

Columbia Exhibit 2096
Illumina, Inc. v. The Trustees
of Columbia University in the
City of New York
IPR2018-00291, 318, 322, 385 & 797

**Illumina, Inc. vs. The Trustees of Columbia
University in the City of New York**

**Videotaped Deposition of
FLOYD ROMESBERG, PH.D.
September 19, 2018
Volume I**

<p>Page 1</p> <p>1 UNITED STATES PATENT AND TRADEMARK OFFICE 2 BEFORE THE PATENT TRIAL AND APPEAL BOARD 3 4 ILLUMINA, INC., Case No. IPR2018-00291 5 Petitioner, U.S. Patent 9,718,852 6 v. IPR2018-00318 7 THE TRUSTEES OF COLUMBIA U.S. Patent 9,719,139 8 UNIVERSITY IN THE CITY OF 9 NEW YORK, IPR2018-00322 10 Patent Owner. U.S. Patent 9,708,358 11 IPR2018-00385 12 U.S. Patent 9,725,480 13 14 VIDEOTAPED DEPOSITION OF FLOYD ROMESBERG, PH.D. 15 VOLUME I 16 SAN DIEGO, CALIFORNIA 17 SEPTEMBER 19, 2018 18 19 Reported By: 20 PATRICIA Y. SCHULER 21 CSR No. 11949 22 Job No. 10047002 23 24 25</p>	<p>Page 2</p> <p>1 UNITED STATES PATENT AND TRADEMARK OFFICE 2 BEFORE THE PATENT TRIAL AND APPEAL BOARD 3 4 ILLUMINA, INC., Case No. IPR2018-00291 5 Petitioner, U.S. Patent 9,718,852 6 v. IPR2018-00318 7 THE TRUSTEES OF COLUMBIA U.S. Patent 9,719,139 8 UNIVERSITY IN THE CITY OF 9 NEW YORK, IPR2018-00322 10 Patent Owner. U.S. Patent 9,708,358 11 IPR2018-00385 12 U.S. Patent 9,725,480 13 14 Videotaped deposition of Floyd Romesberg, Ph.D., 15 Volume I, taken on behalf of the Patent Owner at 16 12790 El Camino Real, San Diego, California, 17 beginning at 9:04 a.m. and ending at 3:48 p.m., on 18 September 19, 2018, before PATRICIA Y. SCHULER, 19 Certified Shorthand Reporter No. 11949. 20 21 22 23 24 25</p>
<p>Page 3</p> <p>1 APPEARANCES: 2 FOR PETITIONER: 3 KNOBBE MARTENS - SAN DIEGO, CA 4 BY: NATHANAEL R. LUMAN, ESQ. 5 12790 El Camino Real 6 San Diego, California 92130 7 (858) 707-4000 8 nate.luman@knobbe.com 9 - and - 10 KNOBBE MARTENS - WASHINGTON, DC 11 BY: WILLIAM R. ZIMMERMAN, ESQ. 12 1717 Pennsylvania Avenue 13 Suite 900 14 Washington, DC 20006 15 bill.zimmerman@knobbe.com 16 FOR PATENT OWNER: 17 FITZPATRICK, CELLA, HARPER & SCINTO 18 BY: ROBERT S. SCHWARTZ, ESQ. 19 BY: ZACHARY L. GARRETT, ESQ. 20 1290 Avenue of the Americas 21 New York, New York 10104-3800 22 Also Present: Dr. Steven Menchen 23 John White, Esq. 24 John Murnane, Esq. 25 Videographer: Daniel Bermudez</p>	<p>Page 4</p> <p>1 I-N-D-E-X 2 WITNESS: EXAMINATION 3 FLOYD ROMESBERG, PH.D. 4 BY MR. SCHWARTZ 8 5 6 7 E-X-H-I-B-I-T-S 8 PATENT OWNER'S PAGE 9 Exhibit 1012 Declaration of Floyd Romesberg, 12 10 Ph.D., in Support of Petition for 11 inter Partes Review of U.S. 12 Patent No. 9,718,852 13 14 Exhibit 1013 International Application 15 15 Published Under the Patent 16 Cooperation treaty, Title: "DNA 17 Sequencing" 18 Exhibit 2007 Declaration of Floyd Romesberg, 16 19 Ph.D. 20 21 Exhibit 2035 Video Deposition Transcript of 21 22 Floyd Romesberg, Ph.D. dated July 23 8, 2014 24 25 Exhibit 1015 Copy of US Patent No. 5,547,839 25 26 27 Exhibit 2080 Video Deposition Transcript of 32 28 Floyd Romesberg, Ph.D. dated 29 January 14, 2014 30 31 Exhibit 2082 Video Deposition Transcript of 73 32 Floyd Romesberg, Ph.D. dated 33 April 10, 2014 34 35 Exhibit 2083 Substitute Declaration of Floyd 75 36 Romesberg, Ph.D. in Support of 37 Patent Owner's Motion to Amend 38 39 40 41 42 43 44 45</p>

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1	SAN DIEGO, CALIFORNIA; WEDNESDAY, SEPTEMBER 19, 2018		1	And at the end is John Murnane from Fitzpatrick.	
2	9:04 a.m.		2	MR. ZIMMERMAN: Bill Zimmerman of Knobbe	
3	THE VIDEOGRAPHER: Good morning. We are		3	Martens Olson & Bear on behalf of Illumina and the	
4	now on the record. Today's date is September 19,		4	witness. With me is my partner Nate Luman and	
5	2018, and the time is 9:04 a.m. This is the video		5	Marcus Burch of Illumina.	
6	deposition of Floyd Romesberg Ph.D. being taken in		6	THE VIDEOGRAPHER: The court reporter is	
7	the matter of Illumina Inc. versus Trustees of		7	Patricia Schuler, and she may now swear in the	
8	Columbia University and the City of New York		8	witness.	
9	pending in the United States Patent and Trademark		9		
10	Office before the Patent Trial and Appeal Board,		10	FLOYD ROMESBERG, PH.D.,	
11	case numbers IPR2018-00291, IPR2018-00318,		11	having been administered an oath, was examined and	
12	IPR2018-00322, IPR2018-00385.		12	testified as follows:	
13	We are at Knobbe Martens, San Diego,		13		
14	12790 El Camino Real. My name is Daniel Bermudez		14	EXAMINATION	
15	of Aptus Court Reporting located at 600 West		15	BY MR. SCHWARTZ:	
16	Broadway, Suite 300, San Diego, California 92101.		16	Q. Good morning, Dr. Romesberg. As I said,	
17	Will counsel please identify yourselves		17	my name is Robert Schwartz, I'm usually referred to	
18	and state whom you represent.		18	as Bob Schwartz. I am an attorney representing	
19	MR. SCHWARTZ: My name is Robert		19	Columbia University in these IPRs.	
20	Schwartz. I'm an attorney with Fitzpatrick, Cella,		20	Would you please state your full name and	
21	Harper & Scinto in New York. I represent Columbia		21	a home address for the record.	
22	University, and with me is my colleague Zack		22	A. Floyd Romesberg, and my home address is	
23	Garrett also from Fitzpatrick. And sitting next to		23	8109 Camino del Sol, La Jolla, California.	
24	him is Dr. Steven Menchen and then sitting next to		24	Q. And you have been deposed before, have	
25	him is John White from the firm Cooper & Dunham.		25	you not?	

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1 A. I have.

2 Q. And the rule that we follow in

3 depositions is that unless your counsel instructs

4 you not to answer a question, you should attempt to

5 answer that question to the best of your ability.

6 You understand that, correct?

7 A. Yes, I do.

8 Q. And if at any time you don't understand

9 my question, please let me know. If you do not say

10 otherwise I'll assume that if you answered my

11 question that you understood that question, okay?

12 A. Yes.

13 Q. And you've heard this before, but the

14 other rule we try to follow -- it's broken,

15 unfortunately, all the time -- is that we try not

16 to talk over one because the court reporter -- it

17 becomes impossible for the court reporter to take

18 down questions and answers. So we'll try to talk

19 one at a time, okay?

20 A. I will try.

21 Q. And the other rule is that we give

22 audible answers, so head shaking or nodding is not

23 acceptable, okay?

24 Did you meet with your attorneys in

25 preparation for your deposition today?

Page 11

1 Q. And I guess maybe my question was not

2 clear, but I was specifically referring in

3 preparation for the deposition, so when did the

4 meetings take place in preparation for the depo?

5 A. I'm sorry. These last two -- this week.

6 Q. And approximately how much time did you

7 spend preparing for the depo?

8 A. 20 hours, maybe, approximately.

9 Q. Outside of those meetings, did you meet

10 with your attorneys at any other time -- and I

11 think you probably went into that. You met earlier

12 over the past couple of months; is that correct?

13 A. Yes.

14 Q. And did you speak to anybody else other

15 than your attorneys about this case?

16 A. No, I have not.

17 Q. And what did you do to prepare for

18 today's deposition?

19 A. Mostly read literature and documents and

20 refreshed my memory of all of the issues.

21 Q. And you understand that today's

22 deposition is for four IPRs, which are

23 IPR2018-00291, IPR2018-00318, IPR2018-00322,

24 IPR2018-00385. That is your understanding that the

25 deposition is in relation to those IPRs, correct?

Page 10

1 A. Yes.

2 Q. I am only asking for a yes or no.

3 A. Yes.

4 Q. What are the names of the attorneys you

5 met with?

6 A. Kerry and Nate.

7 Q. How many times did you meet with those

8 attorneys in preparation for your deposition today?

9 A. In person?

10 Q. Let's start with in person.

11 A. I didn't count, but I believe it would

12 have been, I think, three times, three or four

13 times sounds right.

14 Q. And then you had other meetings that were

15 I assume by telephone or something?

16 A. Yes, that's correct.

17 Q. How many times did you have meetings by

18 telephone?

19 A. I am going to guess about the same, three

20 or four times.

21 Q. And when did those meetings take place?

22 Let's start with the in person.

23 A. Over the past three or so months. One

24 pretty early on, and then one in the middle maybe a

25 month ago, and then a couple this week.

Page 12

1 A. I believe so. I don't, unfortunately,

2 recognize the numbers, but they are the four

3 nucleotide cases, yes.

4 Q. And you prepared an expert declaration in

5 each of those IPRs, correct?

6 A. I did.

7 Q. I am ready to put the first exhibit out.

8 I'm going to put in front of you what has been

9 marked as Exhibit 1012.

10 (Exhibit 1012 was previously marked for

11 identification.)

12 BY MR. SCHWARTZ:

13 Q. Exhibit 1012. These are the four --

14 these are the expert declarations that you

15 submitted in these IPRs, correct?

16 A. That is correct.

17 Q. And that's the first one. I can provide

18 you with the others if you want them, maybe for the

19 time being, we'll just leave one out on the table

20 if that's okay with you, Counsel, or unless you

21 want them all in front of him?

22 MR. ZIMMERMAN: That is fine with me.

23 MR. SCHWARTZ: It is just a lot of paper

24 to put in front of you, so we'll just leave those

25 out, but we have them all here.

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1 BY MR. SCHWARTZ:
2 **Q. Just look at the end of that declaration.**
3 **I just want to confirm that that's your signature.**
4 MR. ZIMMERMAN: Just so we have a clear
5 record, we're looking at Exhibit 1012 in the 291
6 IPR.
7 BY MR. SCHWARTZ:
8 **Q. Correct. That is what we're looking at**
9 **now.**
10 **Is that your signature?**
11 A. That is my signature, yes.
12 **Q. Do you recall signing the three expert**
13 **reports in these cases as well?**
14 A. Yes.
15 **Q. And what did you do to prepare your**
16 **expert declarations in this case?**
17 A. A lot of reading, discussions with my
18 lawyers, and a lot of writing and editing.
19 **Q. Did you receive any materials such as**
20 **scientific references or patents from your**
21 **attorneys that you used to prepare any of your**
22 **declarations?**
23 A. I did, yes.
24 **Q. And are all of those materials listed in**
25 **your reports?**

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1 **provide us any materials that you relied on to form**
2 **the opinions that are in your report that are not**
3 **listed. So I'm making that request on the record,**
4 **okay?**
5 MR. ZIMMERMAN: Okay.
6 BY MR. SCHWARTZ:
7 **Q. You've been an expert for Illumina in**
8 **other IPR proceedings, correct?**
9 A. That is correct.
10 **Q. And in some of those proceeding**
11 **Intelligent Bio-Systems challenged Illumina**
12 **patents; is that right?**
13 A. Yes.
14 **Q. And you submitted expert declarations on**
15 **behalf of Illumina in those proceedings?**
16 A. I did.
17 **Q. And you were deposed in those**
18 **proceedings, correct?**
19 A. I was.
20 **Q. And there was a court reporter at those**
21 **depositions who created a transcript of those**
22 **depositions, correct?**
23 A. Correct.
24 (Exhibit 1013 was previously marked for
25 identification.)

