

In the Matter Of:
GENE CO. V. TRUSTEES OF COLUMBIA

RE47,405

F. PETER GUENGERICH, PH.D.

January 24, 2025



ESQUIRE
DEPOSITION SOLUTIONS

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1 UNITED STATES PATENT AND TRADEMARK OFFICE

2
3 BEFORE THE PATENT TRIAL AND APPEAL BOARD

4
5 CASE IPR2024-00313

6 U.S. Patent No. RE47,405

7
8 GENE COMPANY PTY LTD,

9 Petitioner,

10 vs.

11 THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF
12 NEW YORK,

13 Patent Owner.

14
15 ORAL DEPOSITION OF

16 F. PETER GUENGERICH, PH.D.

17 Friday, January 24, 2025

18 9:00 a.m. CT

19
20
21 Reported by: Elisabeth A. Lorenz: RMR, CRR

22 Job No. J12249647



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ORAL DEPOSITION of F. PETER
GUENGERICH, PH.D., conducted at Courtyard Nashville
Vanderbilt, 1900 West End Avenue, The Cumberland
Room, Nashville, Tennessee:

Pursuant to notice, before Elisabeth A.
Lorenz, Registered Merit Reporter and Certified
Realtime Reporter.



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A P P E A R A N C E S

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INDEX OF EXAMINATIONS

WITNESS: F. PETER GUENGERICH, PH.D.

Exhibit	Description	Page
2208	1957 Hall Paper	97

1 *STENOGRAPHER'S NOTE: All quotations from exhibits
2 are reflected in the manner in which they were read
3 into the record and do not necessarily indicate an
4 exact quote from the document.

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P R O C E E D I N G S

* * *

F. PETER GUENGERICH, PH.D.

was called as a witness, and after having been first
duly sworn, testified as follows:

E X A M I N A T I O N

BY MR. CHRISTIE:

Q Good morning, Dr. Guengerich.

A Good morning.

Q I see you have a large number of binders
there in front of you.

What's in that?

A These contain my declaration and all of
the -- well, many of the exhibits that are relevant
to that. They're clean and haven't been marked at
all.

Q And that's your declaration, Exhibit 1080?

A I think that's it. Yeah, 1080. Yeah, 1080.
Sorry it was out of order, not in numerical order.
Yeah, that's correct.

Q And then the exhibits, that's all the
exhibits cited in Exhibit 1080 or all the exhibits



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1 cited in Exhibit 1080 and your prior declaration,
2 Exhibit 1002?

3 A I don't know that. I don't think it's --
4 I'm not sure that it's all of them. I think it's
5 certainly the most relevant ones.

6 Q Let me back up.

7 You authored a first declaration in this
8 case, Exhibit 1002?

9 A Yes.

10 Q And this binder contains most of the
11 exhibits cited in that declaration?

12 MR. MILLS: Objection.

13 THE WITNESS: I don't think it does.
14 In fact, the entire declaration, Exhibit 1002, this
15 is an excerpt. It's not the complete declaration.
16 I understand I'm here to answer questions about the
17 new declaration, 1080, today.

18 BY MR. CHRISTIE:

19 Q So the binder does include at least the
20 exhibits cited in Exhibit 1080 or just most of them?

21 A Yes, I think most of them.

22 MR. MILLS: If I can, perhaps -- as I



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1 understand it, the intent of the binder is to
2 include the exhibits that are cited in Exhibit 1080.

3 MR. CHRISTIE: Thank you. That's
4 helpful.

5 BY MR. CHRISTIE:

6 Q Dr. Guengerich, do you recall discussing a
7 paper by Roth in this case?

8 MR. MILLS: Objection to scope.

9 THE WITNESS: I believe it's in -- it's
10 in the exhibits, Exhibit 1015, Roth and König.

11 BY MR. CHRISTIE:

12 Q That's the one.

13 Can you flip to that tab for me?

14 A So that is 1015.

15 Q Do you see on page 1 of Exhibit 1015 the
16 abstract?

17 A Yes.

18 Q Can you just describe generally what this
19 paper is discussing?

20 A The paper -- well, the abstract is pretty
21 short, and the title pretty much says it all. It is
22 talking about the kinetic isotope effect on -- well,



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1 we'll call it a 1.5-hydrogen shift. Here it says
2 hydrogen displacement in a compound called
3 cis-pentadiene.

4 Q In the first sentence of the abstract there,
5 it says, The thermal 1.5-hydrogen displacement.

6 Do you see that?

7 A Yes.

8 Q Is there any other kinds of 1.5-hydrogen
9 displacements?

10 MR. MILLS: Objection to form, scope.

11 THE WITNESS: Well, if you're talking
12 specifically about the retinoids in your question
13 today?

14 BY MR. CHRISTIE:

15 Q Just generally speaking.

16 A Yeah, there are different kinds of
17 rearrangements, yes. And, in fact, I think one
18 of -- some of the exhibits, you know, by one of your
19 experts actually talk about the possibility of a
20 different kind of rearrangement that involves proton
21 shifts.

22 Q In this paper, is Roth extrapolating --



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1 scratch that.

2 What type of experiment did Roth run in this
3 paper?

4 A The basic experiment is something called NMR
5 spectroscopy, and they're looking at -- well,
6 they're doing -- not just that. They're also
7 apparently doing gas chromatography analyses of
8 products, and they're heating a sample for various
9 amounts of time and looking at the products of
10 relevance here.

11 And in the title, they're looking at the
12 effect of deuterium substitution on the material --
13 I'm sorry, deuterium substitution on the reaction.
14 I should say the reaction, not the material.

15 Q Can you look at page 27.

16 Do you see the first full paragraph starts,
17 We determined?

18 A Yes.

19 Q It says, We determined the kinetics of the
20 rearrangement in the temperature range 185 to
21 205 degrees.

22 Do you see that?



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1 A Yes.

2 Q Does that mean the actual test was run over
3 that range of temperatures?

4 A Yes, that's my understanding then, and --
5 yeah.

6 Q And then if you flip to page 29, the second
7 to last full paragraph starts, If secondary isotope
8 effects are neglected?

9 A Yes.

10 Q And following that, they come up with a
11 value of 12.2 at 25 degrees?

12 A Yes, I see that.

13 Q And how is that value -- how are they
14 calculating that value?

15 A There's an equation there. I'm trying to
16 keep this simple. Basically, it's what we call an
17 exponential function. Basically, the faster the --
18 and it goes -- up above there, it actually talks
19 about something called the Arrhenius equation.
20 Basically, you actually plug in your values and
21 change the value T, which is the temperature, and do
22 an extrapolation.



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1 Q So they ran the experiment at a higher
2 temperature, 185 to 205, and then they calculated
3 from that the kinetic isotope effect that they would
4 expect at 25 degrees; is that --

5 A That's correct.

6 Q And was this test done in the gas phase?

7 A I believe it was. I'm looking specifically
8 at page 27 at the last full sentence.

9 Q So is that a yes?

10 A Yes, my understanding is that it is. And
11 I'm also looking at page 31. Although it doesn't
12 say gas phase, it says that these were done in
13 ampules, which means sealed glass vessels. I don't
14 know offhand what the boiling point of this molecule
15 is. From what I read here, I believe it is in the
16 gas phase.

17 In fact, I can be more affirmative. At the
18 top of page 27, in the -- well, it's the second
19 paragraph, it says, The hydrogen displacement is a
20 noncatalyzed, homogenous first-order gaseous phase
21 reaction.

22 Q What does that mean, homogenous reaction?



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1 A That means that -- well, it's one phase as
2 opposed to being a combination of liquids and solid
3 with gas.

4 Q So it's a single gas phase; there's nothing
5 else in it?

6 A Yes, you can describe it as that. Yeah, I
7 don't think there's anything else in it, so it's a
8 single entity.

9 Q If you turn back to page 24 to 25, it's kind
10 of spanning it, they're discussing the symmetry of
11 the transition states.

12 A Yes.

13 Q What determines the symmetry of the
14 transition state in a reaction like this?

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

17 THE WITNESS: Symmetry is a term --
18 there's not a direct way to observe this in isotope
19 effect experiments. But basically, it's the
20 similarity of the distance between the product and
21 the transition state with the starting material and
22 the transition state.



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1 That is, basically, is the transition
2 state and an intermediate value between those two in
3 what we call a reaction coordinate.

4 BY MR. CHRISTIE:

5 Q So what factors can influence the distance
6 between the product and the transition state with
7 the starting material?

8 MR. MILLS: Objection to form and
9 scope.

10 THE WITNESS: There are many, and it's
11 not generally a predictable. This happens in
12 enzymes. It happens with purely chemical reactions.

13 BY MR. CHRISTIE:

14 Q Can you give me an example of one factor?

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

17 THE WITNESS: Well, I can. This is --
18 I don't know if it's really speculation but,
19 basically, how much the product and substrate differ
20 in terms of their structures. That's one of the
21 things. There are many things. It's not readily
22 predictable.



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1 BY MR. CHRISTIE:

2 Q Can a composition of a compound itself
3 influence the symmetry of the transition state?

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

6 THE WITNESS: When you say the compound
7 itself, are you referring to the starting material
8 or the product or both?

9 BY MR. CHRISTIE:

10 Q That was a poor question.

11 For example, a nitrogen or an oxygen or a
12 carbon atom?

13 MR. MILLS: Objection to form;
14 objection to scope.

15 THE WITNESS: Well, that's kind of an
16 open-ended question, because when we change those
17 atoms, we have different chemicals.

18 Okay. I suppose there the answer is
19 yes, but that's kind of basically intuitive. The
20 composition of molecules can change all their
21 chemical properties.

22



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1 BY MR. CHRISTIE:

2 Q Let's just use this model compound in Roth
3 as an example.

4 Would introducing an oxygen or a nitrogen to
5 this compound potentially affect the symmetry of the
6 transition state?

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

9 THE WITNESS: I don't know. Possibly;
10 possibly not. I didn't address that specifically in
11 my declaration.

12 BY MR. CHRISTIE:

13 Q I'm just asking generally though.
14 It could influence it?

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

17 THE WITNESS: As I mentioned, whenever
18 you change the chemistry, you have a different
19 molecule, and different things can happen.

20 BY MR. CHRISTIE:

21 Q Now, after Roth, there were others that
22 studied this same reaction with this same compound?



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1 A That's my recollection, yes.

2 Q Do you recall reviewing a paper by Doering?

3 A Doering, yes, I do.

4 Q Doering, excuse me.

5 Do you have that in your binder there?

6 A Let me check. Oh, yeah, there's an

7 Exhibit 2025.

8 Is that the one you're referring to?

9 Q Yeah.

10 Can you pull that up?

11 A I have it.

12 Q And this is a paper by Doering from 2006,
13 Exhibit 2025?

14 A Yes.

15 Q Great.

16 Do you see about halfway down the abstract
17 there there's a sentence that starts, An average
18 kinetic isotope effect?

19 A I'm sorry, where are you reading from?

20 Q This is page 1 in the abstract about halfway
21 down.

22 A Oh, yes, I see it.



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1 Q Can you just read that sentence there?

2 A An average kinetic isotope effect of 4.2
3 plus or minus 0.5 obtained from all values for k_H/k_D
4 and $k_{H/k_{H/D}}$ may be compared with a value
5 of 5.0 plus or minus 0.3, recalculated from data in
6 the pioneering publication of Roth and König.

7 Q Is it your understanding when they say Roth
8 and König they're referring to the paper there in
9 Exhibit 1015 that we just reviewed?

10 A Yes, specifically -- well, it's not
11 editorial policy to include footnotes in abstracts
12 because abstracts have to stand alone.

13 But if you start reading in the
14 introduction, there's a citation to Reference 7A,
15 which is the Roth and König paper we just talked
16 about.

17 Q And what is Doering studying in this paper?

18 A Doering is studying some molecules,
19 basically the compound called a 1,3-pentadiene, and
20 specifically one called
21 2-methyl-1-methylenebicyclo[4.4.0]dec-1-ene.

22 Q And is that the same molecule that Roth and



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1 König studied?

2 A Can you refresh my memory, what was the
3 exhibit number?

4 Q 1015.

5 A Before I answer your question, I want to
6 look at that again.

7 Yes, it appears to be. The nomenclature is
8 different in the two papers, but it appears to be
9 the same molecule, but there are other molecules as
10 well. There are also some other molecules that were
11 studied, including some bicyclic molecules.

12 Q And earlier in the abstract, that sentence
13 you read, and it starts, An average kinetic isotope
14 effect?

15 A Yes.

16 Q So Doering is comparing their reported
17 average isotope effect of 4.2 to the average isotope
18 effect reported by Roth of 5?

19 MR. MILLS: Objection, form.

20 THE WITNESS: It says, yeah, Doering
21 and Zhao report 4.2, and they compared that with a
22 value of 5, which is their recalculated value from



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1 Roth and König.

2 BY MR. CHRISTIE:

3 Q Did Doering measure that isotope effect at
4 the same temperatures as Roth?

5 A The temperature was measured in the Doering
6 paper actually from a high temperature down to a
7 lower temperature over a range of 33 degrees
8 centigrade.

9 Q And that was the range of 167.7 to 201.6?

10 A Yes, that's correct. I recall that the --
11 yeah, the temperature was higher at the Roth and
12 König value in their paper.

13 Q And then like Roth, Doering is extrapolating
14 down to an expected KIE at a lower temperature?

15 MR. MILLS: Objection.

16 THE WITNESS: Yes, I think that's one
17 of the main points of the paper.

18 BY MR. CHRISTIE:

19 Q Can you turn to page 2 of Exhibit 2025, and
20 the first full paragraph starts, As reported?

21 A Yes, I see it.

22 Q Is this paragraph describing the same method



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1 of extrapolation as Roth and Doering?

2 MR. MILLS: Objection to form.

3 THE WITNESS: I don't know if it's
4 exactly the same. They are doing an extrapolation
5 from more temperatures to reduce any uncertainty.

6 BY MR. CHRISTIE:

7 Q What do you mean by reduce the uncertainty?

8 A Well, the -- basically, if you have more
9 points at different temperatures, you can actually
10 get a better fit with less question about what the
11 temperature dependence is. That's a simple way of
12 trying to explain it.

13 Q And in that second paragraph there, the last
14 sentence says, Here, also, the uncertainties in the
15 calculated method for k_H/k_D are too large for a
16 credible extrapolation to room temperature?

17 MR. MILLS: Objection, form.

18 THE WITNESS: I see that. I understand
19 that they're referring to the Roth and König paper.

20 BY MR. CHRISTIE:

21 Q And then that next paragraph there, it says,
22 Stimulus for the present paper stems less from a



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1 desire to confirm the experimental values for the
2 ratios of k_H/k_D at the higher temperature than from
3 a hope to provide a more reliable basis for
4 extrapolation of the ratio to room temperature?

5 A Yes, I see that.

6 Q So Doering doesn't think that his experiment
7 is going to be a credible extrapolation to room
8 temperature, right?

9 MR. MILLS: Objection to form,
10 mischaracterizes the document.

11 THE WITNESS: As I read this, I believe
12 he's referring to Roth and König. I think part of
13 the issue here is that -- well, we're talking about
14 40 years later, and there's -- the instruments are
15 actually much better.

16 BY MR. CHRISTIE:

17 Q So is Doering saying that his method does
18 allow for extrapolation at room temperature
19 reliably?

20 A That's my impression from reading Doering.
21 By the way, I've discussed this in my own -- you
22 know, briefly in my own declaration, I think in



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1 paragraph 53.

