

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3
4 ILLUMINA, INC.,

5 Plaintiff,

6 vs.

Case No.:

IPR2018-00291; Patent 9,718,852

IPR2018-00318; Patent 9,719,139

IPR2018-00322; Patent 9,708,358

IPR2018-00385; Patent 9,725,480

IPR2018-00797; Patent 9,868,985

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8
9 THE TRUSTEES OF COLUMBIA UNIVERSITY
10 IN THE CITY OF NEW YORK,

11 Defendant.
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15 VIDEOTAPED DEPOSITION OF FLOYD ROMESBERG, PH.D.

16 SAN DIEGO, CALIFORNIA

17 FRIDAY, FEBRUARY 1, 2019
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23 Reported by:
24 Linda E. Marquette
RPR, CLR, CSR No. 11874
25 Job No. 10051818

Columbia Exhibit 2140
Illumina, Inc. v. The Trustees
of Columbia University in the
City of New York
IPR2018-00291, 318, 322, 385 & 797

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19 VIDEOTAPED DEPOSITION of FLOYD ROMESBERG, PH.D.,

20 taken at 12790 El Camino Real, Suite 100, San Diego ,

21 California, commencing at 9:05 a.m., and concluding at

22 3:20 p.m., on Friday, February 1, 2019, before Linda E.

23 Marquette, RPR, CLR, Certified Shorthand Reporter No.

24 11874.
25

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1 SAN DIEGO, CALIFORNIA; FRIDAY, FEBRUARY 1, 2019

2 9:05 A.M. to 3:20 P.M.

3
4 THE VIDEOGRAPHER: Good morning. Time on the
5 record is approximately 9:05 a.m. Today's date is
6 February 1st, 2019.

7 My name is Gianni Ortiz of Aptus Court
8 Reporting.

9 The court reporter today is Linda Marquette,
10 also of Aptus Court Reporting, located at 600 West
11 Broadway, Suite 300, San Diego, California 92101.

12 This begins the video-recorded deposition of
13 Dr. Floyd Romesberg testifying in the matter of
14 Illumina, Inc. versus the Trustees of Columbia
15 University in the City of New York. Pending in the
16 United States Patent and Trademark Office before the
17 Patent Trial and Appeal Board.

18 This deposition is taking place at
19 12790 El Camino Real San Diego, California 92130.

20 The video and audio recording will take place
21 at all times during this deposition unless all counsel
22 agree to go off the record. The beginning and end of
23 each video recording will be announced.

24 Will counsel please identify yourselves and
25 state whom you represent.

1 MR. SCHWARTZ: My name is Robert Schwartz from
2 the firm of Venable Fitzpatrick. And I represent
3 Columbia in this matter, and with me is my colleague
4 Zachary Garrett.

5 MR. ZIMMERMAN: Bill Zimmerman of Knobbe
6 Martens Olsen & Bear on behalf of Illumina and the
7 witness.

8 With me is my partner Nate Luman and Marcus
9 Burch, in-house at Illumina.

10 I understand that the deposition is also being
11 streamed in real time to somebody else for you. If we
12 could identify that person.

13 MR. SCHWARTZ: Yes.

14 MR. ZIMMERMAN: Just so it's clear for the
15 record.

16 MR. SCHWARTZ: This is being streamed to John
17 Murnane of Venable Fitzpatrick. And there's a
18 possibility that Steven Menchen will join but it's not
19 clear.

20 MR. ZIMMERMAN: Okay.

21 THE COURT: Thank you.

22 Will the reporter please swear in the deponent
23 to start the deposition.

24 ///

25 ///

1 FLOYD ROMESBERG, PH.D.,
2 having been first duly administered an oath, was
3 examined and testified as follows:

4 EXAMINATION

5 BY MR. SCHWARTZ:

6 Q. Good morning, Dr. Romesberg.

7 A. Good morning.

8 Q. Now, you were deposed in this case before?

9 A. Yes, I was.

10 Q. And is there any reason you will -- you will
11 not be able to give truthful testimony today?

12 A. No, there's not.

13 Q. You understand that unless your counsel
14 instructs you not to answer my questions, you should
15 attempt to answer my questions to the best of your
16 ability?

17 A. I do.

18 Q. And if at any time you do not understand my
19 question, please let me know. And if you do not say
20 otherwise, I will assume that if you answered my
21 question, that you understood my question.

22 Is that fair?

23 A. That is fair.

24 Q. The other rules that we follow, of course we
25 went through this before, we try to talk one at a time,

1 those sort of things. We don't have to go through all
2 of that.

3 Did you meet with your attorneys in
4 preparation for today's deposition?

5 A. Yes, I did.

6 Q. And what are the names of the attorneys you
7 met with?

8 A. Marcus, Nate, and one day of Kerry, Kerry
9 Taylor. And then one day of Kerry, Nate Luman, and
10 Marcus Burch.

11 Q. So a total of how many days did you meet with
12 your attorneys in preparation for today's deposition?

13 A. Two.

14 Q. And approximately how much time did you spend
15 at each of those meetings?

16 A. Approximately seven hours.

17 Q. And outside of those meetings, did you meet
18 with your attorneys at any other time?

19 A. In preparation for this?

20 Q. Yes.

21 A. No, I did not.

22 Q. And did you speak to anybody else other than
23 your attorneys about today's deposition?

24 A. No, I did not.

25 Q. And what did you do to prepare for today's

1 deposition?

2 MR. ZIMMERMAN: I'll caution the witness that
3 you can respond generally without revealing the
4 substance of your communications.

5 A. Outside of meeting with the attorneys, I spent
6 maybe two hours, maybe two and a half hours, just
7 reading and thinking. Mostly reading over past material
8 from the last parts of this.

9 BY MR. SCHWARTZ:

10 Q. Okay. And you understand that today's
11 deposition is for all five of the IPRs in this case?

12 A. I do.

13 Q. Okay. And for the record, those are
14 IPR2018-00291, IPR2018-00318, IPR2018-00322,
15 IPR2018-00385 and IPR2018-00797.

16 And you prepared a second declaration for
17 those IPRs, correct?

18 A. That is correct.

19 Q. And I'm going to put in front of you that
20 declaration. It's been marked as Exhibit 1119.

21 (Exhibit 1119 was previously marked
22 for identification by the Certified
23 Shorthand Reporter.)

24 BY MR. SCHWARTZ:

25 Q. Do you recognize this as your second

1 **declaration?**

2 A. Yes. It appears to be.

3 Q. And that's your signature at the end of the
4 **declaration?**

5 A. Yes, it is.

6 Q. And I'm also going to put in front of you the
7 **materials considered, which was part of your**
8 **declaration, and that's marked as Exhibit 1138.**

9 (Exhibit 1138 was previously marked
10 for identification by the Certified
11 Shorthand Reporter.)

12 MR. SCHWARTZ: Court reporter, do you need
13 one?

14 COURT REPORTER: It's okay.

15 MR. SCHWARTZ: Sorry. I guess we're one
16 short.

17 BY MR. SCHWARTZ:

18 Q. Are all of -- are all of the materials that
19 you relied on to form the materials expressed in your
20 **second declaration listed in this Materials Considered,**
21 **Exhibit 1138?**

22 A. I believe so. This is out of my dec, I
23 believe. And it certainly was correct there, so to the
24 extent that this is an accurate reproduction of that,
25 then yeah.

1 Q. Okay. Is there anything you want to change
2 about the Materials Considered list today?

3 A. No.

4 Q. Is there anything you want to change about
5 your declaration today?

6 A. No.

7 Q. Did you do any of your own independent
8 searches for references outside of what was provided you
9 by the attorneys?

10 MR. ZIMMERMAN: You can answer that yes or no.

11 A. For this particular deposition?

12 BY MR. SCHWARTZ:

13 Q. Yes.

14 A. Not for the prior depositions?

15 Q. No. We're talking about this deposition.

16 MR. ZIMMERMAN: Just so we're clear, he's
17 talking about your declaration, not the deposition, I
18 assume.

19 MR. SCHWARTZ: Yes.

20 MR. ZIMMERMAN: Okay.

21 A. Yes. This declaration.

22 Frankly, I don't remember. I -- I -- I don't
23 think so. I apologize. I've been looking at a lot of
24 different references over the past six months for this
25 case, and I don't think there were any new ones for this

1 dec.

2 BY MR. SCHWARTZ:

3 Q. And if there had been new ones, would you have
4 listed them in your Materials Considered exhibit?

5 A. If I used them in the dec, yes.

6 Q. Okay. And we talked about this last time.
7 You have been an expert for Illumina in other IPR
8 proceedings, correct?

9 A. That is correct.

10 Q. And you submitted expert declarations on
11 behalf of Illumina in those proceedings?

12 A. That is correct, yes.

13 Q. And you were deposed under oath in those
14 proceedings?

15 A. Yes.

16 Q. And the court reporter took down your
17 questions and answers in those depositions?

18 A. Yes.

19 Q. And a transcript of those question and answers
20 was prepared; is that correct?

21 A. Yes.

22 Q. You never designed nucleotides for use in
23 Sanger sequencing; is that correct?

24 A. Not explicitly and -- and not analogs that we
25 then took on to examine in that way, but we certainly

1 were aware of the -- of what analogs for Sanger
2 sequencing required. We looked at hundreds of -- we, my
3 lab, has looked at hundreds of nucleotide analogs, and
4 we have gotten close to various times publishing results
5 that were consistent with Sanger sequencing
6 requirements. I don't think that we ever particularly
7 emphasized that.

8 **Q. Okay. But so my question was, is that you**
9 **never explicitly designed nucleotides for the use in**
10 **Sanger sequencing; is that correct?**

11 MR. ZIMMERMAN: Objection. Asked and
12 answered.

13 A. That is correct.

14 BY MR. SCHWARTZ:

15 **Q. And the same question. You never explicitly**
16 **designed nucleotides for use in SBS; is that correct?**

17 A. No, I don't think that's correct.

18 How do you mean designed? How actively did I
19 have to participate in the design process?

20 We certainly sat around and discussed -- we
21 had a collaboration with a sequencing company called
22 Helicos. And we published a paper and -- yeah, I was
23 probably involved in talking about those designs.

24 **Q. But in your laboratory, did you actually make**
25 **nucleotides for use in SBS?**

1 A. We did not make them in my laboratory, but it
2 was in a collaboration with -- my laboratory was in that
3 collaboration, and so we had discussed it. So the
4 answer to your first part of your question, was I -- did
5 I ever help design, is yes. We then did not make them
6 in my laboratory.

7 Q. Okay. Please open the declaration I put in
8 front of you, your second declaration, Exhibit 1119.
9 And please turn to page 9. And please look at
10 paragraph 25. And in paragraph 25 you refer to
11 Exhibit 1099, which is a document from IUPAC; is that
12 correct?

13 A. That is correct. And I'm going to put in
14 front of you that document. I'm putting in front of you
15 Exhibit 1099, which is entitled Nomenclature of Organic
16 Chemistry, Sections A, B, C, D, E, F and H.

17 (Exhibit 1099 was previously marked
18 for identification by the Certified
19 Shorthand Reporter.)

20 BY MR. SCHWARTZ:

21 Q. And carries a 1979 publication date. This is
22 the same IUPAC document you referred to in your
23 declaration; is that correct?

24 A. It appears to be, yes.

25 Q. And please go back to your declaration. And

1 turn to paragraph 26 on page 9. And please draw your
2 attention to the first sentence. And in that sentence
3 you state your opinion that:

4 "The IUPAC nomenclature
5 represents the standard terminology
6 used to describe chemical
7 compounds."

8 That's what you state, correct?

9 A. Yes. That is what is written, yes.

10 Q. And please turn to paragraph 27. And in
11 paragraph 27 you state, in the last sentence in that
12 paragraph, your opinion is that a skilled artisan would
13 understand that the term "allyl ethers" refers
14 exclusively to the chemical structure CH^2 CH double bond
15 CH^2 . Correct?

16 MR. ZIMMERMAN: Objection. Mischaracterizes
17 the document.

18 You said "ethers."

19 MR. SCHWARTZ: Oh, excuse me. Allyl.

20 BY MR. SCHWARTZ:

21 Q. Let me ask the question again.

22 Your opinion as a skilled artisan would
23 understand that the term "allyl" refers exclusively to
24 the chemical structure CH^2 CH double bond CH^2 ; is that
25 correct?

1 MR. ZIMMERMAN: Objection. Mischaracterizes
2 the document.

3 A. You didn't say "ether."

4 BY MR. SCHWARTZ:

5 Q. I thought you just told me that I shouldn't
6 say "ether."

7 A. No, you said "ethers" before.

8 Q. Okay. I'm getting confused.

9 Let me read it directly from your document.

10 You state:

11 "As a result, in my opinion, a
12 skilled artisan would understand the
13 disclosure of an allyl ether to
14 refer to the [sic] specific
15 modification of a hydroxyl group
16 with the chemical structure CH² CH
17 double bond CH².

18 MR. ZIMMERMAN: Objection. Mischaracterizes
19 the document. You read it incorrectly.

20 MR. SCHWARTZ: What did I read incorrectly?

21 MR. ZIMMERMAN: You read referred to "the
22 specific modification."

23 MR. SCHWARTZ: Referred to "a specific
24 modification."

25 MR. ZIMMERMAN: I just want to make sure that

1 we have an accurate record.

2 BY MR. SCHWARTZ:

3 Q. I'll read it again.

4 "In my opinion, a skilled artisan
5 would understand the disclosure of
6 an allyl ether to refer to a
7 specific modification of a hydroxyl
8 group with the chemical structure
9 $\text{CH}^2 \text{CH double bond CH}^2$."

10 Did I read it correctly this time?

11 A. You read it --

12 Q. Thank you.

13 A. You read it correctly.

14 Q. Thank you.

15 Is $\text{CH}^2 \text{CH double bond CH}^2$ also referred to as
16 2-propenyl?

17 A. It can be, although it's not IUPAC.

18 Q. What can it also otherwise be referred to?

19 MR. ZIMMERMAN: Object as to form.

20 A. Three carbons with a double bond. I mean, I
21 guess I don't understand the question, what else could
22 it be referred to.

23 The IUPAC -- the IUPAC name for that moiety is
24 an allyl group. Could it be propynyl [ph]? That's --
25 yes.

1 What else -- are you asking what else in
2 addition to those two it could be?

3 BY MR. SCHWARTZ:

4 Q. No. I thought you were suggesting it could be
5 something else.

6 A. No. The name for that compound is allyl.

7 Q. Okay. But it's also referred to as
8 2-propenyl.

9 The question is, if I referred to it as
10 2-propenyl in this deposition, will you understand I'm
11 referring to that structure?

12 A. In this deposition I would.

13 The honest truth is, if you would have -- if
14 you would have referred to it that way before I was
15 thinking about it this -- for this deposition, I would
16 have just for a second been, like, what? Because that's
17 a -- yes, I would have quickly figured out what you were
18 talking about.

19 Q. Okay. So -- and your opinion is that after
20 the 1979 publication of IUPAC, Exhibit 1099, the term
21 "allyl ether" always means a single moiety, the CH² CH
22 double bond CH² moiety, which I am calling a 2-propenyl.
23 That's your understanding, correct?

24 A. Not really.

25 MR. ZIMMERMAN: Object as to form.

1 A. My -- my understanding is that this group has
2 always been referred to as allyl. IUPAC formalized it.
3 I don't know if this was the first formal --
4 formalization of that or -- but it -- that -- as long as
5 I've been working in this field, people have referred to
6 that as an allyl. My impression is that they've
7 referred to that as an allyl for a very long time.
8 IUPAC, at least in this document, formalizes that.
9 BY MR. SCHWARTZ:

10 Q. So whenever you've used the term "allyl" in
11 your work, you've always referred to that particular
12 structure; is that correct?

13 MR. ZIMMERMAN: Object as to form.

14 A. First of all, I will not -- without being
15 given a document, I will, first of all, not say that I
16 haven't made a mistake.

17 Secondly, I believe that I would have always
18 used them in what is the standard way. I -- I -- I
19 would hope that I've always used them in -- that word in
20 the standard way.

21 BY MR. SCHWARTZ:

22 Q. So in your work, whenever you referred to the
23 term "allyl," you would have always referred to that
24 specific group?

25 A. Let me be clear. Calling it the other name,

1 the propynyl, is not wrong. It's just not the accepted
2 nomenclature. In a manuscript there's not -- in a
3 paper -- I don't know if you've gone through my papers
4 or other papers. Would it surprise me if -- that if I
5 have used the term "allyl" or called that a "propynyl
6 group," you know, wouldn't -- wouldn't necessarily have
7 been wrong, but it's not what the standard is. It's not
8 the standard name.

9 And in a manuscript there's not that -- that
10 standard where people will reject a manuscript because
11 of that. Like I said, though, I do hope that I've
12 always used it in what is the most -- in what is the
13 IUPAC accepted way.

14 **Q. What about a patent? Would it have been**
15 **rejected if -- if that structure had been called by a**
16 **name other than allyl?**

17 **A.** If I were writing a patent and I wanted to be
18 clear, I would use the clearest language possible.

19 **Q. And in all of your patents, whenever you've**
20 **used the term "allyl," you've always referred to that**
21 **exclusive structure?**

22 **A.** You would have to show me the patent because,
23 again, I'm not sure that I haven't made a mistake or
24 that, you know, a lot of times maybe I was in a rush and
25 I wasn't -- anytime that I was writing any document,

1 patent or a manuscript, if I would have used that in an
2 incorrect way -- like, anything that I was using
3 maybe -- if anything was used in an incorrect way, if
4 someone would have sat down and said, "Which do you
5 mean?" I would have chosen the very specific IUPAC
6 definition.

7 Q. Okay. I'm going to put in front of you Tsien,
8 which has been marked as Exhibit 1013.

9 (Exhibit 1013 was previously marked
10 for identification by the Certified
11 Shorthand Reporter.)

12 BY MR. SCHWARTZ:

13 Q. Please draw your attention to page 28, and
14 draw your attention to line 23 that starts with "There
15 are several." Do you see that?

16 A. I do.

17 Q. And Tsien writes:

18 "There are several cleavable
19 tethers that permit removing the
20 fluorescent group before the next
21 successive nucleotide is added --
22 for example, silyl ethers are
23 suitable tethers which are cleavable
24 by base or fluoride. Allyl ethers
25 are cleavable by mercury (II)."

1 Do you see that?

2 A. I do.

3 Q. And please turn to page 29 of Tsien. And
4 Tsien writes:

5 "Typical tethers are from about two to about
6 20" --

7 MR. ZIMMERMAN: Can you point him to where?

8 MR. SCHWARTZ: At the very top.

9 BY MR. SCHWARTZ:

10 Q. Are you with me?

11 A. I am there.

12 Q. Okay. And Tsien writes:

13 "Typical tethers are from about 2
14 to about 20, and preferably from
15 about 3 to about 10 atoms in
16 length."

17 That's what Tsien writes, correct?

18 A. That is what is written, yes.

19 Q. So Tsien, which was published in 1991, many
20 years after the IUPAC 1979 document you referred to,
21 uses the term "allyl ethers" to refer to moieties that
22 range from 2 to 20 atoms in length, correct?

23 MR. ZIMMERMAN: Objection. Mischaracterizes
24 the document.

25 A. (No response.)

1 BY MR. SCHWARTZ:

2 Q. That's how Tsien is using the term "allyl
3 ethers," correct?

4 MR. ZIMMERMAN: Same objection.
5 Mischaracterizes the document with the omitted material.

6 A. Yes. Can I spend a second to read this?

7 MR. SCHWARTZ: Sure.

8 THE WITNESS: Can I also have a pen?

9 MR. ZIMMERMAN: Sure.

10 A. No. I don't believe that's what he says.

11 BY MR. SCHWARTZ:

12 Q. And why don't you believe that?

13 A. The statement that tethers can be 2 to 20
14 atoms or preferably 3 to 10, that refers to tethers. He
15 proposes several different tethers, one of which has an
16 allyl group in it. The others do not.

17 Q. He's referring to allyl ethers as tethers,
18 correct?

19 A. He's referring to them as an example of
20 several tethers, of several types of tethers that he
21 includes.

22 Q. Right. And those allyl ethers are from 2 to
23 20 in length.

24 MR. ZIMMERMAN: Objection.

25 ///

Floyd Romesberg, Ph.D.

1 BY MR. SCHWARTZ:

2 Q. That's what he states in Tsien?

3 MR. ZIMMERMAN: Objection. Mischaracterizes
4 the document.

5 A. I -- I don't believe he says that. The
6 statement that you're referring to says "typically
7 tethers are," so he's referring to tethers in general.
8 He immediately before discusses, for example, three
9 tethers.

10 BY MR. SCHWARTZ:

11 Q. And one of them is allyl tethers, correct?

12 A. Yeah. I'm not -- that is correct. But I'm
13 not a legal expert, so I don't know if everything he
14 lists as an example must satisfy this. But the common
15 reading of this would be that this length description is
16 referring to tethers in general.

17 My common reading of that would be that that
18 refers to all of the tethers, and it includes three,
19 which would be a standard allyl group. So I don't see
20 in any way that it is a contradiction of including
21 allyl. But I read that as being referring to tethers.

22 Q. And the tethers that he specifically points to
23 are allyl tethers, among other tethers. He specifically
24 points to that, right?

25 A. It is one of, I think, three examples that he

1 gave.

2 Q. Okay. And he refers to those allyl tethers,
3 including the allyl tethers as encompassing from 3 to
4 20, correct?

5 MR. ZIMMERMAN: Objection. Mischaracterizes
6 the document.

7 A. He does -- for example, I'm not trying to be
8 difficult here, but this is just my reading of it.
9 "Typical tethers," he doesn't say which tethers. He
10 doesn't say each of these example groups of tethers
11 must -- can be this. He just says "typically tethers
12 are from about" -- I read that as a general statement
13 about tethers.

14 BY MR. SCHWARTZ:

15 Q. So your opinion is that a POA reading this
16 portion of Tsien would understand that tethers that he's
17 referring to on the top of page 29 exclude the allyl; is
18 that correct?

19 A. Exclude the allyl?

20 Q. Yes.

21 A. No.

22 MR. ZIMMERMAN: Objection. Mischaracterizes
23 the testimony.

24 BY MR. SCHWARTZ:

25 Q. Does it include the allyl?

1 MR. ZIMMERMAN: Objection. Mischaracterizes
2 his testimony.

3 You've got to let him answer one question
4 before you move on to the next.

5 BY MR. SCHWARTZ:

6 Q. Does it include the allyl?

7 A. I think it is -- he's saying that typically
8 tethers -- he lists a series of tethers before.
9 Whether -- what the -- what the legal requirements are
10 of that, I'm not a lawyer.

11 As a human being, not as a POSA, reading this,
12 I would have read this as he gives three examples of
13 tethers, and then he says "typically tethers are this."
14 I think that would imply that the group of tethers that
15 he is suggesting are typically of these requirements.
16 It's certainly not inconsistent with including allyl,
17 because allyl is three carbons. And he says from about
18 2 to 20, which includes 3. And he says from about 3 to
19 10, which again, includes 3, so it's certainly not
20 inconsistent.

21 Does that answer your question?

22 Q. Are you finished?

23 A. If that answers your question, yes.

24 Q. Okay. I'm going to put in front of you
25 another document.

1 MR. ZIMMERMAN: Whenever you need a break.

2 THE WITNESS: Yeah, I apologize.

3 MR. SCHWARTZ: Need a break?

4 THE WITNESS: Yeah.

5 MR. SCHWARTZ: Of course.

6 THE VIDEOGRAPHER: We're going off the record
7 at 9:31 a.m.

8 (Recess taken from 9:31 a.m. to
9 9:34 a.m.)

10 THE VIDEOGRAPHER: All right. We're back on
11 the record at 9:34 a.m.

12 BY MR. SCHWARTZ:

13 Q. So just to close the loop on -- on -- on that
14 testimony, Dr. Romesberg, you agree that there is in
15 Tsien a description of allyl ethers as part of a group
16 of three tethers, correct?

17 You can look at Tsien if you like.

18 A. No. I'm just -- I want to make sure that I
19 understand the exact words that you used. Could you
20 please repeat the question?

21 Q. You agree that there is in Tsien a description
22 of allyl ethers as part of a group of three tethers?

23 A. As a part of a group of three tethers?

24 Tsien describes using the allyl group as part
25 of a linker. The allyl group has three carbons. Oh,

1 oh, no. You're asking if it's one -- sorry.

2 The allyl group is -- linkers with allyl
3 groups are one of three that he -- that he gives as
4 examples, yes.

5 Q. And he calls them "allyl ethers"?

6 A. Yes.

7 Q. Okay.

8 A. Let me check.

9 Q. Page 28. Line 27.

10 A. Yes.

11 Q. And immediately after his disclosure of the
12 three groups of tethers, he talks about tethers that are
13 ranging in size from 2 to 20, and preferably from about
14 3 to 10 atoms, correct?

15 MR. ZIMMERMAN: Objection. Mischaracterizes
16 the document.

17 BY MR. SCHWARTZ:

18 Q. Does he say that?

19 A. Immediately after --

20 MR. ZIMMERMAN: Wait a minute.

21 Which question are you asking him?

22 MR. SCHWARTZ: You know --

23 MR. ZIMMERMAN: You now have two questions
24 pending, and the first one is different from the second
25 one. I objected as to the first one as to

1 mischaracterizes.

2 Are you withdrawing the first one or asking
3 the second?

4 MR. SCHWARTZ: I'm not withdrawing any
5 questions.

6 MR. ZIMMERMAN: Okay. You have two questions
7 pending, so object as to form. Compound.

8 Which question would you like him to answer?

9 BY MR. SCHWARTZ:

10 Q. I want you to -- you agree that on page 28 of
11 Tsien he describes a group of tethers and includes three
12 different types of groups of tethers, one of which is an
13 allyl ether group of tethers, correct?

14 A. He describes three; one of which has the allyl
15 group as part of the tether, yes, that's correct.

16 Q. Allyl ether. That's what he says.

17 A. Yes.

18 Q. He calls them allyl ethers?

19 A. Yeah.

20 Q. Okay. And on the top of page 29, when he's
21 referring to those tethers that he's referred to on
22 page 28, he says that "the tethers are from about 2 to
23 about 20 and preferably from about 3 to about 10 atoms
24 in length." He writes that, correct?

25 A. With the only correction that he prefaces it

1 by saying "typically," but yes. There's typically
2 tethers, and then -- yes.

3 Q. Okay. Do you have any reason to believe that
4 when he talks about these tethers on the top of page 29
5 he is not referencing the tethers that he refers to on
6 page 28?

7 A. You know, I think as the -- as just a normal
8 reading of this, actually having nothing to do with
9 being a POSA, it would seem that he is giving a group of
10 examples, and then he says, typically they have these
11 characteristics. So, you know, I think the meaning is
12 plain and clear.

13 Q. Okay. I'm going to move on to another
14 exhibit. And I'm going to put in front of you your
15 first declaration in IPR 2018-00797, which was marked as
16 Exhibit 1078.

17 (Exhibit 1078 was previously marked
18 for identification by the Certified
19 Shorthand Reporter.)

20 BY MR. SCHWARTZ:

21 Q. And do you recognize this document to be your
22 first declaration in IPR 2018-00797?

23 A. It certainly appears to be.

24 Q. And please turn to page 95.

25 A. Page 95. I'm there.

1 Q. And please look at paragraph 135. I see it.

2 And in paragraph 135 you write:

3 "Allyl linkers were common in the
4 prior art. For example, Seitz
5 discloses a cleavable allyl linker
6 for attaching a fluorescent Fmoc
7 group (compound 8b) to a molecule
8 having an amine group
9 (beta-Ala-OPac)."

10 Do you see that?

11 A. I do.

12 Q. And that's what you wrote, right?

13 A. That is what is written, yes.

14 Q. And if you'd turn the page, you have some
15 drawings of the allyl linkers in Seitz that you're
16 referring to, correct?

17 A. They are -- they are reproduced from -- from
18 Seitz's paper, that is correct.

19 Q. Okay. And the allyl linkers in Seitz
20 compounds 5 and 8b are not 2-propenyls, correct? They
21 are not the CH² -- you know, the structure that you
22 referred to as allyl; they are not those; is that
23 correct?