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1 A. To the best of my knowledge, yes.
2 **Q. And did you do any of your own literature**
3 **searching independent of the materials that were**
4 **provided to you by the attorneys?**
5 A. Yes, I did.
6 **Q. And are all of those materials listed in**
7 **your reports?**
8 A. No, they are not.
9 **Q. How did you decide what to list and what**
10 **not to list?**
11 A. I chose ones that I thought were most
12 relevant without diluting out into the many
13 articles that I examined.
14 **Q. Did you rely on any materials to form the**
15 **opinions in any of your reports that are not**
16 **listed?**
17 A. Yes, in a general way. For several of
18 the issues I looked at many papers, many more than
19 you would have wanted me to list and bring here.
20 And I just wanted to make sure that my
21 recollections of the time period were correct, my
22 impressions were correct. And the ones that I
23 included were the ones that I thought represented
24 that the best.
25 **Q. I am going to request that your counsel**

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1 MR. SCHWARTZ: I am going to put in front
2 of -- it is marked as Exhibit 1013. It is entitled
3 "DNA Sequencing."
4 MR. ZIMMERMAN: Just so we're clear, it's
5 1013 in which IPR?
6 MR. SCHWARTZ: 1013 in the 00385 IPR, but
7 I believe it's the same in all of them.
8 MR. ZIMMERMAN: I'm just not sure that
9 they all line up. But I want to make sure we are
10 clear as to which one it is.
11 BY MR. SCHWARTZ:
12 **Q. And that exhibit I just put in front of**
13 **you is entitled "DNA Sequencing." And it's a**
14 **patent application number WO91/06678 by Tsien. And**
15 **just for the court reporter, the Tsien is spelled**
16 **T-S-I-E-N.**
17 **And, Dr. Romesberg, this is the Tsien**
18 **reference that you referred to in your declarations**
19 **in the four IPRs in this case, right?**
20 A. Yes, it is.
21 (Exhibit 2007 was previously marked for
22 identification.)
23 BY MR. SCHWARTZ:
24 **Q. I'm going to put in front of you**
25 **Exhibit 2007, so this happens to be from the 00385**

<p style="text-align: right;">Page 17</p> <p>1 case. It's an expert declaration in IPR2013-00517. 2 Dr. Romesberg, this is one of the expert 3 declarations that you submitted on behalf of 4 Illumina in the IPR challenges made by Intelligent 5 Bio-Systems against Illumina; is that correct? 6 A. It appears to be, yes. 7 Q. And the Illumina patents at issue in 8 those IPRs related to SBS, correct? 9 A. Yes. 10 Q. Would you please go to Page 14 of your 11 declaration. And on Page 14, towards the bottom of 12 the page there is a header entitled "PCT 13 publication" -- W-zero -- I'm sorry. WO91/00678 to 14 Tsien. Do you see? 15 A. It's 06678. 16 Q. 00678? Thank you. 17 A. One zero. 18 Q. To Tsien, right? 19 A. Yes. 20 Q. That's the same Tsien reference as 21 Exhibit 1013 in the present IPRs, correct? 22 A. Yes, it is. 23 Q. Please draw your attention to the last 24 three sentences in paragraph 36. And in paragraph 25 36 you write -- and this is on Page 15, the last</p>	<p style="text-align: right;">Page 18</p> <p>1 three sentences in paragraph 36: "One of ordinary 2 skill in the art would have understood these 3 teachings of Tsien as stating that Tsien's 4 invention was nucleotide sequenced determination 5 using DNA polymerase, and in particular, sequencing 6 by synthesis." 7 That is what you wrote, correct? 8 A. Yes. 9 Q. And it is your opinion that a person of 10 ordinary skill in the art understood that Tsien's 11 invention was SBS, correct? 12 MR. ZIMMERMAN: Objection. Vague as to 13 time. 14 BY MR. SCHWARTZ: 15 Q. I am referring to a person of ordinary 16 skill as you defined it in your declarations. 17 MR. ZIMMERMAN: And, again, objection. 18 Vague as to time. 19 BY MR. SCHWARTZ: 20 Q. Well, in your declaration you say as of 21 2000, October 2000. So it's your understanding 22 that a person of ordinary skill -- and again, 23 whenever I use that term I am referring to how you 24 define it in October 2000 -- understood that 25 Tsien's invention was SBS?</p>
<p style="text-align: right;">Page 19</p> <p>1 A. Yes. 2 Q. And I'll specifically, again, for the 3 record refer to Dr. Romesberg's definition of POSA 4 in paragraph 24 of his declarations in these cases. 5 So whenever I use the word person of ordinary skill 6 or if I abbreviate it as POSA, we'll understand 7 we're using your definition as you have it in your 8 declarations as of October 2000, correct? 9 A. Okay. 10 Q. Can you please go back to the Tsien 11 reference, 1013. And again, this is the same Tsien 12 reference that you write about in Exhibit 2007, the 13 declaration that we just looked at, correct? 14 A. Yes. 15 Q. Please turn to Page 16 of Tsien and draw 16 your attention to lines 21 to 23. 17 Are you there? 18 A. I am. 19 Q. Tsien writes "One obvious potential 20 shortcoming of the present invention is that it 21 employs a long sequence of serial reactions." 22 Do you see that? 23 A. I do. 24 Q. So a reader of Tsien, a POSA reading 25 Tsien understood that Tsien's SBS method requires</p>	<p style="text-align: right;">Page 20</p> <p>1 multiple serial cycles, correct? 2 A. Yes. 3 Q. And earlier I asked you about whether you 4 had been -- 5 A. I would have to think that. I believe it 6 requires serial reactions. I guess I'm not 7 100 percent positive that simply reading a single 8 nucleotide, a sequence of one -- I would have to 9 check to see if that was covered in this patent or 10 not. 11 Q. No, I am just saying Tsien writes. When 12 Tsien writes that "One obvious potential 13 shortcoming of the present invention is that it 14 employs a long sequence of serial reactions." A 15 person reading that understood that Tsien was 16 referring to a method that requires multiple serial 17 reactions, correct? 18 A. That is what he wrote, and that is what a 19 POSA would have understood. 20 Q. And that's in relationship to his SBS 21 methods? 22 A. Yes. 23 Q. And earlier I asked you about whether you 24 had been deposed in the Illumina versus Intelligent 25 Bio-Systems IPRs.</p>

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1 Do you remember that?

2 A. I do.

3 Q. And you testified you had been deposed,

4 correct?

5 A. Correct.

6 Q. And you testified that there were

7 deposition transcripts from those depositions,

8 correct?

9 A. Correct.

10 Q. Did you review any of those deposition

11 transcripts in preparation for your deposition

12 today?

13 A. I looked over them, yes.

14 Q. I am ready to mark my next exhibit, which

15 is exhibit -- let me get this to the court

16 reporter.

17 (Exhibit 2035 was marked for

18 identification.)

19 BY MR. SCHWARTZ:

20 Q. I am putting in front of Dr. Romesberg

21 Exhibit 2035, which is entitled video deposition of

22 Floyd Romesberg Ph.D. dated July 8, 2014. And

23 please turn to the last page of Exhibit 235, I

24 believe it is page 190. And is that your signature

25 on page 190?

Page 23

1 nucleotide reads that he would have to assemble to

2 be able to reassemble a genome and uniquely place

3 that sequence within the genome.

4 Q. So, again, just so I have a clean record,

5 it is your opinion that SBS requires sequencing of

6 about 25 base pairs. That's what you said, right?

7 MR. ZIMMERMAN: Same objection.

8 MR. SCHWARTZ: And, again, vague

9 objections are actually not allowed in patent

10 office proceedings, just so you know. You can just

11 say "objection," but you can't say anything else.

12 MR. ZIMMERMAN: I'm just trying to give

13 you an opportunity to correct the question so we

14 are clear as to what time frame you are talking

15 about.

16 MR. SCHWARTZ: I am always talking about

17 the time frame of October 2000, okay, as he defines

18 what a POSA would understand, okay?

19 THE WITNESS: I think you have to be a

20 little bit careful to define what you mean by

21 sequencing by synthesis, but you can read a

22 sequence, and you can read a sequence of one. I

23 assume that what I was talking about here -- I'd

24 have to take a few seconds to refresh my memory,

25 but I assume what I'm talking about is the ability

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1 A. It is.

2 Q. Please turn to page 179 of the

3 transcript. And please draw your attention to

4 line 2 on page 179. And starting at line 2 the

5 transcript reads "Question: Dr. Romesberg, you

6 testified that approximately 25 base pairs would be

7 needed for sequencing by synthesis. Do you recall

8 that."

9 And you answered, "Yes, I do."

10 That was your testimony, correct?

11 A. That is what is written, yes.

12 Q. It is your opinion that SBS requires

13 sequencing about 25 base pairs, correct?

14 MR. ZIMMERMAN: Objection. Vague as to

15 time.

16 THE WITNESS: I would have to also --

17 BY MR. SCHWARTZ:

18 Q. And I'm referring always to the

19 October 2000 time frame, as I mentioned earlier,

20 whenever I use the word POSA.

21 A. I would have to look back through this to

22 refresh my memory to see the context of which I was

23 describing this, but it would not surprise me that

24 I would say that. I would imagine I was talking

25 about, as it goes on to explain, the amount of

Page 24

1 to, in a practical way, sequence a genome or

2 sequence an unknown piece of DNA, in which case

3 something like 25 would seem like a reasonable

4 answer.

5 BY MR. SCHWARTZ:

6 Q. But did you testify just -- your

7 testimony I'm just reading it from your transcript

8 is approximately 25 base pairs would be needed for

9 sequencing by synthesis.

10 That is what your testimony was, right?

11 A. That's what is written, yes.

12 Q. So when Tsien states in this patent

13 application that a long sequence of serial

14 reactions is required for his SBS method, that's

15 consistent with your opinion that SBS requires

16 sequencing about 25 base pairs, correct? It's

17 consistent?

18 MR. ZIMMERMAN: Object as to form.

19 MR. SCHWARTZ: You can just object.

20 THE WITNESS: Given the caveat that I

21 just described, but I believe that that statement

22 is correct.

23 BY MR. SCHWARTZ:

24 Q. I'm going to put in front of you my next

25 exhibit. Let me get it to the court reporter.

<p style="text-align: right;">Page 25</p> <p>1 Thank you.</p> <p>2 (Exhibit 1015 was marked for</p> <p>3 identification.)</p> <p>4 BY MR. SCHWARTZ</p> <p>5 Q. I put in front of you Exhibit 1015, which</p> <p>6 is patent No. 5547839. And again, this is from one</p> <p>7 of the IPRs, but I believe they are all the same.</p> <p>8 This is actually Illumina's exhibit, so it was used</p> <p>9 in all of your declarations.</p> <p>10 The first named inventor is Dower.</p> <p>11 Exhibit 1015 is the same Dower patent that you rely</p> <p>12 on in your expert declarations in the present IPRs,</p> <p>13 correct?</p> <p>14 A. It is.</p> <p>15 Q. And the Dower patent relates to SBS,</p> <p>16 correct?</p> <p>17 A. That is correct.</p> <p>18 Q. And so, like Tsien's SBS method, Dower's</p> <p>19 SBS method, since it's about SBS, requires</p> <p>20 sequencing about 25 base pairs. That's your</p> <p>21 opinion?</p> <p>22 A. Again, it is a little bit dependent on</p> <p>23 what your goal of sequencing by synthesis would be.</p> <p>24 But if it is to determine the unique -- to uniquely</p> <p>25 determine the sequence of an unknown piece of DNA</p>	<p style="text-align: right;">Page 26</p> <p>1 that is long and of practical use, the sort of way</p> <p>2 people would have wanted to use this, then yes.</p> <p>3 Q. So practical use of SBS would require</p> <p>4 that about 25 base pairs be sequenced?</p> <p>5 A. As long as that practical use required</p> <p>6 determining the sequence of a large piece of DNA</p> <p>7 that you don't know, yes.</p> <p>8 Q. And that's consistent with your testimony</p> <p>9 that about 25 base pairs is required for SBS?</p> <p>10 A. Yes. The reason I'm qualifying this is</p> <p>11 because there was a lot of interest, especially at</p> <p>12 this time, in determining single nucleotide</p> <p>13 polymorphisms. And that would be a specific single</p> <p>14 nucleotide. And so it is entirely possible that</p> <p>15 someone could have wanted to use these sorts of</p> <p>16 things for that, but that would not be the de novo</p> <p>17 sequencing that we're talking about.</p> <p>18 Q. But that would still require about 25</p> <p>19 base pairs of sequencing to do snips, right?</p> <p>20 A. Well, it depends on how you would do it.</p> <p>21 If you had a small piece of DNA and you just wanted</p> <p>22 to know what the nucleotide was at position -- at</p> <p>23 the position immediately following a primer, then</p> <p>24 no.</p> <p>25 Q. Let's go back to your deposition</p>
<p style="text-align: right;">Page 27</p> <p>1 transcript that was Exhibit 2035. And go back to</p> <p>2 that page 179 we actually looked at before. And we</p> <p>3 were looking at the top of the page where you</p> <p>4 testified that approximately 25 base pairs would be</p> <p>5 needed for sequencing by synthesis. That was your</p> <p>6 testimony, right?</p> <p>7 A. Yes.</p> <p>8 Q. And would you look just down to about</p> <p>9 line 12. And you were asked a question "If you</p> <p>10 were looking for a single nucleotide polymorphism</p> <p>11 using a sequencing by synthesis method, what</p> <p>12 minimum read length would you need?" And then</p> <p>13 there was -- you started to answer that. There was</p> <p>14 an objection. And then you were instructed you can</p> <p>15 answer.</p> <p>16 And then you said -- your answer was: "It</p> <p>17 would not change, because the SNP identification</p> <p>18 comes from the assembled genome, so you still need</p> <p>19 to assemble the genome, you still need to place the</p> <p>20 sequence within the genome to know or not a</p> <p>21 specific nucleotide is a SNP. So the SNP is</p> <p>22 determined after you assemble the genome, so it</p> <p>23 doesn't change anything."</p> <p>24 That was your testimony, correct?</p> <p>25 A. That is correct.</p>	<p style="text-align: right;">Page 28</p> <p>1 Q. And that is in relation to your testimony</p> <p>2 above that SBS requires sequencing of 25 base</p> <p>3 pairs, correct?</p> <p>4 A. That is correct.</p> <p>5 Q. So even if you are sequencing using SBS</p> <p>6 for SNPs, your testimony is it still requires about</p> <p>7 25 base pairs of sequencing, correct?</p> <p>8 A. So again, as I tried to explain a second</p> <p>9 ago, it would depend on how you were doing it. So</p> <p>10 if you simply had a genome or a large piece of DNA</p> <p>11 and you wanted to identify all the differences, the</p> <p>12 SNPs, then what I said in this testimony is</p> <p>13 correct. The reason I caveated it a minute ago was</p> <p>14 because I could also imagine cases where one would</p> <p>15 have a small piece of DNA and one would need to</p> <p>16 simply know the identity of a nucleotide at a given</p> <p>17 position, in which case then you would not need a</p> <p>18 read length of 25.</p> <p>19 So it really depends on the application,</p> <p>20 but for the sort of practical applications that I</p> <p>21 think we're going to spend most of our time</p> <p>22 discussing here, you would need read lengths that</p> <p>23 were longer than one.</p> <p>24 Q. So for a practical application of SBS,</p> <p>25 whether it would be for SNP or some other reason,</p>

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1 it is your opinion that you need to sequence about
2 25 base pairs?
3 MR. ZIMMERMAN: Objection. Asked and
4 answered.
5 MR. SCHWARTZ: You can't make that
6 objection. It's just objection.
7 BY MR. SCHWARTZ
8 **Q. I'm just looking at your testimony. I**
9 **just want to make sure that we understand what your**
10 **testimony is.**
11 A. What I was referring to here was a
12 certain sort of application. I think it's very
13 possible that people would have other applications
14 in mind where they would not need read lengths of
15 25.
16 BY MR. SCHWARTZ:
17 **Q. But you did testify that for SBS you need**
18 **a read length of 25. That is your testimony?**
19 A. The context of what I was talking about
20 at the time, which I hope I made clear, would
21 require read lengths of 25, yes.
22 **Q. And that would be the same if it was for**
23 **SNPs?**
24 A. In the context of what I was describing
25 here, which I hope I have made clear.

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1 And lots of people are interested in lots of
2 different things.
3 **Q. But you were asked specifically about**
4 **SBS, and your testimony was that 25 base pairs**
5 **would be required.**
6 A. Everything that we just talked about is
7 SBS. SBS in the context of my testimony here was
8 in a specific situation where you would need a read
9 length of 25. I can certainly imagine other
10 applications of SBS where you would not need that.
11 **Q. And the practical applications that you**
12 **need 25 when you're sequencing for purposes of**
13 **determining a gene, how it fits into the genome, is**
14 **that something like that?**
15 A. Yeah. So if you don't know anything
16 about the piece of DNA that you're sequencing, for
17 example, and you need to assemble it, you need
18 certain overlap with other sequences to be able to
19 do that, and so you would need longer read lengths
20 there.
21 **Q. Going back to the Tsien patent**
22 **application. Tsien doesn't disclose any sequencing**
23 **data using a 30 allyl nucleotide, correct?**
24 A. He does not have data for a three prime
25 allyl nucleotide, that is correct.