2 Q Can you turn to page 4 of the paper, 2025.

3 Do you see on the right-hand side the first
4 full paragraph?

5 A Yes.

6 Q And towards the end, there's a sentence that
7 starts, That the precision of these data.

8 Do you see that?

9 A I'm sorry, you're talking about Column 2 of
10 page --

11 Q 4.

12 A Is that 9083?

13 Q Yeah.

14 A And which paragraph is it?

15 Q On the right-hand side about halfway down in
16 the first full paragraph.

17 A I'm sorry, the first full paragraph starts,
18 The closest our design comes to freedom.

19 Am I following you?

20 Q No.

21 It should start, Temperature dependence of
22 the KDIE.



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1 A You meant the second full paragraph then?

2 Q Yes.

3 A And you're talking about a sentence that
4 begins, That the precision of these data is
5 insufficient?

6 Q Yeah.

7 A Yes, I see that.

8 Q So that sentence -- referring to, it says,
9 That the precision of these data is insufficient to
10 warrant extrapolation to room temperature emerges
11 starkly from calculation of the temperature
12 dependence of kH/kD from the eight values in
13 Table 3.

14 MR. MILLS: Objection, form.

15 BY MR. CHRISTIE:

16 Q Did I read that correctly?

17 A Yes, you read it correctly. I see that.

18 Q So Doering is concluding that, like Roth,
19 their data was insufficient to extrapolate to room
20 temperature?

21 MR. MILLS: Objection, mischaracterizes
22 the document.



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1 THE WITNESS: They go on and discuss --
2 the rest of that entire paragraph, which leads into
3 the next page, talks about that in more detail, and
4 ultimately they come to the conclusion in the
5 abstract that their value is -- let's see, it's 4.2
6 for their isotope effect.

7 BY MR. CHRISTIE:

8 Q That 4.2 isotope effect is based on the
9 experimental data, right?

10 MR. MILLS: Objection to form.

11 THE WITNESS: Yes, it's based on their
12 experiments, and then they also -- in the abstract,
13 they compare this with a value of 5 -- they
14 recalculate it from Roth and König using the very
15 values, a slightly different approach.

16 BY MR. CHRISTIE:

17 Q And then back on page 4 in that same
18 paragraph, second full paragraph.

19 A Yes.

20 Q The last sentence says, The resulting
21 Arrhenius equation.

22 Do you see where I'm reading there?



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1 A Yes.

2 Q And that sentence says, Leads to a value
3 extrapolated to a room temperature of 16.8?

4 A Correct.

5 Q (2-67)?

6 A Yes.

7 Q What does that 2 to 67 mean?

8 A I believe -- I'm not quite sure, but that
9 might be the confidence intervals, at least with one
10 of the calculations.

11 Q So that means their extrapolation to 16.8
12 has a confidence interval of 2 to 67?

13 MR. MILLS: Objection, form.

14 THE WITNESS: Actually, I'm not sure
15 about that. I don't really know that that's
16 specifically a confidence interval. It might be,
17 but I'm not positive.

18 I would also -- by the way, while we're
19 on this, I'd go up to the -- well, the first
20 paragraph in that column where they say, A value --
21 at the last sentence, A value for kH/kD of about 4.5
22 plus or minus .5 appears trustworthy.



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1 BY MR. CHRISTIE:

2 Q And that's, again, the -- that 4.5 number is
3 based on the experimental data that they conducted
4 at the temperatures from 167 to 201?

5 MR. MILLS: Objection to form.

6 THE WITNESS: That's my understanding.

7 BY MR. CHRISTIE:

8 Q And earlier we saw they compared that value
9 of 4.5 to Roth's value of 5 also calculated at the
10 higher temperatures from experimental data, right?

11 MR. MILLS: Objection to form.

12 THE WITNESS: Well, calculated by
13 extrapolation from the higher temperatures, yes.

14 BY MR. CHRISTIE:

15 Q Right.

16 But the -- what do you mean by that?

17 A They looked at the isotope effects at the
18 higher temperatures and used basically an Arrhenius
19 equation to extrapolate 25 degrees.

20 Q And Roth extrapolated a value of 5 at the
21 higher temperatures to a value of 12.2 at room
22 temperature?



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1 A I believe that was the number, yes.

2 Q And then Doering did the same thing,
3 measured a value of 4.2 and extrapolated to 16?

4 MR. MILLS: Objection, form.

5 THE WITNESS: I'm a little confused --
6 now I'm a little confused about the first part about
7 what was concluded by Roth and Doering.

8 Well, yeah, Roth and Doering reported a
9 high isotope effect. This was reevaluated by
10 Doering and came out lower and is apparently fairly
11 consistent with the value that Doering obtained
12 experimentally.

13 BY MR. CHRISTIE:

14 Q So Roth's experimental data is consistent
15 with Doering, the 5 and 4.2?

16 MR. MILLS: Objection to form.

17 THE WITNESS: Yeah. The abstract is
18 pretty clear about that, I think, in terms of
19 summarizing these studies. As I said, you can read
20 the abstract. It says, An average kinetic isotope
21 effect of 4.2 plus or minus 0.5 obtained from all
22 values for k_H/k_D and k minus H/k minus D may be



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1 compared with a value of 5.0 plus or minus 0.3,
2 recalculated from data in the pioneering publication
3 of Roth and König.

4 BY MR. CHRISTIE:

5 Q Then the next sentence there in the abstract
6 says, From a highly problematic extrapolation of the
7 temperature dependence, a value of 16.6 was
8 calculated?

9 MR. MILLS: Objection to form.

10 THE WITNESS: Yes, I see that.

11 BY MR. CHRISTIE:

12 Q What do you understand that to mean, highly
13 problematic extrapolation?

14 A Probably because -- well, I don't know
15 exactly, though I -- probably dealing with the
16 precision of the measurements at the higher
17 temperature and the extrapolation.

18 Q So Doering is saying the experimental data
19 is consistent with Roth, but the extrapolation still
20 is unreliable?

21 MR. MILLS: Objection to form,
22 mischaracterizes the document.



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1 THE WITNESS: My impression as I read
2 this is that they both conclude that there are high
3 isotope effects, you know, with some variability in
4 exactly what they are going to be at room
5 temperature.

6 BY MR. CHRISTIE:

7 Q And the variability that we just looked at
8 on page 4 was anywhere from 2 to 67 at room
9 temperature?

10 MR. MILLS: Objection, form.

11 THE WITNESS: I'm not sure what the
12 2 to 67 actually refers to.

13 BY MR. CHRISTIE:

14 Q So fair to say that's some measure of
15 variability?

16 MR. MILLS: Objection to form.

17 THE WITNESS: I don't know exactly what
18 it is. It might be a confidence interval; it might
19 not be.

20 BY MR. CHRISTIE:

21 Q Turn to page 5 of Exhibit 2025.

22 A I have it.



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1 Q On the left-hand side, in the first full
2 paragraph, starts Curvature?

3 A Yes.

4 Q About halfway down that paragraph, it says,
5 After 339 days?

6 A Yes.

7 Q What is that referring to?

8 A That's the length of time that the
9 experiment was done.

10 Q That doesn't mean that the reaction took
11 339 days, right?

12 MR. MILLS: Objection, form.

13 THE WITNESS: Well, what do you mean,
14 the reaction?

15 BY MR. CHRISTIE:

16 Q Let me recall it here. The thermally
17 activated 1.5-hydrogen shift.

18 A Well, there's an equilibrium, so that's why
19 I asked about the reaction. So there's an
20 equilibrium of products.

21 But my understanding is, yes, they actually
22 did do this experiment for 339 days at high



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1 temperatures.

2 Q Right.

3 They ran the experiment for 339 days, but
4 that doesn't mean that a single reaction took
5 339 days, right?

6 MR. MILLS: Objection, form.

7 THE WITNESS: My impression is that it
8 was very slow, as I think I pointed out, and that
9 was the reason that they used very long time periods
10 to calculate the rates; the same reason they used
11 very high temperatures.

12 BY MR. CHRISTIE:

13 Q So it's your opinion the single reaction
14 took 339 days?

15 A Well, I'm not sure I like the idea of a
16 single reaction, because as they indicated in
17 Figure 2, for instance, there's actually forward
18 reactions and back reactions going on. What they're
19 looking at is a single -- at time points is the
20 mixture of the products in the starting material.

21 I don't know that I can say it's a single
22 reaction.



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1 Q What do you mean forward and back reactions?
2 Can you just explain that to me?

3 A Well, if we look at Figure 2 in that
4 exhibit, you can see that there's an arrow going, it
5 says, $3kH$, and then there's a back reaction that
6 says k minus H .

7 Q So does that mean reaction is reversible?

8 MR. MILLS: Objection to form.

9 THE WITNESS: Yes, that's my
10 impression. And there are other possibilities too.
11 Yes, they're actually teasing these apart.

12 BY MR. CHRISTIE:

13 Q So the 339 days isn't the time it takes for
14 the reaction to proceed in one direction, right?

15 MR. MILLS: Objection to form.

16 THE WITNESS: Well, the reaction will
17 proceed and also reverse. And at different times --
18 or one could actually look at the rate and see from
19 the mixture from the products what they were.
20 That's my impression of -- or that's how you would
21 do this experiment.

22 It's not going to go completely one



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1 way, because, if you'll look carefully at this,
2 you'll see that aside from the deuterium there, it's
3 actually a symmetrical molecule.

4 BY MR. CHRISTIE:

5 Q I'm sorry, what are you looking at?
6 Figure 2?

7 A I'm looking at Figure 2 and specifically
8 looking at Compounds 1 and 2. They're actually the
9 same thing aside from the deuterium, and that's in
10 the position.

11 Q And the conversion from 1 to 2, that's the
12 thermal 1,5 sigmatropic rearrangement hydrogen
13 shift?

14 A Yeah. Actually, so is the reverse reaction.

15 Q And this is the same reaction that's
16 reported in Roth?

17 MR. MILLS: Objection to form.

18 THE WITNESS: It's a similar reaction.
19 The reaction in Figure 2 has a bicyclic compound
20 instead of a monocyclic one.

21 BY MR. CHRISTIE:

22 Q So it's a similar compound to Roth but not



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1 the same one?

2 A That's correct.

3 Q But it's the same reaction mechanism, the
4 1,5 sigmatropic rearrangement?

5 A Yes, it is.

6 Q And the 339 days, that is the time it takes
7 to go from Compound 1, Figure 2, to Compound 2 in
8 Figure 2, right?

9 MR. MILLS: Objection.

10 THE WITNESS: It takes a lot of time
11 and temperature for the rearrangement to occur,
12 because, obviously, they would not have run the
13 reaction for a year at high temperature if the
14 reaction were complete quickly.

15 BY MR. CHRISTIE:

16 Q Aren't they just running the experiment
17 together with reliable data points?

18 MR. MILLS: Objection, form.

19 THE WITNESS: I'm sorry, would you
20 repeat the question? I didn't understand it.

21 BY MR. CHRISTIE:

22 Q The longer you run the experiment, the more



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1 data points you're going to have, right?

2 MR. MILLS: Objection, form.

3 THE WITNESS: It depends on -- I don't
4 know. It depends on exactly how you set up the
5 experiment. You can take data points at different
6 times, or you can wait a long -- take fewer points.
7 I don't know that.

8 BY MR. CHRISTIE:

9 Q Can you look at page 3, in that first full
10 paragraph, the last sentence starts, The small
11 differences?

12 A Yes.

13 Q It says, The small differences in
14 concentrations at 201.6 degrees Celsius for reaction
15 times of 112 and 205 hours are not significant
16 within experimental uncertainties?

17 A I see that.

18 Q What is that 112 and 205 hours referring to?

19 A Presumably these were intermediate time
20 points. It refers to Table SI-6. That is in the
21 supporting information. I don't have the supporting
22 information here, so I can't comment on the --



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1 exactly what that means.

2 Q What's an intermediate time point? What do
3 you mean by that?

4 A That would be a time point prior to the
5 final time point. That's just a general term.

6 Q What does it mean in this context?

7 A It means they measured samples at those
8 times, which would be, you know, in the order of
9 about a week.

10 Q So when you say the reaction is slow, how
11 long do these reactions take to go from 1 to 2, for
12 example, in Figure 2?

13 A Well, I'm not exactly sure how long it takes
14 to go from 1 to 2 because it's also going back. And
15 they teased these apart. They don't -- perhaps it's
16 in the supporting information, but I don't actually
17 have -- I don't see the actual values of the rate
18 constants in here -- or the rates I should say more
19 correctly. I don't see the rates listed here.

20 It could be calculated -- well, you can't
21 calculate them. Yeah, I don't know exactly. You
22 know, since the -- both the -- Doering and Roth ran



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1 their reactions for a very long time at high
2 temperature, they must be slow. Slow is a relative
3 term, I realize, but I don't have a specific number.

4 MR. MILLS: We've been going for about
5 an hour. We're ready for a break.

6 MR. CHRISTIE: Yeah, we can take a
7 break.

8 MR. MILLS: Off the record.

9 (Recess: 10:03 a.m. to 10:16 a.m.)

10 MR. CHRISTIE: Ready to go.

11 THE WITNESS: Before we go any further,
12 could I actually make a small correction to one of
13 my answers previously?

14 BY MR. CHRISTIE:

15 Q Yeah.

16 A I believe you asked me how fast or how slow
17 the reactions were in the Doering paper.

18 Q Are you asking me?

19 A Yeah.

20 Was that the question you asked me
21 previously?

22 Q Yeah, I was asking if a single reaction took



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1 339 days.

2 A Well, let me just say, if I can amend my
3 previous answer, the specific rates -- or they call
4 them rate constants -- are given in Table 2.

5 They're on the order of, oh, I don't know, about 10
6 to the minus 4th per second, which is pretty slow,
7 I'll just leave it at that, even at about
8 200 degrees.

9 Q So how does that compare to 339 days?

10 A Well, I'm not sure exactly. I have to do
11 the math. I don't know exactly how far they would
12 have gone or exactly what the half-life would be.

13 Q And this Doering paper, this was also a
14 thermally activated 1,5 sigmatropic rearrangement?

15 MR. MILLS: Objection to form.

16 THE WITNESS: Yes, that's why they used
17 high temperatures to expedite that.

18 BY MR. CHRISTIE:

19 Q Is there a photochemical 1,5 sigmatropic
20 rearrangement?

21 MR. MILLS: Objection, form and scope.

22 THE WITNESS: I'm not sure. I didn't



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1 address that in my review of this material.

2 BY MR. CHRISTIE:

3 Q I just mean generally.

4 Can a 1,5 sigmatropic rearrangement be
5 photochemical?

6 MR. MILLS: Objection to form, outside
7 the scope, calls for speculation.

8 THE WITNESS: I don't know. I can't
9 answer.

10 My suspicion is there probably is, but
11 this is speculation. I can't really comment on that
12 because I didn't look for one.

13 MR. MILLS: I'll caution the witness
14 not to speculate.

15 BY MR. CHRISTIE:

16 Q Just to be clear, earlier you were talking
17 about Roth is a gas phase reaction?

18 MR. MILLS: Objection to form.

19 THE WITNESS: We did.

20 BY MR. CHRISTIE:

21 Q And Doering, likewise, was done in the gas
22 phase?



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1 MR. MILLS: Objection to form.

