

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENE COMPANY PTY LTD.,

Petitioner,

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF

NEW YORK,

Patent Owner.

Case IPR2024-00313
U.S. Patent No. RE47,045

Friday, November 15, 2024

CROSS-EXAMINATION

GLENN D. PRESTWICH, Ph.D.

REPORTED BY: SUSAN L. CIMINELLI, CRR, RPR

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GENE COMPANY - EXHIBIT 1070

1 Cross-Examination of GLENN D. PRESTWICH,
2 Ph.D., a witness herein, called for examination by
3 counsel for Petitioner in the above-entitled matter,
4 pursuant to notice, held at Finnegan, Henderson,
5 Farabow, Garrett & Dunner, LLP, 901 New York Avenue,
6 Washington, D.C., the witness being duly sworn by
7 SUSAN L. CIMINELLI, CRR, RPR, a Notary Public in and
8 for the District of Columbia commencing at 9:00 a.m.

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1 APPEARANCES:

2 On behalf of the Patent Owner:

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1 C O N T E N T S

2 GLENN D. PRESTWICH, Ph.D.

3 EXAMINATION PAGE

4 By Mr. Mills 5

5

6 E X H I B I T S

7 (Previously marked exhibits referred to.)

8 EXHIBIT NO. PAGE NO.

9 Exhibit No. 2053 Curriculum vitae 22

10 Exhibit No. 1010 Mata article 133

11 Exhibit No. 2019 Kim 2004 article 140

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

2 Whereupon,

3 GLENN PRESTWICH, Ph.D.,

4 was called as a witness, and having been duly sworn,

5 was examined and testified as follows:

6 EXAMINATION BY COUNSEL FOR PETITIONER

7 BY MR. MILLS:

8 Q. Please state your name for the record.

9 A. **Glenn, with two Ns, Prestwich,**
10 **P-r-e-s-t-w-i-c-h.**

11 Q. Please provide your business address.

12 A. **Business address is Post Office Box 2087,**
13 **Port Townsend, Washington, 98368.**

14 Q. Have you been deposed before?

15 A. **Yes.**

16 Q. How many times?

17 A. **I think this would be number 20 or so.**

18 Q. When was the most recent?

19 A. **Good question. One or two months ago.**

20 Q. And because you've been deposed so many
21 times, you know the standard rules of the
22 deposition. I'll address kind of the most important

1 ones just to make sure we all remember, but the
2 first one is the court reporter is, after you, the
3 next most important person here today. She is
4 trying to write everything down. And so it's
5 important that we don't talk over one another,
6 whether it's you and me or counsel sitting next to
7 you. Can you agree to that?

8 **A. Understood.**

9 Q. And it's also important to do like you
10 have been doing so far, to make sure that your
11 answers are audible, spoken answers. And not just a
12 gesture. Does that make sense?

13 **A. Understood.**

14 Q. If, at any time that you need a break
15 today, please let me know and we can take a break.
16 I just want to make sure that we don't take a break
17 while a question is pending. Can you agree to that?

18 **A. I can agree to that.**

19 Q. If, at any point, you don't understand my
20 question, will you let us know, so we can make sure
21 the record is clear?

22 **A. Yes, I will.**

1 Q. Is there any reason that you can't give
2 your best most accurate testimony today?

3 A. **No reason.**

4 Q. You have some documents in front of you.
5 Can you tell us what you have?

6 A. **I have a clean copy of my declaration
7 provided by counsel. And I have a clean copy of all
8 of the cited exhibits associated with that
9 declaration, also provided in clean form by counsel.**

10 MR. FELDSTEIN: If I may, it's not --
11 some of the larger ones are not included.

12 MR. MILLS: Okay. Do you have a list of
13 which ones are not there? Okay.

14 BY MR. MILLS:

15 Q. And when you say clean copy, I think you
16 mean by that, that there aren't any handwritten
17 notes or additions that have been made subsequent to
18 their being printed for the record, is that correct?

19 A. **That's correct. It's an untarnished
20 printed copy.**

21 Q. Okay. This most recent deposition, can
22 you tell me, in a general way, what was the subject

1 matter of that deposition?

2 **A. General matter, the subject of the last**
3 **deposition. Let's see, which one was that? One of**
4 **them had to do with a process of making a peptide.**
5 **Another one had to do with trade secrets in a -- in**
6 **a monoclonal antibody case.**

7 **Q. Of the 20 depositions approximately that**
8 **you've had, how many of those were in patent cases?**

9 **A. I would say 80 to 85 percent of them.**

10 **Q. So that's most of -- maybe one or two**
11 **that are not patent cases, is that fair?**

12 **A. One or two that were not patent cases,**
13 **yes.**

14 **Q. Did any of those cases involve retinol?**

15 **A. None of those cases involved retinol.**

16 **Q. The same question -- I said retinol, but**
17 **vitamin A?**

18 **A. To my recollection, none of those cases**
19 **involved vitamin A.**

20 **Q. Did any of those cases involve**
21 **deuteration?**

22 **A. To the best of my recollection, none of**

1 **them specifically called out deuteration, although I**
2 **don't know if a deuterated molecule is used in some**
3 **of them.**

4 Q. How did you come to be involved in this
5 proceeding?

6 A. **I --**

7 MR. FELDSTEIN: Doctor, I'll just direct
8 you to be cautious. He is not asking for work
9 product or communications with us. I assume that he
10 is just asking generally.

11 THE WITNESS: Generally, I was contacted
12 by counsel.

13 BY MR. MILLS:

14 Q. And when were you first contacted by
15 counsel regarding this case?

16 A. **I don't remember precisely, but it was**
17 **earlier this year. Earlier in 2024.**

18 Q. Just to help you with the timeline, can
19 you take a look at the date on the front of your
20 declaration and remind yourself when you filed it?

21 A. **Yes, the date on the declaration is**
22 **September 22nd, 2024.**

1 Q. Does that help you to give a more
2 specific timeframe as to when you were contacted?

3 A. Not really. It was earlier in 2024.
4 That's all I can remember.

5 Q. Do you know who Dr. Sessler is?

6 A. I have known of Dr. Sessler. And
7 sometime in the last 40 years of my career, I may
8 have met Dr. Sessler.

9 Q. Have you had any communications with
10 Dr. Sessler regarding this case?

11 A. None, not at all.

12 Q. Have you had any communications with any
13 individuals at Alkeus regarding this case?

14 A. No, I was unaware of Alkeus until I was
15 contacted regarding this case.

16 Q. Have you had any conversations with any
17 of the authors of any of the references that you
18 relied on in this case about this case?

19 A. Have I had any conversations with the
20 authors on the references relied on in this case
21 about this case. The answer to that is no.

22 Q. When you were preparing for your

1 deposition today, did you review any documents that
2 are not documents that are already identified in
3 your declaration?

4 MR. FELDSTEIN: He is just asking for a
5 yes or no, Doctor.

6 THE WITNESS: Not that I recall.

7 BY MR. MILLS:

8 Q. Have you -- do you know who Dr. Del
9 Priore is?

10 A. **No. I've heard his name yesterday, and I**
11 **don't know who he is.**

12 Q. Okay. Is it correct that you've never
13 spoken with Dr. Del Priore?

14 A. **That's correct.**

15 Q. And you haven't read Dr. Del Priore's
16 declaration?

17 A. **That's correct.**

18 Q. And you have not read any deposition
19 transcript from Dr. Del Priore, correct?

20 A. **I have not read any deposition transcript**
21 **from Dr. Del Priore.**

22 Q. Have you prepared any new opinions to

1 offer today during your deposition?

2 **A. No, I have not. My opinions are**
3 **summarized here.**

4 Q. Before you signed your declaration on
5 September 22nd, 2024, did you have an adequate
6 opportunity to review that declaration and satisfy
7 yourself as to its contents?

8 **A. Yes.**

9 Q. Are there any retractions or corrections
10 that you need to make to your declaration?

11 **A. There are -- there may be some minor**
12 **typos that we would -- that we may run across.**

13 Q. Are there any that you specifically have
14 in mind as you answer that question?

15 **A. I remember one thing where I had an A2P1**
16 **instead of A2PE, or something like that. And at one**
17 **point, there was a -- the word "not" transformed**
18 **itself into the word -- or the word -- sorry, the**
19 **word "not" transformed itself into the word "to."**
20 **So there were things like that.**

21 Q. And I think the first typo was instead of
22 A2PE-H2, it was A2P2-H2?

1 **A. That was it, yes.**

2 Q. And just to make sure we are talking
3 about the same thing, that A2PE-H2, is that the same
4 thing as dihydro A2PE?

5 **A. It may be, yes.**

6 Q. You reviewed the Guengerich declaration
7 prior to preparing your declaration in this case,
8 correct?

9 **A. Yes.**

10 Q. Did you read the entirety of the
11 Guengerich declaration?

12 **A. Yes.**

13 Q. Did you do that before you sat down with
14 counsel to discuss your opinions in the case?

15 **A. To the best of my recollection, yes.**

16 Q. Where you have cited a reference in your
17 declaration, does that indicate that you personally
18 reviewed that reference?

19 **A. Let me be clear. When I have cited it in**
20 **my declaration, did I personally review that**
21 **citation? Generally speaking, and to the best of my**
22 **recollection, yes.**

1 Q. And when you were reviewing a reference
2 that you cited, did you read the entire reference or
3 just the portion of it that you were citing?

4 A. **That depends. Most of the references**
5 **that I cited, particularly the scientific ones, I**
6 **would read the whole thing.**

7 Q. Prior to beginning work on this case, had
8 you already reviewed any of the references that you
9 cite in your declaration?

10 A. **To the best of my recollection, no.**

11 Q. Do you know what the institution decision
12 is?

13 A. **I know what the words mean.**

14 Q. Prior to preparing your declaration, had
15 you reviewed personally the institution decision in
16 this case?

17 A. **No.**

18 Q. Prior to preparing your declaration in
19 this case, did you review any institution decision
20 in a companion case for a related patent?

21 A. **I'm not aware of any companion cases, nor**
22 **any decisions.**

1 Q. I'm going to ask specifically about an
2 Alkeus employee named Dr. Saad, S-a-a-d. Is it
3 correct that you have never spoke within Dr. Saad
4 about this case?

5 A. **I don't know who Dr. Saad is, so, no, I**
6 **have not spoken with him.**

7 Q. You can turn there if it's helpful, but
8 in paragraph 13 of your declaration, you list a
9 variety of companies that you have been involved
10 with during your career. Is that correct?

11 A. **Yes, I see that at paragraph 13.**

12 Q. It's a fairly extensive list, you'd
13 agree?

14 A. **Yes, there are a number of them.**

15 Q. And in the very first sentence, you use
16 the word "entrepreneur."

17 A. **That's correct.**

18 Q. Are you familiar with the company Bain
19 Capital?

20 A. **I've heard the name8.**

21 Q. Are you aware that Bain Capital is a
22 major investor in Alkeus?

1 MR. FELDSTEIN: Objection, form,
2 foundation.

3 THE WITNESS: I'm unaware of that.

4 BY MR. MILLS:

5 Q. In any of the companies that you've been
6 involved in during the course of your career, have
7 you had any interactions with Bain Capital?

8 A. **None at all, to my knowledge.**

9 Q. I'd like to talk about your
10 qualifications.

11 A. **Okay.**

12 Q. You mention in your declaration that you
13 have four publications in which you're a joint
14 author with Dr. Nakanishi, is that correct?

15 A. **I don't remember the exact number, but if**
16 **I put four down, those are the four that I remember.**

17 Q. And all four of those had to do with
18 termite hormones, is that correct?

19 A. **Termite natural products, yes.**

20 Q. So I used the word hormone. You said
21 natural product. So some of the -- so first of all,
22 hormones are or can be natural products, is that

1 correct?

2 **A. Yes.**

3 Q. So of those four publications, did some
4 of those have to do with natural hormones from
5 termites?

6 **A. No.**

7 Q. So what is a trinervitene congener from a
8 Trinervitermes soldier?

9 **A. If you'll excuse me in correcting that,**
10 **it's Trinervitene. And the termite's name is**
11 **Trinervitermes, which is why I called the compound**
12 **that was discovered -- that I discovered**
13 **Trinervitene.**

14 Q. Okay. And what is that compound?

15 **A. It is a tetracyclic diterpenoid.**

16 Q. And what is its role in the termites?

17 **A. It is one of the components of the**
18 **termite soldiers' defense secretion that acts as a**
19 **glue.**

20 Q. What are Kempene-1 and 2?

21 **A. Kempene-1 and 2 are also cyclic**
22 **diterpenoids from a different species of termite**

1 **known as *Nasutitermes kempae*, thus the name Kempene.**

2 Q. And in the first compound, you said it
3 was a tetracyclic --

4 A. **Yes.**

5 Q. -- terpene. And the second one, you
6 didn't say tetra. You said cyclic.

7 A. **Mentally, I'm counting the rings. There**
8 **are four rings, so it's tetracyclic, but there are**
9 **multiple Kempenes, and I can't remember if one of**
10 **them has five rings or not.**

11 Q. So both those references that we've
12 talked about so far in which you're a co-author with
13 Dr. Nakanishi relate to tetracyclic Kempenes?

14 A. **I would say more fairly polycyclic.**

15 Q. And then what is cubugene?

16 A. **Cubugene is another termite defense**
17 **secretion from a very different family of termites**
18 **called *Cubitermes*. Cubugene, if I recall it -- I**
19 **think it has two rings, and it is based on the**
20 **macrocyclic diterpenoid known as cembrene.**

21 Q. And then your fourth publication is
22 titled Chemical Ecology Studies from East Africa.

1 **A. I recognize that title, yes.**

2 Q. And what was the subject matter of that
3 publication?

4 **A. That publication described a number of**
5 **different projects that I and one of my other**
6 **co-authors on that paper, Dr. Kubo, worked on with**
7 **Professor Nakanishi and Professor Meinwald, who were**
8 **our U.S.-based supervisors. And it describes a**
9 **number of the projects that each of us worked on in**
10 **chemical ecology in Nairobi, Kenya.**

11 Q. On your CV, it says from 1974 to 1976
12 that you were a research scientist at something
13 called ICIPE in Nairobi, Kenya. Do you recall that?

14 **A. Yes, that's accurate.**

15 Q. Is that what you were referencing just a
16 moment ago when you were talking about your
17 publications with Dr. Nakanishi?

18 **A. Yes.**

19 Q. Is it fair to say that all of your four
20 publications with Dr. Nakanishi arose from your work
21 in Nairobi, Kenya from 1974 to 1976 with ICIPE?

22 **A. They originated with my work with**

1 **Dr. Nakanishi when I was a post doctoral associate**
2 **under his mentorship.**

3 Q. And they all related to termite natural
4 compounds, is that correct?

5 A. **I believe -- I'm trying to remember if we**
6 **talked in the Science chemical ecology paper about**
7 **any non-termite compounds. And I just don't recall.**

8 Q. Now, in your declaration, you identify
9 some later -- well, I guess before we get to that,
10 just to make things clear. These four publications,
11 they were from 1976 to 1984, correct?

12 A. **That sounds accurate, yes.**

13 Q. Did you have any collaboration with
14 Dr. Nakanishi after your 1984 publication?

15 A. **Any academic collaboration? Not to my**
16 **recollection.**

17 Q. And you identify in your declaration some
18 later papers where individuals in Dr. Nakanishi's
19 lab are publishing on the topic of lipofuscin
20 synthesis. Is that fair?

21 A. **Could you say that again, please?**

22 Q. Your declaration discusses later papers

1 from individuals in the Nakanishi lab that discuss
2 lipofuscin synthesis, A2E?

3 **A. Yes, this occurred after my involvement**
4 **with Dr. Nakanishi.**

5 Q. It was long after your involvement,
6 correct?

7 **A. Some -- yes, decades after.**

8 Q. The team in Dr. Nakanishi's lab that you
9 worked with was not -- other than Dr. Nakanishi, is
10 not the same team that was doing the A2E research
11 decades later, correct?

12 **A. I'm thinking back on some of the names,**
13 **and I don't recall knowing any of those people at**
14 **the time. At my time.**

15 Q. Did you read Dr. Nakanishi's A2E papers
16 when they were published?

17 **A. No.**

18 Q. And you never collaborated with
19 Dr. Nakanishi on 7retinoid synthesis, is that
20 correct?

21 **A. To the best of my recollection, no, I**
22 **have not. I did not.**

1 Q. So I was looking through your
2 publications list, which is extensive. And I was
3 looking for certain terms. I just want to find out
4 if I missed any of those. So the first term I
5 looked for, and there were lots of great research.
6 But one term I did not find is lipofuscin. Do you
7 know what lipofuscin is?

8 A. **As a result of the research on this case,**
9 **I do now.**

10 Q. And you agree that none of your
11 publications are specific to lipofuscin. Is that
12 correct?

13 A. **I would have to look through some of the**
14 **later publications, because as I say in my**
15 **declaration, I did work with some ophthalmology**
16 **groups on reducing -- lowering intraocular pressure,**
17 **and potentially addressing age-related macular**
18 **degeneration much later in my career. And I don't**
19 **remember whether or not I called out lipofuscin in**
20 **one of the articles that I wrote with one or more of**
21 **those scientists.**

22 **(Exhibit No. 2053 was referred to.)**

1 BY MR. MILLS:

2 Q. So feel free to take a look at your CV.
3 You have it in front of you, right?

4 A. Which exhibit is that?

5 Q. It's 2053.

6 A. I'm refreshing my memory from my
7 declaration as well, and the two papers that were
8 involved with ophthalmology, in one way or the other,
9 I don't believe had anything to do with lipofuscin
10 and AMD.

