11,13, 14,18 70:1, 2,12,13 71:13 72:10, 17,24 73:2 74:10 76:22, 23 77:9,11, 14,19,20,21, 23,25 82:20, 24,25 83:1 84:1,8,11, 12,13,25 87:8,9 88:23 89:1 92:25 93:17,24 94:14,15,16, 20 95:9,10, 12,17,19 96:2,8,15, 17,24,25 97:7,11,13, 19,20 98:1, 11 99:4,6,8, 17 101:7 102:12,15,16 104:1,5 106:20,22 118:10,19	122:11 123:2,3 125:13 137:16 144:7,21 146:7,12 148:3 149:18,23 150:25 151:1,2 154:14 159:8,17,19, 20,22 162:8, 25 163:10, 16,17 164:2, 10 165:17, 21,22 166:7, 8,15,16 167:12,16 171:10,12, 14,19,20,25 172:1,22 173:22,25 174:14 176:23 177:18 178:16 181:2,8,13 182:1,16,17 185:7,11,12 186:3 189:7 190:10,12 194:17 199:1 questions 12:10,11 13:9 17:15 20:21 21:18 77:2,3,5 78:3,4 86:8 87:6 98:8 99:1,15,19 148:7 161:10,12,13 163:25 167:5 198:3 200:4 201:3,14 Quinn 11:6
---	--	--	---

R	164:19	45:19 76:9	referring
	167:11	116:19 149:8	50:16 81:12
	175:23	180:7 196:11	104:6 111:7
raise	176:19 177:4	201:9	114:25
96:13 97:24	185:17	recognize	135:19
140:12	188:2,15,21	123:10	136:17
raised	189:23	144:24	165:13
178:20	191:7,17	165:12	166:18,22
Ralph	195:9 196:1	recognized	169:14 170:4
11:5	198:19,25	101:4,11	193:19,20,23
random	reads	recognizing	refers
134:7	158:15	170:9	54:9,16,23
range	ready	recollection	111:8,25
14:5 59:21	100:4	185:20 186:5	113:20
ranges	reason	189:1	170:7,14
55:22 62:14	13:12 86:13,	recombinant	refold
ranging	16 91:12	156:6 157:18	132:20,25
57:13 58:16	161:1	164:23	refolded
192:18	reasonable	record	37:23,25
rat	71:8	10:5,20	133:2,4
176:7	reasoning	11:16 45:18,	refuse
reacting	192:2,9	21 76:7,11	99:15
40:17	reasons	98:17 116:18	refuses
read	85:5,17	117:4 149:6,	98:7 99:1,14
15:3,13	87:11	10 173:16	refusing
18:18,19	recall	180:5,9	99:7,24
90:11 91:14	18:22 19:2	181:23	165:21
115:2,7	22:23,25	182:24,25	regard
160:9,24	23:1,14,21	196:8,13	17:18
161:9 162:2,	33:4,20 36:6	201:6,8,11,	regarding
7,21 163:15,	44:23 46:10	19,22	194:8
24 164:9	61:22 62:13	recorded	region
165:18	63:8 64:11	65:20	129:5
166:4,12	77:11 98:7	records	regulation
167:6 186:3	99:13 100:2	21:25 65:12	119:22
197:16	175:19	refer	reiterate
201:15	176:15 178:8	50:3,24 54:2	45:1
reading	185:7	92:18 128:7,	relate
81:14 90:14,	189:18,20,25	11 193:4	18:25 19:10
20,21 110:10	196:2 197:22	reference	28:15
115:6 135:15	recently	17:16 127:20	related
136:19	15:9	referenced	15:15 27:12
137:23	receptor	164:13	28:21 46:3
151:20	115:22	referencing	76:19 118:23
157:22 158:3	receptors	81:10	161:10
159:6,16	114:14	referred	relating
160:8 163:18	recess	63:21 147:20	181:13,25

relative	154:15	required	23 94:19
102:5 133:20	159:22 168:5	55:13	95:16 96:14
139:24	171:12	requirements	97:25 103:6,
199:16 200:8	174:14	74:21	17 105:7
relevance	177:18	research	106:7,13,17
30:7,15	185:11	24:16 35:14	110:5,7