2 THE WITNESS: I'm actually not sure,
3 especially with the bicyclic molecules, if these are
4 in the gas phase or not.

5 BY MR. CHRISTIE:

6 Q Wouldn't these necessarily have to be in the
7 gas phase?

8 MR. MILLS: Objection to form, outside
9 the scope, and to the extent it calls for
10 speculation.

11 THE WITNESS: The reactions, you know,
12 they could occur at lower temperatures. I don't
13 know what the boiling point of some of these
14 bicyclic molecules is without looking it up. I
15 don't know if that's actually given here.

16 BY MR. CHRISTIE:

17 Q Let's shift gears a little bit. In your
18 report and this whole case we've been discussing the
19 rate-limiting step in the A2E pathway.

20 MR. MILLS: Objection to form.

21 BY MR. CHRISTIE:

22 Q Does that sound familiar?



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1 A Yes. I think there's -- actually, I
2 discussed this a considerable amount in my
3 declaration and particularly in the concept of what
4 they -- "the" rate-limiting step is versus what is
5 "a" rate-limiting step.

6 Q Do you have Exhibit 2003 in your binder
7 there?

8 MR. MILLS: I'll object to outside the
9 scope.

10 THE WITNESS: 2003?

11 BY MR. CHRISTIE:

12 Q 2003.

13 A I do not believe that I do.

14 Q I've got a copy here.

15 MR. MILLS: I'm going to object to this
16 document as outside the scope. I don't believe that
17 it's discussed in Dr. Guengerich's reply
18 declaration.

19 BY MR. CHRISTIE:

20 Q Doctor, do you see this is a paper by Travis
21 from 2007?

22 MR. MILLS: Objection to form;



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1 objection as outside the scope. I'll object to the
2 extent the question calls for the witness to
3 speculate and lacks foundation.

4 THE WITNESS: Yeah, I see the paper. I
5 don't recall that I've actually seen this before.

6 BY MR. CHRISTIE:

7 Q Did you rely on this in your first
8 declaration in forming your opinions?

9 A I don't recall that I did. I don't
10 particularly remember -- I don't think I remember
11 this. I probably would have.

12 Travis was with the -- with Mata in one of
13 the important papers, and I also recognize the name
14 Palczewski, who actually I know personally. I don't
15 remember seeing this particular review, though.

16 MR. MILLS: I'm going to register an
17 objection based on scope. The deposition today is
18 about Dr. Guengerich's reply declaration; it's not
19 about his declaration presented with the case in
20 chief. He was already cross-examined on that
21 declaration, so the scope today is limited to the
22 reply declaration.



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1 BY MR. CHRISTIE:

2 Q Doctor, can you turn to page 35 of the
3 exhibit, 2003?

4 A I have a page 35. It has a Figure 5 on it.
5 Is that what you're referring to?

6 Q Yeah.

7 I just want to clarify what we're talking
8 about when you say the A2E pathway.

9 So Figure 5 -- let me just ask you, what do
10 you understand Figure 5 to be showing?

11 MR. MILLS: I object to the question as
12 outside the scope of the deposition. Dr. Guengerich
13 did not discuss Exhibit 2003, Figure 5, in the
14 declaration. And the deposition today is limited to
15 cross-examination on his reply declaration.

16 THE WITNESS: What is your question?

17 BY MR. CHRISTIE:

18 Q Do you understand that Figure 5 is showing
19 the visual cycle and then the A2E side reaction?

20 MR. MILLS: I object to the questions
21 about Figure 5, Exhibit 2003, as outside the scope
22 of the deposition. Dr. Guengerich did not discuss



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1 Exhibit 2003, including Figure 5 of Exhibit 2003, in
2 his reply declaration.

3 He was cross-examined previously on his
4 original declaration, which also does not discuss
5 Exhibit 2003. And for that reason, questions about
6 Exhibit 2003 are outside the scope of the
7 deposition.

8 I'll also note, I don't think we've had
9 a single question yet about Dr. Guengerich's reply
10 declaration, so I would ask counsel to focus the
11 deposition from here on out on Dr. Guengerich's
12 reply declaration.

13 BY MR. CHRISTIE:

14 Q Dr. Guengerich, you discuss the concept of
15 the "a" and "the" rate-limiting step in your reply
16 declaration, right?

17 A Yes.

18 Q I just want to establish what we're talking
19 about when we're talking about the A2E reaction.

20 In Figure 5 of Exhibit 2003, this is the
21 visual cycle?

22 MR. MILLS: I object to --



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1 BY MR. CHRISTIE:

2 Q Is that right?

3 MR. MILLS: I object to the questions
4 about Figure 5, Exhibit 2003, as outside the scope
5 of Dr. Guengerich's reply declaration. Exhibit 2003
6 is not discussed in Dr. Guengerich's reply
7 declaration.

8 There are a number of exhibits that are
9 discussed in his reply declaration. They are
10 identified in the declaration, and they are sitting
11 in the binders on the table in front of
12 Dr. Guengerich and are available for counsel to
13 inquire regarding those exhibits.

14 BY MR. CHRISTIE:

15 Q Are you refusing to answer the question,
16 Doctor?

17 A I really have not seen this document.
18 Figure 5 seems relatively straightforward. However,
19 there are actually other papers, such as Fishkin and
20 Kim, which actually have this -- these elements in
21 more detail in terms of the A2E. I don't even have
22 a structure here for A2E.



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1 Q Do you have Exhibit 1035 there?

2 A Yes, I do.

3 This is the Radu paper, Radu 2003?

4 Q Yeah.

5 Sorry, just before we move on, just to be
6 clear, you didn't consider Exhibit 2003 in forming
7 any of your opinions in this case?

8 MR. MILLS: Objection to form,
9 mischaracterizes the witness's testimony.

10 THE WITNESS: I believe I already
11 indicated, I don't recall having seen this paper
12 specifically.

13 BY MR. CHRISTIE:

14 Q So you didn't consider it in forming any of
15 your opinions in this case?

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

19 THE WITNESS: I don't recall. Correct
20 me if it's on the list. I don't really remember
21 seeing this particular review, though.

22



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1 BY MR. CHRISTIE:

2 Q Looking at Exhibit 1035, this is a paper by
3 Radu from 2003?

4 A Correct.

5 Q And this paper is discussing targeting A2E
6 formation?

7 A Yes, A2E -- well, just to be clear, it is --
8 well, the -- yeah, yeah. It actually -- if you read
9 the abstract, it says, Lipofuscin pigments such as
10 A2E, which means probably it includes -- that, to
11 me, would include other things like ATR-dimer and
12 possibly other materials as well. But, yeah,
13 definitely A2E is listed there and seems to be the
14 focus here.

15 Q And they use isotretinoin?

16 A Isotretinoin.

17 Q Tretinoin. Thank you.

18 A You can call it Accutane if you want to.
19 Well, maybe we should say isotretinoin. Accutane is
20 actually a brand name.

21 Q And how were they using Accutane to target
22 A2E lipofuscin formation?



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1 A Very briefly, it's actually being used as an
2 inhibitor of an enzyme called 11-cis-retinol
3 dehydrogenase. Figure 1 actually shows this quite
4 clearly, which is on page 2.

5 Q So there in Figure 1 on page 2, Section A is
6 the visual cycle, right?

7 MR. MILLS: Objection to the form.

8 THE WITNESS: Well, it's part of the
9 visual cycle, yes. It shows what's going on in the
10 RPE cell, the retinal pigment epithelial cell. But,
11 of course, some of this is also occurring in the
12 visual cycle in the rod outer segment. We call it
13 the ROS here.

14 BY MR. CHRISTIE:

15 Q What do you mean when you say visual cycle?

16 A The sequence of transformations that occur
17 with retinoids that allow for vision.

18 Q And there in Figure A, is this the sequence
19 of transformations of the retinoids?

20 A In part.

21 Q What do you mean, in part?

22 A Well, this paper was written in 2003. It



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1 seems to be missing what's now known as the RPE65
2 protein.

3 Q Aside from that?

4 A Well, yeah, actually -- yeah, I think so.
5 It's a -- drawn in a little bit different way, and
6 I'm not sure what IMH is. I think that might be --
7 well, I shouldn't speculate on that without reading
8 it more carefully.

9 Most of the elements are here in the visual
10 cycle.

11 Q So Figure A is the mostly complete visual
12 cycle; and then on the right-hand side, Figure B is
13 the A2E pathway, and that's a side reaction of the
14 visual cycle?

15 A Yeah, I would agree with what you said, yes.
16 I think that's an accurate way of putting it.

17 Q And here they're using Accutane to limit
18 all-trans RAL, what they're calling atRAL here?

19 MR. MILLS: Objection, form.

20 THE WITNESS: Yeah, I think I would
21 agree with that. I think that's the basic idea
22 behind isotretinoin.



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1 BY MR. CHRISTIE:

2 Q So in that sense, it's rate limiting on A2E
3 formation?

4 MR. MILLS: Objection, form.

5 THE WITNESS: I'm sorry, what's rate
6 limiting? Are you referring to the particular
7 dehydrogenase step that's inhibited?

8 BY MR. CHRISTIE:

9 Q The availability of ATR becomes rate
10 limiting when you inhibit -- let me start over.

11 In Figure A, the Accutane is inhibiting
12 11cRDH?

13 A Yes.

14 Q And that produces less -- by doing that, you
15 produce less 11cRAL?

16 A That is correct, yes.

17 Q And then by doing that, you eventually
18 produce less all-trans RAL, which is the following
19 step, right?

20 A Well, it's not exactly the following step.
21 You actually have to go through binding to
22 rhodopsin, and actually the light transformation.



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1 And basically that's how you see.

2 It should inhibit the formation of atRAL
3 down there in the -- we'll call it the southwest
4 corner of that Part A, yes.

5 Q So by inhibiting 11cRDH, the availability of
6 all-trans RAL becomes rate limiting on the final A2E
7 formation?

8 A I can't agree with that. I don't know that
9 it's rate limiting. The inhibition of that
10 particular dehydrogenase doesn't really necessarily
11 tell you anything about what's rate limiting in
12 the -- certainly the side reaction. That is Part B.

13 Q What do you mean by rate limiting there?

14 MR. MILLS: Objection, form.

15 BY MR. CHRISTIE:

16 Q I think we might just be talking past each
17 other.

18 A What do I mean by rate limiting?

19 Q Yeah.

20 A Well, it's a simple concept inherently.

21 When you have a series of reactions, which
22 they're in linear array or a cyclic array, the



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1 rate-limiting step -- a rate limiting -- a
2 rate-limiting step will be the slowest one. Now,
3 that doesn't have anything to say about how much
4 rate limiting it is compared to other steps. And
5 you may have more than one rate-limiting step too.

6 So it's a qualitative statement -- well, it
7 depends on quantitative numbers, but it's a bit of a
8 qualitative term.

9 Q This 11cRDH, than an enzyme?

10 A Yes, it's a -- what we call a dehydrogenase.

11 Q And in your work studying enzyme kinetics,
12 you look at rate-limiting steps in enzymatic
13 reaction?

14 A Yes. I'm actually covering that in my
15 course this semester.

16 Q So there could be -- there's a rate-limiting
17 step in that reaction from 11cROL to 11cRAL, right?

18 MR. MILLS: Objection to form, outside
19 the scope.

20 THE WITNESS: It could be, but it
21 doesn't have to be. And moreover, when you start
22 adding an inhibitor, you're actually slowing down



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1 one reaction, so something else may become rate
2 limiting.

3 BY MR. CHRISTIE:

4 Q So saying there's a slow step in the visual
5 cycle is different than saying there's a slow step
6 in the A2E pathway?

7 A Yes. That's certainly my opinion.

8 Q Those are two different things?

9 A That is correct.

10 Q And slowing down the visual cycle, like they
11 did here with Accutane, can limit the formation of
12 A2E, right?

13 A Apparently so. Unfortunately, it also slows
14 down the visual -- perturbs the visual cycle, so
15 people aren't able to see as well.

16 Q Those are two -- the A2E pathway -- do you
17 consider the A2E pathway part of the visual cycle?

18 A No. It's side reaction. It's actually,
19 frankly, an unwanted, an undesirable side reaction
20 of products that are in the normal visual cycle. I
21 think that may be the best way to describe it.

22 Q And these authors, Radu, when they say



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1 they're targeting A2E and lipofuscin formation, they
2 don't mean they're targeting the A2E pathway
3 specifically, right?

4 A I would agree with that, yes.

5 Q They're targeting A2E formation?

6 A Yes.

7 Q And likewise, the other visual cycle
8 inhibitors aren't targeting the A2E pathway
9 specifically, right?

10 MR. MILLS: Objection to form.

11 THE WITNESS: When you say the others,
12 I guess could you be more specific just before I
13 answer the question?

14 BY MR. CHRISTIE:

15 Q Sure.

16 Do you know what HPR is?

17 A Is that the fenretinide? I don't remember
18 that abbreviation. If it's fenretinide, that's
19 actually inhibiting the ability of retinol to get
20 into the system, so it's not exactly inhibiting the
21 pathway, but I believe it competes with the
22 transport from the serum to the eye.



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1 Q Right.

2 A And I believe -- well, I don't want to make
3 up any answers without any questions here.

4 Q Right. HPR is used to inhibit retinol
5 binding protein, right?

6 A I believe that's what HPR is, yes.
7 Fenretinide is what I think of, but I can't remember
8 if it's called HPR. If that's true, then, yeah.

9 Q And for hydroxyphenyl retinamide --

10 A Yeah, that's it. The phenal --

11 Q And HPR inhibits the -- or reduces the
12 availability of ATR eventually?

13 A Yes, indirectly it inhibits the availability
14 of retinol, which, therefore, will -- should lead to
15 a lower retinal, yeah.

16 Q And like Accutane, that's not targeting the
17 A2E pathway in Figure B specifically, right?

18 A I agree. It's not directly inhibiting that.

19 Q Dr. Guengerich, in your declaration,
20 Exhibit 1080, you rely on the transcript of
21 Dr. Del Priore.

22 A Just a minute.



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1 Is that the right number? I'm showing a
2 1069.

3 Q Yeah, that's the deposition transcript of
4 Dr. Del Priore.

5 A Did you say 1080 before? I don't have a
6 1080, so...

7 Q 1080 is your declaration.

8 A Oh, I'm sorry. Okay. I apologize for that.
9 Yeah, so 1069 is what I've commented on.

10 Q So are you relying on Dr. Del Priore's
11 opinions when you cite that transcript, or are you
12 forming your own opinions based on your review of
13 it?

14 A To some extent, both.

15 Q So just look at paragraph 34 of your
16 declaration.

17 A All right. I have it.

18 Q So is this your opinion, or is this just
19 reciting Dr. Del Priore's opinion?

20 MR. MILLS: Objection, form.

21 THE WITNESS: As I'm looking at this, I
22 think most -- I have a lot of quotes there, so I



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1 think a lot of it is actually coming from
2 Del Priore's transcript, yes.

3 BY MR. CHRISTIE:

4 Q Paragraph 34 says that, The patent owner's
5 expert testified that these predictable effects of
6 inhibiting the visual cycle.

7 Do you see that?

8 A Yes.

9 Q So is it your opinion based on your review
10 of literature that these predictable effects of
11 inhibiting the visual cycle were so undesirable that
12 they rendered such approaches impractical as a
13 therapy; or are you just saying that that's what
14 Del Priore testified to?

15 A I think I concur with Del Priore's comments
16 here. I think I agree with the deficiencies in the
17 current treatments, which is pretty much what this
18 paragraph 34 is all about.