11 Q. I did a search for intraocular pressure,
12 and I came up with a reference 585 that was looking
13 at TRPV4 signals related to intraocular pressure in
14 glaucoma. Does that sound correct?

15 A. Yes, that's the TRPV4 paper, yes.

16 Q. So in fact, I searched also just for the
17 words "eye" and "ocular," and that's the only
18 reference I found. Okay.

19 I looked for visual cycle. I didn't see
20 anything come up that said, "visual cycle." Does
21 that sound right?

22 A. That sounds correct.

1 Q. And I also looked for deuteration and
2 deuterium. I didn't find anything. Does that sound
3 correct?

4 A. **It might not have been in a title.**

5 Q. I did see tritium labeling. Is that
6 correct?

7 A. **Yes.**

8 Q. I looked for the words retinoid, retinol,
9 retinal, and retinyl. I didn't find any of those
10 listed. Does that sound correct?

11 A. **Again, they may -- they would not have**
12 **been in a title.**

13 Q. I looked for NRPE. Do you know what NRPE
14 is?

15 A. **Yes.**

16 Q. I guess just to connect it, can you tell
17 me the long form of NRPE?

18 A. **N-retinylidene-phosphatidylethanolamine.**

19 Q. Thank you. I'm not going to try and do
20 that, because I will butcher it. I'm just going to
21 call it NRPE. So I didn't find NRPE listed. Does
22 that sound correct?

1 **A. That sounds correct.**

2 Q. I also didn't find A2E listed. Does that
3 sound correct?

4 **A. In the publications, you would not have**
5 **found that.**

6 Q. And just to keep the record clear, what
7 is A2E?

8 **A. A2E is one of the fluorophores that is**
9 **isolated from lipofuscin and is the subject of**
10 **several of these Nakanishi and team papers.**

11 Q. I also looked for the word ATR-dimer. I
12 did not find that anywhere. Does that sound
13 correct?

14 **A. That also sounds familiar. Sounds**
15 **correct, yes.**

16 Q. And ATR-dimer is another one of 8those
17 fluorophores, correct?

18 **A. Yes.**

19 Q. What is a GAG? And I'll give you the
20 context of an anti-inflammatory GAG?

21 **A. GAG is an abbreviation for**
22 **glycosaminoglycan. I can spell that for you later.**

1 **Glycosaminoglycan. We call them GAGs.**

2 Q. And what is that?

3 A. **It's a type of polysaccharide**
4 **characterized by having amino sugars and non-amino**
5 **sugars alternating in the polymer backbone.**

6 Q. Is it a retinoid?

7 A. **No.**

8 Q. Is it a terpene?

9 A. **No.**

10 Q. What is a terpene?

11 A. **A terpene -- terpenes include, generally,**
12 **compounds that are referred to as isoprenoids. Now,**
13 **it's terrible to define something with another**
14 **vocabulary word, but isoprenoids are five carbon**
15 **units. Terpenoids are made up of five carbon units.**

16 **So your typical terpenoid is monoterpene,**
17 **which would be two isoprenoids, C10. Sesquiterpene,**
18 **C15. Diterpene, C20. And then it goes up to much**
19 **more complicated things. Carotenoids, which are**
20 **C40.**

21 Q. So I don't know if I have this right, but
22 when I hear terpene, I think of turpentine.

1 **A. Yeah.**

2 Q. So is that correct, and why -- like, why
3 do I have that association?

4 MR. FELDSTEIN: Object to form.

5 THE WITNESS: I don't know what's in your
6 head or how you learned that, but I can understand
7 the sound of the words being similar and some
8 turpentine comes from, say, pine trees, and pine
9 trees have a characteristic smell that's due to
10 terpenes.

11 BY MR. MILLS:

12 Q. So terpenes are also what give the aroma
13 of cannabis, is that correct?

14 **A. Maybe.**

15 Q. What are other common things that we know
16 -- common aromas that we are familiar with that are
17 attributable to terpenes?

18 **A. Limonene.**

19 Q. So that's the compound?

20 **A. That's the compound.**

21 Q. What's the aroma?

22 **A. Lemon. And citronella, a different kind**

1 of lemon smell. The smell of rose is a terpene
2 ether. The smell of lavender is a terpene. If
3 you've ever had Vicks VapoRub, menthol is a terpene.
4 There are a lot of very familiar things in our
5 consumer products that are terpenes.

6 Q. The smell of orange peel?

7 A. That would be another one.

8 Q. Natural rubber. Is that also a terpene?

9 A. Natural rubber, I believe, is a polymeric
10 form of a terpene.

11 Q. Are steroids terpenes?

12 A. Steroids, in fact, are also terpenes.

13 Q. What is lysolipid signaling?

14 A. So let's take a step back. Lipid
15 signaling is how cells communicate with other cells,
16 and internally. Lipids, when I say -- or the art
17 says lipids, we refer to amphiphilic molecules, so a
18 polar head group, and usually two tails of fatty
19 acid chains. And to your point, a 7lysolipid is
20 missing one of those fatty acid tails. So a
21 lysolipid means that it's missing one of the fatty
22 acid tails.

1 Q. So does lysolipid signaling imply that
2 the compounds are retinoids?

3 A. **No.**

4 Q. What is phosphoinositide?

5 A. **Phosphoinositides are a category of**
6 **signaling lipids.**

7 Q. What's characteristic of phosphoinositide
8 signaling lipids?

9 A. **The characteristic feature is the**
10 **inositol ring in the head group of the**
11 **phosphoinositide.**

12 Q. Does phosphoinositide signaling
13 phospholipid imply being a retinoid?

14 A. **No.**

15 Q. And I'm sure you've gathered this. The
16 reason I'm asking about this, I'm just looking at
17 your research interests in your CV, but your
18 research interests are phosphoinositide and
19 lysolipid signaling, therapeutic biomaterials; and
20 anti-inflammatory GAGs, correct?

21 A. **In the current -- the last, most recent**
22 **period, those were the focuses of my research.**

1 Q. I have another question about your CV.
2 So seven lines from the bottom of your professional
3 experience listing on your CV, it says you are
4 currently, and have been since 2014, an adjunct
5 professor of surgery, Division of Otolaryngology.

6 So my question is, what is
7 otolaryngology?

8 A. **ENT. Ear, nose, and throat.**

9 Q. In paragraph 15 of your declaration, you
10 mention that you have a specialty in insect
11 olfaction. That's the last -- on the last line of
12 the portion of paragraph 15 on page 10, is that
13 correct?

14 A. **Yes, specifically purification, cloning,**
15 **expression, and mechanistic studies of polypeptides**
16 **and proteins important in insect olfaction. And it**
17 **continues.**

18 Q. Okay. And then in paragraph 17 of your
19 declaration, you mention that you received in 2001 a
20 Lifetime Research Achievement Award in the
21 chemistry, biology, and biochemistry of insect
22 chemical communication, is that correct?

1 **A. Yes, I see that.**

2 Q. In your declaration, you also mention
3 several publications by a Boehm, B-o-e-h-m. Do you
4 recall that?

5 **A. Yes.**

6 Q. And who is Marcus Boehm?

7 **A. He often pronounces it "boom," which**
8 **would be the German pronunciation, or "bame" is how**
9 **he Anglicizes it. Marcus Boehm was one of my**
10 **students at Stony Brook.**

11 Q. And the publications that you have with
12 him in Stony Brook range in chronology from 1986 to
13 1990. Is that correct?

14 **A. That sounds like his dissertation period,**
15 **yes.**

16 Q. And these were focused on labeling of
17 various compounds, is that correct?

18 **A. Yes, generally speaking.**

19 Q. There is an article on radio iodine
20 labeling.

21 **A. Let me -- let's take me to the particular**
22 **papers, because this was indeed 30 years ago.**

1 Q. Okay, yes. Entry 90.

2 A. **Okay.**

3 Q. On your publication list.

4 A. **Yes.**

5 Q. And in particular, it's radioiodinated
6 juvenile hormone analogs, right?

7 A. **That's what the title says.**

8 Q. When we are talking about juvenile analog
9 hormones, are those human juveniles or what's the
10 source of the hormones?

11 A. **Insect. It's an insect juvenile hormone.**

12 Q. In entry 91, it uses the short form, JH
13 homologs. That refers to juvenile insect hormone
14 analogs?

15 A. **Insect juvenile hormone, or JH homologs,**
16 **yes.**

17 Q. And there is both iodine labeled and
18 tritium labeled, is that correct?

19 A. **Yes, publication 91 includes a number of**
20 **authors. And that overview article summarizes a**
21 **number of different species that we made to follow**
22 **the action of juveniles.**

1 Q. The publication Insects by Chemistry,
2 correct?

3 A. **That's the journal, yes.**

4 Q. So all of the hormones were insect
5 hormones?

6 A. **Those were all insect hormones, yes.**

7 Q. Publication 94, here we are talking about
8 high specific activity hydroprene, correct?

9 A. **Yes.**

10 Q. And what is hydroprene?

11 A. **Hydroprene is an analog of juvenile**
12 **hormone that was commercially synthesized and used**
13 **for -- I don't remember, flea control or something.**

14 Q. So that's also an insect hormone?

15 A. **It's an insect hormone analog. A**
16 **synthetically made one.**

17 Q. Entry 101, here we are discussing
18 methoprene, correct?

19 A. **Yes.**

20 Q. That's also an insect hormone analog?

21 A. **Yes, that's also a juvenile insect**
22 **juvenile hormone analog.**

1 Q. This one is tritium labeled, correct?

2 A. And this one is tritium labeled, yes.

3 Q. And it's a 7di-tritium labeled compound,
4 is that correct?

5 A. Indeed. In making that, we put two
6 tritium atoms on each molecule.

7 Q. Entry 109 relates to fenoxycarb and
8 S-31183. Do you see that?

9 A. Yes.

10 Q. What is fenoxycarb?

11 A. Fenoxycarb and S-31183 are both
12 fenoxyphenyl ether insect growth regulators. And so
13 they interfere with how insect growth occurs. And
14 those, again, are commercial analogs that were
15 developed as products for insect control.

16 Q. And then the last one is entry 120.
17 That's also about insect juvenile hormone receptors,
18 and here it's in larval epidermis, correct?

19 A. Yes.

20 Q. And there you're using photoaffinity
21 labeling correct?

22 A. Yes.

1 Q. Having walked through those publications,
2 does that refresh your recollection that the time
3 period is 1986 through 1990?

4 A. **Yes.**

5 Q. You mentioned in your declaration that
6 Marcus Boehm --

7 A. **Boehm.**

8 Q. -- later had a patent that was considered
9 during the prosecution of the patent at issue in
10 this case, do you recall that?

11 A. **Yes.**

12 Q. Did you have any involvement with that
13 later patent?

14 A. **None whatsoever.**

15 Q. It's unrelated to the work that you were
16 doing with Marcus Boehm?

17 MR. FELDSTEIN: Object to form,
18 foundation.

19 THE WITNESS: It was work that I
20 understand Marcus did after he left my lab.

21 BY MR. MILLS:

22 Q. Did you ever speak with Marcus about that

1 later work?

2 A. No, not to my recollection.

3 Q. Is it correct that you never collaborated
4 with Marcus Boehm on retinoids?

5 A. Yes, that would be correct.

6 Q. You are not a lawyer, correct?

7 A. I am not a lawyer.

8 Q. You're not testifying as a legal expert?

9 A. I am not testifying as a legal expert.

10 I'm a technical expert.

11 Q. You're not an ophthalmologist, correct?

12 A. I am not an ophthalmologist, no.

13 Q. You're not an optometrist?

14 A. I don't measure eye vision either.

15 Q. You're not a medical doctor?

16 A. I am not an MD.

17 Q. You're not testifying as a medical expert
18 in this case, are you?

19 A. No, I'm not.

20 Q. Please take a look at paragraph 27 of
21 your declaration. The very first line, you say,
22 "based on my experience, having worked in the

1 field." Do you see that?

2 **A. Yes.**

3 Q. When you said, "based on my experience,
4 having worked in the field," what field are you
5 referring to?

6 **A. The field of -- let's see. Let me look
7 at the context of this. I'm referring to paragraph
8 26, which would be the field of chemistry,
9 biochemistry, pharmaceutical science, medicine, or
10 related field.**

11 Q. And under that definition of the field,
12 you consider yourself to be a person of ordinary
13 skill in the art in that field as of September 2007,
14 correct?

15 **A. I consider myself to be at least a person
16 of ordinary skill in the art as of September 2007.**

17 Q. And you reviewed Dr. Guengerich's
18 declaration, right?

19 **A. Yes, I did.**

20 Q. Did you review his CV?

21 **A. I looked at his CV, and I read his
22 description of his background.**

1 Q. Are you disputing in this case that
2 Dr. Guengerich is also at least a person of ordinary
3 skill in the art, as we've just discussed?

4 MR. FELDSTEIN: Object to form,
5 foundation, beyond the scope.

6 THE WITNESS: I haven't formed an opinion
7 on whether or not he is a person of ordinary skill.

8 BY MR. MILLS:

9 Q. So you haven't offered any opinion in
10 this case that Dr. Guengerich is not a person of
11 ordinary skill in the art, correct?

12 A. **Not to my knowledge, in my declaration.**

13 Q. You don't have any published work
14 discussing the work of slowing lipofuscin
15 accumulation, correct?

16 A. **Not that I recall.**

17 Q. You don't have any published work
18 addressing the treatment or amelioration of macular
19 degeneration, correct?

20 A. **Can you say that one again, please?**

21 Q. You don't have any work addressing the
22 treatment or amelioration of macular degeneration,

1 correct?

2 **A. Do I have any work?**

3 **Q. Sorry. Let me withdraw that question and**
4 **start over.**

5 **You don't have any published work**
6 **addressing the treatment or amelioration of macular**
7 **degeneration?**

8 **A. I do not have any published work**
9 **addressing the treatment of macular degeneration.**

10 **Q. You don't have any published work**
11 **addressing the treatment or amelioration of**
12 **Stargardt's syndrome?**

13 **A. That's correct. I don't have any**
14 **published work addressing the treatment or**
15 **amelioration of Stargardt disease.**

16 **Q. What is Stargardt's disease?**

17 **A. To the best of my understanding, it's a**
18 **genetic disorder with what is referred to in a**
19 **number of different acronyms, but ABCR minus minus,**
20 **which is the deletion of a specific gene that codes**
21 **for a protein that we'll talk about later, I'm sure.**

22 **Q. And at a high level, what is macular**

1 degeneration, as you understand it?

2 A. It's the loss of ability to -- of the
3 macula to receive signals from light. And
4 therefore, reduction of the ability to perceive
5 light at the center of the retina. That's the best
6 I can do.

7 Q. And now a more particular question. But
8 the same question about age-related macular
9 degeneration.

10 A. My understanding of age-related macular
11 degeneration is that as we age, a number of things
12 happen. Vascular bed changes. The amount of
13 pigments, these so-called lipofuscin and other
14 related deposits form.

15 And just generally, aging, the macula
16 starts to degenerate. I'm not an ophthalmologist.
17 I don't know the pathophysiology, but, yes, there
18 are a number of general phenomena that occur as we
19 age that result, and can result in macular
20 degeneration.

21 Q. You agree that age-related macular
22 degeneration is a disease that was associated before

1 September 2007 with the accumulation of lipofuscin?

2 **A. That got a little convoluted, so can you**
3 **ask that again, or have the reporter restate the**
4 **question, so that I can follow the whole thing?**

5 **(The question was read back.)**

6 THE WITNESS: Yes, that's what I read in
7 the background materials.

8 BY MR. MILLS:

9 Q. And you also agree that Stargardt's
10 syndrome is also a disease that was associated
11 before September 2007 with the accumulation of
12 lipofuscin?

13 **A. Yes. From the background citations that**
14 **I've read, that seems to be the case.**

15 Q. You read some papers that said that
16 Stargardt's can be characterized as an accelerated
17 form of age-related macular degeneration, is that
18 right?

19 MR. FELDSTEIN: Object to form.

20 THE WITNESS: No, that's not what I read.

21 BY MR. MILLS:

22 Q. Going back to your published work, you

1 don't have any published work that discusses the
2 slowing or limiting of lipofuscin in the retinal
3 pigment epithelium, correct?

4 **A. Not to my recollection. I don't believe**
5 **that I published on slowing of lipofuscin.**

6 Q. You also don't have any published work on
7 the field of retinal degeneration, correct?

8 **A. I don't know that for a fact. The paper**
9 **on intraocular pressure and TRVB4 may have made**
10 **references to retinal degeneration, so we would have**
11 **to go back and read that paper to answer the**
12 **question accurately.**

13 Q. That paper was from 2016, correct?

14 **A. I believe that's correct, yes.**

15 Q. In reviewing Dr. Guengerich's
16 declaration, and at least taking a look at his CV,
17 did you come to an understanding that Dr. Guengerich
18 has been involved in the synthesis of retinoids?

19 **A. Did I come to the understanding that he**
20 **had been? No, I did not come to that understanding.**

21 Q. So you didn't know that Dr. Guengerich
22 has published on the biosynthesis of retinoids?

1 MR. FELDSTEIN: Object to form and
2 foundation.

3 THE WITNESS: I might correct myself that
4 I may have seen one paper from Dr. Guengerich. I
5 can't remember what paper it was. It was a
6 testosterone paper, and there may have been a
7 retinoid. I just don't remember.

8 BY MR. MILLS:

9 Q. So you've preempted my next question,
10 which I was also going to ask, when you signed your
11 declaration, were you aware that Dr. Guengerich has
12 published on the biosynthesis of steroids?