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1 **Q. And that's a practical application of**
2 **SBS, is that what you are saying?**
3 A. No. In the particular practical
4 application that I was talking about in this
5 testimony, yes. But as I just said, I can imagine
6 there would be other practical applications -- I
7 don't know all practical applications that people
8 might be interested in -- where you would need a
9 read length of one.
10 **Q. What practical application would you need**
11 **a read length of one?**
12 A. As I described a minute ago, I'll try to
13 be clear now. You might have a piece of DNA. And
14 you might say I want to know what the nucleotide is
15 at position 28. You could design a primer of 27
16 length or a primer that terminates immediately
17 before the nucleotide in the template that you're
18 interested in, and you could get a read length of
19 one and determine what that nucleotide was.
20 Now, that was not the applications that I
21 was describing in the context that we're
22 discussing. But it would seem to be an application
23 that someone might be interested in. I'm just
24 trying to be clear about what people might have
25 read Tsien or Prober and been interested in doing.

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1 **Q. I am going to mark another exhibit.**
2 MR. SCHWARTZ: Court reporter, before
3 you hand that over, this is an exhibit that has not
4 yet been marked. Could you please mark this as
5 Exhibit 2080.
6 (Exhibit 2080 was marked for
7 identification.)
8 MR. SCHWARTZ: You might want to put the
9 numbers on the bottom in case we have to come back
10 to it. This is going to be 2080.
11 BY MR. SCHWARTZ:
12 **Q. And this is a document entitled "Video**
13 **Deposition of Floyd Romesberg Ph.D." dated**
14 **January 14, 2014.**
15 **Do you see that?**
16 A. I do.
17 **Q. And this is the transcript of your**
18 **deposition in IPR2013-00128, correct?**
19 A. It would seem to be, yes.
20 **Q. Again, the Illumina patents that were**
21 **being challenged in this IPR relate to SBS,**
22 **correct?**
23 A. Yes.
24 **Q. Please turn to page 101 of the**
25 **transcript. Please draw your attention to line 6.**

<p style="text-align: right;">Page 33</p> <p>1 And starting at line 6 of the transcript it reads.</p> <p>2 "Question: And would you agree with me</p> <p>3 that in 2002 it was known that you could cleave a</p> <p>4 linker and a protecting group under identical</p> <p>5 conditions?</p> <p>6 "Answer: No, I would not agree with</p> <p>7 that.</p> <p>8 "Question: So if we can turn to start</p> <p>9 Exhibit 1012, that is the Tsien reference. And in</p> <p>10 particular, if can you turn to page 28 of Tsien."</p> <p>11 Now I'd like to stop here, because I just</p> <p>12 want to clarify something about the transcript.</p> <p>13 In the transcript, Tsien, the T-S-I-E-N</p> <p>14 paper is misspelled as C-H-E-N, correct? That is</p> <p>15 just a misspelling, correct?</p> <p>16 A. I believe so, yes.</p> <p>17 Q. So what you're actually -- the question</p> <p>18 and answer in the section relates to the Tsien,</p> <p>19 T-S-I-E-N, reference that is the same Tsien that we</p> <p>20 have been looking at in these IPRs, correct?</p> <p>21 A. I believe so, yes.</p> <p>22 Q. Let's jump to line 25 of the same page,</p> <p>23 and starting at line 25, the transcript reads, "So</p> <p>24 you see there that Tsien says the one method</p> <p>25 involves the use of a tag attached to the base</p>	<p style="text-align: right;">Page 34</p> <p>1 moiety, correct?</p> <p>2 "Answer: Yes, correct.</p> <p>3 "Question: And that is a fluorescent</p> <p>4 label attached to the base of the nucleotide,</p> <p>5 correct?</p> <p>6 "Answer: yes.</p> <p>7 "Question: Okay. And then the next</p> <p>8 sentence says the tag may be chemically cleaved,</p> <p>9 either separately or simultaneously with the</p> <p>10 deblocking step. Do you see that?</p> <p>11 "Answer: I do.</p> <p>12 "Question: And the deblocking step that</p> <p>13 Tsien is referring to there is the three prime OH</p> <p>14 blocking group, correct?</p> <p>15 "Answer: Yes.</p> <p>16 "Question: So then would you" -- strike</p> <p>17 that.</p> <p>18 "Question: So then you would agree that</p> <p>19 the concept that it was known in the art that you</p> <p>20 could cleave a base labeled, a cleavable linker</p> <p>21 attaching a label to a base in a three prime</p> <p>22 protecting group.</p> <p>23 "Answer: Just to be clear, I guess what I</p> <p>24 am -- I think what we are disagreeing here is</p> <p>25 whether -- with here is whether the suggestion had</p>
<p style="text-align: right;">Page 35</p> <p>1 been made or whether it was known that you could.</p> <p>2 I see that Tsien is suggesting that, and that was</p> <p>3 known in, and that had been suggested in the</p> <p>4 literature built before. I don't believe that</p> <p>5 Tsien provides any data.</p> <p>6 "Question: But the prior art did show,</p> <p>7 and Tsien is an example of that, that a person of</p> <p>8 skill in the art could cleave a cleavable linker,</p> <p>9 attaching a label to the base and a three prime</p> <p>10 protecting group.</p> <p>11 "Answer: I don't.</p> <p>12 "Question: Correct?</p> <p>13 "Answer: No. I don't know that Tsien</p> <p>14 provided that. I don't know that anyone -- I don't</p> <p>15 know that that was known. I'm unaware of that."</p> <p>16 That was your testimony, correct?</p> <p>17 MR. ZIMMERMAN: Objection.</p> <p>18 Mischaracterizes.</p> <p>19 BY MR. SCHWARTZ:</p> <p>20 Q. That was your testimony, correct?</p> <p>21 A. That is what -- you read the transcript</p> <p>22 correctly. It's a little bit hard for me, because</p> <p>23 I haven't read and thought about this particular --</p> <p>24 Q. I am just asking you about that piece.</p> <p>25 That was your testimony, correct?</p>	<p style="text-align: right;">Page 36</p> <p>1 A. You read it correctly.</p> <p>2 Q. And in your deposition testimony in</p> <p>3 IPR2013-00128, you specifically pointed out that</p> <p>4 Tsien does not provide any data for simultaneously</p> <p>5 cleaving a cleavable linker, attaching a label to a</p> <p>6 base in a three prime protecting group, correct?</p> <p>7 A. That seems to be correct, yes.</p> <p>8 Q. And you testified that you were not aware</p> <p>9 of any other prior art that provided data showing</p> <p>10 simultaneous cleavage of the cleavable linker in a</p> <p>11 three prime protecting group, correct?</p> <p>12 A. That seems to have been my testimony.</p> <p>13 Q. And without having such data it was your</p> <p>14 testimony that it was not known that a cleavable</p> <p>15 linker in a three prime protecting group could be</p> <p>16 cleaved, correct?</p> <p>17 A. That seems to have been my testimony.</p> <p>18 Q. And going back to Tsien, Tsien doesn't</p> <p>19 disclose any data showing that a nucleotide with a</p> <p>20 3'-O-allyl protecting group could be cleaved under</p> <p>21 conditions that are compatible with SBS, correct?</p> <p>22 A. Tsien shows no data after that, correct.</p> <p>23 Q. And sitting here today, are you aware of</p> <p>24 any prior art -- and again, I'm dealing with your</p> <p>25 definition as of October 2000 -- that provided any</p>

<p style="text-align: right;">Page 37</p> <p>1 data that a nucleotide with a 30 allyl protecting 2 group could be used successfully for SBS? 3 A. No. I think there was data that 4 suggested that it could be used. 5 Q. What data was that? 6 A. Reaction showing that you could 7 efficiently deprotect the -- you could efficiently 8 remove the deprotecting group. 9 Q. That wasn't in the context of SBS, was 10 it? 11 A. No, but you asked about any data. 12 Q. I asked specifically -- let me ask the 13 question again, okay? 14 Are you aware of any prior art prior to 15 October 2000 that provided any data that a 16 nucleotide with a 3'-O-allyl protecting group could 17 be used for SBS? 18 A. I think that the way you asked the 19 question, the way I would interpret that is that 20 any data would include data that a person of 21 ordinary skill in the art would look at a 22 particular reaction, let's say, and draw an 23 impression about the same or similar reaction that 24 could be used in SBS. And I believe there was data 25 for that.</p>	<p style="text-align: right;">Page 38</p> <p>1 Q. I'm not asking you about drawing 2 inferences. I'm asking you for any direct data -- 3 just the way you testified that you weren't aware 4 of any data that showed cleavable linker on three 5 prime protecting group cleavage. Are you aware of 6 any data -- in the context of actually using it for 7 SBS -- in an SBS reaction, are you aware of any 8 data that a 3'-O-allyl protecting group on a 9 nucleotide that was used for SBS? 10 A. So let me be clear about the answer. My 11 testimony here referred to simultaneously 12 deprotecting a blocking group and a linker on a 13 base. And I testified, and I would have to rethink 14 this, but I believe I understand the context, and I 15 believe that that answer was correct, because no 16 one had ever shown the simultaneous deprotection of 17 two things like that. 18 This is a rather different question, and 19 I'm going to again explain that if one was simply 20 asking if an O-allyl could be deprotected from a 21 nucleotide, it is common, and any person of 22 ordinary skill in the art would have exercised this 23 exact procedure, you would look for -- he or she 24 would have looked for similar reactions, and then 25 it's more than just an inference. This is the way</p>
<p style="text-align: right;">Page 39</p> <p>1 you draw an impression about how optimistic or 2 pessimistic you are about whether or not 3 something's feasible, whether or not you're 4 interested in it. And there was a lot of data, not 5 on an exact nucleotide that would have been used 6 for sequencing by synthesis. So this is not 7 exactly in a sequencing by synthesis reaction, but 8 there were very similar reactions where people 9 would have drawn an impression. 10 So there certainly was data, but there 11 was not data that was used within the context of an 12 exact sequencing by synthesis reaction. 13 Q. So it's your testimony here today that 14 you are not aware of any data prior to October 2000 15 where an 3'-O-allyl nucleotide was used precisely 16 in a SBS reaction? 17 A. That is correct. 18 So can I add one qualifier to that? 19 Metzker did report prior to 2000 a reaction that 20 was getting very, very close. It examined parts of 21 what you would use for sequencing by synthesis 22 reaction, but it was not the complete sequencing by 23 synthesis. 24 Q. But Metzker didn't show any data using 25 the 3'-O-allyl nucleotide for SBS, he did?</p>	<p style="text-align: right;">Page 40</p> <p>1 A. No, but he did look at steps that would 2 be involved in that. 3 Q. But he didn't do it for SBS. He never 4 evaluated that nucleotide for SBS, correct? 5 A. He never used it for sequencing by 6 synthesis, but I just want to be clear that there 7 were examples in literature that was very close 8 that any person of ordinary skill in the art would 9 have relied on to draw an opinion. And more 10 importantly, an opinion was available in 2000 is 11 the point I am trying to make. 12 Q. There was no data. There was no data 13 using a 3'-O-allyl nucleotide for SBS, because that 14 nucleotide would have required a label attached to 15 it as well, correct? 16 A. Just to be clear, sequencing by synthesis 17 is a multi-step process, and there were reports of 18 some of those steps, not all of them. So in a 19 complete sequencing by synthesis reaction, there 20 was no data, no one had tried to my knowledge. But 21 there were examples of different part components of 22 this -- different steps of the overall reaction 23 that had been reported. 24 Q. But not for the complete nucleotide for 25 SBS?</p>

<p style="text-align: right;">Page 41</p> <p>1 A. That's right. Not for the complete 2 scheme for all the steps of the sequencing by 3 synthesis reaction. 4 Q. And without having any data, the best you 5 could do is speculate at that point? 6 A. Well, this is the problem I'm having. I 7 disagree with the statement that there would not 8 have been any data, because there are multiple 9 steps. And you have data that shows whether or not 10 the O-allyl -- the 3'-O-allyl variant would have 11 satisfied individual steps of the overall reaction. 12 You did not have any data on the overall reaction, 13 but you did have data on very relevant steps of 14 that overall reaction. And I think that would have 15 been -- I call that data, and I think a person of 16 ordinary skill in the art would have viewed that as 17 data relevant to how he felt -- he or she felt 18 about the O-allyl groups. 19 Q. But you didn't refer to that kind of 20 steps data when you were testifying about the 21 simultaneous cleavage. There was data. You were 22 asked about data for the individual steps, and you 23 said there was no data for the combined cleavage 24 reaction. That it was not enough to just look at 25 the individual data. You were not aware of any</p>	<p style="text-align: right;">Page 42</p> <p>1 data showing simultaneous cleavage, correct? 2 MR. ZIMMERMAN: Objection. Compound. 3 BY MR. SCHWARTZ: 4 Q. That was your testimony? 5 MR. ZIMMERMAN: Objection. Compound. 6 MR. SCHWARTZ: Again, you can object. 7 MR. ZIMMERMAN: The rules allow me to 8 succinctly state my objection. Objection. 9 Compound. 10 BY MR. SCHWARTZ: 11 Q. Okay. 12 A. What I was referring to in that testimony 13 was a specific step, and no one had ever shown that 14 step. 15 Q. Okay. And no one has ever shown all of 16 the steps involved in SBS for the 3'-O-allyl 17 nucleotide, correct? 18 A. That is correct. No one has shown all of 19 the steps for a 3'-O-allyl nucleotide. That is 20 correct. 21 Q. And without that data, you can only 22 speculate that it would work? 23 A. I disagree with that. 24 Q. But let's go to an Exhibit 2007. It's an 25 exhibit that is already on the table. It's your</p>
<p style="text-align: right;">Page 43</p> <p>1 expert declaration in IPR2013-00517. Please turn 2 to paragraph 37, page 15. 3 In paragraph 37 you write: "According to 4 Tsien, the criteria for the successful use of 5 3'-O-allyl blocking groups include, one, the 6 ability of a polymerase enzyme to accurately and 7 efficiently incorporate the DNTPs carrying the 8 3'-O-allyl blocking groups into the CNA chain; two, 9 the availability of mild conditions for rapid and 10 quantitative deblocking; and, three, the ability of 11 the polymerase enzymes to reinitiate the cDNA 12 synthesis subsequent to the deblocking stage. And 13 you cite to Tsien at column 20, lines 28 to column 14 21, line three. 15 That was what you wrote, correct? 16 A. That is correct. 17 Q. And the Tsien reference that you are 18 referring to in this exhibit is the same Tsien 19 reference that is marked 1013 in these IPRs, 20 correct? 21 A. That is correct. 22 Q. So going to the first criteria: "If a 23 nucleotide analog with a 3'-O-allyl blocking group 24 was not accurately and efficiently incorporated 25 into the DNA chain by the polymerase, it would not</p>	<p style="text-align: right;">Page 44</p> <p>1 be expected to be successful in Tsien's SBS 2 method," correct? 3 A. I think it is important to be careful 4 about what you mean by "accurately and 5 efficiently," because those are absolute 6 statements. And it is certainly true that there is 7 a efficiency and an accuracy requirement for 8 sequencing by synthesis. So I would not want to 9 quantitatively assign any meaning to "accurately 10 and efficiently," but there certainly is a 11 requirement, yes. 12 Q. I was not asking you at this point to 13 assign any numbers or anything. I'm just saying 14 that you cite to Tsien's three requirements. And 15 I'm just asking you if a nucleotide with 16 three-prime blocking group was not accurately and 17 efficiently incorporated as Tsien requires, then it 18 would not be expected to work for his method? 19 A. Are you asking me to confirm that that's 20 what Tsien says, or what my opinion is? 21 Q. I'm asking you -- well, you wrote this. 22 This is what you wrote. You cited this about 23 Tsien's requirements? 24 A. Right. So according to Tsien, that is 25 correct.</p>