19 Q And what is your basis for concurring with
20 Dr. Del Priore? Is it just Dr. Del Priore's
21 testimony?

22 A I think that's the main thing. I agree



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1 there are, you know, quite a few other exhibits that
2 actually talk about problems. And although I
3 haven't read in detail your Exhibit 2003, I think
4 that is also there. There are a couple of other
5 papers as well that point out many of the problems.

6 And I don't believe that -- well, I don't
7 know if any of these things are currently used, some
8 of these things that are veiled, such as fenretinide
9 and isotretinoin, anymore or not.

10 I agree they are problematic based on not
11 only Del Priore's comments but also my own reading
12 of the literature as well.

13 Q So your opinion here in paragraph 34 is
14 based on Dr. Del Priore's testimony and your review
15 of the A2E literature?

16 A Well, yes, I would say the A -- yeah, the
17 general literature here, yeah.

18 Q Okay.

19 A I'm not restricting it to A2E. There are
20 other pigments like ATR-dimer and some others
21 that -- ISO A2E, I-S-O A2E things.

22 I'm not actually convinced that all these



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1 pigments have even been characterized to this day.

2 Q Did you review the entirety of
3 Dr. Del Priore's transcript?

4 A I read it all. Some I skimmed; some I read
5 in more detail. It's pretty long.

6 Q Let's look at the transcript.

7 Do you have it there in your binder?

8 A Do I have it? I'm not sure I have the whole
9 one. 1069. Yeah, I think I do.

10 Yeah, it is long, isn't it?

11 Q In paragraph 34, you cite pages 203, line 15
12 to 204 of line 21 of Exhibit 1069, the transcript.

13 A Yeah.

14 What were those again? 203, page 203 of the
15 transcript?

16 Q Yeah, page 203.

17 And page 203, Dr. Del Priore is discussing a
18 reference from 2006.

19 A Yeah. I don't -- I'm not sure. I'm trying
20 to see exactly what that's referring to, which
21 specific reference.

22 Q I want to go back to page 197 of the



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1 transcript. I think there's the first mention of
2 Exhibit 2111.

3 A Okay.

4 Q Did you review Exhibit 2111?

5 A Well, I'm not sure. First let me check
6 my -- see if it's in my file here. It's not in the
7 file.

8 Can you tell me what it is? Since it's not
9 in my file, I don't specifically remember it.

10 Q I'm just asking, have you reviewed the
11 references cited in this transcript?

12 A I'm sure I've done some of them. I don't
13 know that I've done all of them. And I don't see an
14 index with the transcript. I can't answer that.

15 Q Do you know which ones you reviewed?

16 A I'd have to look at the list.

17 Q Let's just look at 2111.

18 A No, I don't have 2111.

19 MR. MILLS: Do you have another copy?

20 THE WITNESS: Do you have to stamp
21 this?

22 MR. CHRISTIE: No.



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1 THE WITNESS: I don't recall seeing
2 this particular paper.

3 BY MR. CHRISTIE:

4 Q You didn't consider this paper in forming
5 your opinions?

6 MR. MILLS: Objection to form,
7 mischaracterizes the witness's testimony.

8 THE WITNESS: I don't have a
9 recollection of this specific paper, no.

10 BY MR. CHRISTIE:

11 Q In paragraph 34, the testimony you're citing
12 at page 203 is quoting this paper, right? This is
13 203, lines 15 to page 204, line 21.

14 A I guess so.

15 Q But you haven't reviewed Exhibit 2111?

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

19 THE WITNESS: I don't really think I
20 have. I've read other papers about the status of
21 treatments that were tried, as I indicated, but I
22 don't remember this specific paper.



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1 BY MR. CHRISTIE:

2 Q Look at page 3 of Exhibit 2111.

3 Do you see the heading Targeting lipofuscin,
4 A2E Formation?

5 A Yes.

6 Q And then there's a sentence in -- the third
7 sentence starts, As such, recent efforts?

8 A Yes.

9 Q It says, As such, recent efforts have
10 centered on targeting A2E formation in RPE cells as
11 a therapeutic strategy for AMD and AMD-like retinal
12 disorders.

13 Do you see that?

14 A Yes.

15 Q And then if you go to page 4 of
16 Exhibit 2111, they're discussing Accutane and HPR?

17 A Yeah, right. It is -- HPR is fenretinide.

18 Q So when this paper says it's -- is
19 discussing targeting lipofuscin for an A2E
20 formation, it's discussing the same visual cycle we
21 looked at in the Radu paper, right?

22 A I think that's a reasonable statement. The



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1 HPR, the fenretinide, it's actually not specifically
2 targeting the visual cycle, but it's inhibiting the
3 retinol supply to the eye. So it's -- yeah,
4 indirectly, that's correct.

5 Q And neither of those inhibitors target the
6 A2E pathway specifically?

7 A I would agree with that.

8 Q So page 3 of Exhibit 2111 when the authors
9 say, Recent efforts have centered on targeting A2E
10 formation, they're referring to reducing the
11 availability of ATR with HPR or Accutane?

12 MR. MILLS: Objection to form.

13 BY MR. CHRISTIE:

14 Q Right?

15 A Well, right -- well, in addition, it's also
16 talking about reducing dietary levels of Vitamin A,
17 which is another strategy that has been tried, not
18 terribly successfully.

19 Q Right.

20 I'm sorry, just to be clear, the -- reducing
21 dietary levels of Vitamin A that you mentioned a
22 moment ago, that doesn't target the A2E pathway



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1 specifically, right?

2 A I agree.

3 MR. CHRISTIE: Let's take another short
4 break here.

5 MR. MILLS: Off the record.

6 (Recess: 11:13 a.m. to 11:29 a.m.)

7 BY MR. CHRISTIE:

8 Q Welcome back, Dr. Guengerich.

9 A Thank you.

10 Q I think when we left we were discussing
11 paragraph 34 of your declaration, Exhibit 1080.

12 A All right, fine.

13 Q In paragraph 34, after that first sentence,
14 you cite Exhibit 1069, page 215 to 216.

15 Do you see where I'm looking? Do you see
16 that?

17 A Yes.

18 Q Can you go to page 215 of Exhibit 1069?

19 A I have it.

20 Q And on page 215, they're discussing --
21 Dr. Del Priore is discussing a Wolf paper from 2003?

22 A Right.



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1 Q Did you review that reference?

2 A I believe I did, yeah. I can't remember if
3 that's cited on my list or not, but I do remember a
4 Wolf paper. No, it's not on my list -- no, I take
5 that back. I apologize. It's my Exhibit 1034.
6 Right.

7 Q And this is not on the exhibit list in your
8 Exhibit 1080?

9 A Oh, it is. It's -- yeah, it's on my list.
10 It's 1034, yeah, which I think is the second page of
11 my list.

12 Q When you say your list, do you mean the
13 appendix of exhibits in Exhibit 1080 on page 54?

14 A No. I'm sorry, I have another -- I have an
15 index to these, the documents that I brought.

16 Q And that's not the same list of exhibits you
17 provided in Exhibit 1080 on page 54?

18 A That's correct. This is more extensive.

19 Q Was that list submitted in this case, filed?

20 A I don't think it was. I mean, the
21 exhibits -- as I understand it, you should have all
22 of the exhibits that I have access to. I think the



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1 point was -- I don't think all of them were actually
2 mentioned in my declaration. I think only the ones
3 cited in the declaration are actually in that
4 appendix list.

5 MR. MILLS: Counsel, I'll provide a
6 clarification.

7 Paragraph 56 of Dr. Guengerich's reply
8 declaration cites Exhibit 1034. I mentioned earlier
9 the intention of the binders is to provide all of
10 the documents, exhibits that are cited in the
11 declaration, Exhibit 1080.

12 BY MR. CHRISTIE:

13 Q Doctor, what is this list of appendix --
14 appendix list of exhibits on page 54 of your
15 Exhibit 1080?

16 A It's a list of exhibits, at least the main
17 ones that I relied on.

18 Q But it's not all the exhibits cited in this
19 declaration?

20 A I don't think it caught all of -- I don't
21 think all of them are cited -- I'm sorry, I don't
22 think all of them are listed that have been cited.



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1 I apologize.

2 Q So this appendix list of exhibits is just a
3 list of some things that are cited in Exhibit 1080?

4 A That's my understanding. As I said, the
5 exhibits are the exhibits, so I'm not really hiding
6 them. It's just that they aren't listed here
7 because they weren't apparently some of the main
8 ones I used.

9 Q The reference we were just looking at,
10 Exhibit 2011 [sic], that isn't on your exhibit list?

11 MR. MILLS: Objection to form.

12 THE WITNESS: 2011 was which one? Is
13 that the Howes?

14 BY MR. CHRISTIE:

15 Q Yeah.

16 A 2111, is that what you meant?

17 Q Yeah.

18 A No, I don't think so. As I said, I don't
19 remember seeing this either.

20 Q In paragraph 34 -- this is on page 21 now --
21 you cite page 49, 19 to 59?

22 A That is in the Del Priore?



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1 Q Yes. Sorry, this is Exhibit 1069.

2 A I'm sorry, which was that again? Which
3 page?

4 Q This is page 49.

5 A Okay. All right. I have it.

6 Q And on page 49, it's discussing
7 Exhibit 2120?

8 A I'm sorry, I don't see that.

9 Q Page 49.

10 A Oh, never mind. My fault. I apologize. I
11 got into the Prestwich deposition instead of
12 Del Priore. It was page 49, okay. Thank you.

13 Q On page 49 of Exhibit 1069, the transcript
14 is discussing Exhibit 2120?

15 MR. MILLS: Objection.

16 BY MR. CHRISTIE:

17 Q Do you see that?

18 A Yes.

19 Q Have you reviewed Exhibit 2120?

20 MR. MILLS: I want to make a note for
21 the record here, the portion of the transcript that
22 he cited that you asked him about first is different



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1 from the portion you're asking about now. I want to
2 kind of put you on notice -- I just want to be
3 careful about the scope and make sure we're asking
4 him about the portions that he's cited.

5 THE WITNESS: I don't know what 2120
6 is. I don't seem to have it here. I don't think
7 it's listed in my materials either. I don't know
8 what it is.

9 BY MR. CHRISTIE:

10 Q So it's fair to say you haven't reviewed
11 Exhibit 2120?

12 MR. MILLS: Objection to form,
13 mischaracterizes testimony.

14 THE WITNESS: Yeah, I don't know. I
15 don't know what 2120 is. If you could tell me the
16 name of the author or show me the paper, I might be
17 able to answer.

18 Just looking at the previous page,
19 apparently it's a paper by Baehr, but I don't
20 remember Baehr offhand.

21 BY MR. CHRISTIE:

22 Q So you think that Exhibit 2120 is a paper by



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1 Baehr, but you don't remember a Baehr paper?

2 A Not offhand. I might recognize -- I might
3 or might not recognize it if I see it. I'm not
4 sure. The name doesn't really ring a bell.

5 Q Paragraph 33 of your declaration, you're
6 citing Dr. Del Priore, Exhibit 1069, at page 135?

7 A Oh, yeah.

8 Q If you go back to page 130 of Exhibit 1069,
9 do you see that it's discussing Exhibit 1041?

10 A Yes, I see that.

11 Q Did you review Exhibit 1041?

12 MR. MILLS: I'm going to object.
13 Again, I don't think -- I'm not sure that the
14 reference that you're pointing to is the one that's
15 cited in the portions of the transcript that you
16 cited.

17 THE WITNESS: I don't have that one.
18 The first author is Jacobson. I don't remember that
19 specifically. Perhaps I saw it. Perhaps I didn't.
20 I don't recall a Jacobson, though.

21 BY MR. CHRISTIE:

22 Q Can you just look at paragraph 76 of your



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1 declaration.

2 At the top of page 50, you're citing
3 Dr. Del Priore transcript Exhibit 1069, page 131,
4 line 10, to page 132, line 6?

5 A Okay.

6 Q You should still be on page 131 of
7 Exhibit 1069.

8 A I have it.

9 Q And on page 131 of Exhibit 1069, they're
10 discussing Jacobson, a reference by Jacobson?

11 A Yes, that's the one I think I indicated I --
12 that's 1041. I don't have it here. I can try to
13 answer any questions you have.

14 Q So you're citing -- in paragraph 76, you're
15 citing the transcript of Dr. Del Priore discussing
16 the Jacobson reference, but it's not in your
17 materials; is that right?

18 A Apparently not; although, I don't recall
19 Jacobson. You know, I did read some papers about
20 the use of added Vitamin A, of course, as a therapy
21 method, but I don't think I read all of these.

22 Q Do you recall which papers you read



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1 regarding the use of added Vitamin A as a course of
2 therapy method?

3 A Well, the AREDS paper, I can't remember who
4 the first author was; and also I think I definitely
5 looked at the Ortho Pharma patent material.

6 Q And on page 54 of your declaration,
7 Exhibit 1080, lists an Exhibit 1022?

8 A Right. This is the AREDS study I mentioned.

9 Q And on page 54, you list an Exhibit 1008?

10 A Right.

11 Q Is that the Ortho you're referring to?

12 A Yes.

13 Q Aside from those listed in this appendix,
14 would you consider any other references --

15 A I think --

16 Q -- of the use of Vitamin A?

17 A Yeah, there was the Centrum label. I don't
18 know exactly what you'd call that. It's not a
19 paper, but it lists the Vitamin A and beta carotene
20 content in Centrum vitamin supplements.

21 Q And that's Exhibit 1065 listed on page 55 of
22 your appendix -- page 55 of Exhibit 1080?



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1 A That's correct, yes.

2 Q So sitting here today, you don't think
3 you've reviewed Exhibit 1041 that's cited in
4 Dr. Del Priore's transcript?

5 MR. MILLS: Object to form,
6 mischaracterizes the witness's testimony.

7 THE WITNESS: This is a Jacobson
8 reference. I don't recall that.

9 BY MR. CHRISTIE:

10 Q Looking at paragraph 76 of your
11 Exhibit 1080, you cite Dr. Del Priore's transcript
12 at page 159?

13 MR. MILLS: Objection to form.

14 THE WITNESS: I have it.

15 BY MR. CHRISTIE:

16 Q On page 159 of Exhibit 1069, they're
17 discussing Exhibit 1042 on page 158.

18 Do you see that?

19 A Yeah, I see 1042. I don't think I have that
20 either. Let me check. No, I don't believe I know
21 what that is offhand.

22 This is a Penniston 2006. I don't recall



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1 that. Apparently it was the results of a clinical
2 trial.

3 Q You don't have it in your binder there?

4 A No. At least certainly not in order. No.

5 Q This is 1042.

6 MR. CHRISTIE: I'm sorry, to be clear
7 for the record, I've just handed Dr. Guengerich
8 Exhibit 1042.

9 MR. MILLS: I just want to make sure I
10 have the right document. So this is Alberts, not
11 Pennington [sic].

12 THE WITNESS: Wait a minute. No, 2150
13 is apparently -- I apologize for interrupting.
14 Apparently Penniston must be 2150, but...

15 BY MR. CHRISTIE:

16 Q Let me just clear this up.

17 Paragraph 76 of your declaration, you're
18 citing Dr. Del Priore's transcript at page 159?

19 MR. MILLS: Objection.

20 THE WITNESS: Yeah.

21 BY MR. CHRISTIE:

22 Q Do you see that?



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1 A Yes.