13 MR. FELDSTEIN: Object to form and
14 foundation.

15 THE WITNESS: That would not be the way I
16 would characterize it.

17 BY MR. MILLS:

18 Q. So that's not something you were aware of
19 when you signed your declaration?

20 MR. FELDSTEIN: Object to form, misstates
21 testimony.

22 THE WITNESS: That's not what I said.

1 Could you ask your question again?

2 BY MR. MILLS:

3 Q. When you signed your declaration, were
4 you aware that Dr. Guengerich has published on the
5 biosynthesis of steroids?

6 MR. FELDSTEIN: Object to form and
7 foundation.

8 THE WITNESS: I would not characterize
9 his work as the biosynthesis of steroids.

10 BY MR. MILLS:

11 Q. Were you aware that Dr. Guengerich has
12 published on the subject of steroid catalysis?

13 MR. FELDSTEIN: Object to form and
14 foundation.

15 THE WITNESS: I don't know what the term
16 steroid catalysis means. And if you showed me a
17 paper, I could answer your question.

18 BY MR. MILLS:

19 Q. Were you aware that Dr. Guengerich has
20 published on steroid oxidation?

21 MR. FELDSTEIN: Object to form and
22 foundation.

1 THE WITNESS: I haven't reviewed all of
2 his publications, and I may or -- I may have seen
3 that in a title, but I don't -- it wasn't a paper
4 that I reviewed, so I can't answer the question.

5 BY MR. MILLS:

6 Q. Were you aware that Dr. Guengerich has
7 published on steroid metabolism?

8 MR. FELDSTEIN: Object to form and
9 foundation.

10 THE WITNESS: The paper that I recall, I
11 can say yes to that, because it was metabolism of a
12 steroid.

13 BY MR. MILLS:

14 Q. Were you aware that Dr. Guengerich has
15 published papers on the body's use of P450 to lead
16 to novel biological sterols?

17 MR. FELDSTEIN: Object to form and
18 foundation.

19 THE WITNESS: I'm not aware of any of
20 those, no.

21 BY MR. MILLS:

22 Q. What is a sterol?

1 A. What is a sterol? It's often used
2 interchangeably with the word steroid, and they are
3 the triterpenes that our body uses, such as
4 cholesterol, to make hormones in our own bodies.

5 Q. What is P450?

6 A. My understanding of P450 is -- the full
7 name is cytochrome P450, which is an enzyme that is
8 involved in degradation of xenobiotics, foreign
9 compounds, as well as natural processes in the body.

10 Q. When you signed your declaration, were
11 you aware that Dr. Guengerich had published on the
12 subject of deuteration?

13 MR. FELDSTEIN: Object to form and
14 foundation.

15 THE WITNESS: I believe that I read some
16 of his articles in which deuterium labeled
17 compounds, including steroids, were mentioned.

18 BY MR. MILLS:

19 Q. And I asked about retinoids and you
20 answered about steroids, so I'll just ask the
21 question again. Are you aware that Dr. Guengerich
22 has published specifically on deuterated retinoids?

1 MR. FELDSTEIN: Object to form and
2 foundation.

3 THE WITNESS: I recall looking at some of
4 his publications to see if he had published on
5 retinoids, and I have a recollection that I saw one,
6 at least one, but I don't recall at this time.

7 BY MR. MILLS:

8 Q. What's squalene?

9 A. **Squalene is a triterpene, which means it**
10 **has 30 carbons. And squalene is the precursor to**
11 **steroids.**

12 Q. Squalene synthesis is an example of
13 biosynthesis of the natural terpene product,
14 correct?

15 MR. FELDSTEIN: Object to form and
16 foundation, beyond the scope.

17 THE WITNESS: Could you say that again,
18 because it didn't sound right?

19 BY MR. MILLS:

20 Q. Let me start with this question.
21 Squalene is involved in the biosynthesis of a
22 natural terpene product.

1 MR. FELDSTEIN: Object to form,
2 foundation, beyond the scope.

3 THE WITNESS: Squalene is involved in the
4 synthesis of a natural terpene compound. Is that
5 the question? Yes.

6 BY MR. MILLS:

7 Q. Desaturated retinoid is still a retinoid,
8 correct?

9 A. **Yes, I think so.**

10 Q. Desaturated retinoid is still a terpene?

11 A. **May or may not be, depending on what**
12 **happened to it.**

13 Q. A desaturated -- or let me withdraw that
14 question and start over.

15 Biosynthesis of a desaturated retinoid is
16 still biosynthesis of a retinoid, correct?

17 MR. FELDSTEIN: Object to form.

18 THE WITNESS: Not necessarily.

19 BY MR. MILLS:

20 Q. So you're saying it's possible that if
21 you desaturate a retinoid, it can stop being a
22 retinoid?

1 **A. There are some retinoids which are not**
2 **terpenes.**

3 Q. Okay. So I think there was some
4 confusion there. So my -- before I had asked a
5 question about terpenes. Could you be a retinoid
6 without being a terpene. My question just now is
7 whether biosynthesis of a desaturated retinoid is
8 still biosynthesis of a retinoid?

9 MR. FELDSTEIN: Object to form.

10 THE WITNESS: The answer is, it depends.

11 BY MR. MILLS:

12 Q. So you're saying it's possible that a
13 desaturated retinoid can stop being a retinoid by
14 virtue of the desaturation?

15 **A. I didn't say that. That's not my**
16 **testimony.**

17 Q. Do you want to explain what you mean?

18 **A. It might not have been a terpene to start**
19 **with.**

20 Q. I'm sorry, I think there is still some
21 confusion. In this question, I'm not asking about
22 terpenes. I'm just asking about retinoids. So my

1 question is, if it's a retinoid to start with and
2 you desaturated the retinoid, is it still the
3 retinoid? Do you understand the question?

4 **A. The answer to that is, most likely, yes.**

5 Q. All right. And now that I think we've
6 cleared up the confusion, I just want to have a
7 clean question and answer. So biosynthesis of a
8 desaturated retinoid is still biosynthesis of a
9 retinoid, correct?

10 MR. FELDSTEIN: Object to form,
11 incomplete hypothetical.

12 THE WITNESS: No.

13 BY MR. MILLS:

14 Q. Okay. So I thought that we had worked
15 this out. What's the problem now?

16 MR. FELDSTEIN: Object to form.

17 THE WITNESS: Biosynthesis implies the
18 retinoid is a natural product.

19 BY MR. MILLS:

20 Q. And what is it that makes something -- a
21 retinoid a natural product?

22 **A. It's biosynthesized.**

1 Q. And how are you defining biosynthesized?

2 A. **Made metabolically by the -- by an**
3 **organism and/or a tissue of an organism.**

4 Q. And I'm not trying to be difficult, but
5 now we have the word metabolically. So what does
6 that mean, when you say that it's made metabolically
7 by an organism or a tissue of an organism?

8 A. **That the organism is capable of making**
9 **that compound.**

10 Q. Okay.

11 A. **From what it has naturally occurring.**

12 Q. So I appreciate that clarification. I'm
13 not sure if it really makes a difference to my
14 question, because my question is kind of parallel.
15 I'm saying if it's biosynthesis of an unsaturated --
16 let me start the question again, because I was --
17 dehydrogenated and unsaturated. So let me just
18 withdraw the question and start over.

19 So I had biosynthesis on both sides of
20 the question. My question is biosynthesis of an
21 unsaturated retinoid is still biosynthesis of a
22 retinoid, correct?

1 MR. FELDSTEIN: Object to form,
2 incomplete hypothetical, beyond the scope.

3 THE WITNESS: Not necessarily.

4 BY MR. MILLS:

5 Q. Okay. Why not?

6 MR. FELDSTEIN: Object to form.

7 THE WITNESS: It may not be
8 biosynthesized to start with.

9 BY MR. MILLS:

10 Q. So that's, I guess, a different
11 hypothetical. The hypothetical I'm giving you, it
12 is biosynthesis. It's biosynthesis of a retinoid
13 that happens to be unsaturated. Does the fact that
14 it's unsaturated mean that it's not biosynthesis of
15 a retinoid?

16 MR. FELDSTEIN: Object to form,
17 incomplete hypothetical.

18 THE WITNESS: It depends.

19 BY MR. MILLS:

20 Q. Why does it depend?

21 MR. FELDSTEIN: Object to form.

22 THE WITNESS: Whether or not the process

1 was a biosynthetic process.

2 BY MR. MILLS:

3 Q. So that assumption is built into the
4 question. And so the question is, is a biosynthetic
5 process that makes an unsaturated retinoid, is the
6 product of that process is still a biosynthetic
7 retinoid, correct?

8 MR. FELDSTEIN: Object to form.

9 THE WITNESS: If I accept the assumptions
10 in that long hypothetical, my answer is still, it
11 depends.

12 BY MR. MILLS:

13 Q. You agree that enzymes -- let me withdraw
14 the question and start over.

15 You agree that the body can use enzymes
16 for biosynthetic processes, correct?

17 A. Yes.

18 Q. Now, earlier, we were talking about the
19 definition of a POSA in paragraph 26 of your
20 declaration. Do you recall that?

21 A. Yes.

22 Q. And you testified that you are a POSA

1 under that definition, that you have not offered any
2 opinion that Dr. Guengerich is not a POSA under that
3 definition. Am I correct so far?

4 **A. I believe that's what our conversation**
5 **was.**

6 Q. That same set of questions regarding the
7 definition of a POSA under paragraph 28.

8 **A. Okay.**

9 Q. So if you can read that paragraph to
10 yourself and let me know when you're ready.

11 **A. Okay.**

12 Q. Are you offering an opinion in this case
13 that Dr. Guengerich is not a POSA under the
14 definition that you identify in paragraph 28 of your
15 declaration?

16 MR. FELDSTEIN: Object to form, beyond
17 the scope.

18 THE WITNESS: I don't see where I offer
19 any such opinion.

20 BY MR. MILLS:

21 Q. To the best of your knowledge, you don't
22 offer any such opinion, correct?

1 **A. I'm looking at paragraphs 27 and 28 and**
2 **29. I don't see such an opinion.**

3 Q. I'd like to go into a new line of
4 questioning. Do you want to take a break now?

5 MR. FELDSTEIN: We can keep going.

6 THE WITNESS: I'm happy to keep going.

7 BY MR. MILLS:

8 Q. Do you have the patent at issue in front
9 of you?

10 **A. I believe that's Exhibit 1001.**

11 Q. Yes.

12 **A. In that case, the answer is yes.**

13 Q. Did you review the Exhibit 1001 patent in
14 preparation for your deposition today?

15 **A. Yes, I did.**

16 Q. Did you review the patent prior to
17 signing your declaration?

18 **A. Yes, I did.**

19 Q. Did you read the entirety of the patent?

20 **A. Yes, I did.**

21 Q. If you could just take a look at the
22 headings of examples 1 through 6 to refamiliarize

1 yourself with the general subject matter of the
2 examples.

3 **A. You're asking me to review the titles of**
4 **the examples, which are -- which start on column 18,**
5 **is that correct?**

6 Q. I don't have the column number in front
7 of me right now, but starting with example 1 and
8 continuing through example 6.

9 **A. Would you like me to --**

10 Q. Just to yourself.

11 **A. Okay. I've reviewed the titles of the**
12 **six examples.**

13 Q. If you need to look at something more to
14 answer the questions I have, we can do that.

15 **A. Okay.**

16 Q. But I think the titles might be enough.
17 My first question is examples 1 through 2 of the
18 patent are in vitro experiments, correct?

19 **A. Example 1 is slowing the formation of A2E**
20 **in vitro. Example 2 is slowing the formation of A2R**
21 **dimer in vitro, yes.**

22 Q. Examples 3 through 5 are all in mice,

1 correct?

2 **A. Yes, I see the word mice in each one of**
3 **the titles.**

4 Q. There is -- there is no humans in --
5 being administered the treatment in examples 3
6 through 5, correct?

7 **A. No, there are no humans involved, other**
8 **than the experimentalists.**

9 Q. And the same is true of examples 1 and 2.
10 There is no humans being administered the treatment?

11 **A. That is correct. 1 and 2 are simply in**
12 **vitro.**

13 MR. FELDSTEIN: Doctor, you need to give
14 him a second to ask his question. Give me a second
15 to object, too.

16 BY MR. MILLS:

17 Q. So in example 6, there it's rats instead
18 of mice, correct?

19 **A. Yes, I see rats in example 6.**

20 Q. But there is no humans in example 6,
21 correct?

22 **A. That's correct.**

1 Q. Now, this question may seem silly. I
2 don't mean it to be comical, but the rats in example
3 6, these are not smokers. The patent doesn't
4 indicate that those are rats that smoke tobacco, is
5 that correct?

6 MR. FELDSTEIN: Object to form.

7 THE WITNESS: I can't tell because they
8 identify these as CD IGS rats. And I don't know if
9 those have been or have not been exposed to tobacco
10 smoke.

11 BY MR. MILLS:

12 Q. Based on your review of the patent that
13 you've done before you signed your declaration, and
14 in preparation for your deposition today, you don't
15 have any reason to believe that the rats in example
16 6 were smoker rats, correct?

17 MR. FELDSTEIN: Object to form.

18 THE WITNESS: I don't have any reason to
19 believe that they were smoker rats.

20 BY MR. MILLS:

21 Q. And the same question about the mice in
22 examples 3 through 5.

1 MR. FELDSTEIN: Object to form.

2 THE WITNESS: I don't see any evidence
3 that they were exposed to cigarette smoke.

4 MR. FELDSTEIN: Are you going to ask
5 about example 1 and 2 also?

6 BY MR. MILLS:

7 Q. We can do that. Do you see any evidence
8 that the in vitro experiments are the experiments
9 directed to evaluating the effect of the drug in
10 smokers?

11 A. I don't see any evidence of that in the
12 in vitro experiments either.

13 Q. You can look there if you want, but I'm
14 not going to dwell on it. But in your declaration
15 in paragraph 48, you're talking about the claim
16 construction. And you're talking about -- you say
17 it's necessary to identify the patient in need. Do
18 you recall that testimony?

19 A. Paragraph 48?

20 Q. In paragraph 48.

21 A. Yes, I recall.

22 Q. So go ahead and look at the claims of the

1 patent now. And you've done maybe 18 patent case
2 depositions, so you understand that the claims are
3 what define the property right for the patent,
4 correct?

5 **A. Yes, that's what I understand.**

6 Q. The claims are what we are evaluating for
7 purposes of that, correct?

8 **A. That's what I understand, generally, yes.**

9 Q. So my question is about this concept of
10 its necessary to identify the patient in need. So
11 all of the claims of this patent require
12 administration to a patient in need. To the retina
13 of -- let me look at the language and start my
14 question again.

15 All of the claims of the challenged
16 patent require administering an effective amount of
17 a pharmaceutical composition to a patient in need,
18 correct?

19 **A. Are we talking about all of the claims or**
20 **1 and 28 and 29? I'm not sure what you're referring**
21 **to.**

22 Q. Let's start with claim 1.

1 **A. Okay. I've refreshed my memory of claim**
2 **1.**

3 **Q. Claim 1 requires administration to a**
4 **patient in need thereof, right?**

5 **A. Specifically, claim 1 is a method of**
6 **retarding the accumulation of a lipofuscin pigment**
7 **in a retina comprising of administering an effective**
8 **amount of a pharmaceutical composition to a patient**
9 **in need thereof. And that goes on to define the**
10 **composition.**

11 **Q. You understand that claim 1 is an**
12 **independent claim?**

13 **A. That's my understanding, yes.**

14 **Q. And you understand that all of the claims**
15 **that depend on claim 1 also require that**
16 **administration that's recited in claim 1, correct?**

17 **A. I understand that dependent claims depend**
18 **on the claim 1, yes.**

19 **Q. And when you say they depend on it, it**
20 **means that they also have that same requirement?**

21 **A. That's my understanding, yes.**

22 **Q. All right.**

1 **A. I'm not a patent attorney.**

2 Q. Yes.

3 **A. That's my understanding.**

4 Q. You mentioned claim 28?

5 **A. Yes.**

6 Q. So claim 28 also requires administration
7 to a patient in need thereof, correct?

8 MR. FELDSTEIN: Objection to form.

9 THE WITNESS: Yes. And for claim 28,
10 it's a method of treating a macular degeneration
11 comprising administering an effective amount of a
12 substituted C20-D1 through 3 retinoid to a patient
13 in need thereof.

14 BY MR. MILLS:

15 Q. And claim 29 also has that claim language
16 of administering to a patient in need thereof?

17 MR. FELDSTEIN: Object to form.

18 BY MR. MILLS:

19 Q. Is that right?

20 **A. Specifically, it's administering an**
21 **effective amount of a pharmaceutical composition to**
22 **a patient in need thereof.**

1 Q. Okay. So I have a question about the
2 patient.

3 A. **Okay.**

4 Q. So in this patent, in the examples that
5 we discussed earlier -- I'll break it down into a
6 specific question. But in examples 3 through 5, the
7 patients are mice, is that correct?

8 A. **I wouldn't call them patients. They are**
9 **experimental animals.**

10 Q. The same is true for example 6. You
11 wouldn't call the rats patients?

12 A. **That's the example showing the clinical**
13 **result.**

14 Q. So in your opinion, there are no examples
15 in the challenged patent where they are actually
16 giving the treatment to a patient, is that correct?

17 A. **At the time of this -- that's correct.**
18 **There are no patients being treated in this patent**
19 **application as written.**

20 Q. When you were preparing your opinions in
21 this case, did you evaluate whether the claims
22 require that the patient be a human patient?