<p>Page 45</p> <p>1 Q. So according to Tsien, if any of these</p> <p>2 criteria are not met, Tsien says it wouldn't be</p> <p>3 expected to work for his SBS method, correct?</p> <p>4 A. Yes.</p> <p>5 Q. Let's go to Tsien's second requirement,</p> <p>6 which is the availability of mild conditions for</p> <p>7 rapid and quantitative deblocking. We'll talk</p> <p>8 about that for a little bit, okay?</p> <p>9 A. Yes.</p> <p>10 Q. Please go back to your declaration,</p> <p>11 Exhibit 2007, it was your declaration in</p> <p>12 IPR2013-00517. Do you have that?</p> <p>13 A. Yes, I do.</p> <p>14 Q. Please go to page 29. Please draw your</p> <p>15 attention to paragraph 55, and please look down</p> <p>16 about five lines to a sentence that starts with "in</p> <p>17 fact most."</p> <p>18 Do you see that?</p> <p>19 A. I do.</p> <p>20 Q. And in paragraph 55 you write: "In fact,</p> <p>21 most organic solvents, including tetrahydrofuran,</p> <p>22 THF, and methanol were known to denature DNA." And</p> <p>23 you cite the Lee paper of 1981, and you say "(such</p> <p>24 unwinding of the DNA duplex caused by dehydration</p> <p>25 is likely to be a common phenomenon in organic</p>	<p>Page 46</p> <p>1 solvents.)"</p> <p>2 That's is what you wrote, correct?</p> <p>3 A. That is what I wrote.</p> <p>4 Q. So it is your opinion that most organic</p> <p>5 solvents, including methanol, were known to</p> <p>6 denature DNA, correct?</p> <p>7 A. Under conditions where they dehydrate the</p> <p>8 DNA, yes.</p> <p>9 Q. Your testimony is most organic solvents,</p> <p>10 including methanol, were known to denature DNA.</p> <p>11 You cite to the Lee paper, correct?</p> <p>12 A. Yes. And I was also trying to be clear</p> <p>13 that it was due to dehydration.</p> <p>14 Q. Let's turn to page 23 of your</p> <p>15 declaration. And please draw your attention to the</p> <p>16 second line on the top of the page that starts with</p> <p>17 "This reaction was performed in methanol."</p> <p>18 Do you see that?</p> <p>19 A. Yes, I do.</p> <p>20 Q. And you write: "This reaction was</p> <p>21 performed in methanol which was known to denature</p> <p>22 DNA, required two hours, and resulted in only</p> <p>23 75 percent to 91 percent yield." You cite to a</p> <p>24 paper by Loubinoux. "Further, stannous chloride</p> <p>25 was known to damage DNA by causing nicks in DNA</p>
<p>Page 47</p> <p>1 strands." And you cite to a Dantas paper. Then</p> <p>2 you write: "Any one of these considerations would</p> <p>3 have led one of ordinary skill to have expected</p> <p>4 stannous chloride to be incompatible which ends in</p> <p>5 Ju's requirements for sequencing by synthesis."</p> <p>6 That is what you wrote, correct?</p> <p>7 A. That is what I wrote, correct, yes.</p> <p>8 Q. And, again, the Tsien reference that you</p> <p>9 referred to in that statement is the same Tsien</p> <p>10 reference as Exhibit 2 -- 1013, correct?</p> <p>11 A. It is.</p> <p>12 Q. And the reaction you are referring to in</p> <p>13 your declaration is a deprotection reaction of the</p> <p>14 3'-O-allyl protecting group, correct?</p> <p>15 A. Correct.</p> <p>16 Q. It is your opinion that 3'-O-allyl</p> <p>17 deprotection reactions that denature DNA, such as</p> <p>18 those that are performed in methanol, are</p> <p>19 incompatible with Tsien's SBS method.</p> <p>20 It's what you wrote?</p> <p>21 A. It is what I wrote.</p> <p>22 Q. And in fact, you also wrote in your</p> <p>23 opinion that 3'-O-allyl deprotection reactions that</p> <p>24 are performed in most organic solvents are</p> <p>25 compatible with SBS.</p>	<p>Page 48</p> <p>1 That's what you wrote, correct?</p> <p>2 A. Could you point me to where I wrote that,</p> <p>3 please?</p> <p>4 Q. We just looked at that before, remember?</p> <p>5 A. Right. So due to dehydration.</p> <p>6 Q. Most organic solvents?</p> <p>7 A. Yes. Due to dehydration, yeah. They're</p> <p>8 not damaging the DNA is what I mean. But they're</p> <p>9 incompatible if they're denaturing the DNA, yes.</p> <p>10 Q. And what we looked at, you don't say</p> <p>11 anything about dehydration. You just say the</p> <p>12 reaction was performed in methanol, which is</p> <p>13 incompatible with Tsien's SBS method. That is what</p> <p>14 you wrote?</p> <p>15 MR. ZIMMERMAN: Objection.</p> <p>16 Mischaracterizes.</p> <p>17 BY MR. SCHWARTZ:</p> <p>18 Q. That's what you wrote?</p> <p>19 A. That is what I wrote in the section, but</p> <p>20 I do believe I was trying to be clear in the</p> <p>21 document that that was due to dehydration.</p> <p>22 Q. So you're saying that the mechanism of</p> <p>23 denaturation by methanol is dehydration?</p> <p>24 A. The mechanism of denaturation is</p> <p>25 dehydration, yes.</p>

<p style="text-align: right;">Page 49</p> <p>1 Q. Let's go back to Tsien, please, 2 Exhibit 2013. And please turn to page 23. And 3 please draw your attention to line 27. There is a 4 section entitled "deblocking methods." Do you see 5 that? 6 A. I do. 7 Q. And starting at line 33, Tsien teaches 8 that the deblocking method used in his SBS method 9 must, A, proceed rapidly; B, yield a viable 10 3'-O-allyl O-H function in high yield; and, C, not 11 interfere with future enzyme function or denature 12 the DNA strand." 13 Those are Tsien's requirements for 14 deblocking the 3'-O-allyl protecting group, right? 15 A. He lists those requirements, yes. 16 Q. And Tsien expressly requires that the 17 deblocking conditions used to remove the 3'-O-allyl 18 protecting group does not denature the DNA, 19 correct? 20 A. Yes. 21 Q. Will you please go back to Exhibit 2035, 22 that was your transcript from your deposition in 23 IPR2013-00517. 24 A. Okay. 25 Q. You have it?</p>	<p style="text-align: right;">Page 50</p> <p>1 A. Yes. 2 Q. Can you please turn to page 174. Please 3 draw your attention to line 19, and starting at 4 line 19 the transcript reads: 5 "Question: And is it reasonable for 6 someone looking to develop an SBS method to consult 7 synthetic chemistry papers? 8 "Answer: Yes, it is. 9 "Question: Does that -- and does it 10 depend on what is disclosed in those papers? 11 "Answer: Yes. So I mean, if I were 12 looking to develop a sequencing by synthesis 13 method, I would certainly consult synthetic 14 chemistry papers that showed things like efficiency 15 of protecting group cleavage. I would look at the 16 conditions that were explored to see if they were 17 compatible with sequencing by synthesis, and I 18 would look at yield to see if they were compatible 19 with the high efficiencies required for sequencing 20 by synthesis. 21 "Question: And if the conditions 22 disclosed in a particular reference were 23 incompatible with sequencing by synthesis, would 24 there be any expectation of success? 25 "Answer: That would not provide an</p>
<p style="text-align: right;">Page 51</p> <p>1 expectation of success." 2 That was your testimony, correct? 3 A. Yes. 4 Q. So your opinion is that it is reasonable 5 for someone looking to develop SBS methods to 6 consult synthetic chemistry papers, correct? 7 A. Yes. 8 Q. And your opinion is, if the condition 9 disclosed in a synthetic chemistry paper for 10 cleavage of the three-prime protecting group is 11 incompatible with SBS, then there would not be any 12 expectation of success, correct? 13 A. If a synthetic chemistry paper did not 14 provide conditions that were compatible with DNA 15 sequencing, then that paper itself would not 16 provide an expectation of success. 17 Q. And that would be true for Tsien's SBS 18 method, correct? 19 A. Yes. 20 Q. And it would be true for Dower's SBS 21 method, correct? 22 A. Yes. 23 Q. While we have the transcript open, please 24 turn to page 177. And please draw your attention 25 to line 17. And starting at line 17 the transcript</p>	<p style="text-align: right;">Page 52</p> <p>1 reads: 2 "Question: Would you expect DNA to be 3 denatured at 20 degrees Celsius in aqueous 4 pyrimidine sufficient to solubilize 5 triphenylphosphine?" 6 There was an objection. 7 "Answer: That depends on the DNA. Large 8 pieces of DNA like chromosomal DNA or maybe even 9 plasma DNA at 20 degrees in pyrimidine might 10 actually not, although it might be denatured, but 11 certainly primer templates of the sort used in 12 sequencing by synthesis would be denatured at 13 20 degrees in pyrimidine. 14 "Question: Can you explain why. 15 "Answer: Well, because they're already 16 not very stable. They're only marginally stable 17 because they are reasonably short." 18 That was your testimony, correct? 19 A. That is correct. 20 Q. And your opinion is that DNA denaturation 21 is an especially important consideration in SBS, 22 because SBS uses short primer and DNA templates 23 that are only marginally stable due to their short 24 length, correct? 25 A. I don't know that I would characterize it</p>

<p style="text-align: right;">Page 53</p> <p>1 as an especially critical step, but it is a</p> <p>2 required step that you do denature -- that you do</p> <p>3 not dissociate the primer from the template.</p> <p>4 Q. And because the primers and the templates</p> <p>5 are short in length, they are more susceptible to</p> <p>6 denaturation?</p> <p>7 A. Shorter than chromosomal double-stranded</p> <p>8 DNA, so certainly, yes.</p> <p>9 Q. They're already not very stable. That</p> <p>10 was your testimony.</p> <p>11 A. Well, they're certainly less stable, so</p> <p>12 they're more prone to lose structure when you</p> <p>13 perturb them by any method; heating or</p> <p>14 denaturational, whatever.</p> <p>15 Q. And so that's why my question was, so</p> <p>16 they are -- that's a particularly important</p> <p>17 consideration in SBS because the primers and the</p> <p>18 templates are short and only marginally stable,</p> <p>19 they are even more susceptible to denaturing</p> <p>20 conditions, correct?</p> <p>21 A. Yes. I was just a little -- I was</p> <p>22 commenting on that I did not think that the</p> <p>23 denaturation was any more critical than any other</p> <p>24 requirement. But relative to a chromosome, the</p> <p>25 conditions that usually would be used for</p>	<p style="text-align: right;">Page 54</p> <p>1 sequencing by synthesis would be more prone to</p> <p>2 denaturation.</p> <p>3 Q. I'm going to ask you to go back to your</p> <p>4 declaration in IPR2013-00517 that was marked as</p> <p>5 Exhibit 2007. Okay?</p> <p>6 A. I am there.</p> <p>7 Q. Please go to page 34. And please draw</p> <p>8 your attention to paragraph 60. And please look at</p> <p>9 the third line down in paragraph 60 that starts</p> <p>10 with "For example, it was known that."</p> <p>11 Do you see that?</p> <p>12 A. I do.</p> <p>13 Q. In paragraph 60 you write: "For example,</p> <p>14 it was known that stringent requirements for</p> <p>15 nucleotide analogs with removable 3'-OH terminators</p> <p>16 presented a formidable obstacle to developing</p> <p>17 stable and efficiently deprotected 3'-OH protecting</p> <p>18 groups for SBS." And you cite to Metzker at 4259.</p> <p>19 That is the Metzker paper that you also use in your</p> <p>20 declarations, correct?</p> <p>21 A. I believe that is correct, yes.</p> <p>22 Q. And you continue to say "And it was a</p> <p>23 major challenge in the field to develop 3'-OH</p> <p>24 terminators that were removable under aqueous SBS</p> <p>25 conditions." And you cite to the Welsh paper,</p>
<p style="text-align: right;">Page 55</p> <p>1 correct?</p> <p>2 A. Correct.</p> <p>3 Q. That's what you wrote?</p> <p>4 A. That is what I wrote.</p> <p>5 Q. It is your opinion that stringent</p> <p>6 requirements for nucleotide analogs with removable</p> <p>7 3'-OH terminators presented a formidable obstacle</p> <p>8 to developing stable and efficiently deprotected</p> <p>9 3'-OH protecting groups for SBS. That was your</p> <p>10 opinion, correct?</p> <p>11 A. Again, that is what is written there,</p> <p>12 yes.</p> <p>13 Q. And one of those obstacles is that SBS</p> <p>14 requires aqueous conditions for cleavage of the</p> <p>15 3'-OH protecting group, correct?</p> <p>16 A. That is correct.</p> <p>17 Q. And you agree it was a major challenge in</p> <p>18 the field to develop 3'-OH terminators for SBS that</p> <p>19 were removable under aqueous conditions, correct?</p> <p>20 A. Well, as I say, they were a stringent</p> <p>21 requirement for any sequencing by synthesis method</p> <p>22 of this sort, yes.</p> <p>23 Q. And you say though specifically it was a</p> <p>24 major challenge. I'm just reading from your</p> <p>25 declaration.</p>	<p style="text-align: right;">Page 56</p> <p>1 A. Yes, I think I was quoting a paper there.</p> <p>2 If you want me to describe what I'm trying to say,</p> <p>3 if I can remember the context, any sequencing by</p> <p>4 synthesis method stringently requires you simply --</p> <p>5 of the sequencing by synthesis methods that we're</p> <p>6 describing, you simply have to remove that</p> <p>7 protecting group.</p> <p>8 Q. Under aqueous conditions?</p> <p>9 A. Under conditions where the DNA is not</p> <p>10 going to denature, so, yeah, it's very likely there</p> <p>11 is going to have to be water there.</p> <p>12 Q. Well, you actually say that there, it was</p> <p>13 required that they were removable under aqueous</p> <p>14 conditions?</p> <p>15 A. Yes.</p> <p>16 Q. That is your testimony that it was</p> <p>17 required that it be removable under aqueous</p> <p>18 conditions?</p> <p>19 A. Yeah, that's -- just to be clear, that is</p> <p>20 what I meant to just say.</p> <p>21 Q. I am going to put another exhibit in</p> <p>22 front of you.</p> <p>23 MR. ZIMMERMAN: We've been going for a</p> <p>24 little over an hour. Do you need a break?</p> <p>25 THE WITNESS: Yeah, actually.</p>