24 A. No, that's not really correct.

25 To the extent that they are allyl ethers, they

1 are 2-propynyl [ph] -- 2-propynyl ethers. They are
2 referring to a moiety that is characteristic of this
3 group of linkers.

4 Q. So when you were writing paragraph 135 about
5 the allyl linkers in Seitz, which linkers were you
6 referring to in that picture?

7 A. The ones I call out.

8 Q. Okay. And -- and -- and those are four carbon
9 linkers there, correct?

10 A. Can you show me which one you're referring to?
11 8b?

12 Q. 8b and 5.

13 A. Both of them have -- both of them have many
14 more than four carbons, those linkers. Each of them
15 have the allyl group in it. The allyl group is a C3
16 carbon unit.

17 Q. So why don't you take a red pen and draw a
18 circle around the allyl ether that you are referring to
19 in paragraph 135 from the Seitz drawing.

20 A. So let me -- let me be clear. It is not
21 uncommon to refer to -- the allyl group is a group. You
22 can incorporate it into a larger thing. And you can
23 then describe that larger thing as having that group in
24 it. You want to emphasize that that is an allyl linker.
25 That's a linker with an allyl group in it because it

1 would tell everyone how to cleave it. It would tell
2 everyone why you're using it.

3 So are you asking me to draw a circle around
4 the entire molecule that includes the allyl group, or
5 are you asking me to draw a circle around the allyl
6 group?

7 Q. I'm asking you to draw a circle around the
8 allyl ether linker that you referred to in paragraph 135
9 of your decla -- of your declaration.

10 A. The entire linker containing the allyl group?

11 Q. Dr. Romesberg, you referred to allyl linkers
12 and then you refer to the Seitz paper and you draw some
13 pictures from the Seitz -- from Seitz, correct?

14 A. Yes, that is correct.

15 Q. Okay. Let's look at figure -- at compound 5.
16 There's a bromine, correct?

17 A. There is.

18 Q. Then there's a carbon. There's a carbon,
19 double bond carbon, and there's a carbon attached to the
20 oxygen. Is the carbon, carbon, double bond carbon,
21 carbon, the allyl linker?

22 A. You mean the double bond carbon, carbon,
23 carbon, oxygen?

24 Q. Yes.

25 A. The -- the -- the -- that is the O-allyl

1 portion of the linker.

2 Q. And likewise, in Figure 8b, we have Fmoc
3 attached to an amino acid, attached to an oxygen. And
4 then we have a carbon, carbon, double bond carbon,
5 carbon, oxygen. Is the carbon, carbon, double bond
6 carbon, carbon, oxygen the allyl linker in compound 8b?

7 A. I apologize, but I think you are adding a
8 carbon.

9 Can I just repeat it and you tell me if it's
10 correct?

11 Q. Right.

12 A. You're referring to the carbon, double bond
13 carbon, carbon, oxygen?

14 Q. Yes. Carbon -- there's four carbons in there,
15 correct? One of which is doub -- two of which are
16 double bonded?

17 A. That is correct.

18 Q. Okay. And that's the allyl linker?

19 A. That's part of the allyl linker. That's part
20 of the allyl that's in the linker. Yes. That double
21 bond carbon, yes.

22 Q. And that's what you're referring to when you
23 say "allyl linkers" in paragraph 135?

24 A. Well, this is the source of confusion. I'm
25 referring to some linkers and the allyl is referring to

1 that they are allyl units in the linker. And so I'm
2 simply asking, do you want me to circle the entire
3 linker, which you could call an allyl linker, and I did
4 call an allyl linker, so I'm not trying to ply games, or
5 do you want me to circle the allyl -- formerly the allyl
6 group that is within the linker?

7 **Q. I'm just asking you when you referred to allyl**
8 **linkers on -- in paragraph 135, and you say that they**
9 **are common in the prior art, you refer to a paper by**
10 **Seitz. And you reproduced two compounds, at least, on**
11 **the left side?**

12 A. Yes.

13 **Q. Both of those compounds, the allyl ethers are**
14 **four carbon compounds; is that correct?**

15 A. An allyl group is never four compounds.
16 That's a substituted allyl. Substituted allyls are
17 common as parts of linkers.

18 And so I'm simply asking, would you like me to
19 circle the entire linker or the formerly allyl part?
20 I'm just trying to be clear.

21 **Q. Where are these substituted?**

22 A. Well, there's a -- there's a carbon and a
23 bromine substituted to one end of the allyl in compound
24 5 and --

25 **Q. I'm not talking about the ends of it. I'm**

1 talking about the carbons. There are four carbons in
2 those allyl linkers, correct, that are attached to the
3 oxygen?

4 A. No. There's a carbon that's substituted onto
5 the end of one of the allyl -- of the allyl, and that is
6 also attached to a bromine.

7 Q. There's a bromine. There's a carbon.
8 There's --

9 A. Yes.

10 Q. -- a carbon?

11 A. Yes.

12 Q. There's a carbon?

13 A. Yes.

14 Q. And there's a carbon?

15 A. Yes.

16 Q. And there's an oxygen?

17 A. Yes.

18 Q. There were four carbons?

19 A. You -- yes, there are four carbons there.

20 Q. And on 8b, there's the oxygen that has the --
21 Fmoc amino acid has attached to a carbon?

22 A. Yes.

23 Q. A carbon?

24 A. Yes.

25 Q. A carbon?

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1 A. Yes.

2 Q. And a carbon?

3 A. Yes.

4 Q. Those are four carbons, correct?

5 A. That is correct.

6 Q. And that is the allyl linker?

7 A. It's a sub --

8 MR. ZIMMERMAN: Objection. Mischaracterizes
9 his testimony.

10 A. That is a substituted allyl linker. It is an
11 allyl linker -- it is an allyl group --

12 (Court reporter clarification.)

13 A. I don't know. Let me just repeat.

14 I'm sorry. Could you just repeat the
15 question?

16 Q. The four carbons that we just looked at in
17 each of the structures 8b and 5, they are the allyl
18 linkers that you referred to in paragraph 135 when you
19 say "allyl linkers were common in the prior art"?

20 A. No, that is incorrect. The allyl linkers, as
21 I'm referring to them and as I think Seitz -- Seitz was
22 referring to them, is the entire linker. Embedded in
23 that linker is an allyl group. It has three carbons and
24 an oxygen. If it's an allyl ether, it has three carbons
25 and an oxygen.

1 **Q. And we counted four carbons.**

2 A. Well, that's because you're counting part of
3 the larger linker. I mean by that logic you could say
4 that doesn't an allyl group have a bromine in it because
5 there's a bromine attached to the carbon that you're
6 evoking.

7 **Q. So the term "allyl linker" has a different**
8 **meaning than the term "allyl ether"?**

9 A. No. Allyl is a group. You can incorporate it
10 into anything you want. If you're incorporating it into
11 a linker, it's logical to call it an allyl linker. That
12 doesn't change the fact that it's an allyl group in a
13 linker. And you're sort of -- I guess the reason you
14 would do that is you would emphasize that there's an
15 allyl group in there, so if you wished to cleave it, you
16 know the chemistry.

17 **Q. So allyl linker refers to a genus that**
18 **includes substituted allyls, correct?**

19 A. An allyl linker refers to a genus that
20 includes substituted -- as I've just described it. I've
21 never thought of it that way, but yeah, I guess. An
22 allyl linker could be lots of different things as long
23 as it's being used as a linker, and it has an allyl
24 group in it. Okay. I guess I'm okay with that.

25 **Q. And so when Tsien refers to "allyl ether**

1 linkers" -- remember we looked at Tsien and he said --
2 he called them allyl ether linkers?

3 A. Yeah. Can I --

4 MR. ZIMMERMAN: Objection. Mischaracterizes
5 the document.

6 A. Can I grab that?

7 BY MR. SCHWARTZ:

8 Q. He calls them allyl ether tethers.

9 MR. ZIMMERMAN: Just -- objection.

10 BY MR. SCHWARTZ:

11 Q. Is that the same as --

12 MR. ZIMMERMAN: Mischaracterizes the document.

13 A. I would like -- I would like to see it just
14 because I don't want to say something incorrect.

15 And this is page 28 of Tsien; is that right?

16 BY MR. SCHWARTZ:

17 Q. Uh-huh.

18 A. So where is the specific sentence you're
19 referring to?

20 Q. Line 28 on page 28.

21 A. And please repeat the question.

22 Q. When Tsien refers to allyl ether linkers or
23 tethers, whatever word you want to use, he's referring
24 to the three carbon linker? Is that what you're saying?

25 MR. ZIMMERMAN: Objection. Mischaracterizes

1 the document.

2 A. No. He's referring to a group of linkers
3 and -- that all have the allyl group in it, so he's sort
4 of telling you how to cleave them.

5 BY MR. SCHWARTZ:

6 Q. In terms of nomenclature, though, he is
7 referring, then, to a genus of allyl ether linkers; is
8 that what you're saying?

9 A. I guess you could say that he's referring
10 to -- he's being nondescript. He's not describing what
11 the exact linker is. He's telling you that whatever it
12 is he's -- he's teaching you that you should have an
13 allyl group in it. And obviously the reason he's doing
14 that is he wants to be able to cleave it.

15 Do you want your red pen back? Actually, I
16 really like these kind of pens.

17 Q. I'll give it to you at the end of the depo.

18 Okay. I'm ready to mark a new exhibit. And
19 I'm going to put in front of you the Gigg & Warren
20 paper, which was marked as Exhibit 1046.

21 (Exhibit 1046 was previously marked
22 for identification by the Certified
23 Shorthand Reporter.)

24 BY MR. SCHWARTZ:

25 Q. And do you recognize this document to be the

1 Gigg & Warren paper you referred to in your declarations
2 in this case?

3 A. I do.

4 Q. And please turn to page 1968 -- 9 -- 1908 is
5 it? I'm sorry. I know it's confusing because they have
6 the date up there. It's 1904 on the left side.

7 And do you see on the left side there's a
8 reaction scheme?

9 A. The one labeled (1)?

10 Q. Yes.

11 A. Yes, I see that.

12 Q. And Gigg & Warren uses mercury (II) to cleave
13 vinyl ethers, correct?

14 A. I believe that's right, yes.

15 Q. And Gigg & Warren does not use mercury (II) to
16 cleave allyl ethers, correct?

17 A. I believe that he does.

18 Q. Can you point me to where he does?

19 A. This will take a minute to find. Well, I mean
20 I can just -- I mean, I haven't read this -- I mean, I'm
21 sure I've read this document. I haven't -- I mean, I've
22 read lots of them, so just looking at it now, and I'm
23 certainly not saying this is the best example of it, but
24 it's the first -- one of the first ones that I came
25 across. He's talking about in the very opening sentence

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1 we have previously described the application of the
2 allyl ethers as a protecting group in carbohydrate
3 chemistry. And then he says:

4 "The allyl group is conveniently removed by
5 isomerization" --

6 (Court reporter clarification.)

7 A. Sorry.

8 [As read.]

9 "The allyl group is conveniently
10 removed by isomerization to the
11 cis-prop-1-enyl group and subsequent
12 ... hydrolysis."

13 So he's talking about removing allyl groups.

14 Q. Right. But on -- on -- on the structure (1)
15 that he draws, the first step you said is isomerization.
16 That's an isomerization of a vinyl with mercury (II),
17 correct?

18 A. Isomerization to a vinyl?

19 Q. No. Isomerization of the vinyl, correct?

20 A. In scheme (1)?

21 Q. Yes.

22 A. No. He's just showing cleavage.

23 Q. Oh, cleavage of the -- of the vinyl with an
24 ether -- with a mercury?

25 A. Yeah. Because he's saying the isomerizes the

1 allyl to a vinyl, and then he's -- in that particular
2 scheme he's showing cleavage of that vinyl.

3 Q. So in -- in this paper, the only place that
4 you can point to me where he actually discloses using
5 mercury (II) in a reaction is the reaction of vinyl with
6 mercury (II)?

7 MR. ZIMMERMAN: Objection. Mischaracterizes
8 his testimony and the document.

9 A. So to be clear, he's referring to cleavage.
10 Let me read this, because he's probably expressly
11 calling this cleavage.

12 He's talking about allyl ethers with mercuric
13 chloride and the presence of mercuric oxide. And then
14 he's citing some previous workers that showed cleavage
15 of the vinyl group with mercury.

16 Q. But he is showing in -- in equation one a
17 vinyl cleavage with mercury?

18 A. He is -- he is showing a cleave -- he is
19 showing -- he is showing one step of the allyl
20 deprotection. And he's showing the cleavage step, and
21 that is with vinyl. But it's -- he's clear that he's
22 talking about the allyl group by isomerizing to it.
23 But, you know, you are correct in that it would
24 cleave -- these conditions would cleave a vinyl group
25 that was prepared by another means as well.

1 Q. So the cleavage that he shows in equation one
2 is cleavage of the vinyl?

3 A. Yes. But he's showing lots of examples, lots
4 of compounds that are allyl groups that are reacting
5 with mercury that are -- that are deprotecting. For
6 example, look at all the compounds that are on the
7 right-hand side of that page.

8 Q. Right.

9 A. Some of them are allyls.

10 Q. Some of them are the -- what you referred to
11 as an allyl. That's what you're referring to in that
12 specific structure?

13 A. I'm referring to them the way IUPAC does.

14 Q. Okay. And can you point to me where -- in
15 those structures, in this paper, where he shows that he
16 is cleaving them with something other than a vinyl --
17 other than with the mercury using the vinyl?

18 A. It goes through a vinyl.

19 MR. ZIMMERMAN: Object as to form.

20 BY MR. SCHWARTZ:

21 Q. That was a confusing question. Okay. Okay.
22 I'm trying to -- you're pointing me to
23 structures on the right side.

24 And can you point to me anywhere where he is
25 actually cleaving those three carbon allyls with

1 **anything other than mercury?**

2 A. I'd have to look through this, but I think
3 cleaving them with mercury was his point. I think. I'd
4 have to look to see if he talks about any other cleavage
5 mechanisms, but my recollection is that this paper was
6 about mer -- cleavage with mercury.

7 Q. Okay. But that's with the vinyl. With the --
8 with the allyls, what you're calling the allyls, the
9 three carbon groups, he doesn't show that he's cleaving
10 them with mercury?

11 MR. ZIMMERMAN: Objection. Mischaracterizes
12 the document.

13 A. I believe he does. He doesn't draw them out
14 in scheme (1) because that vinyl group came from an
15 allyl group.

16 So -- so a lot of things happened in situ.
17 They happen during the reaction. Multiple steps. You
18 can draw one of them. That doesn't mean that -- if you
19 go from A to D spontaneously in a reaction, you can draw
20 a step from C to D to talk about it because maybe you
21 think it's interesting, but that still doesn't change
22 the fact that the reaction converted from A to D.

23 BY MR. SCHWARTZ:

24 Q. Okay. I understand you're going through a
25 reaction scheme. But I'm asking you specifically, as

1 taught by Gigg & Warren, when he refers to using mercury
2 (II), he is using mercury (II) to cleave the vinyl. And
3 then I understand you're saying that that vinyl then
4 goes through additional steps and you end up with --

5 A. No. The vinyl came from the allyl. So the
6 additional steps I'm --

7 Q. Okay.

8 A. -- referring to were in the front.

9 Q. So there were additional steps in the front,
10 but when he actually uses mercury (II), he's cleaving a
11 vinyl?

12 A. Yes.

13 Q. Okay. You can put that away.

14 I'd like you to go back to Tsien.

15 Exhibit 1013. And please turn to page 20.

16 A. I'm there.

17 Q. And please look at line 17.

18 A. I'm there.

19 Q. And Tsien writes:

20 "In addition, to force the
21 reaction, especially with
22 derivatized dNTPs, it may often be
23 helpful to use substantial excesses
24 (over stoichiometry) of the dNTPs or
25 to modify other conditions such as

1 the salt concentration."

2 That is what Tsien writes, correct?

3 A. That's correct.

4 Q. And the "substantial excess" Tsien is
5 referring to here is an excess of the modified dNTPs
6 over the DNA primer template, correct?

7 A. He doesn't say that, but I think a POSA would
8 have assumed that. He said "over stoichiometry," which
9 is a little bit of a weird language. But I think a POSA
10 would have interpreted -- technically, he could have
11 been thinking about relative to the polymerase as well.

12 So I think he's just talking about an excess
13 of dN -- of those dNTPs. He's not explicitly saying
14 whether he refers to it as a ratio to the -- to the
15 concentration of the polymerase stoichiometry or to the
16 concentration of the primer template. But he's talking
17 about in excess of a -- an increase in concentration of
18 the dNTP.

19 Q. Is it reasonable to -- to understand that he
20 might -- is referring to an excess over the primer
21 template?

22 A. Is it reasonable?

23 What he's -- to achieve what he's suggesting,
24 you would not have to have that. What you would have to
25 have is an excess relative to the primer template bound

1 to the polymerase. So if you've got -- it's -- it's
2 very common to add excess primer template to a
3 polymerase and then add triphosphate. The triphosphate
4 doesn't bind the primer template. So its ratio doesn't
5 actually matter. They don't interact in the absence of
6 the polymerase.

7 When the primer template binds to the
8 polymerase, that now has affinity and provides an
9 opportunity for the triphosphate to bind. So it's
10 really relative to that complex that it makes sense.

11 Q. Okay. But when he's talking about it might be
12 helpful to use substantial excesses of the dNTPs, one
13 excess that he is referring to could be excess over the
14 primer template, for example, correct?

15 MR. ZIMMERMAN: Objection. Mischaracterizes
16 the document.

17 BY MR. SCHWARTZ:

18 Q. I mean, you said --

19 MR. ZIMMERMAN: Calls for speculation.

20 BY MR. SCHWARTZ:

21 Q. -- that originally.

22 MR. ZIMMERMAN: Calls for speculation.

23 MR. SCHWARTZ: Okay.

24 A. Look, the only -- what he is suggesting is a
25 mechanism to increase the efficiency of incorporation.

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1 BY MR. SCHWARTZ:

2 Q. Uh-huh.

3 A. The only metric that matters there, in terms
4 of excess, is relative to the primer template complex
5 bound to the polymerase. I -- I -- I -- let me answer
6 this question in two ways. Let me answer what my
7 opinion is, and then let me take a second to think about
8 exactly what he was thinking. Is that okay? To
9 describe exactly what his words say, to say -- I mean,
10 I'm trying to think through this.

11 So let me first tell you what I think is real
12 or correct or physically reasonable, and then let me
13 tell you what he seems to be saying and make sure -- and
14 maybe they are the same thing.

15 Is that okay?

16 Q. Well, I think you answered my question. You
17 said that it was reasonable that he was talking about an
18 excess of the dNTP over the primer template bound to the
19 polymerase.

20 A. Well, reasonable --

21 Q. Maybe I'm using a word that confuses you,
22 "reasonable." Is a -- when a POSA reads that, would
23 they understand that he is referring to an excess of the
24 dNTP, the modified dNTP, over the primer template bound
25 to the polymerase?

1 A. Oh, bound to the polymerase. That makes
2 absolute sense. I think a POSA would have understood
3 that -- that to achieve what -- what -- what Tsien is
4 suggesting, you would look at the concentration of
5 the -- the stoichiometry -- the excess stoichiometry that
6 he's referring to, to make sense, would be relative to
7 the polymerase bound to the primer template. I believe
8 that's correct.

9 Q. Okay. And is 1,000 -- strike that.
10 Is a hundredfold, in your opinion, a
11 substantial excess?

12 A. It -- I -- I -- in this context, what excess
13 is being used for is for an efficiency. I'd have to
14 know exactly what deficiency challenge that you're
15 trying to overcome with that excess is.

16 If you have something that's -- if you're
17 trying to increase the efficiency something, only
18 marginally, only need a little, then you need less
19 excess. If you're having to increase it a lot, then you
20 would need more excess. So I can't answer that question
21 in the absence of knowing what you're trying to do.

22 Q. Well, when he talks about forcing the reaction
23 by having an excess of the modified dNTPs over the
24 primer template bound to the polymerase, in your
25 opinion, would a hundredfold excess of modified dNTPs be

1 **a substantial excess, in Tsien's words?**

2 MR. ZIMMERMAN: Objection. Incomplete
3 hypothetical.

4 A. I can't really answer that. It's an excess.
5 It's a ratio that's greater than one to one.
6 "Substantial" is a relative term. And so it depends on
7 what you're trying to -- people are trying -- what Tsien
8 is suggesting that you do is if you want to increase the
9 efficiency of incorporation of your modified
10 triphosphate, add more of it. That's a totally
11 reasonable thing to do. It's based on something called
12 entropy. The more you add --

13 (Court reporter clarification.)

14 A. Entropy. The more you add, the more complex
15 you'll find, form. And you form that complex. That's
16 what reacts, and that's what you're trying to do.

17 So it depends on a good bit on what the
18 affinity is. If the affinity that you're having -- if
19 you have very low affinity, you would have to add more
20 excess. So what substantial would be changes in that
21 case.

22 BY MR. SCHWARTZ:

23 Q. So a POSA reading this section of Tsien, would
24 they have an understanding of what Tsien meant when he
25 talked a "substantial excess" of the modified dNTPs?

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1 A. Yeah. I think -- I think they would have -- I
2 think they would have intuitively understood that. They
3 would not known -- they would have had to known for --
4 they would have had to know the particular application
5 and the details of what -- of -- of the triphosphate
6 they were using in order to put -- to make that a more
7 quantitative understanding. But they certainly would
8 have qualitatively understood what he was saying.

9 Q. Okay. And this -- and this is in reference to
10 Tsien's SBS's methods, correct?

11 A. It's in his SBS.

12 Q. Okay.

13 A. Yeah.

14 Q. So what would a POSA consider to be a
15 substantial excess of the modified dNTPs over the primer
16 template polymerase complex?

17 MR. ZIMMERMAN: Objection. Asked and
18 answered.

19 MR. SCHWARTZ: Well, I don't believe he has
20 answered that question.

21 MR. ZIMMERMAN: He's answered it twice now.
22 BY MR. SCHWARTZ:

23 Q. Would a person understand what Tsien was
24 saying when he said "substantial excess"?

25 MR. ZIMMERMAN: Objection. Asked and

1 answered.

2 BY MR. SCHWARTZ:

3 Q. Would he? Would they? Would a POSA
4 understand what Tsien meant by "a substantial excess"?

5 A. Not --

6 MR. ZIMMERMAN: Same objection.

7 A. Not quantity.

8 MR. SCHWARTZ: You're cutting him off. Yeah.

9 A. Not quantitatively.

10 BY MR. SCHWARTZ:

11 Q. So they wouldn't know what that number would
12 be?

13 A. Precisely what that number would be? What
14 would represent "a substantial excess"?

15 Q. Correct. That's my question.

16 MR. ZIMMERMAN: Incomplete hypothetical.

17 A. We're mincing what "substantial" means.

18 When I read this, and you're asking me about
19 what Tsien meant, what he means is that you can go to a
20 substantial excess to favor incorporation of the
21 triphosphate. I think a POSA would have read that as
22 being able to increase the concentration sufficiently to
23 get the triphosphate to incorporate. You can't
24 infinitely increase it.

25 So I would have to know what the

1 concentrations were, and I would have to know how much
2 of a defect -- how much of a defect in binding you are
3 having to overcome in order to -- to gauge -- to put
4 some more qualitative answer to that.

5 BY MR. SCHWARTZ:

6 Q. Okay. So in reference to Tsien's SBS methods,
7 when Tsien teaches this to use a substantial excess,
8 what would a POSA understand to be "a substantial
9 excess"?

10 Would they understand it to be a one-to-one
11 excess? Would they understand it to be a fivefold
12 excess? Would they understand it to be a tenfold
13 excess? Or would they have no understanding about the
14 excess?

15 I'm trying to understand what your
16 understanding of this phrase is.

17 MR. ZIMMERMAN: Please wait. Objection.
18 Asked and answered three times now. Objection,
19 incomplete hypothetical.

20 You can go ahead and answer.

21 A. I'll try to answer this, but honestly, I feel
22 like I have.

23 BY MR. SCHWARTZ:

24 Q. And this is in context of Tsien's SBS methods,
25 okay. So this is not a hypothetical. He's making this

1 statement in context of his SBS methods. Are you
2 correct -- you agree with that?

3 A. I do.

4 Q. Okay. All right. So in the context of what
5 he's saying about his SBS method, and he's referring to
6 "a substantial excess" of the modified dNTP, what does a
7 POSA understand that to be in the context of Tsien's SBS
8 method?

9 MR. ZIMMERMAN: And just so we're clear,
10 objection. Incomplete hypothetical. You keep trying to
11 make it the whole method. You haven't given him the
12 specific pieces at issue, so that's why it's an
13 incomplete hypothetical. And he's told you it differs
14 based on what the scheme is.

15 MR. SCHWARTZ: All right. You have to stop
16 that, Bill. You can't be testifying for him, please.

17 MR. ZIMMERMAN: The fact that you don't like
18 his answer when he's given it three times is not my
19 fault.

20 BY MR. SCHWARTZ:

21 Q. Do you understand my question, Dr. Romesberg?

22 MR. ZIMMERMAN: Objection. Asked and
23 answered.

24 A. To be honest, kinda. What "substantial"
25 means, there will be limitations on it. Could you go to

1 10-molar triphosphate? That would be substantial. But
2 you certainly couldn't achieve that.

3 Frankly, 1 micromolar could be substantial if
4 your concentration of your primer template were
5 picomolar. That would be an excess. So -- "an excess"
6 is a relative term, so "substantial excess" is a
7 relative term. I don't know what it's an excess to.

8 BY MR. SCHWARTZ:

9 Q. We just talked about that. And you told me
10 that your understanding of it was an excess to the
11 primer template polymerase complex?

12 A. Yes. So tell me what the concentration of the
13 primer template complex is.

14 Q. Let's take that as a 1. Let's say that the
15 primer template complex is a 1.

16 A. Okay.

17 Q. What would be the "substantial excess" that
18 Tsien is referring to?

19 A. What's the affinity of the triphosphate in
20 question for the polymerase complete complex?

21 (Court reporter clarification.)

22 A. Affinity. The triphosphate in question for
23 the polymerase complete complex.

24 Q. Tsien doesn't say. So would a person not
25 understand what Tsien is referring to if Tsien doesn't

1 **say that?**

2 A. No. I believe that a person of ordinary skill
3 in the art would have known it depends on -- on the
4 specific triphosphate you're talking about. Tsien is
5 giving a general statement -- point about any
6 triphosphate.

7 **Q. Okay. And then what would a POSA understand**
8 **about Tsien's statement about a general triphosphate?**

9 MR. ZIMMERMAN: Objection. Asked and
10 answered.

11 A. The more triphosphate you add, the -- you --
12 like -- it's likely that you'll get better
13 incorporation. That's all Tsien is saying. They are
14 trying to suss out what "substantial excess" means in a
15 quantitative sense isn't in this statement, so there's
16 nothing that -- I can't provide you any more detail
17 other than qualitatively what he's saying is that if you
18 increase the triphosphate concentration, you're likely
19 to increase the rate of insertion.

20 **Q. And again, I'm asking you if you had a**
21 **hundredfold excess of your modified dNTP over your**
22 **stoichiometry of your primer template polymerase**
23 **complex, would a POSA understand that that is of**
24 **substantial excess as taught by Tsien?**

25 MR. ZIMMERMAN: Objection. Incomplete

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1 hypothetical.

2 A. It all depends on what you're -- what your
3 definition of "substantial" means. And that is --
4 intuitively what that comes from is how much you need to
5 bind. So if you only need a little bit to bind, then
6 frankly tenfold is a substantial excess. If you need a
7 lot to bind because it's a weak binder, then a
8 hundredfold might not be a substantial excess.

9 So it's just -- it's just impossible to take
10 what Tsien is writing as a qualitative guide that any
11 POSA frankly would have known. You increase the
12 concentration, you increase the incorporation rate
13 probably. It's just not -- I don't feel comfortable
14 putting a more quantitative statement on it past what
15 I've tried to explain.

16 BY MR. SCHWARTZ:

17 Q. And that would be true for a POSA reading this
18 statement in Tsien? Is that also -- is that correct?
19 Is that what you're saying?

20 A. I think a POSA would have known that there was
21 a limit at the high end that you wouldn't want to go to.
22 But where exactly, what would represent a functional of
23 substantial, a sufficient excess, he would have to know
24 the particular polymerase, the particular primer
25 template. He would have to know what the -- the ability

1 of the triphosphate in question to bind that complex.