1 **A. Yes. And in reviewing the claims, I**
2 **don't see any further subcategorization of patient.**

3 Q. You don't see anything in the claims that
4 tells you that the patient has to be a human,
5 correct?

6 **A. Not to my knowledge. I wasn't able to**
7 **see that.**

8 Q. Please take a look at column 8 of the
9 patent, starting around line 58.

10 **A. Let me go back to that question. You're**
11 **talking about the claims.**

12 Q. My question before was about the claims.

13 **A. Okay. The claims. I want to be sure**
14 **about that.**

15 Q. Yes.

16 **A. Because, obviously, they talk about human**
17 **patients elsewhere in the specifications. Column 8?**

18 Q. Yes. So line 58 through 59. It says, in
19 the present invention, a patient may be a mammal,
20 preferably a human. Do you see that?

21 **A. Yes, I do see that.**

22 Q. So when it says, the patient may be a

1 mammal, in the examples, the mice, those were
2 mammals, correct?

3 **A. Yes.**

4 **Q. And the rats, those were mammals?**

5 **A. Rodents are, in fact, mammals.**

6 **Q. So you agree that the way the patent**
7 **defines patient, that includes rodents, mice, and**
8 **rats?**

9 **MR. FELDSTEIN: Object to form,**
10 **foundation, misstates the reference, beyond the**
11 **scope.**

12 **THE WITNESS: In the specifications, they**
13 **do talk about the patient being a mammal, preferably**
14 **a human in the embodiment.**

15 **BY MR. MILLS:**

16 **Q. Going back to the claims, so just like**
17 **the claims don't specify that the patient has to be**
18 **a human, it doesn't say anything about they have to**
19 **be smokers versus nonsmokers, right?**

20 **A. I didn't see those terms in the claims.**

21 **The term smoker or nonsmoker, I didn't see.**

22 **Q. As best as you can tell, if the patient**

1 in need thereof happens to be a nonsmoker, they
2 still qualify as a patient in need thereof, correct?

3 MR. FELDSTEIN: Object to form, beyond
4 the scope.

5 THE WITNESS: To the best of my
6 understanding.

7 BY MR. MILLS:

8 Q. I want to ask you, in these claims, while
9 it's still fresh in your mind, there is a lot of
10 notations that say C, little 20, and then they have
11 a dash, and then it says D, little 1 through 3. Do
12 you see that?

13 A. Yes.

14 Q. So I just want to ask about when it has
15 that D1 through 3, that means it can be
16 monodeuterated, bideuterated, or trideuterated, is
17 that correct?

18 A. That's my understanding of C-D1 through
19 3.

20 Q. Okay. And then when it says just C
21 little 20 dash D little 3, that requires it to be
22 trideuterated, correct?

1 **A. The C20 carbon, yes.**

2 Q. Okay. In these independent claims that
3 we looked at, none of those independent claims
4 require that the administration be an oral
5 administration, correct?

6 **A. 1, 28, and 29?**

7 Q. Yes, those are the independent claims.

8 MR. FELDSTEIN: Objection, beyond the
9 scope.

10 THE WITNESS: The independent claims 1 --
11 can you state your question again, please?

12 BY MR. MILLS:

13 Q. None of the independent claims require
14 oral administration, correct?

15 MR. FELDSTEIN: Same objections.

16 THE WITNESS: They don't specify, one way
17 or the other.

18 BY MR. MILLS:

19 Q. And, in fact, you can take your time,
20 none of the claims specify oral administration,
21 correct?

22 MR. FELDSTEIN: Same objections.

1 THE WITNESS: I've reviewed a few
2 sections of the specifications, as well as the
3 claims. And I think I can answer your question now.

4 BY MR. MILLS:

5 Q. None of the claims specify oral
6 administration, correct?

7 A. **No, that's not correct.**

8 Q. Which claim do you think specifies oral
9 administration?

10 A. **Claim 3. The method according to claim**
11 **1, whereas the pharmaceutical composition is**
12 **suitable for use as a neutral composition.**

13 Q. Other than claim 3, none of the claims
14 specify oral administration?

15 MR. FELDSTEIN: Objection, form,
16 foundation, beyond the scope.

17 THE WITNESS: I'm not a patent attorney,
18 but I read the claims in the context of the
19 specifications. And the specifications say that the
20 administration step includes replacing the component
21 of a patient's diet that includes a retinoid or
22 vitamin A of the component that contains the

1 substituted C20 retinoid.

2 To me, I read that to mean oral
3 administration, especially in the case of a
4 nutraceutical, which is not administered any other
5 way except orally.

6 BY MR. MILLS:

7 Q. So my question is, that's a requirement
8 of claim 3, but other than claim 3, none of the
9 claims require oral administration?

10 MR. FELDSTEIN: Object to form,
11 foundation, beyond the scope.

12 THE WITNESS: I don't see the words in
13 the claims.

14 BY MR. MILLS:

15 Q. You don't see any words in any of the
16 claims other than claim 3 indicating a requirement
17 for oral administration, correct?

18 MR. FELDSTEIN: Same objections.

19 THE WITNESS: Ask the question again?

20 BY MR. MILLS:

21 Q. So you've told me that -- I asked you if
22 any of the claims require oral administration. And

1 you pointed to claim 3, and said that a
2 nutraceutical implies taking it as part of the diet,
3 that it's replacing what the people eat in their
4 diet, correct?

5 MR. FELDSTEIN: Object to form, misstates
6 testimony.

7 THE WITNESS: I'd have to hear back the
8 testimony to make sure that that was -- what you
9 just said was accurate.

10 BY MR. MILLS:

11 Q. So I guess you can just tell me. So what
12 is your basis for concluding from the word
13 nutraceutical that that requires oral
14 administration?

15 A. It's a -- the way they are regulated, to
16 my understanding, is that they are not regulated as
17 drugs, so you can't inject them, for example.
18 Nutraceutical means eating it as part of your diet.
19 That's what the words mean.

20 BY MR. MILLS:

21 Q. So claim 3, nutraceutical, that's the one
22 claim in which you see claim language that you

1 interpret to require oral administration, correct?

2 MR. FELDSTEIN: Object to form,
3 foundation, beyond the scope.

4 THE WITNESS: That's one that I see that
5 suggests oral administration.

6 BY MR. MILLS:

7 Q. And you don't see any other claims that
8 suggest that requirement, correct?

9 MR. FELDSTEIN: Objection, form,
10 foundation, beyond the scope.

11 THE WITNESS: Ask your question again,
12 please?

13 BY MR. MILLS:

14 Q. So you've identified claim 3. Sitting
15 here today, you are not identifying any other claim
16 that you believe requires oral administration,
17 correct?

18 MR. FELDSTEIN: Object to form,
19 foundation, beyond the scope, misstates testimony.

20 THE WITNESS: I don't see the words oral
21 administration in the claims.

22 BY MR. MILLS:

1 Q. Please take a look at claim 27.

2 A. I can see claim 27.

3 Q. You agree that claim 27 does not require
4 oral administration, correct?

5 MR. FELDSTEIN: Object to the form,
6 foundation, beyond the scope.

7 THE WITNESS: I can read claim 27 as the
8 method according to claim 1, wherein the
9 pharmaceutical composition is administered directly
10 to the eye.

11 BY MR. MILLS:

12 Q. What is your understanding of what it
13 means for the pharmaceutical to be administered
14 directly to the eye?

15 MR. FELDSTEIN: Same objections.

16 THE WITNESS: I understand it would be
17 some kind of eye drop or some kind of other
18 administration directly to the eye. I don't know.

19 BY MR. MILLS:

20 Q. So administration directly to the eye is
21 different than oral administration, correct?

22 A. My understanding is that those are

1 **different routes of administration.**

2 Q. Please take a look at in the patent,
3 column 8. Sorry, column 9, on -- beginning on line
4 8. Sorry, it's -- actually, it's column. I'm going
5 to restart my question because that was awful.
6 Okay.

7 Column 10, beginning on line 8, the
8 patent discusses administration directly to the eye.
9 Do you see that?

10 A. **I see a sentence starting, "for example,**
11 **the substrate replacement may take place in the eye**
12 **of the patient." Is that the one you're talking**
13 **about.**

14 Q. Yes, that's the sentence.

15 A. **Okay.**

16 Q. Do you see where it says the substrate
17 may be administered directly to the eye?

18 A. **Yes.**

19 Q. It gives three examples of administration
20 directly to the eye. Do you see that?

21 A. **Yes, I see that.**

22 Q. Can you tell me what those three methods

1 of administration directly to the eye are in the
2 patent?

3 **A. Reading specifically, it says, "the**
4 **substrate may be administered directly to the eye**
5 **via eye drops, ointment, or injection."**

6 Q. So when I was asking you first about
7 claim 27, you identified eye drops as one means to
8 administer directly to the eye. Do you recall that?

9 **A. I do.**

10 Q. Do you agree that the patent also
11 explains that that direct administration to the eye
12 can include administration of an ointment or an
13 injection directly to the eye, correct?

14 MR. FELDSTEIN: Object to form,
15 foundation, beyond the scope.

16 THE WITNESS: Those are the words I'm
17 reading in the patent.

18 BY MR. MILLS:

19 Q. Do you want to break now?

20 **A. Let's take a break.**

21 **(Recess.)**

22 BY MR. MILLS:

1 Q. My next series of questions are about the
2 figures in your declaration.

3 A. **Okay. Can I put the patent away for now?**

4 Q. Yes. So let's start on page 137 of your
5 declaration. Page number, not paragraph number.

6 A. **Okay.**

7 Q. So I think this is the last figure that
8 you have for your declaration. It's figure 14.

9 A. **That sounds right.**

10 Q. So my first question is, you have figures
11 1 through 14 that are -- that figure numbering is
12 your figure numbering for your declaration, correct?

13 A. **Yes, those figure numberings are my**
14 **figure numbering.**

15 Q. Maybe hold your place on page 137, and
16 then let's go to page 27. That's what you labeled
17 figure 2 in your declaration, correct?

18 A. **Yes, I see that.**

19 Q. Okay. So for your declaration, figure 2
20 on page 27, in the caption after the word figure 2,
21 you have citation to an exhibit. Do you see that?

22 A. **I see that.**

1 Q. And figure 14 on page 137, there is a
2 caption with a figure number and a title, but there
3 is no source cited, correct?

4 A. **That's correct.**

5 Q. Okay. So am I correct in understanding
6 that when you put a source, that means that source
7 is -- you basically copy that figure content from
8 that source?

9 A. **That's my modus operandi, yes. I'm**
10 **indicating what the source of the figure is that I**
11 **used.**

12 Q. Okay. And where you didn't indicate a
13 source in the figure caption, this is something that
14 you generated, rather than copied from the record.
15 Is that fair?

16 A. **Yes, I drew it myself.**

17 Q. For figure 14, you drew it yourself, is
18 that correct?

19 A. **Yes.**

20 Q. Okay. And then figure 12 on page 127,
21 you drew that yourself?

22 A. **Yes.**

1 Q. Figure 10 on page 90, you drew that
2 yourself.

3 A. **90? Yes.**

4 Q. Figure 4 on page 30, you drew that
5 yourself.

6 A. **Figure 4, page 30, yes.**

7 Q. And then figure 1 on page 25. You drew
8 that yourself, too, correct?

9 A. **I believe there is a footnote there, and
10 the citation is given in footnote 2, where that
11 figure came from.**

12 Q. Okay. All right. Let's take a look at
13 figure 4 on page 30?

14 A. **Figure 4 on page 30. Okay.**

15 Q. And here, this is, as you say in the
16 caption of figure 4, that this is you drawing
17 all-trans-retinal?

18 A. **This is the structure of
19 all-trans-retinal, yes.**

20 Q. And when we talk about all-trans, what
21 does all-trans mean?

22 A. **Okay. It refers to the double bonds in**

1 the -- in the linear chain that comes off of the
2 cyclohexene ring. And so, specifically, when we say
3 all-trans, that refers to the 7-8 double bond being
4 trans, the 9-10 double bond being trans, the 1-12
5 double bond being trans, and the 13-14 double bond
6 being trans.

7 Q. And when you use the word trans, what
8 that means is if I'm focusing on a particular double
9 bond, the carbon on the left side is coming off that
10 double bond, going in one direction, and the carbon
11 in the -- from the other side of the double bond is
12 coming off in the opposite direction.

13 A. Yes. I mean, it's an old terminology.
14 Currently, we use the term E and Z. E for opposite
15 sides and Z for same side of the double bond. But
16 in this nomenclature, before the kind of the
17 nomenclature was changed, these are called cis. And
18 cis and trans, to make sure nobody gets lost.

19 Q. Please take a look at figure 6 on page
20 38.

21 A. Figure 6. Okay.

22 Q. Okay. So in figure 6, on page 38, and

1 I'll look at the NRPE. Do you see the structure of
2 NRPE depicted in figure 6 of page 38 of your
3 declaration?

4 **A. Yes, the top right corner of figure 6 of**
5 **the declaration.**

6 Q. And that's the compound that earlier you
7 told us what NRPE stands for. Do you remember that?

8 **A. Yes.**

9 Q. And in NRPE, the structure around each of
10 those double bonds in the elongated carbon chain are
11 trans, correct?

12 **A. The double bonds on the chain that comes**
13 **off the cyclohexene ring are trans.**

14 Q. Okay. Are there any cis bonds in that
15 molecule?

16 **A. The imine is depicted as -- well, it's**
17 **hard to say, because it's only got three things**
18 **coming off of it. So it's -- it's shown in one**
19 **configuration, but all of the double bonds in the**
20 **chain are carbon-carbon double bonds or trans.**

21 Q. When you say imine, that's the carbon
22 with the double bond to the nitrogen?

1 **A. To the nitrogen, yes.**

2 Q. And when you say it's depicted in one
3 configuration, what configuration is it depicted in?

4 **A. It happens to be shown with the double**
5 **bond to the hydrogen pointing up, but it could just**
6 **as equally be shown with the double bond to the**
7 **right pointing the same direction, and it would**
8 **still be the same molecule.**

9 Q. So the nitrogen is connected by a double
10 bond to carbon 15. Am I correct so far?

11 **A. Let me just make sure I'm getting it**
12 **right. Carbon 15 is the aldehyde carbon, yes.**

13 Q. And so in NRPE, the nitrogen has a double
14 bond to carbon 15, correct?

15 **A. Yes.**

16 Q. And as depicted in figure 6 of your
17 declaration, that imine is pointed up?

18 **A. That's how Fishkin 2005 drew that.**

19 Q. And then -- but you said it just as
20 easily could have been depicted down?

21 **A. Yes, it's the same molecule.**

22 Q. So that that imine is freely rotating

1 through space?

2 A. That would not be accurate.

3 Q. How would you describe it?

4 A. The molecule, NRPE, exists in a place, in
5 a biological context. And depending on the
6 biological context would determine what the minimum
7 energy conformation of that molecule would be in
8 that context.

9 Q. So -- and I may not be getting this
10 exactly right, but I think you're telling me that
11 there is a probability for a given molecule of that
12 type that's going to be up or down. And depending
13 on the context of it, it might be more likely to be
14 up or more likely to be down?

15 MR. FELDSTEIN: Object to form.

16 THE WITNESS: That's not what I said. I
17 think the accurate way to say it is that the
18 rotation around the sigma bond, the single bond that
19 is the single bond between C14 and C15 can occur.

20 BY MR. MILLS:

21 Q. And the compound may be different, but in
22 path B, after the 1-4 conjugate addition, now it

1 looks like that imine is no longer pointing up. Do
2 I have that correct?

3 **A. Almost.**

4 Q. Go ahead and fix it for me.

5 **A. It's no longer an imine, it's an iminium.**

6 Q. So in the -- after the 14 conjugate
7 addition in path B of figure 6 of your declaration,
8 the imine has become an iminium and it's no longer
9 pointing up, correct?

10 **A. It has been drawn differently by Fishkin**
11 **2005.**

12 Q. Okay. Let's take a look at figure 8 of
13 your declaration on page 50.

14 **A. Okay.**

15 Q. So in the caption, you say, "ROS lipid
16 membrane." Do you see those words?

17 **A. Yes.**

18 Q. Do you agree that ROS stands for rod
19 outer segment?

20 **A. That's my use of the term ROS in that**
21 **caption.**

22 Q. Do you have an understanding that the

1 outer segment is a portion of the photoreceptor
2 cell?

3 **A. That it's a portion of the photoreceptor**
4 **apparatus.**

5 Q. You understand that in addition to rods,
6 another type of photoreceptor cell is a cone?

7 **A. Yes, I understand that there are rods and**
8 **cones.**

9 Q. Cones also have an outer segment,
10 correct?

11 **A. From what I understand, yes.**

12 Q. So here, in particular, we are focused on
13 the outer segment of a photoreceptor cell, and in
14 particular, it happens to be a rod, is that correct?

15 **A. In this example, that's the focus.**

16 Q. Okay. Now, there is -- I think there is
17 two lipid membranes depicted in this figure. Do I
18 have that correct?

19 **A. Yes. Roughly speaking, yes.**

20 Q. One of them is denominated as PM?

21 **A. Yes.**

22 Q. And one of them is denominated as DM. Do

1 you see that?

2 **A. I see those.**

3 Q. The DM stands for the disc membrane, is
4 that correct?

5 **A. That's what I understand.**

6 Q. And the PM stands for the photoreceptor
7 membrane, is that correct?

8 **A. Either that or plasma membrane. PM is
9 commonly used for -- can be used for either.**

10 Q. Okay. So in any case, all of the
11 material on the right side of that PM, you agree
12 that's within the photoreceptor cell, correct?

13 **A. The model that Weng 1999 is depicting.
14 This is meant to be a graphical illustration of his
15 or their concept of what this -- how it's -- how
16 it's the symbol in a gross sense. Not the specific
17 details.**

18 Q. What I'm trying to get at, and I don't
19 mean to make it difficult, but we are going to talk
20 about the rim protein.