<p style="text-align: right;">Page 57</p> <p>1 MR. ZIMMERMAN: If now is a good time.</p> <p>2 THE WITNESS: It will only take a second.</p> <p>3 MR. SCHWARTZ: Fine. And, of course,</p> <p>4 you've been through this, you've been to this rodeo</p> <p>5 before. If you ever need a break, you are entitled</p> <p>6 to have a break.</p> <p>7 THE WITNESS: Yeah, I can't understand</p> <p>8 why I have to go to the bathroom all the time.</p> <p>9 THE VIDEOGRAPHER: We are off the record</p> <p>10 at 10:07 a.m.</p> <p>11 (Recess taken.)</p> <p>12 THE VIDEOGRAPHER: We are on the record</p> <p>13 at 10:19 a.m.</p> <p>14 BY MR. SCHWARTZ:</p> <p>15 Q. Dr. Romesberg, would you please go back</p> <p>16 to Tsien. That is Exhibit 1013. And please turn</p> <p>17 to page 23. We may have looked at this before. At</p> <p>18 the bottom of the page, that's where Tsien lists</p> <p>19 the deblocking requirements. And we discussed this</p> <p>20 earlier, one of Tsien's deblocking requirements is</p> <p>21 rapid deblocking of the 3'-OH protecting group,</p> <p>22 correct?</p> <p>23 A. Proceed rapidly, yes.</p> <p>24 Q. Please turn back to Exhibit 2007, your</p> <p>25 declaration in IPR2013-00517. Please go to</p>	<p style="text-align: right;">Page 58</p> <p>1 page 25. Please draw your attention to the second</p> <p>2 line on page 25 that starts with "Furthermore,</p> <p>3 the."</p> <p>4 Do you see that?</p> <p>5 A. Yes.</p> <p>6 Q. And you write: "Furthermore, the amount</p> <p>7 of time required to achieve those yields, three</p> <p>8 hours to multiple days, would not have been</p> <p>9 expected to fulfill the rapid deprotection</p> <p>10 requirement of Tsien's DNA sequencing method, or</p> <p>11 provide a fast sequencing system capable of the</p> <p>12 ultrahigh-throughput in accordance with Ju's DNA</p> <p>13 sequencing method."</p> <p>14 That is what you wrote, correct?</p> <p>15 A. That is correct.</p> <p>16 Q. It's your opinion that if it takes three</p> <p>17 hours to achieve high-yield deprotection of the 3'</p> <p>18 protecting group, it would not have been expected</p> <p>19 to fulfill Tsien's rapid deprojection requirement?</p> <p>20 That's what you wrote?</p> <p>21 A. That is what I wrote.</p> <p>22 Q. Let's go back to Exhibit 2035, your</p> <p>23 deposition transcript in this case, in the 00517</p> <p>24 case I should say. Please turn to page 97. Please</p> <p>25 draw your attention to line 22, and starting at</p>
<p style="text-align: right;">Page 59</p> <p>1 line 22, the transcript reads:</p> <p>2 "Question: Does the rapid removal of a</p> <p>3 3' protecting group relate to the eventual</p> <p>4 application of the SBS method?"</p> <p>5 And there was an objection.</p> <p>6 "Answer: So you are asking if the</p> <p>7 efficiency of removal depends -- required depends</p> <p>8 on the application?</p> <p>9 "Question: Sure. That is a better way</p> <p>10 of asking it. Thank you.</p> <p>11 "Answer: So that depends. I mean, so</p> <p>12 that depends. Are you talking about sequencing by</p> <p>13 synthesis applications?</p> <p>14 "Question: Yes.</p> <p>15 "Answer: Sure, but they all have to be</p> <p>16 efficient. There is a minimum that you are going</p> <p>17 to have to be. You are going to have to get 30</p> <p>18 nucleotide read lengths minimum in a time that is</p> <p>19 not -- in a time that's feasible.</p> <p>20 "Question: What is a feasible time?</p> <p>21 "Answer: You know, that's a relative</p> <p>22 term. I mean, I threw out the idea of five hours</p> <p>23 being not reasonable. And I think that is probably</p> <p>24 right. What is a reasonable time? I don't know.</p> <p>25 An hour. That would not be great, I don't think,</p>	<p style="text-align: right;">Page 60</p> <p>1 but that would at least maybe be in the realm of</p> <p>2 doable."</p> <p>3 That is your testimony, correct?</p> <p>4 A. Yes.</p> <p>5 Q. Is it fair to say that your opinion is</p> <p>6 that SBS requires sequencing somewhere between 25</p> <p>7 to 30 bases?</p> <p>8 A. I think it's my opinion that I'm not sure</p> <p>9 doable is a word, but, yes, I think depending on</p> <p>10 the specific application, and, again, getting back</p> <p>11 to the discussion that we had earlier, if you are</p> <p>12 doing the -- if your goal is the application that</p> <p>13 we are describing here, and that is de novo</p> <p>14 sequencing of unknown sequences of DNA, then, yeah,</p> <p>15 you would need read lengths of on that order.</p> <p>16 Q. And then the testimony we just read you</p> <p>17 testified that a reasonable time for deprotection</p> <p>18 of the 3'-O-allyl protecting group in SBS is an</p> <p>19 hour or less.</p> <p>20 That is what you testified, right?</p> <p>21 A. Well, I am hemmed and hawed a little bit</p> <p>22 because I think that is kind of a tough question.</p> <p>23 If an hour would have been all that is available,</p> <p>24 then people probably would have gone with that.</p> <p>25 But certainly people wanted faster, the fastest</p>

<p style="text-align: right;">Page 61</p> <p>1 possible.</p> <p>2 Q. But your testimony was that an hour or</p> <p>3 less. That was your testimony?</p> <p>4 MR. ZIMMERMAN: Objection.</p> <p>5 Mischaracterizes.</p> <p>6 THE WITNESS: Let me look at what I said.</p> <p>7 "I threw out the idea of five hours being not</p> <p>8 reasonable, and I think that is probably right.</p> <p>9 And what time is reasonable? I don't know. An</p> <p>10 hour, that would not be great I don't think, but</p> <p>11 that would at least maybe be in the realm of</p> <p>12 doable."</p> <p>13 Yeah, so there's not -- I don't have an</p> <p>14 answer, an exact answer to this question. People's</p> <p>15 standards would have adapted to what was required,</p> <p>16 but clearly faster is better.</p> <p>17 BY MR. SCHWARTZ:</p> <p>18 Q. I am just asking about your testimony.</p> <p>19 And your testimony was that an hour might be</p> <p>20 doable.</p> <p>21 A. I certainly believe that an hour might be</p> <p>22 doable.</p> <p>23 Q. But you also said that an hour would not</p> <p>24 be great.</p> <p>25 A. Great is kind of a relative term. I</p>	<p style="text-align: right;">Page 62</p> <p>1 think, you know, today, looking at what we have, I</p> <p>2 think an hour would not be great.</p> <p>3 Q. But in terms of this testimony, that</p> <p>4 wasn't today. That testimony was in the past. And</p> <p>5 you were asked about sequencing by synthesis, and</p> <p>6 your testimony was that an hour might not be great,</p> <p>7 but it would be doable. So my question is, it was</p> <p>8 your testimony that in your opinion SBS required</p> <p>9 that it occur in an hour or less?</p> <p>10 MR. ZIMMERMAN: Objection. Compound.</p> <p>11 BY MR. SCHWARTZ:</p> <p>12 Q. That was your testimony, correct?</p> <p>13 MR. ZIMMERMAN: Objection. Compound.</p> <p>14 THE WITNESS: I don't believe that was my</p> <p>15 testimony. If it -- put it this way, if it was, it</p> <p>16 shouldn't have been. But I don't believe it was.</p> <p>17 Could you direct me to where I said that it would</p> <p>18 have to be an hour or less.</p> <p>19 BY MR. SCHWARTZ:</p> <p>20 Q. "What is a reasonable time? I don't</p> <p>21 know. An hour, that would not be great, I don't</p> <p>22 think, but at least that would be in the realm of</p> <p>23 doable."</p> <p>24 A. If you ask me does it have to be an hour</p> <p>25 or faster to be a great sequencing by synthesis</p>
<p style="text-align: right;">Page 63</p> <p>1 method, I think we could discuss what great means,</p> <p>2 but I think the point I was making was that an hour</p> <p>3 is -- you certainly could have hoped faster, but I</p> <p>4 don't think an hour would have precluded using it.</p> <p>5 It wouldn't necessarily have been great, but it</p> <p>6 still -- it certainly would have been doable.</p> <p>7 I think probably -- I mean, in reality,</p> <p>8 10 hours would have been doable. It would have not</p> <p>9 been great. It would have started to be pretty bad</p> <p>10 because you just would not have been able to</p> <p>11 desequene -- your read lengths wouldn't have been</p> <p>12 limited by time, but would you still be able to do</p> <p>13 it? Yes. Would you be able to do it in the</p> <p>14 high-throughput way that Ju describes? No.</p> <p>15 So it really comes down to what does</p> <p>16 high-throughput mean. And the problem is that</p> <p>17 scientists use these kinds of terms loosely. So</p> <p>18 when I used -- when I said "I don't know. An hour,</p> <p>19 that would not be great, I don't think, but that</p> <p>20 would at least be in the realm of doable," what I</p> <p>21 was saying was that an hour, you know, that's</p> <p>22 doable. It certainly could have been better, but I</p> <p>23 don't believe I ever intended to define an hour as</p> <p>24 any sort of cutoff.</p> <p>25 ///</p>	<p style="text-align: right;">Page 64</p> <p>1 BY MR. SCHWARTZ:</p> <p>2 Q. But you did testify what is a reasonable</p> <p>3 time. I don't know, an hour. That would not be</p> <p>4 great.</p> <p>5 That was your testimony?</p> <p>6 A. Yes. That is what I wrote, but, again, I</p> <p>7 don't believe I was -- I don't believe there's</p> <p>8 anything in that statement that defines an hour as</p> <p>9 some cutoff. I think it is exactly what it says.</p> <p>10 I didn't know. An hour. I was speculating that</p> <p>11 wouldn't be great, but doable.</p> <p>12 Q. An hour would not be great?</p> <p>13 A. But it would be doable.</p> <p>14 Q. So Tsien teaches that his SBS method</p> <p>15 requires rapid and quantitative deblocking. A</p> <p>16 POSA -- and, again, a POSA in terms of the way you</p> <p>17 defined it in October 2000 -- understood that to</p> <p>18 mean that the 3' protecting group should be cleaved</p> <p>19 quantitatively in what you consider to be around an</p> <p>20 hour?</p> <p>21 A. I would not be comfortable imposing my</p> <p>22 speculation of an hour being doable but not great.</p> <p>23 I guess you could interpret that as saying my</p> <p>24 reading of Tsien in a doable but not great way</p> <p>25 would have suggested, I don't know, an hour as a</p>

<p style="text-align: right;">Page 65</p> <p>1 deprotection time. But I don't think I meant to 2 ever state that that was any sort of an absolute 3 requirement in time, you know, 59 minutes okay, 61 4 minutes not.</p> <p>5 Q. Around an hour?</p> <p>6 A. Would be good, I guess. It would 7 certainly be doable.</p> <p>8 Q. The question was, you asked yourself what 9 is a reasonable time. And your answer to what is a 10 reasonable time was an hour.</p> <p>11 A. I agree that one hour would probably be 12 reasonable for a good, but not great sequencing by 13 synthesis implementation of Ju's method.</p> <p>14 Q. We are talking about Tsien.</p> <p>15 A. I'm sorry. Of Tsien's method.</p> <p>16 Q. Please go back to your declaration in 17 IPR2013-00517. That is Exhibit 2007. Please turn 18 to page 27, and please draw your attention to 19 paragraph 52. In paragraph 52 you write: "Tsien 20 and Ju's DNA sequencing methods require high and 21 quantitative efficiency using nucleotides. See 22 example Tsien at column 20, lines 28 to 34, stating 23 that the criteria for the successful use of 24 3'-O-allyl blocking groups include, one, the 25 ability of polymerase enzyme to accurately and</p>	<p style="text-align: right;">Page 66</p> <p>1 efficiently incorporate the DNTPs, i.e., deoxy 2 nucleotide triphosphates; and, two, the 3 availability of mild conditions for rapid and 4 quantitative deblocking."</p> <p>5 That is what you wrote, correct?</p> <p>6 A. That is what I wrote.</p> <p>7 Q. And Tsien's SBS method requires 8 quantitative deblocking of the 3'-O-allyl 9 protecting group, correct?</p> <p>10 A. I'm sorry. I was distracted by an error 11 in my -- please repeat the question.</p> <p>12 Q. Tsien's SBS method requires quantitative 13 deblocking of the 3'-O-allyl protecting group, 14 correct?</p> <p>15 A. It requires very high efficient 16 deblocking, yes.</p> <p>17 Q. You wrote that it "requires high and 18 quantitative efficiency using nucleotides," right?</p> <p>19 A. That is what I wrote.</p> <p>20</p> <p>21</p> <p>22 Q. Please go back to Exhibit 2080, which is 23 your deposition transcript in IPR2013-00128. 24 Please turn to page 200, and please draw your 25 attention to line 3 on page 200. And starting at</p>
<p style="text-align: right;">Page 67</p> <p>1 line 3, the transcript reads: 2 "Question: Okay. And it's greater than 3 the 90 percent that you cite here in paragraph 58 4 as the disulfide cleavage conditions that would 5 provide an expectation that the disulfide cleavage 6 conditions, looking at cleavage of an OH protecting 7 group with greater than 90 percent efficiency." 8 There was an objection by counsel. Some 9 back and forth between you and counsel. You 10 answered, "I never suggested that greater than 11 90 percent was sufficient. It's certainly 12 necessary, but necessary is not necessarily 13 sufficient. And 91 percent is greater than 90, but 14 that would not be sufficient. 95 percent would not 15 be sufficient. Sufficiency is really something 16 approaching 100." 17 That was your testimony, correct?</p> <p>18 A. That is what is written, yes.</p> <p>19 Q. So it is your opinion that 95 percent 20 deblocking efficiency of the 3' protecting group is 21 not sufficient for SBS, correct?</p> <p>22 MR. ZIMMERMAN: Objection. 23 Mischaracterizes. 24 THE WITNESS: I would have to read this. 25 If you want me to, I am happy to. I believe what I</p>	<p style="text-align: right;">Page 68</p> <p>1 am talking about is the disulfide cleavage. Do you 2 want me to take a minute to read this to get 3 context?</p> <p>4 BY MR. SCHWARTZ:</p> <p>5 Q. You can read all you want to get context, 6 but when you worked specifically in the portion 7 that we just read referring to cleavage of a 3'-OH 8 protecting group, when you looked at that, you 9 stated that, that was the question. Cleavage 10 conditions, getting cleavage of a 3'-OH protecting 11 group, and your answer was that "95 percent would 12 not be sufficient. Sufficiency is really something 13 approaching 100."</p> <p>14 That was your testimony?</p> <p>15 A. Well, I look and I see that what's 16 written is "and it's greater than 90 percent that 17 you cite here in paragraph 58." This is what the 18 question -- as the disulfide cleavage conditions. 19 So I want to make sure I'm talking about not the 20 disulfide cleavage.</p> <p>21 Q. You are talking about the cleavage of a 22 3'-OH protecting group?</p> <p>23 A. Can I take a moment?</p> <p>24 Q. Okay. But do you see that you say that 25 here in the testimony we just read?</p>

