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

GENE COMPANY PTY LTD,	)	
	)	
Petitioner,	)	
	)	
v.	)	
	)	
THE TRUSTEES OF COLUMBIA	)	CASE NO.
UNIVERSITY IN THE CITY	)	IPR2024-00313
OF NEW YORK,	)	
	)	Patent No.
Patent Owner.	)	RE47,045
	)	
	)	
	)	
	)	

DEPOSITION OF:
PETER GUENGERICH, PH.D.
Taken on behalf of the Patent Owner

August 16, 2024

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I N D E X

Examinations	Page
BY MR. FELDSTEIN	6

E X H I B I T S

No.	Description	Page
2054	Metals in Biology 2016: Molecular Basis of Selection of Metals By Enzymes	18
2056	E-mail	142
2061	Journal of Biological Chemistry (one page)	147
2057	September 2010 E-mail	150
2051	Article	156
2066	Maiti publication	184
2064	Maeda paper	190
2070	Annual Reviews of Pharmacological	193

1 The deposition of PETER GUENGERICH,
2 PH.D., taken on behalf of Patent Owner, on the
3 16th day of August, 2024, commencing at 10:00
4 a.m., in the offices of Marriott, West End,
5 Nashville, Tennessee, for all purposes under the
6 United States Patent and Trademark Office Rules
7 of Civil Procedure.

8 The formalities as to notice,
9 caption, certificate, et cetera, are waived.
10 All objections, except as to the form of the
11 questions, are reserved to the hearing.

12 It is agreed that Jennifer Haynie,
13 being a Notary Public and Court Reporter for the
14 State of Tennessee, may swear the witness, and
15 that the reading and signing of the completed
16 deposition by the witness are reserved.

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1 MR. FELDSTEIN: Doctor, before I get
2 to questions, I just need to make a statement,
3 and counsel knows this -- that I was going to do
4 this.

5 We have deposition notices in two
6 different IPRs. IPR2024-00312, which is for US
7 patent number 9,486,423, with a second
8 deposition notice for IPR2024-00313, which is
9 for US patent RE 47045.

10 I'm intending to ask questions on
11 Dr. Guengerich's declaration regarding the
12 RE 47045 patent, which is the 313 IPR. My
13 colleague Ms. Pirraglia may have questions at
14 the end directed to Dr. Guengerich's declaration
15 to the extent it's different in the 312 IPR.

16 We intend to reserve opportunity for
17 Ms. Pirraglia to do that. We understand we
18 haven't reached an agreement with opposing
19 counsel on that. If necessary, we'll close this
20 record under the 313 IPR and the 313 deposition
21 notice and open a second record under the 312
22 IPR and its corresponding deposition notice.

23 MR. MILLS: I'll go ahead and make a
24 statement for the record. The parties agree to
25 a single deposition today. There were notices

1 submitted in both cases which is the ordinary
2 course. It would be highly unusual to have two
3 different attorneys questioning the same witness
4 -- two different attorneys for the same side
5 questioning the witness in a single deposition.
6 And so we're reserving all rights, and we'll
7 address and dispute it if one arises during the
8 deposition.

9 PETER GUENGERICH, PH.D.,

10 Having been sworn to tell the truth,
the whole truth and nothing but the
11 truth, testified as follows:

12 DIRECT EXAMINATION

13 BY MR. FELDSTEIN:

14 Q. Okay. Sorry about that, Dr. Guengerich.
15 Nice to you see you again, as I said.

16 In this case, I'm going to focus on, as I
17 mentioned, your declaration in -- regarding the
18 reissue 47045 patent. It's Exhibit 1002, and
19 I'm going to refer only to exhibits using the
20 313 numbering.

21 You have a copy of that, I believe, in
22 front of you, maybe the left-most folder from
23 your counsel.

24 A. I'm sorry. This is the 1002 tab, my
25 declaration.

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1 Q. Your declaration 1002.
2 A. This is the 432. You said the other one,
3 the 405?
4 Q. Correct. '045.
5 A. '045, I'm sorry. Oh, here it is.
6 Q. So you have that.
7 A. I do.
8 Q. I'm going to focus my questions on that,
9 and you're addressing in your declaration --
10 you're addressing the understanding of the
11 person of ordinary skill in the art regarding
12 the formation of A2E, which is the letter A, the
13 number 2, the letter E formation, correct?
14 A. Let me look and see where it defined the
15 POSA in that case. Oh, here we go.
16 Q. And if you tell me where you're reading.
17 And to be clear, Doctor, I really wasn't
18 really asking you what the definition of a POSA
19 is. I was just asking if you were addressing
20 the person of ordinary skills understanding of
21 A2E formation in your declaration in
22 Exhibit 1002.
23 A. Well, okay. Go to paragraphs 52,
24 following from there, and I don't really mention
25 A2E there. The -- yeah, specifically 54, I

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1 don't mention A2E. I mention in paragraph 54
2 that -- oh, it talks about an advanced degree in
3 a field related to pharmacology, chemistry,
4 biochemistry, ophthalmology, or related field
5 and talks about working with a practicing
6 physician who diagnoses and treats
7 ophthalmic -- ophthalmological --
8 ophthalmologic disorders such as macular
9 degeneration. I did not specifically mention
10 A2E.

11 Q. Do you understand I'm not asking about
12 the definition of a person of ordinary skill in
13 the art in my question? Do you understand that?

14 A. I'm not sure that I do.

15 Q. Okay. Maybe not.

16 A. Could you rephrase the question again?

17 Q. In your report, which is 170-some pages,
18 you're addressing some subject matter from the
19 perspective of a person of ordinary skill in the
20 art as you defined it, correct?

21 A. Yes.

22 Q. And one of the subject matters you
23 address from the perspective of a person of
24 ordinary skill in the art as you defined is the
25 formation of A2E; is that correct?

1 A. I did not specifically mention A2E in
2 this section. I did mention in paragraph 54 --
3 well, it does mention the '045 patent states
4 that the compounds may be used to treat or
5 ameliorate an ophthalmologic disorder such as,
6 e.g., macular degeneration by slowing or
7 limiting the accumulation age pigments or
8 lipofuscin in the retinol pigment of epithelial
9 cells of the retina. I didn't specifically at
10 this point define what those pigments were
11 and --

12 Q. Let me try to clarify and maybe modify
13 the question to help a little bit. I'm not
14 asking you to limit you to paragraphs 54 and 55.

15 I'm asking, throughout the context of
16 your report, the entirety of it, do you address
17 the understanding of a person of ordinary skill
18 in the art regarding the formation of lipofuscin
19 pigments?

20 A. I don't recall that. It's a lot; as you
21 mentioned, it's a long report. I don't recall
22 that I specifically addressed that, but if I
23 did, I'll be glad to look and comment.

24 Q. In paragraph 54, which you had directed
25 us to, you're analyzing perspective of a person

1 of ordinary skill in the art as of
2 September 2007, correct?

3 A. Yes.

4 Q. Do you have an opinion on what a person
5 of ordinary skill in the art as of
6 September 2007 would have understood about the
7 formation of a lipofuscin pigments?

8 A. It depends. I mean, there are a number
9 of people, types of people, who would qualify as
10 a person of ordinary skill in the art. Some
11 might come from different backgrounds, from
12 chemistry, some people from ophthalmology, and
13 the person, I think, regardless of the number of
14 different specialists, would probably be working
15 in a team together to work on a problem like
16 this.

17 Q. Could you tell me what opinion, if any,
18 you have regarding what a person of ordinary
19 skill in the art would have known as of
20 September 2000 regarding the formation of
21 lipofuscin pigments?

22 MR. MILLS: Objection to form.

23 THE WITNESS: I can try to answer
24 that question by basically commenting on the
25 available literature, which I think I have in my

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1 report. There were a number of reports from --
2 well, there was a -- what we call a Mata paper.
3 I can't remember exactly from the Dallas group.
4 There were several papers from the Columbia
5 group as well. This was all available in the
6 literature, in the open literature, at the time.
7 There was other exhibits too. For instance, the
8 Ortho -- we'll call it the Ortho patent, others
9 as well.

10 BY MR. FELDSTEIN:

11 Q. And do you have an opinion on what a
12 person of ordinary skill in the art would have
13 known as of September 2007 regarding the
14 formation of lipofuscin pigments?

15 A. Well, based on the available literature,
16 they would have -- you know, if they read these
17 papers, then they would have known that
18 lipofuscin pigments were formed, and these were
19 considered detrimental, and they know something
20 about the process by which they were formed.

21 Q. Do you have an opinion on whether -- on
22 anything else that a person of ordinary skill in
23 the art would have known as of September 2007
24 regarding the formation of lipofuscin pigments?

25 A. Well, I mentioned that some of the papers

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1 that were in the available literature -- and I
2 think they're all exhibits here -- were
3 available, and they would have known that
4 these -- how -- generally how these were formed.

5 Q. And how generally would a person have
6 understood that lipofuscin pigments were formed,
7 in you're opinion?

8 A. I think I already mentioned -- answered
9 the question. I mentioned some of the exhibits
10 we have the -- we'll call it the Mata paper and
11 the Fishkin paper, others too.

12 Q. And to back up a little bit, what are
13 lipofuscin pigments?

14 A. They are complex structures formed by the
15 dimerization of the retinoids in the eye.

16 Q. And what lipofuscin pigments would a
17 person of ordinary skill in the art been aware
18 of as of September 2007?

19 A. Well, I'd have to look at one of the
20 exhibits if I could. The -- do you mind if I do
21 that?

22 Q. Sure. Let me just ask the question: Do
23 you have offhand, without looking, what
24 lipofuscin pigments a person of ordinary skill
25 in the art would have been aware of as of

1 September 2007?

2 A. Well, they go by some complex
3 nomenclature. But I think it's A2E, and then
4 there's a dihedral form, and then there a -- I
5 think it's called ATR; it's a dimer. Those are
6 some of them.

7 And -- for some of these, I'm not even
8 sure it's been totally characterized yet. So
9 it's a little bit complicated. But they're in
10 the -- they're in the schemes of the papers I
11 mentioned, just offhand without looking them up.
12 But I could give you a better answer if you give
13 me time to look at my --

14 Q. Sure. And we're going to get into some
15 of the references. I'm just trying to get some
16 background now.

17 Were you working as of 2007 in the field
18 of -- related to the formation of lipofuscin
19 pigments?

20 A. No, I was not.

21 Q. Have you ever worked the field related to
22 the formation of lipofuscin pigments?

23 A. No, I haven't. I've worked with
24 retinoids, but I haven't worked with lipofuscin
25 pigments.

1 Q. And so what you -- you're under -- let me
2 start again.

3 Your knowledge regarding lipofuscin
4 pigments is based on the literature you've
5 reviewed and cited in your report, Exhibit 1002;
6 is that correct?

7 A. Yes, I think -- well, that. Yes, there
8 may be -- I can't remember if there are any
9 other papers that didn't turn into exhibits,
10 but, yes, basically, yes, that's my
11 understanding.

12 Q. And what I'm trying to clarify is that
13 you didn't have separate knowledge prior to your
14 work on this case regarding the formation of
15 lipofuscin pigments; is that correct?

16 A. That is correct.

17 Q. Okay. Prior to your work in this case,
18 had you done any work related to treatments for
19 age-related macular degeneration?

20 A. No, I had not.

21 Q. And so is it fair to say that the
22 information addressed in your report regarding
23 age-related macular degeneration is based on
24 your review of the literature that you've cited
25 in your report?

1 A. Yes, generally. I have some knowledge
2 about macular degeneration. Mother had some
3 problems with it, and I have a cousin with
4 problems, so I had -- one of my fellow editors
5 had problems with this. But this is not
6 involving any of the details.

7 Q. So regarding the mechanisms, for example,
8 of age-related macular degeneration, that's
9 something you've learned from your work on this
10 case, correct?

11 A. I had not specifically studied that area
12 before. I'll agree with that.

13 Q. And when asked the same for Stargardt's
14 disease, are you familiar with Stargardt's
15 disease?

16 A. I am now. Well -- well, I don't know the
17 details of Stargardt's disease. It's another
18 visual problem disease, and I only know what
19 I've read about it.

20 Q. And what is your understanding generally
21 of Stargardt's disease?

22 A. I can't remember did [sic] I -- I don't
23 know. If I didn't mention that specifically in
24 my report, I don't remember.

25 Q. Okay.

1 A. And I don't remember any specific
2 exhibits dealing in -- well, specializing in
3 Stargardt's disease.

4 Q. So it -- again, fair to say that any
5 information or opinions you offer in your
6 declaration related to Stargardt's disease are
7 based on what you gleaned from the references
8 you've cited; is that correct?

9 A. I would agree with that.

10 Q. Okay. We'll go on to maybe more
11 comfortable territory.

12 Your -- the focus of your research over
13 the years has been enzyme metabolism, correct?

14 MR. MILLS: Objection to form.

15 THE WITNESS: It's been a central
16 feature. I describe myself as an enzymologist.

17 BY MR. FELDSTEIN:

18 Q. As a what?

19 A. Enzymologist.

20 Q. Okay. And am I right that when we're
21 talking about enzyme metabolize -- metabolism,
22 we're talking about things like P450, correct?

23 MR. MILLS: Objection; form.

24 THE WITNESS: That's one of the
25 enzymes I've worked with probably more than any

1 other -- than any other.

2 BY MR. FELDSTEIN:

3 Q. And so you describe yourself as an
4 enzymologist, and P450 is the enzyme you worked
5 with more than any other enzyme, correct?

6 A. That is correct. I do work in other
7 areas too. I'm accomplished in the areas of
8 toxicology, and I also have worked in
9 endocrinology and cancer research.

10 Q. Is any of your toxicology, endocrinology,
11 or cancer research work related to retinal
12 diseases?

13 MR. MILLS: Objection; form.

14 THE WITNESS: Retinal, you mean eye
15 diseases?

16 BY MR. FELDSTEIN:

17 Q. Yes.

18 A. No, not specifically.

19 Q. Where in the body is the P450 enzyme
20 located?

21 A. Well, there are -- I don't want to get --
22 I could talk all day about this, obviously, but
23 we have -- humans have 57 cytochrome P450
24 enzymes, P-4-5-0. They are located in different
25 places; different ones are in different places.

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1 As a whole, the main concentration is in the
2 liver. Other enzymes have -- other cytochrome
3 P450 enzymes have roles in places like the
4 renals, renal glands, skin, places like that.

5 Q. There's P450 in the skin?

6 A. Definitely.

7 Q. Is there P450 enzyme in the eye?

8 A. I am not aware of anyone who's reported
9 that, but I may be overlooking some. I did not
10 specifically address that question in my report.

11 Q. Okay. Mark Exhibit 2054.

12 (Exhibit Number 2054 was marked.)

13 BY MR. FELDSTEIN:

14 Q. Just one page. And I'm marking
15 Exhibit 2054. It says mini review prolog at the
16 top, and the title is "Metals in Biology 2016:
17 Molecular Basis of Selection of Metals By
18 Enzymes." And it's authored by Peter
19 Guengerich.

20 Are you familiar with Exhibit 2054,
21 Doctor?

22 A. I authored this. I haven't looked at it
23 in some time.

24 Q. Generally, is this a paper you published
25 related to your work as an enzymologist?

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1 A. Kind of. The -- I pub- -- this is
2 actually an introduction to a pneumatic series
3 of -- in the Journal of Biological Chemistry.
4 This was when I was an associate editor for that
5 particular journal. I guess I was also deputy
6 editor at the same time.

7 But basically I was just introducing for
8 mini reviews that I had solicited; none of these
9 dealing with cytochrome P450, yes.

10 MR. MILLS: For this line of
11 questions, I'm just going to register objections
12 to them under Federal Rules of Evidence 402
13 through 403.

14 BY MR. FELDSTEIN:

15 Q. And I'm sorry. You were saying you were
16 an editor for what journal, Doctor?

17 A. The Journal of Biological Chemistry.

18 Q. Which is at the bottom?

19 A. Yes. It's listed at the bottom and the
20 top.

21 Q. And you're the only author of
22 Exhibit 2054, correct?

23 A. I am. As I said, this is an introduction
24 to papers by four sets of authors that I
25 solicited.

1 Q. Do you have acknowledgment at the bottom
2 right? Is that a coauthor, K. Trisler?

3 A. Kathy Trisler is my secretary.

4 Q. Your secretary at the Journal of
5 Biological Chemistry?

6 A. No. At Vanderbilt -- well, yes, she was
7 paid part-time by the Journal of Biological
8 Chemistry, so she was working half-time for me
9 at Vanderbilt and half-time for the journal.

10 Q. And so it's not -- Exhibit 2054 is not
11 P450 enzymology specifically, but it is in that
12 general field of enzymology that -- where you
13 specialize?

14 A. Yes, it is. It's about -- well, it's
15 specifically about metals in biology. I ran
16 these series per -- looks like at least eight
17 different papers. About once a year I would
18 solicit -- decide on some proteins that had
19 metals in and solicit mini review articles and
20 put these together into a pneumatic series to
21 actually further develop to the interest in
22 biochemistry of metals, but none of these
23 specifically deal with cytochrome. In fact,
24 they don't deal with cytochrome P450 at all.

25 Q. Okay. Thank you.

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1 Can we turn back to your report? You had
2 directed me, I think, to paragraph 55 in Exhibit
3 1002 earlier regarding a person of ordinary
4 skill in the art.

5 A. Yes.

6 Q. You say in paragraph 55: A person of
7 ordinary skill in the art would have had
8 practical knowledge and experience about
9 metabolism studies.

10 And it continues. And my question is:
11 Why would a person of ordinary skill in the art
12 related to the subject matter of the '045 patent
13 have had practical knowledge and experience
14 about metabolism?

15 A. Well, retinoids do get metabolized. They
16 are -- you know, the pathways are actually
17 fairly complicated. They involve not only
18 oxidation, but also things like binding to
19 specific binding proteins and distribution in
20 the body.

21 As you probably know, we get our
22 retinoids from vitamin A or carotenoids like
23 beta carotene, and these are processed in the
24 body, and the retinoid metabolism is tightly
25 controlled. So somehow we take in vitamin A;

1 that's why it's called a vitamin, and this is
2 distributed throughout the body, not just to the
3 eye. Retinoids derived from vitamin A have
4 important functions in regulation in many
5 systems in our body.

6 Q. Okay. In terms of oxidation, where is
7 vitamin A oxidized?

8 MR. MILLS: Objection to form.

9 THE WITNESS: That wasn't a specific
10 issue I addressed, but I can address that just
11 from my general knowledge.

12 It's -- I'm sorry -- vitamin A --
13 well, it's a little more complicated because we
14 have several forms. We have retinol, retinal,
15 and retinoic acid.

16 BY MR. FELDSTEIN:

17 Q. And for the court reporter, the first one
18 ended -OL; the second one ended -AL; and the
19 third one was retinoic acid.

20 A. Right. Correct.

21 Yeah, so with those, these -- retinoic
22 acid is oxidized at the four position, primarily
23 is the main product. All three of the retinoids
24 as shown in my own laboratory are also --
25 they're dehydrogenated at the three, four

1 position of the cyclohexyl ring.

2 Q. And that's my fault. I was actually --
3 meant to ask, not where on the molecule they are
4 oxidized, but where on the body are they
5 oxidized?

6 A. Well, okay. I can answer that question.
7 Retinoic acid is oxidized primarily in
8 the liver, and this last process, this
9 dehydrogenation that I mentioned that we
10 published on, is actually in the skin in humans.

11 Q. Would a person of ordinary skill in the
12 art have understood whether oxidized forms of
13 vitamin A still feed into the visual cycle?

14 MR. MILLS: Objection; scope.

15 THE WITNESS: Yes. I would -- I
16 would answer that, that I think that would be
17 clear from the literature.

18 BY MR. FELDSTEIN:

19 Q. Are you aware of what a person of
20 ordinary skill in the art would have understood
21 as of 2007 as to whether oxidized vitamin A
22 species feed into the visual cycle?

23 MR. MILLS: Objection; scope.

24 THE WITNESS: I thought I answered
25 that question.

1 I think that's -- well, I don't have
2 a specific reference, but I think this was
3 well-known from the retinoid literature at the
4 time.

5 BY MR. FELDSTEIN:

6 Q. And what are you aware that a person of
7 ordinary skill in the art would have understood
8 as of 2007 as to whether oxidized vitamin A
9 species feed into the visual cycle?

10 MR. MILLS: Objection; scope.

11 THE WITNESS: I'm sorry. I thought
12 I answered that question.

13 BY MR. FELDSTEIN:

14 Q. I'm asking -- maybe -- I'm sure the
15 question is not clear, and I apologize for that.
16 What I'm getting at -- and I'll ask the question
17 again because I'm trying to understand from you
18 what you know that a person of ordinary skill in
19 the art would have known, so let me ask the
20 question with that background again.

21 What are you aware of that a person of
22 ordinary skill in the art would have known as of
23 2007 regarding whether oxidized vitamin A
24 species feed into the visual cycle?

25 MR. MILLS: Objection; form, as to

Page 24

1 the scope.

2 THE WITNESS: Well, maybe your
3 question is too complicated.

4 When you say oxidized, I mentioned
5 already that there are actually multiple
6 oxidation products. There's a 4-hydroxyl
7 product, the 4-oxyl product, the 3,4-D-saturated
8 product. I think the literature at the time was
9 clear that most of these things -- or there was
10 no evidence that any of these things were active
11 in the visual cycle.

12 BY MR. FELDSTEIN:

13 Q. Thank you, Doctor.

14 In paragraph 55, you also say that a
15 person of ordinary skill in the art would have
16 had -- would have had practical knowledge and
17 experience about the deuterium kinetic isotope
18 effect, right?

19 A. Yes.

20 Q. Why, in your opinion, would a person of
21 ordinary skill in the art have had practical
22 experience regarding the deuterium kinetic
23 isotope effect?

24 A. Well, this is a concept. The deuterium
25 isokinetic isotope effect, it's been around

1 chemistry for probably roughly 100 years and --
2 or nearly 100 years. It's also very well known
3 to biochemists and medicinal chemists, and --
4 and, yeah, so it's not unusual.

5 This is basically something that's
6 covered in advanced to certainly advanced
7 organic chemistry classes. I teach about this
8 in my own graduate course.

9 Q. In the literature related to the
10 formation of lipofuscin pigments, the deuterium
11 isotope effect had not come up by 2007, correct?

12 MR. MILLS: Objection; form.

13 THE WITNESS: I'm not aware that it
14 had been specifically applied to retinoids at
15 that time.

16 BY MR. FELDSTEIN:

17 Q. You don't indicate that the person of
18 ordinary skill in the art had any practical
19 knowledge of age-related macular degeneration,
20 right?

21 A. Well, I -- no, I did not specifically
22 mention that. I do mention in paragraph 54
23 and -- well, this is, e.g., an example. This
24 would be a practicing physician who diagnoses
25 and treats ophthalmic -- ophthalmologic

1 diseases such as macular degeneration.

2 Q. But you know, in your view, the person of
3 ordinary skill in the art wouldn't need even
4 practical knowledge related to age-related
5 macular degeneration specifically, correct?

6 MR. MILLS: Objection to form.

7 THE WITNESS: Well, if I could
8 answer that, I think that somehow someone would
9 have to collaborate. For instance, a medicinal
10 chemist would probably be collaborating with
11 somebody who did have more specific knowledge
12 about some of the details of macular
13 degeneration in order to pursue development of
14 drugs in this area.

15 BY MR. FELDSTEIN:

16 Q. And you understand that there are claims
17 in the '045 patent specifically directed to
18 treatment of age-related macular degeneration,
19 correct? It's Exhibit -- should be 1001.

20 A. You said the '045 patent?

21 Q. Correct.

22 A. Let me look at that.

23 As I recall, there were about 54 claims.

24 Q. Yeah, if you need copies, we have
25 everything.

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1 A. I have it. Okay.

2 Can you repeat the question?

3 Q. I'm going -- I'm going to back up a
4 little bit since we have the patent in front of
5 us. Can you turn to Claim 1 of '045?

6 A. I have it.

7 Q. And it's directed to a method of
8 retarding accumulation of lipofuscin pigment in
9 the retina, correct?

10 A. Yes.

11 Q. And in your view, would a person of
12 ordinary skill in the art as of 2007 have
13 practical knowledge regarding the accumulation
14 of lipofuscin pigments in the retina?

15 Would -- in your opinion, would a person
16 of ordinary skill as of 2007 had practical
17 knowledge and experience related to the
18 accumulation of lipofuscin pigment in retina?

19 MR. MILLS: Objection to form.

20 THE WITNESS: My answer would be
21 that some of the people who would qualify as
22 POSAs would; others would be more specialized in
23 other areas.

24 And if I could get back to your
25 previous question, Claim 4 does talk about the

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1 method used for treatment for macular
2 degeneration. Well, more of the claims do too,
3 like 5.