21 **A. Okay.**

22 Q. Which is the RmP in this figure, correct?

1 **A. Yes.**

2 Q. The rim protein is going to take
3 something from within that circle to outside that
4 circle, correct?

5 **A. It's going to -- more or less, yes.**

6 Q. Okay. When it gets outside the circle,
7 it's still within the photoreceptor cell, correct?

8 **A. That's my understanding.**

9 Q. And in fact, it's still within the outer
10 segment of the photoreceptor cell. Do you agree?

11 **A. Yes.**

12 Q. Okay. So that inside that circle, that's
13 the 7luminal side of the disc membrane. Is that
14 fair?

15 **A. I want to be sure I know what you mean by**
16 **the circle, because there is a -- there is a**
17 **circular shape, but it's got things coming out of**
18 **the side.**

19 Q. Yes. So I mean, that is what I'm
20 referring to. We can use different language if you
21 want to.

22 **A. Okay. So let's call it the circle.**

1 Q. So within the circle, that's the luminal
2 space for the disc membrane, correct?

3 A. That is representing some of the luminal
4 space. The rest of the luminal space is represented
5 by the white space between the two gray bars
6 extending off to the right.

7 Q. And then when we get outside the circle
8 in the bar that accompanies the circle, now we are
9 in the cytosolic space of the photoreceptor outer
10 segment, correct?

11 A. I believe that's what Weng was trying to
12 depict.

13 Q. And the circle with the bar on it, that's
14 also sometimes called the interdisc space, is that
15 correct?

16 A. I don't know if I'd call it that, or Weng
17 calls it that, but it sounds more or less -- I don't
18 know. I just don't know.

19 Q. Okay. So the job of the rim protein is
20 to get retinal out from the luminal side of the disc
21 membrane to the cytosolic side of the disc membrane,
22 correct?

1 MR. FELDSTEIN: Object to form, beyond
2 the scope, foundation.

3 BY MR. MILLS:

4 Q. And if it's helpful, you might take a
5 look at paragraph 89 of your declaration, footnote
6 15.

7 A. That was the other paragraph I was
8 looking for. Can you ask your question again? I
9 wasn't prepared to answer it, because it didn't
10 sound right.

11 Q. So my question is about the role of the
12 rim protein?

13 A. Okay.

14 Q. It might help if I ask a predicate
15 question.

16 A. Okay.

17 Q. Earlier in the deposition, you brought up
18 an ABCA4 gene. Do you recall that?

19 A. I did.

20 Q. And you understand that the ABCA4 gene
21 encodes for the rim protein, correct?

22 A. That's what I understand, yes.

1 Q. And you brought up the ABCA4 gene, you
2 told me a little bit about its role. So I'm just
3 trying to get you to connect the dots for me about
4 the rim protein.

5 A. **Okay.**

6 Q. So my question is that the role of the
7 rim protein is to take retinal out from the luminal
8 side of the disc membrane, put it on the cytosolic
9 side of the disc membrane?

10 MR. FELDSTEIN: Object to form,
11 foundation.

12 THE WITNESS: I'll read what I wrote.
13 "The rim protein, RmP, was believed to act as a
14 flippase, i.e. an energy requiring enzyme that uses
15 ATP to facilitate the reduction of ATR by physically
16 flipping the NRPE from the interface of the ROS disc
17 membrane to the outer leaflet of the disc membrane."

18 And then I continue, "in the absence of
19 RmP, NRPE and ATR accumulate in the disc interior,
20 rather than being translocated to the outer leaflet,
21 thus providing the 'excess' ATR believed to be the
22 substrate for A2E formation in Mata's proposed

1 pathway."

2 So that's -- that's the answer to your
3 question, is that -- that's the full answer to your
4 question.

5 Q. So is it different than what I asked?

6 MR. FELDSTEIN: Object to form.

7 THE WITNESS: I was answering from what I
8 wrote in the declaration to make sure I was accurate
9 in my testimony.

10 BY MR. MILLS:

11 Q. And I just want to understand. Is there
12 anything that you think is different about your
13 answer as compared to my question?

14 MR. FELDSTEIN: Object to form.

15 THE WITNESS: We can see. But I heard
16 something different, and that's why I decided I
17 would read from the testimony that I produced.

18 BY MR. MILLS:

19 Q. Okay. And what is it that you heard that
20 you thought was different?

21 A. I don't recall.

22 Q. I'm just trying to make sure we are

1 communicating. But if there is something that you
2 don't understand or think is -- we're
3 miscommunicating, I just want to know is all.

4 Okay. So here in paragraph 89, it refers
5 to a disc interior. Do you see that?

6 **A. Yes.**

7 **Q. And it also uses the term outer leaflet?**

8 **A. I see those words.**

9 **Q. So if we correlate that to figure 8, so**
10 **the disk interior is the space within the disc**
11 **membrane within the circle with the bar on it, is**
12 **that correct?**

13 **A. Yes, I think the way we described it is**
14 **the luminal space, the white space, if you will,**
15 **between the two gray bars.**

16 **Q. And the outer leaflet is a portion that's**
17 **outside the circle and the bar, correct?**

18 **A. It's not the way I would have said it.**
19 **There is an inner leaflet and an outer leaflet. So**
20 **for example, if you look at the gray bar that sticks**
21 **off to the right, you see some yellow balls with**
22 **black tails. And the yellow balls are on the**

1 **inside, the luminal side.**

2 **And you see some yellow balls with black**
3 **tails and the yellow balls are on the outside of the**
4 **gray bar. And so the ones on the inner, that's the**
5 **inner leaflet. The ones on the outer, that's the**
6 **outer leaflet. But the lipid bilayer has two**
7 **leaflets. You don't see that in the gray bar.**

8 Q. So what does it mean in paragraph 89
9 where you say, "rather than being translocated to
10 the outer leaflet"?

11 A. **I'm trying to find where you're reading**
12 **from.**

13 Q. Paragraph 89, five lines down. It's the
14 sentence you read just a moment ago. "Rather than
15 being translocated to the outer leaflet."

16 A. **I'm sorry, counsel, I don't see any word**
17 **"rather."**

18 Q. So it's a sentence that starts, "in the
19 absence of RmP." Do you see that sentence?

20 A. **"In the absence of RmP, NRPE and ATR**
21 **accumulate in the disc interior, rather than being**
22 **translocated to the outer leaflet." Yes.**

1 Q. So what is that telling us with respect
2 to figure 8?

3 A. Relative to figure 8, the NRPE that's on
4 the inner leaflet in figure 8, and it's specifically
5 labeled N-RPE. And it has a red ball and a black
6 tail stuck to a yellow ball on the inner leaflet.

7 That would not be able to be taken out in
8 the absence of RmP, and flipped out as it were.
9 Flipped out to the outer leaflet. So that protein,
10 RmP, is functioning as what is called -- it's called
11 a flippase. It's moving it from the inner leaflet
12 to the outer leaflet.

13 Q. And when you said taken out, taken out of
14 what?

15 A. If the RmP protein is not present because
16 of a genetic defect, for example, then that
17 function, the flippase function doesn't occur. And
18 in that case, the NRPE ends up stuck on the inside
19 of the inner leaflet.

20 Q. And in figure 8, that's the inside of the
21 circle with the bar on it?

22 A. Yes.

1 Q. Okay. Now, you've been talking about the
2 rim protein flipping NRPE. Does the rim protein
3 flip ATR?

4 A. **Not to my understanding. It's a**
5 **flippase -- flippase is flipped phospholipids and**
6 **phospholipid atoms.**

7 Q. And what's the difference between ATR and
8 NRPE?

9 A. **ATR is all-trans-retinal. That's in**
10 **figure 8. That's the little red ball with the long**
11 **squiggly black tail.**

12 Q. So all-trans-retinal doesn't have the --
13 doesn't have the phospholipid atoms of NRPE,
14 correct?

15 A. **That's approximately correct, yes.**

16 Q. And I just want to make sure we have the
17 sequence correct. So essentially, there is an
18 all-trans-retinal molecule that's in the disc
19 interior. And in order for the body to move that
20 all-trans-retinal molecule from the disc interior
21 and on to the cytosolic side, the ATR molecule is
22 converted into NRPE, is that correct?

1 MR. FELDSTEIN: Object to form.

2 THE WITNESS: It's not an accurate
3 overall depiction of the process.

4 BY MR. MILLS:

5 Q. Go ahead and tell me what's wrong with
6 it.

7 MR. FELDSTEIN: Object to form.

8 THE WITNESS: If we refer back to figure
9 8, just to make one or two observations. The
10 retinal is shown in a number of places in this
11 figure besides the so-called NRPE.

12 One place is metarhodopsin II, labeled
13 MII. And that's where it's covalently bound to a
14 rhodopsin protein. Another one is opsin AT Ral, and
15 I don't know what the depiction there is meant to
16 be, but it's a retinal molecule which is associated
17 with a different protein in the disc membrane.

18 And as I said before, there is the one
19 retinal that isn't attached to anything that's just
20 hanging out there on the white space. So this
21 graphic depiction shows a couple of places that ATR
22 might be.

1 BY MR. MILLS:

2 Q. Okay. So my first question is focused on
3 just the correlation of NRPE to all-trans-retinal.

4 A. Okay.

5 Q. So when an all-trans-retinal molecule is
6 conjugated with phospholipid, then it becomes NRPE,
7 correct?

8 A. Yes.

9 Q. And at that point, because it has
10 phospholipid on it, the rim protein is able to
11 translocate it from the disc interior to the disc
12 exterior, correct?

13 MR. FELDSTEIN: Object to form.

14 THE WITNESS: That's the belief of the
15 authors and the belief of the community as to what
16 the function and mechanism might be.

17 BY MR. MILLS:

18 Q. Okay. Now, in this figure 8 in your
19 declaration, after the translocation by the rim
20 protein, now I see the letters A-T-R-O-L. What does
21 that stand for?

22 A. In this figure, they are distinguishing

1 **ATR, which is the all-trans-retinal, from the**
2 **all-trans-retinol, which is the reduced form.**

3 Q. Okay. So when the NRPE was formed in the
4 disc interior, it was the all-trans-retinal form,
5 correct?

6 A. The all-trans-retinal, the aldehyde is
7 required to react with the phosphatidylethanolamine
8 to get NRPE.

9 Q. Does the rim protein itself reduce the
10 all-trans-retinal to all-trans-retinol?

11 A. No.

12 Q. So that reduction happens outside the
13 disc interior, is that correct?

14 A. Outside of the interior of the disc
15 membrane compartment, yes.

16 Q. And what is it that accomplishes that
17 reduction?

18 A. Well, in their graphic depiction, there
19 are two little curvy arrows and there are at least
20 two different enzymes, but not limited to two
21 enzymes.

22 Q. And what are those enzymes, if you know?

1 A. I'm trying to remember.

2 Q. If it helps, look on page 27 of your
3 declaration.

4 A. Thank you. And in addition to the
5 enzymes, there are binder proteins. So it's --
6 there is a lot going on. 27. Wait, page 27. Yes,
7 the primary enzyme involved there is the -- I guess
8 is the ATR-DH, which is the all-trans-retinal
9 dehydrogenase.

10 Q. So if we go back to figure 8 of your
11 declaration, it's ATR-DH enzyme that converts
12 all-trans-retinal to all-trans-retinol, it's on the
13 outside of the inner disc space, correct?

14 A. That's what they are illustrating there,
15 yes.

16 Q. Okay. So if the body wants to use a rim
17 protein to move the all-trans-retinal out of the
18 inner disc space across that membrane, it needs to
19 convert it into NRPE, correct?

20 MR. FELDSTEIN: Object to form,
21 foundation, beyond the scope.

22 THE WITNESS: The characterization -- the

1 body doesn't have -- if the body wants to do
2 something, the -- a function of rim protein is
3 believed to be this flippase activity that binds --
4 recognizes, binds to, and changes the orientation of
5 the NRPE from the inner membrane to the outer disc
6 membrane.

7 BY MR. MILLS:

8 Q. Without the formation of the NRPE, the
9 flippase wouldn't be able to translocate the
10 all-trans-retinal process, right?

11 MR. FELDSTEIN: Object to form,
12 foundation, scope.

13 THE WITNESS: I am unaware of all of the
14 research on NRPE translocation. But in this
15 simplified depiction, that appears to be the case,
16 but I do not know all of the experiments that were
17 done to verify or to test the structural specificity
18 of the flippase, what its substrate specificities
19 were, or any of the details of how it does the
20 flipping. That's all -- at the time of this, I
21 believe, was all poorly understood.

22 BY MR. MILLS:

1 Q. Earlier, you talked about Stargardt
2 patients lacking ABCR -- or ABCRA4 gene, correct?

3 A. **Yes, they have a reduced or missing ABRC**
4 **gene. And as a result, more often than not, the**
5 **gene product, which is the rim protein.**

6 Q. Do you have an understanding as to
7 whether age-related macular degeneration similarly
8 results from an absence or reduction of rim protein?

9 MR. FELDSTEIN: Object to form,
10 foundation, scope.

11 THE WITNESS: That's very much beyond the
12 scope of the -- of my declaration.

13 BY MR. MILLS:

14 Q. So it's not a question that you've
15 addressed?

16 A. **The role of rim protein in other macular**
17 **degeneration type pathologies, I don't believe**
18 **that's in my declaration.**

19 Q. So functionally, when the flippase, the
20 rim protein, it grabs NRPE, moves it on to the other
21 side -- it translocates it to the other side of the
22 membrane. Then what happens?

1 MR. FELDSTEIN: Objection, form.

2 THE WITNESS: Well, I'm not comfortable
3 with the term "grab."

4 BY MR. MILLS:

5 Q. You can use your own word.

6 A. There is some binding event which has
7 selectivity for certain structures, and certain
8 affinities for these structures. And after the
9 binding, energy is required to allow that protein
10 NRPE complex to be translating. That was not very
11 well understood at the time for a POSA in 1999 or
12 2007. That was not well understood how that all was
13 taking place.

14 And like I said, this is a graphical
15 depiction. This is not a molecular detail of what's
16 going on.

17 Q. I'm not trying to get so far into the
18 molecular details, but after the translocation of
19 the NRPE outside the disc membrane, does the NRPE
20 stay attached there to the membrane forever?

21 MR. FELDSTEIN: Object to form,
22 foundation, beyond the scope.

1 THE WITNESS: My impression from this
2 graphic and my general understanding of the reaction
3 between NR -- let me take that back.

4 The reaction between
5 phosphatidylethanolamine, PE, and ATR, that reaction
6 is the reversible reaction. It's reversible inside
7 the disc membrane. It's reversible outside the disc
8 membrane environment.

9 So the role of this rim protein, the way
10 I look at this graphic depiction, and the way I
11 understand what was known in the art as of 1999 or
12 2007 is that the NRPE is translocated from the inner
13 disc leaflet to the outer disc leaflet, and it
14 dissociates.

15 It's a non -- it's a reversible reaction.
16 And after the ATR comes off, then it can be reduced.
17 It may or may not in all other transport proteins.
18 Other stuff can be going on that was not known at
19 the time. It's just not enough information.

20 But at some point, that then -- that
21 released all-trans-retinal, ATR, it then binds to
22 and is reduced to retinol, all-trans-retinol by the

1 retinal dehydrogenase.

2 BY MR. MILLS:

3 Q. Thank you. So that's reflected in your
4 footnote 15 in paragraph 89, right? Because you're
5 quoting the Rozanowska reference, and it says that
6 there is formation of a reversible Schiff base
7 linkage phosphatidylethanolamine8, PE, that forms
8 NRPE. Am I right so far?

9 A. **I'm looking at reference -- footnote 15**
10 **on page 44.**

11 Q. Yes. So footnote 15 of your declaration
12 on page 44 conveys that there is -- first, there is
13 this conjugation of the all-trans-retinal with
14 phosphatidylethanolamine that forms NRPE, correct?

15 MR. FELDSTEIN: Object to form.

16 THE WITNESS: And that's what I'm
17 reading. I say that removal refers to -- I'll just
18 read what I wrote. It's easier.

19 The rate of -- and this is quoting from
20 Rozanowska, 2005: "The rate of accumulation of ATR
21 in the inner leaflet of the OS disc membrane must
22 exceed the rate of removal of ATR, where removal

1 refers to its direct enzymatic reduction to
2 all-trans-retinol or formation of a reversible
3 Schiff base linkage with phosphatidylethanolamine
4 (PE) and N-retinylidene phosphatidylethanolamine
5 (NRPE), and its transport across to the outer
6 leaflet of the OS disc membrane, where subsequent
7 reduction to all-trans-retinol can occur."

8 So that's what I wrote as a quote from
9 Rozanowska.

10 Q. So I had a question about the two words,
11 "its transport." Do you see those words?

12 A. Yes.

13 Q. So its transport across the outer leaflet
14 of the outer segment disc membrane. Do you see
15 those words?

16 A. I see those words.

17 Q. That's what we've been discussing in
18 figure 8 with the rim protein, correct?

19 MR. FELDSTEIN: Object to form.

20 THE WITNESS: I believe so.

21 BY MR. MILLS:

22 Q. Okay. "Its." Its transport. What is it

1 that's being transported? Is that the NRPE?

2 **A. I believe the authors -- I don't know**
3 **what was in their head, but to me, this reads as**
4 **though the authors are talking about the transport**
5 **of NRPE from one side of the disc membrane leaflet,**
6 **inner leaflet to the outer, the other side, the**
7 **outer disc membrane leaflet. That's the way it**
8 **reads to me.**

9 Q. Thank you. Now I'm going to ask you
10 about removal. You say removal refers -- so is it
11 correct that they are saying removal refers, and it
12 gives two possibilities. One is direct enzymatic
13 reduction to all-trans-retinol, correct?