<p style="text-align: right;">Page 69</p> <p>1 A. Can I answer that in a second?</p> <p>2 Q. Sure.</p> <p>3 A. It seems to me I'm talking about</p> <p>4 disulfide cleavage.</p> <p>5 Q. In relation to cleavage of the 3'-OH</p> <p>6 protecting group, correct?</p> <p>7 A. I think I'm talking about the efficiency</p> <p>8 of disulfide cleavage.</p> <p>9 Q. Of the 3'-OH protecting group.</p> <p>10 A. No.</p> <p>11 Q. You're talking about cleavage conditions</p> <p>12 could get cleavage of a 3'-OH protecting group.</p> <p>13 A. I'm sorry. I don't follow that. I know</p> <p>14 one of the issues that we were talking about in</p> <p>15 this case was disulfide cleavage of a nucleobase.</p> <p>16 Q. Okay, but let's look at the transcript</p> <p>17 again. Starting at page 200, line 3.</p> <p>18 "Question."</p> <p>19 Are you with me?</p> <p>20 A. Yes.</p> <p>21 Q. "Okay. And it's greater than 90 percent</p> <p>22 that the cite here in paragraph 58. It's the</p> <p>23 disulfide cleavage conditions that would provide an</p> <p>24 expectation that the disulfide cleavage conditions</p> <p>25 could get cleavage of a 3'-OH protecting group with</p>	<p style="text-align: right;">Page 70</p> <p>1 greater than 90 percent efficiency."</p> <p>2 That was your question. And your answer</p> <p>3 was: "95 percent would not be sufficient.</p> <p>4 Sufficiency is really something approaching 100."</p> <p>5 A. The problem that I'm having here is that</p> <p>6 at the time, we were talking about -- and I don't</p> <p>7 know if that's what we are talking about here, but</p> <p>8 one of the issues was simultaneous deprotection of</p> <p>9 a nucleobase linker and the 3' blocking group. So</p> <p>10 I'm not sure I'm talking about conditions where you</p> <p>11 get simultaneous cleavage.</p> <p>12 Let me answer the question that I think</p> <p>13 you're getting at is that I think that we would</p> <p>14 need -- you would need for Tsien's sequencing by</p> <p>15 synthesis method, I think the answer is applicable</p> <p>16 to that, that you would need something greater than</p> <p>17 95 percent for cleavage of the 3' hydrox group, if</p> <p>18 that's the question that you're asking.</p> <p>19 Q. Yes.</p> <p>20 A. Then I would agree with it. I want to</p> <p>21 caveat that I'm not absolutely sure that that is</p> <p>22 specifically precisely what I am talking about</p> <p>23 here, but I am happy to answer that question.</p> <p>24 Q. Okay. And, in fact, you said that</p> <p>25 sufficiency is really something approaching 100?</p>
<p style="text-align: right;">Page 71</p> <p>1 A. The closer you get to 100, the better the</p> <p>2 method's going to be.</p> <p>3 Q. Sufficiency is really something closer to</p> <p>4 100, correct?</p> <p>5 MR. ZIMMERMAN: Objection. Asked and</p> <p>6 answered.</p> <p>7 BY MR. SCHWARTZ:</p> <p>8 Q. That is what you testified, right?</p> <p>9 A. I think sufficiency is a relative term.</p> <p>10 Sufficient for what? But certainly you would have</p> <p>11 wanted to get as efficient as possible.</p> <p>12 Q. So do you agree with your testimony that</p> <p>13 sufficiency is something approaching 100?</p> <p>14 MR. ZIMMERMAN: Objection.</p> <p>15 Mischaracterize.</p> <p>16 THE WITNESS: I wish to characterize that</p> <p>17 based on what sufficient -- what your application</p> <p>18 is and what sufficiency you need. It would depend</p> <p>19 on read length. It would depend on things, all</p> <p>20 sorts of things. So you would have to give me a</p> <p>21 set of conditions. I don't know the context that I</p> <p>22 testified here to know whether I would agree with</p> <p>23 myself or not. I think it's clear that the closer</p> <p>24 you get to 100 the better.</p> <p>25 ///</p>	<p style="text-align: right;">Page 72</p> <p>1 BY MR. SCHWARTZ:</p> <p>2 Q. Let's go back to Exhibit 2035, your</p> <p>3 deposition transcript in the IPR2013-00517 case.</p> <p>4 Please turn to page 156. Please draw your</p> <p>5 attention to line 12. And starting at line 12, the</p> <p>6 transcript reads:</p> <p>7 "Question: Would the efficiency also</p> <p>8 include the efficiency of incorporation of a</p> <p>9 nucleotide; is that right?</p> <p>10 "Answer: To the extent that the step</p> <p>11 limited things, then sure. The nucleotide has to</p> <p>12 be efficiently incorporated."</p> <p>13 That was your testimony, correct?</p> <p>14 A. That was what was written, yes.</p> <p>15 Q. And it is your opinion that SBS requires</p> <p>16 efficient incorporation of the nucleotide by the</p> <p>17 polymerase, correct?</p> <p>18 A. Well, I would like to caveat this in that</p> <p>19 efficiency is not a quantitative term; it is a</p> <p>20 relatively qualitative term, but it is certainly</p> <p>21 true.</p> <p>22 Q. And so to successfully practice SBS,</p> <p>23 there must be both efficient incorporation of the</p> <p>24 nucleotide and deblocking efficiencies that are</p> <p>25 efficient?</p>

<p style="text-align: right;">Page 73</p> <p>1 A. Yes.</p> <p>2 Q. I'm putting in front of you another</p> <p>3 document that has not yet been marked. I am</p> <p>4 putting you in front of you, Dr. Romesberg, a</p> <p>5 document entitled "Video Deposition of Floyd</p> <p>6 Romesberg Ph.D. in IPR2013-00266.</p> <p>7 MR. SCHWARTZ: Court reporter, could you</p> <p>8 please mark this as Exhibit 2082?</p> <p>9 THE WITNESS: I'm sorry, so this is going</p> <p>10 to be --</p> <p>11 MR. SCHWARTZ: 2082.</p> <p>12 THE WITNESS: In the future, this is</p> <p>13 going to be today, this will be referred to as?</p> <p>14 (Exhibit 2082 was marked for</p> <p>15 identification.)</p> <p>16 BY MR. SCHWARTZ:</p> <p>17 Q. 2082. Please turn to page 66. And</p> <p>18 please draw your attention to line 17. And</p> <p>19 starting at line 17 the transcript reads:</p> <p>20 "Question: Okay. So what is the</p> <p>21 concentration needed to reach high incorporation?</p> <p>22 "Answer: Of these substrates would be</p> <p>23 one millimolar.</p> <p>24 "Question: Does that same sentence</p> <p>25 mention whether or not it is -- it's an efficient</p>	<p style="text-align: right;">Page 74</p> <p>1 chain terminator?</p> <p>2 "Answer: The sentence on page 3?"</p> <p>3 And there was an objection.</p> <p>4 "Question: Yeah, we -- yes.</p> <p>5 "Answer: It says that they are not very</p> <p>6 efficient chain terminators.</p> <p>7 "Question: And what does that mean to be</p> <p>8 a not very efficient chain terminator?</p> <p>9 "Answer: That it is not a good</p> <p>10 substrate.</p> <p>11 "Question: And what do you mean by not a</p> <p>12 good substrate?</p> <p>13 "Answer: It is not recognized well and</p> <p>14 incorporated by the polymerase."</p> <p>15 That was your testimony, correct?</p> <p>16 A. That is what is written, yes.</p> <p>17 Q. And when you are referring to a chain</p> <p>18 terminator, you are referring to the 3' protecting</p> <p>19 group, correct?</p> <p>20 A. I would have to check. A 3' protected</p> <p>21 nucleotide is certainly a chain terminator.</p> <p>22 Q. So a 3' protecting group that is not</p> <p>23 efficiently incorporated by a polymerase means that</p> <p>24 it is not a good substrate for the polymerase,</p> <p>25 correct?</p>
<p style="text-align: right;">Page 75</p> <p>1 A. Yes.</p> <p>2 Q. And the 3' protecting group that is not a</p> <p>3 good substrate means that it is not recognized well</p> <p>4 and it is not incorporated well by the polymerase,</p> <p>5 correct?</p> <p>6 A. I think I agree with if it is not</p> <p>7 incorporated well, it is not a good substrate. I</p> <p>8 think that's what you mean by incorporation is that</p> <p>9 it is taken as a substrate so, yes.</p> <p>10 MR. SCHWARTZ: And before it gets handed</p> <p>11 to you, maybe it would be easier, Court Reporter,</p> <p>12 this is a new exhibit, so could you mark this 2083.</p> <p>13 (Exhibit 2083 was marked for</p> <p>14 identification.)</p> <p>15 BY MR. SCHWARTZ:</p> <p>16 Q. Dr. Romesberg, I've put in front of you a</p> <p>17 document entitled "Substitute Declaration of Floyd</p> <p>18 Romesberg Ph.D. in Support of Patent Owner's Motion</p> <p>19 to Amend in IPR2013-00128." Please turn to page 37</p> <p>20 of that exhibit. And I'm just going to ask you if</p> <p>21 that is your signature on that page?</p> <p>22 A. Yes, it is.</p> <p>23 Q. Please go back to page 21. Please draw</p> <p>24 your attention to the last line on page 21. Do you</p> <p>25 see there's a sentence that starts with "A person</p>	<p style="text-align: right;">Page 76</p> <p>1 of ordinary skill"?</p> <p>2 A. I do.</p> <p>3 Q. You write: "A person of ordinary skill in</p> <p>4 the art would have been well aware that</p> <p>5 incorporation of each sequential nucleotide and any</p> <p>6 related deprotection of a 3' protecting group or</p> <p>7 cleavage of a linker from the nucleotide in a DNA</p> <p>8 sequencing by synthesis process must be highly</p> <p>9 efficient to permit accurate sequencing."</p> <p>10 That's what you wrote, correct?</p> <p>11 A. That is what is written.</p> <p>12 Q. So each cycle of that SBS requires highly</p> <p>13 efficient nucleotide incorporation and highly</p> <p>14 efficient 3' deprotection, correct?</p> <p>15 A. Those words are qualitative but, sure,</p> <p>16 yes. And as I go on to do, you can simply do the</p> <p>17 math for anything that is not 100 and see what the</p> <p>18 ramifications are.</p> <p>19 Q. I will. We'll do some of that math</p> <p>20 later, since you invited it. Thank you.</p> <p>21 A. I'll invite triple integrals as well, if</p> <p>22 you would like to do some of that.</p> <p>23 Q. That's above me.</p> <p>24 So inefficient incorporation of the 3'</p> <p>25 protected nucleotide or inefficient deprotection of</p>

<p style="text-align: right;">Page 77</p> <p>1 the 3' protecting group, that would result in an 2 SBS system becoming out of phase, correct? 3 A. The sequencing read would lose phase, 4 yes. 5 Q. And when the sequencing -- I'm trying to 6 use your words. When the sequencing system loses 7 phase, it's no longer capable of generating 8 reliable sequencing information, correct? 9 A. Certainly once it's lost phase, that is 10 correct. 11 Q. Please go back to Exhibit 2080. That's 12 your deposition transcript in IPR2013-00128. And 13 please turn to page 252. Please draw your 14 attention to line 6. And starting at line 6 the 15 transcript reads: 16 "Question: If more than half of the 17 strands were out of phase after a given number of 18 cycles, would that be sufficient for SBS? 19 "Answer. No. No." 20 That was your testimony, correct? 21 A. Yes. 22 Q. It's okay. You can smile. 23 It is your opinion that if more than half 24 the strands are out of phase after a given number 25 of SBS cycles, then that would not be sufficient</p>	<p style="text-align: right;">Page 78</p> <p>1 for SBS, correct? 2 A. That was the answer to the question that 3 I was answering. 4 Q. That's your opinion, right? That if more 5 than half of the strands are out of phase after a 6 given number of cycles, that would not be 7 sufficient for SBS? 8 A. I think there are ways that you can 9 recover data, and where exactly it fails to be 10 recoverable, I'm not exactly sure. But this sounds 11 about right to me. 12 Q. So you stand by your testimony? 13 A. More or less. Certainly losing phase is 14 a problem for sequencing. 15 Q. And if more than half the strands were 16 out of phase, you testified that would not be 17 sufficient for SBS? 18 MR. ZIMMERMAN: Objection. Asked and 19 answered. 20 THE WITNESS: I think there are methods 21 that allow you to still sequence as you are losing 22 phase. I don't know how far currently people can 23 do that. I don't know that the specific software 24 algorithms that allow you to do that as to how far 25 you can read into a lost phase sequence, a losing</p>
<p style="text-align: right;">Page 79</p> <p>1 phase sequence. So I don't know exactly at what 2 point. I think that intuitively I would more or 3 less agree with what I said here, although I don't 4 know the exact value. 5 BY MR. SCHWARTZ: 6 Q. I am going to take you up on your 7 suggestion that we do some calculations. 8 Does anybody have a piece of paper? 9 A. You're going to make me do calculations? 10 Q. You bet. 11 Let's assume that we have 93 percent 12 efficiency of cleavage of the 3' protecting group 13 at each cycle. After 10 cycles there would be .93 14 to the 10th of the sequence polynucleotide 15 containing the correct sequence, correct? 16 A. Um-hmm. Sorry, yes. 17 Q. And so I just want you to do that 18 calculation, .93 -- 19 A. Can I use my calculator? 20 Q. Absolutely. 21 A. Actually, I am not sure my calculator 22 has -- 23 Q. Mine doesn't either. You'll have to do 24 it 10 times. 25 A. Okay.</p>	<p style="text-align: right;">Page 80</p> <p>1 MR. ZIMMERMAN: The answer is the answer. 2 You're going to make him sit here and punch in .93 3 ten times on a calculator? 4 MR. SCHWARTZ: Yes, I am going to ask him 5 to confirm that is 48.4 percent. 6 MR. ZIMMERMAN: Take as much time as you 7 need, Dr. Romesberg. 8 THE WITNESS: The answer I get is 9 48 percent. 10 BY MR. SCHWARTZ: 11 Q. And that means that 93 percent cleavage 12 efficiency of the 3' protecting group, more than 13 half of the strands are out of phase after 10 14 cycles, correct? 15 A. Yes. 16 Q. Go back to Exhibit 1012, which is your 17 declaration. Take your time. 18 MR. ZIMMERMAN: Declaration in this case? 19 BY MR. SCHWARTZ: 20 Q. Okay, so we're at Exhibit 1012? 21 A. Yes. 22 Q. That's your declaration in IPR2018-00291, 23 correct? 24 A. Yes. 25 Q. And please turn to page 16. Right above</p>

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1 paragraph 40 you have a header which reads: "It was
2 known that the 3' capping group should be small."
3 Do you see that?
4 A. I do.
5 Q. Please keep that open, but I'd like you
6 to go back to Exhibit 2007. That is your
7 declaration in IPR2013-00517. And please go to
8 page 32. Please draw your attention to paragraph
9 58, and please draw your attention to the second
10 sentence. And you write: "One skilled in the art
11 would have understood that the physical properties
12 underlying, one, nucleotide stability; two,
13 polymerase recognition; and, three, reinitiation of
14 DNA synthesis following deprotection are not
15 necessarily related to; four, size; and, five, the
16 chemical reversibility. A protecting group can
17 have any subset of the aforementioned properties
18 independent of the other properties."
19 And to save time, I'm not going to read
20 the rest of paragraph 58 into the record, but I
21 would ask that you turn to page 34 where you have a
22 concluding sentence. It starts with "Thus, a
23 person of ordinary skill in the art."
24 Do you see that?
25 A. Yes.