32:17 67:20	190:10 199:1	43:23 44:15,	112:1 120:1,
68:7 69:5	repertoire	17,19,21	19 121:4,16
70:24 72:9	41:13,16,19	84:19 133:7	126:6 142:2
73:25 158:14	42:9 80:16,	168:14	156:11
159:15	24 83:22	researchers	169:25 171:8
160:7,23	105:5,14,25	35:11 38:7,	182:16 193:5
161:7	106:5,16	18 40:5 41:9	198:15
relevant	119:25	126:24	responses
31:18	repertoires	130:18,21	28:19 29:3,
relied	86:3	191:8	8,19 30:2
180:21	replaced	reserve	43:21 44:4
187:6,16,20	50:11 51:3	99:12	62:3 64:23
188:16	replacing	reside	65:7 71:7,
rely	63:2	11:18,19	11,16 73:1
15:14 180:16	report	96:20	82:17,19
188:13	191:8	residues	83:4,10,20
remainder	reported	65:10	84:21 89:16
32:11	41:10 126:19	respect	92:14 93:10
remember	156:2 175:13	17:21 20:21	94:11 95:25
14:4 65:1	192:6 195:21	35:1,24	101:18
76:20 152:5,	reporter	respond	102:2,11
7 189:21	10:16,21	12:11 88:1	103:2,3,13,
remotely	27:20 78:24	118:3,17	14,24 104:17
11:7	reporting	responded	105:12,18
remove	108:18	94:23	109:14,16
119:1,3	191:11 200:7	responding	110:1 112:13
removing	reports	96:24 119:4	113:12
132:21	154:2 189:19	response	117:21,24
render	194:22	12:5,17 13:9	119:13
71:21	represent	41:14,21	120:23
rendered	16:9	42:10,16,19	121:7,11,20
21:20	represented	43:17 53:4	122:16,20
repeat	198:16	80:15 82:13	123:15 124:9
22:3 40:12	reproductive	83:7,18	125:20,24
42:5 60:22	44:1 74:7	85:3,11,13,	126:4 128:9,
63:18 67:21	108:2,3,6	18,23 86:8,	13 130:24
92:25 101:7	111:14,18	12,19 87:3,	131:18
102:16 104:5	113:1,10	4,16,18,23	134:14
118:10 123:2	114:1,11	88:5,17	141:15,22
125:13	148:10,18,21	91:24 92:1,	142:7,22
137:16 146:7		3,4,13 93:6,	143:8 144:13
			145:3
			146:20,21,

23,25 147:10 150:23 154:9 155:4 172:14 173:2 174:8 175:10 176:3,8 179:4,7,13, 18,21 187:15,24 191:1,12,24 192:8,20 194:15	retrieved 100:8	35:21 38:15 39:7 42:24 43:15 44:6 49:21 50:15 52:9 53:3,10 57:15 58:21 69:3 72:21 74:23 76:20 77:1 79:11, 14,20 80:1,7 81:13,21 86:16,24 91:17,22 99:12 100:13 103:3,14,25 104:8,9,10 107:8 108:22 109:2,5 110:15 111:14,24 112:22 113:10 117:25 118:21 119:2,7,14 121:17 123:7,11 125:4 128:2 129:25 134:8 136:1,18 137:22 144:16 147:6,13,24 149:24,25 150:6,10,12 151:18 152:10,18 153:4,10,15 155:23 157:2,4 158:1 160:14 161:15 165:14,20 167:13 168:19 169:13 170:2,5,18 171:16,19 172:10 174:5	176:12,23 179:24 180:18,23 183:18 186:12,16 187:2,4 189:15 193:4,17,22, 25 194:4,12 195:7 196:4 199:17 200:4,15 201:15
responsible 38:19 41:1	returns 185:3	reveal 183:12	rise 97:1 153:24
rest 162:8	revealing 14:25 172:22 173:22 181:8 184:15	review 17:7 21:22, 24 22:4,7,9, 14,17 23:7,9 28:19,22 41:7 90:8	risks 126:20
result 62:2 65:7 75:20 103:12,23 111:12 124:9 131:7 133:13,18 134:3 138:21 139:4,12 140:19 142:7,21 147:9,11	reviewed 14:15,18 15:5,9 17:8 18:4,8,11, 14,23 19:14, 17,23 21:10 22:12,16,19 23:15,17 28:12 174:7 180:20	reviewing 179:15	role 11:25 115:1 141:17