14 **A. That's one of the possibilities they say.**

15 Q. And then the second possibility is that
16 the all-trans-retinal is converted to NRPE,
17 transported across the membrane, and then subsequent
18 to being transported, it is converted to
19 all-trans-retinol, correct?

20 **A. I believe -- yes, that's what the quote**
21 **is saying, more or less.**

22 Q. Okay. I want to ask about the rate of

1 accumulation of ATR in the inner leaflet of outer
2 segment disc membrane. Do you see that phrase?

3 **A. The rate of accumulation of ATR in the**
4 **inner leaflet of the OS disc membrane, yes.**

5 Q. And OS refers to outer segment?

6 **A. Outer segment, yes.**

7 Q. Under the photoreceptor cell?

8 **A. That, I believe we are referring to**
9 **figure 8, yes.**

10 Q. Okay. So when it says the inner leaflet
11 of the outer segment disc membrane, if we are
12 translating that into figure 8, it's saying that the
13 accumulation of all-trans-retinal within the circle
14 and the bar, on that side of the membrane, correct?

15 **A. Yes.**

16 Q. Now I have a question about the word
17 "must."

18 **A. Okay.**

19 Q. So when it says, "it must exceed," so the
20 accumulation of all-trans-retinol -- retinal within
21 that circle and bar must exceed the rate at which
22 it's removed. Do you see that sentence?

1 **A. "The rate of accumulation of ATR in the**
2 **inner leaflet of the OS disc membrane must exceed**
3 **the rate of removal of ATR." That's what I see.**

4 Q. So what does it mean by "must"?

5 MR. FELDSTEIN: Object to form.

6 THE WITNESS: Well, as I said previously,
7 this is a quote from Rozanowska. And you would have
8 to ask the authors of the paper what they meant by
9 "must."

10 BY MR. MILLS:

11 Q. So you cited that quote. When you cited
12 it, did you have an understanding as to what they
13 meant by "must"?

14 A. I think they were simply -- to me, if it
15 accumulates, they are saying the rate of
16 accumulation must exceed the rate of removal.
17 Otherwise, if it's removed, it can't accumulate.
18 That's kind of a tautology.

19 Q. Okay, so -- and this footnote 15, you
20 know, that comes from your paragraph 89, right?

21 MR. FELDSTEIN: Object to the form.

22 THE WITNESS: Footnote 15 is a footnote

1 to the phrase where I'm referring to Rozanowska 2005
2 and their characterization of the rim protein that
3 they believed -- or they characterized by saying
4 they believed it acted as a flippase, and we talked
5 about this.

6 BY MR. MILLS:

7 Q. Right. So you say there in paragraph 89,
8 "in the absence of rim protein, NRPE and ATR
9 accumulate in the disc interior, rather than being
10 translocated to the outer leaflet, thus providing
11 the excess ATR believed to be the substrate for A2E
12 formation in Mata's proposed pathway," correct?

13 A. I see what I wrote. I see that after I
14 cited footnote 15, the next sentence of my
15 declaration is that "in the absence of rim protein,
16 NRPE and ATR accumulate in the disc interior, rather
17 than being translocated to the outer leaflet, thus
18 providing the 'excess' ATR believed to be the
19 substrate for A2E formation in Mata's proposed
20 pathway." That's what I said.

21 Q. So I just want to make sure that I
22 understand these two concepts in paragraph 89,

1 footnote 15. Earlier, you called it a tautology.
2 But basically, what you're saying here is that Mata
3 was teaching that excess ATR in that -- inside the
4 circle and bar portion, when you have an imbalance
5 of that, you have too much because the amount being
6 made in there is happening faster than it's being
7 pulled out, that's what leads to this formation of
8 A2E?

9 MR. FELDSTEIN: Object to form, misstates
10 the document and testimony.

11 THE WITNESS: Actually, all that quote
12 says is that if -- to accumulate, it has to
13 accumulate. That's what it says. That's how I read
14 what Rozanowska said.

15 BY MR. MILLS:

16 Q. I mean, to be fair, it's saying a little
17 bit more than that. It's -- it's saying it
18 accumulates in the inner disc space. And I mean,
19 the problem is if it were outside the membrane, then
20 it's going to get reduced, right? So it's
21 accumulating in the inner disc space, because it
22 needs to move outside that membrane, so that it can

1 get reduced and become retinol, right?

2 MR. FELDSTEIN: Object to form.

3 THE WITNESS: That's not my
4 characterization, nor Rozanowska's. I'm reading the
5 words here. It doesn't say what you just said.

6 BY MR. MILLS:

7 Q. Let me ask you this. Well, in footnote
8 15, it says, you know, there could be direct
9 enzymatic reduction to all-trans-retinol, right?
10 Removal could refer to direct enzymatic reduction to
11 all-trans-retinol, right?

12 A. I don't see the word "could."

13 Q. So it says, "removal refers to direct
14 enzymatic reduction to all-trans-retinol," correct?

15 A. **"Or formation of a reversible Schiff base
16 linkage with phosphatidylethanolamine and its
17 transport to the outer leaflet."**

18 Q. So if the all-trans-retinal in the disc
19 space were being directly enzymatically reduced to
20 all-trans-retinol at a sufficient rate, it would no
21 longer be -- the all-trans-retinol would no longer
22 be accumulating in that space, right?

1 MR. FELDSTEIN: Object to form, beyond
2 the scope, incomplete hypothetical.

3 THE WITNESS: I have to hear that again,
4 because I heard things that were wrong.

5 BY MR. MILLS:

6 Q. So I'm not -- I may be asking a bad
7 question, but I'm not trying to ask a complicated
8 question.

9 It seems to me that this paragraph in
10 your footnote tells us very clearly that Mata
11 teaches that A2E formation happens when you have too
12 much all-trans-retinal inside the disc space, the
13 disc interior. Do I have that part correct?

14 MR. FELDSTEIN: Object to form.

15 THE WITNESS: That's way
16 overcharacterizing what I wrote. I can read what I
17 wrote.

18 BY MR. MILLS:

19 Q. Well, let's focus on the location.
20 What's the location of the excess ATR believed to be
21 the substrate for A2E formation in Mata's proposed
22 pathway?

1 MR. FELDSTEIN: Object to form.

2 THE WITNESS: I don't think I have enough
3 information looking at the Rozanowska paper or the
4 Mata paper. Or the citation, the limited citation
5 to the Mata pathway. I'm not sure I can answer that
6 question. Maybe you could ask it a different way.

7 BY MR. MILLS:

8 Q. So in the sentence, you say, "in the
9 absence of rim protein, NRPE and ATR accumulate in
10 the disc interior." Do you see that?

11 A. Yes.

12 Q. So they accumulate in the disc interior,
13 thus providing the excess ATR believed to be the
14 substrate for A2E formation in Mata's proposed
15 pathway, correct?

16 A. Believed to be the substrate for the A2E
17 formation. Yes, that's what I heard.

18 Q. So the location we are discussing in this
19 sentence is the disc interior, correct?

20 A. That's what we are discussing in that
21 sentence, yes.

22 Q. You agree that all-trans-retinal is not

1 itself a substrate for the rim protein?

2 MR. FELDSTEIN: Object to form,
3 foundation.

4 THE WITNESS: I don't believe I've seen
5 any characterization of the substrate specificity
6 for the rim protein that would include
7 all-trans-retinal.

8 BY MR. MILLS:

9 Q. The same question for all-trans-retinol?

10 MR. FELDSTEIN: Same objection. Object
11 to form, foundation.

12 THE WITNESS: I haven't seen all of the
13 substrate specificity data for the rim protein, so I
14 don't know, one way or the other.

15 BY MR. MILLS:

16 Q. Sitting here right now, you can't point
17 to any prior art literature indicating that the rim
18 protein operates on all-trans-retinol as a
19 substrate, correct?

20 MR. FELDSTEIN: Object to form,
21 foundation, scope.

22 THE WITNESS: I haven't seen that in any

1 of the references that I recall reviewing the
2 details of.

3 BY MR. MILLS:

4 Q. And the same question with respect to
5 all-trans-retinal that has not been converted into
6 NRPE?

7 MR. FELDSTEIN: Object to form,
8 foundation, scope.

9 THE WITNESS: And the same answer.

10 BY MR. MILLS:

11 Q. Please take a look at figure 2 of your
12 declaration on page 27.

13 A. **Page 27.**

14 Q. Yes. So in this figure, there is a
15 depiction of the basic steps of the visual cycle, is
16 that correct?

17 A. **That's correct.**

18 Q. There is also a depiction of a side
19 reaction or byproduct reaction, is that correct?

20 A. **That's the purpose of this, yes.**

21 Q. This -- the component of the visual cycle
22 that is a substrate to that side reaction is

1 all-trans-retinal, correct?

2 **A. That's what I have -- that's what Kim**
3 **2004 depicted, and which I have reproduced from his**
4 **article.**

5 Q. And the -- in this particular case, there
6 are two downstream products of this side reaction.
7 One of those is ATR-dimer, correct?

8 MR. FELDSTEIN: Object to form, misstates
9 the document.

10 THE WITNESS: I see that on the right
11 side of figure 2. All-trans-retinal has a curved
12 arrow in front of it with PE in front of the curved
13 arrow. And that curved arrow takes you to A2PE.
14 And another kind of a little branched arrow goes
15 down to ATR-dimer. That's what I see in this very
16 oversimplified depiction.

17 BY MR. MILLS:

18 Q. As a chemist, you understand that the
19 arrow is indicating that ATR-dimer is a product of
20 this side reaction of all-trans-retinal, correct?

21 **A. It depends on what the authors wrote**
22 **about their figure. And the figure by itself,**

1 without a legend or a text surrounding it, may or
2 may not tell you the whole story of what the authors
3 were thinking or what they -- how they want this
4 interpreted.

5 Q. So I mean, so you put this figure in your
6 declaration, right?

7 A. I did.

8 Q. So you chose that and put it here on this
9 page in your declaration, correct?

10 A. Yes.

11 Q. Are you telling me that you think you
12 left out context to interpret the figure in your
13 declaration?

14 MR. FELDSTEIN: Object to form, misstates
15 testimony.

16 THE WITNESS: No, I'll state exactly what
17 I wrote. As shown below in figure 2, just referring
18 to that figure 2, these products -- referring back
19 to paragraph -- my paragraph 55, these products,
20 referring to fluorescent pigments such as A2E and
21 ATR-dimer, were believed to be produced -- were
22 believed to be produced as a byproduct of the visual

1 cycle from excess all-trans-retinal.

2 And that is the purpose of figure 2, to
3 show the fact or the proposal by Kim and co-workers
4 that this byproduct pathway -- how that byproduct
5 pathway interacts with, impinges on, comes off from
6 the visual cycle, as is generally understood for
7 vision.

8 BY MR. MILLS:

9 Q. Thank you. And I think you have answered
10 my question, which is about the language you use
11 where you say, "these products." "These products"
12 refers to A2E and ATR-dimer, correct?

13 MR. FELDSTEIN: Object to form,
14 misstates.

15 THE WITNESS: Yes. Almost. What I said
16 is that when I say these products, I'm referring
17 backwards to all of paragraph 55 -- parts of
18 paragraph 55, where I say -- I talk about lipofuscin
19 accumulation and comprises fluorescent pigments,
20 such as A2E and ATR-dimer.

21 And then I go on to say, "the buildup of
22 these pigments was associated with macular

1 degenerative diseases, including Stargardt's disease
2 and age-related macular degeneration, AMD."

3 And then in the next paragraph, which we
4 were just referring to, 56, "as shown below in
5 figure 2, these products," the antecedent to that
6 was the pigments A2E and ATR that build up during
7 the disease process.

8 BY MR. MILLS:

9 Q. Thank you. Okay. So now that we've
10 identified the products, I want to make sure that
11 we've identified the starting reactant. So in this
12 diagram, the starting reactant that I see that is
13 part of the visual cycle is all-trans-retinal,
14 correct?

15 A. **That's the connection between the visual**
16 **cycle and the byproduct pathway.**

17 Q. Okay. So my question now is going to be
18 about all-trans-retinol.

19 A. **Okay.**

20 Q. Any of the documents that you looked at
21 in this case, have any of them provided a teaching
22 prior to September 2007 that all-trans-retinol is a

1 compound of the visual cycle that becomes A2E or
2 ATR-dimer through a direct byproduct reaction?

3 MR. FELDSTEIN: Object to form.

4 BY MR. MILLS:

5 Q. I think my question maybe is a little
6 sloppy, but what I'm getting at is, I get
7 all-trans-retinol can become all-trans-retinal, and
8 then it can go down the byproduct option. But if we
9 are just all-trans-retinol, at that point, we've
10 reached at least as far as the literature told us at
11 the time, a safety point.

12 Then the retinal is no longer going to go
13 down that byproduct pathway, because it's a retinol
14 instead of a retinal.

15 MR. FELDSTEIN: Object to form. Twice.

16 THE WITNESS: Retinol does not have the
17 chemical functionality to form A2E unless it's
18 transformed into A2 -- unless it's transformed into
19 retinal.

20 BY MR. MILLS:

21 Q. Thank you. Let's turn to paragraph 103
22 of your declaration.

1 **A. Paragraph 103.**

2 Q. Let me know when you've had a chance to
3 read paragraph 103, as well as footnote 22.

4 **A. Okay. Okay. I've reviewed that**
5 **paragraph and the footnote.**

6 Q. Okay. So my first question is about the
7 word "ROS," the acronym "ROS" in paragraph 103.

8 **A. Yes.**

9 Q. So that's the word on which you've added
10 the footnote 22, correct?

11 **A. Yes.**

12 Q. Okay. So my first question is right
13 there, where you wrote, ROS, that's the same thing
14 as the ROS in figure 8 that we've been talking about
15 today, correct?

16 **A. The rod outer segment.**

17 Q. And then I have a question about footnote
18 22. So here you say, "by September 2007, it was
19 known that the initial reaction between ATR and PE
20 and the bimolecular condensation reaction took place
21 as described in the preceding section of V.B.2.b.3."
22 Do you see that?

1 **A. Yes.**

2 **Q. So my first question is, when it says the**
3 **initial reaction between ATR and PE, is that the**
4 **conjugation of all-trans-retinal with**
5 **phosphatidylethanolamine that creates NRPE that we**
6 **were discussing today?**

7 **A. Yes.**

8 **Q. And then the bimolecular condensation**
9 **reaction. What does that refer to?**

10 **A. Which are you referring to, the footnote**
11 **for paragraph 104, or what are you referring to with**
12 **that question?**

13 **Q. In footnote 22.**

14 **A. Footnote 22. Well, I'm going to read the**
15 **context of 22 -- footnote 22 in the context of**
16 **paragraphs 103 and 104, because the footnote relates**
17 **to the overall context of my declaration.**

18 **So in 103, I say, "returning to Mata's**
19 **hypothetical pathway, a POSA would have understood**
20 **that the rates of each of the reactions that took**
21 **place within the immediate proximity of this**
22 **protein-chiral, "c-h-i-r-a-l, "lipid environment of**

1 the ROS, reference 22, would be influenced by the
2 crowded protein and lipid rich nature of this
3 dynamic environment."

4 And then I go on to say, "the rate of the
5 bimolecular condensation between NRPE and a second
6 molecule of ATR would likely have been particularly
7 susceptible to this influence." And then I
8 continue.

9 But in the context of footnote 22, I say,
10 "a POSA would have understood that the rates of each
11 of the reactions that took place within the
12 immediate proximity of the protein-chiral lipid
13 environment of the ROS would be influenced by a
14 crowded protein lipid rich nature of this dynamic
15 environment."

16 And I say in 22, "by September 2007, it
17 was known that the initial reaction between ATR and
18 PE and the biomolecular -- sorry, bimolecular
19 condensation reaction" -- and when I say bimolecular
20 reaction condensation, that's NRPE plus the second
21 molecule of ATR -- "took place as described in the
22 preceding section." So I'm referring back to a

1 **section in the declaration.**

2 Q. Okay. So I think I heard -- it was a
3 long answer. I think I did hear the answer to my
4 question. I want to make sure that the record is
5 clear.

6 A. **Okay.**

7 Q. My question is just specifically, what do
8 you mean when you're referring to the bimolecular
9 condensation reaction? And what I heard you say is
10 that is the condensation of NRPE with a second
11 molecule of ATR. Is that correct?

12 A. **There are two bimolecular condensation**
13 **reactions. The first forms an RPE. The second --**
14 **that's paragraph 103. The second is paragraph 104.**
15 **And in the -- what I'm saying is that both**
16 **bimolecular reactions are influenced by these same**
17 **environments that they are occurring in.**

18 Q. So my question is specifically about
19 footnote 22?

20 A. **Okay.**

21 Q. So in footnote 22, you agree that you
22 identify two reactions in that footnote, right?

1 **A. Yes, I call it the initial reaction**
2 **between ATR and PE, and the bimolecular condensation**
3 **reaction, referring to the second reaction of NRPE**
4 **with ATR.**

5 **Q. Okay. So when you, in footnote 22, refer**
6 **to the bimolecular condensation reaction, you're**
7 **referring to the condensation of NRPE with the**
8 **second molecule of ATR, correct?**

9 **A. Indeed. Both reactions are bimolecular,**
10 **because two molecules are coming together.**

11 **Q. So that -- I understand you want to point**
12 **out that they are both bimolecular. In your**
13 **footnote, one you call the initial reaction between**
14 **ATR and PE. The second one you call the**
15 **biomolecular [sic] condensation reaction, right?**

16 **A. To distinguish between the initial**
17 **reaction and the second reaction.**

18 **Q. Okay. And when you're talking about the**
19 **second one, that is the condensation of NRPE with a**
20 **second molecule of all-trans-retinal, correct?**

21 **A. That's what I say in paragraph, for**
22 **example, 104.**

1 Q. And you say that these reactions -- those
2 two reactions took place as described in the
3 preceding section. So what do you mean by that?