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1 group?
2 A. Yes.
3 Q. Go back to Tsien, please. That is
4 Exhibit 1013, back to pages 20 and 21. And, again,
5 Tsien's required properties for successfully
6 practicing his SBS method include; one, the ability
7 of a polymerase enzyme to accurately and
8 efficiently incorporate the dNTP carrying the 3'
9 blocking groups into the CD nature -- my mouth is
10 dry. Let me read that again.
11 "Tsien's required properties for
12 successfully practicing his SBS method include;
13 one, the ability of a polymerase enzyme to
14 accurately and efficiently incorporate the dNTPs
15 carrying the 3' blocking groups into the cDNA
16 chain," correct?
17 A. That is listed as a criteria for the
18 successful use of the 3' blocking group, yes.
19 Q. And Tsien's required properties include;
20 two, the availability of mild conditions for rapid
21 and quantitative deblocking, correct?
22 A. That is listed as well, yes.
23 Q. And Tsien's required properties include;
24 three, the ability of a polymerase enzyme to
25 reinitiate the cDNA synthesis subsequent to the

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1 Q. And you write: "Thus, a person of
2 ordinary skill in the art would not have had an
3 expectation that a small and removal protecting
4 group would also possess all of the listed
5 properties of Ju and Tsien's protecting group."
6 That is what you wrote, correct?
7 A. Yes.
8 Q. And, again, the Tsien reference that
9 you're talking about is the same Tsien reference
10 that we have been talking about in this case?
11 A. It is.
12 Q. It is your opinion that a person of
13 ordinary skill in the art would not have had an
14 expectation that a small and removable protecting
15 group would also possess all of the listed
16 properties of the Tsien's protecting group,
17 correct?
18 A. Sure, yes. I assume that you're going to
19 have me clarify this, but ...
20 Q. No, I'm just asking you that you heard
21 the question. I could repeat it again. It is your
22 opinion that a person of ordinary skill in the art
23 would not have had an expectation that a small and
24 removable protecting group would also possess all
25 of the listed properties of Tsien's protecting

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1 deblocking stage, correct?
2 A. That is listed as No. 3, yes.
3 Q. It is your opinion that "a person of
4 ordinary skill in the art" -- and, again, I'm using
5 it in the way you do in October 2000 -- "would not
6 have had an expectation that just because 3'
7 blocking group is small, it would be expected to be
8 accurately and efficiently incorporate the DTNPs
9 carrying 3' blocking groups into the cDNA chain,"
10 correct?
11 A. That is what I testified.
12 Q. And it is your opinion that a person of
13 ordinary skill in the art "would not have had an
14 expectation that just because the 3' blocking group
15 is small, it would be expected that mild conditions
16 for rapid and quantitative deblocking are available
17 for that blocking group," correct?
18 A. That is correct.
19 Q. It is your opinion that a person of
20 ordinary skill in the art would not have had an
21 expectation that just because 3' blocking group is
22 small, it would be expected that the polymerase
23 enzyme is able to reinitiate cDNA synthesis
24 following deprotection, correct?
25 A. That is correct.

<p style="text-align: right;">Page 85</p> <p>1 (Exhibit 1035 was previously marked for 2 identification.) 3 BY MR. SCHWARTZ: 4 Q. I am going to put in front of you a 5 different exhibit. 6 I am putting in front of you Exhibit 1035 7 entitled "Cleavage of Allyl Ethers with Palladium 8 Carbon" by Boss and Scheffold. You relied on this 9 paper to form your opinions about deprotection 10 efficiency of allyl groups, correct? 11 A. Actually, no. 12 Q. Okay. Why don't we take you back to your 13 declaration that we looked at in IPR2018-00291. 14 MR. ZIMMERMAN: 10 of 12. Go to page 64. 15 THE WITNESS: On what page? 16 BY MR. SCHWARTZ: 17 Q. Page 32. And do you see where it says 18 "It was also known -- it's paragraph 64 -- "it was 19 also known that allyl groups were generally 20 efficiently removed using palladium including under 21 aqueous conditions," and you cite to Exhibit 1035, 22 which is Boss? 23 A. Yes. 24 Q. So you relied on this paper to form your 25 opinions about deprotection efficiencies of allyl</p>	<p style="text-align: right;">Page 86</p> <p>1 protecting groups, correct? 2 A. Including conditions that -- under which 3 you could get deprotection. 4 Q. But you relied on this paper to form your 5 opinions about deprotection efficiencies. You say 6 so in your declaration. 7 A. So I included two specific examples of 8 deprotection. This is a paper that I relied 9 particularly strongly on some aspects that 10 weren't -- there certainly is data in here that 11 lead -- that I included in -- to form my opinion 12 that it was efficient, but this paper also was used 13 for other -- to inform my opinion on other aspects 14 of the reaction as well. 15 Q. As an additional question, none of the 16 compounds in Boss are nucleotides or nucleosides, 17 correct? 18 A. They are not. 19 Q. And when you opined that Boss talked that 20 allyl groups were efficiently removed, you were 21 referring to the first four entries in table one 22 that reported yields of greater than 95 percent, 23 correct? 24 A. I was. 25 Q. And that data comes from structures four,</p>
<p style="text-align: right;">Page 87</p> <p>1 five, six and seven, correct? 2 A. That is correct. 3 Q. Is it fair to say that yields of 4 74 percent or 84 percent as shown for the last 5 three compounds in Table 1 would not be understood 6 to exhibit efficient removal of allyl groups? 7 A. That's correct. 8 Q. So in forming your opinion that Boss 9 thought that the allyl groups were efficiently 10 removed, you relied only on 8, 9, and 10 to form 11 that opinion, correct? 12 I'm sorry. You relied only on -- 4, 5, 13 6, and -- let me ask the question again because I 14 messed it up. 15 In forming your opinion that Boss thought 16 that the allyl groups were efficiently removed, you 17 did not take into account the yields of compounds 18 8, 9 or 10, correct? 19 A. I would not say that I did not take them 20 into account. Because I never said or meant to 21 imply that all groups could be efficiently removed 22 at any level. I was looking through there and saw 23 a wide variety of deprotection efficiencies. And 24 certainly reactions 4 through 7 which show greater 25 than 95 percent yield were the ones that</p>	<p style="text-align: right;">Page 88</p> <p>1 represented the efficient deprotection so, yes. 2 Q. Let me ask you a few questions about 3 those compounds in Table 1. As an initial 4 question, the allyl protecting group on a 5 nucleotide, 3'-OH. Let me go back. 6 I'm going to ask you about a few 7 questions about the compounds in Table 1, okay? 8 And as an initial question, the allyl protecting 9 group on a nucleotide, 3'-OH, it's a secondary 10 alcohol, correct? 11 A. That is correct. 12 Q. And the only secondary alcohol in Boss is 13 compound 10, correct? 14 A. That is correct. 15 Q. Compound 4 is an aromatic alcohol, 16 correct? 17 A. That is correct. 18 Q. And compounds five, six, seven, and nine 19 are primary alcohols, correct? 20 A. That is correct. 21 Q. And compound 8 is also a primary alcohol, 22 but it would be considered to be a hindered 23 alcohol, correct? 24 A. Maybe. It is certainly in an environment 25 that might suggest steric hindrance.</p>

<p style="text-align: right;">Page 89</p> <p>1 Q. And it's a primary alcohol? 2 A. It is a primary. 3 Q. So a person of ordinary skill in the art 4 understood that the structure that is most relevant 5 in terms of the type of alcohol that is on the 6 protecting group is compound 10 to a nucleotide 7 3'-OH because they're both secondary alcohols, 8 correct? 9 A. I think that is hard to say. You have to 10 understand the mechanism of these reactions. They 11 are very complex, and even to understand any one 12 even today, it's a mechanistic study. What you're 13 getting at is whether or not the departure of the 14 hydroxyl, that deprotection step, whether that 15 weight limits the reaction. Sometimes it does; 16 sometimes it doesn't. And so sometimes the 17 efficiency of the stability, what you're getting at 18 is whether or not the stability of that leaving 19 group would impinge -- will affect the reaction. 20 And that is not known. It could, but it might not, 21 and so I think it is a little bit risky to say that 22 that compound in particular represents the sort of 23 yield, the sort of reaction that you would expect 24 with a nucleotide, because that step is often not 25 rate limiting.</p>	<p style="text-align: right;">Page 90</p> <p>1 And if it -- to be clear, if it is not 2 rate limiting that means that in a series of steps, 3 if you have a step that is slower than everyone 4 else, that step is called rate limiting, and that 5 is the step that is going to determine the rate of 6 the reaction. And if you are competing with other 7 things, that determines the efficiency of the 8 deprotection in this case. 9 These Palladium-catalyzed reactions are 10 multi-step. The palladium has to bind. A 11 nucleophile has to attack. You then have to do a 12 rearrangement that involves displacement of that 13 leaving group. That step may or may not be rate 14 limiting, so the nature of the actual leaving group 15 may or may not identify commonalities between them. 16 Q. Is it true that in terms of the compounds 17 that we are looking at in the allyl on an aromatic 18 alcohol is generally easier to cleave than an allyl 19 on a secondary alcohol? 20 A. It might be, but it is not an absolute. 21 Q. And is it true that an allyl on a primary 22 alcohol is generally easier to cleave than a allyl 23 on a secondary alcohol? 24 A. If it's the rate limiting step, then, 25 yes; if it is not, then, no. Let me rephrase that.</p>
<p style="text-align: right;">Page 91</p> <p>1 The actual step itself, what you said is correct. 2 But whether you actually can even see that because 3 whether that -- those differences contribute to the 4 rate of the reaction and the efficiency for the 5 reaction that you're looking at, that may make no 6 difference at all. Because they're simply not rate 7 determining. 8 Q. Suppose in your hypothetical that the 9 deprotection was the rate limiting step? 10 A. If the -- no, to be clear, all of the 11 steps are the deprotection step. That step is a 12 complex series of steps, and if the specific step 13 that evolves the accumulation of negative charge on 14 the oxygen and its departure and cleavage of that 15 bond, if that specific elementary step is rate 16 limiting for the deprotection, then what you're 17 saying would be -- you would then see those 18 differences in the rates and the efficiencies for 19 the deprotection. 20 If that particular elementary step were 21 not rate limiting to the overall deprotection step, 22 then you would not see it. 23 Q. Okay. I think I understand that. But 24 again, we're talking about if we just get down to 25 the simpler level of the primary, secondary, and</p>	<p style="text-align: right;">Page 92</p> <p>1 aromatic alcohols that we're talking about here, 2 generally speaking, the aromatic is easier to 3 cleave than a secondary? 4 A. It depends if that step is what limits 5 the reaction. 6 Q. Would you agree that all of Boss's 7 compounds are much simpler in structure than 8 nucleotide, particularly one that has a cleavable 9 label on a base? 10 A. Simpler? 11 Q. I asked simpler in the sense that a 12 nucleotide with cleavable label on the base 13 contains additional functional groups, right? For 14 example, amines on the base, amides in the linkers 15 double bonds in the bases, all of those could also 16 react with palladium under the conditions of Boss's 17 method, correct? 18 MR. ZIMMERMAN: Objection. Compound. 19 BY MR. SCHWARTZ: 20 Q. Do you understand my question? 21 A. Yes, I believe so. I mean, you're asking 22 if any of the functionality in DNA would interfere 23 with the palladium-catalyzed reaction. I don't 24 think so. You know, these reactions -- I see 25 hydroxyl groups here. So first of all, I don't</p>