2 Q. Okay. So with all of the caveats that you're
3 saying a person would understand when they read this
4 portion of Tsien, the POSA would not be able to
5 quantitatively determine what Tsien meant by a
6 "substantial excess."

7 Is that your testimony?

8 MR. ZIMMERMAN: Objection. Mischaracterizes
9 the testimony.

10 A. A POSA would have known -- a POSA would have
11 understood that Tsien was teaching that -- if your -- if
12 your incorporation efficiencies weren't sufficient, he's
13 teaching you to increase the concentration. He's saying
14 that you can increase it a lot. What "a lot" means
15 depends on the specifics of the situation.

16 BY MR. SCHWARTZ:

17 Q. But he uses a specific term, "substantial
18 excess," right?

19 A. Yeah. And I switched that to "a lot," because
20 I think that is what he's saying. And -- because they
21 are both sort of the same quantitative --

22 Q. And I'm asking you, then, what is "a lot"?
23 What is "a lot" in terms of if we set as 1 the
24 stoichiometry of the primer template polymerase complex,
25 when you set that as 1, what is a lot excess --

1 MR. ZIMMERMAN: Objection.

2 BY MR. SCHWARTZ:

3 Q. -- in your opinion?

4 MR. ZIMMERMAN: Objection. Asked and
5 answered. Incomplete hypothetical.

6 A. It depends -- it depends on how much is
7 needed.

8 BY MR. SCHWARTZ:

9 Q. And a POSA reading this would understand that
10 it depends on what is needed?

11 A. Yeah, I think so.

12 Q. And so they wouldn't be able to come to any
13 understanding of how much Tsien said when he said
14 "substantial excess"; is that your testimony?

15 A. No.

16 MR. ZIMMERMAN: Objection. Mischaracterizes
17 the testimony.

18 A. It is not that they would have had no
19 understanding. I want to say --

20 BY MR. SCHWARTZ:

21 Q. Quantitatively, I asked you.

22 A. Quantitatively would they have been able to
23 say, oh, 96-fold? No, they would not have been able to
24 say that. They would not have been able to say
25 218-fold.

1 Q. Would they have been able to say fivefold?

2 A. They would have known fivefold is different
3 than a hundredfold. But no, they would not have been
4 able to say fivefold.

5 Q. Okay. Let's move on.

6 MR. SCHWARTZ: Why don't we take a short
7 break, because I have been going for more than an hour.

8 THE VIDEOGRAPHER: All right. We're going off
9 the record at 10:14 a.m.

10 (Recess taken from 10:14 a.m. to
11 10:27 a.m.)

12 THE VIDEOGRAPHER: We're back on the record at
13 10:27 a.m.

14 BY MR. SCHWARTZ:

15 Q. Dr. Romesberg, if you would take a look at
16 page 38 of Tsien. And if you would look at Example 4.
17 And in Example 4 of Tsien, Tsien gives an embodiment of
18 his SBS method.

19 Do you see that?

20 A. Example 4?

21 Q. Yes.

22 A. I do.

23 Q. Okay. And in the context of Example 4, he
24 talks about using 30 micromolars of the fluorescently
25 labeled 3'-blocked dNTP.

1 Do you see that?

2 A. Oh, let me read it, please.

3 That seems to be correct, yes.

4 Q. Okay. So in the context of what Tsien is
5 teaching in Example 4, would you be able to determine
6 what Tsien means by "substantial excess" of
7 stoichiometry of the modified nucleotide in the portion
8 of Tsien we were looking at?

9 A. I would be able to give you slightly more
10 clarity on it but -- but still not in any quantitative
11 sense, no. I would able to give you a little bit more
12 clarity on it, because I think he gives the
13 concentration of a lot of other things. He gives the
14 concentration of the natural triphosphates.

15 I'm looking to see if he gives a concentration
16 of the polymerase and the template -- on the primer
17 template. If he does, could you point me to that, or do
18 you want me to -- single strand -- proximally.

19 So the single-stranded primed subject DNA is
20 present at 0.1 molar. I don't see a concentration of a
21 polymerase being used. Regardless, that's slightly more
22 clarity, because at least I could now tell you what the
23 ratio of the triphosphate to the DNA primer is. But as
24 we've discussed before, that's not particularly
25 relevant.

1 What would be relevant would be the ratio of
2 the triphosphate to the primer template polymerase
3 complex gauged adjusted for how high -- what the
4 affinity of primer template polymerase complex was for
5 the triphosphate in question.

6 Q. Okay. And so can you put more granularity,
7 then, on when Tsien talks about a substantial excess of
8 the modified nucleotide? Can you -- looking at Example
9 4, does that -- does that help you?

10 A. Not --

11 MR. ZIMMERMAN: Objection. Asked and
12 answered.

13 A. Not particularly. Again, the -- the critical
14 thing is missing is how much -- it's not clear to me
15 that in this example he's trying to overcome low
16 efficiency. So I'm not -- I'm not sure what the
17 relationship of this example is to that couple of
18 sentences that we talked about that are earlier.

19 What the subject matter of those couple
20 sentences were, was he's telling a reader that if your
21 triphosphates are not incorporated with sufficient
22 deficiency for whatever your application is, add more
23 triphosphate. You could go up to a lot. I couldn't put
24 more granularity on what "a lot" meant there,
25 substituting "a lot" for "sufficient excess." And I

1 can't give you much more here, because I don't know what
2 you're trying -- I don't -- it's not even clear.

3 He's using this as a concentration to overcome
4 an efficiency that wasn't sufficient for an application.
5 And if -- even if he is, I don't know what the affinity
6 of the triphosphate for the polymerase complex is, so I
7 can't gauge whether that would be a lot or not.

8 BY MR. SCHWARTZ:

9 Q. So is it possible that in Example 4, when
10 Tsien talks about 30 micromolar of the fluorescently
11 labeled 3'-modified nucleotide, that he's taking into
12 account the substantial excess that he's referring to
13 earlier?

14 A. I don't know that -- I'd have to read to see
15 if he says he's taking that into account. But I
16 don't -- I don't see that he says that he's taking that
17 into account. I see this as an example of a set of
18 concentrations that he's using as an example.

19 I don't -- I don't see from looking at it at
20 this instant that it's an example to overcome poor
21 triphosphate insertion, insufficient for whatever
22 application he's -- a POSA might be interested in. I
23 don't know if he's using this to illustrate the use to
24 increase incorporation efficiency. I don't see that he
25 says that anywhere. This seems to be an example.

1 Q. Is one reasonable interpretation of Example 4
2 is that he is taking that into account?

3 A. He just doesn't address it.

4 Q. So a POSA, when they read this, they couldn't
5 understand that he's taking that into account?

6 A. They couldn't?

7 MR. ZIMMERMAN: Objection. Mischaracterizes
8 the document.

9 MR. SCHWARTZ: I'm also going to -- you know,
10 I'm going to ask you to not jerk your head around a lot
11 when I -- when I ask questions because you're just --
12 you're coaching your witness every imaginable way. So
13 please --

14 MR. ZIMMERMAN: I haven't coached the witness
15 once today.

16 MR. SCHWARTZ: You know --

17 MR. ZIMMERMAN: You don't like his answers, so
18 you're asking the questions multiple times.

19 MR. SCHWARTZ: I'm not getting the answers
20 that I'm asking, and I would appreciate if you
21 wouldn't --

22 MR. ZIMMERMAN: He is giving you answers.

23 MR. SCHWARTZ: I'm just -- I'm just asking
24 you, please, Bill, don't jerk around like you're on a,
25 you know, hot seat or something.

1 BY MR. SCHWARTZ:

2 Q. Dr. Romesberg, you can continue, please.

3 A. Could you please repeat the question?

4 Q. Is one reasonable interpretation of Example 4
5 in Tsien is that the concentrations of the nucleotides
6 that he provides takes into account his earlier
7 suggestion to use an excess of modified nucleotides?

8 MR. ZIMMERMAN: Objection. Asked and
9 answered.

10 A. I -- I find that a difficult question to
11 answer, because he doesn't -- there's no -- there's no
12 clarification on what this -- whether -- there's no
13 indication at all that this is being used as a
14 mechanism -- if this is being used in relation to that
15 statement about increasing triphosphate concentration.
16 There's a lot in this application that would not,
17 according to -- to -- to Tsien in what I believe he's
18 writing, that would not require you to do that.

19 I don't see that this is referring -- I don't
20 see that he -- I don't see any reason that I would have
21 associated this with that same statement.

22 BY MR. SCHWARTZ:

23 Q. And again, if he is referring to using 30
24 micromolars of the labeled capped nucleotide here, would
25 a hundredfold concentration excess be a substantial

1 **excess that he's teaching?**

2 MR. ZIMMERMAN: Objection. Incomplete
3 hypothetical. Asked and answered.

4 A. For the same reason that we discussed when you
5 were asking me about it in the context of the other part
6 of the patent, I -- I -- I don't know. He's not giving
7 the triphosphate affinity. And as we talked about
8 there, I would not feel comfortable answering that
9 question without knowing that. He's simply giving you a
10 concentration. I don't know what the affinity would be.

11 BY MR. SCHWARTZ:

12 Q. So there -- if Tsien doesn't provide that
13 information in his application, then a POSA reading his
14 suggestion to use a substantial excess without all the
15 information you say a POSA would need to understand
16 quantitatively what that would mean, if Tsien doesn't
17 provide that information, a reader wouldn't understand
18 what "a substantial excess" means in Tsien; is that
19 right?

20 A. I think a reader would have understood that
21 Tsien in that former section that we were talking about
22 was suggesting that insufficient incorporation
23 efficiencies could be in some cases dealt with by
24 increasing the triphosphate concentration. I don't
25 think there would have been -- I don't think Tsien

1 intended anything more quantitative in that. I think by
2 "substantial excess" he simply was saying you could
3 increase it substantially. I don't think he intended to
4 make it quantitative. And I don't think a POSA would
5 have read anything more quantitative than what I just
6 described into it.

7 Q. Okay. Let's move on. I'm going to mark
8 another exhibit. I'm going to put in front of you U.S.
9 Patent No. 5,808,045 to Hiatt and Rose. That is marked
10 as Exhibit 1106.

11 (Exhibit 1106 was previously marked
12 for identification by the Certified
13 Shorthand Reporter.)

14 BY MR. SCHWARTZ:

15 Q. And this is an exhibit offered by Illumina in
16 these proceedings.

17 Please look at the title of the patent. And
18 the title reads "Compositions For Enzyme Catalyzed
19 Template-Independent Creation of Phosphodiester Bonds
20 Using Protected Nucleotides."

21 Do you see that?

22 A. I do.

23 Q. And please turn to Column 1 where there is a
24 heading entitled "Technical Field."

25 Do you see that?

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1 A. Can I ask -- I don't recall seeing this. Have
2 I seen this?

3 Is this in my -- is this in my list of
4 Material Review?

5 **Q. You can check.**

6 **Have you seen this? You don't remember.**

7 A. I saw a lot of papers, and I could -- I could
8 take a few minutes to see if -- if it jogs my memory.
9 At this exact moment, it does not, so I would like to do
10 exactly as you just recommended. 1106.

11 Yes. I appear to not have seen this. I
12 appear to not have used this in my dec so ...

13 **Q. So you have not seen this?**

14 A. I don't at this moment recall seeing it, but
15 again, over the past year or so, I've read a lot of --
16 I've read a lot of these. At the moment, I do not
17 recall seeing it.

18 **Q. Okay. So again, we were at the section called**
19 **"Technical Field."**

20 MR. ZIMMERMAN: I'm going to object as outside
21 the scope of his declaration.

22 MR. SCHWARTZ: This is -- this is a document
23 that was marked by Illumina.

24 MR. ZIMMERMAN: Yes, but it's not within his
25 declaration. He's testified that he hasn't seen it.

1 It's not on his list of Materials Considered. I'm
2 objecting as outside the scope of his declaration, which
3 is the proper scope for this deposition.

4 BY MR. SCHWARTZ:

5 Q. Do you see where it says "Technical Field"?

6 A. No. Could you tell me what column?

7 Q. One.

8 A. Column 1. Yes.

9 Q. Okay. And the patents reads:

10 "This invention relates to the
11 synthesis of oligonucleotides and
12 other nucleic acid polymers using
13 template independent enzymes."

14 That's what is written, correct?

15 A. That is what is written. Yes, correct.

16 Q. And please turn to Column 3. At the bottom of
17 Column 3 there's a heading entitled "Summary of the
18 Invention." Do you see that?

19 MR. ZIMMERMAN: Can I have a standing
20 objection to questions on this document as outside the
21 scope?

22 MR. SCHWARTZ: Sure.

23 A. Summary of the Invention, yes, I see that.

24 BY MR. SCHWARTZ:

25 Q. Okay. And the summary Of the Invention reads:

1 "A number of methods have been
2 discovered by which the 3'-hydroxyl
3 group of a deoxynucleotide
4 triphosphate can be effectively
5 protected and deprotected and
6 wherein the protected nucleotide is
7 utilized by a template-independent
8 polymerase to create a
9 phosphodiester bond permitting the
10 synthesis of oligonucleotides or
11 polynucleotides having a desired
12 predetermined sequence."

13 That's what's written, correct?

14 A. I read that along with you.

15 Q. Okay. So Exhibit 1106 relates to synthesizing
16 single-stranded polynucleotides, correct?

17 A. I have not read this document. The part that
18 you just read was about -- well, it's what the words
19 say, so 3 hydroxyl -- a number of methods have been
20 discovered, hydroxyl group. Wow. I'm just going to
21 read that to myself.

22 MR. ZIMMERMAN: And I will object as outside
23 the scope and calling for speculation.

24 A. It does not say single-stranded. It's a
25 template-independent polymerase. Single-stranded jumps

1 to mind there. But again, I have not read this.

2 BY MR. SCHWARTZ:

3 Q. Well, we just read that the patent said this
4 invention relates to the synthesis of oligonucleotides
5 and other nucleic acid polymers. Those are
6 single-stranded molecules; is that correct?

7 MR. ZIMMERMAN: Hold on. Objection. Outside
8 the scope. Calls for speculation. Lacks foundation.

9 You can answer to the extent you can.

10 A. I -- oligonucleotides, no. I think people
11 refer to duplex DNA as an oligonucleotide.

12 BY MR. SCHWARTZ:

13 Q. And would you use a template-independent
14 polymerase to make --

15 A. Well, that's why I said that using -- the fact
16 that they are using a template-independent polymerase
17 brings that to mind. I don't see that it's written
18 there. But it's certainly suggestive. I don't know if
19 it -- I haven't read this document, so I -- I don't know
20 if that's what they are suggesting, but it certainly
21 comes to mind.

22 Q. And DNA sequencing, whether it be Sanger or
23 SBS, requires a template-dependent polymerase, correct?

24 A. Sanger sequencing or sequencing by synthesis
25 requires a template-dependent polymerase.

1 Q. We can move -- sorry.

2 A. Certainly -- certainly in the versions that
3 we're talking about, I cannot immediately think of a
4 case -- could you repeat the question?

5 Is the question, does sequencing by synthesis
6 require a template-dependent polymerase?

7 Q. Yes. In the context that we are referring to
8 in these proceedings.

9 A. In the context of Tsien and the Ju patent, the
10 Dower patent -- you know, the problem is, is that it's
11 certainly an application that is certainly a use. And
12 that is certainly the use that I've spent a lot of time
13 thinking about.

14 Whether or not there's a template-independent
15 application in there, I'm not comfortable saying. I
16 would have to go back and look at them. But certainly
17 the sort of meat of what I've been testifying in my
18 declaration, what I wrote about in my declaration, and
19 what I've thought about has been the use of a
20 template-directed polymerase.

21 I'm not -- I've got to say I'm not sure that
22 they didn't talk about -- I mean, there's lots of
23 possible ways that you could sequence, and I'm not
24 comfortable without looking at them specifically to
25 address whether they talk about other -- there might be

1 a paragraph that says, by the way, you could do this.
2 And I didn't look for that. And so at the -- at the
3 moment, I cannot --

4 Q. When we talk about Tsien's SBS methods and we
5 talk about Dower's SBS's methods and we talk about Ju's
6 patents SBS methods, they require a template-dependent
7 polymerase, correct?

8 A. What I am talking about and what I'm
9 testifying about and what I'm writing in my declaration
10 about and what I've thought about has all been with a
11 template-directed polymerase.

12 Q. Okay. You can put that away.

13 I'm putting in front of you a document
14 entitled "Protective Groups in Organic Synthesis" by
15 Greene & Wutz, which was marked as Exhibit 1101.

16 (Exhibit 1101 was previously marked
17 for identification by the Certified
18 Shorthand Reporter.)

19 BY MR. SCHWARTZ:

20 Q. Have you seen this exhibit before?

21 A. Yes, I have.

22 Q. Please turn to page 67 where there's a header
23 entitled "Allyl Ether (Allyl-OR.)"

24 Do you see that?

25 A. I do.

1 Q. And please turn to page 72 of this exhibit.
2 And starting at page 72 and running through page 74 is a
3 list of references cited in this section for examples of
4 the allyl ether (Alco-OR), correct?

5 A. They -- I'm glancing at a couple -- there are
6 a couple I recognize, and that would be correct. I
7 don't know that all of them are, but there's certainly
8 at least some. I recognize the first --

9 Q. No, I'm just asking you if this is the list of
10 references that are cited in this portion of Greene &
11 Wutz.

12 A. Well, it starts at reference 27. The
13 references start --

14 Q. Right.

15 A. -- two earlier, but -- but starting with
16 reference 27, that -- that's at the beginning of
17 page 72.

18 Q. I'm looking at references 1 through 40 --
19 sorry -- 1 through 60. You're looking at 27 to
20 something else. The reference --

21 MR. ZIMMERMAN: There may be some confusion.
22 And it's at the top of 72. It starts 27.

23 MR. SCHWARTZ: Right.

24 MR. ZIMMERMAN: He's talking about where it
25 starts 1, midway down that page.

1 THE WITNESS: Oh. Oh.

2 MR. ZIMMERMAN: Not to testify, but just to
3 get you on the same page.

4 A. Yeah. No, I apologize. Yeah, I see. The
5 references start midway down page 72.

6 BY MR. SCHWARTZ:

7 Q. Okay.

8 MR. ZIMMERMAN: So now that you're looking at
9 the same references, proceed.

10 BY MR. SCHWARTZ:

11 Q. And please draw your attention to reference 18
12 on page 73. And this is the same Gigg & Warren
13 reference as Exhibit 1046, correct?

14 A. Yes, it is.

15 Q. Okay. Please go back to page 68 of Greene &
16 Wutz. And please draw your attention to the header at
17 the bottom of the page entitled "Cleavage."

18 Do you see that?

19 A. I do.

20 Q. And starting on the bottom of page 67 and
21 running through page 72 is a collection of cleavage
22 reactions for allyl ethers; is that correct?

23 MR. ZIMMERMAN: Do you want to look at that
24 question and change it? Object as to form. You said
25 "page 67," I think you meant page 68.

1 MR. SCHWARTZ: Sorry. Page 68.

2 BY MR. SCHWARTZ:

3 Q. You understand what section I'm referring to?

4 A. No. Because I was actually looking back at --

5 Q. The cleavage section.

6 A. The section titled "Cleavage?"

7 Q. Yes.

8 A. Yes.

9 Q. Starting at that page and running through
10 page 72 is a collection of cleavage reactions for the
11 allyl ethers, right?

12 A. It looks like it.

13 Q. Did you review each of those cleavage
14 reactions?

15 A. How do you mean "review"? Did I look for
16 references, or did I just -- I certainly read this
17 document. How do you mean, did I -- did I review?

18 Q. Did you look at each one of those 30 cleavage
19 reactions that are listed in Greene & Wutz?

20 A. You mean the ones that are actually listed
21 here?

22 Q. Yes.

23 A. I read them.

24 Q. Okay. And sitting here today, can you point
25 to any of those cited cleavage reactions where the allyl

1 ether is cleaved quantitatively and rapidly under
2 aqueous mild conditions?

3 A. Do you want me to look now? I did look at one
4 point. And I think if one would have satisfied that, I
5 would have taken it out and used it as a reference.
6 Since I did not, my guess is that there's not. So I'm
7 comfortable saying my guess is there is not. If you
8 want me to look and confirm that, I'll do so.

9 Q. But your understanding is that you did look
10 for one and you didn't find one?

11 A. That is my understanding.

12 Q. Okay. You can put that away.

13 I'm putting in front of you the Metzker paper
14 that was marked as Exhibit 1016.

15 (Exhibit 1016 was previously marked
16 for identification by the Certified
17 Shorthand Reporter.)

18 MR. SCHWARTZ: Sorry.

19 BY MR. SCHWARTZ:

20 Q. Please turn to page 4263. And on the right
21 side of page 4263 is a header entitled "Terminator
22 screen."

23 Do you see that?

24 A. I do.

25 Q. And Table 2 summarizes the data for the

1 terminator screen, correct?

2 A. It does so in a way. My recollection is when
3 I read this, I didn't quite understand how it
4 summarized, but yes, it summarizes.

5 And do you want me to explain what I mean by
6 that?

7 Q. Well, let me ask the next question. About
8 five lines down in the terminator screen section there
9 is a sentence that starts with "Inhibition was
10 revealed."

11 Do you see that?

12 A. I do.

13 Q. And Metzker writes:

14 "Inhibition was revealed when the
15 presence of the test compound
16 prevented the polymerase from
17 incorporating the natural
18 nucleotides."

19 That's what Metzker writes, correct?

20 A. That is what is written.

21 Q. So if a test compound is an inhibitor, there
22 won't be any termination bands on the gel because it
23 will not incorporate the three capped nucleotides,
24 correct?

25 A. No. Are you asking inhibition the way it's

1 defined in the sentence that you just read, or are you
2 asking a broader statement about a compound that acts as
3 an inhibitor?

4 **Q. Let's start with the way that he uses the term**
5 **"inhibitor."**

6 A. The way -- so he's using -- so there are two
7 types of inhibitors. One is sort of a nonspecific
8 inhibitor. It just inhibits all of the activities the
9 polymerase might have. And your comment is probably
10 right there. So it would simply prevent DNA synthesis.
11 So you would see a very strong primer band with very
12 little extension or maybe just extension that's all very
13 faint.

14 **Q. Okay. So it -- there won't -- there won't be**
15 **a termination band?**

16 A. In that -- well, there would be. There might
17 be. But they might just be faint because over -- the
18 entire synthesis is less.

19 **Q. And -- well, I'm sorry. Maybe I don't**
20 **understand you here, because Metzker is saying that:**

21 **"Inhibition was revealed when the**
22 **test compound prevented the**
23 **polymerase from incorporating the**
24 **... nucleotide."**

25 A. Yeah. So what he means is a nonspecific

1 inhibitor. So what he means by "prevent" is he's
2 reducing the ability of the polymerase to incorporate --
3 to have any of its functions. No inhibitor is perfect.
4 It depends upon the concentration. So you can get
5 partial inhibition. You can get full inhibition.

6 If you had a partial inhibition, you would
7 still get your termination bands, but they would all be
8 fainter because they would all be -- that would be
9 partial inhibition. If it were acting as a full-blown
10 potent inhibitor with complete inhibition, you would get
11 no extension at all.

12 Q. And if it -- if it -- if it was a full-blown
13 inhibitor, you wouldn't get a failure band either
14 because you didn't get any bands, right?

15 A. You would get no -- you would get no DNA
16 synthesis at all.

17 Q. Okay.

18 A. I don't know what a failure band is.

19 Q. That's what Dr. Menchen refers to as -- as the
20 band below the termination band.

21 A. His test efficiency band?

22 Q. Efficiency band. You wouldn't get that band
23 when you had full failure in terms of inhibition,
24 correct?

25 A. If you were getting no DNA synthesis, that's a

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1 band that results from DNA synthesis, so if you're
2 getting no DNA synthesis, you would not get that band.

3 Q. Okay. So when you have -- when you have total
4 inhibition, you wouldn't get any band, except for
5 perhaps the band at the bottom of the gel?

6 A. Again, we're talking about two types of
7 inhibition, and you suggested that we first talk about
8 the specific inhibition that --

9 Q. Metzker.

10 A. -- that Metzker --

11 Q. Yes.

12 A. -- is describing here?

13 Correct.

14 Q. Okay. And please turn to page 4262. And
15 please look at Table 1. And please draw your attention
16 to the column labeled "PFU exo minus DNA polymerase."

17 Do you see that?

18 A. I do.

19 Q. And please look at the bottom of the column
20 where Metzker tested incorporation ddATP, ddGTP, and
21 ddTTP.

22 Do you see that?

23 A. I do.

24 Q. And Metzker reports incomplete termination for
25 these ddNTPs using PFU (exo-) DNA polymerase, correct?

1 A. That is what the table says.

2 Q. Okay. And please look at page 4263 again.
3 And please draw your attention to the left side of the
4 page. And please draw your attention to the last full
5 sentence on the left side that starts with PFU minus --
6 sorry. Strike that. "PFU (exo-) DNA polymerase."

7 Do you see that?

8 A. I do.

9 Q. And Metzker writes:

10 "PFU (exo-) DNA polymerase was
11 excluded from the oligo template
12 assay since a ddNTP concentration
13 that yielded complete termination
14 for this enzyme could not be
15 identified."

16 That's what Metzker writes, correct?

17 A. That is what is written, yes.

18 Q. And please draw your attention to Table 2,
19 Metzker's screening assay. Metzker did not test the
20 3'O-capped nucleotides with PFU (exo-) DNA polymerase,
21 correct?

22 A. PFU is not listed in Table 2.

23 Q. Okay. And so Metzker makes clear that he
24 abandoned the use of PFU (exo-) DNA polymerase in this
25 screening assay because it was only capable of

1 **incomplete termination, correct?**

2 A. Actually not. He -- what he says is he
3 abandoned it -- he excluded it from the oligo template
4 assay, which was one of three that he used. And so
5 I'd -- I'd have to think -- I'd have to read more to see
6 if he abandoned it from all of the -- all three of the,
7 assays, but what you just read says that he excluded it
8 from the oligo template assay.

9 **Q. Because of incomplete termination?**

10 A. He says since a dideoxy NTP concentration that
11 yielded complete termination for this enzyme could not
12 be identified.

13 **Q. And he does not then go forward with it in**
14 **Table 2 where he tests the 3'-modified nucleotides,**
15 **correct?**

16 MR. ZIMMERMAN: Objection. Asked and
17 answered.

18 A. It is not in Table 2.

19 BY MR. SCHWARTZ:

20 **Q. Okay. Okay. Please go back to page 4262 and**
21 **please draw your attention to the left side of the page**
22 **where there's a header entitled "Polymerase**
23 **incorporation assays."**

24 Do you see that?

25 A. I do.

1 Q. In this section Metzker is describing the
2 conditions he used for the DNA incorporation assays,
3 correct?

4 A. For -- for, I believe, two of the assays he
5 is.

6 Q. And please look around 11 lines down in this
7 section, where there's a sentence that starts with "For
8 the second assay." Do you see that?

9 A. I do.

10 Q. And Metzker writes:

11 "For the second assay, designated
12 the 'oligo template assay'
13 [P32]-labeled [sic] universal primer
14 was annealed to an oligonucleotide
15 template (0.05 picomoles to 0.1
16 picomoles respectively per 5
17 microliters) in the same fashion."
18 That's what Metzker writes, correct?

19 A. That is what is written.

20 Q. And if you look down to the next paragraph,
21 Metzker writes:

22 "For each reaction, 5 microliters
23 ... of the annealed primer template
24 samples were dispensed into separate
25 tubes containing 5 microliter

1 mixtures of each enzyme and
2 nucleotides in their special
3 buffers."

4 MR. ZIMMERMAN: Objection. Mischaracterizes
5 the document.

6 BY MR. SCHWARTZ:

7 Q. **"In their specific buffers."**

8 MR. ZIMMERMAN: Objection. Mischaracterizes
9 the document.

10 MR. SCHWARTZ: Are you saying I read it wrong?

11 MR. ZIMMERMAN: Yes.

12 BY MR. SCHWARTZ:

13 Q. **Then I'll read it again.**

14 **"For each reaction, 5 microliter**
15 **aliquots of the annealed primer**
16 **template samples were dispensed into**
17 **separate tubes containing-five**
18 **microliter mixtures of each enzyme**
19 **and nucleotides in their specific**
20 **buffers."**

21 **Metzker writes that, correct?**

22 A. That is what is written.

23 Q. **And so the total volume of the template primer**
24 **enzyme nucleotide mixture in these assays is 10**
25 **microliters, correct?**

1 A. It would seem to be. Let's leave it at -- he
2 said -- he then goes on in the next sentence to say:

3 "The final buffer conditions,
4 concentrations" -- yeah, he doesn't -- it would say they
5 would be seem to be 10 microliters.