2 Q And on page 159 of Dr. Del Priore's
3 transcript, they're discussing Exhibit 1042?

4 MR. MILLS: Objection to form.

5 THE WITNESS: Actually, that says that
6 on 158.

7 BY MR. CHRISTIE:

8 Q Right.

9 A So that's 1042. I apologize, I flipped back
10 and I saw something about Penniston.

11 Is Alberts 1042?

12 Q Yeah.

13 A I do not recall having seen this paper
14 before.

15 Q And you didn't review Exhibit 1042 in
16 forming your opinions in this case?

17 MR. MILLS: Objection to form.

18 THE WITNESS: No, only indirectly in
19 terms of what I got out of Del Priore's material.

20 BY MR. CHRISTIE:

21 Q The next citation you have there in
22 paragraph 76 is page 164 of Dr. Del Priore's



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1 transcript?

2 MR. MILLS: Objection, form.

3 BY MR. CHRISTIE:

4 Q Do you see that, Doctor?

5 A Yes.

6 Q And on page 164 of Dr. Del Priore's
7 transcript, it's discussing Exhibit 2154?

8 A Yes.

9 Q Did you review Exhibit 2154?

10 A If I did, it's not in my exhibit binders. I
11 don't know the name either.

12 Q Just to be clear, Exhibit 2154 appears
13 within the citation, Exhibit 1069, 164, 15 to 167,
14 14, you're using in paragraph 76 of your
15 declaration.

16 A Correct. I am citing Dr. Del Priore's
17 testimony.

18 Q And on page 164 of Dr. Del Priore's
19 declaration, it says, towards the bottom, they are
20 quoting from Exhibit 2154?

21 A Yes.

22 On line 24?



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1 Q Yes.

2 A Yeah.

3 Q And then you use that same quote in
4 paragraph 76, tour de force?

5 A I do. It said the Berson study, yes.
6 Again, quoting Del Priore.

7 Q Right.

8 Del Priore is just reading Exhibit 2154 on
9 page 164 of his transcript, right?

10 A Right. He's -- well, I don't know if he's
11 reading it -- right, he is reading it.

12 Q I'm sorry --

13 A Well, he is responding to apparently
14 Mr. Mills reading it and asking questions about it.

15 Q So that quote is Mr. Mills reading
16 Exhibit 2154?

17 A That seems to be the case, yes.

18 Q On page 165 of Dr. Del Priore's
19 transcript -- do you have that?

20 A Yes.

21 Q It's citing Exhibit 2153?

22 A Yes.



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1 Q Did you review Exhibit 2153 in forming your
2 opinions in this case?

3 A I don't recall that I did. If I flip over
4 to the next page, it's a paper written by Marmor,
5 and I don't recall reading the Marmor paper.
6 Perhaps I did, but I don't remember it.

7 Q And Exhibit 2153 isn't listed in your
8 appendix exhibits?

9 A No, it isn't.

10 Q And it's not in your binder of materials you
11 have with you today?

12 A No.

13 Q And the same is true of Exhibit 2154?

14 A That's correct.

15 Q Sitting here today, you can't say that you
16 reviewed either Exhibit 2153 or Exhibit 2154?

17 A I can't say conclusively one way or the
18 other.

19 Q Now, on page 165 of Dr. Del Priore's
20 transcript, towards the bottom is a question from
21 Mr. Mills that says: This study was meticulously
22 designed and extraordinarily well performed and



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1 represents an important scientific contribution.

2 A Yes, I see that.

3 Q And in paragraph 76 of your declaration, is
4 that what that portion of the transcript that we
5 just looked at, meticulously designed, is that what
6 you're quoting there?

7 A Apparently so, yes -- well, no -- I don't
8 know if that -- it seems to be referring to
9 Berson -- oh, but I think Marmor was actually just a
10 commentary on the Berson paper, from what I can
11 surmise of this.

12 Q My question is just, is what's written in
13 your declaration here quoted, meticulously designed
14 and extraordinarily well performed, quoting
15 Mr. Mills' question on page 165 of Exhibit 1069?

16 A Well, it is his question, but he's actually
17 reading from 2153.

18 Q Right.

19 So what you're quoting in paragraph 76 is
20 Mr. Mills reading Exhibit 2153; is that right?

21 A Yes, that's my understanding of the
22 discourse here.



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1 Q And you never reviewed Exhibit 2153?

2 A I don't remember that I have or have not.

3 MR. CHRISTIE: Do you guys want to get
4 lunch?

5 MR. MILLS: Let's go off the record.

6 (Recess: 12:08 p.m. to 12:49 p.m.)

7 BY MR. CHRISTIE:

8 Q Welcome back, Dr. Guengerich.

9 A Welcome back to you.

10 Q When we left, we were looking at
11 paragraph 76 of your declaration.

12 A Okay.

13 Q In that parenthetical on page 50, it's
14 discussing a Bernson [sic] study.

15 Do you see that? Berson?

16 A Hang on.

17 Q On page 50.

18 A Yeah, I'm looking at this. Oh, yeah, right
19 at the top, yeah, Berson study.

20 Q What is the Berson study?

21 A I believe this is the one that we were
22 talking about. I believe it's Exhibit 21 -- I'm



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1 looking here. Correct me if I'm wrong, but I think
2 this was 2153. It had the number 2153.

3 Q You think that the Berson study was
4 Exhibit 2153?

5 A Yeah. I believe this was a clinical trial
6 or at least some kind of clinical study in terms of
7 how much -- 2154 -- no, it wasn't that. I believe
8 it was a study in terms of giving fortified
9 retinoids.

10 Q You believe the Berson study was a study of
11 administering fortified retinoids?

12 A I think so -- I'm sorry, I think it was a
13 supplementation. I should say supplementation, not
14 fortification.

15 Q Did you review the Berson study in forming
16 your opinions in this case?

17 A I don't remember specifically if I did or
18 not.

19 Q And there's no Berson study listed on
20 page 54 and 55 of your appendix of exhibits?

21 A No. That's correct. There is not.

22 Q Do you remember anything else about the



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1 Berson study aside from the fact there was a
2 clinical trial of fortified retinoids?

3 MR. MILLS: Objection to form and
4 mischaracterizes the witness's testimony.

5 THE WITNESS: Yeah, my recollection is
6 it was a higher dose Vitamin A study. But I
7 can't -- without actually seeing this again, I can't
8 comment on it further on the details.

9 BY MR. CHRISTIE:

10 Q You didn't review the Berson study in
11 forming the opinions in this case, right?

12 A I don't specifically remember if I reviewed
13 Berson or not.

14 Q Do you know what year the Berson study was
15 conducted?

16 A No, not offhand.

17 Q Can we go back to paragraph 34 of your
18 declaration?

19 A I have it.

20 Q In paragraph 34, you cite page 214 of
21 Dr. Del Priore's transcript?

22 MR. MILLS: Objection, form.



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1 THE WITNESS: That's correct.

2 BY MR. CHRISTIE:

3 Q Can you look at page 214 of Dr. Del Priore's

4 transcript.

5 Do you have it?

6 A I have it.

7 Q Do you see on page 214 of the transcript,

8 it's discussing his declaration in paragraph 184?

9 MR. MILLS: Objection, form.

10 THE WITNESS: Sorry, what was the

11 paragraph? 184 or 284?

12 BY MR. CHRISTIE:

13 Q 284.

14 A Yes.

15 Q Did you review paragraph 284 of

16 Dr. Del Priore's declaration in this case?

17 A Not in depth. I do remember skimming his

18 declaration. I don't specifically remember

19 paragraph 284.

20 Q Dr. Del Priore's declaration isn't cited in

21 your listed appendix?

22 A It is not.



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1 Q Do you have Dr. Del Priore's declaration in
2 your binder there?

3 A No, I don't. Only the transcript.

4 Q So when you're citing Dr. Del Priore's
5 transcript, you're not responding to his
6 declaration, right?

7 A No, I'm not really. I'm using information
8 from his transcript, but I'm not really addressing
9 this. This was more dealing with the clinical
10 issues, which I wasn't focused on.

11 Q So is it fair to say that your declaration
12 is responding to Dr. Prestwich but not to
13 Dr. Del Priore?

14 MR. MILLS: Objection to form.

15 THE WITNESS: I think in the main I'm
16 responding to Dr. Prestwich, but I'm not -- this is
17 not exclusive because some of what Del Priore has is
18 actually relevant.

19 But on the main, I would agree that
20 it's primarily Prestwich.

21 BY MR. CHRISTIE:

22 Q You didn't review Dr. Del Priore's



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1 declaration?

2 A I have obtained it. I read it. As I said,
3 I skimmed most of it, but I don't remember a lot of
4 the details. I didn't rely heavily on it.

5 Q Why isn't it in the listed appendix or your
6 binder?

7 MR. MILLS: Objection, form.

8 THE WITNESS: Well, it was one of -- I
9 didn't put everything in the binder or the appendix
10 that I actually read on this case.

11 BY MR. CHRISTIE:

12 Q How did you select what went in the binder?

13 A Decided which were the most important things
14 or the things the -- I should say the things most
15 relevant to my declaration.

16 Q And Dr. Del Priore's declaration was not
17 relevant to your declaration?

18 MR. MILLS: Objection, form.

19 BY MR. CHRISTIE:

20 Q Is that fair?

21 A Basically, what it was in the transcript of
22 his deposition was probably more to be the point, I



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1 think, or I should say it covered the main points
2 that I was interested in.

3 Q Can you identify anything in Exhibit 1080
4 where you're responding to Dr. Del Priore?

5 A In looking at my declaration again, I don't
6 think I'm taking any -- I don't recall seeing any
7 issues I had with Dr. Del Priore's material.
8 Certainly the transcript and/or to my recollection
9 his declaration of most of -- this is actually
10 agreeing with the point he's raised.

11 Q So you can't identify anything in
12 Exhibit 1080 where you're disagreeing or responding
13 to Dr. Del Priore?

14 A I don't think there's any disagreement. As
15 I said, I -- you know, I haven't dealt with
16 everything that he's done. I think the points that
17 I have -- where I have mentioned Del Priore, I think
18 I've always agreed with these points. That doesn't
19 specifically mean that I necessarily agree with
20 everything, but it wasn't enough to -- that I
21 thought I should mention.

22 Q Let's shift gears a little bit.



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1 Earlier you were talking about -- or you had
2 mentioned Dr. Prestwich's testimony about acid-base
3 catalysis.

4 A This morning? I don't specifically remember
5 that, but please go on.

6 Q Do you recall that Dr. Prestwich discussed
7 acid-base catalysis?

8 A Yes. I don't remember discussing it at this
9 point.

10 Q I may have imagined it.

11 Can you tell me just what a base is?

12 MR. MILLS: Objection to form, scope.

13 THE WITNESS: A base is a chemical
14 entity that wants to pick up a proton.

15 BY MR. CHRISTIE:

16 Q And by pick up --

17 A Well, that's -- let me rephrase that.

18 Either that or something that easily loses a
19 proton. That's probably a better way of looking at
20 it.

21 Q And a proton is a hydrogen?

22 A Yeah, it's a -- hydrogen with a plus charge



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1 on it. So bases -- this gets a little

2 complicated -- well, not really complicated. Some

3 things might not be so obvious.

4 That is, a base can have a negative charge
5 on it and then tend to pick up a proton. But we can
6 also talk about a base as something that's going to
7 easily lose a proton.

8 Q In our context here where we're talking
9 about base catalysis, does that mean that the base
10 is taking a hydrogen --

11 A Yes.

12 Q -- off --

13 MR. MILLS: You've got to let him
14 finish his question.

15 THE WITNESS: Sorry. Go ahead. I
16 apologize.

17 MR. MILLS: Did you finish your
18 question?

19 MR. CHRISTIE: Yeah.

20 MR. MILLS: I object to the question on
21 the basis of form; I object to the question on the
22 basis of scope.



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1 You can answer.

2 THE WITNESS: You're probably -- may be
3 referring to -- I think it's Figure 12 in the
4 Prestwich declaration where he postulates that there
5 is a base on a protein perhaps that is actually
6 picking off a proton from the C20 methyl group of
7 retinal.

8 So in that case, the base would have a
9 negative charge, and it would be taking a proton to
10 itself and then leave -- and that would be acting as
11 a base, yes.

12 BY MR. CHRISTIE:

13 Q So a base can be a protein?

14 A Protein --

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

17 THE WITNESS: Proteins have basic
18 groups on. That's probably the way we usually talk
19 about it.

20 BY MR. CHRISTIE:

21 Q What do you mean basic groups?

22 A Well, you could have -- probably the best



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1 example is a lysine, L-Y-S-I-N-E. Lysine has an NH2
2 group hanging off of its amino acid. And that NH2
3 can abstract a hydrogen, a proton from something
4 else.

5 Q And the lysine is an amino acid?

6 A That is correct.

7 Q So the lysine is part of the protein?

8 A That is correct.

9 Q Are there any other amino acids that can act
10 as bases?

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

13 THE WITNESS: Yes, there are.
14 Arginine; in some cases, cysteine.

15 BY MR. CHRISTIE:

16 Q Are there any other proteins in the body
17 that can act as a strong base -- excuse me, as a
18 base?

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

21 THE WITNESS: Well, I can answer your
22 question. I think almost all proteins that have a



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1 basic group on could, yes, in principle.

2 BY MR. CHRISTIE:

3 Q Lysine, the base group is NH₂?

4 A That's correct.

5 Q Is that an amide?

6 A Amine, A-M-I-N-E.

7 Q Lysine has an amine?

8 A Yes.

9 Q What's a strong base?

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

12 THE WITNESS: Well, a strong base is
13 sodium hydroxide. Another one, which it's actually
14 mentioned here, or at least somewhere, is sodium
15 hydride.

16 BY MR. CHRISTIE:

17 Q I'm sorry, I should have been more precise
18 there.

19 What's the definition -- what makes a strong
20 base strong?

21 MR. MILLS: Objection.

22



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1 BY MR. CHRISTIE:

2 Q What's the definition of a strong base?

3 MR. MILLS: Objection to form, scope.

4 THE WITNESS: Well, it's the tendency
5 to abstract protons.

6 BY MR. CHRISTIE:

7 Q How is a strong base differentiated from a
8 weak base?

9 MR. MILLS: Objection to form, outside
10 the scope.

11 Counsel, if you don't have any more
12 questions about Dr. Guengerich's declaration, then
13 perhaps we can end the deposition.

14 THE WITNESS: It has -- I can answer
15 your question. Its basic chemistry is something
16 called a pKa value.

17 BY MR. CHRISTIE:

18 Q And what's a pKa value?

19 MR. MILLS: Objection to scope.
20 Dr. Guengerich is here to be cross-examined on his
21 reply declaration. The question is not about his
22 reply declaration.



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1 Counsel, you know I have a flight to
2 catch. It seems at this point you're just wasting
3 time.

4 I ask you to ask questions about
5 Dr. Guengerich's declaration. If you don't have any
6 more, then we can end the deposition.

7 BY MR. CHRISTIE:

8 Q What's a pKa?

9 MR. MILLS: Same objections.

10 THE WITNESS: A pKa is the negative
11 logarithm to the base ten of the association
12 constant, the association constant for the base with
13 a proton.

14 BY MR. CHRISTIE:

15 Q And so a lower pKa is a weaker base or a
16 stronger base?

17 MR. MILLS: Object to the question as
18 outside the scope of cross-examination of
19 Dr. Guengerich's reply declaration.