4 A. Well, let me refer back to section 5,
5 which is the complex via the visual cycle.
6 Lipofuscin biosynthesis to -- there is V.B.2.

7 Q. Take a look at page 45, and let me know
8 if that's the right place for the beginning of that
9 section.

10 A. This is V.B. Where was footnote 22 we
11 were just looking at?

12 Q. On page 51.

13 A. Thank you. I think I've got the roadmap.
14 Now, what was the question?

15 Q. So my first question is going to be, the
16 section V.B.2.B.3 that you reference in footnote 22
17 in your declaration, the heading of that section is,
18 "location of reactions," correct?

19 A. That's the subheading for that subsection
20 of a subsection, yes.

21 Q. Okay. So in footnote 22, you were
22 telling us that, you know, for the initial -- what

1 you call the initial reaction, what you call the
2 bimolecular condensation, those took place as
3 described in section V.B.2.B.3, correct?

4 MR. FELDSTEIN: Objection to form.

5 THE WITNESS: So let me refer back, now
6 that we've found where this V.B.2.B.3 is. When I
7 say, for example, in paragraph 91 is the formation
8 of lipofuscin in the visual cycle was known to occur
9 in both the ROS and RPE.

10 And a POSA would have understood that the
11 rate of the chemical reactions in the above reaction
12 schemes would vary significantly, depending on the
13 physiological compartment or compartments in which
14 each of the reactions occurred. So then I go on.

15 BY MR. MILLS:

16 Q. Okay. I don't need you to read me
17 everything in there, because really, I'm trying to
18 understand what footnote 22 is saying first.

19 A. Okay.

20 Q. So number one, in the first sentence, you
21 say you identify two reactions that you say took
22 place as described, and you refer to a specific

1 section. Do you agree with me so far?

2 **A. That's the way I read it.**

3 Q. Okay. And the section that you refer to
4 is titled, "location of reactions"?

5 **A. That's what I see.**

6 Q. And the second sentence of footnote 22,
7 you say that there was no consensus as to where the
8 subsequent steps in the reaction took place. Do I
9 have that correct?

10 **A. That's what I say, yes.**

11 Q. Okay. So I understand your footnote 22
12 to say, it was known by September 2007 where the
13 initial reaction between ATR and PE and the
14 bimolecular condensation reaction took place, even
15 though there may be some lack of consensus regarding
16 subsequent steps. Do I have that correct?

17 MR. FELDSTEIN: Object to form.

18 THE WITNESS: The art described the work
19 of the investigators that disclosed where they
20 thought it was taking place. And there was not 100
21 percent agreement among all investigators, which is
22 why I have all these other paragraphs and sections.

1 BY MR. MILLS:

2 Q. All right. In footnote 22, you say, "by
3 September 2007, it was known," right?

4 A. I say it was known that it took place as
5 described in the preceding section.

6 Q. And the section that you're pointing to
7 is the section that says, "location of reactions."

8 A. Yes. And one of those is -- says
9 specifically, as of September 2007, there was no
10 consensus over where many of these individual
11 reactions leading to the formation of this retinoid
12 lipofuscin pigments took place.

13 Q. So many of those -- at the beginning of
14 the deposition, you told me you weren't retracting
15 any of your testimony. So what I'm trying to
16 understand is, in footnote 22, you seem to be
17 identifying consensus as to two steps in the
18 reaction, and saying there is a lack of consensus as
19 to others?

20 MR. FELDSTEIN: Object to form.

21 BY MR. MILLS:

22 Q. Is that an accurate characterization of

1 footnote 22?

2 MR. FELDSTEIN: Object to form.

3 THE WITNESS: I mean, reference 22 sends
4 you to the description in V.B.2.b.3, where there is
5 a caveat in paragraph 29 that as of September 2007,
6 there was no consensus over where many of the
7 individual chemical reactions leading to the
8 formation of this retinoid lipofuscin pigments took
9 place.

10 BY MR. MILLS:

11 Q. So paragraph 91 is a general or a
12 nonspecific statement about which ones there is
13 consensus, and which ones there is not. So for
14 some, there is consensus. For others, there is not.
15 It doesn't tell you which ones?

16 MR. FELDSTEIN: Object to form.

17 THE WITNESS: I don't understand what the
18 question is.

19 BY MR. MILLS:

20 Q. Well, you keep pointing to paragraph 91
21 to explain what you mean in footnote 22. And in
22 footnote 91, you say that there is a lack of --

1 **A. Paragraph 91.**

2 Q. Yes, in paragraph 91, you say, there is a
3 lack of consensus regarding -- it's actually
4 paragraph 92. So in paragraph 92, you say, "there
5 is no consensus over where many of the individual
6 reactions take place."

7 MR. FELDSTEIN: Objection, misstates the
8 reference.

9 THE WITNESS: And in paragraph 91, I --
10 paragraph 92 is a -- follows paragraph 91. And
11 paragraph 91 says, "the formation of lipofuscin in
12 the visual cycle was known to occur in both the ROS
13 and RPE. A POSA would have understood that the rate
14 of the chemical reactions in the above reaction
15 schemes would vary significantly, depending on the
16 physiological compartment or compartments in which
17 each of these reactions occurred."

18 And 92, "as of September 2007, there was
19 no consensus over where many of the individual
20 chemical reactions leading to the formation of this
21 retinoid lipofuscin pigments took place."

22 BY MR. MILLS:

1 Q. So, Dr. Prestwich, I think you need to be
2 cognizant about your credibility here. You seem to
3 be reluctant to rephrase what you said in paragraph
4 22 of your declaration. In the first sentence, you
5 identify two specific reactions and you say, "by
6 2007, it was known." And then you say, but there
7 was no consensus as to where the subsequent steps
8 took place?

9 MR. FELDSTEIN: I'm going to object on
10 form and just being rude.

11 BY MR. MILLS:

12 Q. Dr. Prestwich, you agree in footnote 22,
13 paragraph 103 of your declaration, on page 51, you
14 state, by September 2007, it was known that the
15 initial reaction between ATR and PE and the
16 bimolecular condensation reaction took place as
17 described in the preceding section, section
18 V.B.2.B.3. However, as also discussed, there was no
19 consensus as to where the subsequent steps in the
20 reaction took place?

21 A. **I see those words.**

22 Q. Thank you.

1 **A. Time for a short one.**

2 **(Recess.)**

3 BY MR. MILLS:

4 Q. Welcome back.

5 **A. Thank you.**

6 Q. So, Dr. Prestwich, I was looking at your
7 figures. And I see -- I see a couple of different
8 schematics for A2E formation among the 14 figures
9 that you included in your declaration. Does that
10 sound right?

11 MR. FELDSTEIN: Object to form.

12 THE WITNESS: Each figure from a
13 different reference may depict things differently.

14 BY MR. MILLS:

15 Q. Can you tell me the numbers of the
16 figures that you included in your declaration that
17 depict A2E formation pathways?

18 MR. FELDSTEIN: Object to form.

19 THE WITNESS: If you allow me to page
20 through them, I can probably point them out.

21 BY MR. MILLS:

22 Q. And when you find one, tell me the figure

1 number, and also the reference that you got it from.

2 A. Okay. The first one that I see is figure
3 5. Maybe it's not the first one. Let me go back
4 and see if I can see it in an earlier one. The
5 first one I see is the proposed A2E pathway of
6 Fishkin 2003, on page 36. And that's figure 5.

7 Q. Thank you. Is there another one?

8 A. Looks like the next one that I see is
9 figure 6, which is Fishkin 2005's proposed A2E
10 proposed pathway on page 38.

11 Q. Thank you. Is there another one?

12 A. I think figure 7, Kim 2007's proposed A2E
13 pathway. From Kim 2007 on page 39.

14 Q. Thank you. Is there another one?

15 A. I'm not sure this meets your criteria,
16 but there is figure 9, which shows the phagocytosis
17 of the ROS by the RPE, and shows some of these
18 pigments being moved around or changed.

19 Q. Anything else?

20 A. I see figure 12, in which I depict the
21 NRPE general passive base tolerization.

22 Q. Figure 12, that's one that doesn't have

1 any evidentiary source cited in the caption,
2 correct?

3 **A. That one is one that I drew. That's**
4 **correct.**

5 Q. Anything else?

6 **A. I think that is it.**

7 Q. There is at least one prior art reference
8 providing a mechanism for A2E formation. You didn't
9 include it in any of your figures in your
10 declaration, right?

11 **A. I don't see the Mata 2000 figure per se,**
12 **but I talk about it quite a bit.**

13 Q. Let's look at the Mata reference. That's
14 Exhibit 1010.

15 **A. Okay.**

16 Q. Figure 5 appears on page 7158 of Exhibit
17 1010, correct?

18 (Exhibit No. 1010 was referred to.)

19 THE WITNESS: Figure 5 in Mata appears on
20 page 7158 of the article.

21 BY MR. MILLS:

22 Q. And figure 5 of Mata is the biosynthetic

1 pathway that -- figure 5 in Mata is the biosynthetic
2 pathway for A2E that Mata proposed, correct?

3 MR. FELDSTEIN: Object to form, misstates
4 the document.

5 THE WITNESS: I'll read what his title
6 sentence for figure 5 is. "Hypothetical
7 biosynthetic pathway for A2E in mice and humans
8 lacking the RmP transporter."

9 And then he continues -- or they
10 continue, "this model is based on the proposed
11 scheme for A2 biogenesis by Parish et al., reference
12 24." And then it continues.

13 BY MR. MILLS:

14 Q. Do you disagree that figure 5 provides a
15 schematic of the biosynthetic pathway that Mata
16 proposes for A2E formation?

17 MR. FELDSTEIN: Object to form,
18 misstates.

19 THE WITNESS: I'm going to read back to
20 you what he describes and what -- Mata describes
21 this as a hypothetical biosynthetic pathway for A2E
22 in mice and humans lacking the RmP transporter.

1 BY MR. MILLS:

2 Q. But I haven't asked to you read me what
3 Mata says. I'm asking you if you would agree that
4 figure 5 provides the schematic for the biosynthetic
5 pathway that Mata proposed?

6 MR. FELDSTEIN: Object to form.

7 THE WITNESS: I agree that figure 5 shows
8 a hypothetical biosynthetic pathway, and that's what
9 I can agree to.

10 BY MR. MILLS:

11 Q. So in your declaration, Dr. Prestwich,
12 you refer repeatedly to Mata's proposed pathway.

13 A. Yes.

14 Q. Do you recall that?

15 A. I do.

16 Q. Okay. We can look at paragraph 89 of
17 your declaration if you want to refresh your
18 recollection.

19 A. And I see the words, "excess ATR believed
20 to be the substrate for A2E formation in Mata's
21 preferred pathway."

22 Q. Are those your words?

1 **A. Yes.**

2 Q. When you wrote Mata's proposed pathway in
3 paragraph 89 of your declaration, that refers to
4 what is depicted in the schematic of figure 5 of
5 Exhibit 1010?

6 **A. That is what I'm referring to as Mata's**
7 **proposed pathway.**

8 Q. And that schematic in figure 5 was not
9 included in any of the 14 figures that you selected
10 for inclusion in your declaration, correct?

11 **A. That appears to be the case.**

12 Q. On that same page in Exhibit 1010, in the
13 right-hand column for the reference -- do you have
14 that reference in front of you?

15 Starting seven lines from the bottom of
16 that paragraph, I want to make sure we are talking
17 about the right place. The paragraph begins by
18 saying, "we confirmed," and it ends with the words
19 "RPE phagolysosomes." Have you found the paragraph?

20 **A. I found the paragraph.**

21 Q. Okay. Seven lines up from the bottom of
22 that paragraph, there is a sentence that begins,

1 "the stability." Do you see that?

2 A. Yes.

3 Q. Okay. That sentence says, "the stability
4 of A2PE-H2 in a non-oxidizing environment suggests
5 that reaction 2 in figure 5 is effectively
6 irreversible." Do you see that sentence?

7 A. I see that sentence.

8 Q. I have a couple of questions about this.
9 So at the beginning of your deposition, I identified
10 a typo in your declaration, where there was a
11 compound that you had called A2P2-H2, and you said
12 it was supposed to be A2PE-H2?

13 A. Yes.

14 Q. This is the compound that we are talking
15 about is what's referenced here in this sentence,
16 right?

17 MR. FELDSTEIN: Object to form.

18 THE WITNESS: I believe that's what I was
19 referring to as A2PE-H2 from this Mata paper.

20 BY MR. MILLS:

21 Q. And then that A2PE-H2, that is -- the
22 structure is depicted for that in figure 5 on that

1 same page above, correct?

2 **A. Yes, it's one of the structures here in**
3 **figure 5. Kind of at the middle.**

4 Q. It's on the right-hand side. It's the
5 third one down from the top, correct?

6 **A. Yes.**

7 Q. And it's immediately downstream of the
8 [3,3] sigmatropic rearrangement, correct?

9 MR. FELDSTEIN: Object to form.

10 THE WITNESS: There is an arrow which has
11 a circle 2 over it that shows a proposed reaction
12 going from the one labeled [3,3] sigmatropic
13 rearrangement, and the one going to A2PE-H2 on the
14 other side. That's what I see.

15 BY MR. MILLS:

16 Q. The arrow, do you disagree with
17 characterizing that the schematic is indicating that
18 A2PE-H2 is downstream of the [3,3] sigmatropic
19 rearrangement?

20 **A. The term is not generally used in organic**
21 **chemistry or biosynthetic chemistry. It's showing a**
22 **proposed hypothetical transformation.**

1 Q. I mean -- so downstream isn't a term that
2 you would use?

3 A. **I'm not familiar with that term in**
4 **synthetic chemistry or biosynthetic chemistry.**

5 Q. Can you take a look at the structure for
6 A2PE-H2 in figure 5 of the Mata reference?

7 A. **You're asking me to look at the structure**
8 **of A2PE-H2 (500 nanometers). Is that the one?**

9 Q. Yes. And it's also -- in the figure,
10 they also call it dihydro A2PE, is that right?

11 A. **Yes.**

12 Q. So have you had an adequate opportunity
13 to look at the structure of A2PE-H2 in figure 5?

14 A. **Yes.**

15 Q. Do you have any disagreement with the
16 veracity of the depiction of the structure for that
17 compound?

18 MR. FELDSTEIN: Object to form.

19 THE WITNESS: Not of that compound, no.

20 BY MR. MILLS:

21 Q. Okay. You reviewed the Kim 2004
22 reference for this case, right?

1 **A. Kim 2004. I believe that was where I**
2 **cited one of the figures.**

3 Q. Okay. Let's take a look. It's Exhibit
4 2019.

5 (Exhibit No. 2019 was referred to.)

6 THE WITNESS: Should I keep Mata out?

7 BY MR. MILLS:

8 Q. Sure. Keep it handy.

9 **A. 2019. Okay.**

10 Q. Okay. And you can also pull out your
11 declaration, paragraph 94.

12 **A. 94?**

13 Q. Yes.

14 MR. FELDSTEIN: Kim 2004?

15 MR. MILLS: I'm sorry, I misspoke. So
16 Exhibit 2019 is Kim 2007, and that is the document
17 that I intended, but I said the wrong year.

18 THE WITNESS: So I have Kim 2007.
19 Exhibit 2019.

20 BY MR. MILLS:

21 Q. Perfect. Thank you. Okay. And you also
22 have paragraph 94 of your declaration?

1 **A. I see paragraph 94 now, yes.**

2 Q. And paragraph 94 bridges two pages. Your
3 reference to Kim 2007 bridges pages 46 and 47,
4 correct?

5 **A. I see that.**

6 Q. Okay. Can you read to yourself what you
7 wrote about Kim 2007 in paragraph 94 of your
8 declaration.

9 **A. I've re-informed myself of what this is**
10 **about.**

11 Q. Did you have an opportunity to compare
12 the sentence about Kim in paragraph 94 with the
13 footnote 19, where you quote Kim?

14 **A. Let's start with the footnote, since I'm**
15 **looking at that.**

16 Q. Can you go ahead and read to me the text
17 from Kim that's quoted in footnote 19 in your
18 declaration?

19 **A. Yes. "Several lines of investigation**
20 **also demonstrated that A2PE forms with photoreceptor**
21 **outer segments."**

22 Q. What does it mean to you when Kim says

1 that several lines of investigation demonstrated
2 that A2PE forms with photoreceptor outer segments?

3 **A. It says what it says. And I would need**
4 **to go back and review how they, Kim and six other --**
5 **six or eight other authors came to that conclusion**
6 **by looking at their various lines of evidence.**

7 Q. Let's look at page 6 of the Kim
8 reference, Exhibit 2019. Let's just begin on that
9 page at the very top, there is a big heading in
10 capital letters that says, "discussion."

11 **A. Got it, yes.**

12 Q. There is a very long paragraph that
13 follows immediately after that in discussion. Do
14 you see that?

15 **A. I see a very long paragraph.**

16 Q. Okay. About six or seven lines up from
17 the bottom of that paragraph, there is a cite to
18 references 13 and 17. And after that, there is a
19 sentence that begins, "several lines of
20 investigation." Do you see that?

21 **A. I see that, yes.**

22 Q. Okay. So that sentence, "several lines

1 of investigation also demonstrated that A2PE forms
2 within photoreceptor outer segments." Do you see
3 that sentence?