6 Q. Right. First he talks about 5 microliters of
7 the oligonucleotide template, and he -- and he talks
8 about then 5 microliters of the remaining materials.
9 Correct?

10 A. That would seem to be correct.

11 Q. And that 5 plus 5 is 10 microliters, correct?

12 A. Do you want me to calculate that?

13 Q. I'm not trying to be tricky here. I'm just
14 trying to get -- you know, I'm going to ask you to do a
15 calculation, a very simple calculation, but we have 10
16 microliters, correct?

17 A. But this is not the simple calculation you
18 want me to do?

19 Q. It's not much harder than that but -- no. I
20 just want you to agree first that we're talking about 10
21 microliters of a reaction volume.

22 A. To the best of my knowledge, 5 plus 5 is 10.

23 Q. Okay. And so I'm going to put a piece of
24 paper in front of you.

25 A. I thought you might do that.

1 Q. So let's just write down that the total volume
2 is 10 microliters. And Metzker says that he used 0.05
3 picomoles of primer, correct?

4 A. 0.05 to 0.1 picomole of primer respectively.
5 So primer was annealed to -- so, yes, 0.05 picomole of
6 primer.

7 Q. Of primer.

8 A. Okay.

9 MR. ZIMMERMAN: Just so we have a clear
10 record, you're asking him to assume that concentration
11 of primer, .05 as opposed to --

12 MR. SCHWARTZ: I'm asking him just to -- just
13 to -- not to assume anything, just to say this is what
14 Metzker has in his assay.

15 MR. ZIMMERMAN: And he took -- but he told you
16 it was a range.

17 MR. SCHWARTZ: No, he didn't tell me in a
18 range. Okay. He told me that -- he talks about
19 picomole of the primer. And then the other one was for
20 the template. So I asked him specifically about the
21 primer, and Dr. Romesberg agreed with me that it was .05
22 picomole of primer.

23 BY MR. SCHWARTZ:

24 Q. Is that correct, Dr. Romesberg?

25 A. In this particular section, that is correct.

1 Q. Okay. And -- and -- and Metzker used in
2 Table 2, 250 micromolars of the modified nucleotides,
3 correct?

4 A. In Table 2?

5 Q. Yes.

6 A. That is correct.

7 Q. Okay. So you can write that down. 250
8 micromolars of the modified nucleotides. And 250
9 micromolars is equivalent to 250 micromoles per liter,
10 correct?

11 A. 250-micromolar is equal to 250 micromoles per
12 liter.

13 Q. Okay. And 250 micromoles per liter is
14 equivalent to 250 nanomoles per milliliter, correct?

15 A. You divided each by a thousand.

16 Q. So that's correct?

17 A. I -- so you said that 250 micromoles -- I'm
18 going to write this down.

19 Q. Yes.

20 A. 250 micromoles per --

21 Q. Liter.

22 A. Per liter, is equal to 250.

23 Q. Nanomoles per milliliter?

24 A. That is correct.

25 Q. And 250 nanomoles per milliliter is equivalent

1 to 250 picomoles per microliter?

2 A. 250 picomoles per microliter is correct.

3 Q. Okay. So since the total volume of the assay

4 is 10 microliters, that means that there is 2500

5 picomoles of the modified nucleotide in his Table 2

6 assay; is that correct?

7 A. It would be 10 times 250.

8 Q. That's 2500 picomoles in the Table 2 assay,

9 correct?

10 A. I believe that is correct.

11 Q. Okay. That's of the modified nucleotide?

12 A. That is of the modified nucleotide.

13 Q. And as we determined, the amount of primer in

14 the assay is 0.05 picomoles, correct?

15 A. That is correct.

16 Q. So 2500 divided by .05 is 50,000, correct?

17 A. Sounds right. Did you want me to --

18 Q. I don't want you to guess.

19 A. All other things being equal, I have a

20 calculator on my cellphone. Can I use it?

21 Q. Of course.

22 A. It's like comfort.

23 You asked for 2,500 picomoles ratio to 0.05,

24 correct?

25 Q. Yes. Picomoles.

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1 A. That number is 50,000.

2 Q. Okay.

3 A. That ratio.

4 Q. So Metzker used a 50,000-fold excess of the
5 modified nucleotide over the primer in his Table 2
6 assay, correct?

7 A. I don't know. And the reason I don't know is
8 earlier I alluded to that I wasn't sure exactly how
9 Table 2 summarized. So here's the confusion. I was not
10 able to figure out if Table 2 referred to only the
11 oligonucleotide template assay or the M13 long synthesis
12 assay. I don't think he actually gives clarification on
13 that.

14 It certainly is in part reflective in a way
15 that I couldn't suss out how much of it was contributing
16 from which assay, because there are certain assays where
17 they didn't agree, yet he gave them a value in this
18 assay. So for example, the 3' -- the -- well, there
19 were several examples.

20 I could not find a spot where it says the
21 Table 2 came from that first screen, which is the M13
22 screen, or the second screen, which is what he calls the
23 oligo template assay, or, for that matter, the third
24 screen which he called the biotinylated assay. I could
25 not find clarification on which data led to Table 2.

1 A big part of the paper is the oligo template
2 assay that you are describing. These concentrations are
3 right for that assay. Presumably they went in some way
4 to collecting the data from Table 2. But the data that
5 you're describing is from the oligonucleotide assay.
6 Imputatively two assays could go into this data for
7 Table 2 for all of the compounds except the nitrobenzyl
8 terminator, in which case three assays led -- this is a
9 summary of three assays.

10 **Q.** But you do agree for the oligo template assay,
11 according to the calculations we just did, and the
12 description of the assay conditions in Metzker, he used
13 a 50,000-fold excess of the modified nucleotide over the
14 template -- over the primer, correct?

15 A. That is correct, yes.

16 **Q.** Yeah. I'm going to mark those as 2139.

17 A. These?

18 **Q.** Yes.

19 MR. SCHWARTZ: 2139.

20 2139.

21 (Court reporter clarification.)

22 (Exhibit 2139 marked for

23 identification by the Certified

24 Shorthand Reporter.)

25 THE WITNESS: That may be the most important

1 thing I've ever written.

2 BY MR. SCHWARTZ:

3 Q. I'm going to put in front of you another
4 exhibit. It's a document entitled "DNA Sequence
5 Determination Using Exonuclease-Deficient PFU DNA
6 Polymerase in a Cycle Sequencing Format" by Hedden,
7 H-E-D-D-E-N, et al., which was marked by Illumina as
8 Exhibit 1109.

9 (Exhibit 1109 was previously marked
10 for identification by the Certified
11 Shorthand Reporter.)

12 BY MR. SCHWARTZ:

13 Q. Have you seen this document before?

14 A. I believe so. I believe this is a document
15 that shows a bunch of abstracts. And I believe, yes.
16 Best I can tell, this -- I have considered this in my
17 declaration.

18 Is this on my declaration list?

19 Q. I just want to draw your attention to the
20 third sentence in the abstract.

21 A. I'm sorry. Can I ask you, is this on my
22 declaration list of declar -- articles that I
23 considered? I believe I considered it. I don't see it
24 on my list.

25 Q. I was just asking you whether you had seen

1 this document before, and I think you said you had.

2 A. Well, I mean, that's always the problem is
3 that a lot of these documents look the same. I believe
4 that I have.

5 Q. Okay.

6 A. I don't see it on my list, but I believe -- I
7 believe that I considered it.

8 Q. Okay. And I want to draw your attention to
9 the third -- the third sentence in the abstract, which
10 starts with "We have chosen to use." Do you see that?

11 A. I do.

12 Q. And it reads:

13 "We have chosen to use 3'-5 prime
14 exonuclease deficient Pyrococcus
15 furiosus (PFU) polymerase, because
16 it shows no discrimination against
17 alpha-thionucleotides. This allows
18 the efficient labeling of the
19 sequencing reactions with S35-dATP."
20 That's what's written, correct?

21 A. That appears to be, yes.

22 Q. So in Exhibit 1109, the authors used 35S-dATP
23 and PFU polymerase to make S35 labeled nucleic acids,
24 correct?

25 A. That is by definition, correct.

1 Q. And S35 dATP is not a ddNTP, correct?

2 A. No. But they are using it in a cycle
3 sequencing format so ...

4 Q. I'm just asking you whether or not 35S-dATP,
5 that's not a dideoxy nucleotide?

6 A. No.

7 Q. Okay. And incorporation of 35S-dATP by PFU
8 DNA polymerase will not result in chain termination,
9 correct?

10 A. That is correct.

11 Q. I'm going to move on to another exhibit. I'm
12 putting in front of you the Metzker 1998 paper that was
13 previously marked as Exhibit 2131.

14 (Exhibit 2131 was previously marked
15 for identification by the Certified
16 Shorthand Reporter.)

17 BY MR. SCHWARTZ:

18 Q. Have you seen this paper before?

19 A. Yes, I have.

20 Q. And please look at Figure 3 at the bottom of
21 the page on page 816.

22 A. I'm there.

23 Q. And you've seen Figure 3 before?

24 A. I have.

25 Q. And please focus on the lanes that are labeled

1 5, 25 and 50 micromolars. Do you see that?

2 A. I do.

3 Q. In this experiment, Metzker is increasing the
4 concentration of 3'-O-methyl-dATP from 5 to 50
5 micromolars, correct?

6 A. That is correct.

7 Q. And the enzyme used in this experiment is
8 AMV-RT, correct?

9 A. That is correct.

10 Q. The enzyme used in this experiment is not
11 vent (exo-) polymerase, correct?

12 (Court reporter clarification.)

13 Q. Vento (exo-) polymerase, correct?

14 A. That is correct.

15 Q. And the highest concentration of
16 3'-O-methyl-dATP used in this experiment is 50
17 micromolars, correct?

18 A. That is correct.

19 Q. At 50 micromolars, the 3'-O-methyl-dATP
20 produces complete termination, correct?

21 A. In the case where you do not have
22 contaminating dATP, in other words, lane B of the 50
23 micromolar sample, correct.

24 Q. Yes. And I am referring to the lane B's.

25 A. Okay.

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1 Q. So all of my questions relate to lane B.

2 Okay?

3 A. Okay.

4 Q. And so again, at 50 micromolars the
5 3'-O-methyl-dATP produces complete termination in the
6 absence of the contaminant, correct?

7 A. There might be a trace amount of -- of a N
8 minus one band there. It would be arguable whether
9 that's a shadow of the strong band above it. I would
10 not feel comfortable myself sitting here saying that
11 there's none, that it's only complete termination. It's
12 certainly dominating -- and it might be complete. I'd
13 have to see the gel. And --

14 Q. Okay.

15 A. Frankly, it's not the experiment to actually
16 test that, because if you really wanted to say there's
17 no N minus one band, you would run the gel much bigger.
18 You would get rid of the shadow. It's neither here nor
19 there.

20 Q. Okay. But Metzker does not show that
21 increasing the concentration of 3'-O-methyl-dATP above
22 50 micromolar increases termination, right?

23 A. He only --

24 MR. ZIMMERMAN: Wait.

25 A. In this figure he only exceeds -- he only goes

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1 up to 50 micromolar.

2 BY MR. SCHWARTZ:

3 Q. Right. So he's not testing anything greater
4 than 50?

5 A. In this figure.

6 Q. Okay.

7 A. I -- I -- I don't think anywhere -- actually,
8 there are higher concentrations in other parts of the
9 paper. But for the gel in question that you're
10 referring to, then that is correct.

11 Q. Okay. And 50 micromolars is five times lower
12 than the concentration of nucleotides that was tested in
13 Table 2 of Metzker 1994, correct, where it was 250?

14 A. Given the caveat that we already described for
15 the oligo, meaning that if you're asking in template --
16 for any of the data in Table 2 that came from the oligo
17 template assay, the second assay described by Metzker
18 where we figured the concentrations, which are now been
19 entered into the record, that statement is true.

20 Q. Well, actually, if you go back and look at
21 Metzker 1994 and look at Table 2, he says that all of
22 the compounds were assay --

23 A. I'm sorry. Could I have a second to find --

24 Q. Sure.

25 A. -- the Metzker paper?

1 Here. Table 2, yes.

2 Q. And he says in the legend that all of the
3 compounds were assayed at a final concentration of 250
4 micromolars. That's what he states, right?

5 A. Yes.

6 Q. Okay.

7 A. So I -- I'm sorry. I thought the question was
8 related to the amount of primer present.

9 Q. No. No. I'm only asking you whether or not
10 in Table 2 Metzker tested the nucleotides at 250 --

11 A. Yes.

12 Q. -- micromolar.

13 Okay. And when you compare the 50 micromolar
14 that was tested in Metzker 1998, that's fivefold lower
15 concentration than the nucleotides -- the nucleotide
16 concentrations tested in Table 2 of Metzker 1994,
17 correct?

18 A. 250 divided by 50 is 5, correct.

19 Q. Let me go -- ask you to go back to Metzker
20 1998. And look again at that figure. I see it's right
21 in front of you.

22 There is no experimental data in Figure 3 of
23 Metzker 1998 showing that increasing the concentration
24 of 3-O-methyl-dATP [sic] above 250 micromolar has any
25 effect on incorporation efficiency of 3-O-methyl-dATP

1 with AMV reverse transcriptase, correct?

2 A. He goes up to 50 micromolar.

3 Q. So you agree there's no experimental data for
4 anything above 50 micromolar?

5 A. That is correct.

6 Q. And there's no experimental data in Figure 3
7 of Metzker 1998 showing that increasing the
8 concentration of 3-O-allyl-dATP above 250 micromolar
9 would have any effect on the incorporation efficiency of
10 3' O-allyl dATP with vent (exo-) polymerase. There's no
11 experimental data in this figure, correct?

12 A. There's no experimental data -- there's no
13 data. There's no mention of O-allyl in this paper at
14 all. I never suggested there was.

15 Q. Okay.

16 A. I guess passively aggressively saying I wasn't
17 the one who suggested that there was.

18 Q. Okay. Let's go back to Metzker 1994.

19 A. Yeah.

20 Q. And please turn -- for the record, that's
21 Exhibit 1016. Please turn to page 4265. And please
22 look at Figure 4 and, in particular, at Figure 4B. And
23 you reviewed Figure 4B, correct?

24 A. I did, yes.

25 Q. And please look at lanes 7, 8, and 9 in Figure

1 **4B.**

2 A. So there are two Figure 4B, 7, 8, and 9s.

3 **Q. On the right side.**

4 A. They are both on the right side. One is --
5 there are four different polymerases. So it's an upper
6 panel of B and a lower panel of B.

7 MR. ZIMMERMAN: The top one and the middle one
8 are both labeled B. And they --

9 MR. SCHWARTZ: Oh.

10 MR. ZIMMERMAN: -- both have 7, 8, and 9.

11 BY MR. SCHWARTZ:

12 **Q. I'm sorry. Let's look at the one that's in**
13 **the middle.**

14 A. The middle one.

15 **Q. Correct.**

16 A. So just to be clear, we're looking at
17 vent (exo-)?

18 **Q. Yes, uh-huh.**

19 A. Okay.

20 **Q. And the data shown in lane 7 through 9 in that**
21 **figure are for 3'-O-methyl-dTTP, correct?**

22 A. That is correct.

23 **Q. There are no experiments in Figure 4B using**
24 **3'-O-allyl-dATP, correct?**

25 A. That is correct.

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1 Q. And there's no experimental data in Metzker
2 1994 showing that increasing the concentration of
3 3'-O-allyl-dATP above 250 micromolars increases the
4 efficiency of incorporation of that nucleotide with
5 vent (exo-) polymerase, correct?

6 A. There was only one concentration of O-allyl
7 ever examined, and that was 250. So there was nothing
8 above or below that.

9 Q. And that's true for any of the enzymes tested,
10 correct?

11 A. I -- I think so. I'd have -- I'd have to
12 reread this to be careful, but I think that, frankly,
13 the description of O-allyl is rather brief. He says
14 it's incorporated. And I don't even think that he -- I
15 think you have to go back and look at the materials and
16 methods to figure out that it was only done at 250
17 micromolar.

18 And I think that for any polymerase that he
19 then used -- it's frankly a little bit of a mixed thing
20 because he switches polymerases around. He then
21 characterizes in Table 2 the behaviors, so he must have
22 examined each of those polymerases.

23 Q. Right. But I'm just asking you whether --
24 there is no experimental data in Metzker 1994 showing
25 that increasing the concentration of 3-O-allyl-dATP

1 above 250 micromolar increases the efficiency of
2 incorporation of that nucleotide by any of the enzymes
3 he tested?

4 A. As I said, he only examined a single
5 concentration of 250 micromolar. He doesn't exam --
6 examine lower concentrations or higher concentrations.

7 Q. So that's a yes, correct?

8 A. Yes.

9 Q. Okay. And if you go back to Table 2, Metzker
10 tested eight different 3'-O-modified nucleotides with
11 eight different enzymes in these assays, correct?

12 A. In Table 2 there are eight analogs reported
13 with eight different polymerases.

14 Q. And different 3'-O-modified nucleotides gave
15 different results both when tested against the same
16 polymerase and when tested with different polymerases,
17 correct?

18 A. I'm sorry. Could you -- did you say the same
19 3'-modification gave different results? Is that --

20 Q. Yes.

21 A. I think that the only case that that's
22 provided -- that's the only case where it's possible,
23 because it was only tested with T, and that is with
24 compound -- he looked at the O-methyl and -- he looked
25 at O-methyl-dTTP. And he looked at O-methyl-dATP.

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1 Sorry.

2 Q. That's correct. I think you said that
3 correctly.

4 In fact, I'll ask you the question.

5 A. Yeah. Compound 1 and compound 8.

6 Q. So Metzker showed that the same polymerase
7 with the same 3'-O-modification but with different bases
8 gave different results, correct?

9 A. He provided a case where it did.

10 Q. And Metzker taught termination asterisks for
11 the 3'-O-allyl-dATP with vent (exo-) polymerase?

12 A. I'm sorry. Could you repeat the question?

13 Q. Metzker taught termination asterisks for the
14 3'-O-allyl-dATP with vent (exo-) polymerase?

15 A. Termination asterisk, that's correct.

16 Q. Would a POSA reasonably expect the
17 3'-O-allyl-dTTP to be incorporated by vent (exo-)
18 polymerase?

19 A. Yeah, I think a POSA would have expected that.
20 Sorry. Make sure I answered the question. You asked
21 would a POSA have expected the O-allyl T analog --

22 Q. Correct.

23 A. -- to be incorporated by vent?

24 Q. Yes.

25 A. I think he would have expected it to be

1 incorporated.

2 Q. Would it surprise you if 3'-O-allyl-dTTP is
3 not incorporated by a vent (exo) polymerase?

4 A. To the same extent that it surprised Metzker
5 that the T analog of the O-methyl was not incorporated
6 the same as the A analog. I think that to the same
7 level it would surprise me. I guess it would depend on
8 how different they were. If they were orders and orders
9 of magnitude different, I would be very surprised.

10 If they were twofold different or 1.5-fold
11 different, I would be very much less surprised. Meaning
12 there will be small variation. I don't think it would
13 be variation that rose to the level of competing -- of
14 the difference between a correct pair and a mispair, for
15 example.

16 Q. And why would it surprise you if
17 3'-O-allyl-dTTP was not incorporated by vent (exo-)
18 polymerase?

19 A. Well, because polymerases recognize -- there's
20 two things that's going on when a triphosphate's
21 incorporated. One is the polymerase is pairing the
22 nucleobase part of the incoming triphosphate. That's
23 the part that differs between them, G, C, A, or T. And
24 it's testing it for sampling for hydrogen bonding to
25 whatever is in the template. So G likes to pair with C.

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1 A likes to pair with T. So it's sampling that. And if
2 it satisfies that, then it's favorable, and it
3 contributes to it incorporating.

4 Now, the polymerase is also sampling
5 everything else in the triphosphate, and those have to
6 be accommodated as well. In all of these analogs, the
7 nucleobase portion is the same. So it's sampling a G
8 pairing with a C and A pairing with a T, and it's
9 presumably contributing favorably when it's correct and
10 disfavorably when it's incorrect, independently of
11 what's going on at the sugar.

12 Now, at the sugar the polymerase is a little
13 surprised. It doesn't have its expected hydroxyl group
14 there. It's got this blocked hydroxyl group. That
15 will -- presumably that could interfere with the
16 polymerase's recognition to some extent. But one would
17 expect it to be independent. One wouldn't expect it to
18 not be independent certainly.

19 And so you're satisfying a GC or you're
20 satisfying an AT. And you're getting some penalty for
21 having an O-methyl or an O-allyl there. And whatever
22 that penalty is probably doesn't impact the -- the
23 favorability of a correct pair. So if you're forming --
24 so the -- the ability to tolerate the 3'-modification at
25 first principle would depend on what the nucleobase

1 pairing was. And as long as it was satisfied correctly,
2 it's good.

3 So whatever -- to whatever extent it's
4 interfering with the synthesis -- to whatever extent
5 it's interfering with the insertion of T against A, you
6 would expect it to interfere or not to interfere to a
7 similar extent with the insertion of G against C,
8 correspondingly C against G, and A against T, so all
9 four possibilities.

10 Is that clear?

11 Q. Well, I guess. That is your answer as to why
12 you would be surprised that the T was not incorporated.
13 That's -- that was your answer to why that you were
14 surprised?

15 A. That I -- that I would be surprised if they
16 were dramatically different, yes.

17 Q. Well, I asked you about incorporated versus
18 not incorporated. I didn't ask you about dramatic
19 differences. It's just incorporated versus not
20 incorporated.

21 A. Well, now you're asking me about whether I'd
22 be surprised or not, so I would like to be a little
23 careful about what is surprising me or not surprising
24 me. There's very little detail in this paper,
25 incorporated and not incorporated. I guarantee you

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1 that's not in an absolute sense correct.

2 It's -- there was some trace amount in the
3 cases you're calling that incorporated. Maybe it was
4 below your detection limit. I don't know what the
5 detection limit was, so I can't really gauge that.
6 Things aren't that black and white, so I would have to
7 know. In order to really be -- to know if I'm
8 surprised, I would have know what the cutoff was, what
9 the limit of detection was. I would have to know
10 exactly what you're describing as incorporated or not
11 incorporated.

12 **Q. So are you standing by your testimony that you**
13 **would be surprised, or are you changing the testimony?**
14 **I'm trying to understand your answers.**

15 A. What I'm -- let me be clear. If you ask me
16 would I be surprised if there were significant
17 differences between similar modifications on the sugar
18 leading to effects on one insertion of one triphosphate
19 against its cognate template versus another triphosphate
20 against its cognate template, if you're asking me would
21 I be surprised that there were significant large
22 differences between them? Yes. Hundreds of fold?
23 Thousands of fold? Yes. Twofold? Not so much.

24 So it depends on what the assay is picking up.
25 So I would -- in order for -- really to tell you whether

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1 I'd be surprised or not, I'd have to know -- I would
2 like to know a little more clarity about what this data
3 means. This is very qualitative data. Inhibited/not
4 inhibited? Terminated/partial termination.

5 I would -- I would -- if -- if -- I would like
6 to know how big the differences are in order to really
7 engage my surprise. If they were really different, then
8 yes, I'd be surprised. If they were trivially
9 different, only small differences, then I would be less
10 surprised.

11 Q. Okay. But if you did an assay under similar
12 conditions to what Metzker did, and you found that the
13 dTTP was not incorporated by vent (exo-) polymerase,
14 would that surprise you?

15 MR. ZIMMERMAN: Incomplete hypothetical.

16 A. You're asking if I -- if I repeated these --
17 if I repeated the assays that Metzker describes and if I
18 then tested the O-allyl derivative of T and it was not
19 incorporated at all, in whatever detection limit I could
20 arrange on whatever gel I ran, and it was not detected
21 at all, no incorporation?

22 BY MR. SCHWARTZ:

23 Q. Well, let's start with that.

24 A. Given that Metzker seems to describe the
25 O-allyl A incorporation as moderate to significant, if

1 you then tell me that the T analog was zero?

2 **Q. It was undetectable.**

3 A. Well, then that -- what's the detection limit?
4 What could you detect? That's -- that's -- that's kind
5 of the problem of what I'm struggling with. Some assays
6 are exquisitely sensitive and some are not at all. So
7 if you ask --

8 Forgive me for a second, but let me indulge in
9 some kinetic numbers. Let's say that the T analog was
10 incorporated with an efficiency of 10 to the 6. And the
11 A analog was 10 to the 7. But your limited detection is
12 5 times 10 to the 6. It's going to look like a big
13 difference, but I'm going to know my limit of detection
14 was 5 times 10 to the 6.

15 So I'm going to write, and I've done this
16 many, many times in papers, is that this is at least
17 fivefold better. It might be 5,000-fold better. But I
18 mean, I know it sounds like I'm obfuscating here, but
19 I'm not.

20 If I'm going to be surprised, I have to know
21 what I'm being surprised by. Is it really night and
22 day? Is it really, really efficient? Really fast
23 kinetics versus zero? That's -- that would surprise me.
24 If it were orders of magnitude different in terms of
25 rates, then I would be surprised. If in a given assay I

1 could only say, given the detection limit, this is
2 threefold better, then that wouldn't surprise me so
3 much.

4 Q. All right. So going back to my original
5 question -- strike that.

6 Okay. Is it fair to say that a POSA
7 understood from Metzker's data in Table 2 that different
8 polymerases have different substrate specificities?

9 A. Table 2 suggests that. And I think that would
10 have been a -- I think that would have been a
11 reasonable -- I think a POSA would have read that, yeah.
12 Likely.

13 Q. And is it fair to say that a POSA understood
14 from Metzker's data in Table 2 that whether a polymerase
15 incorporates and how well a polymerase incorporates a
16 3'-modified nucleotide by a polymerase is unpredictable?

17 A. I'm sorry? Could you --

18 Q. Is it fair to say that a POSA understood from
19 Metzker's data in Table 2 that whether a polymerase
20 incorporates a 3'-modified nucleotide and how well it
21 incorporates that nucleotide is unpredictable?

22 A. I'd have to think about that question more.
23 For example, I would have to see whether the ones that
24 show some similar behavior -- let's say that they are
25 similar to each other. And let's say I knew -- so this

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1 is called phylogenetics, when people reconstruct how
2 close polymerases are -- how close any given protein is
3 to something else. For example, you and I, all of our
4 proteins are very close to each other, much more close
5 than a plant.

6 So I would say if all of these polymerases --
7 if you're in my polymerase, has a fingerprint shown here
8 to be closer to each other than something else, then
9 that gives a level of predictability. And someone could
10 have looked at that and said, hm, human polymerases look
11 like they are taking this analog better.

12 So I think that there -- I would not be
13 comfortable saying that there's zero predictability. I
14 would have to think about that and look carefully at
15 this. I would say that from 30,000 feet, just from
16 glancing at this, I don't see any predictability there.
17 But I'd have -- in order to really think about that, I
18 would want to look at crystal structures. Maybe --
19 maybe polymerases that have a certain residue at a
20 certain spot tend to incorporate analogs better.

21 Q. I'm just referring to the data that's in
22 Table 2. So, for example, for compound 1, with AMV-RT,
23 Metzker reports termination, right? And with a cleanout
24 fragment, he reports no activity.

25 Does that suggest that it's not predictable

1 **what happens when given a modified nucleotide --**

2 A. No, no.

3 MR. ZIMMERMAN: Objection. Asked and
4 answered.

5 A. Just so -- no, to put a little more clarity on
6 that. This is a good point. If you look at the
7 O-methyl derivative, he only looked at two reverse
8 transcriptases. He looked at AMV and the Murine, MMULV.
9 And both reverse transcriptases handled the O-methyl
10 derivative of A better than in the others. So one might
11 have then thought, well, the O-methyl derivative, I
12 think maybe reverse transcriptases handle them better.