4 BY MR. FELDSTEIN:

5 Q. Sticking with Claim 1 for a minute, in
6 your view, a person of ordinary skill in the art
7 may or may not have had practical knowledge and
8 experience related to the accumulation of a
9 lipofuscin pigment in a retina as of 2007,
10 correct?

11 MR. MILLS: Objection to form.

12 THE WITNESS: I can answer that. I
13 think, you know, many of the people who would be
14 considered persons of ordinary skill in the art
15 by themselves, for instance, a medicinal chemist
16 would know how to make compounds and deal with
17 that. And on the other hand, I don't think
18 every medicinal chemist understands all of the
19 details of every disease target that he or she
20 is working with.

21 BY MR. FELDSTEIN:

22 Q. So in your view, a person of -- one --
23 I'm sorry.

24 In your view, one could be a person of
25 ordinary skill in the art without practical

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1 knowledge or experience related to retarding the
2 accumulation of lipofuscin pigment in the
3 retina, correct?

4 MR. MILLS: Objection to the form,
5 asked and answered.

6 THE WITNESS: The information about
7 this was all in the open literature, so anyone
8 who was interested in the subject matter, yeah,
9 I think this would have been readily -- the
10 information would have been readily available in
11 the open literature for a POSA.

12 BY MR. FELDSTEIN:

13 Q. Well, in paragraph 55, you talk about
14 having deuterium -- experience related to
15 deuterium kinetic isotope effect. That's also
16 in the literature, correct?

17 A. Yes.

18 Q. But you're saying it's a requirement that
19 in your definition of a person of ordinary skill
20 in the art that they have practical experience
21 and knowledge related the deuterium kinetic
22 isotope effect. That's a requirement according
23 to your definition, correct?

24 MR. MILLS: Objection to form.

25 THE WITNESS: My understanding of

1 the person of ordinary skill in the art is that
2 it doesn't necessarily have to be a single
3 person who understands every aspect of the
4 problem. Again, a POSA could effectively be a
5 team of individuals who understand different
6 aspects of the problem, going from the clinical
7 work back to very basic chemistry and synthesis
8 of molecules.

9 BY MR. FELDSTEIN:

10 Q. But that -- that person as you defined
11 must have practical knowledge and experience
12 related to deuterium kinetic isotope effect,
13 correct?

14 MR. MILLS: Objection to form.

15 THE WITNESS: Well, somebody has --
16 somebody in the team must know something about
17 deuterium isotope effect, I guess is what I'm
18 saying.

19 BY MR. FELDSTEIN:

20 Q. Okay.

21 A. Even if it's a rudimentary understanding.

22 Q. And in your definition, there's no
23 requirement that any individual person or team
24 persons have practical knowledge and experience
25 directed to the accumulation of a lipofuscin

1 pigment in a retina, correct?

2 MR. MILLS: Objection to form.

3 THE WITNESS: Well, I think this
4 would probably be included in the paragraph 54
5 talking about macular degeneration. I think it
6 was -- well, there was certainly plenty of
7 literature in macular degeneration literature by
8 that time about the accumulation of pigment.

9 BY MR. FELDSTEIN:

10 Q. So would or wouldn't a person of ordinary
11 skill in the art had have to had a practical
12 knowledge regarding the accumulation of a
13 lipofuscin pigment in the retina?

14 MR. MILLS: Objection to form, asked
15 and answered.

16 THE WITNESS: I think I've answered
17 that.

18 As I said, there are individuals,
19 for instance, a medicinal chemist who
20 wouldn't -- may not have worked on this specific
21 disease area, but would have been very
22 knowledgeable about other areas and been able to
23 develop this by, you know, reading more and
24 addressing the problem.

25 BY MR. FELDSTEIN:

1 Q. And as of 2007, you didn't have a
2 practical knowledge and experience regarding the
3 accumulation of a lipofuscin pigment in the
4 retina, correct?

5 MR. MILLS: Objection; form.

6 THE WITNESS: I had not worked in
7 the specific area, no.

8 BY MR. FELDSTEIN:

9 Q. Okay. And you recognize there are claims
10 directed to the treatment of Stargardt's
11 disease, correct? For example, Claim 38.

12 A. Yes.

13 Q. And in your definition of a person of
14 ordinary skill in the art, in your view, they
15 would not have had to have knowledge regarding
16 Stargardt's disease, correct?

17 MR. MILLS: Objection to form.

18 THE WITNESS: My answer is that
19 there are actually a number of diseases here.
20 If we go down to Claim 43, there are more
21 diseases, you know, in addition to the
22 Stargardt's, and then there are -- also in 37,
23 there's something called dry non neovascular
24 age-related macular degeneration.

25 So there are a variety of, probably,

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1 related diseases here, and my opinion is that a
2 specific person would not have to be an expert
3 in all of these to actually start working on
4 this.

5 BY MR. FELDSTEIN:

6 Q. Would a person of ordinary skill in the
7 art have had to -- you -- let me back up.

8 You answered with respect to an
9 expertise. I'm asking along the lines of what
10 you have in paragraph 55.

11 Would a person of ordinary skill have
12 had -- had to have practical knowledge and
13 experience related to Stargardt's disease?

14 MR. MILLS: Objection to form, asked
15 and answered.

16 THE WITNESS: I didn't mention
17 Stargardt's disease or any specific disease in
18 paragraph 55. Well, wait a minute. Let me read
19 the rest. No, I didn't.

20 BY MR. FELDSTEIN:

21 Q. So your opinion, a person of ordinary
22 skill in the art would not have had to have
23 practical knowledge and experience regarding
24 Stargardt's disease; is that correct?

25 MR. MILLS: Objection to form, asked

1 and answered.

2 THE WITNESS: I didn't mention
3 Stargardt's disease or these other diseases in
4 all the claims.

5 BY MR. FELDSTEIN:

6 Q. And by not mentioning it, what you're
7 saying is that -- that's not a requirement,
8 practical knowledge and experience regarding
9 Stargardt's disease to be a POSA, correct?

10 MR. MILLS: Objection to form.

11 THE WITNESS: I think I did answer
12 the question to the best of my ability.

13 Again, I didn't, you know -- I think
14 in -- usually with these POSA statements, you
15 don't -- my experience is that you don't try to
16 overspecialize, so -- a lot of these things. I
17 think that I've made it fairly general. I think
18 that the people working in these areas would
19 qualify as POSAs.

20 BY MR. FELDSTEIN:

21 Q. Okay. You didn't, as of 2007, have a
22 practical knowledge and experience regarding
23 Stargardt's disease, correct?

24 MR. MILLS: Objection to form, asked
25 and answered.

1 THE WITNESS: I did not.

2 BY MR. FELDSTEIN:

3 Q. And even today you don't have practical
4 knowledge and experience regarding Stargardt's
5 disease treatment, correct?

6 MR. MILLS: Objection; form.

7 THE WITNESS: I do not have
8 practical experience with Stargardt's disease.

9 BY MR. FELDSTEIN:

10 Q. Okay.

11 A. Or treating any ophthalmologic disease.

12 Q. Do your opinions in this case change as
13 to whether the claim is directed to the
14 treatment of Stargardt's disease or whether it's
15 treated to age-related macular degeneration?

16 MR. MILLS: Objection to form.

17 THE WITNESS: I have not written --
18 I've really not commented on that specifically
19 or any of these other diseases, for instance, in
20 Claim 43.

21 BY MR. FELDSTEIN:

22 Q. You don't have an opinion specific to the
23 treatment of Stargardt's disease different from
24 the treatment of age-related macular
25 degeneration, correct?

1 MR. MILLS: Objection to form.

2 THE WITNESS: I do not.

3 There's another expert that's filed
4 a report in this case. I believe Dr. Calman,
5 and he's actually practicing -- practicing
6 clinician, and he's the expert and I'm not on
7 that.

8 BY MR. FELDSTEIN:

9 Q. Did you consult with Dr. Calman at all?

10 A. No.

11 Q. Did you consult with anyone else for your
12 work in this case besides counsel?

13 A. No.

14 Q. Let's go backwards a little bit here.

15 In your declaration, paragraph 19.

16 Paragraph 19 generally is the standard you
17 applied for the determination of obviousness,
18 correct?

19 A. Yes. This is under the legal standards
20 section.

21 Q. And you've offered opinions in this case
22 on obviousness, correct?

23 A. Yes.

24 Q. The fourth enumerated point in paragraph
25 19 is secondary indicia of obviousness.

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1 A. Yes.

2 Q. What secondary indicia of obviousness did
3 you consider?

4 A. I don't remember specifically.

5 Q. Are there any that you remember at all?

6 A. No.

7 Q. Do you remember generally what you
8 considered?

9 A. First secondary indicia -- no, I don't.

10 Q. Do you remember if you considered
11 secondary indicia of obviousness?

12 A. I have to look at the
13 specific possibilities -- or specific points in
14 order to try to address that.

15 Q. Sitting here, you don't remember whether
16 or not you addressed secondary indicia of
17 obviousness, correct?

18 MR. MILLS: Objection to form.

19 THE WITNESS: Again, this is a
20 fairly legal definition, and it gets into some
21 of the -- well, what we'll call the weeds of the
22 legal interpretation, and, again, I -- I don't
23 remember specifically what constitutes exactly
24 secondary indicia as opposed to primary.

25 BY MR. FELDSTEIN:

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1 Q. And you don't remember what, if any,
2 secondary indicia you considered in forming your
3 opinions in this case, correct?

4 A. I think I answered that. I do not.

5 Q. Okay. Going to paragraph 25.

6 Let's skip paragraph 25. We'll go to
7 paragraph 184. I'm sorry for going out of
8 order.

9 In the second sentence of paragraph 184,
10 you say: The 1,5, which is -- excuse me -- you
11 say: The 1,5, which is in square brackets,
12 sigmatropic shift step in the pathway in the
13 '045 patent is just upstream of the intermediate
14 that results in both A2E and ATR dimer.

15 And then you continue, correct?

16 A. Yes.

17 Q. How are you relying on the '045 patent in
18 your opinions regarding the 1,5-sigmatropic
19 shift that you're referring to?

20 A. I'm relying -- well, let me look at the
21 patent again. I don't remember if there is a
22 scheme or not. I think there is.

23 Yeah, there's a Figure 2 in the '045
24 patent, and also I'm relying on the papers by
25 Mata, Fishkin -- Mata, Fishkin, and others in

1 terms of their presentations of the pathway.

2 Q. And why are you relying on the '045
3 patent for its presentation of pathway?

4 A. Why am I relying on the '045 patent?

5 Q. Correct.

6 A. Well, it's because it's there, and
7 although it's not in as much detail as it is in
8 the two other papers, the PNAS papers by Mata
9 and Fishkin and some others.

10 Q. Are -- I'm sorry.

11 Are you relying on the '045 patent as a
12 basis for your -- your opinion regarding the
13 1,5-sigmatropic shift?

14 MR. MILLS: Objection to form.

15 THE WITNESS: It's -- not really
16 because it's presented in more detail in other
17 papers.

18 BY MR. FELDSTEIN:

19 Q. So then why are you mentioning the '045
20 patent in Figure 2?

21 A. Because you asked me a question about
22 that.

23 What was the original question?

24 Q. Why are you relying on the '045 patent in
25 paragraph 183 and 184 of your report?

1 Do you want an extra copy of the '045
2 patent?

3 A. No, it's fine. Back to 184.

4 Q. I'll ask the question again.

5 Why are you relying on the '045 patent in
6 paragraphs 183 and 184 of your report regarding
7 obviousness of the '045 patent?

8 MR. MILLS: Objection to form.

9 THE WITNESS: I can answer your
10 question again.

11 Okay. I'm not relying on it. If
12 you read the sentence, it says: The
13 1,5-sigmatropic shift step in the pathway in the
14 '045 patent is just upstream, et cetera.

15 That doesn't mean that I'm relying
16 on this. What I'm -- it just says that it's in
17 the patent, but it is also in the open
18 literature before -- that was published well
19 before the patent was applied for.

20 BY MR. FELDSTEIN:

21 Q. And so what was your thought process,
22 then, for including it -- including the '045
23 patent in your discussion here of the pathway?

24 A. Well, I mentioned that it appears there.
25 That's not it, though. The first sentence --

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1 actually, it says it was disclosed in Mata.

2 Q. And I'm asking you what your thought
3 process was for including the '045 Patent's
4 description of the 1,5 step.

5 A. It could have been done without leaving
6 it. I could have just said the 1,5-sigmatropic
7 shift step in the pathway is just upstream, and
8 I could have referenced Mata or other papers
9 instead.

10 Q. Right. But you didn't, and so I'm asking
11 why you did include it?

12 A. Well, I did reference it in Mata. It's
13 just a matter of reference to the patent, and
14 the fact is that the patent was actually using
15 the scheme, basic scheme, that was already
16 published.

17 Q. So was there a reason or was there no
18 reason for including the 45 patent in paragraphs
19 183 and 184 of your report?

20 MR. MILLS: Objection to form, asked
21 and answered.

22 THE WITNESS: I think I answered the
23 question.

24 I basically pointed out that this
25 step in the patent, you know, if you go back and

1 use the previous sentence, is that it was
2 already disclosed in Mata as well as other
3 papers.

4 BY MR. FELDSTEIN:

5 Q. Okay. Could you go back to paragraph 49?
6 And you say -- read the whole paragraph to
7 yourself, but you say in the middle: The patent
8 applicant apparently never informed the examiner
9 about art references that expressly disclosed
10 the Claim C20 deuterated retinoids.

11 Do you see that?

12 A. Yes.

13 Q. Do you still believe that to be accurate?

14 A. Well, okay. The prosecution history is
15 actually pretty long, and I'm not -- don't want
16 to go search through that specifically again,
17 but I indicated that I found no mention
18 informing the examiner that Pho in 1988 -- and I
19 believe that is either Pho or -- I forgot the
20 other first author; it's from Olson's Laboratory
21 at Iowa State -- that these hadn't been actually
22 cited.

23 Q. The sentence says, among other things:
24 Patent applicant apparently never informed the
25 examiner about prior art references that it

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1 expressly disclosed the claimed C20 deuterated
2 retinoids.

3 Do you stand by that statement as
4 accurate, Doctor?

5 MR. MILLS: Objection; form.

6 THE WITNESS: Well, can you point me
7 to information in the patent process that that
8 specific reference from Olson's Lab was
9 mentioned in the application?

10 BY MR. FELDSTEIN:

11 Q. I'm asking a different question, Doctor.

12 Sitting here today, do you believe the
13 statement you make in paragraph 49 to be
14 accurate?

15 A. I believe it's accurate unless you can
16 show me evidence that I missed something when I
17 put this report together.

18 Q. And how did you form your opinion that
19 patent applicant apparently never informed the
20 examiner about prior art references that
21 expressly disclosed claimed C20 deuterated
22 retinoids?

23 A. The -- well, I did read the patent
24 proceedings and the objections and also -- I
25 also found this -- or discussed this with

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1 counsel.

2 Q. Did counsel give you this information
3 that applicant never informed the examiner about
4 prior art references that expressly disclosed
5 the claimed C20 deuterated retinoids?

6 MR. MILLS: I'm going to issue a
7 cautionary instruction. So unless you're
8 relying on a statement from counsel as the basis
9 for your opinion, I'll instruct you not to
10 disclose the content of the confidential
11 communications you may have had with counsel.

12 THE WITNESS: Yeah. I don't
13 specifically remember the exact history about
14 this, but that -- again, I stand by that unless
15 you can show me that this is missing -- that I
16 was wrong about that.

17 BY MR. FELDSTEIN:

18 Q. The statement may have relied on
19 information provided to you from counsel; is
20 that correct? You don't remember?

21 MR. MILLS: Objection to form,
22 mischaracterizes the witness's testimony.

23 THE WITNESS: I have no further
24 answer on that.

25 BY MR. FELDSTEIN:

1 Q. Your testimony -- is it your testimony
2 that you formed that opinion independently of
3 counsel?

4 A. I can't say that.

5 Q. Okay. And is it your testimony that you
6 read the entirety of the file history of the
7 applications underlying the '045 patent?

8 A. I did read the entire file.

9 Q. Okay.

10 A. It was pretty boring.

11 Q. And you considered all the references
12 that were cited in the file history of the
13 application leading to the '045 patent; is that
14 correct?

15 A. I don't remember that I read all of them.

16 Q. Okay. And in paragraph 50, you have a
17 similar sentence.

18 Patent applicant apparently never
19 informed the examiner that the prior art, e.g.,
20 Mata, publically attributed in vivo lipofuscin
21 formation to reactions involving removal of a
22 hydrogen from carbon-20, C20, of vitamin A and
23 its active analogues. Do you stand by that as
24 being accurate, to the best of your knowledge?

25 A. I do unless you can show me something

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1 that specifically that goes against that.

2 Q. So when you reviewed the file histories
3 underlying the application related to the '045
4 patent and the references cited therein, you
5 didn't see any references attributing in vivo
6 lipofuscin formation to reactions involving
7 removal of a hydrogen from carbon-20 of vitamin
8 A and its active analogues?

9 MR. MILLS: Objection to form.

10 THE WITNESS: The -- I don't think
11 there was a specific comment. I can't remember.
12 I'm just thumbing through the patent now as to
13 whether Mata was cited or not.

14 The -- of course, the scheme in the
15 '045 patent actually does show that missing;
16 although, the point is that the removal of the
17 carbon would have to inferred in -- in that. In
18 that process. I'm sorry.

19 BY MR. FELDSTEIN:

20 Q. So to be clear, it's your understanding
21 that none of the references submitted during
22 prosecution of the applications leading to the
23 '045 patent disclosed removal of a hydrogen from
24 carbon-20 of vitamin A and its active analogues
25 in the in vivo formation of lipofuscin?

1 MR. MILLS: Objection to form,
2 misstates the witness's testimony.

3 THE WITNESS: Well, let me try to
4 answer your question. I'm looking at the
5 reference list in the '045 patent. I don't
6 specifically -- unless I missed this. I don't
7 specifically see the Mata, et al., paper cited.

8 BY MR. FELDSTEIN:

9 Q. And is it your understanding that none of
10 the references cited in the '045 patent or in
11 the prosecution history leading to the '045
12 patent disclosed a similar step of attributing
13 in vivo lipofuscin formation to reactions
14 involving removal of a hydrogen from carbon-20
15 of vitamin A and its active analogues?

16 MR. MILLS: Objection to form,
17 misstates the witness's declaration testimony.

18 THE WITNESS: I don't see anything
19 else. I don't know if that particular Fishkin
20 paper, which is reference 13, did or not.

21 MR. FELDSTEIN: I'm going to switch
22 topics if anybody wants to take a break.

23 MR. MILLS: It's been about an hour.

24 (Brief break was observed.)

25 BY MR. FELDSTEIN:

1 Q. Can you turn, Doctor, to Exhibit 1011?

2 A. 1011.

3 Q. If you want copies of anything, we have
4 copies too, if you want them separate from your
5 binder.

6 A. For some reason, I don't seem to find
7 1011.

8 MR. FELDSTEIN: Drew, could you
9 pull --

10 THE WITNESS: Oh, yes, I do. Never
11 mind. My fault.

12 BY MR. FELDSTEIN:

13 Q. This is a paper by Fishkin, Sparrow,
14 Allikmets, and Nakanishi, correct?

15 A. Nakanishi, yes.

16 Q. Are you familiar with these authors,
17 Doctor?

18 A. I know Nakanishi, or the late Nakanishi,
19 by his reputation. I don't know him personally.

20 Q. Do you know any of the other authors?

21 A. Nope.

22 Q. Would a person of ordinary skill in the
23 art recognize them as leading researchers in the
24 field of formation of lipofuscin pigment?

25 MR. MILLS: Objection to form,

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1 scope.

2 THE WITNESS: My answer would be
3 yes. You know, I -- based on my experience
4 here, Nakanishi has -- seemed to be involved in
5 a number of these papers. He was actually a
6 very well-known chemist.

7 BY MR. FELDSTEIN:

8 Q. Okay. Can you turn to Figure 10 in
9 Exhibit 1011?

10 A. I have it.

11 Q. There's the species with the description
12 tautomer X under it. Do you see that?

13 A. Yes. Yes, I do.

14 Q. Is that species and Figure 10 as a whole
15 attributing in vivo lipofuscin formation to
16 reactions involving removal of hydrogen from the
17 carbon-20 of vitamin A or its active analogues?

18 A. Yes, it is.

19 Q. Okay. And can we go back to the patent,
20 '045 patent, and can you go to Column 22?

21 A. The '045 patent column --

22 Q. 22.

23 A. Okay. That's the reference list.

24 Q. Reference Number 13, do you see Fishkin?

25 A. Yes.

1 Q. Reference Number 13 in the '045 patent is
2 the same as Exhibit 1011, correct?

3 A. Yes.

4 Q. And so now, if we turn back to your
5 declaration, paragraph 50, your statement on
6 page 29 that applicant never informed -- 28 to
7 29, the statement that patent applicant
8 apparently never informed the examiner that the
9 prior art attributed in vivo lipofuscin
10 formation to reaction involving removal of a
11 hydrogen from carbon-20 of vitamin A and its
12 active analogues. That statement's incorrect?

13 MR. MILLS: Objection. Form,
14 mischaracterizes the testimony.

15 THE WITNESS: What was the question?

16 BY MR. FELDSTEIN:

17 Q. Your statement or your belief that patent
18 applicant never informed the examiner that the
19 prior art attributed in vivo lipofuscin
20 formation to reactions involving removal of the
21 hydrogen from carbon-20 of vitamin A and its
22 active analogues, that is incorrect, correct?

23 MR. MILLS: Objection to form,
24 mischaracterization.

25 THE WITNESS: The specific -- well,

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1 specifically, Mata is not cited but Fishkin is.
2 And Fishkin does -- although it's not really
3 discussed in the patent, Fishkin's scheme does
4 show the removal of the hydrogen at C20.

5 BY MR. FELDSTEIN:

6 Q. Applicant did inform the examiner of
7 prior art attributing in vivo lipofuscin
8 formation to a reaction involving removal of a
9 hydrogen from carbon-20 of vitamin A and its
10 active analogues, correct?

11 MR. MILLS: Objection to form,
12 mischaracterization.

13 THE WITNESS: If you give me a
14 minute, I'm trying to find where this is
15 actually -- how this was cited.

16 BY MR. FELDSTEIN:

17 Q. If you want to look in Column 21 where it
18 says "The following documents which are cited
19 above and not -- are incorporated by reference
20 as cited in the (inaudible)."

21 A. I'm sorry. Where are you? In Column 21
22 of the patent?

23 Q. Actually, I will withdraw that and let
24 you look wherever you want.

25 A. Okay. Okay. The patent does cite

1 reference 13. I'm looking on column 2. I don't
2 think there's any further discussion of that,
3 and it does again reference -- that reference,
4 the Fishkin reference, actually does show there
5 actually involved the breaking of the
6 carbon-hydrogen bond at carbon-20.

7 Q. Do you recall how it was that you came to
8 the opinion that the patent applicant never
9 informed the examiner that the prior art
10 attributed in vivo lipofuscin formation to
11 reactions involving removal of hydrogen from
12 carbon-20 of vitamin A and its active analogues?

13 MR. MILLS: Objection; form.

14 THE WITNESS: I don't remember any
15 of the discussion in the process here from the
16 patent agency then, specifically. Perhaps they
17 missed that. I don't know. They didn't discuss
18 -- well, they certainly didn't discuss this in
19 the patent; they just cited the reference.

20 BY MR. FELDSTEIN:

21 Q. And you testified that you came to that
22 opinion independent of information provided to
23 you by counsel?

24 MR. MILLS: Objection to form, asked
25 and answered.

1 THE WITNESS: I don't specifically
2 remember that progress. This was actually back
3 in -- you know, at least back in December, or if
4 not before, and I can't remember specifically
5 how we came to that particular statement.

6 BY MR. FELDSTEIN:

7 Q. So sitting here today, you can't testify
8 that you came to the statement in paragraph 50,
9 that we've read, independently from information
10 provided to you by counsel; is that correct?

11 MR. MILLS: Object to form,
12 mischaracterizes the witness's testimony.

13 THE WITNESS: As I said, I don't
14 remember the specifics.

15 BY MR. FELDSTEIN:

16 Q. Okay. Can we now talk about the Mata
17 reference that's referred to there and you
18 referred to in Exhibit 1010?

19 A. I -- have it.

20 Q. Okay. And you're familiar with Exhibit
21 1010, the Mata reference?

22 A. Yes, I am.

23 Q. Can you turn to Figure 5? You're
24 familiar with Figure 5 from Mata Exhibit 1010?

25 A. Yes, I am.

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1 Q. Okay. Is it your opinion that the -- is
2 it your opinion that's what -- excuse me.