20 THE WITNESS: A lower pKa is a weaker
21 base.

22



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1 BY MR. CHRISTIE:

2 Q A lower pKa is a weaker base; higher pKa,
3 strong base?

4 A Strong base.

5 Q And do you know what the pKa of lysine is?

6 MR. MILLS: Object to the question as
7 not cross-examining Dr. Guengerich on his reply
8 declaration.

9 THE WITNESS: It's typically 9 to 10.

10 BY MR. CHRISTIE:

11 Q And do you know what the pKa of arginine is?

12 MR. MILLS: Objection to the question
13 as outside the scope to Dr. Guengerich's reply
14 declaration.

15 THE WITNESS: I can answer. It's 12
16 approximately.

17 BY MR. CHRISTIE:

18 Q Arginine is a stronger base?

19 A It is.

20 Q And sodium hydroxide, what's the pKa
21 roughly?

22 MR. MILLS: Object to the question as



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1 outside the scope.

2 THE WITNESS: We don't normally talk
3 about a pKa for sodium hydroxide. It's a stronger
4 base, but that actually involves different things.
5 That is different because basically it's dissociated
6 so it's actually hydroxyl ions in solution. It's a
7 very strong base.

8 BY MR. CHRISTIE:

9 Q And that's because it completely
10 disassociates?

11 MR. MILLS: Objection, scope.

12 THE WITNESS: Yes, because it
13 completely dissociates from the sodium ion.

14 BY MR. CHRISTIE:

15 Q Is n-Butylamine a base?

16 MR. MILLS: Objection, outside the
17 scope, incomplete hypothetical, relevance.

18 THE WITNESS: N-Butylamine? Yes, it's
19 a base.

20 BY MR. CHRISTIE:

21 Q And does that have the NH₂ group as well?

22 MR. MILLS: Objection, outside the



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1 scope.

2 THE WITNESS: Yes, I think so. I have
3 to think about the structure again, but, yeah, I
4 think so. It's a strong base.

5 BY MR. CHRISTIE:

6 Q N-Butylamine is a strong base?

7 A Wait a minute --

8 MR. MILLS: Objection, outside the
9 scope.

10 THE WITNESS: I thought you said
11 something else.

12 N-Butylamine would be -- well, it's a
13 base. I don't know exactly what its pKa is.

14 MR. CHRISTIE: Can we have a sticker
15 there, 2208.

16 (Marked Exhibit 2208.)

17 MR. MILLS: I object to the document
18 that has been marked as Exhibit 2208 as outside the
19 scope of Dr. Guengerich's declaration. At this
20 point, I object to it on the basis of authenticity,
21 lack of foundation, the lack of a sponsoring
22 witness, and object on the base of relevance.



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1 I object to it on the basis of
2 untimeliness of patent owner's intent to rely on the
3 exhibit. It should have been submitted with the
4 patent owner response.

5 And I reserve additional objections. I
6 also object to the exhibit on the basis of hearsay.

7 BY MR. CHRISTIE:

8 Q Dr. Guengerich, this Exhibit 2208 that I
9 just handed you, this is a paper by Hall from 1957.
10 Do you see that?

11 MR. MILLS: Objection, lacks
12 foundation, assumes facts not in evidence, outside
13 the scope, calls for speculation.

14 BY MR. CHRISTIE:

15 Q I see on page 1 of this paper, it's a paper
16 by Hall from 1957?

17 MR. MILLS: Objection, lack of
18 foundation, assumes facts not in evidence, outside
19 the scope, calls for speculation.

20 BY MR. CHRISTIE:

21 Q Do you see that?

22 MR. MILLS: Same objections.



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1 THE WITNESS: Do I see what?

2 BY MR. CHRISTIE:

3 Q That on the first page, this is a paper by
4 Hall from 1957.

5 MR. MILLS: Objection, lacks
6 foundation, assumes facts not in evidence, outside
7 the scope, calls for speculation.

8 THE WITNESS: It is a paper by Hall.
9 I'm actually not sure what journal it's in. I'd
10 have to guess on that.

11 MR. MILLS: I'm going to caution the
12 witness not to speculate and not to offer testimony
13 that exceeds his personal knowledge or his expertise
14 as applied to the knowledge and facts in front of
15 him reliably applied.

16 BY MR. CHRISTIE:

17 Q Can you look at page 5443?

18 A I'm looking at it.

19 Q You have it? Okay.

20 On the left-hand side there, there's
21 Table 1?

22 A Yes.



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1 Q Is this table showing the pKa values we were
2 discussing a moment ago?

3 MR. MILLS: Objection to form, outside
4 the scope, lacks foundation, calls for speculation,
5 assumes facts not in evidence.

6 THE WITNESS: There are pKa values. I
7 can't really comment on this paper. I would have to
8 consider this at considerably greater length in
9 terms of the issues involved here with sigma values,
10 et cetera. I'm not prepared to discuss this.

11 BY MR. CHRISTIE:

12 Q In Table 1, it lists a value of 10.43 for
13 n-Butyl?

14 MR. MILLS: Objection, assumes facts
15 not in evidence, outside the scope, lacks
16 foundation.

17 THE WITNESS: Yeah, I'm seeing a pKa
18 value there for n-Butyl.

19 BY MR. CHRISTIE:

20 Q Does that seem approximately correct?

21 MR. MILLS: Objection to form,
22 incomplete hypothetical, outside the scope, lacks



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1 foundation, assumes facts not in evidence.

2 THE WITNESS: I can't actually comment
3 on that. This paper would require considerably more
4 analysis.

5 The pKas also can depend on solvents
6 and other things -- the pKa values can be influenced
7 by the solvents, the temperature in some cases,
8 particularly with amines.

9 BY MR. CHRISTIE:

10 Q In neutral solution, does that seem
11 approximately a pKa of n-Butyl?

12 MR. MILLS: Objection to form,
13 incomplete hypothetical, outside the scope, assumes
14 facts not in evidence, lacks foundation.

15 THE WITNESS: I said before that the
16 amine and lysine has a pKa of about 9 or 10
17 depending on the conditions. This is roughly
18 similar. That's about as much as I can really
19 answer.

20 MR. CHRISTIE: Let's set that aside.

21 BY MR. CHRISTIE:

22 Q Dr. Guengerich, can you turn to



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1 Exhibit 2052? It's the Prestwich declaration.

2 A All right. I have that.

3 Q Let's turn to paragraph 3.

4 A Paragraph 3?

5 Q About halfway down, it says, During these
6 studies, my research team and I synthesized and
7 evaluated many deuterium- and tritium-labeled lipids
8 and also deuterium-labeled hyaluronic acid.

9 Do you see that?

10 A Yes.

11 Q Would evaluating deuterium- and
12 tritium-labeled lipids and deuterium-labeled
13 hyaluronic acid involve knowledge of the KIE,
14 kinetic isotope effect?

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

17 THE WITNESS: My answer is not
18 necessarily.

19 BY MR. CHRISTIE:

20 Q Can you turn to paragraph 13? About
21 three-fourths of the way down the paragraph,
22 Dr. Prestwich mentions that he's the cofounder and



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1 manager of Deuteria Agrochemicals and the cofounder
2 and manager of Deuteria Biomaterials?

3 A Yes.

4 Q Is it fair to say that those companies
5 involve deuterium modification of some kind?

6 MR. MILLS: Objection to form,
7 foundation, incomplete hypothetical, calls for
8 speculation.

9 THE WITNESS: I do know I did find
10 Deuteria -- or at least one of these,
11 Deuteria biomaterials or -- I don't know if it was
12 that or Agrochemicals, they actually either were
13 developing or they are selling deuterated hyaluronic
14 acid and also deuterated ethanol for human
15 consumption. That's all I know about those
16 companies.

17 BY MR. CHRISTIE:

18 Q Would the cofounder of those companies have
19 practical experience with the kinetic isotope
20 effect?

21 MR. MILLS: Objection to form,
22 foundation, calls for speculation.



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1 THE WITNESS: Maybe, I don't know.

2 BY MR. CHRISTIE:

3 Q What's the purpose of selling -- excuse me.

4 What's the purpose of deuterating hyaluronic
5 acid?

6 MR. MILLS: Objection to form,
7 foundation, calls for speculation, outside the
8 scope.

9 THE WITNESS: I could only speculate,
10 which I shouldn't really do. It may be to slow the
11 metabolism of hyaluronic acid. I'm not aware that
12 there's actually any literature available in the --
13 I should say open literature on their materials, so
14 I can't really say anything about what their
15 strategy is exactly or how effective it is.

16 MR. MILLS: I'll caution the witness
17 not to speculate.

18 BY MR. CHRISTIE:

19 Q What, in your opinion, constitutes practical
20 knowledge of kinetic isotope effect?

21 A Practical knowledge of kinetic isotope
22 effect?



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1 That would involve mechanistic studies on
2 the application of isotope effect to scientific
3 questions, which is something I've been doing since
4 the 1980s.

5 Q So mechanistic studies, that's understanding
6 the mechanistic details of biochemical reactions?

7 MR. MILLS: Objection, form.

8 THE WITNESS: Or chemical reactions. I
9 should say not only mechanisms but rates of
10 reactions.

11 BY MR. CHRISTIE:

12 Q Mechanistic details of biochemical reactions
13 would qualify as practical experience with kinetic
14 isotope effect?

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

17 THE WITNESS: It depends on the study,
18 whether isotope effects were involved in the study
19 of the mechanism or not. You can study a mechanism
20 without looking at isotope effects.

21 BY MR. CHRISTIE:

22 Q How do you study a mechanism with deuterium



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1 without having knowledge of the kinetic isotope
2 effect?

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

5 THE WITNESS: There are possible --
6 there is one possible -- one way to do that is to
7 actually look where the isotope winds up in the
8 product. You don't have to know the rates in that
9 case. There are other ways too.

10 BY MR. CHRISTIE:

11 Q So practical knowledge of the kinetic
12 isotope effect requires carrying out mechanistic
13 studies that actually involve deuterium changing the
14 rate?

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

18 THE WITNESS: I think -- as I
19 understand your answer, I think that's correct, or
20 at least it's one way, yes.

21 BY MR. CHRISTIE:

22 Q Turn to Exhibit 2053.



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1 And this is Dr. Prestwich's CV?

2 A Okay.

3 Q Can you turn to page 63, I think -- one
4 moment, sorry -- 64.

5 And on page 64 of Exhibit 2053, there's
6 several patents or patent applications directed
7 towards deuterium-enriched hyaluronan?

8 MR. MILLS: Objection to form, scope,
9 and objection to foundation and to the extent the
10 question calls for speculation.

11 BY MR. CHRISTIE:

12 Q I'm sorry, do you see that?

13 A Yeah, I see several -- five or six patents
14 that are all entitled Deuterium-Enriched Hyaluronan.

15 Q Is that the same hyaluronan that you
16 mentioned earlier when we were discussing the
17 Deuteria companies?

18 MR. MILLS: Objection to form,
19 foundation, calls for speculation, outside the
20 scope.

21 THE WITNESS: Maybe, maybe not. I
22 don't know. I haven't read the patents. I haven't



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1 examined what they're doing in each company -- or
2 that particular company of his.

3 BY MR. CHRISTIE:

4 Q But you agree that his CV lists him as the
5 cofounder of Deuteria Agrochemicals and
6 Deuteria Biomaterials and that he has several
7 patents directed to deuterium-modified compounds?

8 MR. MILLS: Objection, form,
9 foundation, calls for speculation, mischaracterizes
10 the CV.

11 THE WITNESS: I can't -- yeah, I agree
12 that these are -- things are listed as you
13 mentioned. I don't know anything else about them.

14 BY MR. CHRISTIE:

15 Q So you can't tell, based on his CV and his
16 statements in his declarations, whether or not he
17 has practical experience with kinetic isotope
18 effect?

19 MR. MILLS: Objection.

20 THE WITNESS: When I examined his
21 publications in the peer-reviewed literature, I
22 didn't see any that provided me with any evidence of



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1 use of kinetic isotope effects at all.

2 BY MR. CHRISTIE:

3 Q And my question was just based on the CV and
4 statements we looked at in his declaration, you
5 can't tell one way or another whether he has
6 practical experience with the kinetic isotope
7 effect?

8 MR. MILLS: Objection, form, asked and
9 answered.

10 THE WITNESS: I don't know anything
11 about how they're using the deuterium in the
12 hyaluronan derivatives or exactly what they are.

13 BY MR. CHRISTIE:

14 Q So you can't tell one way or another whether
15 he has practical experience with respect to kinetic
16 isotope effect based on his statements in his CV and
17 his declaration?

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

20 THE WITNESS: I've already answered it.
21 All I see is something about a company and some
22 patents that I haven't looked at.



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1 BY MR. CHRISTIE:

2 Q Can we turn to paragraph 280 of
3 Dr. Prestwich's declaration?

4 A I have it.

5 Q Do you understand that Dr. Prestwich is
6 opining that the 1,5 shift is a base-catalyzed
7 tautomerization?

8 MR. MILLS: Objection to form,
9 foundation.

10 THE WITNESS: Could you repeat the
11 question, please?

12 BY MR. CHRISTIE:

13 Q Do you understand Dr. Prestwich's
14 declaration as opining that the 1,5 shift in NRPE is
15 via a general base-mediated tautomerization
16 mechanism?

17 MR. MILLS: Objection to form,
18 foundation.

19 THE WITNESS: I understand that's the
20 proposal.

21 BY MR. CHRISTIE:

22 Q Would you turn to paragraph 274 of



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1 Dr. Prestwich's declaration.

2 Dr. Prestwich isn't opining that the base
3 catalyzed tautomerization occurs via -- is enzyme
4 mediated?

5 A I'm sorry, you said that he is or isn't?

6 Q Let me try that again.

7 Dr. Prestwich isn't opining that the base
8 catalyzed mechanism is enzyme mediated, right?

9 MR. MILLS: Object --

10 BY MR. CHRISTIE:

11 Q He's not?

12 MR. MILLS: Objection to form,
13 foundation.

14 THE WITNESS: Well, he has something
15 there labeled as a protein, and it's got some
16 hypothetical base, which is actually participating
17 in catalysis, so I would call that an enzyme. So I
18 would disagree with you. I think he is proposing
19 that there's an enzyme doing this.

20 BY MR. CHRISTIE:

21 Q Does a base catalyzed tautomerization imply
22 enzyme mediated?



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1 MR. MILLS: Objection.

2 BY MR. CHRISTIE:

3 Q Is it necessarily enzyme mediated?

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

6 THE WITNESS: You can do things with,
7 for instance, small molecules. For instance, you
8 can use things like acetate or imidazole to do
9 acid-base catalysis. There have been a number of
10 model studies in this regard. I'm pretty familiar
11 with those.

12 BY MR. CHRISTIE:

13 Q And earlier we were talking about amino
14 acid, lysine, arginine?

15 A Yes.

16 Q Those can mediate general base catalyzed
17 tautomerizations?

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

20 THE WITNESS: They can when they're at
21 their appropriate positions in enzymes. That's how
22 enzymes work.



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1 That doesn't mean that all proteins
2 that have lysine on them will just start doing all
3 kind of catalysis on their own. Enzymes are highly
4 specific.

5 BY MR. CHRISTIE:

6 Q But a lysine residue can act as a base
7 without being enzyme mediated, right?

8 MR. MILLS: Objection to form,
9 incomplete hypothetical, calls for speculation,
10 outside the scope.

11 THE WITNESS: You can make model
12 systems. I don't know if any specifically used
13 lysine, but you can do that. It's very inefficient.

14 For that matter, I suppose any of the
15 amino acids could theoretically do that. As I said,
16 it would be extremely inefficient.