13 So that's a level of predictability, and
14 that's exactly what I'm referring to.

15 **Q. How about for nitrobenzyl, compound 7? He**
16 **reported inhibition for Sequenase whereas he got**
17 **termination with the Bst, correct? Is that predictable?**

18 A. Well, those are very distantly related
19 enzymes, so no that's not predictable, but those are not
20 related enzymes. I mean, Sequenase is a viral T7
21 polymerase from a virus where Bst is from a bacteria,
22 and so they are very distant.

23 **Q. Could you have predicted before you did that**
24 **experiment that two nitrobenzyl would be incorporated by**
25 **Sequenase but not by Bst?**

1 A. No. No. But I would have predicted that the
2 reverse transcriptases might show more similar behavior
3 than the others. So that's a level of predictability.
4 And that would have been partially true. I'm just
5 saying that there's not no predictability here.

6 Q. What do you mean by "no predictability"?

7 A. Well, I just described the two reverse
8 transcriptases, I would have predicted ahead of time
9 that they would be prone to show more similar behavior
10 to each other than to the rest of the DNA polymerases,
11 which are not reverse transcriptases, because they are
12 structurally similar. They evolved from a common
13 ancestor, same protein, and so one would expect them to
14 behave more similarly.

15 Q. Okay. What if you scan all of the data in
16 Table 2? Does that suggest to a POSA looking at this
17 data that how -- whether a polymerase incorporates a
18 nucleotide and how well it incorporates a nucleotide
19 doesn't carry with it predictability?

20 MR. ZIMMERMAN: Objection. Asked and
21 answered.

22 MR. SCHWARTZ: I'm talking about all of the
23 data in this table.

24 A. I would have to be --

25 MR. ZIMMERMAN: Objection. Asked and

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1 answered.

2 A. I would like to think about that more
3 carefully. The example I'm using is that the two
4 reverse transcriptases have similar behavior.
5 Sequences -- the actual sequence of all of these, or at
6 least most of them, I believe were known at the time.

7 So for example, if I would have wanted to
8 answer that question as a POSA in 1999 or 2000, I would
9 have looked at the sequences. And I would have said
10 which ones are more similar to each other. And I would
11 have predicted them to have similar behaviors.

12 Now, I don't know if that turned out to be
13 true or not because I haven't done that exercise. I
14 haven't compared their sequences. So I'm a little
15 uncomfortable saying that there would be zero
16 predictability there. I would have to try it. I would
17 have to look. I would have to see.

18 The way you predict is you see what things are
19 in common and you expect those things that are in
20 common, some of them might lead to the same behavior.
21 That's what predictability is. I haven't done that. So
22 the example that I'm using is that I know that the two
23 reverse transcriptases are structurally, both primary
24 structure and secondary structure, are more similar to
25 each other than they are to the other polymerases. I

1 just happen to know that.

2 So I haven't -- I didn't have to do a sequence
3 comparison. I didn't have to do a structure comparison.
4 Nothing. I just happened to know that. They both
5 O-methyl. They both recognize O-methyl similarly.

6 Q. But you would agree that you have
7 extraordinary knowledge with polymerases, correct?

8 You don't take -- a POSA wouldn't have your
9 level of experience with polymerases?

10 A. A POSA would have known --

11 MR. ZIMMERMAN: Objection to form. Compound.

12 A. A POSA would have known that reverse
13 transcriptases are more similar to each other than they
14 are to a DNA polymerase.

15 BY MR. SCHWARTZ:

16 Q. All right. So taking a look at all of the
17 data in Table 2 through the eyes of a POSA, would you
18 agree that the POSA would understand from Table 2 that
19 whether a polymerase incorporated at any given modified
20 nucleotide and how well it incorporated it at any given
21 modified nucleotide carried with it a significant degree
22 of unpredictability?

23 MR. ZIMMERMAN: Hold on one second.

24 Objection. Asked and answered twice now.

25 You can go ahead and answer.

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1 A. There would have been some predictability, I
2 imagine. I -- I don't think it would have taken extreme
3 expertise to say that, look, if I'm going predict, I'm
4 going to take the time to look at what I'm predicting.
5 I haven't done that. I haven't and I -- but I think a
6 POSA certainly would have if they wanted to predict.
7 And they had a bunch of polymerases, probably more than
8 here.

9 They would have started by looking at
10 sequences. If they would have known that vent
11 incorporates an O-methyl analog or an O-allyl analog,
12 they would have found polymerases that are close to that
13 in sequence. It makes complete sense that you would
14 predict those would have a higher likelihood of
15 recognizing and behaving in a way that vent did.

16 You would look at Sequenase, which is a viral
17 polymerase. You would look at Klenow fragment, which
18 is -- technically it's called a Type 1 DNA polymerase.
19 And you would look at other Type 1 DNA polymerases.

20 And I think that a POSA would have expected
21 there would have been some level of predictability
22 there, because similar things behavior similarly. And
23 different polymerases are more similar to each other
24 than others.

25 These two reverse transcriptases are a

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1 different class of polymerase than a DNA-dependent DNA
2 polymerase. So I think a POSA, as I just did on the
3 fly, a POSA would have thought, yeah, I think it's
4 likely that the two reverse transcriptases might behave
5 more similarly than either of them behaved to a totally
6 different DNA polymerase.

7 BY MR. SCHWARTZ:

8 Q. So are you saying that Metzker really didn't
9 need to do these assays in Table 2 because he could have
10 predicted which ones were going to be incorporated and
11 which ones were not and how well each of them would be
12 incorporated, and he would have known that without
13 testing?

14 A. I never said that. I said that you would have
15 predicted similarities between similar polymerases. You
16 would have predicted similarities between different
17 polymerases. And on top of that, you would have to
18 check those polymerases, and then after you had them
19 with Metzker's data, you'd then -- I think a POSA would
20 have thought, well, similar polymerases might behave
21 similarly, so ...

22 Q. The very fact that Metzker did this testing in
23 Table 2, these screening studies, that suggests that
24 Metzker could not have predicted beforehand what the
25 results would be, correct?

1 A. Well, you're asking two different questions.
2 No. 1, could Metzker have predicted them before he ran
3 the experiments.

4 **Q. That's my question.**

5 A. No. Metzker could have predicted that the
6 reverse transcriptases would probably be similar.

7 **Q. Okay. Thank you.**

8 MR. ZIMMERMAN: We've been going well over an
9 hour. Is now a good time for a break?

10 MR. SCHWARTZ: Sure.

11 THE VIDEOGRAPHER: All right. We're going off
12 the record at 11:42 a.m.

13 (Recess taken from 11:42 a.m. to
14 11:50 a.m.)

15 THE VIDEOGRAPHER: All right. We're back on
16 the record at 11:50 a.m.

17 BY MR. SCHWARTZ:

18 **Q. Dr. Romesberg, if we go back to -- are we in**
19 **Metzker 1994? Yes. Okay, good.**

20 So if you turn to page 4266. And please look
21 at the second full paragraph on the right side that
22 starts with "Several unexpected results."

23 Do you see that?

24 A. I do.

25 **Q. And Metzker writes:**

1 "Several unexpected results were
2 observed in the use of the
3 3'-O-methyl-dNTPs as terminators in
4 DNA sequencing. First, the
5 3'-O-allyl-dTTP, compound 8, reduced
6 enzyme fidelity. Also, we have not
7 identified a polymerase that will
8 incorporate both 3'-O-methyl,
9 compound 1, and 3'-O-methyl-dTTP,
10 compound 8. These problems could be
11 resolved by increasing the
12 concentration of dATP in the former
13 case to titrate away artifact
14 termination bands and by testing
15 more polymerases in the later [sic]
16 case."

17 Do you see that?

18 A. I do.

19 Q. That's what Metzker writes, correct?

20 A. That is what is written, correct.

21 Q. And this paragraph -- and in this paragraph
22 Metzker teaches increasing the concentration of the
23 unmodified dATP to solve the problem of reduced enzyme
24 fidelity of 3'-O-methyl-dTTP, correct?

25 A. He -- he -- he suggests increasing the amount

1 of dATP, natural dATP, to reduce the amount of O-methyl
2 TTP that's incorporated against T in DNA. Because
3 surprisingly, what Metzker found is that the O-methyl
4 analog of dTTP was behaving in some cases like it were
5 A. And it was going in against T. And so Metzker is
6 suggesting that you could outcompete that process by
7 increasing the concentration of dATP.

8 Q. All right. But he -- he is referring in these
9 unexpected results to two different issues, right? He
10 has a first?

11 A. That's the one we just discussed.

12 Q. Okay. And in the first he says, the
13 3-O-methyl-dTTP reduced enzyme fidelity. That's what he
14 says. That's -- that's the problem that he has,
15 correct?

16 A. That is what's written.

17 Q. Okay. And then he says these problems could
18 be resolved by increasing the concentration of dATT --
19 dATP in the former case to titrate away artifact bands
20 and by testing more polymerases in the latter case.

21 The former case he's referring to is the
22 O-methyl-dTTP reducing enzyme fidelity, correct?

23 A. It's a specific flavor of fidelity. It's a
24 specific problem, but it is a fidelity problem. So I'm
25 okay calling it that.

1 Q. Okay. Well, I mean, that's what he states.
2 He's stating -- he's actually saying here that he has
3 two issues, correct? One of them has to do with reduced
4 enzyme fidelity?

5 A. It's not overall fidelity, just to be clear.
6 It's the fidelity problem that he ran into, which he is
7 very clear about in the paper, is the O-methyl TTP
8 analog going in against T.

9 Q. What does "fidelity" mean to you?

10 A. That is a form of fidelity. Fidelity is the
11 rate at which correct pairs are synthesized relative
12 to -- I think it would be very common to use it as
13 relative to the most efficiently synthesized mispair.

14 Q. Does "fidelity" refer to the accuracy of the
15 sequencing?

16 A. That's what I just said. So it would be the
17 rate at which a correct pair was synthesized, and for
18 sequencing, that means sequenced versus the rate at
19 which it's misread, which means the fastest rate of
20 the -- the rate of the fastest mispair.

21 Q. Okay. So for -- and turn -- and to solve the
22 first issue, Metzker suggests -- or he teaches
23 increasing the concentration of the unmodified dATP to
24 solve the problem of reduced enzyme fidelity, correct?

25 A. Sure. It's nothing to do with it being

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1 natural. It's simply a substrate. He's increasing the
2 concentration of a substrate just like Tsien taught, and
3 he's getting it to outcompete something else.

4 Q. Okay.

5 A. Sure.

6 Q. Okay. That's -- that's not -- that's not --
7 that's not a capped nucleotide. That's an unmodified
8 nucleotide, correct?

9 A. The concentration dependence, that doesn't
10 matter.

11 Q. But what he's teaching is, he's teaching him
12 to reduce -- to reduce the problem of enzyme infidelity,
13 he's increasing the concentration of an unmodified
14 nucleotide?

15 A. Yes.

16 (Court reporter clarification.)

17 Q. Let me ask you a question. In SBS, if there
18 is inefficient incorporation of a 3 cap nucleotide into
19 the growing DNA strands, in the time frame that the
20 terminating nucleotide and polymerase are together, that
21 will result in less than all of the growing strands
22 incorporating the 3' capped nucleotide, correct?

23 MR. ZIMMERMAN: Object as form.

24 A. Let me -- let me just state that in a way that
25 I think is exactly what you just said. But if it is,

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1 then I agree with you.

2 BY MR. SCHWARTZ:

3 Q. The result of inefficient incorporation of a
4 3'-O cap nucleotide is incomplete termination, correct?

5 A. Not necessarily. You may have had to wait
6 longer. You may have had to add more of the
7 triphosphate if it was less efficient, but the result
8 of -- in the end, if it -- if it -- if -- if -- if the
9 analog does not go in, then you don't read that template
10 in that strand.

11 Q. Right. And that's the result of an
12 inefficient incorporation?

13 A. Inefficient incorporation is -- could lead to
14 that. They are not the same thing. Inefficient
15 incorporation doesn't mean it doesn't go in -- under
16 some set of conditions that it didn't go in well. It
17 just means that you would have to, for example, as Tsien
18 suggests and as Metzker suggests as well, you might have
19 to increase the concentration if it was less efficient,
20 or if it was competing with something that was more
21 efficient.

22 Q. But an effect of inefficient incorporation of
23 a 3'-O cap nucleotide would be incomplete termination,
24 correct?

25 A. That could be.

1 Q. And for Metzker's assay, what would
2 inefficient incorporation look like on the gel if you
3 had 1 percent contamination of the natural nucleotide?

4 A. For Metzker's assay, what would inefficient
5 incorporation look like?

6 Q. Yes.

7 A. If you had 1 percent contamination of dATP.

8 Q. Like -- like he says in his assay. What would
9 that look like on the gel?

10 A. You'd have to tell me how inefficient. If it
11 were only a little less efficient, then -- let me start
12 by the easy case where it's crazy less efficient, it's
13 terrible. It's not incorporated at all. Eventually,
14 you would get only full length band because your amount
15 of your natural dATP present is in excess of primer
16 template. And eventually, because the polymerase is
17 essentially ignoring the modified analog, it will
18 eventually synthesis through.

19 If it were only a little bit less inefficient,
20 it will incorporate competitively with dATP, and you'll
21 get some termination band and some full length band. If
22 it were somewhere in between, you could get -- if you
23 don't give it enough time or if the concentrations are
24 low enough of both the natural and the modified, you
25 could get some of what your expert witness -- which is

1 what the field calls N minus 1 bands. You would get
2 some N minus 1 band if you didn't have enough of the
3 triphosphate of both of them.

4 Does that answer your question?

5 **Q. Yes. And let me -- let me ask the question**
6 **now. What would it look like -- what would inefficient**
7 **incorporation look like on the gel if you had no**
8 **contamination?**

9 A. What would inefficient incorporation look
10 like?

11 Under conditions where it manifests as
12 incomplete incorporation? Because again, inefficient
13 termination is -- describes a property.

14 **Q. Inefficient incorporation was my question, not**
15 **inefficient --**

16 A. Oh, oh. If you actually got inefficient
17 incorporation and there was no contaminants.

18 **Q. What would that look like?**

19 A. In any given time it would look like -- at an
20 early time point it would look like a lot of N minus 1
21 band and maybe just a little bit of the correct N
22 termination band. And then as you gave it more time, it
23 would eventually convert from the N minus 1 to the N
24 band.

25 **Q. Let me mark another exhibit. I'm going to**

1 mark -- I'm putting in front of you a document entitled
2 Determinants of Nucleotide Sugar Recognition in an
3 Archaeon DNA Polymerase, by Gardener and Jack, which was
4 previously marked by Illumina as Exhibit 1122.

5 (Exhibit 1122 was previously marked
6 for identification by the Certified
7 Shorthand Reporter.)

8 BY MR. SCHWARTZ:

9 Q. In your declaration you refer to this paper as
10 support for your proposition that mutations to
11 polymerases made them more tolerant to nucleotides with
12 modifications at the 3' positions.

13 Do you recall that?

14 A. Yes.

15 Q. Gardener tested dideoxy nucleotides with
16 mutated vent (exo-) polymerase in a Sanger sequencing
17 reaction, not SBS, correct?

18 A. I believe that is correct.

19 Q. The modified nucleotides examined in Gardener
20 are not 3'-O cap nucleotides, correct?

21 A. That is correct.

22 Q. And dideoxy nucleotides don't have an ether
23 protecting group at the 3' position, correct?

24 A. By definition.

25 Q. And there is no testing in Gardener of 3'-O

1 **reversibly terminating nucleotides, correct?**

2 A. No. But there is a statement about
3 substituted analogs, which those are a subset of.

4 **Q. Okay. But there's no testing in Gardener?**

5 A. No, but there's a statement.

6 **Q. Okay.**

7 A. Personal communication, which is common.

8 **Q. And there's no testing in Gardener of a 3'-O,**
9 **what I call propenyl, modified nucleotide, correct?**

10 A. There is no testing of what I call a
11 3'-O-allyl modified.

12 **Q. And there's no experimental data in Gardner**
13 **that demonstrates efficient incorporation of a**
14 **3'-O-propenyl modified nucleotide with mutated**
15 **vent (exo-) polymerase, correct?**

16 A. No. What I was suggesting this as is that a
17 POSA would have known that there were mutants of vent
18 that were more tolerant to the 3' position. He would
19 not have known the accepted 3'-O-allyl. My only point
20 in the dec, to be clear, was that a POSA would have
21 known to go look. He would -- he would not have known.
22 He would have known to look and try.

23 **Q. Okay. But there is no data --**

24 A. No, that's right.

25 **Q. Okay.**

1 A. Just to be clear, I never said there was.

2 Q. Would you expect a 3'-O-azidomethyl nucleotide
3 to be incorporated by Gardener's mutated vent (exo-)
4 polymerase?

5 MR. ZIMMERMAN: Objection. Calls for
6 speculation. Outside the scope of his declaration.

7 MR. SCHWARTZ: You can answer.

8 A. I didn't consider it but -- I didn't consider
9 it.

10 BY MR. SCHWARTZ:

11 Q. Would you expect it to?

12 MR. ZIMMERMAN: Objection. Asked and
13 answered.

14 BY MR. SCHWARTZ:

15 Q. I'm asking. Would you expect it to?

16 A. You're asking --

17 MR. ZIMMERMAN: Outside the scope.

18 A. You're asking me to consider it now?

19 BY MR. SCHWARTZ:

20 Q. Yes.

21 A. Certainly less predict -- less predictable
22 than an O-allyl. Would I -- what Gardner suggests is
23 that there are analogs that take 3'-O modified analogs.
24 As you pointed out, he doesn't show data. I suggested
25 in my dec that that would have motivated someone to

1 examine those.

2 The problem -- the -- the hope for success
3 that someone would have had would have been
4 perturbations are tol- -- are more tolerated, but you
5 would have wanted the least perturbation possible. So
6 does that mean that you would have taken fluorescein
7 substituents? They're large substituents.

8 Sorry.

9 You -- you could have made the argument that
10 they are more tolerant. The more -- the less the
11 perturbation, the smaller the perturbation, the more
12 optimistic you would have been, the more motivated you
13 would have been to go check.

14 Q. Okay. So --

15 A. So an O-allyl is smaller than is an
16 azidomethyl. So it would have -- I would have to think
17 carefully about this to come up with an answer, because
18 I don't want to testify incorrectly.

19 Certainly less confident than an O-allyl. How
20 confident you would have been? I would have to think
21 about. They are very different analogs. It's not just
22 shape. The azido group is a large and -- I'm just
23 speculating now, and you've asked me to.

24 So -- the azido group is a hydrogen bond
25 acceptor, so it's going to need a hydrogen bond. So

1 it's not just shape, because the O-allyl is a bit unique
2 in that it kind of is just shape because it isn't
3 demanding an H band acceptor, for example, whereas an
4 azido kind of is. The azido has a large dipole moment,
5 so it's going -- the electric -- the dielectric median
6 in the environment is going -- is going to matter. So
7 it's certainly less predictable.

8 For the moment, I'm certainly comfortable
9 saying that a POSA would have been optimistic about an
10 O-allyl. It's nonhydrogen bonding. It doesn't have a
11 significant dipole. It's just not as perturbative. To
12 really think about an azido, I would have to think about
13 it.

14 Q. So sitting here today, you don't have any
15 opinion on whether or not you would expect an
16 azidomethyl to be incorporated by a mutated vent (exo-)
17 polymerase?

18 A. I don't have an opinion on that right now.
19 I -- I'd have to think about that. What I've thought
20 about is the allyl.

21 Q. Okay. I'm going to put another exhibit in
22 front of you. And this is U.S. Patent No. 5,614,365, by
23 Tabor and Richardson, which was previously marked by
24 Illumina as Exhibit 1130.

25 ///

1 (Exhibit 1130 was previously marked
2 for identification by the Certified
3 Shorthand Reporter.)

4 BY MR. SCHWARTZ:

5 Q. And this is another one of the references you
6 cite in your declaration as support for your proposition
7 that mutations to polymerases made them more tolerant to
8 nucleotides with modifications at the 3' positions.

9 Do you recall that?

10 A. I believe I testified that they could make
11 them more tolerant, that the -- that a POSA would have
12 expected that there was an opportunity. I don't think I
13 said that they -- they would be more tolerant of the
14 O-allyl substituent.

15 Q. And like the Gardner paper we just looked at,
16 the Tabor patent only tested dideoxy nucleotides, not
17 3'-O reversible terminating nucleotides, correct?

18 A. I believe that is correct.

19 Q. And like the Gardner paper we just looked at,
20 the DNA sequencing platform in this paper is Sanger
21 sequencing, not SBS, correct?

22 A. I believe that is correct. But the reason
23 I -- I believe that is correct. But the reason I used
24 it for supporting the statement in the dec was that the
25 incorporation step in a Sanger sequencing reaction is

1 the same thing as the incorporation step in the --

2 (Court reporter clarification.)

3 A. -- sequencing by synthesis methods that we're
4 talking about here.

5 **Q. The incorporation step in Sanger uses a**
6 **dideoxy, correct?**

7 A. Yeah. They are different analogs, just as the
8 O-methyl and the O-allyl in -- in Metzker are different
9 analogs, but they are both being incorporated, so the
10 step is the same.

11 **Q. But they have different parameters of the 3'**
12 **position of the ribos, correct? One of them has a**
13 **hydrogen and one of them has a capping group, correct?**

14 A. True. Yeah, I don't -- I don't view that as a
15 difference that's more tangible than the allyl and the
16 methyl in Metzker or the allyl and the nitrobenzyl in
17 Metzker or one's got -- they've got different
18 substituents at that position.

19 **Q. Okay. So the -- the -- the geometry in the**
20 **shape of the 3' position of the ribos in a dNTP in that**
21 **of an SBS capped nucleotide, they are different,**
22 **correct?**

23 A. They are all different. The analogs are
24 different to each other, and they are different to the
25 dideoxy.

1 Q. Okay. And -- and like we just looked at for
2 Gardner in the Tabor patent, there's no actual testing
3 of the 3'-O-propenyl modified nucleotide, correct?

4 A. I'd have to look carefully through it to give
5 you a definitive answer, but I have looked through this
6 patent, and I certainly think I would have remembered it
7 if there were no allyl.

8 Q. Okay. So there's no experimental data in
9 Tabor that demonstrates efficiency incorporation of a
10 3'-O-propenyl modified nucleotide with a polymerase?

11 A. So we can't agree to use IUPAC nomenclature
12 here?

13 Q. I'm asking you -- at the -- at the beginning
14 of the deposition, I said, if I use the word 'propenyl,'
15 you'll understand that it refers to that structure, the
16 three carbon structure.

17 A. It just -- and I told you every time it will
18 take a second to click, so okay. We'll continue that --

19 Q. Do you agree that there's no experimental data
20 in Tabor with 3'-O -- three carbon propenyl capped
21 nucleotide?

22 A. I believe I would remember that if there was,
23 so I think there's not.

24 Q. Okay. I'm going to mark another paper. I'm
25 putting in front of you a document entitled DNA

1 Sequencing with Dye-labeled Terminators and T7 DNA
2 Polymerase; Effect of Dyes and dNTPs on Incorporation of
3 Dye-terminators and Probability Analysis of Termination
4 Fragments, by Lee, et al. It was published in 1992.

5 MR. SCHWARTZ: Court reporter please mark this
6 as 2137.

7 You might want to write "2137" on the bottom
8 of that or somewhere --

9 THE WITNESS: I can write that.

10 MR. SCHWARTZ: Or unless the court reporter is
11 going to give you the marked copy.

12 THE WITNESS: I'm happy writing it if that's
13 sufficient.

14 MR. SCHWARTZ: That's fine with me.

15 MR. ZIMMERMAN: That's fine.

16 THE WITNESS: 2137?

17 MR. SCHWARTZ: Yeah.

18 (Exhibit 2137 marked for
19 identification by the Certified
20 Shorthand Reporter.)

21 BY MR. SCHWARTZ:

22 **Q. Please turn to page 2472.**

23 A. So to be clear, just to let you know, I do not
24 believe I've looked at this document before, so any
25 specific questions I'm prone to likely ask you for a

1 second to read the context.

2 Q. Sure.

3 A. I'm sorry. What page?

4 Q. 2472.

5 And please draw your attention to the right
6 side of the page where there's a section entitled
7 "Materials and Methods."

8 Do you see that?

9 A. Yep. Yep, I do.

10 Q. Okay. And that continues for some time, and
11 it continues onto page 2473. And I'd like to draw your
12 attention to the right side of the page on 2473 where
13 there's a section entitled "Extension Reaction."

14 Do you see that?

15 A. Yep.

16 Q. Okay. Please read that section to yourself
17 and let me know when you're done.

18 MR. ZIMMERMAN: Objection. Outside the scope
19 of his declaration.

20 MR. SCHWARTZ: This paper goes directly to
21 Illumina's arguments relating to incorporation of
22 efficiencies and Sanger sequencing.

23 MR. ZIMMERMAN: Outside the scope of his
24 declaration and lacks foundation.

25 MR. SCHWARTZ: I just gave you the foundation.

1 MR. ZIMMERMAN: And I'm telling you we
2 disagree and we would like to move to exclude.

3 MR. SCHWARTZ: Okay.

4 BY MR. SCHWARTZ:

5 Q. And while you're reading that, Dr. Romesberg,
6 the question I'm going to ask you is that, this relates
7 to Sanger sequencing, correct, this paper?

8 MR. ZIMMERMAN: Objection. Outside the scope.
9 Lacks foundation.

10 A. Okay. I think I've read it. I've read it. I
11 think I've followed.

12 BY MR. SCHWARTZ:

13 Q. And the question is just that, this paper
14 relates to Sanger sequencing, correct?

15 A. I read --

16 MR. ZIMMERMAN: Same objections.

17 A. I read one paragraph in the "Materials and
18 Methods" that seems to apply to Sanger sequencing. I
19 have not read the entire document.

20 BY MR. SCHWARTZ:

21 Q. Understood.

22 Okay. And please draw your attention to
23 Equation 1 on the top of page 2481. And it says
24 Equation 1 is $P_{subscript N}$ equal $R_{subscript N}$
25 concentration ddNTP over concentration dNTP.

1 Do you see that?

2 MR. ZIMMERMAN: Objection. Outside the scope.
3 Lacks foundation.

4 A. I do see it.

5 BY MR. SCHWARTZ:

6 Q. And if you'll look at the left side of the
7 page, down towards the bottom of the page, there's a
8 section entitled "Analysis of a Repeating Sequence."

9 Do you see that?

10 MR. ZIMMERMAN: Objection. Outside the scope.
11 Lacks foundation.

12 A. I do.

13 BY MR. SCHWARTZ:

14 Q. And if you look down four lines in that
15 section, there's a sentence that starts with "We can
16 write Equation 1."

17 Do you see that?

18 MR. ZIMMERMAN: Objection. Outside the scope.
19 Lacks foundation.

20 A. I do.

21 BY MR. SCHWARTZ:

22 Q. And the paper states:

23 "We can write Equation 1, where
24 R, subscript N, is an
25 enzyme-dependent discrimination

1 constant that describes the extent
2 of discrimination of the enzyme
3 between each ddNTP and dNTP pair.
4 For T7 DNA polymerase, which does
5 not discriminate against
6 dideoxynucleotides when manganese is
7 used, the value of R is unity for
8 each ddNTP/dNTP pair ($R_{\text{subscript A}}$
9 equals $R_{\text{subscript C}}$ equals $R_{\text{subscript G}}$
10 equals $R_{\text{subscript T}}$
11 equals 1), and is independent of
12 sequence.

13 The value of R is also unity for
14 each ddNTP/($S_{\text{subscript P}}$)-dNTP
15 alpha S pair."

16 That's what's written, correct?

17 MR. ZIMMERMAN: Objection. Outside the scope.
18 Lacks foundation.

19 MR. SCHWARTZ: You can make a standing
20 objection to this paper, if you wish.

21 MR. ZIMMERMAN: Okay.

22 MR. SCHWARTZ: But as I said, it has
23 foundation because it responds directly to Illumina's
24 arguments.

25 MR. ZIMMERMAN: It's an attempt to admit a new

1 exhibit at a time in the proceedings when you can't.

2 MR. SCHWARTZ: Okay.

3 A. I read that sentence with you.

4 BY MR. SCHWARTZ:

5 Q. Okay. Now, look at the right side of the page
6 down towards the bottom. Do you see a paragraph that
7 starts with "To maximize"?