3 Is it your opinion that what is referred
4 to as a 1,5-sigmatropic rearrangement of APE is
5 the rate-limiting step in the reaction sequence
6 shown in Figure 5?

7 MR. MILLS: Objection to form.

8 THE WITNESS: You said the
9 rate-limiting step?

10 BY MR. FELDSTEIN:

11 Q. Yes.

12 A. I don't think I could say that. It may
13 be a rate-limiting step in the overall process.

14 Q. Why do you say -- why can't you say it is
15 the rate-limiting step?

16 A. Well, first of all, this is a concept we
17 usually don't talk in enzyme kinetics, and
18 that's with enzymes, but the same thing applies.
19 It's strictly chemical processes. There often
20 are more than one rate-limiting step; that is
21 two steps made to attribute to rate limitation.

22 So an example would be -- okay. Let's
23 say you're driving from Washington to Nashville
24 and there are two -- let's say you're going --
25 whatever road you want to take, but on the

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1 highway, you know, normally it would be four
2 lanes, but there are two places where you're
3 down to two lanes, and these go for several
4 miles. So either of those, if it gets congested
5 and gets cut down one lane, it's going to be a
6 problem for you. So that's kind of analogous
7 to the deuterium issue that we're talking about
8 here and what's really rate limiting. So you
9 may have more than one rate-limiting step on the
10 process.

11 Q. What other rate-limiting steps, are --
12 excuse me.

13 What other steps in Mata Figure 5 would a
14 person of ordinary skill in the art understood
15 to also be rate limiting?

16 A. Well, the one -- it would be -- the first
17 step is the 1,5-sigmatropic rearrangement
18 involves the breaking of carbon-hydrogen bond,
19 so that's an obvious possibility. Without
20 further knowledge, it could be the
21 3,3-sigmatropic rearrangement or the
22 dimerization process or perhaps even one of the
23 other following the steps then.

24 Q. And are you saying that one of them --
25 one of those other steps could be the overall

1 most rate-limiting step in the reaction?

2 MR. MILLS: Objection to form.

3 THE WITNESS: As I said, we tend not
4 to use the concept of the overall rate-limiting
5 step unless there's particular evidence about
6 rates of specific steps. That is, in my own
7 research with cytochrome p450, that it worked on
8 retinoid oxidation.

9 We found that there were actually
10 two rate-limiting steps. One involved
11 carbon-hydrogen bond breaking, leading to a
12 deuterium isotope effect. And another
13 rate-limiting step was the reduction of the
14 enzyme; they both contributed.

15 BY MR. FELDSTEIN:

16 Q. So would a person of ordinary skill in
17 the art as of 2007 be able to rank the relative
18 degree of -- excuse me.

19 When we say rate limiting, you're
20 referring to a slow step, generically, correct?

21 MR. MILLS: Objection; form.

22 THE WITNESS: As I said, you can
23 have multiple slow steps, and I'd also like to
24 make a point that this is a little -- somewhat
25 different than what we see in normal enzyme

1 reactions.

2 These are strictly chemical
3 reactions, and in many ways, they're actually
4 simpler. So if you inhibit the first step,
5 which is the one involved -- well, effectively,
6 the first step after the condensation of the
7 phosphatidyl at the nolamine, if you inhibit
8 that step, you will block the accumulation of
9 the APE intermediate, and then you'll actually
10 have less material to go on to the subsequent
11 products, regardless of how slow or fast they
12 are.

13 BY MR. FELDSTEIN:

14 Q. Would a person of ordinary skill in the
15 art as of 2007 been able to evaluate the
16 relative speed of each step in Figure 5 of Mata
17 compared to the other steps in Mata?

18 MR. MILLS: Objection to form.

19 THE WITNESS: Two -- well, the point
20 is, in a way, it doesn't really matter what the
21 relative rates are for these individual
22 reactions if you can block the first step of
23 them, and the first step is the one that would
24 be the easiest to actually deter.

25 BY MR. FELDSTEIN:

1 Q. The first step being the biomolecular
2 reaction of --

3 A. No. I'm sorry. The first -- the
4 numbering's a little funny in this Figure 5 in
5 the Mata paper. The step in which you get -- I
6 should be more specific. The 1,5-sigmatropic
7 rearrangement, that is actually very -- should
8 be very susceptible to kinetic isotopic effect.

9 Q. So let me try to get an answer to my
10 question, though.

11 My question was: Would a person of
12 ordinary skill in the art as of 2007 have been
13 able to evaluate the relative speed of each step
14 in Figure 5 of Mata Exhibit 1010?

15 MR. MILLS: Objection to form, asked
16 and answered.

17 THE WITNESS: Of every step, my
18 general answer would be no. But as I said, I
19 don't know that -- I don't think that that's
20 actually an issue in this particular case, and a
21 person of ordinary skill in the art would have
22 been led to attack the -- the 1,5-sigmatropic
23 rearrangement based on literature precedent
24 about kinetic isotopic effects and the ease of
25 preparing material with deuterium.

1 BY MR. FELDSTEIN:

2 Q. Isn't it true that in early 2000s CH bond
3 breaking was regarded as generally being
4 relatively rapid?

5 MR. MILLS: Objection to form.

6 THE WITNESS: No, I wouldn't say
7 that. Why -- no, I don't have any basis to say
8 that I wouldn't agree with that.

9 BY MR. FELDSTEIN:

10 Q. So --

11 A. Are you talking specifically about this
12 process in Figure 5 of Mata or just in general?

13 Q. Just in general, sir.

14 A. Well, it's very hard to generalize, first
15 of all, because there are many ways in which we
16 break CH bonds, both in strictly chemical
17 reactions and -- so, for instance, the -- if we
18 go back to precedent here for 1,5-sigmatropic
19 rearrangement, it'd have been known since 1966
20 at least that there was a high kinetic deuterium
21 isotope effect in that reaction, which is
22 basically the model for this.

23 And also different enzymes, you know --
24 well, different enzymes would actually be --
25 some of these would be highly susceptible to

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1 deuterium isotope effects; others would not.

2 I also should have put this in earlier
3 before the enzymes. Other chemical processes
4 are also -- strictly chemical processes with no
5 enzymes are also subject -- where you would
6 break carbon-hydrogen bonds are actually also
7 susceptible to deuterium isotope effects. For
8 instance, racemization is one in which more
9 recently deuterium -- deuteration has actually
10 been applied as a way of slowing that down.

11 Q. You're referring to kinetic isotopic
12 effect measured in 1966. You're talking about
13 Roth; is that correct?

14 A. Roth and König.

15 Q. And in that reaction, which you seem to
16 know well, am I -- is that correct?

17 A. I've studied that paper considerably.

18 Q. There's only one step involved -- the
19 only step involved is the 1,5-sigmatropic shift,
20 correct?

21 A. Yes.

22 Q. It's not a multistep reaction in Roth,
23 correct?

24 A. No, it's not. The Itou and I guess
25 all -- During later on talked about -- also talk

1 about reverse reaction, but basically it's an
2 irreversible step, yes.

3 Q. So it's necessarily the slowest step
4 because it's the only step in Roth, correct?

5 MR. MILLS: Objection; form.

6 THE WITNESS: Well, I suppose one
7 could say that, yeah, it's the only step. It's
8 a single reaction, yes.

9 BY MR. FELDSTEIN:

10 Q. Okay. And so it doesn't -- Roth doesn't
11 tell you whether sigmatropic shift in a
12 different multistep sequence is going to be
13 overall rate limiting, correct?

14 MR. MILLS: Objection; form.

15 THE WITNESS: It does not. But as I
16 mentioned, that's not really the point. The
17 point is, if you can block the -- slow down the
18 first step, which is the 1,5-sigmatropic
19 rearrangement in Mata, you can slow down the
20 supply of material for subsequent steps then,
21 and ultimate -- that would actually have an
22 effect regardless of how fast or slow these
23 particular ones are.

24 BY MR. FELDSTEIN:

25 Q. In Mata Figure 5, how many of the steps

1 would a person of ordinary skill in the art
2 understand contribute to the overall reaction
3 rate?

4 MR. MILLS: Objection; form.

5 THE WITNESS: To the overall
6 reaction rate to form what? To form A2E or
7 A2PE?

8 BY MR. FELDSTEIN:

9 Q. All the way to the end of the sequence
10 from the very first species reacting to the very
11 last product of A2E.

12 MR. MILLS: Objection to form.

13 MR. FELDSTEIN: I'm sorry. What's
14 form problem, Counsel?

15 MR. MILLS: Can you repeat the
16 question?

17 BY MR. FELDSTEIN:

18 Q. Did you understand the question, Doctor?

19 A. I understand your question, but I think
20 I've answered that. I guess the point is that
21 it doesn't matter if the subsequent steps are
22 slow if you can actually inhibit the first one.
23 Or I should say attenuate the first one. Then
24 you will actually lead to less of a final
25 product.

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1 This is different. I think you may be
2 more familiar with the concept of deuterium
3 isotope effects in enzyme reactions, and as you
4 know, I worked with your firm before on -- in
5 this and some other situations.

6 This is not a cyclic process. Enzymes go
7 through a cycle where they have multiple steps,
8 and one of those can slow down the overall rate
9 of reaction.

10 This is a linear reaction. Basically,
11 you start with something; you end up with
12 something; so if you block any step here, you
13 will actually slow down the production of the
14 final product.

15 Q. So you're saying that as of 2007 a person
16 of ordinary skill in the art would have
17 understood that, of the sequence in Mata
18 Figure 5, that every step is a plausible
19 rate-limiting step?

20 MR. MILLS: Objection to form,
21 mischaracterizes the witness's testimony.

22 THE WITNESS: I would say -- well,
23 it was very -- this is difficult research to do
24 because some of these intermediates are very
25 hard to isolate and study these specific steps

1 and their rates. So it may -- in fact, I'm not
2 even sure this has been done to date.

3 However, one -- if one could inhibit
4 any of these steps or attenuate any of these
5 steps, one should slow down the overall
6 production of the undesirable materials, that
7 being the A2PE and the A2E.

8 It turns out that the
9 1,5-sigmatropic rearrangement presents what I --
10 what I think a POA would consider the easiest
11 route to inhibition because all one had to do
12 was introduce the different isomer of hydrogen
13 at a particular position, which was already
14 known and reported in the literature.

15 BY MR. FELDSTEIN:

16 Q. Different isotope?

17 A. Different isotope. Deuterium instead of
18 hydrogen -- protium.

19 Q. You said isomers. I just want to
20 clarify.

21 A. I'm sorry. Did I? I meant isotope.

22 Q. So backing up a little bit, the very
23 first reaction is a reaction between
24 all-trans-retinaldehyde, and I'll just say PE,
25 okay?

1 A. Okay. Phosphatidylethanolamine, yeah.

2 Q. PE for short, yeah?

3 A. All right. We'll do that.

4 Q. Okay. What would a person of ordinary
5 skill in the art understand about the rate of
6 that reaction?

7 MR. MILLS: Objection to scope.

8 THE WITNESS: That is the formation
9 of a shift base. That reaction actually is
10 reversible. That's, again, a pure chemical
11 reaction, and I'm not -- I don't know if
12 anybody's actually tried this, but the addition
13 of the phosphatidylethanolamine may not be
14 required for the 1,5-sigmatropic rearrangement.

15 Well, I shouldn't say -- let me --
16 you know, let me qualify that. I don't know if
17 that's required or not; it may be. Somebody
18 might have tried that.

19 BY MR. FELDSTEIN:

20 Q. My question is: What would a person of
21 ordinary skill in the art understand about the
22 rate of that biomolecular reaction?

23 MR. MILLS: Objection to form, asked
24 and answered.

25 THE WITNESS: Well, I don't think

1 anybody would know the specific rate; however,
2 it's a very facile reaction. It's a reversible
3 reaction. It happens very quickly because all
4 you're doing is combining the amine and the
5 aldehyde and taking out the element of water.

6 BY MR. FELDSTEIN:

7 Q. And doesn't it depend on the
8 concentration of the two reactants?

9 MR. MILLS: Objection to form,
10 incomplete hypothetical.

11 THE WITNESS: That's true. It's a
12 biomolecular reaction, so it would depend on the
13 concentrations on original components.

14 BY MR. FELDSTEIN:

15 Q. And so what would a person of ordinary
16 skill in the art as of 2007 have known about the
17 concentration of those pure reactants and their
18 effect on the reaction rate?

19 MR. MILLS: Objection to form,
20 scope.

21 THE WITNESS: Well, it's a very --
22 it would be expected in the absence of more
23 complicating factors, such as an enzyme bringing
24 these together or something like that, to
25 actually be a biomolecular reaction and be first

1 order -- what we call first order in each of the
2 two components.

3 BY MR. FELDSTEIN:

4 Q. So second order overall?

5 A. Second order overall, that is correct; I
6 agree with that.

7 Q. And so the rate depends on the
8 concentration of each of the two components,
9 correct?

10 MR. MILLS: Objection to form and
11 scope.

12 THE WITNESS: Yes. That's the
13 definition of a second order chemical reaction.

14 BY MR. FELDSTEIN:

15 Q. And what would a person have
16 understood -- a person of ordinary skill in the
17 art as of 2007 have understood about those
18 concentrations?

19 MR. MILLS: Objection to form,
20 scope, asked and answered.

21 THE WITNESS: I don't know that
22 those concentrations have actually been measured
23 in -- well, specifically in the cells in the
24 eye, and I'm not quite sure how one would
25 actually do that, in fact, then.

1 Well, you could -- well, I guess you
2 could. No, it'd be very difficult in a very
3 specific localization. But the point is it is a
4 reversible reaction.

5 BY MR. FELDSTEIN:

6 Q. Okay. What the patent calls APE -- I
7 mean -- excuse me.

8 What Mata Figure 5 calls APE, is that
9 undergoes a 1,5-sigmatropic rearrangement
10 according to Mata, correct?

11 A. Yes.

12 Q. And that's spontaneous due to molecular
13 reaction, correct?

14 MR. MILLS: Objection to form.

15 THE WITNESS: It's an unimolecular
16 reaction; yes, it is. And it's specifically --
17 and it's also what's called a synchronous
18 reaction.

19 And what was your other part?

20 BY MR. FELDSTEIN:

21 Q. Spontaneous.

22 A. Yeah. Well, we can say -- I don't like
23 to use the word spontaneous in chemistry because
24 you don't -- although you don't need a specific
25 catalyst, this happens very, very slowly unless

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1 you have, for instance, a lot of heat present.
2 So I don't like the word spontaneous. That
3 means that it's happening immediately.

4 Q. What is your basis saying that it happens
5 very slowly?

6 A. Well, if we look at the models that were
7 done with 1 -- or 1,5-sigmatropic
8 rearrangements, these required long time periods
9 and a lot of heat then. So basically you're
10 talking about things up around 200 degrees for
11 at least days, weeks, or perhaps even months in
12 some of the experiments there.

13 This reaction also happens very slowly in
14 the eye because -- well, people -- babies
15 generally don't have macular degeneration; old
16 people do. So it may take decades for this
17 process to develop and accumulate amounts of
18 lipofuscin except in unusual disease states.

19 Q. The formation of A2E is slow based on the
20 "baby versus old person" comment you made,
21 correct?

22 A. I don't know.

23 Q. But you also don't know that babies don't
24 have it, a lipofuscin accumulation, because of
25 the 1,5-sigmatropic rearrangement is slow. It

1 could be that something else is slow.

2 MR. MILLS: Objection; form.

3 BY MR. FELDSTEIN:

4 Q. Correct?

5 A. Well, I don't -- my understanding is --
6 unless some ophthalmologists know more than I do
7 about this, that babies don't have accumulated
8 things like A2PE and A2E.

9 Q. Right. But you don't get to --

10 A. Lipofuscins. Sorry.

11 Q. You don't get to those until, for
12 example, you have a second biomolecular reaction
13 with all-trans-retinol, correct?

14 A. As far as I know, retinal --
15 retinaldehyde itself does not undergo a
16 1,5-sigmatropic rearrangement. But I'm not sure
17 that anybody's ever actually compared those
18 rates as far as I'm aware.

19 Q. But to be clear, Doctor, you can't
20 conclude from babies not having high levels of
21 lipofuscin deposits that the 1,5-sigmatropic
22 rearrangement in Mata Figure 5 itself is slow,
23 correct?

24 MR. MILLS: Objection to form.

25 THE WITNESS: Well, no, I cannot do

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1 that. I just mentioned that because you brought
2 up the Mata just being spontaneous. I mentioned
3 the model chemistry, which required very high
4 temperatures, and I also just added this
5 because, as far as we understand, this is not a
6 rapid process in humans at physiological
7 temperatures.

8 BY MR. FELDSTEIN:

9 Q. No one's ever measured the reaction rate
10 for the 1,5-sigmatropic rearrangement, correct?

11 MR. MILLS: Objection; form.

12 BY MR. FELDSTEIN:

13 Q. In -- in -- excuse me. Let me start
14 again. Thank you.

15 No one's ever measured the reaction rate
16 of the 1,5-sigmatropic rearrangement of APE,
17 correct?

18 A. I'm not aware that that's been done, no.

19 Q. And so no one knows what the reaction
20 rate is for the 1,5-sigmatropic rearrangement of
21 the APE, correct?

22 MR. MILLS: Objection to form.

23 THE WITNESS: As far as I
24 understand, that hasn't been done. I'm actually
25 not sure it's possible, but -- to do that.

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1 BY MR. FELDSTEIN:

2 Q. Why would it not be possible?

3 A. Well, if you actually have to apply a lot
4 of heat to get this reaction to go, it might
5 break down other parts of the molecule.

6 Q. And the model system that applies a lot
7 of heat, that's again Roth, correct?

8 A. That's one of the those. There's also
9 theoretical work by Itou, and I think these
10 things are cited, and also there's another
11 experimental study later by During as well.

12 Q. And Itou is just reanalyzing the data
13 from Roth, correct?

14 A. No, it's not. It's actually a
15 computational paper using calculations -- well,
16 they're using data, experimental -- or dealing
17 with experimental data, but they're also using
18 computational work of their own then.

19 Q. I may have asked that badly and not
20 giving enough credit to Itou. But my question
21 is Itou did not create new raw data on the
22 reaction rates, correct? They were relying
23 on -- for data, they were relying on Roth?

24 A. Well, they were -- I can't comment on
25 exactly whether they were doing (inaudible) --

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1 what we call (inaudible) work or not. I don't
2 remember the details of all their computational
3 work. The During was certainly doing
4 experimental work.

5 Q. Okay. Well, Roth, then -- Roth was
6 simplified molecule gas phase, correct?

7 A. By necessity because the temperatures had
8 to be so high that this was actually -- those
9 simple molecules actually wouldn't be liquid
10 anymore.

11 Q. Okay. And Roth didn't measure anything
12 in the in vivo environment of the retina,
13 correct?

14 A. No, he didn't.

15 Q. And Roth didn't make any measurements of
16 the molecule nearly as complicated as APE,
17 correct?

18 MR. MILLS: Objection to form.

19 THE WITNESS: I agree that Roth and
20 König use a simplified molecule. That was the
21 whole point of it. That's also the case with
22 During and with Itou too.

23 BY MR. FELDSTEIN:

24 Q. And it was a simplified, symmetric
25 hydrocarbon, correct?

1 MR. MILLS: Objection; form.

2 THE WITNESS: Yes, it was.

3 BY MR. FELDSTEIN:

4 Q. Okay.

5 A. Or I think there were more than one in
6 During, actually, as I recall.

7 Q. And AP is not symmetric, correct?

8 MR. MILLS: Objection; form.

9 THE WITNESS: It is not symmetric
10 because of the nitrogen present, yes.

11 BY MR. FELDSTEIN:

12 Q. Right. And it's also not a simple
13 hydrocarbon because it has at least a nitrogen
14 as well as other species present, correct?

15 MR. MILLS: Objection; form.

16 THE WITNESS: That is true.

17 BY MR. FELDSTEIN:

18 Q. And are you aware of any references that
19 bridge the gap between Roth's symmetric
20 hydrocarbon and an asymmetric molecule with
21 nitrogen?

22 MR. MILLS: Objection to form,
23 mischaracterize witness's testimony.

24 THE WITNESS: I'm aware of a paper,
25 which I think is an exhibit here by (inaudible).

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1 BY MR. FELDSTEIN:

2 Q. And that paper, you think, addresses the
3 sigmatropic shift in asymmetric molecule with
4 nitrogen?

5 A. It does but the models -- the -- it's
6 also a purely computational paper, no
7 experiments, and it also doesn't actually
8 address the particular transformation here with
9 the CH bond breaking.

10 Q. So are you aware of any references that
11 address the particular situation here of
12 carbon-hydrogen bond breaking in -- by a
13 1,5-sigmatropic rearrangement in an asymmetric
14 molecule having nitrogen?

15 MR. MILLS: Objection; form.

16 THE WITNESS: My recollection, the
17 only one that would come close would be the one
18 I just mentioned, (inaudible), but that still
19 doesn't really rate -- relate directly to this
20 particular type of transformation.

21 BY MR. FELDSTEIN:

22 Q. Okay. I appreciate that.

23 A. And, again, that's a theoretical paper.
24 Well, I shouldn't say a theoretical -- just say
25 a computational paper is probably a better term.

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1 Q. Would a person of ordinary skill in the
2 art have understood that the reaction between --
3 well, let me back up a second.

4 What Mata refers to as APE, is that with
5 or without -- excuse me. Let me start again.

6 What Mata refers to as APE in Figure 5,
7 is that before or after the sigmatropic
8 rearrangement?

9 A. That's -- well, if you take out the
10 arrows -- let me look. Now I'm having trouble
11 seeing. I think -- it's a little fuzzy.

12 My understanding is that the H is still
13 connected to carbon-20 and that there's a only
14 dotted line going over to the nitrogen. Or are
15 there two dotted lines?

16 No, I think -- no, I think what I said is
17 correct. Yeah, I think that's before the
18 sigmatropic rearrangement.

19 Q. So your understanding is that when Mata
20 refers to APE, he's referring to the molecule
21 prior to 1,5-sigmatropic rearrangement?

22 A. Yes. That's my understanding, and I
23 think that's also the case in the Fishkin paper
24 too, as I recall.

25 Q. Are you aware by 2007 whether there was

1 any way to separately measure APE, both before
2 and after sigmatropic rearrangement?

3 MR. MILLS: Objection to form,
4 scope.

5 THE WITNESS: I'm not aware that
6 there was because I don't think the subsequent
7 product would be -- the subsequent products
8 might not -- were probably not that stable. In
9 fact, I think some of the subsequent
10 chromatography was pretty messy.

11 BY MR. FELDSTEIN:

12 Q. Are you aware of APE that has undergone
13 1,5-sigmatropic rearrangement ever having been
14 experimentally verified as of 2007?

15 MR. MILLS: Objection; form.

16 THE WITNESS: I'm not aware of that.
17 As I said, it doesn't look like a particularly
18 stable molecule for chromatography.

19 BY MR. FELDSTEIN:

20 Q. And so if you're doing chromatography,
21 you may be measuring either APE or
22 sigmatropically rearranged APE?

23 MR. MILLS: Objection to form.

24 THE WITNESS: No. I think APE
25 should be stable, at least stable enough to do

1 chromatography. I think you can tell the
2 difference between that and the subsequent
3 products; however, the subsequent products are
4 probably going to be very messy.

5 BY MR. FELDSTEIN:

6 Q. What would happen to sigmatropically
7 rearranged APE in a chromatography experiment?

8 MR. MILLS: Objection to form.

9 THE WITNESS: It's, again -- it is
10 hypothetical. This is a charged species, and it
11 could be a number of things to break down.

12 BY MR. FELDSTEIN:

13 Q. And what number of things would those be?

14 MR. MILLS: Objection.

15 THE WITNESS: Could hydrolyze, react
16 with water.

17 BY MR. FELDSTEIN:

18 Q. The reaction between sigmatropically
19 rearranged APE and all-trans-retinol in the
20 second row of Mata Figure 5, that was understood
21 to be a relatively rare event as of 2007; is
22 that correct?

23 MR. MILLS: Objection to form.

24 THE WITNESS: I'm sorry. Repeat the
25 question again. APE and which one?

1 BY MR. FELDSTEIN:

2 Q. All-trans-retinol in the second row of
3 Mata Figure 5, that was understood to be a
4 relatively rare event as of 2007, correct?

5 MR. MILLS: Objection; form.

6 THE WITNESS: I -- wouldn't be
7 relatively rare.

8 BY MR. FELDSTEIN:

9 Q. It happens infrequently in vivo?

10 MR. MILLS: Objection to form.

11 THE WITNESS: That would be my
12 understanding because, you know, again, we do
13 have, you know, retinoids floating around our
14 bodies, and they don't all turn into lipofuscin
15 rapidly.