resulted 186:15	rheumatoid 88:12	rheumatoid 88:12	room 11:4 13:3 98:18,23 181:18,21 185:4
resulting 95:24 100:19,24 101:16 114:15 134:10 146:22 147:10	rhuph20 156:5,16 157:15 158:5,17 165:1	Rice 25:6,9 26:24	roughly 26:8
results 49:19 102:25 103:8,19 104:15 109:24 164:11 175:13	right 12:12 16:15, 17,22 17:14 18:10 19:6 20:3,23 21:15 23:16, 22 25:5,8,15 26:4 27:14 28:25 29:23, 24 32:25 34:6,21	rows 199:8	route 108:20,21, 22,23,24 110:14 111:22
retained 13:15,16		run 73:2	row 199:9 200:1, 5
			rows 199:8
			run 73:2
			<hr/> s <hr/>
			saline 121:1 122:15
			sat 27:5

satisfy 52:12	search 173:11,12	seeing 90:19 116:1	137:9,11,22
saves 16:16	174:3,10,16,	156:19	138:6
saying 73:9 106:25	20 177:7	segment 112:2	sequence 34:7 36:15,
135:24	178:2,19	selected 41:5 47:6,	17 47:15
137:14 140:8	185:19	10,15 54:13,	50:5,7,19,25
141:2 142:23	186:8,14,17,	20 55:3	51:1,8 52:3,
183:11	19 188:4,23	selection 126:25	6,20,24
192:23	189:11,17	self- 120:12	53:5,10,14,
says 25:11 110:21	searched 172:25	self-antigen 88:8,18,20,	24 54:10,12,
115:9 157:13	searching 167:22	25 120:20,24	17,19,24
158:11	second 16:3,4,6	121:12,16,20	55:1,17
164:21	81:2 94:13	125:18	57:9,13,23
scale 56:3	97:9 129:21	self-antigens 88:5 118:8,	58:16 59:4
scales 112:9,11	secreting 109:20	14 119:2,4	60:16,17,24,
scenario 101:1,8	secretions 111:2 112:3,	self-protein 120:5,8,11,	25 61:2,3,
177:25	5,14,15	25 121:4,18,	14,17,19
Science 197:2	section 18:9 169:14	22 127:2	62:9,15,22
scientific 31:18 106:22	see 18:2,3,6	200:2,3,8	63:9,22
scientist 23:1	19:7 31:8	self-proteins 120:4	64:5,7,9,12,
scope 110:9 111:16	48:24 49:24	seminars 27:10,16	16,20,22,25
112:19	71:17 78:19	sense 29:14 184:14	65:1,2,3,6,
115:5,24	79:14,16	sentence 81:3,15	14,15 66:2,
140:11	81:2,15	90:22 91:11	3,6,8,11,19,
159:5,15	91:11 109:6	111:10	20,23 67:8,
160:7,23	110:18,19	115:25	12 68:5,22
161:7 162:1,	112:6,7,20,	134:22	69:2,22,25
10,16,20	23 113:4,5	135:24	70:21 72:2,
163:14	115:8,25	156:14	4,5 73:17
165:9,16	123:15	157:23	81:24,25
167:3,19	130:3,10,11,	158:10,15,18	122:14,18
172:3	12 134:22	169:12 170:1	131:4 134:25
screen 41:5	147:14	SEQ 50:8 66:10	135:12,20,25
screening 43:8	155:20	81:13 135:5,	136:4,6,8,
	156:1,10,14	13 136:1,18	11,12,14,15,
	157:6,21,23		18,21,22,24
	158:4,6,15		137:4,5,11,
	169:11,12		21,22,25
	170:1 190:20		138:1,3,4
	198:12 200:5		143:6,9,10,
			11,19 144:6,
			10,14,15
			145:5,12,17
			148:17,23
			150:12 151:7
			156:7,16
			166:18,24
			167:22
			169:6,22

170:23	serve	187:13,22	silico
171:7,22	132:17	194:13	49:17
172:5,16	145:19 146:2	showing	similar
173:1,4	148:24 155:3	79:21	54:1 55:19