8 A. I do.

9 Q. And the authors write:

10 "To maximize the size of the
11 500th peak, or 125th A peak in our
12 repeating sequence, the probability
13 of termination ($P_{\text{subscript A}}$) is set
14 to 1 over 125. For T7 DNA
15 polymerase the enzyme discrimination
16 constant, R , is unity for each
17 ddNTP/dNTP or ddNTP/($S_{\text{subscript P}}$)dNTP pair, so the ratio of each
18 ddNTP/dNTP should be 1 over 125 or
19 0.008."
20

21 That's what's written, correct?

22 A. I read that with you.

23 Q. And 0.008 is equivalent to .8 percent,
24 correct?

25 A. It would seem to be, but frankly, I'm not

1 exactly following what they are doing. And it seems odd
2 to me. I'm missing something, but --

3 Q. But as taught by Lee, sequencing 125 bases by
4 Sanger sequencing requires only .8 percent of the
5 growing DNA strands to be terminated, correct?

6 A. I don't see that it says that. I see that it
7 says in a way that I do not understand how they are
8 defining RN. Because it seems to me it's missing a
9 natural log term, but I haven't read this paper and I
10 haven't thought about it, so it might be somewhat
11 incorporate.

12 The ratio of triphosphates DDs DNs should have
13 a natural log on it. They must have somehow
14 incorporated that into RN. I'm not following it. But I
15 will go on and try to address the question you're
16 asking.

17 "For T7 DNA polymerase the enzyme
18 discrimination constant R is unity
19 for each ddNTP/dNTP or
20 ddNTP/(SP)dNTP pair, so the ratio
21 ... should be 1 over 125."

22 I don't know what -- is this for the 100 --

23 MR. ZIMMERMAN: Do you need to read it for
24 context? Please go ahead, since you haven't seen it
25 before.

Floyd Romesberg, Ph.D.

1 A. Is 1 over 500 point --

2 BY MR. SCHWARTZ:

3 Q. Well, this is Sanger sequencing, right? So
4 remember that there --

5 A. Can I do a calculation real quick?

6 Q. Sure.

7 A. All right.

8 Q. But, remember, you have to take a look at what
9 their sequence is. And it's A, C, G, T. A, C, G, T.
10 And that goes on for 500 bases.

11 A. It's a repeating sequence?

12 Q. Yes.

13 A. So again, this is a bit of the problem with me
14 not exactly following because I haven't considered this
15 but ...

16 Q. And if you have a 500 MIR repeating sequence
17 like that, you'll have 125 A's, correct?

18 A. Yeah. Sure.

19 Q. Okay. And so that's what they're referring to
20 here. They're referring to in Sanger sequencing you do
21 each reaction separately.

22 A. Oh, okay. So at the 500th peak you've gone
23 through 125 A's because 120 -- because 500 divided by 4
24 is 125. Okay.

25 Q. All right. And so for Sanger sequencing, what

1 this paper is teaching, that the -- that you only need
2 to get to 125 bases, it requires only .8 percent of the
3 growing DNA strands to be terminated.

4 A. Well, I mean, again, I haven't read this
5 paper, and I haven't thought about this exactly. But
6 you know, I guess as Sanger sequencing gets longer and
7 longer, since the dideoxys are having to -- in order to
8 read are having to incorporate at every base, then by
9 definition, just by definition, you're diluting them out
10 over larger and larger fragments. So your band
11 intensities will get less and less.

12 So I've never thought about that. The dideoxy
13 has a limitation -- that Sanger sequencing has a
14 limitation in length that way. People really didn't
15 think about that because back when I did that, we only
16 sequenced 300 nucleotides using Sanger. But, yeah, I
17 guess that would -- that would -- that would be the
18 case. If you -- if you -- if you're covering 500
19 nucleotides, then you would want to optimize such
20 that -- that you're -- that you competed at that level.

21 Q. Well, actually this refers only to the A's, so
22 they are talking about for 125 incorporation events,
23 correct?

24 A. Sure.

25 Q. Okay.

Floyd Romesberg, Ph.D.

1 A. But -- but what -- but they are never going to
2 be in a row. I mean --

3 Q. Right. But there's 125 incorporation events,
4 and for those -- and -- and for Sanger sequencing to
5 accomplish that, you only need to terminate a very small
6 portion?

7 A. Sanger sequencing, depending on the length,
8 has requirements of how much you want to terminate,
9 because you can't use all of your triphosphate dideoxy
10 to terminate at one position, because if you did,
11 obviously, you wouldn't get any readthrough.

12 You need some -- some -- you need competitive
13 incorporation of both the dideoxy and the natural. And
14 what exactly that competitive incorporation is would
15 depend on, sure, length and how much of the analog is in
16 there.

17 Q. So this paper is teaching that for Sanger
18 sequencing, you really only want a small proportion?

19 A. I'm uncomfortable saying that because that's
20 for a 500 MIR where you have a four repeating sequences.

21 Q. Well, that's what they teach, though, right?
22 I mean --

23 A. It's for a specific example.

24 Q. Yeah. For this specific example?

25 A. I haven't thought about it, but that would

1 seem to be correct. But certainly it's correct that you
2 don't want all -- you don't want your dideoxy inserted
3 so efficiently that it is all consumed in the first
4 position because then you won't be able to go on and
5 sequence anymore. So that is by definition true.

6 So at some level this kind of argument
7 would -- would certainly apply. In all cases, this
8 would seem to be the case for this particular one, 500
9 with that sequence.

10 **Q. And so is that another way of saying that you**
11 **don't want it for Sanger sequencing for the terminator**
12 **to terminate at a very high efficiency because otherwise**
13 **you wouldn't be able to sequence a ladder? You wouldn't**
14 **generate a ladder? Is that correct?**

15 **A. I would like to be careful about the use of**
16 **the word "efficiency." My take is that 8 percent**
17 **efficiency at every position in the template when you're**
18 **competing with a natural triphosphate is remarkably**
19 **efficient.**

20 **Q. But you only -- I'm not talking about**
21 **efficiency. I'm talking about the amount of the growing**
22 **DNA strand.**

23 **A. The fact that you're -- that you're competing**
24 **at the tune of 1 percent-ish.**

25 **Q. Uh-huh.**

1 A. With the natural triphosphates, that's --
2 apparently that's about what you want.

3 **Q. Okay. And so --**

4 A. I just think that -- I thought that you used
5 the word "inefficient" someplace, like that you -- I may
6 have misheard you.

7 MR. ZIMMERMAN: He used the word "efficient."

8 MR. SCHWARTZ: Well, if I used the word
9 "efficient" I'm talking -- I apologize.

10 BY MR. SCHWARTZ:

11 **Q. My question is, for Sanger sequencing the goal**
12 **is not to terminate the -- the -- the strand.**

13 A. By definition, you cannot fully terminate.
14 You want an equal termination across the entire range at
15 which you sequence.

16 **Q. Okay. And would you agree that for SBS the**
17 **goal is different? You do want to be able to terminate**
18 **the strand or else you'll end up with out-of-phase**
19 **sequencing?**

20 A. It's a very different comparison, because
21 in -- in the Sang -- in the sequence by synthesis that
22 we're talking about, you don't have any natural
23 triphosphate present.

24 **Q. Uh-huh.**

25 A. So you're not competing with anything there.

1 Q. Okay. Well, we're just talking about
2 terminating the DNA strands. We agree that for Sanger
3 sequencing, you can't terminate all of the strands
4 because you wouldn't be able to generate a ladder,
5 correct?

6 A. They have different desires for the extent of
7 termination. It just -- it's even weird to talk about
8 calling them termination in this way in Sanger
9 sequencing compared to sequencing by synthesis. But,
10 okay. It's not the way I think about it. I think it
11 more as incorporation. But, yeah, they are blocks, so
12 they are terminating, sure.

13 Q. Okay. But for SBS the goal would be to have
14 very high termination, almost complete termination of
15 the growing DNA strands to prevent out-of-phase
16 sequencing, correct?

17 A. Sure.

18 MR. SCHWARTZ: Okay. I'm going to move on. I
19 don't -- before I move on, did you guys have lunch
20 plans? I don't want to make anybody hypoglycemic. It's
21 about 12:30.

22 MR. LUMAN: We'll have lunch brought in. It's
23 probably here already.

24 MR. SCHWARTZ: Shall we do it now?

25 MR. LUMAN: It's right behind me.

1 MR. SCHWARTZ: Okay. Would it be helpful to
2 take our lunch break now? I don't want you to get
3 hungry or anything.

4 THE WITNESS: I'm fine any -- any way we do
5 it. I'm happy to skip lunch altogether and just power
6 through it or get lunch now.

7 MR. SCHWARTZ: I don't know if your attorneys
8 want to do that, but --

9 MR. ZIMMERMAN: Let's go ahead and -- if now
10 is a good time, let's go ahead and take the lunch break.

11 MR. SCHWARTZ: Okay. Can we try to keep it to
12 about half an hour?

13 MR. ZIMMERMAN: Sure.

14 MR. SCHWARTZ: My goal is to get you out of
15 here as quickly as possible. I'm not sure if that would
16 upset you.

17 THE WITNESS: I'm getting paid for this so ...

18 THE VIDEOGRAPHER: Off the record?

19 MR. SCHWARTZ: We're off the record.

20 THE VIDEOGRAPHER: Okay. Going off the record
21 at 12:25 p.m.

22 (Lunch recess taken from 12:25 p.m.
23 to 1:02 p.m.)

24 THE VIDEOGRAPHER: We are back on the record
25 at 1:02 p.m.

1 BY MR. SCHWARTZ:

2 Q. Dr. Romesberg, during our lunch break, did you
3 have any discussions with your attorneys relating to the
4 substance of today's deposition?

5 A. I did not.

6 Q. During the lunch break, did you have any
7 discussions with your attorneys relating to the
8 questions and answers in today's deposition?

9 A. No.

10 Q. I'm going to put a new exhibit in front of
11 you. And I'm putting in front of you U.S. Patent
12 5,885,813, by Davis, et al., which was previously marked
13 by Illumina as Exhibit 1131.

14 (Exhibit 1131 was previously marked
15 for identification by the Certified
16 Shorthand Reporter.)

17 BY MR. SCHWARTZ:

18 Q. And this is a reference you cite in your
19 declaration as support for your proposition that
20 mutations to polymerases made them more tolerant to
21 nucleotides with modifications to 3' positions.

22 Do you recall that?

23 A. That is correct.

24 Q. And again, the DNA sequencing platform in
25 Davis is Sanger, not SBS, correct?

1 A. Again, like a lot of these things, I read
2 these for a certain -- I used them for a certain
3 purpose. I think that is correct. If you want a
4 statement about the entirety of the document, I'd have
5 to look more carefully, but the part I relied on I
6 believe was -- was from Sanger sequencing -- Sanger
7 sequencing.

8 Q. And Davis only tested dideoxynucleotides, not
9 3' or reversibly modified nucleotides, correct?

10 A. Again, I didn't -- the part that I used was
11 for that. And I don't recall them having something
12 other than dideoxy, but I would not feel comfortable
13 testifying that there were no -- nothing but dideoxy.

14 Q. Well, I'm just really referring to the
15 portions --

16 A. Yes.

17 Q. -- that you relied on. You didn't rely on
18 anything that taught anything but dideoxys, correct?

19 A. I believe that is correct.

20 Q. And there was no experimental data in Davis
21 that you relied on that demonstrates efficient
22 incorporation of a 3'-O-propenyl modified nucleotide
23 with a polymerase, correct?

24 A. There was nothing with a 3'-O-allyl. That is
25 correct.

1 Q. Okay. You can put that aside.

2 I'm going to mark another exhibit. And I'm
3 going to put in front -- I'm going to put in front of
4 you Exhibit 2081, which is your second declaration in
5 IPR2013-00266.

6 (Exhibit 2081 was previously marked
7 for identification by the Certified
8 Shorthand Reporter.)

9 BY MR. SCHWARTZ:

10 Q. And please turn to page 15. And do you see --

11 A. I'm sorry. Could I have one second?

12 Q. Sure.

13 A. I want to refresh my memory.

14 Page 15?

15 Q. Yes, please.

16 A. I'm there.

17 Q. Okay. And please look at the first full
18 sentence on that page that starts with "For example,
19 Canard stated." Do you see that?

20 A. I do.

21 Q. And you write:

22 "For example, Canard stated that
23 'high concentrations of 3' RTa-dNTPs
24 were needed to reach high
25 incorporation levels' for its

1 relatively bulky 3'-group."

2 And then you cite an exhibit.

3 "'The high concentrations" of
4 nucleotide used by Canard were 1
5 millimolar and 2 millimolar."

6 And then you cite to that same exhibit at
7 Figure 3A.

8 That's what you wrote, correct?

9 MR. ZIMMERMAN: Objection. Outside the scope.

10 A. That is what is written.

11 BY MR. SCHWARTZ:

12 Q. So your opinion is that 1 millimolar is a high
13 concentration for SBS, correct?

14 MR. ZIMMERMAN: Objection. Mischaracterizes
15 the document. Outside the scope.

16 A. I don't know that I would say that. What I
17 said here was that -- I referred to them as high
18 concentrations. And 1 millimolar and 2 millimolar are
19 certainly higher than a lot of concentrations, higher
20 than some concentrations. It is not the highest that
21 I've seen used.

22 But what I was stating here and what I would
23 agree today is that those are concentrations where you
24 begin to worry about fidelity.

25 ///

Floyd Romesberg, Ph.D.

1 BY MR. SCHWARTZ:

2 Q. Okay. But you do refer to them specifically
3 in this declaration as high concentrations, and you put
4 that in parens.

5 MR. ZIMMERMAN: Objection. Outside the scope.

6 A. I would have to read this carefully to see,
7 but I believe I'm referring to -- I mean, I quote
8 Canard, the document in question, as high concentrations
9 of 3' et cetera. So then the next sentence says "The
10 high concentrations used by," and so I think I'm using
11 the term "high concentrations" as a quote from Canard.
12 I'm not sure that I'm calling them high.

13 Once again, I would say -- and I believe what
14 I was testifying here to, and this is my recollection
15 from four years ago, and it's something that I would
16 agree with today, those are -- I'd have to see if this
17 is exactly what I'm saying, but I think what I was
18 saying is that those are concentrations that you would
19 begin to worry about fidelity.

20 BY MR. SCHWARTZ:

21 Q. Okay. So do you consider them to be high?

22 MR. ZIMMERMAN: Objection. Outside the scope.

23 BY MR. SCHWARTZ:

24 Q. Do you consider 1 millimolar to be a high
25 concentration of a nucleotide for SBS?

1 MR. ZIMMERMAN: Objection. Compound. Outside
2 the scope.

3 A. I think a quantitative answer to that is
4 exactly like the concentration -- the conversation that
5 we had earlier today where it would -- it would depend.
6 It is -- it is a concentration where you start to worry
7 about fidelity. And -- and so it's -- it's high --
8 it's -- I would consider it a spot that you start -- so
9 obviously I'm considering it high enough that you would
10 start to worry about that. Are the -- is it the highest
11 possible?

12 Q. I didn't ask that question.

13 A. Yeah, but it's sort of baked -- part of your
14 question is that.

15 BY MR. SCHWARTZ:

16 Q. No.

17 My question was, do you consider 1 millimolar
18 to be a high concentration of the nucleotide for SBS?

19 A. But high --

20 MR. ZIMMERMAN: Objection. Outside the scope.

21 A. High is a relative term. High relative to
22 what? And so I'm saying that, in general, it's -- it
23 feels high enough to me that I would start to worry
24 about fidelity. Is it high relative to any possible
25 application or any possible situation? I would

1 certainly worry about fidelity there, but I'd have to
2 look at the application to think about it.

3 BY MR. SCHWARTZ:

4 Q. Okay. And with worrying about fidelity means
5 that you would worry about the accuracy of the
6 sequencing results in SBS, correct?

7 MR. ZIMMERMAN: Objection. Outside the scope.

8 A. That is a concentration range with a typical
9 polymerase that I would begin to worry about that. And
10 I believe that's what I was illustrating -- I believe
11 that's what I was testifying to in this document.

12 BY MR. SCHWARTZ:

13 Q. And you continue writing:

14 "However, polymerases lose the
15 ability to accurately replicate a
16 DNA strand at high nucleotide
17 concentrations because the
18 selectivity of polymerases is
19 hindered at high nucleotide
20 concentrations."

21 And you cite to some Fersht papers, correct?

22 MR. ZIMMERMAN: Objection. Outside the scope.

23 A. That is what is written there.

24 BY MR. SCHWARTZ:

25 Q. Okay. And so your opinion is that polymerases

1 lose the ability to accurately replicate a DNA strand at
2 high nucleotide concentrations because the selectivity
3 of polymerases is hindered at high nucleotide
4 concentrations? That's your opinion?

5 MR. ZIMMERMAN: Objection. Outside the scope.

6 A. Again, and I think it's consistent with what's
7 written here. I think that at high concentrations you
8 begin to worry about that.

9 BY MR. SCHWARTZ:

10 Q. Okay. And the high concentrations that you
11 were referring to directly above that are 1 millimolar
12 and 2 millimolar?

13 MR. ZIMMERMAN: Objection. Outside the scope.

14 A. I don't believe that I actually say that. I
15 think I'm -- I think I'm raising the possibility that at
16 those high concentrations that Canard used, if I were
17 Canard, I would start to worry about that.

18 BY MR. SCHWARTZ:

19 Q. Okay. And you cited some Fersht papers to
20 support your opinion, correct?

21 A. That is correct.

22 Q. And the first -- and it's spelled
23 F-E-R-S-C-H-T [sic]. I'm sorry. It's spelled
24 F-E-R-S-H-T.

25 Thank you.

1 And the first Fersht papers were published in
2 '79 -- 1979 and 1981, correct?

3 A. I don't -- I'd have to look at those -- I
4 don't exactly -- I mean, I -- they are actually famous
5 papers. And I do kind of remember them, and certainly
6 the date is there.

7 Q. Okay. All right. And you continue writing:

8 "Furthermore, polymerases are
9 prone to insert or delete nucleotide
10 residues during synthesis at high
11 nucleotide concentrations."

12 That's what you wrote, correct?

13 MR. ZIMMERMAN: Objection. Outside the scope.

14 A. That is correct.

15 BY MR. SCHWARTZ:

16 Q. And you cite to two papers by Bebenek, et al.,
17 correct?

18 MR. ZIMMERMAN: Objection. Outside the scope.

19 A. That is what is cited there, yes.

20 BY MR. SCHWARTZ:

21 Q. And those papers were published in 1990 and
22 1992, correct?

23 MR. ZIMMERMAN: Objection. Outside the scope.

24 A. I don't have them in front of me, but
25 that's -- that is what I wrote.

1 BY MR. SCHWARTZ:

2 Q. Uh-huh. And please draw your attention to six
3 lines up from the bottom of page 15 where there's a
4 sentence that starts with "A person of ordinary skill."

5 Do you see that?

6 A. I do. Yes.

7 Q. And you write:

8 "A person of ordinary skill in
9 the art seeking to develop
10 sequencing-by-synthesis methods
11 would recognize the need to use a
12 nucleotide with a 3'-protecting
13 group that could be incorporated by
14 a polymerase with high fidelity at
15 moderate to low concentrations."

16 That's what you wrote, correct?

17 MR. ZIMMERMAN: Objection. Outside the scope.

18 A. That is what is written.

19 BY MR. SCHWARTZ:

20 Q. Okay. And your -- so your opinion is that a
21 POSA would be motivated to use moderate to low
22 concentrations of a 3'-O-protected nucleotide for SBS,
23 correct?

24 MR. ZIMMERMAN: Objection. Outside the scope.
25 Mischaracterizes his prior testimony.

1 A. I think that a person would want an analog,
2 depending on the application, of sufficient efficiency.
3 Obviously, something that is a -- is a -- is sufficient
4 enough to be used at the lowest possible concentration
5 would be an attractive aspect of a modification.

6 BY MR. SCHWARTZ:

7 Q. And -- and so are you sticking with your
8 opinion that a POSA would be motivated to use moderate
9 to low concentrations of the 3'-O-protected nucleotide
10 for SBS?

11 MR. ZIMMERMAN: Objection. Outside the scope.
12 Mischaracterizes the document.

13 A. I have not here nor -- I have not today, nor
14 am I here defining precisely what moderate to low is
15 other than it's better to not be very high. And I do
16 cite 2 as a spot that I would begin to worry about that.
17 But there's no more quantitative number ratio here of
18 what an excess nucleotide would require -- how much
19 excess would be required than we talked about earlier.

20 BY MR. SCHWARTZ:

21 Q. So in all of these passages that you're
22 writing about on page 15, the only concentration of a
23 nucleotide that you referred to as high is 1 millimolar
24 and 2 millimolar, correct?

25 MR. ZIMMERMAN: Objection. Outside the scope.

1 A. Again, I'm not absolutely positive I referred
2 to those as high. I'm -- I'm -- I'm clearly quoting as
3 Canard is calling them high. And then I say at high,
4 polymerases are prone to lose fidelity.

5 And then at the bottom, seven lines up, where
6 you asked me to look, it is certainly a truism that
7 people would have preferred to -- to use something that
8 could be used at low to moderate. That is all certainly
9 true. I don't believe that I am here -- at least as I'm
10 seeing here, I do not believe that I'm defining 2 or 1
11 as some cutoff.

12 BY MR. SCHWARTZ:

13 Q. No, I'm not asking you that. I'm only asking
14 you whether or not you're using them as examples of a
15 high concentration.

16 MR. ZIMMERMAN: Objection. Outside the scope.

17 A. I'm saying Canard called it a high
18 concentration.

19 BY MR. SCHWARTZ:

20 Q. I'm going to put in front of you one of the
21 Fersht papers that you referred to in this declaration.
22 I'm going to put in front of you a document entitled
23 Fidelity of Replication of Phage ØX174 DNA by DNA
24 Polymerase III holoenzyme: Spontaneous mutation by
25 misincorporation, by Fersht.

1 MR. SCHWARTZ: And please mark as, court
2 reporter, as 2134.

3 MR. ZIMMERMAN: I'm objecting as outside the
4 scope. Lacks foundation. I'll move to exclude.

5 (Exhibit 2134 marked for
6 identification by the Certified
7 Shorthand Reporter.)

8 BY MR. SCHWARTZ:

9 Q. And this is the same Fersht paper you were --
10 you were referring to in the passage in your declaration
11 we just read, correct?

12 A. I believe.

13 MR. ZIMMERMAN: Outside the scope. Lacks
14 foundation.

15 A. I believe so. It has -- yes, I believe it is.

16 BY MR. SCHWARTZ:

17 Q. Okay. And this is the same Fersht paper that
18 you were referring to when you said that:

19 "Polymerases lose the ability to
20 accurately replicate a DNA strand at
21 high nucleotide concentrations,"
22 correct?

23 MR. ZIMMERMAN: Objection. Outside the scope.

24 A. That is correct.

25 ///

1 BY MR. SCHWARTZ:

2 Q. And let's turn to page 4947, which is the page
3 you actually cite in your declaration. And you were
4 referring to Table 1 on page 4947 in your declaration,
5 correct?

6 MR. ZIMMERMAN: Objection. Outside the scope.

7 A. I don't remember. I'd have to think about it
8 but --1 --

9 BY MR. SCHWARTZ:

10 Q. That's where the data is? You did refer to
11 this page in your declaration?

12 MR. ZIMMERMAN: Objection. Compound.
13 Objection. Outside the scope.

14 A. I don't remember referring to this page. I
15 certainly remember referring to this paper, but I
16 believe you, and that appears to be the date.

17 BY MR. SCHWARTZ:

18 Q. You don't have to believe me. It's right
19 there.

20 MR. ZIMMERMAN: Objection. Outside the scope.

21 BY MR. SCHWARTZ:

22 Q. When you cite the Fersht paper, you cite a
23 page?

24 MR. ZIMMERMAN: Objection. Outside the scope.
25 Compound.

1 A. Yes.

2 BY MR. SCHWARTZ:

3 Q. That is the page you were referring to?

4 A. That is the page.

5 Q. Okay. And so is it likely that you were
6 referring to the data on this page to support your
7 position?

8 MR. ZIMMERMAN: Objection. Outside the scope.
9 Lacks foundation.

10 A. That is likely.

11 BY MR. SCHWARTZ:

12 Q. Okay. Now, Table 1-- so you've reviewed Table
13 1 before, because you've opined on it in your
14 declaration, correct?

15 A. Four years ago.

16 Q. Yes. And Table 1 shows that -- if you look at
17 Table 1, you look at the left side for the concentration
18 of dGTP at 93 micromolars, you start to see nucleotide
19 misincorporation. It's 14-fold above background which
20 becomes much more pronounced at 202 micromolars becomes
21 40 times above background, correct?

22 MR. ZIMMERMAN: Objection. Outside the scope.
23 Lacks foundation. Mischaracterizes the document.

24 A. The prophage revertants increase that is
25 indicative of mutation rate increasing.

1 BY MR. SCHWARTZ:

2 Q. And the results are misincorporation in this
3 assay, right? That's an effect of misincorporation in
4 this assay?

5 MR. ZIMMERMAN: Outside the scope.

6 BY MR. SCHWARTZ:

7 Q. That's how you were using it?

8 MR. ZIMMERMAN: Objection. Compound. Outside
9 the scope. Lacks foundation. Mischaracterizes the
10 document.

11 BY MR. SCHWARTZ:

12 Q. That's how you were using it, correct?

13 MR. ZIMMERMAN: Same objections.

14 A. I'm familiar with these type of reversion
15 assays, and you can set them up to be deletion or
16 mutation. Looking at what I wrote here, it looks like I
17 was referring to them as mutation. So my guess is that
18 this is indeed mutation, if that's right, but I don't
19 remember.

20 I could have been using it for either -- but
21 if you look at what I'm referring to -- let's see.
22 Because it says "selectivity of polymerases," so that's
23 probably mutation.

24 BY MR. SCHWARTZ:

25 Q. Okay. And so at 93 micromolar concentration

1 of the nucleotide that's being examined here, you get
2 18-fold increases in misincorporation according to this
3 assay, correct?

4 MR. ZIMMERMAN: Objection. Lacks foundation.
5 Outside the scope. Mischaracterizes the document.

6 A. I didn't cite 18. Could you tell me where
7 you're getting that value?

8 BY MR. SCHWARTZ:

9 Q. Well, you see where there's a number of 54 in
10 the progeny phage assay?

11 A. I do.

12 Q. And the background is 3?

13 A. Okay. That would appear to be correct.

14 Q. Okay. So at 93 micromolars, you begin to see
15 misincorporation at -- I'm sorry.

16 You would start to see misincorporation at 93
17 micromolars?

18 MR. ZIMMERMAN: Objection. Outside the scope.
19 Lacks foundation.

20 BY MR. SCHWARTZ:

21 Q. Correct?

22 A. No, that's not correct. That's not where you
23 start to see misincorporation. You see misincorporation
24 at all levels. It is increasing there.

25 Q. Okay.

Floyd Romesberg, Ph.D.

1 A. That is not where it starts to increase. Is
2 my -- I mean, from this particular dataset, there is --
3 there is a low background mutation rate, and then it is
4 increasing more at 93.

5 **Q. Okay. So at 93 micromolars you get -- you get**
6 **18-fold increase in mutation rate?**

7 MR. ZIMMERMAN: Objection. Outside the scope.
8 Lacks foundation.

9 A. In this particular assay, yes.
10 BY MR. SCHWARTZ:

11 **Q. Okay. And that represents misincorporation?**

12 MR. ZIMMERMAN: Objection. Outside the scope.
13 Lacks foundation.

14 A. I'd have to check, but it would -- as we
15 discussed a minute ago, my guess -- I -- I think it
16 might. I'm not sure.

17 From what I wrote here, it suggests that. I
18 would have to reread this. But that would be consistent
19 with what I wrote.

20 BY MR. SCHWARTZ:

21 **Q. Okay. And at 202 micromolars of the**
22 **nucleotide, you get a significant increase to 40-fold**
23 **above background of misincorporation, correct?**

24 MR. ZIMMERMAN: Objection. Outside the scope.
25 Lacks foundation.

Floyd Romesberg, Ph.D.