4 **A. I see that sentence.**

5 Q. That's the sentence that you quoted in
6 footnote 19 of your declaration, correct?

7 **A. That's what I see.**

8 Q. Okay. Go ahead and read from that
9 sentence to the end of the paragraph to yourself. I
10 just want to make sure you've had an opportunity to
11 read what comes in that paragraph after that
12 sentence.

13 **A. I'm going to start by reading the**
14 **discussion section and see what gets me to that**
15 **quote. Okay, I've reviewed as much as I think I**
16 **need to for the next question. But we'll see.**

17 Q. Okay. So you read that long paragraph
18 under the discussion.

19 **A. Yes.**

20 Q. Okay. So since you read the whole thing,
21 I'm going to ask you a question in the upper part,
22 since you just read that, too. Do you see there is

1 a citation in the first half of that paragraph to a
2 reference 17 after the sentence that begins, "mass
3 spectrometry"?

4 **A. Was utilized to confirm -- "mass**
5 **spectrometry was utilized to confirm the formulation**
6 **of NRPE and A2PE (reference 17)," which maps to Liu**
7 **et al., Journal of Biological Chemistry.**

8 Q. So reference 17 is -- this is a
9 publication from the Nakanishi lab, correct?

10 **A. Yes, it appears that way.**

11 Q. And Kim itself was also a publication
12 from the Nakanishi lab, correct?

13 **A. Yes.**

14 Q. Okay. So, first, they are citing their
15 own prior publication to say, look at what we did,
16 and we used mass spectrometry to confirm the
17 formation of NRPE and A2PE, right?

18 **A. That's what I'm understanding this to**
19 **mean.**

20 Q. Okay. And then further down, they have a
21 long discussion about what they are looking at. But
22 further down, the very first sentence in the next

1 paragraph, it kind of gets to the point of what
2 their article now is about.

3 They say, "before we confirmed NRPE and
4 A2PE," and then they said, "the results presented
5 here also now corroborate dihydro A2PE as an
6 intermediate in the biosynthetic pathway leading to
7 A2PE and then A2E formation," correct?

8 **A. I agree with that, yes.**

9 Q. Okay. So now back to my question. Right
10 after the reference, the citation references 13 and
11 17 in that first paragraph. We are at the sentence
12 that says, "several lines of investigation also
13 demonstrated that A2PE forms within photoreceptor
14 outer segments," correct?

15 **A. I see that.**

16 Q. That's the line that you quoted in
17 footnote 19 of your declaration, correct?

18 **A. Yes.**

19 Q. Okay. Have you had a chance to read the
20 material that the Nakanishi lab included in this
21 paragraph to describe the several lines of
22 investigation they are talking about?

1 MR. FELDSTEIN: Object to form,
2 foundation.

3 THE WITNESS: I just read them, and I can
4 read them again to myself.

5 BY MR. MILLS:

6 Q. So I'll tell you what my question is.

7 A. Yes.

8 Q. He identifies at least two lines of
9 reasoning or two experiments that they are relying
10 on for this conclusion. Is that fair?

11 A. I think so. They talk about a
12 radiolabeling experiment, and excised whole retinas.
13 And they talk about a mass spec. analysis for A2PE
14 as an orange colored pigment in Royal College of
15 Surgeon rats. I guess that's what they are talking
16 about.

17 Q. Let's start with the first one. Do you
18 have that in your mind?

19 A. Yes.

20 Q. Can you tell me in a sentence or two what
21 they did in that first experiment?

22 MR. FELDSTEIN: Objection to form,

1 foundation.

2 THE WITNESS: Well, this is a discussion,
3 and it's obviously an abbreviated version of the
4 experiment they conducted. And rather than just
5 take what they said in the discussion, I would look
6 at the actual experiment that was done with
7 incorporating carbon-14 ethanolamine and then
8 irradiation to release endogenous all-trans-retinal.
9 I would have to look at that experiment to figure
10 out what they actually did and why they think that's
11 an appropriate line of evidence.

12 BY MR. MILLS:

13 Q. So if I understand you correctly, you are
14 saying there is a one sentence summary of what they
15 did in this reference?

16 MR. FELDSTEIN: Objection, form.

17 THE WITNESS: It's kind of a -- yes, it's
18 a conclusion they have drawn that they are putting
19 in their discussion.

20 BY MR. MILLS:

21 Q. So what I want to understand now is what
22 you understand from that one sentence summary? What

1 is it that you understand that they did from that
2 summary?

3 A. Yeah. Just at a high level, what I
4 understand that they did is that they, in some
5 fashion that I don't know experimentally how they
6 did this, they incorporated ethanolamine that was
7 labeled -- two of the carbon atoms which were
8 labeled with carbon-14, into whole retinas. And
9 like I say, I don't know how they did that. And
10 then it says, "and irradiation to release endogenous
11 all-trans-retinol."

12 I'm not sure how to interpret that until
13 I look at the experiment and see what came first,
14 what came second, what conditions, and how many
15 animals and how the analysis was done. How the
16 counting of the radioisotopes was done. Whether or
17 not it was imaged or whether it was ground up and
18 just counted in a scintillation counter.

19 I have no idea from reading that what
20 they actually did. But they are saying, this is one
21 of the lines of evidence that gives -- that supports
22 where they are saying that A2PE forms within

1 photoreceptor outer segments.

2 Q. Can you explain to me, based on this one
3 sentence summary, what is the significance of the
4 carbon-14?

5 A. In general, it allows you to trace where
6 the chemistry/biochemistry is occurring, where the
7 reactions are occurring. And it's an indication, in
8 general, of where the reaction is occurring, because
9 especially in a situation like this, you have to
10 look carefully at the experimental details to find
11 out how the experiment was done, how the
12 administration of C-14 ethanolamine was done, and
13 how the isolation of the product was done.

14 And the fact that this is -- can only be
15 indicative -- indicative -- indicative because the
16 reaction in vivo takes place with
17 phosphatidylethanolamine, not ethanolamine. So this
18 summary doesn't tell me how they did the experiment
19 and how -- how best to fully interpret it.

20 Q. So carbon-14 began on the ethanolamine,
21 correct?

22 MR. FELDSTEIN: Object to form.

1 THE WITNESS: What I'm reading is that
2 they found the formation of double AC-14 labeled
3 A2PE as the result of taking excised whole retinas,
4 presumably of these rats and incubating them somehow
5 with C-14 labeled ethanolamine irradiation -- I'm
6 sorry, C-14 ethanolamine incorporation, and then
7 irradiating -- irradiating it to release endogenous
8 all-trans-retinal.

9 BY MR. MILLS:

10 Q. So do you have an understanding as to
11 where the source that they are saying there is
12 all-trans-retinal. What are they saying is the
13 source of the all-trans-retinal? Is that something
14 that they are adding to the system, or is it
15 something that's coming from the retina -- the
16 authors?

17 MR. FELDSTEIN: Objection to form.

18 BY MR. MILLS:

19 Q. Do you have my question in mind?

20 A. **I think I have the question in mind. Why**
21 **don't you ask it again?**

22 Q. So I'm really just trying to find out

1 where is the carbon-14 starting and where is the
2 carbon-14 ending up.

3 A. Ah. And this paper does not describe
4 that. They are -- I believe that this is reference
5 17, where that experiment is described which is the
6 Liu et al. paper from reading this.

7 There is nothing in the experimental
8 where they do a radiolabeling experiment in this
9 paper that I'm able to find. But I will look one
10 more time. And I think they are talking about a
11 line of evidence from one of their references.

12 Q. Reading Exhibit 2019, you don't know
13 whether or not, in this experiment, the carbon-14
14 atoms are being introduced into the experiment on
15 the ethanolamine and are being detected on A2PE?

16 MR. FELDSTEIN: Objection, form.

17 THE WITNESS: I heard something wrong in
18 there, so --

19 BY MR. MILLS:

20 Q. Let's see if we can take it one step at a
21 time. So you testified earlier that the carbon-14
22 is there as a tracer, correct?

1 MR. FELDSTEIN: Object to form.

2 THE WITNESS: Yes.

3 BY MR. MILLS:

4 Q. There is two carbon-14 tracer atoms on
5 each molecule of ethanolamine. Is that how it was?

6 A. **There is two carbons in ethanolamine.**

7 Q. Each one is in carbon-14?

8 A. **In this designation, C-14 2 means both of
9 them are partially labeled.**

10 Q. In this experiment, carbon-14 is
11 introduced as a tracer on the ethanolamine
12 molecules, correct?

13 MR. FELDSTEIN: Objection, form,
14 foundation.

15 THE WITNESS: In the formation of C-14 2,
16 A2PE has been measured in excised full retinas
17 following C-14 ethanolamine incorporation and
18 irradiation to release all-trans. That's what I'm
19 reading.

20 BY MR. MILLS:

21 Q. So in this experiment, the carbon-14
22 atoms are introduced as tracers on the ethanolamine

1 molecules, correct?

2 MR. FELDSTEIN: Object to form,
3 foundation.

4 THE WITNESS: That's what the words say.

5 BY MR. MILLS:

6 Q. Okay. And then the reference is telling
7 us that those carbon-14 atoms end up being detected
8 in A2PE, correct?

9 A. **That's what the words say.**

10 Q. Thank you. Okay. So that's the first
11 experiment. So now I'm going to ask about the
12 second experiment. So recognizing that it's a one
13 sentence summary, can you tell us in a sentence or
14 two what it is that they did in this experiment that
15 led them to conclude that they had demonstrated that
16 A2PE forms within photoreceptor outer segments?

17 MR. FELDSTEIN: Objection, form,
18 foundation.

19 THE WITNESS: I think to answer that, I
20 would need to see -- look at the references 13 and
21 17 to which they cite, because reading this here,
22 the context is such that they are citing to two

1 other works that may be involved in determining the
2 location of where A2PE forms.

3 BY MR. MILLS:

4 Q. Right now, I'm asking a question about
5 the last sentence of the paragraph. The sentence
6 that says, "by mass spectrometric analysis, it has
7 also been shown that A2PE is the orange colored
8 pigment present in degenerating photoreceptor outer
9 segment debris in Royal College of Surgeons rats
10 (13)." Do you see that sentence?

11 A. Right. I do.

12 Q. So my question is, can you just tell me,
13 in your own words, what that sentence conveys?

14 MR. FELDSTEIN: Object to form.

15 THE WITNESS: It conveys that I should go
16 look at reference 13 and see what reference 13 says.

17 BY MR. MILLS:

18 Q. I'm asking you what that sentence conveys
19 about what they did.

20 MR. FELDSTEIN: Object to form.

21 THE WITNESS: That sentence is -- the way
22 I read that sentence, when they say it has also been

1 shown that, and then they cite reference 13, they
2 are talking about the work in reference 13.

3 BY MR. MILLS:

4 Q. How are they characterizing the work in
5 reference 13?

6 MR. FELDSTEIN: Object to form.

7 THE WITNESS: Reference 13 has a title
8 also from the -- it's the Ben-Shabat paper. It's
9 biosynthetic studies of A2E and major fluorophore of
10 RPE lipofuscin. And it's from the Nakanishi group.

11 And all I can read from this sentence,
12 "by mass spectrometric analysis, it has also been
13 shown that A2PE is the orange colored pigment
14 present in the degenerated photoreceptor outer
15 segment debris in Royal College of Surgeons rats,"
16 reference 13. That's one of the conclusions reached
17 by reference 13.

18 BY MR. MILLS:

19 Q. So in Exhibit 2019, in their summary of
20 Ben-Shabat, they tell you that there was an
21 experiment conducted using Royal College of Surgeons
22 rats. Do you agree?

1 MR. FELDSTEIN: Objection, form,
2 mischaracterizes.

3 THE WITNESS: I see that they -- that
4 they write, "by mass spectrometric analysis, it's
5 also been shown that A2PE is the orange colored
6 pigment present in degenerated photoreceptor outer
7 segment debris in Royal College of Surgeons rats."
8 That's what I see.

9 BY MR. MILLS:

10 Q. Do you understand from that sentence that
11 mass spectrometric analysis was used to identify
12 A2PE as a compound?

13 A. **It says that mass spectrometric analysis**
14 **showed that A2PE was present and it was an orange**
15 **colored pigment. Those are the two things that I**
16 **can read from that sentence.**

17 Q. Do you understand what mass spectrometric
18 analysis is?

19 MR. FELDSTEIN: Object to form.

20 THE WITNESS: Yes.

21 BY MR. MILLS:

22 Q. What is that?

1 A. Mass spectrometric analysis is the
2 process that is commonly used to determine molecular
3 sizes, molecular weights, or mass to charge ratio,
4 more accurately, in molecules that have been
5 purified, so that you can determine what the
6 molecular weight is. And with the molecular weight
7 and the fragmentation pattern, deduce what the
8 likely structure is.

9 Q. You understand from Exhibit 2019 that
10 members of the Nakanishi lab concluded, as a result
11 of the mass spectrometric analysis, that they had
12 analyzed a compound that was A2PE, correct?

13 MR. FELDSTEIN: Object to form.

14 THE WITNESS: Kim et al., also Nakanishi
15 lab characterized the work by Ben-Shabat et al. as
16 having accomplished that.

17 BY MR. MILLS:

18 Q. Okay. And they identified the source of
19 the A2PE as being degenerated photoreceptor outer
20 segment debris from Royal College of Surgeons rats,
21 correct?

22 MR. FELDSTEIN: Object to form.

1 THE WITNESS: That's -- those are the
2 words that I read.

3 BY MR. MILLS:

4 Q. Thank you. I have a question about a
5 different subject.

6 A. Okay.

7 Q. Are you familiar with sodium hydroxide?

8 A. Sodium hydroxide, yes.

9 Q. What is sodium hydroxide?

10 A. The formula is NaOH. It's a base.

11 Q. Sodium hydroxide is a chemical that
12 you're familiar with?

13 A. Yes.

14 Q. Sodium hydroxide is a strong base?

15 A. It's generally considered a strong base.

16 Q. What is sodium hydride?

17 A. Sodium hydride is a -- also a relatively
18 strong base.

19 Q. Have you ever heard sodium hydride
20 referred to as a super base?

21 A. I don't believe I have heard that
22 terminology in my many years of doing organic

1 **synthesis.**

2 Q. Are you able to make a comparison between
3 the strength of sodium hydroxide versus sodium
4 hydride as a base?

5 MR. FELDSTEIN: Object to form, beyond
6 the scope.

7 THE WITNESS: I don't think that -- I
8 don't -- no, I don't know how to make a direct
9 comparison between those two.

10 BY MR. MILLS:

11 Q. In reaching your opinions in this case,
12 you did not consider whether sodium hydride is a
13 stronger base than sodium hydroxide, correct?

14 A. **They are both bases. And I wasn't**
15 **considering relative bases.**

16 Q. You're aware that sodium hydride is
17 combustible?

18 A. **Yes.**

19 Q. You're aware that sodium hydride is
20 insoluble?

21 A. **I'm aware that --**

22 Q. Sodium hydride is insoluble?

1 **A. Is insoluble?**

2 MR. FELDSTEIN: Object to form.

3 THE WITNESS: I'm generally aware. I've
4 used sodium hydride and it depends what you try and
5 dissolve it in.

6 BY MR. MILLS:

7 Q. You're aware that sodium hydride can
8 ignite in the air spontaneously?

9 **A. It depends how it's packaged, and how you**
10 **use the reagent that you receive.**

11 Q. In all of the references that you
12 reviewed coming to your opinions in this case, you
13 didn't see any references saying that sodium hydride
14 appears endogenously in the outer segments of the
15 photoreceptor cells, correct?

16 MR. FELDSTEIN: Object to form, beyond
17 the scope.

18 THE WITNESS: Can you ask the question
19 again?

20 BY MR. MILLS:

21 Q. In all of the references that you
22 reviewed in coming to your opinions in this case,

1 you didn't see any references saying that sodium
2 hydride appears endogenously in the outer segments
3 of the photoreceptor cells, correct?

4 MR. FELDSTEIN: Object to the form,
5 beyond the scope.

6 THE WITNESS: I did not see any
7 references that placed sodium hydride in the -- in
8 the broad outer segments.

9 BY MR. MILLS:

10 Q. The same is true for the other segments,
11 correct?

12 MR. FELDSTEIN: Same objections.

13 THE WITNESS: That would be true also.

14 MR. MILLS: Thank you. I have no further
15 questions.

16 MR. FELDSTEIN: Take a break.

17 (Recess.)

18 MR. FELDSTEIN: No questions for
19 Dr. Prestwich from Patent Owner. We are off the
20 record. Thank you.

21 (Whereupon, 1:29 p.m., the instant
22 deposition concluded.)

1 CERTIFICATE OF REPORTER

2 I, Susan L. Ciminelli, Registered Professional
3 Reporter and Notary Public in and for Washington,
4 D.C., the officer before whom the proceedings were
5 taken, do hereby certify that the foregoing
6 transcript is a true and accurate record of these
7 proceedings; that said proceedings were taken in
8 Stenotype notes by me on the 15th day of November,
9 2024, commencing at 9:00 a.m. and ending at 1:30
10 p.m. I further certify that present on behalf of
11 Party The Trustees of Columbia University, Patent
12 Owner, were Mark J. Feldstein and Drew D. Christie
13 of Finnegan, Henderson, Farabow, Garrett & Dunner,
14 LLP and on behalf of Party Gene Company Pty Ltd. was
15 Jad A. Mills of Wilson, Sonsini, Goodrich & Rosati.
16 I further certify that I am not related to, nor
17 associated with any of the parties or their
18 attorneys, nor do I have any disqualifying interest,
19 personal or financial in the actions within.

20 Dated this 27th day of November, 2024 at
21 Washington, D.C.

22

Susan L. Ciminelli

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