174:11	served	109:14,16,	100:24,25
175:3,9,21,	12:1	18,19 179:16	101:2 109:24
25 176:5,6	service	191:21	137:2 147:14
177:1,23	34:10	192:17	170:20
178:11	session	shown	191:25
179:2,17	77:2,10	72:15 73:5	200:14
185:24 186:8	set	110:1,13	similarity
187:7,13,22	41:20 42:16	112:21,22	200:2,5
189:2,12	45:3 50:13	136:3,10,15,	similarly
190:25	51:10 52:13	22,24 137:3	91:4 199:21
191:22	55:7 56:10,	138:1,4	simple
192:3,7,10,	12,21 57:18	shows	151:3 181:1
18,24,25	75:7 81:10,	189:2,5,11	simpler
193:4,12,18,	11,12,18	shuttle	154:14 159:8
20,24 194:1,	113:11 137:7	114:4	simply
6,10,14,17	138:24	shuttling	73:18
195:4,6,16	sets	113:21	Simpson
sequences	56:2	sic	23:16
34:6 41:1	setting	50:11 88:14	single
50:15,17	191:9	112:13 135:4	55:15 57:12,
51:25 52:4,	several	162:22	21 58:25
12 56:1,3,	130:13	184:17 197:5	99:5 123:13,
11,21 57:19	share	side	23 124:1,7
58:13 62:9	170:23	111:23,24	125:22 139:6
63:3,16,20	171:21	112:10	142:5
65:13,18,23,	174:11	113:22 127:7	sit
24 66:14,18	shared	Sidley	188:25
67:6 71:6,24	122:21,24	10:23	site
73:20,21,23	123:16 124:4	sign	97:1,3,21
74:12,21	Sharp	18:24 201:15	114:4 147:4
75:9,10	10:9	signaling	sites
127:25	Sheldon	182:9	93:3,18
143:13	22:15	signed	94:16 111:9
145:20 151:9	shock	17:2,4,6	113:13
191:14	190:3 191:2,	18:24 51:20	sitting
sera	9,12,19	58:22,24	178:9
42:17,22	short	59:11,25	situations
43:2,6,7,13	71:5	60:4 61:12	177:15
series	show	62:8	size
67:6 100:15	113:6,11	significant	55:7,19
serum	194:7	73:8	198:17,20
111:3,5,6,9,	showed	signing	skill
17 112:1,14	185:23	17:9	31:14 45:2
113:12			

67:13,22	42:1 74:20	sperm	182:24
68:23 70:18	84:4 91:23	136:5 139:9	194:21
71:19 72:1	135:21 178:1	140:13	statement
73:13	species	146:5,17	49:25 80:19
145:11,15	121:24	147:2,6,24	110:20
152:25	122:4,14,18,	148:2,10	125:14
159:9,25	22,25 123:5,	149:1	182:12
160:13	6 124:4	sperm-	193:21
161:16	169:10	associated	statements
skilled	178:21,22	88:21 89:3,	20:18
160:17	179:9 193:16	10 148:14	stay
163:11	species'	spleen	89:14
slightly	122:1 123:18	124:25	stays
59:23	specific	spoke	143:3
smaller	18:22 33:20	45:25 46:3	step
47:21 48:1	47:24 48:24,	117:8	98:18
144:3 199:5,	25 49:7 54:2	spoken	181:15,17
7	55:13,23	22:24	steps
software	56:20 59:10	spreading	159:1 160:18
36:5,12	60:3,10,23	124:9	161:2,22
38:20 48:17	63:2 84:8	STANDARD	163:12
64:19 167:23	104:22	10:2	Sterne
168:3,6,11	106:23 132:2	start	10:12 11:2,5
softwares	144:23	12:6 70:9	13:16
34:25 36:2	154:19	184:14	sticker
38:8 168:1,	163:25 164:7	199:13	27:21
16	167:5 175:19	starting	stimulated
soluble	176:15	48:5 60:17	169:24 171:7
138:7,8,15	178:8,25	65:23 66:22	stimulating
199:11,17,19	179:12	155:13	169:7 193:13
solvent	189:18	starts	stretch
158:22	190:1,18	110:16	143:18,19
159:2,11	specifically	state	144:6