1 A. I'm not sure I agree with your use of the word
2 "significant" there.

3 The reason I cited this paper, and this is
4 clearly here, is that you've got a higher and higher
5 concentration, you do get more and more mutation.
6 That's all I was citing.

7 And certainly -- and when you get up to sort
8 of millimolar concentrations, you've got high mutation
9 rates. You're going in and finding this 8.4 to 93 to
10 202, and you're saying, oh, you get an 18-fold increase,
11 you get a 54-fold increase. That's true enough, but to
12 call that significant is again a bit of an application
13 feeling sort of thing.

14 You've got to remember you're plating out 10
15 to the 6 phage. So would that mutation rate affect your
16 Sanger sequencing or your sequencing-by-synthesis
17 reaction? Maybe not.

18 My point that I had -- that I was -- that I
19 was raising in my dec in 2014 was that high
20 concentrations of even natural triphosphates can lead to
21 mutation -- increase in mutation rates. I -- I don't
22 think that I was -- that I was saying at what point
23 these natural concentrations would inhibit -- would
24 prevent someone from using those -- an analog because of
25 those mutation rates in a sequencing-by-synthesis

1 application.

2 Q. But you do agree that the data that you relied
3 on -- you did -- you relied on this data for the
4 positions you took in that declaration, correct?

5 MR. ZIMMERMAN: Objection. Outside the scope.

6 A. I appear to have relied on the entirety of
7 Table 1. I'm not sure that I relied on the particular
8 data points that you're pointing to. In fact, I think
9 it's fair to say that I was not relying on that at all.
10 I was probably relying on the lowest -- the highest
11 concentration and -- a mutation rate that was high and
12 the fact it monotonically increased as you went across.
13 I was making the point that polymerases lose fidelity at
14 high triphosphate concentrations.

15 BY MR. SCHWARTZ:

16 Q. Right. But you do agree that the data in this
17 table shows that above 100 micromolars of the
18 nucleotide, you get misincorporation?

19 MR. ZIMMERMAN: Objection. Outside the scope.
20 Lacks foundation.

21 A. You get -- you get misincorporation under all
22 sorts of conditions. And I'm not -- and I did not
23 testify here that under those conditions it would be
24 problematic for sequencing by synthesis.

25 ///

Floyd Romesberg, Ph.D.

1 BY MR. SCHWARTZ:

2 Q. So take a look at the GTP concentration of 404
3 micromolar -- I'm sorry, yeah, 404 micromolar. Do you
4 consider the misincorporation rate in this table there
5 to be significant?

6 MR. ZIMMERMAN: Objection. Outside the scope.

7 A. That's -- that's a hard -- I mean, by
8 significant you mean for sequencing-by-synthesis
9 application?

10 BY MR. SCHWARTZ:

11 Q. I'm talking about -- and when you were
12 referring to misincorporation rates increase with
13 increasing concentration of a nucleotide, at 404
14 micromolar nucleotide, do you consider that the data in
15 this table demonstrates that results in significant
16 misincorporation?

17 A. I did not testify --

18 MR. ZIMMERMAN: Objection. Outside the scope.

19 BY MR. SCHWARTZ:

20 Q. I'm asking you now.

21 A. I did not say that then, to be clear. To say
22 now, that would require some thought, because you're
23 asking for sequencing-by-synthesis applications, right?

24 Q. I'm only asking about --

25 A. Significant relative to what? If it's a

1 cancer mutation, absolutely, it would be significant
2 because cancerous mu- cancer cells then have a growth
3 advantage, so all you need is one. So it's just a
4 probabilistic issue.

5 When you're sequencing a population of
6 molecules, this is -- I'm just -- off the top of my head
7 now, so I hope this is correct, and I'm not guaranteeing
8 it. You've got 10 to the 6 phage particles. You're
9 picking up a hundred mutations. That means that you've
10 got, if my math is right, a thousand to one of the
11 correct signal. I think under sequencing by synthesis
12 assays, that might be okay.

13 BY MR. SCHWARTZ:

14 Q. And what about at 400 micromolar G --

15 A. Now you've got --

16 MR. ZIMMERMAN: Objection. Outside the scope.

17 A. Now you've got -- so you've got -- now you've
18 got a ten -- a thousandfold preference for the right
19 signal. So at someplace -- and again, this is very
20 difficult to speculate. At some point high
21 concentrations are going to become a problem.

22 But again, remember these are all
23 concentrations -- these are all -- these are all assays
24 in living cells where you don't have control over the
25 other triphosphate concentrations. You don't have

Floyd Romesberg, Ph.D.

1 control over the polymerases.

2 The only point that I was trying to make in
3 2014 was that mutation rates increase with a function of
4 increasing concentration. That's not in -- that's not
5 in contention here. I agree with that today, just like
6 I said it then.

7 It is -- the argument -- the discussion that
8 we're having is that at what point do they become
9 problematic. I think that's a hard enough question in a
10 sequencing-by-synthesis reaction because it depends on
11 the application. I think it's really very difficult to
12 say that in a living cell does this reversion frequency
13 of a phage translate into problems with
14 sequencing-by-synthesis. I'm not comfortable sitting
15 here saying that now. There's a million moving parts
16 there that I would have to evaluate.

17 The only thing I'm comfortable saying here is
18 exactly what I said in 2014, and that is mutation rates
19 increase with adding triphos- -- with increasing
20 concentrations of triphosphate under -- with other
21 things being equal.

22 BY MR. SCHWARTZ:

23 Q. Okay. And the highest concentration tested
24 here was about 1 millimolar, correct?

25 MR. ZIMMERMAN: Objection. Outside the scope.

1 A. It was about 1 millimolar.

2 MR. SCHWARTZ: Right. And that's consistent
3 with your statement about Canard that that would be a
4 high concentration of a nucleotide because it could
5 cause misincorporation, correct?

6 MR. ZIMMERMAN: Objection. Outside the scope.
7 Mischaracterizes his prior declaration.
8 Mischaracterizes his --

9 MR. SCHWARTZ: You can make a standing
10 objection so you don't have to do this every time.

11 A. I am uncomfortable drawing that conclusion.
12 These concentrations are so different than the
13 concentrations used in sequencing-by-synthesis reaction.
14 BY MR. SCHWARTZ:

15 **Q. But you relied on this in your declaration,**
16 **correct?**

17 A. I relied on it --

18 MR. ZIMMERMAN: Again, outside the scope. And
19 just for clarity, the question is talking about a
20 declaration from four years ago, not a declaration from
21 this case.

22 A. I relied on it for mutation rates increasing
23 with increasing concentration of triphosphate. I relied
24 on it for nothing more than that. And I will not opine
25 on anything more than that today without being given

1 this and a lot of thought. And even then, I'm not sure
2 I would, because the conditions are so wildly different
3 that I'm not sure it's a great comparison even --

4 BY MR. SCHWARTZ:

5 Q. But you agree --

6 A. -- in a quantitative fashion.

7 Q. You agree that the highest concentration of
8 nucleotide tested on this page that you referred to in
9 your declaration was around 1 millimolar?

10 MR. ZIMMERMAN: Objection. Outside the scope.
11 Asked and answered twice now.

12 A. They are both 1 millimolar.

13 BY MR. SCHWARTZ:

14 Q. Okay. Going back to your declaration at
15 page 15.

16 MR. ZIMMERMAN: And when you say
17 "declaration," you're talking about the one from four
18 years ago in a different matter?

19 MR. SCHWARTZ: I'm talking about Exhibit --
20 where we were, Exhibit 2081.

21 THE WITNESS: 2081?

22 MR. ZIMMERMAN: That's an exhibit number from
23 a prior case?

24 MR. SCHWARTZ: No. It's this case.

25 MR. ZIMMERMAN: Oh, okay. I see where you're

1 at.

2 MR. SCHWARTZ: Okay. So we're on the same
3 page?

4 MR. ZIMMERMAN: Yep.

5 BY MR. SCHWARTZ:

6 Q. So in Exhibit 2081, your declaration in that
7 case, when you say "a person of ordinary skill in the
8 art seeking to develop sequencing-by-synthesis methods
9 would recognize the need to use a nucleotide with a
10 3'-protecting group that could be incorporated by a
11 polymerase with high fidelity at moderate to low
12 concentrations," is it your position for SBS today, in
13 this case today?

14 A. A person of ordinary skill in the art would
15 not --

16 Q. In this case. Let me ask the question again.
17 So that statement that you made here that we
18 just read, "a person of ordinary skill," that statement,
19 on page 15, would that be true in this case?

20 A. In this case, just like then, a person would
21 want to use a set of a concentration where you would not
22 have fidelity issues.

23 Q. All right. You actually used the word "need"
24 in this sentence. And you actually turned that around
25 and said "want."

1 Do you agree in this case today that a person
2 of ordinary skill would recognize the need to use a
3 nucleotide with a 3'-protecting group that could be
4 incorporated by a polymerase with high fidelity at
5 moderate to low concentrations?

6 A. You would need -- you would need an analog to
7 be incorporated with at least reasonable fidelity, and
8 that is -- that is certainly incompatible with --
9 with -- with certain concentrations that are high. I --
10 I want to be -- I don't want to be -- I don't want to
11 assign express values to high, moderate or low, but
12 clearly, the lower the better because that's more
13 efficient. And you've got increasingly less risk of --
14 of mutations, so higher fidelity is always good.

15 Q. All right. So I'm asking you, do you agree or
16 disagree with the statement that you have in this
17 declaration, that we've read several times, that it
18 refers -- those are your opinions in this case?

19 MR. ZIMMERMAN: Objection. Outside the scope.

20 A. You know, I always find it a little bit
21 uncomfortable when I take a sentence and say, you know,
22 can -- can we pull the sentence out and write it down
23 and that's what I'm saying.

24 In the context of what I'm saying in this
25 document, I still agree with what I said there.

Floyd Romesberg, Ph.D.

1 BY MR. SCHWARTZ:

2 Q. And that -- and this document was also related
3 to SBS --

4 A. Yes.

5 Q. -- conditions, right?

6 A. Yeah.

7 Q. Okay. So I'm asking you, this case is about
8 SBS, right?

9 A. Yeah.

10 Q. Do you agree -- is this still your opinion in
11 this case?

12 MR. ZIMMERMAN: Objection. Outside the scope.
13 That opinion wasn't offered in this case.

14 BY MR. SCHWARTZ:

15 Q. I'm asking. Is this -- is that your opinion
16 about SBS in this case?

17 A. Polymerases --

18 MR. ZIMMERMAN: Objection. Outside the scope.

19 A. Polymerases lose fidelity at high
20 concentration. Someone developing a
21 sequencing-by-synthesis method would need to have
22 concentrations where -- would need to have triphosphates
23 that could be used at concentrations that did not cause
24 loss in fidelity.

25 So I'm essentially agreeing to what I said

1 here, but I'm just making sure that it's in the context
2 that I meant it at the time.

3 BY MR. SCHWARTZ:

4 Q. Okay. And I'm asking you, do you -- do you
5 agree or disagree that the sentence -- the sentence that
6 we've read several times in that declaration is your
7 opinion in this case?

8 MR. ZIMMERMAN: Objection.

9 BY MR. SCHWARTZ:

10 Q. You can either say it is or it isn't.

11 MR. ZIMMERMAN: Objection. Outside the scope.
12 Asked and answered. It's getting harassing now. He
13 answered your question.

14 A. To be honest, I'm just afraid someone's going
15 to use this statement out of context. So I'm
16 effectively giving you the answer you want in the
17 context of making sure it's used in the context I
18 intended it to be used. So if you want me to say that
19 again, I will. But I'm going to keep saying it that
20 way.

21 BY MR. SCHWARTZ:

22 Q. Okay. I'm going to move to another exhibit.
23 I'm putting in front of you a document entitled
24 Hydrolysis of Esters of oxy acids: PKa values for
25 strong acids; Bronsted -- spelled B-R-O-N-S-T-E-D --

1 relationship for attack of water at methyl; free
2 energies of hydrolysis of esters of oxy acids; and a
3 linear relationship between free energy of hydrolysis
4 and PKa holding over a range of 20 pK [sic] units, by
5 Guthrie. It was published in 1978.

6 MR. SCHWARTZ: Court reporter, please mark
7 this as 2135.

8 You can write on here 2135. Would you mind
9 just marking that as 2135, Dr. Romesberg?

10 Thank you.

11 (Exhibit 2135 marked for
12 identification by the Certified
13 Shorthand Reporter.)

14 BY MR. SCHWARTZ:

15 Q. And would you please turn to page 2345.

16 MR. ZIMMERMAN: Objection. Outside the scope.
17 Lacks foundation.

18 BY MR. SCHWARTZ:

19 Q. Okay. So did you go to 2345?

20 A. I'm on that page. Just to be clear, I do not
21 believe I've seen this document before.

22 Q. Okay. Please draw your attention to Table 2.

23 MR. ZIMMERMAN: Objection. Outside the scope.
24 Lacks foundation.

25 ///

Floyd Romesberg, Ph.D.

1 BY MR. SCHWARTZ:

2 Q. Table 2 has the heading "pKa values which have
3 been reported for strong acids." Do you see that?

4 MR. ZIMMERMAN: Objection. Outside the scope.
5 Lacks foundation.

6 A. I do.

7 BY MR. SCHWARTZ:

8 Q. And the first of the acids listed in Table 2
9 that Guthrie refers to as a strong acid is perchloric
10 acid, correct?

11 MR. ZIMMERMAN: Objection. Outside the scope.
12 Lacks foundation.

13 A. That is correct.

14 BY MR. SCHWARTZ:

15 Q. All right. You understand perchloric acid to
16 be a strong acid, correct?

17 MR. ZIMMERMAN: Objection. Outside the scope.
18 Lacks foundation.

19 A. I do.

20 BY MR. SCHWARTZ:

21 Q. And the second of the acids listed in Table 2
22 that Guthrie refers to as a strong acid is
23 para-toluenesulfonic acid, correct?

24 MR. ZIMMERMAN: Objection. Outside the scope.
25 Lacks foundation.

Floyd Romesberg, Ph.D.

1 A. I do.

2 BY MR. SCHWARTZ:

3 Q. And do you consider para-toluenesulphonic acid
4 to be a strong acid?

5 MR. ZIMMERMAN: Objection. Outside the scope.
6 Lacks foundation.

7 A. You know, like so many things we seem to be
8 talking about, "strong" is a relative term. We just
9 talked about perchloric acid. So this is a weaker acid,
10 but it is a stronger acid than a lot of other things,
11 and so I think most people would call a toxic acid.
12 That's what that common name is -- would -- yes, I would
13 consider that a strong acid.

14 Q. Okay. You can put that away.

15 I'm going to put in front of you a document
16 entit- -- entitled Practical Palladium-Mediated
17 Deprotective Method of allyloxycarbonyl in Aqueous Media
18 by Genêt, et al. That was previously marked by Illumina
19 as Exhibit 1094.

20 (Exhibit 1094 was previously marked
21 for identification by the Certified
22 Shorthand Reporter.)

23 BY MR. SCHWARTZ:

24 Q. Have you seen this document before?

25 A. I have.

1 Q. And please turn to page 499 Table 1. The
2 alcohol protecting groups shown in Table 1 are Alloc,
3 correct?

4 A. They are pronounced Alloc, yes.

5 Q. Alloc.

6 A. I believe the entire paper is Alloc.

7 Q. And that -- the abbreviation for Alloc again
8 is allyloxycarbonyl, correct?

9 A. Uh-huh.

10 Q. When the Alloc protecting group is used to
11 protect an alcohol, it forms an ester bond, not an ether
12 bond, correct?

13 A. When an Alloc is used to protect a what?

14 Q. Alcohol.

15 A. This is silliness, but I have to be careful.
16 I don't know why I'm -- no, I don't think it forms an
17 ester. And I'm drawing a blank on what the name on the
18 compound is.

19 Q. It's not an ether, correct?

20 A. It's not an ether. It's got two oxygens --
21 it's got three oxygens. Carbonate -- carbonate is what
22 I think it is.

23 Q. Okay. It's not an ether?

24 A. Yeah.

25 Q. It is not an ether. I don't know if the court

1 **reporter heard.**

2 MR. ZIMMERMAN: Objection. Asked and
3 answered.

4 MR. SCHWARTZ: I just said it fast. I wanted
5 to make sure the court reporter understood my question.
6 BY MR. SCHWARTZ:

7 Q. **It is not an ether that is being formed,**
8 **correct?**

9 A. Yes, that's correct.

10 Q. **And so Genêt does not show deprotection of any**
11 **ether protected alcohols, correct?**

12 A. Does not show deprotection of any ether, no.
13 He -- this -- this -- this manuscript is about Alloc.
14 And those are not ethers.

15 Q. **Okay. You can put that away.**

16 I'm going to put in front of you a document
17 entitled Selective Deprotective Method Using
18 Palladium-Water Soluble Catalysts by Lemaire Audorie,
19 et al. That was previously marked as Illumina
20 Exhibit 1114.

21 (Exhibit 1114 was previously marked
22 for identification by the Certified
23 Shorthand Reporter.)

24 BY MR. SCHWARTZ:

25 Q. **Have you seen this document before?**

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1 A. I have.

2 Q. And please turn to page 8784 and the
3 protecting group shown on page 8784 are, again, Alloc,
4 correct?

5 A. I believe that all of Genêt's work is with
6 Alloc.

7 Q. This paper included?

8 A. Right.

9 Q. Okay.

10 A. But Ju cites them, and the reason that we
11 would be interested in them is because the initial
12 deprotection is of the allyl group and then subsequent
13 decarboxylation. So the reason Ju -- so, correct, they
14 are not allyl ethers. They are not -- they are not
15 removing --

16 (Court reporter clarification.)

17 A. They are removing an allyl from an oxygen.
18 It's the same first step. The Alloc then does something
19 else afterwards. And the reason Ju cited them for
20 evidence for allyl deprotection, and the reason I agree
21 with Ju, is because the first step is identical.

22 BY MR. SCHWARTZ:

23 Q. But this paper does not disclose any ether
24 protected alcohols, correct?

25 A. Any alcohols protected as an allyl ether?

1 Q. Correct.

2 A. It does not disclose that. People would have
3 known what the first step was. And the reason Ju cited
4 it the way he did and the reason that I would agree with
5 Ju is because the first step is identical. That's the
6 only relevance of Alloc.

7 Q. Okay. But you agree that this paper does not
8 show any deprotection conditions for ether-protected
9 alcohols?

10 A. It does for O-allyls. It does for cleaving an
11 allyl from oxygen, but that oxygen is not part of an
12 alcohol. Correct.

13 Q. Okay. I'm going to put in front of you a
14 document entitled Chemoselective Removal of Allylic
15 Protecting Groups Using Water-Soluble Pd(OAc)₂/TPPTS Catalyst, by again, Lemaire Audorie. That was
16 previously marked by Illumina as Exhibit 1115.

17 (Exhibit 1115 was previously marked
18 for identification by the Certified
19 Shorthand Reporter.)
20

21 BY MR. SCHWARTZ:

22 Q. And have you seen this document before?

23 A. I have.

24 Q. And do you agree that like the other two
25 documents we just looked at, that this paper also

1 describes only Alloc?

2 A. The answer I gave to the last paper is
3 identical to this paper. I believe it's identical to
4 all of Genêt's work.

5 Q. Okay.

6 A. That's cited in this -- in this -- that we're
7 talking about, these three Genêt papers.

8 Q. So there are no reaction conditions disclosed
9 in any of those three papers for cleaving a 3'-O-allyl
10 ether from a --

11 A. I disagree with that. I believe that's
12 exactly what these papers -- I believe these papers
13 explicitly show conditions for deprotecting an O-allyl.

14 Q. But when -- but the Alloc, when it's on the
15 alcohol in this case, is not forming an ether?

16 A. No, but the first step is identical. It's
17 removing -- it's cleaving an oxygen -- it's cleaving an
18 O-allyl between the oxygen and the first carbon. And
19 they are identical in both cases.

20 Ju knew that. Ju cited it as evidence that
21 you would be able to do exactly this reaction with an
22 O-allyl in protecting an alcohol of the sort that we're
23 talking about here, and I agree with Ju. It's the
24 identical first step. And I would have taken this as
25 evidence that that would work.

1 Q. But when -- when it's a protecting group on an
2 alcohol, it's not forming an allyl ether, correct?

3 A. No. But the point I'm trying to make -- and
4 again, this is exactly the point that -- what Ju was
5 looking at when he cited these exact same papers. The
6 first step is identical. And so a person would have
7 expected that to proceed identically.

8 Now, the two reactions with an Alloc and with
9 an O-allyl diverge afterwards. And they are going to go
10 on different routes for different chemistry, but both of
11 them are initiated by the exact same palladium
12 chemistry. And so I think Ju was exactly correct in
13 citing these evidence that O-allyl would be deprotected
14 efficiently and timely under mild conditions, and I
15 agree with him in this case.

16 Q. But all of the Genêt papers that we looked at,
17 the Alloc group is not forming an ether with the alcohol
18 on the sugar, correct?

19 MR. ZIMMERMAN: Objection. Asked and answered
20 twice.

21 A. All of the Genêt papers we've talked about, in
22 fact all of the work of Genêt that I know of is with
23 Alloc. Now, that may not -- in terms of this -- close
24 to what we're talking about. That's what he was
25 interested in. That's -- that's not why Ju cited it.

1 Ju cited it, as I've said now, because that first step
2 was identical, and you would have expected it to be
3 identical. But that is correct, they are carbonates.

4 BY MR. SCHWARTZ:

5 Q. Not ethers?

6 MR. ZIMMERMAN: Objection. Asked and
7 answered.

8 BY MR. SCHWARTZ:

9 Q. You can answer.

10 A. That is correct.

11 Okay. You can put that aside.

12 MR. SCHWARTZ: Let's take a short break.

13 THE VIDEOGRAPHER: We're going off the record
14 at 1:48 p.m.

15 (Recess taken from 1:48 p.m. to
16 2:07 p.m.)

17 THE VIDEOGRAPHER: We are back on the record
18 at 2:07 p.m.

19 BY MR. SCHWARTZ:

20 Q. Dr. Romesberg, would you please go back to
21 your second declaration in this case. It was
22 Exhibit 1119.

23 MR. ZIMMERMAN: It's the big one.

24 THE WITNESS: Oh.

25 MR. SCHWARTZ: Right.

1 MR. ZIMMERMAN: No. The other big one.

2 THE WITNESS: I'm sorry. This is it right
3 here.

4 MR. SCHWARTZ: Got it?

5 MR. ZIMMERMAN: 1119?

6 MR. SCHWARTZ: I believe so.

7 MR. ZIMMERMAN: Okay.

8 THE WITNESS: I have it.

9 BY MR. SCHWARTZ:

10 Q. Got it?

11 So please turn to page 50. Almost at the end.

12 And on page 50 you draw Fmoc attached to an adenine,
13 correct?

14 A. Correct.

15 Q. And Fmoc is 9-fluorenylmethoxycarbonyl,
16 correct?

17 A. Fluorenylmethoxycarbonyl, that's right.

18 Q. And using this pen, would you just draw a
19 circle around the entire Fmoc moiety on your
20 declaration.

21 A. Just to be a little clear, Fmoc is kind of
22 never on its own. It's either Fmoc like chloride or
23 Fmoc attached to something. This is attached to
24 something. So I'm going to draw a circle around the
25 Fmoc part of what it's -- of the bigger thing.

1 Is that okay?

2 **Q. I think I understand you, yes.**

3 **I want you to draw a circle around**
4 **9-fluorenylmethoxycarbonyl.**

5 A. That -- that winds up making me produce a
6 carbonyl group that's not attached to anything.

7 **Q. Okay.**

8 A. But it's attached to a nitrogen.

9 **Q. Okay.**

10 A. And so --

11 **Q. Okay. Fine.**

12 **And now you can keep that red pen because I**
13 **promised. Okay?**

14 A. So I just had to use it.

15 **Q. Okay. I'm going to hand you what's now been**
16 **previously marked as the Dower exhibit.**

17 (Exhibit 1015 was previously marked
18 for identification by the Certified
19 Shorthand Reporter.)

20 MR. SCHWARTZ: And that's Exhibit 1015.

21 BY MR. SCHWARTZ:

22 **Q. Again, you have seen Dower before, correct?**

23 A. I certainly have seen Dower before.

24 **Q. And please turn to Column 5 of Dower.**

25 **And I'll draw your attention to Figure 9. And**

1 Dower's description of Figure 9 reads:

2 "Figure 9 illustrates the
3 synthesis of a representative
4 nucleotide analog useful in the
5 synthetic scheme. Note that the
6 Fmoc may be attached to adenine,
7 cytosine or guanine."

8 That's what's written, correct?

9 A. That is correct.

10 Q. And now please turn to Figure 9 of Dower. And
11 in Figure 9 Dower shows that the Fmoc labeled is
12 attached to the base, correct?

13 A. In what part of Figure 9? The top part?

14 Q. Yeah.

15 A. Yes.

16 Q. And Dower nowhere explicitly describes the
17 fluorenyl moiety as a tag or label in this figure,
18 correct?

19 A. In this figure he doesn't seem to describe the
20 linker or the specific fluorophore part of Fmoc.
21 Whether or not in the entire document he does or not,
22 I'm, again, less confident in discussing, because I'd
23 have to expressly look for that. And I don't recall
24 looking for that expressly, that point exactly.

25 But he's -- in this figure he's just writing

1 Fmoc chloride reacting with a nucleophile on the base to
2 produce Fmoc like that is attached in the figure that I
3 drew that we just discussed.

4 Q. And in Figure 9 and elsewhere in Dower, for
5 that matter, he nowhere explicitly discloses the
6 methoxycarbonyl group as a chemically cleavable chemical
7 linker, does he?

8 (Court reporter clarification.)

9 A. I'd have to check explicitly, but I think he
10 does. Because he talks consistently about having a
11 fluorophore attached via a cleavable linker. And Fmoc
12 is an example that he gives. And so I think that you
13 would look at Fmoc. I think a person in the ordinary
14 skill of the art would have known that Fmoc is exactly
15 that and would have taken it as an example of that.

16 Q. But I didn't ask you that.

17 I asked you whether he explicitly discloses
18 the methoxy oxy -- sorry -- whether he explicitly
19 discloses the methoxycarbonyl group as the chemically
20 cleavable chemical linker, whether he explicitly
21 discloses.

22 A. Explicitly. So I guess your argument is that
23 implicitly by evoking Fmoc as an example but not
24 explicitly stating that the methoxycarbonyl is the
25 cleavable part. I guess he doesn't explicit -- I don't

1 recall him explicitly saying that.

2 Q. Okay. And in Figure 9, in the description we
3 just looked at, Dower teaches that Fmoc may be attached
4 to adenine, cytosine, or guanine, correct?

5 A. That is correct.

6 Q. And Dower does not teach that Fmoc can be
7 attached to a thymine, correct?

8 A. That is correct.

9 Q. It cannot be attached to a thymine, correct?

10 A. Not without modification. But you could
11 modify thymine to attach it.

12 Q. And please go back to your second declaration,
13 Exhibit 119.

14 A. So just to be clear, you could attach it. And
15 you would use the method he suggests by a reference to
16 Prober to attach it.

17 Q. That wasn't my question though.

18 He does -- he doesn't -- he shows the Fmoc
19 being attached to the exocyclic amines. And he refers
20 in Figure 9 only to those three bases, correct?

21 A. He writes them out explicitly, yes. But he
22 teaches cleavable linkers. He cites to Prober. And
23 he's using Fmoc as an example in three cases out of four
24 where you could use it directly. And I think the person
25 of ordinary skill in the art would have -- since he

1 cites Prober, I think six times, I think he would have
2 looked to Prober and simply added Fmoc to those
3 derivatized T versions.

4 So I don't -- I don't think a person of
5 ordinary skill in the art would have considered using
6 this meth- -- Fmoc to tag T with a cleavable linker
7 outside of possibility. But you are correct, in Figure
8 9 he shows it for -- and the caption explicitly says
9 this is for G, C, and A.