16 BY MR. FELDSTEIN:

17 Q. If the rearranged -- if the
18 sigmatropically rearranged APE doesn't react
19 with all-trans-retinol as shown in Row 2 of Mata
20 Figure 5, what happens to it in vivo?

21 MR. MILLS: Objection to form.

22 THE WITNESS: Well --

23 BY MR. FELDSTEIN:

24 Q. Actually, I'm going to try to correct the
25 question with your counsel's objection.

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1 What would a person of ordinary skill
2 understand regarding what would happen to
3 sigmatropically rearranged APE in vivo if it
4 didn't react with all-trans-retinol?

5 MR. MILLS: Objection to form,
6 incomplete hypothetical.

7 THE WITNESS: Yeah. The -- let me
8 try to answer your question. I think perhaps
9 maybe a simplified -- the answer, if we go to
10 Fishkin -- not trying to evade your question.
11 Fishkin is in Exhibit 1011. In Figure 10
12 there's something they call a tautomer X. That
13 is the product of the sigmatropic rearrangement.
14 If you'll agree with me about that, that
15 molecule, as I understand, has not actually been
16 isolated, as far as I know.

17 BY MR. FELDSTEIN:

18 Q. And you're referring to tautomer X?

19 A. Yes. Tautomer X. I don't like the word
20 tautomer, by the way, but I can talk about that
21 later.

22 But that molecule -- I don't know that
23 anyone knows exactly what levels are present in
24 vivo in cells or what other fates that might
25 have other than path A and path B, both of which

1 are dimerizations.

2 Q. So I'm with you on Fishkin. Sticking
3 with Fishkin, if -- they call in the top row on
4 Fishkin Figure 10, they call -- they identify
5 species by the initials NRpe, correct?

6 A. Correct.

7 Q. And that's the same thing that Mata calls
8 APE, correct?

9 A. That's correct, yes.

10 Q. And what would a person of ordinary skill
11 in the art understand from Fishkin as to where
12 -- what alternative paths there are for NRpe
13 other than the -- what Fishkin calls the 1,6
14 proton shift?

15 MR. MILLS: Objection to form.

16 THE WITNESS: Well, I -- there could
17 be -- I think this is hypothetical, and I don't
18 know that anyone really thought as -- thought
19 that much about it or they tried to do anything
20 about it, but, you know, it could be oxidized by
21 other -- by enzymes, for instance. You could
22 stick oxygen at some of the usual places on
23 retinoids; that's a possibility.

24 BY MR. FELDSTEIN:

25 Q. Would the person of ordinary skill in the

1 art as of 2007 understood that there was some
2 alternate paths of consumption of NRpe other
3 than what Fishkin calls the 1,6 proton shift?

4 MR. MILLS: Objection to form, calls
5 for speculation.

6 THE WITNESS: I could only
7 speculate, but I don't know that there was any
8 evidence or anything like that. So in the
9 absence of evidence, I think a POSA would assume
10 that this, you know, could go on to the
11 sigmatropic rearrangement.

12 BY MR. FELDSTEIN:

13 Q. And if you slowed the sigmatropic
14 rearrangement -- let me try again. And maybe go
15 back to Mata Figure 5. Let's go back to Mata
16 Figure 5, Doctor.

17 A. Sure.

18 Q. You had said that the CH bond breaking in
19 the 1,5 rearrangement of APE -- I think you said
20 it was an obvious possibility for being a
21 rate-limiting step.

22 Is that consistent with your opinion,
23 Doctor? Did I get that right?

24 MR. MILLS: Objection to form,
25 misstates the witness's testimony.

1 THE WITNESS: Rather than say a
2 rate-limiting step, I would say that it would be
3 obvious for slowing -- if you attenuate that,
4 you'll get less of a final product.

5 BY MR. FELDSTEIN:

6 Q. So when a POSA -- excuse me -- a person
7 of ordinary skill in the art as of 2007 wouldn't
8 have looked at the 1,5-sigmatropic rearrangement
9 in Mata as being a rate-limiting step; is that
10 correct?

11 MR. MILLS: Objection to form,
12 mischaracterizes the witness's testimony.

13 THE WITNESS: Well, I would say that
14 a person skilled in the art would have looked at
15 this and would have -- it would have been
16 obvious that if you could slow down the CH
17 bond-breaking step, that you would actually slow
18 down the whole process.

19 By the way, I'd like to apologize
20 for this, but I'm looking at this more
21 carefully, and as I look in Mata, I think this
22 is actually showing a sort of almost transition
23 state. I thought before that there was a solid
24 bond through the H, but I think it's actually
25 dotted all the way over to the end. Am I

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1 correct about that?

2 BY MR. FELDSTEIN:

3 Q. I don't know that I can see it any
4 better, but are you answering the earlier
5 question of whether -- when Mata refers to APE,
6 whether he's referring to the pre- or
7 post-sigmatropic shift?

8 A. I think, yes. We had a question like
9 that, and I want to make sure that I didn't make
10 a mistake.

11 Q. And what is your best understanding now?

12 A. Well --

13 Q. What is your understanding now from Mata
14 as to whether APE refers to species before or
15 after the sigmatropic shift or, I suppose, both?

16 A. Well, I think my answer to the question
17 now, if that's a dotted line. Maybe somebody
18 else -- well, no, I guess no one else could
19 answer the question in my eyes even with my
20 glasses. Well, this is the only copy.

21 MR. MILLS: I'm going to issue a
22 cautionary instruction to the witness not to
23 speculate.

24 THE WITNESS: Okay. I think it's
25 actually showing something that we could call a

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1 transition state, which has got the hydrogen
2 bonded to the both nitrogen and the carbon.

3 That's not the way I would have done
4 it. My impression was that this was
5 corresponding to what Fishkin calls the NRpe
6 where there actually is a solid bond to the
7 hydrogen.

8 BY MR. FELDSTEIN:

9 Q. So --

10 A. I want to make sure that I'm not giving
11 you anything misleading here.

12 Q. Sure. And if I could try to dumb down,
13 less science to what you're saying, is
14 it correct that what you're saying now is that
15 Mata appears to be using, to your understanding,
16 APE to refer to both pre- and post-sigmatropic
17 rearrangement?

18 MR. MILLS: Objection to form.
19 And caution the witness not to
20 speculate.

21 THE WITNESS: I can't -- I'm not
22 Mata. I would -- I might have done this
23 differently myself, but I think I know what he
24 means then. He is showing something that looks
25 more like a transition state than the individual

1 compound.

2 BY MR. FELDSTEIN:

3 Q. So would a POSA understand APE in Mata to
4 refer to pre-sigmatropic rearrangement,
5 transition state, post-sigmatropic
6 rearrangement, or some mix of the three?

7 MR. MILLS: Objection to form,
8 outside the scope.

9 Caution the witness not to
10 speculate.

11 THE WITNESS: I could only
12 speculate, but I think the problem was -- I
13 think Mata probably -- again, this is what I
14 would have done. I would have shown the
15 individual steps in that case.

16 BY MR. FELDSTEIN:

17 Q. So that sigmatropic rearrangement, a
18 person of ordinary skill in the art wouldn't
19 look at it as rate limiting per se, but would
20 look at it as a place to slow down the overall
21 reaction rate is my understanding of what you
22 had said earlier, correct?

23 MR. MILLS: Objection to form,
24 mischaracterizes the witness's testimony.

25 THE WITNESS: That's one of the use

1 of the words, but again, the point is that if
2 you -- you know, the whole point is here that
3 you slow down the overall -- some step in the
4 process, you're going to slow down the amount of
5 the end product. Again, as I said, it's
6 different than cyclic enzyme reaction here in
7 terms of what -- when we talk about
8 rate-limiting steps.

9 BY MR. FELDSTEIN:

10 Q. Right. But I'm just trying to clarify
11 the terminology.

12 Are you saying that a person of ordinary
13 skill as of 2007 wouldn't look at the
14 rearrangement as a rate-limiting step per se,
15 but as a step that you could slow down?

16 MR. MILLS: Objection to form,
17 mischaracterizes the witness's testimony.

18 THE WITNESS: Again, the point is it
19 doesn't necessarily matter what's rate limiting
20 in the overall process, but if you can slow down
21 anything on the linear reaction, you'll slow
22 down the final product.

23 Again, it's like my analogy of
24 driving from Washington to Nashville and hitting
25 slow spots on the highway. If you hit a slow

1 spot, regardless of where it is, it's going to
2 take you longer to get here.

3 BY MR. FELDSTEIN:

4 Q. Sure. But can you answer my question?
5 What I'm asking is: Is it correct that a
6 person of ordinary -- is it correct that, in
7 your opinion, a person of ordinary skill in the
8 art would look at the sigmatropic rearrangement
9 in Mata as a step that could be slowed down but
10 not as a rate-limiting step per se?

11 MR. MILLS: Objection to form,
12 mischaracterize the witness's testimony.

13 THE WITNESS: I think I've tried to
14 answer this. As I said, it's not necessarily --
15 I don't think a POSA is looking for the
16 rate-limiting step in a sequence like this. If
17 you can slow down the -- any step in the
18 reaction, including this -- well, first one or
19 after the -- after the initial condensation,
20 then you can slow down the overall reaction.
21 That's the whole point here.

22 MR. MILLS: We've been going for
23 about an hour and because we got -- started late
24 because your flight difficulty.

25 MR. FELDSTEIN: Let me finish a few

1 more questions related to this, Doctor; is that
2 okay?

3 THE WITNESS: What's that?

4 MR. FELDSTEIN: Let me finish a few
5 more questions related to this; is that okay?

6 MR. MILLS: Is your blood sugar okay
7 right now, or do you --

8 THE WITNESS: I haven't measured it,
9 but I probably --

10 MR. MILLS: Okay. We can go --

11 BY MR. FELDSTEIN:

12 Q. Can you give me a couple of questions?

13 A. Okay. We'll do that.

14 Q. Okay. You let me know when you need to
15 take a break. But we'll have to refresh
16 everything all over again.

17 Oh, what you're saying about being able
18 to slow down the overall reaction rate, that
19 would be true for any linear sequential
20 biochemical reaction, that if you can slow down
21 any step, you're saying in essentially any
22 biochemical synthesis, you're going to slow down
23 the overall rate; is that correct?

24 MR. MILLS: Objection to form,
25 incomplete hypothetical.

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1 THE WITNESS: It is hypothetical,
2 but the -- okay. Let's say -- trying to think
3 of a good example. Well, if you -- let's say
4 you -- yeah, if you slow down the -- I'm
5 thinking a little bit outside the box here, but
6 if you -- let's say -- okay. You eat protein.
7 I'll try to keep this simple and not have to
8 involve too much biology.

9 You eat protein and you have -- you
10 inhibit the breakdown of that protein in your
11 stomach by things called proteases, and they
12 break it down into amino acids; therefore, you
13 will have a lower level of individual amino
14 acids, and you will have less of those amino
15 acids to participate in the synthesis of new
16 proteins in your body.

17 BY MR. FELDSTEIN:

18 Q. In other words, if you slow down any
19 linear reaction of a biological chemical
20 reaction, you can slow down any step in any
21 biological -- multi-step biological chemical
22 reaction, you're saying that it will slow the
23 overall reaction rate?

24 A. Well, the --

25 MR. MILLS: Hold on. You got to let

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1 him finish his question and give me a chance
2 to object.

3 THE WITNESS: All right.

4 Sorry, Counsel, are you finished?

5 MR. FELDSTEIN: I'm done.

6 MR. MILLS: Okay. Thank you. My
7 objections are to form, incomplete hypothetical,
8 and outside the scope.

9 THE WITNESS: It is hypothetical,
10 but -- and I can't speak for every reaction. I
11 was just basically thinking of a possible
12 example here that -- there may be others, but
13 the point is it's not really the rate. It's
14 actually how much of the end product you have to
15 work with.

16 In the example I just cooked up for
17 you, it gives you a fewer amino acid to do
18 things with, and therefore, you would be able to
19 -- may be able to make less protein because of
20 that.

21 Perhaps that's oversimplified, but,
22 again, it's the point. This is different than
23 cyclic reactions here. It's not just the rate,
24 but it's actually how much you actually have to
25 go on all the way on.

1 BY MR. FELDSTEIN:

2 Q. And analogized limiting reaction to
3 driving from, I think, D.C. to Nashville,
4 correct?

5 A. Well, it may not be a perfect analogy,
6 but that's one I thought of.

7 Q. And even if you have a roadblock
8 somewhere on the road, everyone still gets to
9 Nashville at the end of the day, right?

10 MR. MILLS: Objection to form,
11 incomplete hypothetical.

12 THE WITNESS: Well, the -- you guys
13 didn't -- well, this was on the airplane. You
14 guys didn't get here last night.

15 BY MR. FELDSTEIN:

16 Q. I know. That's true and that's funny.

17 But if you slow down -- if you have a
18 slow point on a highway between here and
19 Nashville -- assuming that you haven't shut off
20 the highway completely, if you slow down
21 somewhere here between Nashville, everyone still
22 gets to Nashville, just slower, right?

23 MR. MILLS: Objection to form,
24 incomplete hypothetical.

25 THE WITNESS: Well, the -- yeah,

1 this is probably getting too hypothetical. We
2 could look at it different ways.

3 Let's talk about trucks making
4 deliveries on a specific date when they have to
5 be here. Perhaps some trucks won't get there on
6 time and will have fewer raw materials here to
7 whatever the trucks were delivering.

8 BY MR. FELDSTEIN:

9 Q. Congestion on the highway doesn't stop
10 you from getting to the endpoint, correct?

11 MR. MILLS: Objection to form,
12 incomplete hypothetical.

13 THE WITNESS: It may prevent you
14 from getting there in a timely manner to
15 actually accomplish your purpose.

16 MR. MILLS: So we've been going --

17 MR. FELDSTEIN: Let's take a break.
18 Thank you for letting me finish.

19 (Brief break was observed.)

20 BY MR. FELDSTEIN:

21 Q. Dr. Guengerich, could you turn to
22 paragraph number 98 in your declaration?

23 A. Yeah, I have it.

24 Q. And a long paragraph, but on the part
25 that is on page 59 -- well, paragraph 98, you're

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1 discussing the 1,5-sigmatropic rearrangement,
2 correct? I'm just trying to get back here.

3 A. Yeah, right.

4 Q. Okay. And then on -- towards the end of
5 paragraph 98 on page 59, you say: "That
6 enzymatic catalysis was very likely because
7 lipofuscin formation was undesirable," right?
8 Page 59.

9 A. I'm sorry. Where are you exactly?

10 Q. Second line down from the top of the page
11 59.

12 A. Oh, okay.

13 Q. And I'll just read it again.

14 A. Yeah, no, I see where it says --

15 Q. I'm just going to read it for the record
16 again, okay?

17 "Enzymatic catalysis was very likely
18 because lipofuscin formation was undesirable."

19 That was your opinion, correct?

20 A. Well, that's the somewhat general
21 biological statement that, you know, making bad
22 things is something that, you know, animals and
23 organisms generally don't do or we don't get
24 geared up for that. And so we generally don't
25 have enzymes that make bad things for us;

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1 although, there are some exceptions, I suppose.

2 Q. And what you're saying -- you're
3 referring to the 1,5-sigmatropic rearrangement
4 specifically when you say the enzymatic
5 catalysis was very unlikely?

6 A. No.

7 Q. What are you referring to then?

8 A. Cleavage -- well, cleavage of the
9 carbon-hydrogen bond there. Then I talk about
10 the enzyme catalysis, so that could have been
11 cytochrome p450 hydroxylation or some other
12 reaction going on.

13 Q. Maybe I lost the thread here. Paragraph
14 98 starts with "Person of ordinary skill in the
15 art would thus have had good reason to inhibit
16 the 1,5-sigmatropic shift," and then you go on,
17 correct?

18 A. Right.

19 Q. And then isn't the statement on page 59,
20 "enzymatic catalysis was very unlikely because
21 lipofuscin formation was undesirable," referring
22 back to the 1,5-sigmatropic shift?

23 MR. MILLS: Objection to form, asked
24 and answered.

25 THE WITNESS: Well, yeah. This

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1 is -- again, this is kind of hypothetical too.

2 Basically, I suppose one could also
3 argue that we might have enzymes to get rid of
4 lipofuscin, but apparently we don't, as far as I
5 know, so it doesn't -- again, as I think I said
6 before, it doesn't seem to be that there were
7 alternative processes that would work on
8 carbon-20 involving enzymes, in my opinion.

9 BY MR. FELDSTEIN:

10 Q. Could I ask a favor? Could you just read
11 paragraph 98 to yourself first, and then I'll
12 ask questions about it and let me know when
13 you've done that.

14 A. I'm ready.

15 Q. At the bottom of page 58, you say: "A
16 person of ordinary skill in the art would have
17 recognized that cleavage of this carbon-hydrogen
18 bond." Do you see that?

19 A. Yes.

20 Q. You're referring to the cleavage that
21 occurs in the 1,5-sigmatropic rearrangement,
22 correct?

23 A. Yes, the one on carbon-20.

24 Q. And it's the same sentence that continues
25 where you say: "Enzymatic catalysis was very

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1 unlikely because lipofuscin formation was
2 undesirable." You're referring to enzymatic
3 catalysis of the cleavage of the carbon-hydrogen
4 bond in the 1,5-sigmatropic shift, correct?

5 MR. MILLS: Objection to form.

6 THE WITNESS: It's more general in
7 terms of anything that could happen. I'm not
8 aware of enzymes that catalyze 1,5-sigmatropic
9 shift. But I think this is actually more
10 general in terms of alternative reactions by
11 other enzymes as well.

12 BY MR. FELDSTEIN:

13 Q. So you're saying it's more general? Are
14 you saying that none of the steps in Mata
15 Figure 5 -- start again.

16 When you say it's more general, are you
17 saying that it's unlikely that any of the steps
18 in Mata Figure 5 would be enzymatically
19 catalyzed because lipofuscin formation is
20 undesirable?

21 A. Well, I think it's more broader than
22 that. In fact, all of these -- this whole
23 process had been demonstrated in vitro. That is
24 basically you just run the reaction, and you'll
25 get these products slowly, then, you know, all

1 the way, going from -- starting -- of you
2 started with retinal and mixing it with an amine
3 and winding up with things like A2E and ATR
4 dimer.

5 Q. I apologize, but I'm not quite following,
6 Doctor.

7 Would a person of ordinary skill in the
8 art in 2007 have expected that enzymatic
9 catalysis was very unlikely for Mata's
10 1,5-sigmatropic rearrangement?

11 A. It was unlikely? Yes. I'd say so
12 because, as far as -- and I think I already
13 answered this. As far as I know, the
14 1,5-sigmatropic rearrangement was unknown for
15 enzymes.

16 Q. And would a person of skill in the art in
17 2007 have expected that enzymatic catalysis was
18 unlikely for each and every step in Mata
19 Figure 5 --

20 A. Yeah --

21 Q. -- because lipofuscin formation was
22 undesirable?

23 A. Well, if enzymatic catalysis -- as I
24 said -- we talked before. This is known to be a
25 very slow process, so if any enzymatic catalysis

1 was occurring, it would have to be relatively
2 slow.

3 I mean, there are possibilities, for
4 instance, if we're looking -- I'm actually
5 looking at Fishkin right now. But I think --
6 well, let me go back over to -- yeah. Well,
7 that's about -- can you just look at Fishkin,
8 which is next --

9 Q. Sure. I'm going to repeat my question
10 while you're looking so that we're clear on the
11 table.

12 Would a person of ordinary skill in the
13 art as of 2007 have expected that enzymatic
14 catalysis was unlikely for each and every step
15 in Mata Figure 5 because, as you say in
16 paragraph 98, lipofuscin formation was
17 undesirable?

18 MR. MILLS: Objection to form.

19 THE WITNESS: I mean, I think that's
20 one of the reasons. As I said, it's conceivable
21 that some of these reactions could be -- for
22 instance, the autooxidation could actually -- as
23 shown in Fishkin more clearly, could be
24 catalyzed by an enzyme, but since these have
25 been demonstrated to occur in the absence of

1 enzymes, there wasn't really a need to invoke --
2 to suppose that enzymes would be involved.

3 BY MR. FELDSTEIN:

4 Q. So as of 2007, to your understanding, a
5 POSA would have expected that enzymatic
6 catalysis was unlikely for each and every step
7 in Mata Figure 5 because lipofuscin formation
8 was undesirable, correct?

9 MR. MILLS: Objection to form, asked
10 and answered.

11 THE WITNESS: I think it was
12 unlikely, and, you know, one of the possible
13 reasons would be that this would be something
14 that is not favored in the body, and therefore,
15 one could raise the question why you would have
16 enzymes overmaking these things.

17 BY MR. FELDSTEIN:

18 Q. Are there other reasons you're aware of
19 why a person of ordinary skill in the art in
20 2007 would have expected that enzyme catalysis
21 was unlikely for each and every step in Mata
22 Figure 5?

23 MR. MILLS: Objection form.

24 THE WITNESS: Yeah, I think I
25 answered that. Basically, if you -- as shown --

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1 well, in the patent and then by others before
2 that, if you just mix up these things, you'll
3 actually get the end product, as shown both by
4 Mata and also Fishkin, both groups at Columbia
5 and at Dallas.

6 BY MR. FELDSTEIN:

7 Q. Do you know where biologically each step
8 in Mata Figure 5 takes place?

9 A. You're talking about which tissues or
10 organs?

11 Q. Yes. Which tissues.

12 A. Well, apparently it happens in the eye.
13 I'm not aware -- I guess it's conceivable this
14 could be happening in other tissues, but the
15 effects of -- may not be physiologically
16 relevant.

17 Q. Within the structure of the eye, what
18 would a POSA as of 2000 have understood
19 regarding what parts of the eye each step takes
20 place?

21 MR. MILLS: Objection to form.

22 You can answer.

23 THE WITNESS: Sorry.

24 What was the date?

25 BY MR. FELDSTEIN:

1 Q. September 2007.

2 A. Oh, sure. Well, since we're looking at
3 Mata, or I am, I see that they're actually
4 looking at -- in Figure 3, retina and the RPE
5 regions in the eye and showing that you're
6 actually getting at least A2E and A2PE --
7 dihydro-A2PE formed in those. So that -- no,
8 that would be part of the answer.

9 There may be other papers that show
10 these. I can't remember if Fishkin did that or
11 not or any other papers. At least those, it was
12 actually shown in those parts of the eye.

13 Q. Are you aware of different compartments
14 within the eye where visual cycle and A2E
15 formation occur?

16 MR. MILLS: Objection to form and
17 scope.

18 THE WITNESS: I think that maybe --
19 in terms of the fine details of that, I don't
20 really want to comment on that. That's beyond
21 my report, I think.

22 BY MR. FELDSTEIN:

23 Q. Does it matter to your opinion at all
24 where specifically or cellularly each step of
25 Mata takes place in the eye?

1 A. It probably does. Although, the steps --
2 since it's not enzymatic, I would think it'd be
3 similar in terms of what -- wherever the
4 retinaldehyde and phosphatidylethanolamine --
5 wherever they are, this should happen.

6 Now, the consequences of -- you know,
7 different parts may be very different, and also,
8 the concentrations of the retinal, with an A,
9 are going to be variable, I'm sure, in different
10 parts of the eye.

11 MR. FELDSTEIN: I can't read that
12 word.

13 BY MR. FELDSTEIN:

14 Q. Oh, was there consensus by 2007 on the
15 biosynthetic pathway for A2E?

16 A. Well, I think basically the overall
17 details are pretty much described -- well, in
18 the patent itself, but also in Figure 5 of Mata
19 and Figure 10 of Fishkin there.

20 There are some details that are --
21 probably are a little fuzzy in terms of -- maybe
22 still today, in terms of the -- some of the
23 steps, but basically those were the accepted --
24 this was the accepted pathway by individuals in
25 the field.

1 Q. And are you aware of any -- well, Mata
2 Figure 5 and Fishkin Figure 10, there's some
3 common features but also some differences,
4 correct?

5 MR. MILLS: Objection to form.

6 THE WITNESS: There are. Again, I
7 said the basic pathways, I think, were agreed
8 upon. There are some details in the latter
9 steps in terms of what the possibilities are. I
10 think also there was some ambiguity in terms of
11 the spectral assignments of particular
12 intermediates to chromatography.

13 BY MR. FELDSTEIN:

14 Q. And does it matter to your opinion at all
15 whether there were disagreements on the spectral
16 assignments of intermediates?

17 A. In my opinion, not because -- as I tried
18 to point out before, if you stop -- block the
19 initial step or the step after the condensation,
20 the 1,5-sigmatropic rearrangement, then the
21 other materials downstream are going be to
22 attenuated as well, even though there may be
23 some minor differences in terms of what their
24 spectra are or exactly where the electrons are,
25 and bonds in some cases.

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1 Q. And so it also doesn't matter to your
2 opinion whether there was a lack of consensus
3 regarding the biosynthetic pathway for A2E as a
4 whole, correct?