160:3 161:3	59:19 107:18	10:19 11:15	strike
sotto	specified	31:8 33:24	86:25 142:10
186:10	57:13 58:10	81:3 134:23	178:16
source	62:18 93:9	169:17	strong
80:5 183:8	specify	stated	61:6 65:7
sources	58:17	15:15 20:25	122:16
29:18 174:17	speculating	21:5,19 31:5	125:20
speak	177:10,20	32:10 45:5	126:18,20
45:23 46:2	spell	87:24 118:18	127:6
76:13 117:6	46:25	120:18	stronger
149:12	spelled	123:21,23	92:3,14
196:15	47:1	140:24	strongest
speaking	spend	142:11,19	73:1
22:25 23:1	160:9	150:21 156:3	

structural	107:13,17	substance	159:7,19,23
34:9 38:3	191:3	14:22,25	174:15
64:14 141:8	studies	172:19,22	182:14
148:12,17	24:15,16	173:7,19,22	190:20 199:2
150:17	32:5 33:20	181:5,8	surface
151:16	49:19 74:13	182:7	134:3 152:17
168:12	109:25	substitution	153:3,9
structure	130:18	59:2 100:15	160:5 161:5
31:19 32:4,	190:23	142:12,16	surprise
14,21 35:1,	study	substitutions	55:25
6,13,19,24	31:19 32:3	52:20 53:2,	survival
36:7 38:3,14	34:7 35:1,13	7,16,22 57:8	118:7,13
39:11,13,19,	36:7,12 38:8	58:9 59:3	Susan
21 59:6 93:4	39:25 40:3,	substrate	10:16
100:16,18,	6,19 41:8	41:2	swear
20,24 101:1,	46:15,19	successful	10:21
2,3,4,8,10,	47:23 48:14	21:7	SWISS-MODEL
11,21 102:5,	49:9 64:19	sufficient	34:10,20
18,22 103:1,	73:3 109:24	85:20 112:25	35:7,12,25
4,15 104:2,	148:20	177:7	150:10
7,12,15,16	150:4,8	suggest	151:12,21
128:12 129:2	151:22	182:22	166:23
141:16	152:20	suggesting	SWISS-MODELS
145:25 147:5	153:6,11,16	111:4	34:17,23,25
148:20	168:15	suggests	sworn
150:2,8,11,	study/studied	28:17 192:10	11:11
15,20 153:7,	43:12	suitable	synthesis
12,17	studying	68:3 70:20	25:12,16
157:17,20	191:9	71:22	synthesize
158:5,6,7,	subject	summer	63:13
11,16,22	19:20 20:2	13:21,23,24	synthesized
159:2,11	79:24 155:23	support	47:3,12
160:3 161:3	195:1,13	10:16,18	system
162:13,14	subjects	180:22 183:9	26:24 30:5,
165:1,3,7	108:19	187:6,17	13 81:8,20
166:9,24	109:15,17	188:13 194:2	82:6 84:9
167:21	111:2	supported	85:6,18
168:15,18	sublingual	176:25	87:12,25
structures	108:20,21,23	sure	113:25
38:8 84:23	110:8,13	22:4 40:13	114:10
93:21 101:16	111:23	41:18 42:2,	117:23,24
102:3,6,13,	112:12,16	13 45:11,15	118:2,16,20
19 103:9,20	113:8	49:11 63:19	121:3
studied	sublingually	67:22 72:12	124:17,22
30:9 35:6	109:17	86:5 93:1	systemic
38:10,21,22	subsequent	98:20 102:17	109:1,3
41:16 43:20	146:21 147:1	125:14 149:4	111:12
44:3 49:7			

thymus 124:25	tolerance 87:20,22 117:19,23 118:6,12,21, 24 119:5,6, 10,11,12,16, 17,23 120:4, 9,13 121:15 124:3 125:2, 7,21 126:1, 16	152:12	71:20 144:2 147:16 152:9 176:23 177:19,25
time 10:2,5 16:16 18:24 27:4, 16 42:4 51:19 58:22, 24 70:8 90:19 94:13 95:8 96:1 97:9 98:4 113:4 116:1, 6,11 117:2 148:18 152:12 156:19 160:9 161:8 186:13 197:16,18,23 201:13	tolerate 67:16	trains 44:11	TUESDAY 10:1