10 Q. So in the Ju patent claims, Ju has the linker
11 on the thigh position -- strike that.

12 In our claims you wouldn't be -- you wouldn't
13 have Fmoc on the T and R claims?

14 MR. ZIMMERMAN: Object as to form.

15 Just so we're clear, which claims?

16 MR. SCHWARTZ: Any of the claims in any of the
17 patents.

18 BY MR. SCHWARTZ:

19 Q. They have a T, correct?

20 MR. ZIMMERMAN: Object as to form.

21 A. They wouldn't have an Fmoc is the question?

22 BY MR. SCHWARTZ:

23 Q. Dower doesn't teach putting Fmoc?

24 A. Well, Dower doesn't --

25 MR. ZIMMERMAN: Wait a minute. Objection.

1 Compound. You've got two different questions out there
2 now, one about the Ju patent and one about Dower. So I
3 just want to make sure -- whichever one you want an
4 answer to, he's happy to answer, but there's two of them
5 out there now.

6 BY MR. SCHWARTZ:

7 Q. I'm talking about the T in Ju's claims. Okay.
8 Dower doesn't teach putting Fmoc on that T -- on the Ju
9 T.

10 MR. ZIMMERMAN: Object as to form.

11 A. Sorry, I'm confused. Does Dower teach --

12 BY MR. SCHWARTZ:

13 Q. Dower teaches attaching the Fmoc to the
14 exocyclic amines, correct?

15 A. Dower teaches attachment to exocyclic amines
16 implicitly by example, yes.

17 Q. And T doesn't have that?

18 A. Right. But he cites Prober and Prober's
19 produced analogs of T that had exactly that.

20 Q. Not on exocyclic amine?

21 A. On exocyclic amine, yeah.

22 Q. On a T?

23 A. Yeah. He teaches them for all analogs, on
24 both T and C at the 5' position of both pyrimidines.
25 He's got propargylamine linkers that he then uses to

1 attach dyes to. Those propargylamines are exactly what
2 you would want to attach Fmoc.

3 Q. Okay. But maybe -- maybe I'm not -- I'm
4 understanding you now.

5 But my question is, is that what Dower
6 teaches, Dower teaches putting the Fmoc directly
7 attached to the base, correct?

8 A. I think that Dower uses Fmoc as an example.
9 What Dower teaches is the use of linkers to attach
10 labels, fluorophores. He cites to Prober for that.
11 Prober produces those analogs. And one would have done
12 exactly that. One would -- if one would have wanted to
13 label with Fmoc T, Dower cites Prober, you would have
14 looked at Prober and seen what Prober did, and you would
15 have attached Fmoc.

16 Q. But Dower doesn't teach attaching Fmoc to the
17 three bases that he teaches attaching it to through any
18 kind of additional linker, correct?

19 A. Dower gives an example where he uses Fmoc to
20 attach directly to the three of the four that you could
21 directly attach to. T is not. But Dower cites to
22 Prober consistently throughout, six times, and I think
23 expressly says four linkers. Look to Prober. And
24 Prober published T analogs with exocyclic amines that
25 would have been suitable and, in fact, cites -- uses

1 them in the example that we used -- included in my dec
2 for exactly that, a propargylamine linker to attach a
3 linker to it, which he attached a fluorophore to.

4 He didn't attach the Fmoc directly, but it
5 would be an exocyclic amine that you would exactly be
6 able to do that if you chose. Or you would be able to
7 choose an additional linker between them. And that's
8 what Seitz did.

9 (Court reporter clarification.)

10 **Q. I just have to get to Dower. Sorry.**

11 **Going back to Figure 9 of Dower. You agree at**
12 **the bottom of Figure 9, Dower is directing the reader to**
13 **attach the Fmoc linker to the exocyclic amines of the**
14 **three bases shown, correct?**

15 A. He is -- that is explicitly what he is showing
16 in the figure.

17 In the caption that we just talked about, I
18 think he says the same thing. I would like to look at
19 it.

20 So Figure 9 illustrates the synthesis of
21 representative nucleotide analogs in the -- that's kind
22 of my point. It's representative. He's expressly
23 showing Fmoc with its fluorophore, its linker, and that
24 could be directly attached to adenine, cytosine, or
25 guanine.

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1 Like I said, this isn't a representative
2 analog that's useful, but he cites Prober six times
3 expressly for linkers. Prober produces propargylamine
4 linkers that would be exactly analogous to those -- that
5 have exocyclic amines, exactly analogous to what he
6 represents here. And so I think, by reference to
7 Prober, he includes T, as my opinion, from a person of
8 ordinary skill in the art in 1999 to 2000.

9 **Q. But you agree that nowhere in Dower did you**
10 **find any example of where Dower is teaching attaching**
11 **Fmoc to an additional linker?**

12 A. He shows three examples where -- that he says
13 are representative of what he would use. He cites to
14 Prober. Prober provides exactly what you would need to
15 do exactly that. So no, I disagree with that. I think
16 that he does teach attaching Fmoc to all four.

17 **Q. Okay.**

18 A. Three explicitly and one -- and one by
19 reference.

20 **Q. And the only way that you could attach Fmoc to**
21 **something other than an exocyclic amine, sitting here**
22 **today that you're aware of, would be to use some**
23 **additional structure between the base and the Fmoc,**
24 **correct?**

25 A. The only way that you could attach Fmoc to a

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1 T.

2 No, you probably could. It would be ugly. I
3 mean, there's a variety of things you could use.
4 Radical chemistry. You might be able to -- you would
5 not -- I certainly would not say that. It certainly
6 would not -- I would not guess it would be easy, but I
7 would not say you could not do it.

8 Let me be clear. You certainly could do it
9 easily in a way that might -- that you would be very
10 suspicious that it would perturb the ability to act as a
11 substrate. You could attach it to the oxygen, the
12 oxygen-hydrogen bond. So one would be very hesitant to
13 do that.

14 So to -- to clarify -- to clarify it a little
15 bit, to do so in a way that you would be very opt- --
16 that you would remain optimistic that it would be a good
17 substrate. For all intents and purposes what that
18 means, you're asking me today, right? Today that means
19 that you would want the 5 position. You would want a
20 very specific moiety at the 5 position. So you would
21 want to attach it to the 5 position.

22 I don't know that you couldn't do that. I
23 could not sit down and tell you how to do it. But
24 synthetic chemists are very good --

25 (Court reporter clarification.)

1 A. For example, you generate a radical at that
2 alpha position to that carbonyl, that 5 position, you
3 could probably add it in there. I don't think this
4 would be particularly easy. I don't think it would
5 be -- I don't -- but I'm just not comfortable saying you
6 could not do it. In fact, you probably could because
7 synthetic chemists are good today.

8 Q. You haven't cited any references in any
9 declarations in this IPR -- these IPRs with conditions
10 where you could attach Fmoc to the 5 position, correct?

11 A. No. You asked me if I thought you could. And
12 I'm simply speculating.

13 Q. Okay. But you haven't cited any.

14 A. No, nor do I know of any.

15 Q. Okay. And the same for the diaza position,
16 attaching it to the diaza position of a 7 --

17 (Court reporter clarification.)

18 A. Are you -- are you asking if I could come up
19 with a method to do that?

20 Q. I'm asking you whether or not you cited to any
21 references for the synthetic chemistry involved in doing
22 that.

23 A. I did not.

24 Q. Okay. I'm going to move on to another
25 exhibit. And I'm putting in front of you a document

1 entitled Methods for removing the Fmoc Group, by Fields.
2 And it's been previously marked by Illumina as
3 Exhibit 1136.

4 (Exhibit 1136 was previously marked
5 for identification by the Certified
6 Shorthand Reporter.)

7 BY MR. SCHWARTZ:

8 Q. You've seen this exhibit before?

9 A. I have, yes.

10 Q. Fields' paper uses Fmoc for peptides
11 synthesis, correct?

12 A. Yes.

13 Q. The Fields' paper does not disclose
14 deprotecting Fmoc on DNA, does it?

15 A. It does not, but I don't think that anyone
16 would consider that to be -- in terms of the actual
17 mechanism, of the pyridine mechanism, the way Fmoc is
18 protected, it wouldn't matter what else was in the
19 molecule.

20 Q. But the Fields' reference itself doesn't show
21 any deprotection methods for --

22 A. It's for peptides.

23 MR. SCHWARTZ: Could can we take another short
24 break? We're very close to being done.

25 THE VIDEOGRAPHER: We're going off the record

1 at 2:27 p.m.

2 (Recess taken from 2:27 p.m. to
3 2:40 p.m.)

4 THE VIDEOGRAPHER: We are back on the record
5 at 2:40 p.m.

6 BY MR. SCHWARTZ:

7 Q. Dr. Romesberg, I just want to go back to your
8 declaration, the second declaration in this case,
9 Exhibit 1119. And if you would go back to page 50 where
10 you drew the red circle. And just for the record, could
11 you describe what is encompassed by the circle.

12 A. The -- there's a fluorenyl fluorophore. It's
13 a known fluorophore, and there's was a -- a
14 methoxycarbonyl linker. That's a methylene attached to
15 an oxygen attached to a carbon --

16 (Court reporter clarification.)

17 A. There's carbon attached to an oxygen, attached
18 to a carbonyl, which would usually be attached to
19 something like a chloride. That would make something
20 called Fmoc chloride. And that's the reagent that you'd
21 probably actually buy. And that's the activated
22 carbonyl group so that when you react that with an
23 amine, you get a carbamate. That's what's shown here.

24 Earlier we talked about like an Alloc. If you
25 reacted that with an oxygen, you would get a

1 carbonate -- unless I'm screwing the nomenclature up,
2 which I don't think I am. But what I circled here was
3 the link -- I -- I -- I -- I chose to differentiate the
4 fluorophore and the linker from what it was attached to
5 by that bond that was forged by adding Fmoc chloride.

6 Q. Okay. So your circle includes the fluorenyl,
7 the methoxycarbonyl, and it is up through the NH on the
8 6 position of the base?

9 A. It does not include the NH on the 6 position
10 of the base. That was originally there. That was the
11 nucleophile that attacked -- the activated chloride.

12 Q. Okay. Thank you.

13 A. I'm sorry. The activated cloro acid.

14 Q. Thank you.

15 MR. SCHWARTZ: I have no further
16 cross-examination questions.

17 MR. ZIMMERMAN: Can we take a short break?

18 MR. SCHWARTZ: Yes.

19 THE VIDEOGRAPHER: We're going off the record
20 at 2:43 p.m.

21 (Recess taken from 2:43 p.m. to
22 2:59 p.m.)

23 THE VIDEOGRAPHER: We are back on the record
24 at 2:59 p.m.

25 ///

EXAMINATION

BY MR. ZIMMERMAN:

Q. Good afternoon, Dr. Romesberg. I have just a few questions for you that follow up on your testimony earlier today.

The first one is, at any of the breaks did I discuss questions I was going to ask you or the answers you were to give to those questions?

A. No.

Q. Okay. You talked about the Genêt papers earlier in your direct testimony under questioning, correct?

A. Correct.

Q. Okay. And you said that those papers were cited by Dr. Ju?

A. Correct.

Q. Okay. They weren't cited in Dr. Ju's patents, were they?

A. No.

Q. Okay. What were they cited in?

A. They were cited in, I believe, the -- the 2005 paper that I cite, the 2006 paper that I cite, as well as his student's thesis.

Q. Okay. And those papers and thesis were after the patents, correct?

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1 A. Yes.

2 Q. Okay.

3 A. That is correct.

4 Q. Now, you talked in response to questions about
5 increasing concentration to increase efficiency.

6 Do you recall that testimony?

7 A. I do.

8 Q. Okay. Now, that idea of increasing
9 concentration to increase efficiency, is that unique to
10 a particular polymerase?

11 A. No. It's neither unique to a particular
12 polymerase nor to a particular substrate. It is -- it
13 will be true of all substrates and all polymerases.

14 The reason these modified analogs do not
15 incorporate efficiently is because they don't bind as
16 tightly. And as you increase the concentration, you
17 overcome that. So it's -- the polymerase is just
18 binding a substrate. It doesn't matter whether it's a
19 natural substrate or an artificial substrate.
20 Increasing the concentration is expected to facilitate
21 incorporation.

22 Q. So is it correct that that applies regardless
23 of the polymerase or the 3'-protecting group being used?

24 A. Absolutely, it does.

25 Q. Okay. And why is that?

1 A. It's just entropy. It's just the probability
2 forming the complex that is proportional -- the
3 stability of the complex is proportional to the
4 concentrations that they are present at. So as you add
5 more of them, you bind more -- more of it binds. It's
6 actually called Le Chatelier's Principle, is you have an
7 equilibrium bound and unbound. As you add more of the
8 free triphosphate, the equilibrium shifts to more of the
9 bound state, and so it shifts. You bind more. You can
10 just think of it having more and more there. It's more
11 and more likely to keep binding.

12 And so, yeah, it's just a -- it's just a
13 fundamental law that the -- you can shift equilibrium by
14 adding more of -- of -- of a participant.

15 Q. Okay. Can you look at Exhibit 2137, which is
16 the paper where the first author is Linda Lee, the DNA
17 sequencing.

18 A. Oh, yeah.

19 Q. Dye-label terminators.

20 A. Yeah.

21 MR. SCHWARTZ: Just give me a second to get
22 there.

23 MR. ZIMMERMAN: Yeah, it's not a problem.

24 MR. SCHWARTZ: Got it.

25 ///

1 BY MR. ZIMMERMAN:

2 Q. Okay. Do you recall being asked some
3 questions about this paper, Dr. Romesberg?

4 A. I do.

5 Q. Okay. If you'll turn to page 2481. You'll
6 see that there's an Equation 1 in the right-hand column.

7 A. I see.

8 Q. Do you recall being asked about that equation?

9 A. I do.

10 Q. And then if you look in the left-hand column
11 at the bottom, you'll see a section where it says "RA
12 equals RC equals RG equals RT equals 1."

13 A. I see.

14 Q. Do you recall being asked questions about that
15 section?

16 A. Yes.

17 Q. Okay. So I have a question for you. When R
18 equals 1, what does that mean with respect to how
19 efficiently the dTNTp are incorporated compared to the
20 dNTPs?

21 A. Again, I didn't read this paper carefully, but
22 I believe what it means is that the ddNTPs and the
23 dNTPs, the natural substrates, would be equally
24 incorporated at the -- at the same efficiency.

25 Q. Okay. And why would they be equally

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1 **incorporated?**

2 A. Because -- because the dideoxy would probably
3 be at a higher concentration than the dNTP.

4 Wait. Can I have a second to read this?

5 **Q. Uh-huh. You can take as much time as you**
6 **need.**

7 A. So R subscript N in the enzyme dependent
8 discrimination content -- constant that describes the
9 extent of discrimination of the enzyme between each
10 dideoxy dNTP and dNTTP pair. And so an R subscript N
11 value -- an R value of 1 would mean they are equally
12 well recognized.

13 **Q. And when R subscript A equals R subscript C**
14 **equals R subscript G equals R subscript T equals 1, does**
15 **that mean all of the different ddNTPs are recognized at**
16 **the same level as the dNTPs or the natural nucleotides?**

17 A. I believe that's -- I believe that is correct.

18 **Q. Okay. Now, do you recall being asked**
19 **questions about the Metzker '94 article in your direct**
20 **testimony?**

21 A. I do.

22 **Q. Okay. If we could bring up Metzker '94. And**
23 **turn to Table 2 on page 4263.**

24 A. I'm there.

25 **Q. Okay. Do you recall being asked questions**

1 about the predictability of the data in this table and
2 whether you would know it, a priority before running the
3 experiments?

4 A. I recall being asked two types of questions
5 about this table and predictability, one as to whether
6 or not Metzker and coworkers would have had to run the
7 experiments or what one would have predicted after
8 seeing this data.

9 Q. Okay. And I believe you indicated that you
10 would need to actually run the experiments to know what
11 the results were going to be; is that correct?

12 A. Yeah. Metzker would not have been able to sit
13 down and predict. The only predictability that I
14 described at that point would have been Metzker would
15 have said -- might have said, look, there are two
16 reverse transcriptases. So whatever this reverse
17 transcriptase does, I don't know what it is, you've got
18 to run that experiment. But the only predictability
19 would have been that another rescript transcriptase
20 might be predicted to behave similarly.

21 After you got the data -- after he collected
22 the data, someone might have looked at this and said,
23 well, two reverse transcriptases handle it, so maybe
24 another reverse transcriptase will handle it. It's not
25 an absolute cast in stone, but there's some -- there's

1 more than zero predictability there.

2 Q. Okay. And you've reviewed the Ju patents that
3 are at issue in this case, right?

4 A. I have.

5 Q. Okay. Based on your review of the Ju patents,
6 does Ju give you any more predictability of whether a
7 particular polymerase will incorporate an O-allyl
8 protecting -- protected nucleotide than Metzker '94?

9 MR. SCHWARTZ: Objection. Outside of the
10 scope.

11 A. I'm not sure I understand the question.
12 Metzker has data. That's -- that's interesting. Ju
13 doesn't present data in the diaza -- in his -- in his --
14 you're referring to the patent?

15 BY MR. ZIMMERMAN:

16 Q. Yes.

17 A. There's no data in Ju's patents, so there's no
18 predictability.

19 Q. Does Ju give you any more information that
20 would allow you to better predict incorporation of
21 3'-O-allyl protected nucleotides than Metzker '94 does,
22 in your opinion?

23 MR. SCHWARTZ: Objection. Scope.

24 A. No. In -- in -- no.

25 ///

1 BY MR. ZIMMERMAN:

2 Q. Okay. Now, you were -- you were asked a
3 number of questions about incorporation and various
4 3'-protecting groups. And if you have a 3'-protecting
5 group and it diminishes the incorporation of the correct
6 base, what did Seitz do to incorporation of incorrect
7 bases or the wrong base?

8 A. So this is what I was describing. There's --
9 you can think of this as there being two things the
10 polymerase is reading to bind the right substrate. One
11 is the Watson-Crick pair. So if the incoming
12 triphosphate is a G and the templating nucleotide is a
13 C, that stabilizing interaction is going to favor its
14 formation relative to the incorrect triphosphate coming
15 in that gives you a mispair.

16 The other thing is that you have this
17 substituent at the 3' position of the sugar, and it may
18 not fit exactly as the polymerase anticipated. There's
19 no reason to think that those interactions would be
20 aware of each other. They are in different parts of the
21 polymerase. And so there -- there -- one would assume
22 they are going to be additive.

23 So if you think of how efficiently a mispair
24 is inserted -- sorry, a correct pair is inserted, and
25 you think how efficiently a mispair is synthesized, you

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1 have a window. And if you make modifications that
2 doesn't affect the relative stability of a correct
3 Watson-Crick pair, a GC for example, versus an incorrect
4 pair, for example, mediated by some interaction with
5 sugar, that whole window is likely to increase so --
6 because you're simply binding less.

7 But there's -- but that -- but that defect
8 induced in binding by the sugar is not going to affect
9 the difference in stability between a correct and an
10 incorrect Watson-Crick pair where you're pairing. There
11 are two separate things that the polymerase is grabbing
12 on to. You're decreasing the ability to bind due to one
13 interaction, but the differential stability of a correct
14 and incorrect pair at this other part of the polymerase
15 that's forming the Watson-Crick pair, there's no reason
16 to think that those should be related.

17 So if this is the window between a correct and
18 an incorrect pair for a natural triphosphate, if you're
19 simply decreasing the binding and not messing with the
20 pairing, one expects the window to just do this. So
21 there would be a higher concentration required for high
22 fidelity incorporation to get over the binding defect
23 caused by the sugar modification. But that would still
24 be less than the equally increased affinity amount that
25 you need for the incorrect triphosphate to be made, the

1 incorrect pairing.

2 Q. Okay. Now I'd like to shift gears a little
3 bit.

4 You recall toward the end of your testimony
5 you were brought to Exhibit 1119, which is your second
6 declaration and you were brought to page 50.

7 A. Okay. I got it.

8 Q. Before we -- before we shift to this, during
9 your last answer regarding what happens when a
10 3'-protective group diminishes incorporation, you were
11 on the camera with your -- your hands and a shifting
12 window. Can you explain what you meant with respect to
13 the shifting window and why it shifts?

14 A. Without the visual aid of my camera -- my
15 hands or --

16 Q. Well, I'm trying to figure out -- you showed
17 your hands going up, and I'm trying to figure out what
18 that represents, if anything.

19 A. So this -- so lower affinity is good. So this
20 is representative of, let's say, the concentration where
21 a triphosphate binds. This is the concentration where
22 the incorrect triphosphate binds and binds correctly for
23 the incorporation.

24 If you destabilize the interaction in a part
25 that doesn't impact the contribution from correct

1 pairing, that destabilization is expected to decrease
2 the stability of both the correct pair and the incorrect
3 pair by similar amounts. So that way this window will
4 simply shift to higher concentrations. You'll need
5 higher concentrations to achieve the high fidelity only
6 correct binding.

7 But that's -- there's a window between what
8 that will be and the higher concentration needed to bind
9 for the incorrect, as long as that contribution of the
10 incorrect pairing is independent of the modifications
11 and the destabilization caused at the sugar.

12 Q. Okay. So is it correct that the size of the
13 window stays the same?

14 A. To the extent that -- to the extent that they
15 are absolutely independent interactions, the -- the
16 interactions between the polymerase and the sugar and
17 the interactions between the polymerase and the
18 Watson-Crick base pair forming, then yes, they would be
19 completely independent. And that window would precisely
20 shift.

21 Now, maybe small changes. To the extent that
22 they are independent it would -- it would -- they would
23 shift equally.

24 Q. Okay. And if they are not independent, then
25 they would shift different amounts?

1 A. One could imagine them being slightly
2 different. Frankly, I can't imagine them being
3 particularly strongly coupled, so I don't think that
4 they would do this. I think that, you know, they might
5 do -- I'm wiggling my hands as I raise them. There
6 might be some variation, and I don't know exactly what
7 that would be. But it is unreasonable to think that a
8 modification of the sugar is going to destabilize the
9 correct pair and not affect the mispair. I can't
10 imagine that happening.

11 Q. Okay. So going back now to your second
12 declaration, Exhibit 1119. There were some discussions
13 about Fmoc, correct?

14 A. Correct.

15 Q. And then in response you talked about Prober
16 teaching linker chemistry --

17 A. I did.

18 Q. -- correct?

19 And you said that Dower references Prober and
20 Prober taught linker chemistry, correct?

21 A. That is correct.

22 Q. Okay. What is the linker chemistry that's
23 taught by Prober?

24 A. Prober teaches a propargylamine linker
25 attached to the 5 position of pyrimidines or the 7 diaza

1 position of purines.

2 Q. Okay. So the propargylamine chemistry that's
3 taught by Prober, could you use that to attach Fmoc to a
4 T nucleotide?

5 A. That was exactly my point, yes.

6 Q. Okay. And why is that?

7 A. Because you have a primary amine that's a
8 nucleophile. You have an Fmoc with an electrophilic
9 chloride. That's the whole point of the Fmoc -- of
10 having that built-in linker on Fmoc to attach the
11 fluorenyl fluorophore. Yeah, so I think that you would
12 simply -- it would probably be a better reaction than
13 the ones that are shown that are aromatic amines.

14 Q. Okay. Could you use Prober's linker chemistry
15 to attach Fmoc to the 5 position of a C nucleotide?

16 A. Yes.

17 Q. Okay. Could you use Prober's linker chemistry
18 to attach Fmoc to the 7 position of a diaza A
19 nucleotide?

20 A. Yes.

21 Q. And could you use Prober's linker chemistry to
22 attach Fmoc to the 7 position of a diaza G nucleotide?

23 A. Yes. And I think that's exactly why Dower was
24 citing to Prober.

25 Q. And would the use of that Prober chemistry

1 have been within the skill of a person of skilled in the
2 art at the time?

3 A. Yes.

4 MR. ZIMMERMAN: Can we take a short break?

5 MR. SCHWARTZ: Okay.

6 THE VIDEOGRAPHER: We're going off the record
7 at 3:16 p.m.

8 (Recess taken from 3:16 p.m. to
9 3:17 p.m.)

10 THE VIDEOGRAPHER: We are back on the record
11 at 3:17 p.m.

12 MR. ZIMMERMAN: I have no further questions
13 for Dr. Romesberg at this time.

14 MR. SCHWARTZ: I have one question.

15 FURTHER EXAMINATION

16 BY MR. SCHWARTZ:

17 Q. So your counsel just asked you questions about
18 the propargylamine linker in Prober. That's not a
19 cleavable linker, correct?

20 A. It is -- it is -- Prober -- so Prober used it
21 to attach fluorophores that were not cleavable. Dower
22 cites to the attachment of cleavable fluorophores --
23 sorry. Dower, I think at multiple spots, at least
24 three, talks about the need to link the fluorophore via
25 cleavable -- by a removable -- it needs to be removable.

1 He cites to Dower -- he cites to Prober for linkers.
2 The Fmoc group is a cleavable linker. So attaching the
3 Fmoc to the Prober cite would install a cleavable linker
4 as prescribed by Dower. The -- the link -- the -- the
5 modifications that Dower is citing to Prober for are to
6 attach the cleavable linker. They are not the cleavable
7 linker themselves.

8 Q. And in your -- in your testimony about
9 attaching Fmoc, the Fmoc label to the 5 position of the
10 purine or the 7 diaza position --

11 A. Backwards.

12 Q. 5 position of the pyrimidine and the 7
13 position -- 7 diaza of the purine --

14 (Court reporter clarification.)

15 Q. In your testimony about attaching Fmoc to the
16 5 position of the pyrimidine or the 7 diaza position of
17 the purine, the propargylamine linker is a separate
18 structure separate and apart from Fmoc, correct?

19 A. Separate and apart from Fmoc?

20 Q. Yeah.

21 A. Yeah. It's what you would use to attach Fmoc.

22 MR. SCHWARTZ: I have no further questions.

23 Thank you for your time.

24 MR. ZIMMERMAN: I have no further questions
25 either. We're done.

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1 THE VIDEOGRAPHER: We're going off the record
2 at 3:20 p.m.

3 (Deposition concludes at 3:20 p.m.)
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1 STATE OF CALIFORNIA)
)
2 COUNTY OF SAN DIEGO)

3 I, Linda E. Marquette, a Certified Shorthand
4 Reporter, do hereby certify:

5 That prior to being examined, the witness in the
6 foregoing proceedings was by me duly sworn to testify to
7 the truth, the whole truth, and nothing but the truth;

8 That said proceedings were taken before me at the
9 time and place therein set forth and were taken down by
10 me in shorthand and thereafter transcribed into
11 typewriting under my direction and supervision;

12 I further certify that I am neither counsel for,
13 nor related to, any party to said proceedings, nor in
14 anywise interested in the outcome thereof.

15 Further, that if the foregoing pertains to the
16 original transcript of a deposition in a federal case,
17 before completion of the proceedings, review of the
18 transcript ☐ was ☒ was not requested ☐ waived.

19 In witness whereof, I have hereunto subscribed my
20 name.

21
22 Dated: February 04, 2019

23
24 

25 Linda E. Marquette
RPR, CLR, CSR No. 11874,

DECLARATION UNDER PENALTY OF PERJURY

Case Name: Illumina, Inc. vs. The Trustees of Columbia
University in the City of New York

Date of Deposition: 02/01/2019

Job No.: 10051818

I, FLOYD ROMESBERG, PH.D., hereby certify
that I have read the transcript of my deposition and that
this transcript accurately states the testimony given by me,
with the changes or corrections, if any, as noted on an errata
sheet or errata sheets.

Executed this _____ day of
_____, 2019, at _____.

FLOYD ROMESBERG, PH.D.

NOTARIZATION (If Required)

State of _____

County of _____

Subscribed and sworn to (or affirmed) before me on
this _____ day of _____, 20__,
by _____, proved to me on the
basis of satisfactory evidence to be the person
who appeared before me.

Signature: _____ (Seal)

1 DEPOSITION ERRATA SHEET

2 Case Name: Illumina, Inc. vs. The Trustees of Columbia
University in the City of New York
Name of Witness: Floyd Romesberg, Ph.D.
3 Date of Deposition: 02/01/2019
Job No.: 10051818
4 Reason Codes: 1. To clarify the record.
2. To conform to the facts.
5 3. To correct transcription errors.

6 Page _____ Line _____ Reason _____
7 From _____ to _____

8 Page _____ Line _____ Reason _____
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1 DEPOSITION ERRATA SHEET

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22 _____ Subject to the above changes, I certify that the
transcript is true and correct

23 _____ No changes have been made. I certify that the
transcript is true and correct.

24

25 _____
FLOYD ROMESBERG, PH.D.

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