5 MR. MILLS: Objection to form.

6 THE WITNESS: For A2E?

7 BY MR. FELDSTEIN:

8 Q. Correct.

9 A. I think the point in my report is that
10 basically, if you block the 1,5-sigmatropic
11 rearrangement, you will block everything
12 downstream, and some of the fine details of
13 exactly how that happened may not be an issue
14 because you're going to block everything.

15 Q. And Fishkin actually doesn't call
16 1,5-shift -- Fishkin calls it a 1,6-shift and
17 characterizes as a tautomer, correct?

18 A. Well, this is a little confusing, and
19 basically -- I guess, first of all, the
20 difference between 1,5 and 1,6 in the
21 nomenclature depends on whether you include the
22 hydrogen and counting that, and so whether you
23 get the 5 or 6. I prefer -- generally, in the
24 literature, the 1,5 is more common for this,
25 though. So I've use the 1,5-sigmatropic

1 rearrangement in nomenclature.

2 The tautomer X, in a sense, yes, it can
3 be a tautomer in terms of whether you have an
4 enamine or an imine; however, the matter of fact
5 is that the 1,5-sigmatropic shift is not a
6 tautomerization because it's not reversible.

7 Q. And does tautomer imply reversible?

8 MR. MILLS: Objection to form.

9 THE WITNESS: That's the general
10 principle, yes. And I would cite -- I think
11 it's one of the exhibits is the part of the
12 March textbook, which I have on my shelf, by the
13 way, and I'd say it can solve it again.

14 But, yeah, tautomers are things that
15 are reversible, and they may be slow. Some of
16 these may be slow; some may be very fast, but
17 tautomers are reversible.

18 BY MR. FELDSTEIN:

19 Q. And so when earlier you were referring to
20 Figure 5 of Mata, trying to figure out whether
21 it was dotted lines or solid lines, that
22 intermediate state is consistent with reversible
23 tautomerization?

24 A. No.

25 MR. MILLS: Objection --

1 Sorry.

2 THE WITNESS: I'm sorry.

3 MR. MILLS: Were you done?

4 Okay. Objection to form.

5 THE WITNESS: No. I don't interpret
6 that as being reversible. I interpret that as
7 being probably a transition state on the way.
8 If you go to Roth and König, they actually talk
9 about the mechanism, and even by 1966, I think
10 there was general agreement that this was a --
11 what we call a synchronous reaction. That is,
12 basically, we weren't shifting protons or
13 hydride ions. It was something that was an
14 internal reaction.

15 BY MR. FELDSTEIN:

16 Q. That consensus you're referring to is the
17 ultra-simplified symmetric --

18 A. Yes.

19 Q. -- carbohydrate, correct?

20 MR. MILLS: Sorry, Doctor, you got
21 to let him finish his question and give me a
22 chance to object, okay?

23 THE WITNESS: All right.

24 BY MR. FELDSTEIN:

25 Q. That consensus you're referring to is the

1 ultra-simplified symmetric hydrocarbon, correct?

2 MR. MILLS: Objection to form.

3 THE WITNESS: Yes. It was -- the
4 work was done with those models, but my
5 extension, I think -- my opinion, yeah, it
6 applies to other systems as well to interpret
7 the synchronous reaction. I'm not --

8 BY MR. FELDSTEIN:

9 Q. Sorry, keep going.

10 A. Okay. I was still talking, so it's okay.

11 The -- yeah, it's -- I am not aware of
12 any evidence in the literature for the shift of
13 an actual proton or hydrogen atom or a hydride
14 ion, which would involve intermediates.

15 Q. As of 2007, an ordinary person of skill
16 in the art would have understood that there was
17 not consensus on whether the APE rearrangement,
18 what you call 1,5 or 1,6, was irreversible or
19 reversible as of tautomer, correct?

20 MR. MILLS: Objection to form.

21 THE WITNESS: I'm not aware of any
22 evidence that it was reversible.

23 BY MR. FELDSTEIN:

24 Q. People are characterizing it as tautomer,
25 correct?

1 MR. MILLS: Objection.

2 THE WITNESS: The tautomer is not
3 used, I don't think, in the proper sense. One
4 can take a tautomer of -- take tautomer X, and
5 you can actually shift the bond to convert that
6 enamine structure to an imine.

7 And that is tautomerization in the
8 classic sense, but you can't take what's called
9 tautomer X and go back to NRpe. I'm not aware
10 of anybody's ever shown that, and it isn't going
11 to happen.

12 BY MR. FELDSTEIN:

13 Q. But you understand that by 2007 people
14 continued to call that species tautomer,
15 correct?

16 MR. MILLS: Objection.

17 BY MR. FELDSTEIN:

18 Q. Tautomer.

19 A. Well, as I said, certainly, Fishkin and
20 Nakanishi did, but it is a tautomer, but it's
21 the tautomeric -- the tautomeric form of that is
22 not in NRpe. And they don't show that as being
23 reversible either, I might add.

24 Q. Well, no one has been able to directly
25 probe the 1,5 or 1,6 rearrangement, correct?

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1 MR. MILLS: Objection to form.

2 THE WITNESS: Directly probe in the
3 sense of making NRpe and then looking at the
4 direct reaction product?

5 BY MR. FELDSTEIN:

6 Q. Right.

7 A. No, I'm not aware that that's happened.
8 That usual -- apparently breaks down to go on
9 with the following reactions after that.

10 Q. So your -- your statement about no one
11 showing it to actually be a tautomer applies
12 equally to no one's actually shown it to be
13 irreversible, correct?

14 MR. MILLS: Objection to form, asked
15 and answered.

16 THE WITNESS: I think I've answered
17 it. There's no one -- as far as -- I'm not
18 sure. I don't think anybody's even postulated
19 that that would be reversible in this particular
20 case.

21 BY MR. FELDSTEIN:

22 Q. It was unknown as of 2007 whether the
23 rearrangement of NRpe was or wasn't reversible,
24 correct?

25 MR. MILLS: Objection to form, asked

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1 and answered.

2 THE WITNESS: I'm not aware that
3 anybody even proposed that. It seems extremely
4 unlikely to me from my knowledge of chemistry
5 that it would be reversible.

6 BY MR. FELDSTEIN:

7 Q. Sure. But from your investigation of the
8 literature, you didn't see anywhere where it was
9 resolved that it was or was not reversible,
10 correct?

11 MR. MILLS: Objection to form, asked
12 and answered.

13 THE WITNESS: Well, I guess one
14 thing I could say is that the absence of
15 evidence is evidence for the absence of that
16 reaction.

17 BY MR. FELDSTEIN:

18 Q. And so the absence of evidence that it's
19 not -- okay. I'm going to leave that one alone.

20 MR. MILLS: Sorry. Was the answer
21 that reaction or the back reaction?

22 THE WITNESS: I'm sorry. What --
23 what did I say? Are you trying to -- asking me
24 to clarify?

25 MR. MILLS: Go ahead, Jen, ask what

1 you want to clarify.

2 The transcript says "that evidence
3 for the absence of that reaction."

4 THE WITNESS: The back reaction.
5 The back reaction doesn't occur.

6 BY MR. FELDSTEIN:

7 Q. Does it matter to -- maybe I asked this;
8 I apologize.

9 Does it matter to your opinion in this
10 case where each step in Mata Figure 5 takes
11 place in the cellular compartments of the eye?

12 MR. MILLS: Objection to form,
13 incomplete hypothetical.

14 THE WITNESS: I'm think -- I'm not
15 sure. Maybe you asked me that. I don't know if
16 you broke it up into individual steps.

17 I would think it'd be highly
18 unlikely that these intermediates would probably
19 transfer from -- well, compartment to
20 comfortable within the eye.

21 It would matter because I suppose --
22 you know, if it could happen; although, I doubt
23 that it does, and I'm not aware there's any
24 evidence that there is transport or passive
25 defusion from one compartment in the eye to the

1 next.

2 MR. MILLS: Sorry, just so -- did he
3 say would matter or wouldn't matter?

4 MR. FELDSTEIN: Yeah, I mean, we're
5 not going to be able to deal with every
6 question, okay?

7 THE COURT REPORTER: When I go back
8 and listen to it -- I mean, it's hard to hear in
9 here, and I'm doing my best.

10 MR. MILLS: No. You're doing a
11 great job. I don't mean to suggest anything
12 different.

13 THE COURT REPORTER: If you want to
14 ask him that question, and then I have it right
15 on record.

16 MR. FELDSTEIN: I don't think we can
17 do it with every question. You can do it on
18 redirect.

19 BY MR. FELDSTEIN:

20 Q. Doctor, if one or more -- let me start
21 again.

22 If some intermediate in Mata Figure 5
23 were transferred between compartments in the
24 eye, how would that impact your opinion?

25 MR. MILLS: Objection to form.

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1 THE WITNESS: Well, I'm not sure --
2 as I think about this, I'm not sure how much
3 that would really matter. The important thing
4 is the end products which are deleterious to the
5 membranes, and it's where they are.

6 Now, if they're -- now, if you're
7 doing the initial sigmatropic rearrangement in
8 the same compartment or in another space but the
9 materials get to the, you know, relevant or most
10 sensitive part of the eye, that's what really
11 counts.

12 BY MR. FELDSTEIN:

13 Q. So it doesn't matter, then, as relative
14 to your opinion where each substep in Mata
15 Figure 5 occurs within the eye's cellular
16 compartment; is that correct?

17 A. Well, it's probably more complicated than
18 that because it would actually matter about the
19 rates at which they move to other compartments
20 and if there were any alternative fates for
21 those.

22 Again, the bottom line is where the end
23 products are is really the dangerous area. It
24 also might relate to where the retinaldehyde is
25 most concentrated in the first place.

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1 Q. Is it fair to say that the opinions
2 expressed in this case, you didn't consider
3 where in the eye cellular compartments, each
4 step of Mata Figure 5 takes place?

5 MR. MILLS: Objection to form.

6 THE WITNESS: It's been
7 hypothetical, and I did not specifically go into
8 that. The report's already pretty long and
9 could have been -- could have made it a lot
10 longer, I suppose, considering every
11 possibility.

12 BY MR. FELDSTEIN:

13 Q. And where you have multiple partially
14 rate-limiting steps in a reaction, you can't
15 predict whether slowing one of those steps is
16 going to have any significant impact in vivo; is
17 that correct?

18 MR. MILLS: Objection to form.

19 THE WITNESS: Well, that's a good
20 question, and this is actually been kicked
21 around, as you probably know, in terms of drug
22 oxidations and deuterium substitutions and
23 things like that as well.

24 I think when you have a high -- when
25 you have a -- for instance, a high isotope,

1 effect, you're able -- or even any kind of a
2 simple chemical inhibitor for a step, you have
3 the possibility that the in vitro effect will be
4 seen in vivo.

5 In this case, it's -- it's a little
6 bit simpler than for an enzyme reaction because
7 we're just looking at the inhibition of the
8 overall process which is nonenzymatic.

9 Having said that, it would be
10 difficult to predict exactly how much you're
11 going to have an effect for inhibition. This is
12 a typical common problem. I don't want to
13 belabor this, but medicinal chemists and the
14 pharmaceutical industry deal with this all the
15 time. They're trying to develop inhibitors;
16 some of them work very well in vitro or in
17 cells, and then they just don't work in vivo as
18 well.

19 BY MR. FELDSTEIN:

20 Q. I wasn't asking about calculating
21 specific reactions slowly, and I want to make
22 sure that you understood, I was asking about a
23 case where you have multiple partially limiting
24 steps, not merely in vitro to in vivo.

25 Can I ask the question again, Doctor?

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1 A. Yes, why don't you do that.

2 Q. Where you have multiple partially
3 rate-limiting steps in a reaction sequence, you
4 can't predict whether slowing one of those steps
5 is going to have any significant impact on the
6 overall reaction rate in vivo, correct?

7 MR. MILLS: Objection to form,
8 incomplete hypothetical.

9 THE WITNESS: It's hypothetical. I
10 would say yes, one can predict, but one does
11 have to do the testing and to see if this really
12 happens, yes.

13 BY MR. FELDSTEIN:

14 Q. Okay. Are you aware of whether it was
15 understood by a person of ordinary skill in the
16 art as of 2007 whether the mechanism of A2PE H2
17 formation varies with the generic etiology of
18 the disease?

19 MR. MILLS: Objection; form and
20 scope.

21 THE WITNESS: I don't know, and I
22 don't have an opinion about that.

23 BY MR. FELDSTEIN:

24 Q. Mata itself doesn't teach that putting
25 deuterium at the C20 position would materially

1 slow the formation of A2E. That's your
2 interpretation, correct?

3 MR. MILLS: Objection to form.

4 THE WITNESS: Mata doesn't address
5 the deuterium approach, and in the Mata -- yeah,
6 it's not addressed in the Mata paper. No,
7 that's correct.

8 BY MR. FELDSTEIN:

9 Q. Are you aware of anyone prior to the '045
10 patent suggesting that deuteration of carbon-20
11 would slow the formation of A2E?

12 MR. MILLS: Objection to form.

13 THE WITNESS: No, I'm not. I was
14 just looking at Fishkin, and I don't
15 specifically see that mentioned right here;
16 although, obviously, the Columbia group actually
17 was thinking about that shortly thereafter.

18 BY MR. FELDSTEIN:

19 Q. We were talking earlier about paragraph
20 98. Do you still have that opened?

21 A. I do.

22 Q. At the end of -- towards the bottom of
23 page 58, one line up from the bottom, you write:
24 "A person of ordinary skill in the art would
25 have recognized that cleavage of this

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1 carbon-hydrogen bond would have already been
2 relatively slow under physiological conditions
3 absent enzymatic catalysis," and then it goes
4 on, correct?

5 A. Yeah. Yes.

6 Q. There are no references that actually
7 teach that cleavage of this carbon-hydrogen bond
8 would have been relatively slow under
9 physiological conditions, correct?

10 MR. MILLS: Objection; form.

11 THE WITNESS: Well, I think if you
12 actually look at -- well, several papers,
13 including Fishkin and -- and Mata, basically it
14 was a slow reaction. This was not a very
15 efficient reaction, and I can't remember exactly
16 how long they incubated these things. I do know
17 in the patent and the subsequent paper by Kim,
18 but it -- these things took a long time in the
19 artificial systems in vitro, yes.

20 BY MR. FELDSTEIN:

21 Q. Is there anything specific in Mata that
22 you can point to teaching that cleavage of the
23 carbon-hydrogen bond that you reference was
24 recognized to be relatively slow under
25 physiological conditions?

1 A. The Mata actually worked primarily with
2 extracts. I'm just looking at Fishkin to see
3 what their in vitro process involved.

4 Q. So you want to do one at a time?

5 A. Yes, let's do that.

6 Q. For Mata -- the question for Mata: Is
7 there anything specific in Mata that you can
8 point to teaching that cleavage of the
9 carbon-hydrogen bond that you referenced was
10 recognized to be relatively slow under
11 physiological conditions?

12 MR. MILLS: Objection to form.

13 THE WITNESS: I don't see anything
14 specifically in Mata, since they were working
15 primarily with extracts. I'm looking -- can we
16 go on to Fishkin now?

17 BY MR. FELDSTEIN:

18 Q. Sure. Let me ask that question.

19 Is there anything specific in Fishkin
20 that you can point to teaching that cleavage of
21 the carbon-hydrogen bond you referred to in
22 paragraph 98 was recognized to be relatively
23 slow under physiological conditions?

24 MR. MILLS: Objection to form.

25 THE WITNESS: Well, I would say,

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1 looking at Fishkin, I think their conditions
2 were fairly -- they started with
3 all-trans-retinol -- retinal, and they actually
4 did some reactions here, and I think they were
5 fairly long-term, as, apparently, I'm looking
6 here.

7 BY MR. FELDSTEIN:

8 Q. But they didn't isolate the
9 carbon-hydrogen bond cleavage measurements,
10 correct?

11 A. No. No, that's correct.

12 Q. So is it correct that Fishkin does not
13 show recognition that cleavage of the
14 carbon-hydrogen bond referred to in paragraph 98
15 of your report was recognized to be relatively
16 slow under physiological condition?

17 MR. MILLS: Objection to form,
18 mischaracterizes the witness's testimony.

19 THE WITNESS: Probably the best
20 thing here in Figure 4 is Fishkin, which
21 basically deals -- well, that's starting with
22 ATR dimer. I'm sorry. Unless they started
23 everything with ATR dimer. No, no, no.

24 Well, as I'm reading this, the
25 conditions are fairly complicated and in some

1 cases not as clear as I would hope. And they
2 are -- they are not what I call physiological
3 then.

4 I think my opinion would be that
5 these conditions were actually used to force the
6 reaction to make these products.

7 BY MR. FELDSTEIN:

8 Q. So is there something specific in Fishkin
9 showing recognition that cleavage of the
10 carbon-hydrogen bond you referred to in
11 paragraph 98 was recognized as being relatively
12 slow under physiological conditions?

13 MR. MILLS: Objection to form, asked
14 and answered.

15 THE WITNESS: I don't see a
16 specific, you know, reference in Fishkin to
17 that. Obviously, the authors were thinking
18 about this because they came up with the patent
19 the next year or two then, but I don't see a
20 specific comment about this.

21 BY MR. FELDSTEIN:

22 Q. Which patent did they come up with the
23 next year?

24 A. Well, I thought it was the -- the first
25 one was 432, right?

1 Q. The patents and the ITRs?

2 A. Yeah. As I recall, the filing date was
3 2007, or was it -- did they submit -- no --
4 2007, not 2006.

5 Q. So we're turning to paragraph 98 of your
6 report, the sentence that begins two lines up
7 from the bottom of 58.

8 Just to state what's obvious, you don't
9 cite any literature showing recognition in the
10 art that cleavage of the referenced
11 carbon-hydrogen bond would have been recognized
12 as being relatively slow under physiological
13 conditions, correct?

14 MR. MILLS: Objection to form.

15 THE WITNESS: Well, the -- although
16 it's only a model, we do have the general
17 information about 1,5-sigmatropic
18 rearrangements, then, and that goes back to Roth
19 and König, and, you know -- and I guess,
20 actually, subsequent material that was actually
21 published since then before the patent.

22 BY MR. FELDSTEIN:

23 Q. Well --

24 A. Those -- well.

25 Q. Just to be clear, Doctor, the question

1 was a very obvious question.

2 You don't cite any support in paragraph
3 98 for this assertion of what a POSA would have
4 recognized as being slow under physiological
5 conditions, correct? There's just no citation
6 in that paragraph?

7 MR. MILLS: Objection to form.

8 THE WITNESS: Perhaps it would have
9 been better to actually put another citation in,
10 but again, there are, or there were some, that
11 are in the exhibit -- that we put in the
12 exhibits.

13 BY MR. FELDSTEIN:

14 Q. Sure. Can you just confirm that you
15 don't cite any support in paragraph 98 for this
16 assertion?

17 MR. MILLS: Objection to form, asked
18 and answered.

19 THE WITNESS: Yeah, I -- there's no
20 citations in paragraph 98.

21 BY MR. FELDSTEIN:

22 Q. Okay. And in terms of Roth, we've
23 already addressed that Roth was not under
24 physiological conditions, correct?

25 MR. MILLS: Objection to form.

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1 THE WITNESS: I think that's the
2 point. Roth had to use some extreme conditions
3 to get the action to work. So it was definitely
4 not physiological. It was high temperature and
5 long time.

6 BY MR. FELDSTEIN:

7 Q. And Roth was chemically and structurally
8 a very different molecule what Mata called APE,
9 correct?

10 MR. MILLS: Objection to form.

11 THE WITNESS: It was different, but
12 it was the same rearrangement, yeah.

13 BY MR. FELDSTEIN:

14 Q. Okay. What type of evidence would have
15 been needed to determine if that bond breaking
16 really was or not rate limiting in the formation
17 of A2E?

18 MR. MILLS: Objection to form,
19 incomplete hypothetical.

20 THE WITNESS: Well, it's
21 basically -- well, the answer, in part by the
22 experiments that were presented in the patent
23 and also later by Kim -- actually, I think it
24 was the same evidence there.

25 Basically, you synthesize both

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1 molecules and look at their rates of breakdown.

2 BY MR. FELDSTEIN:

3 Q. In your own research, what do you do to
4 determine if a step is rate limiting in a
5 multistep reaction?

6 MR. MILLS: Objection; form.

7 THE WITNESS: There are two
8 things -- and, by the way, I think essentially
9 everything I've done is actually with enzymes,
10 so it's -- some may or may not apply.

11 There are two things: We can either
12 measure a step directly in some cases with --
13 for instance, with a cytochrome p450, we can't
14 measure every step. What we can do is look at
15 the rate of carbon-hydrogen or the -- we look at
16 the -- we can look at a kinetic isotope effect
17 for the breaking to see if that step is at least
18 partially rate limiting.

19 BY MR. FELDSTEIN:

20 Q. And why can't you look at it and say
21 there's a carbon-hydrogen bond breaking;
22 therefore, it'll be partially rate limiting?

23 MR. MILLS: Objection to form,
24 incomplete hypothetical.

25 THE WITNESS: It's -- well, it --

1 you can't do that because, you know, different
2 enzymes -- when we're comparing different
3 enzymes, they have different rates for various
4 steps, and they're controlled in that way, and
5 so there is some variability, yes.

6 BY MR. FELDSTEIN:

7 Q. And does it vary not only by enzyme but
8 by substrate?

9 MR. MILLS: Objection to form and
10 incomplete hypothetical.

11 THE WITNESS: There is some
12 variation by substrate. Yeah, we've publish
13 widely -- widely on that, and so there are a
14 number of different factors. Again, this is a
15 little bit -- it's a different situation.
16 Cytochrome p450 cycle takes nine steps if it's a
17 cyclic reaction, and it's not a matter of just a
18 simple linear chemical reaction.

19 BY MR. FELDSTEIN:

20 Q. And again, what you're saying -- what
21 you've said is that any linear chemical reaction
22 with a CH bond breaking could be slowed by
23 changing hydrogen to deuterium?

24 MR. MILLS: Objection to form,
25 incomplete hypothetical, asked and answered.

1 THE WITNESS: It is hypothetical
2 because you're talking about all carbon-hydrogen
3 bonds and different types of reactions that
4 occur by entirely different mechanisms, so one
5 doesn't -- cannot -- well, you have to consider
6 each one individually or at least in terms of
7 the class of mechanism.

8 BY MR. FELDSTEIN:

9 Q. In general -- even if there are
10 exceptions, in general, is it correct that
11 you're saying that for a linear chemical
12 reaction with the CH bond breaking, that it
13 could be slowed by changing hydrogen to
14 deuterium?

15 MR. MILLS: Objection to form,
16 incomplete hypothetical.

17 THE WITNESS: It's hypothetical; in
18 principle, it could but not necessarily. It
19 just depends. You know, one has to consider the
20 mechanism of how you're doing that, yes.

21 BY MR. FELDSTEIN:

22 Q. And why not necessarily, and what would a
23 person have to consider?

24 MR. MILLS: Objection to form,
25 scope.

1 THE WITNESS: It is out of the scope
2 here. There -- and I could write a whole nother
3 report on that, but there are different ways of
4 breaking CH bonds. In cytochrome p450
5 reactions, which I'm most familiar with, we're
6 abstracting hydrogen atoms, and that kind of
7 mechanism is very sensitive to a kinetic isotope
8 effect. In other types of enzyme reactions,
9 basically, there are deprotonated to form
10 carbon ions.

11 You know, in other cases, you can
12 take off hydrides -- hydride ions to form up
13 carbocation. So these are very different
14 mechanisms, and so the principles are very
15 different. One has to consider this in terms of
16 predicting whether or not you're going to have a
17 kinetic isotope effect.

18 BY MR. FELDSTEIN:

19 Q. And I apologize. I was not trying to ask
20 about enzymatic reactions. So let me try to
21 make a better question.

22 In general, even if there are exceptions,
23 is it correct that for linear nonenzymatic
24 chemical reactions with a CH bond breaking, that
25 it would be slowed by replacing hydrogen to

1 deuterium?

2 MR. MILLS: Objection to form,
3 incomplete hypothetical, scope.

4 THE WITNESS: My answer is the same.
5 It depends on the mechanism. Here we have in
6 1,5-sigmatropic rearrangement, we have a
7 concerted synchronous mechanism which is
8 consistent with a high kinetic isotope effect.

9 Again, you know, have other kinds of
10 purely chemical mechanisms where one is
11 abstracting a hydride ion or -- or a -- I'm
12 sorry -- hydride ion or a proton.

13 BY MR. FELDSTEIN:

14 Q. And in general, even if there are
15 exceptions, is it correct that, in your opinion,
16 for a nonenzymatic hydrogen subtraction
17 reaction, that changing hydrogen to deuterium
18 would slow the overall reaction?