17 BY MR. CHRISTIE:

18 Q Looking at paragraph 280 again, Prestwich is
19 discussing a paper by Verdegem?

20 A Close enough.

21 Q So is that a yes?

22 A I think that's Belgian. Verdegem, Verdegem,



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1 I don't know.

2 Q So in paragraph 280, Dr. Prestwich is
3 discussing a paper by Verdegem, Verdegem.

4 Is the Verdegem paper an enzyme -- describe
5 an enzyme-mediated reaction?

6 MR. MILLS: Objection to form,
7 foundation.

8 THE WITNESS: If I could go to that, I
9 think I have that, 2078.

10 Oh, it's a Dutch paper, not Belgian.

11 No, it's not an enzyme reaction.

12 BY MR. CHRISTIE:

13 Q And Dr. Prestwich is analogizing between the
14 1,5 shift reaction and the reaction in Verdegem?

15 MR. MILLS: Objection to form,
16 foundation, calls for speculation.

17 THE WITNESS: Sorry, would you repeat
18 the question?

19 BY MR. CHRISTIE:

20 Q What is your understanding of why
21 Dr. Prestwich is relying on Verdegem?

22 MR. MILLS: Objection to form.



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1 THE WITNESS: Well, I think he's trying
2 to develop an argument for this case that an isotope
3 effect -- kinetic isotope effect would not be
4 expected.

5 I should point out, while we're on
6 Verdegem, he doesn't use an enzyme. He's actually
7 using a sodium hydride, which is an extremely strong
8 base, as I think I've pointed out. This is actually
9 flammable. You have to be very careful with this
10 and keep it dry. You can't even put it into water.

11 BY MR. CHRISTIE:

12 Q Can you show me where in Dr. Prestwich's
13 declaration he argues that the 1,5 shift was enzyme
14 mediated?

15 A Yeah, Figure 12. He's got a protein with a
16 base on picking off a hydrogen. To me, that's an
17 enzyme.

18 Q Because you're an enzymologist?

19 A I'm sorry, what?

20 Q Because you're an enzymologist?

21 A No, I think any biochemist would see that as
22 an enzyme. You don't just have proteins around with



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1 bases on that go around picking protons off of
2 methyl groups.

3 Q Figure 12 doesn't say enzyme mediated,
4 right?

5 A No, but it says protein, and it has a basic
6 group on there that's actually doing catalysis, so
7 that's an enzyme. I don't know if he specifically
8 calls it an enzyme, but it's an enzyme.

9 Q Can you point me to anywhere in
10 Dr. Prestwich's declaration aside from the word
11 protein in Figure 12 where he says that the 1,5
12 shift is an enzyme mediated?

13 A Well, I'm looking. I can't specifically
14 remember if he used the word enzyme. But that is an
15 enzyme. It's a protein that's catalyzing a
16 reaction, and so, therefore, it's acting as an
17 enzyme.

18 By the way, just to expand on that argument,
19 he's actually showing this as a reversible reaction,
20 so this hypothetical protein is actually doing
21 catalysis. So, therefore, if you have a -- both
22 ways in this so-called proton tautomerization. So



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1 if you have a protein, which is actually catalyzing
2 a reversible reaction, that's catalysis, and that's
3 an enzyme by definition.

4 Q Dr. Guengerich, is there anything else in
5 Dr. Prestwich's declaration that suggests that he's
6 arguing the 1,5 shift is enzyme mediated aside from
7 Figure 12?

8 A I didn't do a specific search for the word
9 enzyme in here. Obviously, I can't do it right now.
10 Basically, whether he uses the word or not,
11 this is an enzyme reaction.

12 Q So is that a no, there's nothing else in
13 this declaration that suggests this is --
14 Dr. Prestwich intended the 1,5 shift to be an
15 enzyme-mediated reaction?

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

19 THE WITNESS: I would have to do --
20 actually, I don't recall that I wrote down that he
21 used the word enzyme, but this is basically an
22 enzyme reaction.



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1 I would have to do a search for the
2 word enzyme to verify that, whether or not he said
3 that.

4 BY MR. CHRISTIE:

5 Q So sitting here today, you can't identify
6 anything other than your interpretation of Figure 12
7 that suggests that Dr. Prestwich is arguing that the
8 1,5 shift is enzyme mediated?

9 A I have --

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

12 THE WITNESS: I've answered this. I
13 think I've answered that, and I would have to read
14 the -- you know, his whole declaration again
15 verbatim to see if I could find the word enzyme or
16 enzymatic.

17 He's apparently not proposing that
18 simple amino acids are doing that because he says
19 protein here.

20 BY MR. CHRISTIE:

21 Q Can you look at Figure 13 in Dr. Prestwich's
22 declaration?



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1 A I see it.

2 Q Can you describe just generally what that's
3 showing?

4 MR. MILLS: Objection to form,
5 foundation, scope.

6 THE WITNESS: It's similar to what's
7 been shown. It's similar to what's been shown in
8 Figure 12 except this is actually with a cis
9 derivative instead of -- I think the other one had a
10 trans. Yeah.

11 Here, this just indicates -- it says
12 base. It doesn't stick a protein on it. He's
13 showing an interconversion -- actually, two
14 interconversions with base.

15 BY MR. CHRISTIE:

16 Q So Figure 13 is similar to Figure 12 except
17 for it doesn't have the word protein in it?

18 MR. MILLS: Objection to form,
19 incomplete hypothetical, foundation,
20 mischaracterizes the witness's testimony.

21 THE WITNESS: Well, yes. As I
22 mentioned already, this is actually cis, not trans.



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1 That is, the entity at the end is pointing down
2 instead of up.

3 By the way, I just noticed this is
4 actually taken directly from -- this is a copy of
5 Figure 5 from Exhibit 2077, Mowery, which is
6 actually cited here.

7 BY MR. CHRISTIE:

8 Q So Dr. Prestwich's Figure 12 is based on a
9 figure from Mowery?

10 A It is --

11 MR. MILLS: Objection to form.

12 THE WITNESS: It is the same figure.

13 MR. MILLS: I'm sorry, he asked about
14 Figure 12.

15 THE WITNESS: Oh, I'm sorry, Figure 12.
16 I apologize.

17 So what was the question again?

18 BY MR. CHRISTIE:

19 Q So Figure 13 is from Exhibit 2077, Mowery?

20 MR. MILLS: Objection to foundation.

21 Caution you not to speculate.

22 THE WITNESS: Well, Figure 13 is



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1 Figure 5. They are identical.

2 BY MR. CHRISTIE:

3 Q And just so the record is clear, you're
4 comparing Figure 13 in Exhibit 2052 to Figure 5 in
5 Exhibit 2077?

6 A That is correct. They are exactly the same.

7 Q And a moment ago, you said that Figure 13 is
8 similar to Figure 12 in Exhibit 2052 except for the
9 protein and the transconfiguration?

10 A Yes.

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

13 BY MR. CHRISTIE:

14 Q So it's fair to say that Figure 12 is based
15 on the same figure in Mowery, Exhibit 2077, except
16 for it has the word protein?

17 MR. MILLS: Objection to form, lacks --

18 BY MR. CHRISTIE:

19 Q And the transconfiguration?

20 MR. MILLS: Lacks foundation,
21 incomplete hypothetical, calls for speculation,
22 mischaracterizes the witness's testimony.



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1 THE WITNESS: It's similar. Like I
2 said, the Figure 13 is deficient in showing some of
3 the electron movement then. But, yeah, there is
4 certainly similarity. I can't -- I can only
5 speculate on which Dr. Prestwich drew first.

6 BY MR. CHRISTIE:

7 Q Mowery, Exhibit 2077, that's not an enzyme
8 catalyzed reaction, right?

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

11 THE WITNESS: Mowery did not use an
12 enzyme. He used a very high concentration of
13 butylamine in the solvent chloroform.

14 BY MR. CHRISTIE:

15 Q Can you look at paragraph 284 of
16 Dr. Prestwich's declaration?

17 A I'm sorry, did you say 284?

18 Q 284.

19 A Yes.

20 Q And the third sentence says, Moreover, basic
21 species such as amino acid side chains (e.g.,
22 lysine, arginine) and other nucleophilic moieties



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1 present in the complex chiral protein-lipid
2 environment of the ROS facilitate the deprotonation
3 of acidic hydrogen atoms.

4 Do you see that?

5 A Yes.

6 Q And that doesn't say that the 1,5 shift
7 reaction is enzyme mediated, right?

8 MR. MILLS: Objection.

9 THE WITNESS: Well, it says that there
10 are basic groups on proteins that are doing
11 catalysis. That's what enzymes do. We went through
12 this on Figure 12.

13 This is total speculation on the part
14 of Dr. Prestwich, by the way. He says something
15 about the photoreceptor cells. But what he's saying
16 is true about every cell in the body. They're full
17 of proteins sitting around, and they don't just do
18 random -- as far as I know, they don't do many
19 random events.

20 BY MR. CHRISTIE:

21 Q Can you describe the rod outer cells, the
22 composition of the rod outer segment?



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1 MR. MILLS: Objection.

2 THE WITNESS: Well, what do you mean,
3 the composition of the rod outer segment? These are
4 the cells that interact with the retinol pigment
5 epithelium.

6 We have rods there. Beyond that, I
7 can't -- I don't know if there's anything unusually
8 specific except for the machinery we use for visual
9 purposes.

10 There are discs in there too, but
11 that's about really all I want to comment on on the
12 anatomy of those cells.

13 MR. MILLS: We've been going for maybe
14 close to an hour and a half, right. We should take
15 a break.

16 MR. CHRISTIE: Yeah, we can take a
17 break.

18 (Recess: 2:13 p.m. to 2:25 p.m.)

19 BY MR. CHRISTIE:

20 Q Welcome back, Dr. Guengerich.

21 Can you tell me what a biomimetic reaction
22 is?



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1 MR. MILLS: Objection, scope.

2 THE WITNESS: Biomimetic is a term we
3 use for things that model biology, that is -- or we
4 think they're modeling the biology. They're usually
5 simplified systems not involving biological -- I
6 shouldn't say -- let me stop. Not involving complex
7 biological molecules. They're models.

8 BY MR. CHRISTIE:

9 Q So they're trying to synthetically mimic in
10 vivo conditions?

11 MR. MILLS: Objection to form,
12 outside-the-scope objection, lacks foundation, calls
13 for speculation, incomplete hypothetical.

14 THE WITNESS: Biomimetic models aren't
15 necessarily used for synthesis. In my field,
16 they've been used to mimic enzyme reactions, not
17 necessarily even in vivo situations, but more
18 complicated reactions with simpler molecules.

19 BY MR. CHRISTIE:

20 Q How do you use it in your work?

21 MR. MILLS: Objection, scope.

22 THE WITNESS: I'm trying to remember



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1 the last time we used a biomimetic model. I don't
2 remember. We probably have, but I don't remember a
3 good case for that. We usually use the enzymes
4 themselves.

5 BY MR. CHRISTIE:

6 Q So a moment ago you said, In my field,
7 they're used to mimic enzyme reactions.

8 MR. MILLS: Objection.

9 THE WITNESS: I think that's what I
10 said, yeah. That can be. That is correct. They're
11 used for other types of things too as models.

12 In my field, enzyme reactions, but they
13 could be used for other biological events.

14 BY MR. CHRISTIE:

15 Q All-trans RAL, the atRAL we were talking
16 about earlier today, do you know what I'm talking
17 about?

18 A All-trans retinaldehyde, yes.

19 What about it?

20 Q Is that an unsaturated aldehyde?

21 MR. MILLS: Objection to scope.

22 THE WITNESS: Yes, it's unsaturated. I



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1 think -- yeah, right, it is. Yeah.

2 BY MR. CHRISTIE:

3 Q Is that also referred to as an
4 a,B-unsaturated aldehyde?

5 MR. MILLS: Objection, outside the
6 scope.

7 THE WITNESS: I'm not familiar with
8 that nomenclature.

9 BY MR. CHRISTIE:

10 Q Alpha beta?

11 MR. MILLS: Objection, outside the
12 scope.

13 THE WITNESS: Oh, that, yes, alpha beta
14 is used. I hadn't heard a,B but alpha beta.

15 BY MR. CHRISTIE:

16 Q Let me just make that clear for the record.
17 All-trans RAL, ATR, is an alpha beta
18 unsaturated aldehyde?

19 MR. MILLS: Objection, outside the
20 scope.

21 THE WITNESS: Yes is the answer for the
22 nomenclature. Yes.



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1 BY MR. CHRISTIE:

2 Q Does it also have a methyl at the beta
3 carbon?

4 MR. MILLS: Objection, outside the
5 scope.

6 THE WITNESS: That's correct. There's
7 a methyl. That's the 20 methyl group.

8 MR. CHRISTIE: I want to just go off
9 the record. Just give me ten minutes here.

10 MR. MILLS: Do you need the room?

11 MR. CHRISTIE: Yeah.

12 (Recess: 2:32 p.m. to 2:39 p.m.)

13 MR. CHRISTIE: Dr. Guengerich, I have
14 no further questions today.

15 THE WITNESS: Thank you.

16 MR. MILLS: Thank you. I have a couple
17 of questions.

18 E X A M I N A T I O N

19 BY MR. MILLS:

20 Q Dr. Guengerich, a few moments ago, you were
21 asked about biomimetics.

22 Do you recall that?



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1 A Yes.

2 Q And you were asked a series of questions
3 about one of the ways that biomimetics can be used
4 in your field.

5 Do you recall that?

6 A Yes.

7 MR. CHRISTIE: Objection to form.

8 BY MR. MILLS:

9 Q When you were discussing the way that
10 biomimetics can be used in your field, one of the
11 ways you identified was enzyme reactions.

12 Do you recall that testimony?

13 A Yes.

14 Q So my question is, is your field and
15 expertise limited to enzyme reactions?

16 A No.

17 Q Do you recall testimony from counsel about a
18 hypothetical random proton removal from basic amino
19 acid residues on proteins?

20 MR. CHRISTIE: Objection to form.

21 THE WITNESS: Do you mean from
22 Mr. Christie?



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1 BY MR. MILLS:

2 Q Yes.

3 A Yes.

4 Q So Mr. Christie's proposal that there could
5 be random proton removal from basic amino acid
6 residues from proteins in the disc space of the
7 photoreceptor cells, do you recall testifying that
8 that would be extremely inefficient? Do you
9 remember using those words?

10 A I think I do.

11 MR. CHRISTIE: Objection to form.

12 THE WITNESS: That's what I would say
13 now.

14 BY MR. MILLS:

15 Q Can you tell us what you meant and why you
16 said that, that that would be extremely inefficient?

17 A Well, the -- basically, you would have
18 things floating around in space but not working like
19 enzymes do where you actually have affinity for
20 groups to actually do -- I shouldn't use my hands --
21 catalysis to occur in a restricted space, which is
22 one of the main reasons enzymes work well.



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1 As I indicated, just having basic proteins
2 around doesn't just start taking protons off of
3 methyl groups and things like that. That's not a
4 very efficient process.

5 Q Would you characterize Mr. Christie's
6 proposal as something that occurs frequently or
7 something that occurs rarely or some other way?

8 A Very rarely.

9 Q And if that were what was happening, what
10 would be the impact of a C20 deuteration to the
11 Vitamin A?

12 MR. CHRISTIE: Objection to form.

13 THE WITNESS: It would slow down the
14 removal of the proton.

15 BY MR. MILLS:

16 Q What impact, if any, would that have on the
17 downstream formation of lipofuscin?

18 A It should slow it down.

19 Q You were also asked some questions about
20 base catalyzed tautomerization.

21 Do you recall that line of questioning?

22 A Yes.



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1 Q What impact would C20 deuteration have on
2 downstream formation of lipofuscin if it were
3 resulting from base catalyzed tautomerization?