times 11:22 154:16 197:10	tool 35:7,8,19	transcytosis 113:16,18, 19,23 114:3, 8,9,13,15 115:1,13,14, 22 116:3	tune 28:2,18
tissues 125:1,7	tools 24:12 38:23 49:8 71:2 72:6 84:19 152:20,22, 23,24 153:1, 6,11,16 154:11 164:13 167:21	translational 110:17	turn 117:10 156:21
titers 111:4 113:7, 9 126:10	top 109:7 157:1	translocate 111:17	twice 11:23
title 22:5 28:17	topic 190:13	translocation 111:8 115:15	two 12:2 36:15 67:7 91:1 121:24 122:5,25 123:5,14,17 124:4 130:12 148:7 168:25 170:3,8,9, 10,15,16,20 171:21 173:3 174:11 175:4,13,20 176:25 177:15,22 178:10,13 185:22,23 186:6 187:7, 13 189:2,12 192:2,23 194:3
titled 21:24	topics 28:20	transport 113:24	
TNF-ALPHA 88:9	tract 44:1,4 74:3, 7,16 108:2, 3,6 111:14, 18 113:1,10 114:1,11 148:11,18,21	transudation 111:5,6	
today 13:6,13 14:13 16:22 17:15 19:1, 13 76:21 77:24 117:12 152:2 154:16 178:9 188:25 197:11 200:4	trained 24:11 88:1 118:3,17 124:16,19,24	Trentham 188:11 194:9	
today's 14:10	training 23:23 26:9 27:11 29:11 30:8,12,17 33:9 39:9 44:7 124:21	trigger 104:16 146:20 147:1,11	
told 76:21 96:22, 23		true 92:2 93:2 140:22 195:5	
		truncated 136:4,12,23 137:4	
		truthful 13:8	
		truthfully 13:13,14	
		try 12:19,24 16:4 36:21 58:21 61:10 77:23 121:23 125:25 144:7,21 153:25 186:12	
		trying 35:17 40:13 61:15 63:19	

<hr/> U <hr/>	96:3,7,9,15	vaccination	variation
	98:1 106:16	73:7 80:21	46:18
	108:5 122:11	vaccine	variations
U.S.	132:16	26:12,13	52:16 56:17
10:15,17	135:16	28:21,25	59:15 60:7
UC	136:3,7,20	29:3,7 30:3	67:12 68:16
24:1,3,6	145:8 154:6	33:3,6,9,17	74:9 75:1,16
26:21	155:2,24	35:2,13	142:6
Um-hum	165:5 176:24	37:12,16	varied
23:24 67:24	181:23	38:6 44:3	47:12
unable	182:11	48:16 67:17	variety
163:17	understanding	68:3,25	29:6,17
uncertainty	47:14 51:24	70:21 71:22	73:19
139:6	55:6 58:12	72:18 77:16	various
undenatured	59:6 65:11	81:9,21 82:7	62:16 125:7
129:13	66:2,8 67:4	87:14 107:5,	173:1
undergoes	73:10 77:14	7,9,13,14,17	varying
148:11,17	88:19 90:22	109:25 110:2	126:5
undergrad	107:21,25	112:24	vast
24:15 26:20	162:18	126:12,21	131:16 137:1
27:2 44:10	understands	130:18,19	versa
undergraduate	182:14	152:13 168:2	132:1
23:25 24:2,	understood	190:24 191:3	version
14 26:19	41:22 42:14	vaccines	66:9 74:15
31:16	49:11 56:16	29:5,22	77:15 107:1
understand	57:1 72:14	30:9,19,21,	136:4,12,23
12:18,21	159:8,19	22 32:8,23	137:4
13:6,7,10,11	underwent	34:15,18	versions
15:8 17:24	130:6	36:2 37:2,19	122:1 197:19
19:9,12	undisrupted	107:3 110:8	versus
35:18 36:4	130:21	127:11	10:9 129:17
40:13 50:23	unfolded	vaccinologist	vessel
52:18 53:7,	131:11	s	26:1
11 54:9,16,	unfolding	47:21	vessels
23 55:12	131:7,10	vaccinology	24:17,19,20