19 MR. MILLS: Objection to form,
20 incomplete hypothetical, outside the scope,
21 asked and answered.

22 THE WITNESS: Yeah. That depends on
23 the mechanism, and one can't say that that's
24 always going to happen or not. Yeah.

25 BY MR. FELDSTEIN:

1 Q. Is it right that oxygenation in a
2 multistep reaction can be slower than CH bond
3 breaking?

4 MR. MILLS: Objection to form,
5 incomplete hypothetical.

6 THE WITNESS: Would you repeat the
7 question? I don't...

8 BY MR. FELDSTEIN:

9 Q. Is it right that oxygenation in a
10 multistep chemical reaction can be slower than a
11 CH bond breaking in that multistep reaction?

12 MR. MILLS: Same objections.

13 THE WITNESS: Is oxy- -- can
14 oxygenation be slower than --

15 BY MR. FELDSTEIN:

16 Q. Carbon-hydrogen bond breaking.

17 Let me just try again.

18 Can the rate of an oxygenation reaction
19 in a multistep process be slower than the rate
20 of a carbon-hydrogen bond breaking in that
21 multistep process?

22 MR. MILLS: Objection; form,
23 incomplete hypothetical.

24 THE WITNESS: Okay. Did you say
25 oxidation or oxygenation?

1 BY MR. FELDSTEIN:

2 Q. Oxidation.

3 A. So can oxidation slower than the rate --
4 well, yes is my best answer; it can be. This is
5 kind of hypothetical and sort of just searching
6 around in my head for what kind of examples one
7 would think about.

8 Q. Is there a difference in the effect of CH
9 bond breaking on the rate of reaction on whether
10 it's an alkele [sic] hydroxylation or some other
11 type of bond breaking?

12 MR. MILLS: Objection to form,
13 incomplete hypothetical.

14 THE WITNESS: Other form of bond
15 breaking. The answer is yes, at least in
16 enzymes.

17 BY MR. FELDSTEIN:

18 Q. And what about in nonenzymatic reactions?

19 MR. MILLS: Objection to form,
20 incomplete hypothetical.

21 THE WITNESS: What was the question
22 again?

23 BY MR. FELDSTEIN:

24 Q. Is there a difference in the effect of
25 deuteration where the bond breaking is an alkele

1 [sic] hydroxylation as compared to other CH
2 bond-breaking nonenzymatic reactions?

3 MR. MILLS: Objection to form,
4 incomplete hypothetical.

5 THE WITNESS: I'm not sure -- I
6 can't answer that without putting a lot of
7 thought into it in terms of an example for a
8 nonenzymatic system. I just haven't thought
9 about it.

10 MR. MILLS: Are you moving to a new
11 line of questions? We're almost to the hour if
12 you're moving to a new line of question.

13 MR. FELDSTEIN: I'm moving.

14 MR. MILLS: Should we take a break
15 now?

16 MR. FELDSTEIN: Sure.

17 (Brief break was observed.)

18 BY MR. FELDSTEIN:

19 Q. Going to switch gears a little bit.
20 Doctor, could we turn to Exhibit 1008.

21 A. Okay. I have it.

22 Q. You've considered Exhibit 1008 in your
23 opinions here, Doctor?

24 A. Yes, this is the German patent.

25 Q. Can we call it Ortho?

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1 A. Yeah, we'll call it Ortho. Yeah.

2 Q. Okay.

3 A. I think I did in the references, in the
4 citations.

5 Q. Is it correct that the only vitamin A
6 taught in Ortho is non-deuterated vitamin A?

7 A. That's correct.

8 Q. And do you understand whether Ortho is
9 teaching use of vitamin A to address vitamin A
10 deficiencies?

11 MR. MILLS: Objection; form.

12 THE WITNESS: That is -- that's a
13 general statement, but, yes, I would agree that
14 basically you're -- it's a vitamin
15 supplementation with a bunch of other stuff
16 added too. Yeah.

17 BY MR. FELDSTEIN:

18 Q. So it's not treating a method of
19 treatment with vitamin A, but for vitamin
20 deficiencies, correct?

21 MR. MILLS: Objection to form,
22 incomplete hypothetical.

23 THE WITNESS: The -- well, it's a
24 little complicated. It certainly is, as the
25 specification started out, it related to

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1 carotenoid containing product, basically as a
2 source of vitamin A, and then they're adding a
3 bunch of antioxidant vitamins and minerals as
4 well to that. Yeah, that's the approach of this
5 is using -- that Ortho is using here, yes.

6 BY MR. FELDSTEIN:

7 Q. And its goal is to get more vitamin A
8 into the eye, correct?

9 MR. MILLS: Objection to form.

10 THE WITNESS: I -- that's -- again,
11 it's kind of general, but that's basically what
12 I think this is, yes. It's -- they're using
13 supplements to do that, and, you know, perhaps
14 they're doing other things as well, but
15 basically the point is it's a vitamin A
16 supplement.

17 BY MR. FELDSTEIN:

18 Q. And vitamin A supplement to the eye will
19 further feed the visual cycle, correct?

20 A. I would -- I think that's the concept
21 that Ortho is pushing here in this application
22 or whatever it is. Or actually vio path.

23 Q. Okay. And Ortho is not addressing
24 Stargardt's disease at all, correct?

25 MR. MILLS: Objection to form.

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1 THE WITNESS: I don't think they
2 specifically said that. In fact, I'm not
3 sure -- well, they talk about, I guess, in their
4 paragraph 2 or whatever it is too, they say
5 age-related eye disease such as macular
6 degeneration or senile cataracts, but they don't
7 really specify very much in terms of the
8 specific eye diseases beyond that.

9 BY MR. FELDSTEIN:

10 Q. And by 2007, the person of ordinary skill
11 would have understood that vitamin A
12 contraindicated for the treatment of Stargardt's
13 disease, correct?

14 MR. MILLS: Objection to form,
15 incomplete hypothetical.

16 THE WITNESS: Yeah, I don't have a
17 comment on that. I didn't address that
18 specifically.

19 BY MR. FELDSTEIN:

20 Q. Does it matter to your opinions in this
21 case at all whether vitamin A was understood by
22 2007 to be contraindicated for Stargardt's
23 disease?

24 MR. MILLS: Objection to form,
25 incomplete hypothetical, asked and answered.

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1 THE WITNESS: I didn't address that
2 issue.

3 BY MR. FELDSTEIN:

4 Q. Sure. I understand you didn't address
5 it, but I'm asking: Does it matter to your
6 opinion whether or not vitamin A was understood
7 to be contraindicated for Stargardt's disease.

8 MR. MILLS: Objection to form,
9 incomplete hypothetical.

10 THE WITNESS: It doesn't matter to
11 my opinion regarding the material I do have in
12 the report.

13 BY MR. FELDSTEIN:

14 Q. Oh, I had one more question about Ortho.
15 Actually, Caroline had one more question about
16 Ortho. But does Ortho teach giving vitamin A
17 alone?

18 MR. MILLS: Objection to form.

19 THE WITNESS: Apparently not. They
20 have a list here, and I don't see offhand
21 anywhere where they talk about vitamin A
22 separately.

23 MR. FELDSTEIN: Did you pull 2006,
24 Drew?

25 BY MR. FELDSTEIN:

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1 Q. Give you 2006, Doctor. Are you familiar
2 with 2006, Doctor?
3 A. Yes, I am.
4 Q. And how are you familiar with 2006?
5 A. Well, I've read it and studied it, and
6 some of it overlaps with the 405 patent.
7 Q. When was it that you read and studied it?
8 A. Oh, I don't know. During the last month,
9 maybe before that; I'm not sure.
10 Q. Do you recall when you first reviewed the
11 text of Exhibit 2006?
12 A. Not specifically.
13 Q. Generally?
14 A. I really don't remember if I looked at it
15 before the last round of preparation or not.
16 Q. This is from the Journal of Biological
17 Chemistry, correct?
18 A. Yes.
19 Q. And that's where you said you were an
20 editor; is that correct?
21 A. Yes. I did not review this paper, as
22 best of my recollection.
23 Q. What time period were you ever at the
24 Journal of Biological Chemistry?
25 A. Well, I was an associate editor from 2006

1 to 2022. I think this is in my report anyway,
2 but I was deputy editor from 2013 to 2022, and I
3 was the interim editor in chief on two
4 occasions, I think from 2015 to '16, and then I
5 forgot the other time, but anyway.

6 Q. And so you were an editor at the time
7 that Exhibit 2006 was published, correct?

8 A. Yes.

9 Q. And what's the process by which a
10 manuscript is reviewed and accepted for
11 publication in the Journal of Biological
12 Chemistry in and around 2011?

13 A. All right. I can comment on that. I'll
14 try to keep it brief and not get into the weeds
15 too much in the interest of time.

16 Basically, authors submit manuscripts to
17 the journal. They are then assigned to the
18 individual associate editors. At that time we
19 had about 20 or 25, and they're assigned by
20 either the editor in chief or the deputy editor,
21 who was sometimes myself.

22 And then the associate editor,
23 depending -- and these are based on the subject
24 matter and the expertise of the individual
25 associate editors. These are then actually sent

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1 out to, usually, at least two editorial board
2 members for comment. On the basis of those
3 comments, the associate editor will make a
4 decision as to whether the paper should be
5 accepted, revised, or rejected.

6 Q. And how are the reviewers selected?

7 A. On the basis of their expertise. Most of
8 reviews are done by members of the editorial
9 board. There -- at least at that time, there
10 were about 6 or 700 people on the editorial
11 board; people throughout the world selected from
12 different areas to give us diversity across the
13 spectrum.

14 Q. And are the reviewers at least persons of
15 ordinary skill in the art in the area they're
16 reviewing?

17 MR. MILLS: Objection to form,
18 incomplete hypothetical.

19 THE WITNESS: That -- I'm not sure I
20 can give you a blanket answer on that. I think
21 they're pretty generally good. I mean,
22 obviously the journal, you know, dealt with
23 thousands or maybe over 10,000 papers a year,
24 and I can't vouch for every single paper.

25 BY MR. FELDSTEIN:

1 Q. Was the intent to give it to reviewers
2 who are at least ordinary skilled in the art
3 they were reviewing?

4 MR. MILLS: Objection to form,
5 incomplete hypothetical.

6 THE WITNESS: Yeah. People are -- I
7 don't disagree with that. Yeah, that was our
8 goal to actually get the most appropriate
9 reviewers who were knowledgeable in the field
10 and also known for their fairness.

11 Q. Okay.

12 MR. FELDSTEIN: Can you mark
13 Exhibit 2056?

14 (Exhibit Number 2056 was marked.)

15 MR. MILLS: I'm going to register
16 objections to this document which has been
17 marked as 2056 on the basis it's not an
18 authenticated document; there is no sponsoring
19 witness to provide authentication or foundation
20 for it. I object on the basis of hearsay. I
21 object on the basis that it's a post-critical
22 date document and for lack of foundation.

23 BY MR. FELDSTEIN:

24 Q. Doctor, can you identify Exhibit 2056?

25 MR. MILLS: Objection; lacks

1 foundation.

2 THE WITNESS: I -- well, perhaps I
3 guess I misspoke. I was the associate editor on
4 this. This is a -- I'm not quite sure legally;
5 it does seem, generally, manuscript reviews are
6 considered confidential, and I don't know if you
7 subpoenaed or what.

8 I did review it, and it appears to
9 have reviewed generally well, and it was
10 published. I apologize if I didn't recognize
11 that I was the editor. On my behalf, at that
12 time I remember one year I handled, I think, 600
13 manuscripts myself as the associate editor, and
14 this was -- went on for years, so I can't -- and
15 at that time I didn't have as much interest in
16 retinoids, so I just forgot about that.

17 BY MR. FELDSTEIN:

18 Q. And just in terms of identifying
19 Exhibit 2056, is it correct that this is an
20 e-mail sent on your behalf by your secretary
21 Kristin Trisler to Ilyas Washington at Columbia
22 University?

23 MR. MILLS: Objection to form,
24 foundation.

25 Caution the witness not to

1 speculate.

2 THE WITNESS: It's Kathy Trisler for
3 the record, but this is my secretary, and she
4 was working for the JBC, but it appears to be.
5 I have no reason to doubt that.

6 BY MR. FELDSTEIN:

7 Q. So it appears to be, and you have no
8 reason to doubt this is an e-mail sent on your
9 behalf by your secretary Kathy Trisler to Ilyas
10 Washington at Columbia University regarding the
11 paper titled "Deuterium Enrichment of Vitamin A
12 at the C20 Position Prevents the Formation of
13 Detrimental Vitamin A Dimers (inaubible)",
14 correct?

15 A. Yes.

16 Q. And can you turn to the second page?
17 Under your name, F. Guengerich, associate
18 editor; do you see that?

19 A. Yes.

20 Q. What's below there where it says
21 "Reviewer 1? What is that?

22 A. Comments for the author. These are
23 what -- since we're going on with this, these
24 are what are actually submitted to the associate
25 editor to be passed on to the authors.

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1 Q. And can you read -- I'll just read what
2 the comment from Reviewer 1 says.

3 "This is an innovative paper on the use
4 deuterium vitamin A to provide a significant
5 kinetic isotope effect to slow the rate of
6 dimerization retinaldehyde that can lead to the
7 production of ATR dimers that proceed the onset
8 of macular degeneration."

9 MR. MILLS: Objection to form.

10 BY MR. FELDSTEIN:

11 Q. That's what you're Reviewer Number 1
12 commented, correct?

13 MR. MILLS: Objection to form.

14 THE WITNESS: Yes.

15 BY MR. FELDSTEIN:

16 Q. And you accepted reviewer number one's
17 comments to accept this manuscript for
18 publication, correct?

19 MR. MILLS: Objection to form.

20 THE WITNESS: Let me clarify this.
21 This is an invitation for revision, okay? So
22 what would happen or what did happen -- and I
23 assume in this case, as always, the author or
24 authors have to actually address the specific
25 questions that were raised in the review, and I

1 as associate editor or any other associate
2 editor would actually consider these.

3 Sometimes we sent these back to the
4 individual reviewers, Reviewer 1 and Reviewer 2,
5 not always. And then those comments come back
6 to the associate editor, and the associate
7 editor makes the final decision as to whether to
8 accept or reject a manuscript.

9 BY MR. FELDSTEIN:

10 Q. And so ultimately you accepted the
11 publication with revisions, correct?

12 A. Apparently I did, yes.

13 Q. And the publication, even with revisions,
14 showed it was an innovative paper on the use of
15 deuterium vitamin A to provide a significant
16 kinetic isotopic effect to slow down the rate of
17 dimerization of retinaldehyde that can lead to
18 production of ATR dimers that proceed the onset
19 of macular degeneration, correct?

20 MR. MILLS: Objection to form,
21 mischaracterize the testimony.

22 THE WITNESS: These are -- you know,
23 those are the verbatim comments of the
24 reviewers, so, yes, I don't -- didn't disagree.
25 Yeah, you know.

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1 BY MR. FELDSTEIN:

2 Q. Okay.

3 A. I don't know -- I don't have -- unless
4 you're going to show it to me -- the further
5 comments of on this or how they addressed the
6 issues.

7 Q. I'm going to mark 2061.

8 (Exhibit Number 2061 was marked.)

9 BY MR. FELDSTEIN:

10 Q. That should be marked 2061. Actually, we
11 have a sticker for that. It was actually
12 marked. Sorry.

13 MR. MILLS: Just give me a moment on
14 this.

15 So let me register my objections to
16 this document as a post-critical date document.
17 Object under Federal Rules of Evidence 801
18 through 803. And also 401 through 403. I also
19 object on the basis of foundation and the lack
20 of a sponsored witness.

21 BY MR. FELDSTEIN:

22 Q. Doctor, can you confirm this publication
23 from the Journal of Biological Chemistry in
24 which you were an editor in 2011?

25 MR. MILLS: Objection. Foundation,

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1 to the extent it calls for speculation.

2 THE WITNESS: It was published
3 that -- you know, in the Journal of Biological
4 Chemistry. I don't know if I was the associate
5 editor involved in the review or not, though.

6 BY MR. FELDSTEIN:

7 Q. Sure. But you were editor or an
8 associate editor at the journal at the time of
9 the publication at least, correct?

10 A. I was. This appears to be what we -- I
11 think it's -- I had not recalled seeing this, at
12 least in this case.

13 It appears to be a companion paper
14 because the page numbers indicated it was
15 published in back to back with this one. I
16 don't know if I was the reviewer. Unless you're
17 going to show me something about that, I don't
18 know if I reviewed that together or not.

19 The general -- if two papers were
20 submitted at the same time by the same authors,
21 usually the same associate editor and reviewers
22 will handle both. That doesn't always happen,
23 though.

24 Q. And when you were referring to the
25 companion paper, the other paper you were

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1 referring to was Exhibit 2006 that we looked at
2 previously?

3 A. No. I'm referring to a 2011 paper.

4 Q. No, Exhibit Number 2006.

5 A. Oh, yes, that's correct.

6 Q. And I'm just going to ask it again.

7 When you're referring to the companion
8 paper of Exhibit 2061, you're referring to
9 Exhibit 2006 that we had previously looked at,
10 correct?

11 A. That's correct.

12 Q. And Exhibit 2006 was also published in
13 the Journal of Biological Chemistry in 2011 at a
14 time when you were an associate editor of the
15 journal, correct?

16 MR. MILLS: Objection; foundation.

17 THE WITNESS: That is correct. As I
18 said, I'm not sure if I also reviewed this one
19 or not.

20 BY MR. FELDSTEIN:

21 Q. You said, though, it's ordinary practice
22 when companion papers come in that they go to
23 the same associate editor, correct?

24 A. Yes. But that doesn't always happen.

25 MR. FELDSTEIN: Mark Exhibit 2057.

1 (Exhibit Number 2057 was marked.)

2 MR. FELDSTEIN: And I'll give you
3 time to object.

4 MR. MILLS: Thank you. I object to
5 Exhibit 2057 on the basis of Federal Rules of
6 Evidence 401 through 403, 801 through 803, as
7 well there as for lack of foundation, absence of
8 sponsoring witness. I will also add an
9 objection to both Exhibit 2057 and 2056. These
10 appear to be portions of correspondence with the
11 journal, and so I make an objection on the basis
12 of potential incompleteness of the record.

13 BY MR. FELDSTEIN:

14 Q. Doctor, can you confirm that Exhibit 2057
15 is an e-mail sent on your behalf by your
16 secretary Kathy Trisler to Ilyas Washington at
17 Columbia University in September 2010?

18 MR. MILLS: Objection; foundation.

19 THE WITNESS: It is. I will note,
20 although I apparently did handle both of these,
21 there's -- it's strange here. They -- these
22 manuscripts did not appear to be reviewed
23 together, and these -- because if they were
24 reviewed by the same reviewers, I would have
25 handled them together.

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1 These decision messages were
2 actually sent on different dates, and I'm not
3 sure -- usually the -- usually when back-to-back
4 papers are considered, you know, as I said,
5 usually it's the same author, so we get some
6 comments together, but these apparently were
7 submitted separately and may or may not have
8 been reviewed by different individuals than the
9 other manuscript.

10 BY MR. FELDSTEIN:

11 Q. And the manuscript in -- being addressed
12 in Exhibit 2057 was directed to prevention of
13 lipofuscin deposits in a mouse model's
14 Stargardt's disease, correct?

15 MR. MILLS: Objection to form.

16 THE WITNESS: That's what the title
17 indicates.

18 BY MR. FELDSTEIN:

19 Q. And what you wrote back in the second
20 paragraph to Dr. Washington was that novelty of
21 using a deuterated version of vitamin A is also
22 considered quite novel?

23 MR. MILLS: Objection to form.

24 BY MR. FELDSTEIN:

25 Q. Correct?

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1 A. That's what the -- basically the reviewer
2 said, or one of the reviewers.

3 By the way, I should point out that one
4 of the ways the associated editors worked -- or
5 at least they did when I was an associate
6 editor -- is that we also ask the reviewers --
7 the reviewing editors of the editorial board
8 members, we asked them to provide confidential
9 comments too that can be actually used in the
10 sending the letter.

11 So in both cases there, I would suspect
12 that the -- that second paragraph in both cases
13 is probably a derivative of the comments I got
14 from the editorial board.

15 Q. Right. And on page 2 of Exhibit 2057,
16 can you look where it says Reviewer Number 2?

17 A. Yes.

18 Q. Would you mind reading into the record
19 the comments from the author?

20 MR. MILLS: Objection; form.

21 THE WITNESS: This manuscript
22 describes the effect of feeding a deuterated
23 version of vitamin A to mice carrying a mutation
24 that predisposed them to developing Stargardt's
25 disease. This is a great -- this is great --

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1 there is great interest in this disorder, and it
2 is of significant clinical importance. The use
3 of a C20, D3 vitamin A is quite novel and
4 interesting.

5 BY MR. FELDSTEIN:

6 Q. And you extracted that statement -- "the
7 novelty of using a deuterated version of vitamin
8 A is also considered quite novel," you extracted
9 that from the reviewer comment for your e-mail
10 directly to Dr. Washington, correct?

11 A. I probably did. I can't say with
12 certainty.

13 Q. Okay. Now, going, back to the Mata a
14 little bit, as of 2007, Mata was understood to
15 teach reducing the flow of retinoids through
16 inhibition of the visual cycle, correct?

17 A. Would you repeat that? I'm sorry.

18 Q. As of 2007, Mata was understood to teach
19 reducing the flow of retinoids through
20 inhibition of the vision cycle, correct?

21 MR. MILLS: Objection to form,
22 incomplete hypothetical, mischaracterizes
23 witness's testimony.

24 THE WITNESS: I don't know if it
25 says that in the document. I -- well, yeah,

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1 they were -- there was -- I know Mata was doing
2 other things to actually, you know, do the
3 inhibition using a couple of drugs in animal
4 models to do that, and that that was their
5 approach.

6 BY MR. FELDSTEIN:

7 Q. And to be clear, when we're talking about
8 inhibiting visual cycle, that is the
9 predecessor, perhaps, to what's in Mata
10 Figure 5, correct?

11 MR. MILLS: Objection; form.

12 THE WITNESS: That's one way to look
13 at it, yeah. There's a cycle, and I can't
14 remember which -- there's a good overview of
15 that somewhere in our exhibits, but it involves
16 the isomerization, et cetera, things like of
17 that too.

18 BY MR. FELDSTEIN:

19 Q. And Mata Figure 5 is not in a visual
20 cycle?

21 A. No, definitely not.

22 Q. Okay. Following -- Mata was published in
23 2000; is that correct?

24 A. Yes.

25 Q. Following --

1 A. June 2000.

2 Q. Following Mata, is it correct that
3 researchers in the field continued to look for
4 ways to either inhibit the visual cycle itself
5 or reduce the serum concentration of vitamin A
6 species?

7 MR. MILLS: Objection to form,
8 incomplete hypothetical.

9 THE WITNESS: I would agree that
10 those were two of the major approaches with the
11 experimental drugs that were in use.

12 The Ortho approach was to actually
13 put in more vitamin A, so I think those are
14 major approaches that were used until the
15 deuterated -- C20 deuterated material approach
16 was tried.

17 BY MR. FELDSTEIN:

18 Q. And until the C20 deuterated approach was
19 tried, no one had attempted to slow the reaction
20 steps in Mata Figure 5, correct, to your
21 knowledge?

22 MR. MILLS: Objection to form,
23 incomplete hypothetical.

24 THE WITNESS: I'm not aware of any
25 in that time period.

1 MR. FELDSTEIN: Can we mark 2051.

2 (Exhibit Number 2051 was marked.)

3 MR. CHRISTIE: Sorry guys. We have
4 a box full.

5 MR. FELDSTEIN: Thank you. Sorry.
6 Give you a chance here to object.

7 MR. MILLS: I'll register objections
8 to Exhibit 2051 on the basis of Federal Rules of
9 Evidence 401 through 403, 801 through 803, and
10 601, lack of sponsoring witness.

11 BY MR. FELDSTEIN:

12 Q. Are you familiar with Exhibit 2051,
13 Doctor?

14 A. I don't believe I am.

15 Q. Taking a look at it, do you agree it's in
16 the field of lipofuscin pigment formation?

17 MR. MILLS: Objection; form,
18 foundation.

19 THE WITNESS: I would agree with
20 that, yes. It's in the subject matter, yeah.

21 BY MR. FELDSTEIN:

22 Q. And do you see where it was published?

23 A. Yes, in the Journal of Biological
24 Chemistry.

25 Q. And that's where you were -- you were

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1 again, correct?

2 A. I don't know if I was -- no, I wasn't an
3 associate editor yet. I can't remember if I was
4 on the editorial board then or not.