4 MR. CHRISTIE: Objection, form.

5 THE WITNESS: The expected effect would
6 be that this would be -- the deprotonation would be
7 more difficult, so this would actually slow down the
8 process.

9 BY MR. MILLS:

10 Q And is that true regardless of whether it's
11 enzyme mediated or not?

12 A My answer would be the same, yes.

13 Q Do you recall being asked some questions
14 about Verdegem?

15 A Yes.

16 Q Do you recall testifying you have to keep it
17 dry; you can't put it into water? Do you recall
18 that?

19 A Yes. This was the case with the use of
20 sodium hydride.

21 Q And why is it that you have to keep it dry?

22 A Well, basically -- I know this from personal



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1 experience. If you put water in sodium hydride,
2 you'll get fire.

3 Q And I just want to ask, are those
4 physiological conditions, but in sodium hydride, is
5 that the physiological conditions that exist in the
6 photoreceptor cells in the eye?

7 A No. Your eyes would burn up.

8 Q Now you were also asked some questions about
9 the Mowery reference.

10 Do you recall that?

11 A Yes.

12 Q Do you recall testifying that the Mowery
13 reference used high concentrations of a particular
14 base?

15 A I recall a value of 100 millimolar
16 butylamine.

17 Q Are those physiological conditions that
18 exist in the rod outer segments of the eye?

19 A No, that's .1 molar. That's a very high
20 concentration of any amine.

21 Q Please take a look at Figure 13 of
22 Dr. Prestwich's declaration.



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1 A Okay. I have it.

2 Q Do you recall being asked questions about
3 this figure by counsel?

4 A Yes.

5 Q And do you recall testifying that the source
6 that Dr. Prestwich identified for his Figure 13 was
7 Figure 5 of Exhibit 2077, Mowery?

8 A Yes.

9 MR. CHRISTIE: Objection to form.

10 THE WITNESS: It says that in the
11 legend to Figure 13.

12 BY MR. MILLS:

13 Q There's a parenthetical right after the word
14 Figure 5.

15 Do you see that?

16 A Yes, redrawn.

17 Q So what do you understand Dr. Prestwich to
18 mean when he says that his Figure 13 is redrawn as
19 compared to Mowery, Figure 5?

20 A I did not see a difference unless I missed
21 something. I think it was just trying -- as opposed
22 to doing a photoclip out of the paper, which I think



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1 was a PDF. I think he probably redrew that in the
2 program KingDraw, that's a software, or a similar
3 program, I suspect. That's my speculation.

4 Q Go ahead and look -- keeping open Figure 13,
5 go ahead and look at Figure 5 of Exhibit 2077.

6 Do you have both of those?

7 A Yes, I do.

8 Q Would you agree that the printing of
9 Figure 5 of the Mowery reference is murky?

10 A Yes, I would.

11 Q Do you agree that Dr. Prestwich appears to
12 have redrawn Figure 5 of Mowery because the figure
13 is somewhat illegible?

14 A That would be my suspicion. Frankly, I
15 would probably do that myself if I had the choice.

16 Q Thank you. You can set that aside.

17 Do you recall being asked questions by
18 counsel about hyaluronan?

19 A Yes.

20 Q My question, is hyaluronan a retinoid?

21 A No.

22 Q Thank you.



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1 Do you recall being asked questions about
2 Exhibit 1065?

3 A 1065 was -- actually, I can't remember if
4 there was a specific question about 1065. This is a
5 Centrum thing.

6 Q Do you recall testifying about the Centrum
7 label during your deposition?

8 A No, I don't think I did.

9 Q You did, but you may not remember it because
10 it's been a long day.

11 MR. CHRISTIE: Counsel, I don't think
12 he testified about the Centrum label.

13 MR. MILLS: It's in the transcript. We
14 can pull it up. Look it up in the realtime.

15 THE WITNESS: I think I mentioned it,
16 but I didn't answer a question.

17 MR. CHRISTIE: Objection, completely
18 outside the scope of redirect. Centrum label was
19 not discussed today.

20 MR. MILLS: It was. It was discussed.

21 Your objection is noted for the record.

22



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1 BY MR. MILLS:

2 Q Dr. Guengerich, do you recall being asked
3 questions about references that you were aware of
4 discussing the Vitamin A that was administered to
5 macular degeneration patients?

6 A Yeah, that was in regard to the Del Priore
7 deposition transcript.

8 Q And as part of that, you were asked
9 references that you had reviewed that supported the
10 use of Vitamin A in macular degeneration patients.

11 Do you recall that question?

12 A Yes, there were several studies, yeah.

13 Q One of the references that you identified in
14 your testimony was Exhibit 1022, the AREDS study.

15 Do you recall that?

16 A Oh, yes.

17 Q And another reference you identified was
18 Exhibit 1008, the Ortho Pharma reference.

19 Do you recall that?

20 A Yes, I do.

21 Q And you were asked if there was any other
22 references that related to that, and that's when you



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1 identified Exhibit 1065, the Centrum label.

2 A That's right.

3 Q Do you recall that?

4 Why is it that you mentioned the Centrum
5 label in relation to the AREDS study?

6 MR. CHRISTIE: Objection to form.

7 THE WITNESS: Well, the AREDS study
8 indicated that there was a benefit to people in
9 terms of preventing further damage to the eyes if
10 they were using more Vitamin A. And, indeed, the
11 Centrum study, I think that -- not the Centrum
12 study.

13 The Centrum label, that indicates, I
14 think, about a milligram per day of Vitamin A or
15 beta carotene included in it, which is about, you
16 know, as much as the normal person consumes anyway.
17 So it was similar.

18 I think the Centrum value was actually
19 based on the AREDS study, is my recollection, in
20 terms of the suggested amount.

21 BY MR. MILLS:

22 Q Did you have an understanding when you



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1 testified about the Centrum label that there were
2 patients in the AREDS study who were taking Centrum
3 multivitamin?

4 A I remember --

5 MR. CHRISTIE: Objection to form.

6 THE WITNESS: I remember now, yeah. I
7 think more than half of the people, maybe two-thirds
8 in the AREDS study, were using Centrum or the
9 equivalent, and they actually showed a better
10 outcome than the rest of the contingent.

11 BY MR. MILLS:

12 Q And you recall counsel asking you whether in
13 addition to those references there were any others
14 that you recalled at the moment, and you didn't
15 recall any others at the moment.

16 Do you recall that?

17 A Yes.

18 Q Please take a look at Exhibit 1088 in your
19 binder.

20 A Oh. Okay.

21 Q And what is Exhibit 1088?

22 A This is an old Centrum label from -- the



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1 year I think is 2006 -- I'm sorry, 2007. Yeah,
2 2007. This is an old Centrum label.

3 Q What month is that?

4 A Well, it looks like it's actually very
5 specifically, if I'm reading this correctly,
6 July 14th.

7 Q And how do you know -- or do you have any
8 knowledge as to the source of this Centrum label --

9 MR. CHRISTIE: Counsel, this is well
10 outside the scope of redirect.

11 THE WITNESS: It was from the -- well,
12 the Wayback Machine, which is the web archive
13 system. I think there's a general validation in one
14 of the other exhibits, yeah.

15 BY MR. MILLS:

16 Q Did you personally go to the Wayback Machine
17 to see Exhibit 1088?

18 A Actually, I did.

19 Q Is the same true of Exhibit 1089?

20 A Yes.

21 Q Are or are not Exhibits 1088 and 1089
22 examples of additional references that disclose the



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1 use of Vitamin A in the Centrum multivitamin?

2 A Yes, they are.

3 Q Thank you.

4 Do you recall being asked questions about
5 rate-limiting steps today?

6 A I certainly do.

7 Q And do you remember being asked questions
8 about "the" rate-limiting step as opposed to "a"
9 rate-limiting step?

10 A Yes, and I actually dwelt on that
11 considerably in my declaration too.

12 Q Do you recall testifying with regard to the
13 impact of whether a step is slow or the slowest in a
14 pathway?

15 A Yes.

16 Q And what is your opinion in regards to the
17 synthesis pathway for A2E in regards to whether the
18 1,5 shift needs to be the slowest step as opposed to
19 a rate-limiting step in the pathway?

20 A I think for a success -- for it to see -- to
21 have a successful outcome here due to deuteration,
22 it can be one of the rate-limiting steps, but it



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1 does not have to be the rate-limiting step.

2 Q And why is that the case?

3 MR. CHRISTIE: Objection.

4 THE WITNESS: Well, it's a linear
5 reaction. And if you block the -- slow down the
6 first reaction, everything will pile up beyond
7 that -- or I should say slow down would be a better
8 term than pile up.

9 BY MR. MILLS:

10 Q Do you recall being asked questions about
11 Roth and Doering?

12 A Yes, I do.

13 Q Do you recall being asked questions about
14 Roth employing forced conditions to make the
15 reaction go forward?

16 A Yes.

17 Q What were those forced conditions?

18 A Well, high temperature and long reaction
19 time.

20 Q Do you recall being asked questions about
21 the gas phase?

22 A Yes, I do.



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1 Q So what is the implication of the forced
2 conditions in the gas phase that were required to
3 force the 1,5 sigmatropic rearrangement to go
4 forward in the Roth reference?

5 A Well, it's an inherently difficult reaction,
6 and so it takes extreme conditions to make this
7 proceed.

8 Q And is there similarity or dissimilarity
9 between that and the conditions used in the Doering
10 reference?

11 A They're very similar in -- well, somewhat
12 different temperatures, but both very high and for
13 long periods of time.

14 Q And what conclusion, if any, do you draw
15 based on your experience and expertise regarding the
16 impact of C20 deuteration of retinol on the
17 formation of lipofuscin based on the Roth and
18 Doering references?

19 A Well, it would be expected to be a very slow
20 reaction, which makes some logic because it's -- you
21 know, it -- for many people, it's actually a very
22 slow, lifelong process.



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1 Q Therefore, what impact would you expect to
2 result from C20 deuteration of retinol?

3 A It should slow down the production of these
4 unwanted molecules by slowing down the reaction.

5 Q Do you recall being asked questions about
6 extrapolation from the forced conditions down to
7 more physiological temperatures?

8 A Yes.

9 Q And there was a point in time where you were
10 reading something talking about highly problematic
11 extrapolation.

12 Do you recall that?

13 A Yeah. I think the Doering actually used
14 that term.

15 Q So did those statements that counsel had you
16 read, do any of them undermine your testimony about
17 the impact of the Roth and Doering studies on the
18 reasonable expectation of success in this case?

19 MR. CHRISTIE: Objection to form.

20 THE WITNESS: No. These
21 extrapolations, even though there were some
22 differences, they still had a very sizable isotope



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1 effect predicted at 25 degrees or 37 degrees, so
2 this would be suggested that this was a good
3 candidate for deuteration to slow down the reaction.

4 BY MR. MILLS:

5 Q Do you recall offering some testimony about
6 in the Doering reference a reverse reaction?

7 A Yes.

8 Q Have you seen any evidence that the 1,5
9 sigmatropic rearrangement that's disclosed in the
10 Mata paper had physiological conditions as a
11 reversible reaction?

12 A I have not. I'm not sure -- I'm not aware
13 that anybody has even tried to do that.

14 Q And then do you recall being asked questions
15 about the potential for a nitrogen if added to the
16 Roth or Doering compounds to impact the KIE? Do you
17 recall that?

18 A I do.

19 Q Does the concept of introducing a nitrogen
20 into the compound, for example, a nitrogen in the
21 NRPE, does that undermine your testimony about a
22 large expected KIE resulting from C20 deuteration?



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1 MR. CHRISTIE: Objection to form.

2 THE WITNESS: No, it does not.

3 BY MR. MILLS:

4 Q Why not?

5 A I think there would still be a large isotope
6 effect expected for that particular reaction
7 regardless of whether you had a nitrogen or not.

8 Q Has Dr. Prestwich identified any evidence
9 that would indicate that you would not have a large
10 KIE in the NRPE when you deuterate at C20?

11 MR. CHRISTIE: Objection to form.

12 THE WITNESS: I don't believe he has.

13 MR. MILLS: Thank you. No further
14 questions.

15 E X A M I N A T I O N

16 BY MR. CHRISTIE:

17 Q Doctor, this new Centrum label that you were
18 just handed or was in your binder, that's not in
19 your declaration, right?

20 A When you say the new one, do you mean the
21 2007? It's actually the old one.

22 Q Whatever, yeah.



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1 A I don't think it -- well, it wasn't -- I
2 don't think it's in the appendix. It was in my
3 binder.

4 Q So this Exhibit 1088 was not in your binder
5 of material -- excuse me, was not cited in your
6 declaration?

7 A I don't think it was.

8 Q It's not listed in the appendix of your
9 declaration?

10 A No. That's a fairly short one anyway.

11 Q Okay.

12 A We only had the newer one, which is after
13 the patent application.

14 Q Right.

15 The only one cited in your declaration is
16 after the priority date of the patent at issue here,
17 right?

18 A Yeah. I would add, though, that the amount
19 of Vitamin A is actually the same though.

20 Q Did you prepare that binder?

21 A No. Wilson Sonsini packaged the binders
22 together.



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1 Q And why did you look at the Wayback Machine?

2 A Well, because in discussions with our
3 counsel, we decided that it would be more relevant
4 to actually know what the Vitamin A content of the
5 Centrum was that was being used at the time of the
6 AREDS study then, which actually hasn't changed.

7 Q Thank you.

8 You didn't do that before you submitted your
9 declaration, Exhibit 1080?

10 A No.

11 Q So you submitted Exhibit 1080, your
12 declaration, and you have since prepared this new
13 exhibit --

14 A Yes.

15 Q -- that was not in the record?

16 A Correct.

17 Q What other exhibits are in that binder that
18 are not cited in your declaration?

19 A Well, I'm not sure.

20 MR. CHRISTIE: Withdraw the question.

21 THE WITNESS: I'm not sure offhand
22 anyway.



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MR. CHRISTIE: No further questions.

MR. MILLS: Thank you. The deposition
is over. The witness reserves the right to review
the transcript.

THE STENOGRAPHER: You want a rough
draft and regular turnaround?

MR. MILLS: Yes.

(Time noted: 3:05 p.m. CT.)

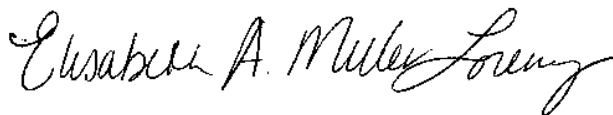


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signing was requested; and that I am neither counsel
for, related to, nor employed by any of the parties
to this case and have no interest, financial or
otherwise, in its outcome.

IN WITNESS WHEREOF, I have hereunto set
my hand this 24th day of January, 2025.



ELISABETH A. LORENZ

NCRA Registered Merit Reporter

NCRA Certified Realtime Reporter



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ACKNOWLEDGMENT OF DEPONENT

I, F. PETER GUENGERICH, PH.D., do
hereby certify that I have read and examined the
foregoing testimony, and that the same is a true,
correct, and complete transcription of the testimony
given by me, and any corrections appear on the
attached Deposition Errata Sheet signed by me.

F. PETER GUENGERICH, PH.D.

DATE

Subscribed and sworn to on the _____ day of
_____, 2025, before me,

Notary Public, in and for the State of

_____.



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