59:9 61:15,	Uniprot	27:12	VI
25 63:14,19	34:4,5,7	vaginal	169:14
66:21 69:12	151:7 166:21	21:8 44:4	vice
70:2,9,15	University	111:1,9	132:1
71:12 72:10	25:10 26:25	112:4,14	video-
73:4 76:24,	unmodified	113:13	recorded
25 77:1,21,	122:15	values	10:7
22 78:2,6,8		112:21,22	videographer
81:16 82:24,	<hr/> V <hr/>	variance	10:4,15
25 84:11,12		148:23	45:17,20
86:6 88:21,	vaccinate	variants	76:7,10
24 89:3,10	84:16 120:8	57:2 138:20	116:17 117:3
		143:7	

149:6,9	23:22 27:20	wild-type	157:22 158:3
180:3,5,8	30:23 42:13	20:11 21:4	159:6,16
196:7,10,12	45:9 49:11	53:18 68:12	160:8 164:19
201:7,10,18,	58:3,4 60:18	75:12,22	167:11
22	63:14 70:8,	81:12 93:15	175:23
view	15 73:10	95:7 100:21	176:19 177:4
151:14,16	78:20 86:5	101:3,10,17	180:14
168:12	87:5 95:11	102:22	181:20
viral	98:8 114:23	103:9,20	182:4,10
29:20,21	149:2,16	107:2 115:18	183:4,25
33:17	156:22	122:7 129:13	184:16
virus	159:7,19,25	131:12	185:2,3,17
107:8,23	160:11	134:16 135:3	186:23
110:24	173:16	136:1,9,22,	188:2,9,15,
viruses	174:15	23 137:3,13	21 189:23
29:13	181:22	138:1,4	191:7,17
visualization	182:11,13	139:9,13,25	196:1
35:8,19	195:20	140:13,20	198:19,25
visualized	198:11	142:2 145:5,	witness's
58:5	wanted	8,12,16	201:15
visualizing	70:9 71:25	146:4 147:2	witnesses
56:10	78:2 197:11	148:25	70:7
vivo	Washington	150:24	wondering
20:12 21:5	10:13	151:25	106:19
25:13,17	waste	153:20	word
68:12 75:23	70:8	154:13	41:19 42:11
115:15	way	179:7,22	130:12
139:14	55:10 99:18	200:14	words
VLP	105:20	withdraw	130:12,15
110:4	111:11 134:7	163:8 189:7	work
voce	184:9,13	witness	24:14 25:19,
186:10	190:15 197:7	10:21 15:20	25 26:11,12,
Vol	ways	24:25 27:25	17,18,19,24
28:3 90:3	24:7,8	45:11,14,16	27:4,6 28:9,
108:16	102:10	70:5 76:4	15,16 29:1
114:18	106:24	79:1,4,7,8	33:13,22
155:13	120:21	81:14 90:14	34:2 37:18,
	121:10,14	97:10,18	20 38:2,13
	125:23	98:4,7,16,	39:4,23
	website	20,23,25	40:8,24 41:6
W	34:5	99:11,13	43:16 46:8
	well-known	100:3 108:13	47:10 48:11,
wait	64:9	110:10 115:6	22 49:14
78:15 157:4	went	116:12	65:23 67:4
173:9,10	63:6	135:15	72:3 73:10
walk	whether...	136:19	107:15
109:8	polyclonal	137:23 149:4	109:22
want	21:2	151:20	149:20 152:3
15:8,23			

153:23 154:1 181:25 192:22 worked 14:2 29:10 37:11,14,19 38:6 39:12, 20 44:23,24 133:6,7 working 29:14 40:6,8 67:14 works 115:22 120:13 workshops 27:5,10,15 write 65:20 67:5, 11 74:12 written 65:12 70:25 73:19 137:19 wrong 163:4 wrote 118:1 175:24	159:24 162:2 173:15 174:15 180:4 182:13 186:10,12 195:22 197:9 198:8 199:12 201:21 year 13:20,22,24 years 26:8 28:13	
<hr/>		
x		
<hr/>		
X-RAY 150:3		
<hr/>		
y		
<hr/>		
yeah 13:25 14:9 15:23 28:8 42:7 45:5, 14,25 46:6 53:21 69:10, 17 72:11,13 76:19 78:17 79:4 84:12 100:5 109:11 117:14 137:18		