5 Q. Okay.

6 A. So I might not have been connected with
7 the journal during that time period.

8 Q. And it published in 2002, correct?

9 A. That's correct.

10 Q. And this is after Mata, correct?

11 A. Correct.

12 Q. Are you familiar with any of the authors
13 of Exhibit 2051?

14 A. Well, I recognize the names of -- Fishkin
15 appears, obviously, and Sparrow appear and
16 Parish appear on some of the other papers.

17 Nakanishi, I mentioned before. I know of -- of
18 the late Dr. Nakanishi, I know of by reputation.

19 Q. Do you have an understanding in 2002
20 people in the art were still trying to determine
21 the steps involved in the biosynthesis of A2E?

22 MR. MILLS: Objection to form.

23 THE WITNESS: That's understandable
24 in terms of the complexity of the latter steps,
25 yes.

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1 BY MR. FELDSTEIN:

2 Q. So you agree that the steps of -- the
3 steps involved in biosynthesis of A2E were not
4 fully determined as of the time of Mata in 2000,
5 correct?

6 MR. MILLS: Objection to form,
7 mischaracterizes witness testimony.

8 THE WITNESS: Well, they certainly
9 weren't cast in stone at that time. As I said,
10 these are -- this is a messy process, and these
11 are difficult structures to work with.

12 BY MR. FELDSTEIN:

13 Q. Can you turn to page number 7189 at the
14 top; it's the full text.

15 A. I have it with the structures.

16 Q. Yes. On the left-hand side at the
17 bottom, it says that it's generally been assumed
18 that the generation of A2E by phosphate
19 hydrolysis of A2-PE occurs within the acidic
20 conditions of RPE lysosomes. Do you see that?

21 A. Yes.

22 Q. Do you have an understanding of what that
23 means?

24 A. Yes. The lysosomes -- this is a
25 subcellular organelle, and it has an acidic

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1 environment, and he's saying that it's been
2 assumed that that chemical reaction that causes
3 the phosphate possibly to break off.

4 Q. And the next sentence says: "Contrary to
5 expectations, we observed that at pH 5.5, an
6 acidic environment similar to that in liposomes
7 (pH 5.5), A2E is generated from A2PE at a slow
8 rate."

9 Do you understand that?

10 A. I see what's being -- what you're
11 reading. I don't know -- unless you can direct
12 me, I don't know what the rate is, though. It
13 says slow, but I don't know what that means.

14 Q. Is this -- was it contrary to
15 expectations in 2002 that A2E is generated from
16 A2PE at a slow rate?

17 MR. MILLS: Objection to form,
18 incomplete hypothetical, misstates --

19 THE WITNESS: I am not offhand
20 familiar with anybody else trying to actually
21 measure that rate.

22 BY MR. FELDSTEIN:

23 Q. Was it known in the art by 2007 that A2E
24 is generated from A2PE at a slow rate in the
25 conditions -- pH conditions of a liposome?

1 MR. MILLS: Objection.

2 BY MR. FELDSTEIN:

3 Q. Liposome?

4 MR. MILLS: Objection. Form,
5 incomplete hypothetical, and outside the scope.

6 THE WITNESS: Well, if one accepts
7 the material and the conclusions in this paper,
8 it was known by 2007 because that's what was
9 said here.

10 Although, I don't know what the rate
11 is or right offhand without reading more of the
12 paper.

13 BY MR. FELDSTEIN:

14 Q. Can you turn to your materials to
15 Exhibit 1035? It's something that you have with
16 you and you considered.

17 A. 1035.

18 Q. 1035 is authored by Radu, correct?

19 A. Correct.

20 Q. This is something you considered,
21 correct?

22 A. I think it's on the list of materials.
23 There was a Radu paper, I think. I can't
24 remember if this is the same one. It does look
25 familiar.

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1 Q. This is -- Mata is second author here,
2 correct?

3 A. Yes. Mata, and the corresponding author
4 is Travis.

5 Q. So it includes the same group members --
6 some of the same group members as the Mata 2000
7 publication?

8 A. That's correct, yes.

9 Q. And Exhibit 1035 is published in
10 April 2003, correct?

11 A. That's what it says, yes.

12 Q. And Figure 1 of Radu Exhibit 1035
13 includes the same proposed mechanism as Mata
14 Exhibit 10, on the right-hand side under B,
15 correct?

16 MR. MILLS: Objection to form.

17 THE WITNESS: Yeah. Without making
18 direct comparison, it looks like the same steps.
19 I will point out that this time the end ret-PE
20 actually does have a single bond -- which is the
21 way it should be -- in contrast to the -- what
22 we talked about originally where there was a
23 dotted bond to the nitrogen.

24 BY MR. FELDSTEIN:

25 Q. So N-ret-PE corresponding to before or

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1 after 1,5 shift?

2 A. Oh, this is before.

3 Q. Okay. And Radu doesn't address
4 pharmacological inhibition of any of the steps
5 in Mata Figure 5 or Radu Figure 1B, correct?

6 MR. MILLS: Objection; form.

7 THE WITNESS: Apparently, the focus
8 is on the isotretinoin or Accutane -- well,
9 whatever it was sold as -- using that to inhibit
10 the 11 CRDH enzymes shown there in part of
11 Figure 1.

12 BY MR. FELDSTEIN:

13 Q. Okay. I'm going to try to break that
14 down so it's clear on record.

15 What Radu Exhibit 1035 is addressing is
16 an inhibitor of the visual cycle, which is
17 Figure 1A, correct?

18 MR. MILLS: Objection to form.

19 THE WITNESS: That is correct.

20 BY MR. FELDSTEIN:

21 Q. And Radu was not addressing
22 pharmacological inhibition of the A2E
23 biosynthesis in Radu Figure 1B, correct?

24 MR. MILLS: Objection to form.

25 THE WITNESS: That is -- I would

1 agree with that. That is correct. This is an
2 approach that this group was, I think, primarily
3 focused on, at least at this time.

4 BY MR. FELDSTEIN:

5 Q. Do you have an understanding of what's
6 depicted in Figure 3A -- excuse me -- 3C Radu
7 Exhibit 1035?

8 MR. MILLS: Objection to form and
9 scope.

10 THE WITNESS: Yes, I do.

11 BY MR. FELDSTEIN:

12 Q. And what's your understanding of what's
13 depicted in Figure 3C of Radu Exhibit 1035?

14 MR. MILLS: Objection to scope.

15 THE WITNESS: Well, it -- basically,
16 they're treating mice and -- with or without a
17 drug, and they're measuring this -- the levels
18 of the N-Ret-PE, and they're looking at the
19 effect of isotretinoin on that, and they show
20 that the levels of that compound are decreased
21 by, oh, approximately 40 percent. They're using
22 a very high concentration -- high dose of
23 isotretinoin, 20 milligrams per kilogram, which
24 is a lot for most drugs.

25 BY MR. FELDSTEIN:

1 Q. And what specifically are they measuring?
2 What's the anolyte in Figure 3C?

3 MR. MILLS: Objection to scope.

4 THE WITNESS: Well, they're using
5 radioactivity, but they're measuring N-ret-PE on
6 Figure 1B, so we're using the same nomenclature,
7 which is -- well, it could be something else.
8 Well, they called it APE way back in the earlier
9 Mata paper.

10 BY MR. FELDSTEIN:

11 Q. Is your understanding that that was based
12 on injecting the mice with trace amounts of
13 tritiated A-T-R-O-L?

14 MR. MILLS: Objection to scope.

15 BY MR. FELDSTEIN:

16 Q. And I can point you to the bottom of --

17 A. Yeah, I found it.

18 Q. Yeah.

19 A. It's all-trans-retinol with a TRITC
20 label, and they injected that apparently into
21 the eye -- no. They didn't time the period
22 incubated. But, yeah, basically they were
23 looking at that coming from all-trans-retinol.

24 Q. And so the same group as Mata 2000 were
25 in 2003 using isotopically labelled retinol to

1 study the mechanisms of the visual cycle,
2 correct?

3 MR. MILLS: Objection to scope.

4 THE WITNESS: Well, yeah, part of
5 the study was done with radioactivity retinol,
6 yes.

7 BY MR. FELDSTEIN:

8 Q. And they didn't suggest in Radu
9 Exhibit 1035 using deuterated vitamin A species
10 to slow down the A2E biosynthesis in Radu
11 Figure 1B, correct?

12 MR. MILLS: Objection.

13 THE WITNESS: In Figure 1 -- I'm
14 sorry, 1C?

15 BY MR. FELDSTEIN:

16 Q. One, B as in boy.

17 A. Oh, Figure 1B. Oh, okay. You're
18 referring to the scheme. Repeat the question,
19 I'm sorry.

20 Q. I'll break it down.

21 The same researchers that were involved
22 in the Mata 2000 publication, in 2003 they were
23 using isotopically labeled retinoids, correct?

24 MR. MILLS: Objection; form.

25 THE WITNESS: Yes. This was

1 tritium. This was actually a tracer, so that's
2 not the same kind of molecule at all.

3 BY MR. FELDSTEIN:

4 Q. Right. And -- but they had at their
5 disposal a way to isotopically label retinoids,
6 correct?

7 MR. MILLS: Objection to form.

8 THE WITNESS: Well, yes and no.
9 They were, I think -- they don't really talk
10 about the source of their material. We have
11 actually purchased tritiated retinol itself, and
12 I don't know where the label is. I would be
13 very shocked to know that it was actually on the
14 20 position. So they probably just bought this
15 from a commercial vendor, I would suspect when
16 they say that.

17 The -- having said that, yeah,
18 they -- it was known from the work of
19 Dr. Olson's lab and a couple of papers that are
20 in the exhibits that some -- that a person could
21 actually synthesize C20 deuterated retinoids,
22 though, sure.

23 BY MR. FELDSTEIN:

24 Q. So the Mata group understood Mata
25 Figure 5, Ragu Figure 1, correct?

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1 MR. MILLS: Objection; form.

2 THE WITNESS: Yes.

3 BY MR. FELDSTEIN:

4 Q. And they knew about isotopic labeled
5 retinoids, correct?

6 MR. MILLS: Objection to form.

7 THE WITNESS: Presumably. Well,
8 they could -- certainly could have if they read
9 the literature and knew about Olson' work.

10 BY MR. FELDSTEIN:

11 Q. And they, in fact, use isotopically
12 labeled retinoids as tracers, correct?

13 MR. MILLS: Objection to form.

14 THE WITNESS: They did. But that's
15 somewhat irrelevant because that was as a tracer
16 and the radioactivity could be in a different
17 place, and they perhaps -- this is -- they
18 left -- for whatever reason, they did not elect
19 to do the chemical synthesis of the deuterated
20 material.

21 BY MR. FELDSTEIN:

22 Q. And so even three years later, the same
23 Radu group, with all the tools at their
24 disposal, weren't attempting to slow the A2E
25 biosynthesis by using C20 deuterated retinoids,

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1 correct?

2 MR. MILLS: Objection to form,
3 foundation, calls for speculation.

4 THE WITNESS: I have no evidence
5 that they considered this. They apparently were
6 more interested in using other drugs, available
7 drugs, to try to achieve the same -- well, I
8 shouldn't say the same endpoint, but to actually
9 address the disease state.

10 BY MR. FELDSTEIN:

11 Q. By inhibiting the visual cycle itself,
12 correct?

13 A. That is correct.

14 Q. Okay. Can you turn to Exhibit 1033?
15 I can give you a copy if you need it.

16 A. I may --

17 MR. FELDSTEIN: Do you have 1033,
18 Drew?

19 THE WITNESS: Let me say -- I'm
20 sorry, what's the --

21 BY MR. FELDSTEIN:

22 Q. 1-0-3-3.

23 A. I have 1032 and 1035.

24 Q. Somebody is going to get fired.

25 A. Huh?

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1 Q. I'll give you a copy. Here's 1033.

2 A. Okay. Thank you.

3 Q. 1033 is a document you considered in the
4 (inaudible); is that correct, Doctor?

5 A. I think so. I'm pretty sure I've seen
6 this, though, it doesn't feel as familiar. This
7 is 2003 paper. Okay. Sure.

8 Q. And it includes authors who are active
9 researchers in the --

10 A. The Nakanishi group; you can call it
11 that. Sparrow and Fishkin and Nakanishi.

12 Q. Okay. First sentence of the introduction
13 says: "Circumstantial evidence gathered over a
14 number of years has implicated retinol pigment
15 epithelial RPE, lipofuscin in the etiology of
16 atropic age-related macular degeneration."

17 Do you see that?

18 MR. MILLS: Objection to form.

19 THE WITNESS: I do. That's what it
20 says.

21 BY MR. FELDSTEIN:

22 Q. Has it not been established by this time
23 that lipofuscin pigments were part of the
24 etiology of atropic age-related macular
25 degeneration?

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1 MR. MILLS: Objection to form.

2 THE WITNESS: Well, it
3 circumstantial evidence, and then it goes on to
4 cite a number of papers. As far as I remember,
5 I don't know that I specifically read these, but
6 they actually provide a synopsis that I think is
7 reasonable.

8 BY MR. FELDSTEIN:

9 Q. Is your understanding at this time it was
10 not yet confirmed whether or not lipofuscin
11 pigments are implemented in etiology of atropic
12 age-related macular degeneration?

13 MR. MILLS: Objection to form.

14 THE WITNESS: Well, for some reason,
15 they use the circumstantial evidence. I don't
16 know exactly what the context of using that word
17 is in terms of -- as opposed to experimental
18 evidence. Perhaps experimental evidence is
19 probably might -- that might be too strong
20 because that would probably imply that
21 everything had been done in human subjects,
22 which may not be the case. Some of this is
23 probably from experimenting on (inaudible).

24 BY MR. FELDSTEIN:

25 Q. Do you understand whether or not there

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1 was consensus by 2007 that lipofuscin pigments
2 were implicated in etiology in atropic
3 age-related macular degeneration?

4 MR. MILLS: Objection.

5 THE WITNESS: From the papers I
6 read, I think there was -- this was actually --
7 I wouldn't say an airtight case, but it was a
8 strong suspicion. I think one has to be -- you
9 know, just in general, one has to be very
10 careful about that. The number of people have,
11 you know, proposed different things. But the
12 basis of Alzheimer's disease and some things
13 sound pretty good for a while, and we're still
14 not making that much progress yet, so...

15 BY MR. FELDSTEIN:

16 Q. Can you turn now to Exhibit 1009? If you
17 need a copy of it, let me know.

18 A. Okay. I have it.

19 Q. And what is Exhibit 1009?

20 A. This is a world patent, W0 patent, by
21 Widder, et al.

22 Q. And is this something you considered and
23 relied upon, Doctor?

24 A. Yes, I read this.

25 Q. And at a high level, was Widder directed

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1 to trying to reduce lipofuscin production?

2 A. I think that's -- yeah, I was going to
3 say I would agree with that, yeah.

4 Q. And is it correct that Widder discloses
5 two methodologies to do that: The first being
6 antagonizing the visual cycle itself; and second
7 being reducing serum retinol?

8 MR. MILLS: Objection; form.

9 THE WITNESS: I think that's
10 appropriate. It's a little more complicated.
11 They -- they tried two different drugs. One was
12 the -- I think fen -- fen -- what is it? The
13 fenretinide is it? Okay. I think that -- yeah,
14 they were using two pharmacological approaches.
15 We call them pharmacological approaches.

16 And those were the main targets. I
17 think that it may be a little more complicated
18 than, you know, just the serum retinoid, but --
19 because I think one of those compounds was also
20 supposed to be inhibiting an enzyme called LRAT,
21 L-R-A-T.

22 BY MR. FELDSTEIN:

23 Q. Right. So just to clarify and make sure
24 the question is clear. Widder is disclosing two
25 mechanisms to reduce lipofuscin formation: The

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1 first is to inhibit the visual cycle; the second
2 is to reduce serum retinol; is that correct?

3 MR. MILLS: Objection; form.

4 THE WITNESS: I would agree. I
5 think that's a reasonable, general conclusion,
6 yes.

7 BY MR. FELDSTEIN:

8 Q. Okay. And why did it make sense to
9 reduce serum retinol levels to reduce formation
10 of the lipofuscin pigments?

11 MR. MILLS: Objection to form,
12 incomplete hypothetical.

13 THE WITNESS: Yeah, it's
14 hypothetical, and actually, if you look at some
15 of the approaches that's historically used, some
16 of those were actually almost countering each
17 other in terms of giving vitamin A and also
18 lowering retinal levels then.

19 And I'm sorry, what was the question
20 again?

21 BY MR. FELDSTEIN:

22 Q. I'll do a better question.

23 A. Okay.

24 Q. Or try to.

25 What would a person of ordinary skill in

1 the art understand from Exhibit 1009 as the
2 benefit of reducing serum retinol levels?

3 MR. MILLS: Objection; form,
4 incomplete hypothetical.

5 THE WITNESS: Well, my understanding
6 was that if you reduce the amount of retinols
7 and, you know, therefore retinal, you'll have
8 less material to go on and form these lipofuscin
9 products.

10 BY MR. FELDSTEIN:

11 Q. And that's --

12 A. That's an oversimplification, but, yeah,
13 something like that.

14 Q. And would a person of ordinary skill in
15 the art have understood the converse is true,
16 that increasing serum retinol levels will
17 increase the production of lipofuscin?

18 MR. MILLS: Objection. Form,
19 incomplete hypothetical, lacks foundation.

20 THE WITNESS: My answer is not
21 necessarily because retinoids -- homeostasis is
22 -- well, there are a lot of controls on that.
23 We have a lot of binding proteins, a lot of
24 enzymes that work on retinoids, and so the body
25 may react in a different ways to that. So

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1 what -- you know, raising it lower may not --
2 the total level may not actually have opposite
3 effects.

4 BY MR. FELDSTEIN:

5 Q. What would a person of ordinary skill in
6 the art have understood as of 2007 as to whether
7 increasing serum retinol levels could increase
8 lipofuscin formation?

9 MR. MILLS: Objection to form,
10 incomplete hypothetical.

11 THE WITNESS: I'm not sure there
12 was direct -- I'm not aware or don't remember
13 direct evidence that this actually would happen.
14 However, the -- apparently, Widder thought that
15 this was a -- well, I'm sorry. Widder thought
16 that this approach -- or did I misstate or
17 understand your question?

18 BY MR. FELDSTEIN:

19 Q. Oh, I can ask it again.

20 A. Okay.

21 Q. What would a person of ordinary skill in
22 the art in 2007 have understood as to whether
23 increasing serum retinol levels could increase
24 lipofuscin infusion formation?

25 MR. MILLS: Objection to form,

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1 incomplete hypothetical, asked and answered.

2 THE WITNESS: It's hypothetical, but
3 I don't know that a POSA would know
4 necessarily -- that was necessarily bad or not.

5 BY MR. FELDSTEIN:

6 Q. I'm sorry, you don't --

7 A. A POSA would know if this was a bad
8 approach or a good one.

9 Q. Let me step back. Widder's approach was
10 to lower serum ret -- excuse me. One of
11 Widder's approaches was to lower serum retinol
12 levels, right?

13 A. Correct.

14 Q. Correct?

15 A. Right.

16 Q. And I'm asking now about the opposite of
17 Widder, increasing serum retinol levels. What
18 would a person of ordinary skill in the art in
19 2007 have known as to whether increasing serum
20 retinol levels could increase lipofuscin
21 formation?

22 MR. MILLS: Objection to form,
23 incomplete hypothetical.

24 THE WITNESS: That is a bit
25 hypothetical because you said "could."

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1 Now, that's different than saying it
2 would. In fact, Ortho -- assuming Ortho had
3 some POSAs working for them, they were actually
4 taking that approach, adding more, giving more
5 vitamin A.

6 So the -- I guess the overall point
7 I'm making when you actually consider Widder and
8 Ortho is that there were a mixture of
9 approaches, and some of them seem almost
10 diametrically opposed to each other.

11 BY MR. FELDSTEIN:

12 Q. Decreasing serum retinol levels for
13 Widder is the opposite of Ortho increasing serum
14 retinol levels?

15 MR. MILLS: Objection to form,
16 incomplete hypothetical, mischaracterizes
17 testimony.

18 THE WITNESS: Yeah. That's a --
19 that may be a gross overgeneralization, but
20 there's some merit to it.

21 BY MR. FELDSTEIN:

22 Q. Let's go to Exhibit 30, which you should
23 have in your materials also.

24 MR. MILLS: Is your line of
25 questioning in this exhibit, is it pretty short?

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1 MR. FELDSTEIN: I have more than a
2 few minutes in this folder if want to take a
3 break now.

4 MR. MILLS: Yeah, I think we've been
5 going about an hour.

6 THE WITNESS: I don't think I have
7 1030, by the way.

8 MR. FELDSTEIN: We're going to go
9 off the record.

10 (Off-the-record discussion was held.)

11 BY MR. FELDSTEIN:

12 Q. Ready, Doctor?

13 A. Yes.

14 Q. Can you jump back to Fishkin for a
15 second? Exhibit 1-0-1-1.

16 A. Sure. All right. I have it.

17 Q. And you recognize that Fishkin criticizes
18 some of the analysis in Mata, correct?

19 MR. MILLS: Objection; form.

20 THE WITNESS: Yeah. I think it's
21 primarily some of the spectral assignments
22 particularly, yeah.

23 BY MR. FELDSTEIN:

24 Q. And the dispute between Fishkin and Mata
25 is that Mata had a 5-nanometer pigment species

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1 that Mata said was A2PE-H2 and Fishkin
2 disagrees, correct?

3 A. I think that was the gist of the major --
4 yeah, disagreement, yes.

5 Q. And what is it that Fishkin thinks that
6 corresponds to?

7 A. I'm sorry, which one? The 500?

8 Q. Yes.

9 A. Yeah, he got a diagram. He thinks it
10 corresponds -- well, it -- probably the best
11 beyond that is to look at Figure 3C.

12 Q. Okay.

13 A. I think he has -- I'm sorry. That's --
14 is that -- okay. He's got the ATR dimer PE
15 conjugate. That's one of the main things that
16 he's showing this -- the 204 is extending there
17 in the bottom half, sort of going down towards
18 the -- we'll call it the southwest side,
19 probably the 506.

20 Q. And why does it not matter to your
21 opinion whether Mata's identification of a
22 species in the biosynthetic pathway is correct
23 or not?

24 A. Well, I think I pointed out before, I
25 think the point is that if you slow down the

1 1,5-sigmatropic shift, you actually slow down
2 production of all the compounds that form after
3 that. So they -- these are complex, but
4 basically my primary opinion is that, you know,
5 they'll all slow down, yeah, and some
6 differences in terms of what they really are may
7 not be so much relevant, yeah, then.

8 I won't say they're irrelevant, the
9 structures, but the point is deuteration should
10 slow down or decrease the pressure of everything
11 downstream.

12 Q. Is deuteration going to affect any other
13 step besides what Mata calls 1,5 and what
14 Fishkin calls 1,6?

15 A. Possibly. The -- let's see. Okay. It
16 could, but may or may not affect -- let's
17 look -- we're looking at Fishkin. I think
18 that's the right paper.

19 We're looking at Fishkin, and we're
20 looking down at the -- in the southeast corner
21 of Figure 10 where you have A2E and iso-A2E.
22 Okay.

23 If you're forming -- they have a step
24 there called, two, auto oxidation, and that is
25 the conversion of an dihydro pyridine to a

1 pyridine, so that's an oxidation. And there,
2 you're actually losing one of the hydrogens that
3 is on the original C20 carbon, so that could
4 possibly be decreased.

5 Q. How would you know, or how would you
6 expect one way or the other?

7 A. Well, if you did a careful experiment,
8 you could actually look at the composition of
9 the final products and see if the balance were
10 actually changed between the ATR dimer and the
11 A2E.

12 Q. One of the authors of Fishkin is
13 Nakanishi that you referred to earlier?

14 A. Yeah, Nakanishi.

15 Q. And you said you knew Nakanishi by
16 reputation, correct?

17 A. Yes.

18 Q. And what's Nakanishi's reputation?

19 A. Well, he's one of the -- he was one of
20 the famous premier chemists. He was still
21 working well into his 90s; he died recently. He
22 also -- I think he was apparently an
23 accomplished amateur magician, and actually --
24 no, seriously, he would sometimes do magic
25 tricks at his seminars and things like that. I

1 never saw that, but it's something I remembered.
2 Q. Was he considered a reliable authority in
3 the field?

4 MR. MILLS: Objection; form.

5 THE WITNESS: As I said, he was
6 viewed as a very accomplished organic chemist,
7 yes. That doesn't mean he was always right, but
8 you know, he was considered one of the important
9 people chemistry.

10 MR. FELDSTEIN: Did we do this one
11 yet?

12 BY MR. FELDSTEIN:

13 Q. Did I ask you about Exhibit 1030, Doctor?
14 I lost track before the break. I don't think I
15 did.

16 MR. CHRISTIE: That is one don't
17 have.

18 THE WITNESS: That was one I don't
19 have.

20 MR. FELDSTEIN: Oh, right.

21 BY MR. FELDSTEIN:

22 Q. Thank you.

23 MR. FELDSTEIN: Do you want a copy,
24 Jad? Do you need time to object?

25 MR. MILLS: This one is in the

1 record.

2 MR. FELDSTEIN: Okay.

3 MR. MILLS: It was yours.

4 BY MR. FELDSTEIN:

5 Q. Are you familiar with Exhibit 1030,
6 Doctor?

7 A. Yeah, I think I've read it.

8 Q. And this is from Mata and colleagues,
9 correct?

10 A. Right.

11 Q. Including Pavis?

12 A. Yeah.

13 Q. And could you turn to the references
14 page? It's the second-to-last page of the
15 document.

16 A. I have it.

17 Q. Number 8, Reference Number 8 is the Mata
18 2000 that you rely on?

19 A. Correct.

20 Q. And there's nothing showing in
21 Exhibit 1030 for recognition of the 1,5
22 sigmatropic step as being a slow step in the A2E
23 biosynthetic pathway, correct?

24 MR. MILLS: Objection.

25 THE WITNESS: I don't recall any

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1 discussion of the pathway itself. I think this
2 was actually using a different -- a fairly
3 different approach with the compound HPR or 4-
4 hydroxyphenyl retinamide, so they were focused
5 on that.

6 BY MR. FELDSTEIN:

7 Q. And that Exhibit 1030, the approach is to
8 reduce serum vitamin A levels, correct?

9 MR. MILLS: Objection; form.

10 THE WITNESS: I think that's the
11 gist of their approach, yes. I don't disagree
12 with that.

13 MR. FELDSTEIN: I'm going to mark as
14 Exhibit 2066 --

15 (Exhibit Number 2066 was marked.)

16 BY MR. FELDSTEIN:

17 Q. -- a publication by Maiti, M-A-I-T-I, in
18 Biochemistry 2006.

19 Let me know if you need time.

20 MR. MILLS: Yeah, just one moment.

21 I object to Exhibit 2066 on the
22 basis of Rules of Federal Evidence 801 through
23 803 and under rule 601, lack of sponsor witness.

24 BY MR. FELDSTEIN:

25 Q. Do you recognize Exhibit 2066 as a

1 publication from Biochemistry 2006?

2 MR. MILLS: Objection to form,
3 foundation.

4 THE WITNESS: That's what it
5 purports to be, yes.

6 BY MR. FELDSTEIN:

7 Q. And it's from the -- includes Dr. Sparrow
8 among others, correct?

9 A. Yes.

10 Q. Is this something you considered in
11 forming your opinions in this case?

12 A. I don't recall that I did. I don't
13 recall seeing this paper before.

14 Q. Is this something a person of ordinary
15 skill would have been aware of as you define
16 that person?

17 MR. MILLS: Objection to form and
18 foundation, incomplete hypothetical.

19 THE WITNESS: Possibly. I don't
20 know actually. I mean, it's a paper that's sort
21 of in the field; although, the -- you know,
22 well, I guess the abstract actually would have
23 keywords in it that would show up in searches.
24 The title doesn't.

25 BY MR. FELDSTEIN:

1 Q. And take your time if you need to, but do
2 you agree that the Exhibit 2066 is directed to
3 inhibition of the visual cycle to prevent
4 formation of lipofuscin pigments?

5 MR. MILLS: Objection to form.

6 THE WITNESS: That seems to be the
7 case. They're using RP65 antagonist here, and
8 they're trying to reduce this -- reduce the
9 lipofuscin, I should say. I'm sorry.

10 BY MR. FELDSTEIN:

11 Q. And this is a couple of years after Mata
12 2000, correct?

13 A. Six years, precisely, and it's apparently
14 just, you know, more the patent application.

15 Q. And in the references, Reference Number 6
16 is, in fact, Mata 2000, correct?

17 A. That's correct.

18 Q. And in 2006 the abstract is recognizing
19 that to prevent formation of lipofuscin pigments
20 requires identification of rate-limiting steps
21 in the visual cycle, correct?

22 MR. MILLS: Objection to form,
23 incomplete hypothetical, mischaracterizes the
24 document.

25 THE WITNESS: Well, I'm not sure.

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1 That's what they say. I'm not sure I'd agree
2 with that necessarily because this is an
3 approach, and actually, as it turned out,
4 subsequently, the visual cycle seems to be
5 rather divorced from the cycle that's actually
6 going to lipofuscin shown by the deuterium
7 effects.

8 BY MR. FELDSTEIN:

9 Q. In 2006, the authors of Exhibit 26 --
10 2066 were focused on inhibiting the visual cycle
11 as opposed to inhibiting the A2E biosynthetic
12 pathway, correct?

13 MR. MILLS: Objection. Form,
14 foundation, calls for speculation.

15 THE WITNESS: Well, it's a little
16 hard to tell, and the -- basically -- well,
17 actually, this is a little misleading.

18 It says: "RPE lipofuscin including
19 A2E" -- I'm reading from the abstract -- "forms
20 as a byproduct of the visual cycle."

21 I mean, I guess in the sense that
22 retinal -- all-trans-retinal is involved in
23 AP -- in lipofuscin formation, I guess that's
24 fits in, in a very vague way.

25 I don't know -- what I can't say is

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1 exactly when the -- or what was in the authors'
2 minds as they considered this approach versus
3 going to the deuterium.

4 BY MR. FELDSTEIN:

5 Q. But they describe here is reducing the
6 supply of ATR by inhibiting the visual cycle,
7 correct?

8 MR. MILLS: Objection; form.

9 THE WITNESS: That's what they say.
10 Yes, this was an approach. I think this
11 probably would have side effects because if you
12 inhibit the visual cycle, you're going to have
13 some problems then, and I don't know if that's
14 all I can really say about this. As I said, I
15 hadn't really considered this previously.

16 BY MR. FELDSTEIN:

17 Q. And can you turn to the third page of the
18 article, 853?

19 A. Yes.

20 Q. You see where it says "experimental
21 procedures" in the bottom right?

22 A. Yes.

23 Q. Immediately above that, it says: These
24 studies provide strong evidence that mRPE65 is
25 rate limiting in the visual cycle function and

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1 A2E formation and that mRPE65 is a valid target
2 for therapies designed to prevent accumulation
3 of lipofuscin and possibly the onset and
4 progression of macular degeneration. Do you see
5 that?

6 MR. MILLS: Objection to form.

7 THE WITNESS: That's what the
8 sentence reads. I read.

9 BY MR. FELDSTEIN:

10 Q. And what would a person of ordinary skill
11 in the art as of 2007 have understood from that?

12 MR. MILLS: Objection to form,
13 incomplete hypothetical, also to scope.

14 THE WITNESS: Well, that the authors
15 were of the opinion that the best approach was
16 to block A2E formation was to get -- to inhibit
17 mRPE65.

18 BY MR. FELDSTEIN:

19 Q. Are you aware of any similar statement in
20 the art as of September 2007 identifying --
21 well, that's a bad question.

22 Are you aware of any statement in the art
23 as of 2007 identifying any other step as rate
24 limiting in A2E formation?

25 MR. MILLS: Objection to form.

1 THE WITNESS: I'm not aware that
2 anyone else used that term about a rate-limiting
3 step in the 2E formation, no.

4 BY MR. FELDSTEIN:

5 Q. Okay. 2-0-6-4. I will mark
6 Exhibit 2064.

7 (Exhibit Number 2064 was marked.)

8 MR. FELDSTEIN: A paper by Maeda
9 M-E -- M-A-E-D-A from Molecular Pharmacology
10 2006.

11 THE WITNESS: Yes.

12 MR. MILLS: I'll register objections
13 to what has been marked as 2064 under Federal
14 Rules of Evidence 401 through 403, 801 through
15 803, and 601.

16 BY MR. FELDSTEIN:

17 Q. Is this a paper you considered, Doctor,
18 Exhibit 2064?

19 A. I have not.

20 Q. Is it something that a person of ordinary
21 in the skill as you defined would have been
22 aware of as of September 2007?

23 MR. MILLS: Objection to form,
24 incomplete hypothetical.

25 THE WITNESS: Could have been. You

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1 know -- you know, it has some of the keywords,
2 and it does deal with some approaches to the
3 matter of reducing the pigments.

4 BY MR. FELDSTEIN:

5 Q. Are you familiar with any of the authors
6 of 2064?

7 A. Yeah, I know Krzys Palczewski. I don't
8 know any of the others. I think this is when he
9 was still at Case.

10 Q. Who is Krzysztof Palczewski?

11 A. He's a scientist; he's very prominent in
12 vision research. I know him from my work at the
13 Journal of Biological Chemistry. He -- I think
14 he was at -- at the University of Washington
15 Seattle, and then he move to Case Western. I
16 think since then, he's moved to the University
17 of California Irvine.

18 Q. In the abstract on the left-hand side,
19 four lines up from the bottom, it says: Thus,
20 there's a need for potent selected inhibitors
21 that can regulate the flux of retinoids through
22 the metabolism pathway termed the visual
23 (retinoid cycle). Do you see that?

24 A. Yes.

25 MR. MILLS: Objection to form.

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1 BY MR. FELDSTEIN:

2 Q. Would a person of ordinary skill in the
3 art understand that term?

4 MR. MILLS: Objection to form,
5 incomplete hypothetical.

6 THE WITNESS: Well, I guess I would
7 have understood that the -- their favorite
8 approach to reducing the undesirable products
9 was to inhibit the normal visual cycle.

10 BY MR. FELDSTEIN:

11 Q. And is it accurate that as of 2006 there
12 was a need for potent selected inhibitors that
13 regulate the flux of retinoids through the
14 visual cycle?

15 MR. MILLS: Objection to form,
16 incomplete hypothetical, outside scope.

17 THE WITNESS: I can't comment on
18 that directly. That was one approach that was
19 being used, as we discussed earlier in the day.
20 Other approaches were being used, and the --
21 and, actually, if we consider the subject matter
22 of this whole discussion, which is the 20
23 deuterated material, that's actually not an
24 inhibitor itself; is actually an alternate
25 substream.

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1 BY MR. FELDSTEIN:

2 Q. Can you look at the last page of
3 Exhibit 264? The print's terribly small and
4 kind of faint, but the references are
5 alphabetically. The second Mata that's listed,
6 that's the Mata 2000 article that you relied on,
7 correct?

8 A. Correct.

9 Q. And so the authors of 2064, likewise,
10 relied on Mata 2000?

11 A. Well, it certainly cited it, yes.

12 Q. And the methodology that the authors of
13 Exhibit 2064 relied on was adding inhibitor to
14 the visual cycle different than inhibiting the
15 A2E biosynthetic pathway that's shown in
16 Figure 5 Mata, correct?

17 A. I would -- yes. I would agree with that,
18 yeah. Again, it's the same approach that we
19 just saw in the previous biochemistry paper,
20 inhibited visual cycles and the approach as
21 opposed to go directly after the pathway
22 formation itself.

23 Q. Okay. We'll mark Exhibit 2070.

24 (Exhibit Number 2070 was marked.)

25 BY MR. FELDSTEIN:

1 Q. Exhibit 2070 is an article by Travis from
2 Annual Reviews of Pharmacological [sic]
3 Toxicology 2007?

4 A. Yes.

5 MR. MILLS: I'm going to register
6 objections to the -- object to Exhibit 2070.
7 The document itself purports, in some places at
8 least, to be a post-critical data information.
9 I object to the document under Federal Rules of
10 Evidence 401 through 403, 801 through 803.
11 Object to the document under rules 601 for
12 lacking a sponsoring witness, and I object to
13 the authenticity of the document to establish
14 prior reiteration.

15 BY MR. FELDSTEIN:

16 Q. Doctor, are you familiar with
17 Exhibit 2070?

18 A. I don't recall that I've seen it before.

19 Q. This is also authored by your friend
20 Krzysztof Palczewski --

21 MR. MILLS: Objection to form.

22 BY MR. FELDSTEIN:

23 Q. -- correct?

24 A. It's authored by Travis and Palczewski.
25 I recognize those names.

1 Q. And would a person of ordinary skill in
2 the art have been aware of this article too?

3 MR. MILLS: Objection. Form,
4 incomplete hypothetical, foundation.

5 THE WITNESS: I don't know the
6 effective date on this publication. It was in
7 2007, so I'm not sure if it was published before
8 or after the patent.

9 BY MR. FELDSTEIN:

10 Q. Okay. Can you turn to page 7? Has the
11 number page 7 at the top.

12 A. I have it.

13 Q. And you see the heading "LCA Due to
14 Mutations"?

15 A. Yes.

16 Q. The sentence immediately above that says:
17 "A2PE-H2 is converted to A2E and A2E-epoxides
18 upon exposure to short wavelength light in the
19 acidic and oxidizing conditions of RPE
20 phagolysosomes."

21 Do you see that?

22 A. Yes.

23 Q. What do you understand that to mean?

24 MR. MILLS: Objection; form,
25 foundation incomplete hypothetical.

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1 BY MR. FELDSTEIN:

2 Q. Sure. Let me ask a foundation question.

3 Do you understand that statement, Doctor?

4 A. Yes. Without looking at the actual
5 references, but I don't remember about the
6 epoxides. It cites the primary references here,
7 actually. One -- yeah, I don't -- haven't read
8 the ones about the epoxides, the 113 and 114.

9 Q. What do you understand it to mean?

10 A. Well, basically, they cite these as
11 evidence that one of the pigments, APT, dihydro
12 A2PE is converted A2E and to epoxides when
13 exposure to short-wavelength light, which would
14 be UV light, and then which would be entering
15 the eye within the acidic and oxidizing
16 conditions of the phagolysosomes. The epoxides
17 are actually formed by oxidation.

18 Q. And so is this indicating that one step
19 in the conversion of A2PE-H2 to A2E is a
20 photoinduced reaction?

21 MR. MILLS: Objection to form,
22 foundation, incomplete hypothetical, and to the
23 extent it calls for speculation.

24 THE WITNESS: I haven't read the
25 original papers, but it certainly apparently can

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1 be converted. I don't know if these are
2 physiological or not, or they just mimicking the
3 conditions in the phagolysosomes, and -- and
4 oxidizing epoxides.

5 BY MR. FELDSTEIN:

6 Q. And so do you know if as of
7 September 2007 whether there was an
8 understanding that part of the A2 biosynthetic
9 pathway included a photoinduced step?

10 MR. MILLS: Objection; form,
11 foundation, incomplete hypothetical.

12 THE WITNESS: I think it's been --
13 it was mentioned in some of the papers in terms
14 of the photo reduction.

15 BY MR. FELDSTEIN:

16 Q. As a possible step in the formation of
17 A2E, or is a consensus step --

18 A. I say --

19 MR. MILLS: Hold on. You got to let
20 him finish, Doctor.

21 THE WITNESS: Okay.

22 MR. MILLS: Let him finish and then
23 let me have a chance, okay?

24 THE WITNESS: Okay.

25 MR. MILLS: All right. Counsel, are

1 you done?

2 MR. FELDSTEIN: Yeah. I'll just
3 repeat the question.

4 BY MR. FELDSTEIN:

5 Q. Do you know -- I may have go back a
6 question.

7 The prior question, Doctor, was: Do you
8 know if as of September 2007 there was an
9 understanding that part of the A2E synthetic
10 pathway included a photoinduced step, and you
11 said something to the effect that -- the record
12 will speak for itself -- but to the effect of
13 that you saw it mentioned, and my question that
14 I get to was, was it mentioned as a possible
15 step or as a consensus conclusion?

16 MR. MILLS: Objection. Form,
17 foundation, incomplete hypothetical, and outside
18 the scope.

19 THE WITNESS: The Fishkin paper in
20 2005 actually does actually use light treatment
21 and show formations of various products. For
22 instance, they're -- I mean, whether or not -- I
23 don't know if this was generally accepted or
24 not, and I don't know how much of a role this
25 was -- the thought really played then either.

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1 BY MR. FELDSTEIN:

2 Q. And did you consider -- in forming your
3 opinions regarding slowing Mata's biosynthetic
4 pathway in Figure 5, did you consider whether
5 any of the steps therein required a
6 photoinduction?

7 MR. MILLS: Objection to form.

8 THE WITNESS: I did not because
9 the -- as I mentioned a number of times today,
10 basically, if their point is to reduce the
11 amount of the material we call APE, then -- or I
12 think it's NRpe elsewhere -- yeah, NRpe
13 elsewhere. If you reduce that, everything will
14 be reduced downstream from that, and you will
15 have accomplished your purpose whether it, you
16 know, involves acid or light or oxygen.

17 BY MR. FELDSTEIN:

18 Q. Can you turn to page 15 of Exhibit 2070?
19 There's "conclusions and perspective." Do you
20 see that?

21 A. I do.

22 Q. And the last sentence of the first
23 paragraph says: Three therapeutic strategies
24 have been considered, correct?

25 MR. MILLS: Objection; form.

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1 THE WITNESS: I see that.

2 BY MR. FELDSTEIN:

3 Q. And the context is treating retinal
4 diseases, right?

5 A. Yes, I will agree with that.

6 Q. And I'm going to ask you -- I want to ask
7 you about each of the three approaches and ask
8 whether you have an understanding of whether as
9 of September 2007 those were -- whether this is
10 an accurate summary of the therapeutic
11 strategies that were being considered by POSA as
12 of September 2007, okay?

13 And so the first one: Is it accurate
14 that one of the three therapies being considered
15 as of September 2007 for retinal disease,
16 inherited retinal disease, was gene therapy?

17 MR. MILLS: Objection to form,
18 foundation.

19 THE WITNESS: That's what's listed.
20 A number of caveat -- well, a number of problems
21 with this are mentioned there, and, you know, my
22 own opinion in 2007 is that gene therapy wasn't
23 really generally very successful, and I think in
24 a case like the eye probably would be much more
25 difficult. In fact, still today gene therapy

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1 was pretty limiting.

2 BY MR. FELDSTEIN:

3 Q. And is it correct that as of 2007 gene
4 therapy was one of the three perspectives being
5 considered to reduce the formation of A2E?

6 MR. MILLS: Objection; form.

7 THE WITNESS: That's what the
8 authors say. Well, they say -- I don't if
9 they -- how -- what they considered. They point
10 out most of the problems with this at that time,
11 which is probably accurate.

12 Q. And then on page 16, the first two
13 chromophore replacement therapy. Do you see
14 that?

15 A. Yes.

16 Q. And that's a third -- a second therapy
17 was that being considered by September 2007 to
18 address A2E-related diseases, correct?

19 MR. MILLS: Objection.

20 THE WITNESS: Yes. It doesn't
21 really explain that too well. I think the
22 problem is that -- well, as they say, the
23 drawback in the approach is the accumulation of
24 toxic or teratogenic retinoic acid with
25 prolonged retinoid supplementation.

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1 BY MR. FELDSTEIN:

2 Q. And then the third therapeutic strategy
3 being considered to reduce A2E as of 2007 was
4 therapeutic inhibition of the visual cycle,
5 correct?

6 MR. MILLS: Objection to form,
7 foundation, incomplete hypothetical.

8 THE WITNESS: Well, the second
9 complete paragraph on that page does deal with
10 therapeutic inhibition, which from everything
11 I've read, seemed to be the Travis favorite
12 approach, at least at that time.

13 BY MR. FELDSTEIN:

14 Q. And are you aware of, by September 2007,
15 any reference teaching another therapy for
16 reducing A2E?

17 MR. MILLS: Objection; form.

18 THE WITNESS: I think -- no. I
19 think this covers most of the literature I'm
20 aware of in that period in terms of the
21 pharmacological intervention and chromophore
22 replacement.

23 I guess I could consider, I suppose,
24 ultimately the 20 deuterated material is
25 chromophore replacement; although, it's probably

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1 not the best way to describe it.

2 BY MR. FELDSTEIN:

3 Q. But there's no one -- there's no paper
4 that says you should deuterate C20 to reduce A2E
5 formation, correct?

6 MR. MILLS: Objection; form.

7 THE WITNESS: Not that I'm aware of.

8 BY MR. FELDSTEIN:

9 Q. Okay. Can you turn in your materials to
10 Exhibit 1019? And if you need a copy, let me
11 know.

12 A. Okay. I have it. This is Furr, et al.,
13 F-U-R-R.

14 Q. Now, what is Furr Exhibit 1019
15 referencing?

16 A. Basically, isotope dilution methods for
17 managing vitamin A and related carotenoids in
18 humans.

19 Q. Does Furr address treatment of ophthalmic
20 disorders?

21 MR. MILLS: Objection.

22 THE WITNESS: No, I don't think so;
23 not directly.

24 BY MR. FELDSTEIN:

25 Q. Is it correct that for a stable isotope

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1 dilution assay, you need to put the isotopes on
2 chemically stable positions?

3 MR. MILLS: Objection; form.

4 THE WITNESS: Yes.

5 BY MR. FELDSTEIN:

6 Q. And anywhere in Furr Exhibit 1019 do they
7 identify positions on retinoids to avoid for
8 that reason?

9 MR. MILLS: Objection; form.

10 THE WITNESS: Actually, I don't
11 think this paper really talks about positions.
12 You know, it's not really that kind of a paper.
13 It's mainly designed for nutritionists.

14 MR. FELDSTEIN: Do you want to take
15 a ten-minute break and regroup?

16 MR. MILLS: So we can take a break,
17 just, the court reporter has to leave at five,
18 right.

19 (Brief break was observed.)

20 BY MR. FELDSTEIN:

21 Q. Doctor, just one question for you.

22 During any of the breaks, did you discuss
23 the substance of the case with your counsel?

24 A. No, absolutely not.

25 MR. FELDSTEIN: Okay. That's all I

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1 have for you, Doctor.

2 MR. MILLS: Let's go off the record.

3 (Off-the-record discussion was held.)

4 MR. MILLS: Deposition is over. The
5 witness reserves the right to review the
6 transcript.

7

8 FURTHER THIS DEPONENT SAITH NOT.

9 (Proceedings concluded at 4:45.)

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REPORTER'S CERTIFICATE

I certify that the witness in the foregoing deposition, was by me duly sworn to testify in the within-entitled cause; that the said deposition was taken at the time and place therein named; that the testimony of said witness was reported by me, a Shorthand Reporter and Notary Public of the State of Tennessee authorized to administer oaths and affirmations, and said testimony, pages 5 through 205 was thereafter transcribed into typewriting.

I further certify that I am not counsel or attorney for either or any of the parties to said deposition, nor in any way interested in the outcome of the cause named in said deposition.

IN WITNESS WHEREOF, I have hereunto set my hand the 1st Day of September, 2024.



JENNIFER HAYNIE (License No. 403)

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1 JAD A. MILLS

2 Jmills@wsgr.com

3 September 4, 2024

4 GENE COMPANY PTY LTD v. The Trustees Of Columbia University

5 8/16/2024, PETER GUENGERICH, PH.D. (#6839153)

6 The above-referenced transcript is available for
7 review.

8 Within the applicable timeframe, the witness should
9 read the testimony to verify its accuracy. If there are
10 any changes, the witness should note those with the
11 reason, on the attached Errata Sheet.

12 The witness should sign the Acknowledgment of
13 Deponent and Errata and return to the deposing attorney.
14 Copies should be sent to all counsel, and to Veritext at
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16
17 Return completed errata within 30 days from
18 receipt of testimony.

19 If the witness fails to do so within the time
20 allotted, the transcript may be used as if signed.

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22 Yours,

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1 GENE COMPANY PTY LTD v. The Trustees Of Columbia University
2 PETER GUENGERICH, PH.D. (#6839153)
3 E R R A T A S H E E T
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24 PETER GUENGERICH, PH.D. Date
25

1 GENE COMPANY PTY LTD v. The Trustees Of Columbia University
2 PETER GUENGERICH, PH.D.(#6839153)

3 ACKNOWLEDGEMENT OF DEPONENT

4 I, PETER GUENGERICH, PH.D., do hereby declare that I
5 have read the foregoing transcript, I have made any
6 corrections, additions, or changes I deemed necessary as
7 noted above to be appended hereto, and that the same is
8 a true, correct and complete transcript of the testimony
9 given by me.

10
11 _____
12 PETER GUENGERICH, PH.D. Date

13 *If notary is required

14 SUBSCRIBED AND SWORN TO BEFORE ME THIS
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Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

(2) Changes Indicated in the Officer's Certificate. The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

DISCLAIMER: THE FOREGOING FEDERAL PROCEDURE RULES ARE PROVIDED FOR INFORMATIONAL PURPOSES ONLY.

THE ABOVE RULES ARE CURRENT AS OF APRIL 1, 2019. PLEASE REFER TO THE APPLICABLE FEDERAL RULES OF CIVIL PROCEDURE FOR UP-TO-DATE INFORMATION.

VERITEXT LEGAL SOLUTIONS

COMPANY CERTIFICATE AND DISCLOSURE STATEMENT

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