<p style="text-align: right;">Page 93</p> <p>1 think any of the functionality in DNA is 2 particularly poisoning to a palladium-catalyzed 3 reaction. 4 I don't see any -- I'm not envisioning 5 any functionality in what I imagine is the standard 6 implementation of a linker, fluora-4, in a 7 sequencing by synthesis methodology that would be 8 incompatible with palladium, I'm not imagining 9 that. I'm not seeing that, if that is what you are 10 asking. 11 MR. ZIMMERMAN: I think we need to change 12 the tape. 13 THE VIDEOGRAPHER: This marks the end of 14 media No. 1 of the deposition of Floyd Romesberg 15 Ph.D. We are off the record at 11:12 a.m. 16 (Recess taken.) 17 THE VIDEOGRAPHER: We are on the record 18 at 11:18 a.m., and this marks the beginning of 19 media No. 2 of the deposition of Floyd Romesberg 20 Ph.D. 21 BY MR. SCHWARTZ: 22 Q. Dr. Romesberg, please go back to 23 Exhibit 2007. It's your declaration in 24 IPR2013-00517. Please turn to page 33, and please 25 draw your attention to the middle of the page where</p>	<p style="text-align: right;">Page 94</p> <p>1 there is a sentence that starts "Furthermore, it 2 was known that a nucleotide." 3 Do you see that? 4 A. I do. 5 Q. And you write: "Furthermore, it was known 6 that a nucleotide having a 3'-O azido ester was not 7 a substrate for polymerases examined by Metzker," 8 and you cite the Metzker '94 paper. And that is 9 the same Metzker paper that you used in your 10 declarations in these cases, correct? 11 A. That is correct. 12 Q. And then you write: "Thus, 3'-O azido 13 esters were known to interfere with polymerase 14 recognition and incorporation of the modified 15 nucleotide despite the small size and removability 16 of this protecting group." 17 That is what you wrote, correct? 18 A. That is what is written. 19 Q. So it is your opinion that Metzker 1994 20 showed that 3'-O azido esters were known to 21 interfere with polymerase recognition and 22 incorporation of the modified nucleotide, despite 23 the small size and removability of this protecting 24 group, correct? 25 A. That is what is written.</p>
<p style="text-align: right;">Page 95</p> <p>1 Q. Please turn to page 34 of the 2 declaration, and please look at the second sentence 3 and you write: "Thus, a person of ordinary skill in 4 the art would not have had an expectation that 3'-O 5 azido esters would also possess all of the listed 6 properties of Ju and Tsien's protecting group." 7 That is what you wrote, right? 8 MR. ZIMMERMAN: Objection. Where are you 9 reading from? 10 MR. SCHWARTZ: On page 34. Am I in the 11 wrong place? Second sentence. 12 THE WITNESS: Yeah, you added azido group 13 in particular, and that's not -- 14 MR. ZIMMERMAN: Mischaracterizes the 15 document. What you read is not what is on the 16 page. 17 MR. SCHWARTZ: Let me get to the right 18 place. 19 Can I go off the record for a second and 20 try to find it? Because I know -- maybe it is in a 21 different document. 22 MR. ZIMMERMAN: Okay. 23 THE VIDEOGRAPHER: We are off the record 24 at 11:22 a.m. 25 (Recess taken.)</p>	<p style="text-align: right;">Page 96</p> <p>1 THE VIDEOGRAPHER: We are on the record 2 at 11:25 a.m. 3 BY MR. SCHWARTZ: 4 Q. We were looking at paragraph 33 where you 5 wrote that -- on page 33, I'm sorry, of the 6 declaration it was known. "Furthermore, it was 7 known that a nucleotide having 3'-O" -- 8 A. I'm sorry. Could you tell me what 9 document we are on? 10 Q. Exhibit 2007. Page 33. 11 A. Yes. 12 Q. And you wrote "Furthermore, it was known 13 that a nucleotide having a 3'-O azido ester was not 14 a substrate for polymerases examined by Metzker." 15 You cite to Metzker 1994. "Thus, 3'-O acetyl 16 esters were known to interfere with polymerase 17 recognition and incorporation of the modified 18 nucleotide, despite the small size and removability 19 of this protecting group." 20 That's what you wrote? 21 MR. ZIMMERMAN: Objection. Asked and 22 answered. 23 BY MR. SCHWARTZ: 24 Q. You wrote that? 25 A. That is what is written.</p>

<p style="text-align: right;">Page 97</p> <p>1 Q. So a person with ordinary skill would 2 have had an expectation that 3'-O acetyl esters 3 would be expected to interfere with polymerase 4 recognition and incorporation of the 3'-O acetyl 5 ester nucleotide, correct? 6 A. With the polymerases examined by Metzker, 7 yes. 8 Q. Sitting here today are you aware of any 9 other polymerases that had been tested prior to 10 October 2000 with the acetyl ester? 11 A. I did not research that, so off the top 12 of my head I could not come up with an example. I 13 am not positive that people did not try, but I 14 don't know of one. 15 Q. Let's go back to your declaration and 16 IPR2013-00517, Exhibit 2007, and please look at 17 paragraph 67 on page 37. In paragraph 67 you 18 write: "I have reviewed several notebook pages 19 provided by Illumina dated" -- blank. And the date 20 is -- and that was redacted. 21 Do you see that? 22 A. Yes, I do. 23 Q. Please look at paragraph 68. In 24 paragraph 68 you write: "Notebook SLB090 describes 25 several experiments conducted in -- it was</p>	<p style="text-align: right;">Page 98</p> <p>1 redacted -- where 3'-O-allyl protecting group was 2 removed from nucleotides under aqueous conditions." 3 Please look at paragraph 75 on page 40. 4 In paragraph 75 you write: "In my opinion, these 5 notebook pages report that even under optimized 6 conditions long time periods are required to 7 achieve 3'-O allyl protecting group cleavage 8 efficiencies that are sufficient for SBS. For 9 example, 3'-O-allyl protecting group was at best 10 only -- redacted -- this is insufficient for SBS." 11 The passages I read into the record is 12 what you wrote, correct? 13 A. That is what is written, yes. 14 Q. And in your opinion, the Illumina 15 laboratory notebooks you reviewed show that even 16 under optimized conditions in aqueous media, long 17 time periods are required to achieve 3'-O-allyl 18 protecting group cleavage efficiencies that are 19 sufficient for SBS, correct? 20 A. Under the optimized conditions that they 21 reported, that is what I'm saying. 22 Q. And you conclude from looking at those 23 notebooks that the 3'-O-allyl protecting group 24 would not work for SBS? 25 A. I don't believe I concluded that. I</p>
<p style="text-align: right;">Page 99</p> <p>1 believe I concluded that the conditions -- the 2 precise result they reported under the optimized 3 conditions that they reported would be insufficient 4 for SBS, yes. 5 Q. And when you came to that conclusion in 6 2014, you were aware of Metzker 1994 and the data 7 in Metzker 1994 for the 3'-O-allyl nucleotide, 8 correct? 9 A. I was, yes. 10 Q. Please go back to Exhibit 2081, that is 11 your second declaration in IPR2013-00266. 12 MR. ZIMMERMAN: I don't think we have 13 2081. 14 THE WITNESS: Yeah, I thought we skipped 15 2081. 2082? 16 MR. SCHWARTZ: You don't have this 17 before. I have skipped it before. 18 (Exhibit 2081 was marked for 19 identification.) 20 BY MR. SCHWARTZ: 21 Q. And so are you ready? 22 A. Um-hmm. 23 Q. I put in front of you Exhibit 2081, which 24 is your second declaration in IPR2013-00266. 25 Please turn to page 15. Starting at six lines up</p>	<p style="text-align: right;">Page 100</p> <p>1 from the bottom of page 15, there is a sentence 2 that starts with "The person of ordinary skill in 3 the art." 4 Do you see that? 5 A. I do. 6 Q. You write: "A person of ordinary skill in 7 the art seeking to develop sequencing by synthesis 8 methods, would recognize the need to use a 9 nucleotide with a 3' protecting group that could be 10 incorporated by a polymerase with high fidelity at 11 moderate to low concentrations." 12 That is what you wrote, right? 13 A. That is what I wrote. 14 Q. And it is your opinion that a person of 15 ordinary skill in the art seeking to develop an SBS 16 method would recognize the need to use a nucleotide 17 with a 3' protecting group that could be 18 incorporated by a polymerase with high fidelity at 19 moderate to low concentrations, correct? 20 A. Again, I believe that is what is written. 21 Q. Please go back to Tsien. To Tsien's 22 paper, Exhibit 1013. 23 A. I have it. 24 Q. Please turn to page 38. On page 38 Tsien 25 has a section entitled "Example four:</p>

<p style="text-align: right;">Page 101</p> <p>1 Incorporation of Labeled Nucleotide Analogs Into 2 DNA." 3 Do you see that? 4 A. I do. 5 Q. You can read through this entire 6 paragraph if you need to in order to answer my 7 question, but for now I'll just ask you to look at 8 lines 14 through 19. And Tsien teaches the use of 9 three unlabeled 3' blocked deoxy nucleotide 10 triphosphate dNTP analogs at a concentration of 1.5 11 micromolar each and one 3' blocked fluorescently 12 labeled dNTP analog at a concentration of 30 13 micromolar for his SBS method, correct? 14 A. That would seem to be correct. 15 Q. And Tsien's teaching of 1.5 to 30 16 micromolar concentrations -- excuse me -- of 17 nucleotides is consistent with your opinion that a 18 person of ordinary skill in the art seeking to 19 develop sequencing by synthesis methods would 20 recognize the need to use a nucleotide with a 3' 21 protecting group that could be incorporated by a 22 polymerase with high fidelity of moderate to low 23 concentrations, correct? 24 A. I think that's just the question that you 25 asked earlier, and if that's the case, then, yes,</p>	<p style="text-align: right;">Page 102</p> <p>1 that is what I wrote, so, yes. 2 Q. A POSA understood that a nucleotide 3 concentration of 200 micromolars is higher than 4 what typically would be expected for SBS, correct? 5 A. Would a person of ordinary skill in the 6 art thought 200 micromolar was higher than what? 7 Q. Well, when you were talking about 8 moderate to low concentrations for SBS, would it be 9 higher than the moderate to low concentrations? 10 A. 200 micromolar, no. That's probably in 11 the moderate range. That is certainly not in the 12 low range. 13 Q. But Tsien himself uses them at much lower 14 concentrations, correct? 15 A. That would seem to be the case here, yes. 16 (Exhibit 1016 was previously marked for 17 identification.) 18 BY MR. SCHWARTZ: 19 Q. I am putting in front of you 20 Exhibit 1016, a paper entitled "Termination of DNA 21 Synthesis by Novel 3' Modified Deoxyribonucleoside 22 5'-triphosphates" by Metzker that was published in 23 1994. 24 This is the same Metzker 1994 paper you 25 refer to in your declarations in these current IPRs,</p>
<p style="text-align: right;">Page 103</p> <p>1 correct? 2 A. That is correct. 3 Q. Please look at the abstract. In the 4 abstract the authors write "Eight modified-dNTPs 5 were synthesized and tested in two different 6 template assays for incorporation activity. From 7 this" -- 8 MR. ZIMMERMAN: You want to read that 9 sentence again? You did not read it correctly. So 10 I just want to make sure, we left out the three. 11 BY MR. SCHWARTZ: 12 Q. "Eight 3'-modified-dNTPs were synthesized 13 and tested in two different template assays for 14 incorporation activity. From this enzymatic screen 15 two 3'-O-methyl-dNTPs were shown to terminate DNA 16 syntheses mediated by a number of polymerases and 17 may be used as alternative terminators in Sanger 18 sequencing." 19 That is what Metzker wrote, correct? 20 A. That is correct. 21 Q. When Metzker refers to the enzymatic 22 screen, he is referring to the tests that are shown 23 in table two on page 4263, correct? 24 A. I believe that is actually slightly 25 vague, because he reports two different assays of</p>	<p style="text-align: right;">Page 104</p> <p>1 which there's a lot of data, and then table two is 2 sort of a summary of that. And so it is not 3 exactly those assays, it is compiled from the 4 assays. 5 Q. But if you look on the right side of 6 page 4263 of Tsien, it talks about a -- 7 A. I'm sorry -- 8 Q. I'm sorry. Of Metzker. And he has a 9 section "terminator screen," and he refers to the 10 table two, correct? 11 A. It summarizes. That's right. And the 12 only reason I point that out is there is an immense 13 amount of little details in this paper that didn't 14 make their way into this table, but I believe all 15 of the things of your interest are going to be in 16 this table. 17 Q. Again, I am just saying when he refers to 18 enzymatic screen in his abstract, he is referring 19 at least to the information in table two, correct? 20 A. At least, yes. 21 Q. You are familiar with the term "screen" 22 as used by scientists, correct? 23 A. I am. 24 Q. And is it fair to say that the screen is 25 used by scientists to -- who are involved in the</p>

<p style="text-align: right;">Page 105</p> <p>1 discovery projects to mean a preliminary test that 2 is used to identify compounds that have promising 3 properties? 4 A. It can be used in that way. That is not 5 the only way it is used. 6 Q. But that is a way that it is used? 7 A. It is used in that way. It is also used 8 as a preliminary analysis that is not superficial. 9 A screen itself does not necessarily have to be 10 rough or approximate. It is somehow limited and is 11 expected to then lead to information that would 12 help you move forward. 13 Q. And is it fair to say that screens are 14 also used to decide which compounds not to move 15 forward with? 16 A. They can be used in that way. 17 Q. And that would be because they don't have 18 necessarily the properties you are looking for in 19 your discovery project, right? 20 A. Yes. 21 Q. Going back to table two of Metzker. 22 Metzker tested modified nucleotides with seven 23 different 3'-O protecting groups to see how they 24 behaved in Sanger sequencing, correct? 25 A. Was it exactly Sanger sequencing? I</p>	<p style="text-align: right;">Page 106</p> <p>1 mean, certainly -- he compares to the dideoxy 2 termination pattern, which sort of is Sanger 3 sequencing. So I didn't ask myself were each of 4 his assays precisely Sanger sequencing, but I think 5 essentially that is correct. 6 Q. Included in that group of seven 3'-O 7 protecting groups is a 3'-O-allyl protecting group, 8 correct? 9 A. It is compound 3, yes. 10 Q. And going back to the abstract we just 11 looked at that from those screening tests that are 12 reported in table two, Metzker identified two 3'-O 13 protected nucleotides that Metzker says may be used 14 as alternative terminators in Sanger sequencing, 15 correct? 16 A. Yes. 17 Q. And Metzker states in the abstract that 18 "the 3'-O methyl dNTPs were shown to terminate DNA 19 synthesis and may be used as alternative 20 terminators in Sanger sequencing." 21 That is what he states, correct? 22 A. That is what is written. 23 Q. Metzker does not say that the 3'-O-allyl 24 dNTP was shown to terminate DNA synthesis and may 25 be used as an alternative terminator in Sanger</p>
<p style="text-align: right;">Page 107</p> <p>1 sequencing, right? 2 A. He does not say that. 3 Q. I would like you to keep Metzker '94 in 4 front of you. I'm going to mark another paper. 5 MR. SCHWARTZ: This will require a new 6 stamp, Court Reporter, 2053. 7 (Reporter clarification.) 8 MR. SCHWARTZ: Some of these are going to 9 be a little bit out of order. I'll be coming back 10 and forth, so instead of changing my whole index, 11 I'm just going to ask you to mark this as 2053. 12 This is actually something already marked in these 13 IPRs, but it wasn't in all four of the early four. 14 MR. ZIMMERMAN: Is it a record only in 15 the method case or is it a record in the four 16 nucleotide cases? 17 MR. SCHWARTZ: It's so far only of record 18 in the method case. 19 MR. ZIMMERMAN: Because we offered the 20 witness today on the method. And you're not taking 21 him on the method, but you're using exhibits from 22 the method case. Just want that to be clear from 23 the record. 24 MR. SCHWARTZ: We're using an exhibit 25 from the method case.</p>	<p style="text-align: right;">Page 108</p> <p>1 (Exhibit 2053 was marked for 2 identification.) 3 BY MR. SCHWARTZ: 4 Q. Dr. Romesberg, I'm putting in front of 5 you a document entitled "Sequencing technologies, 6 the next generation," by Michael Metzker. It was 7 published in 2010. The author of this article is 8 the same Michael Metzker who is an author of the 9 Metzker 1994 paper we were just looking at, 10 correct? 11 A. That is correct. 12 Q. Please turn to page 34 of that paper, and 13 please draw your attention to the left column which 14 contains a section header entitled "Cyclic 15 reversible termination." 16 Do you see that? 17 A. I do. 18 Q. And please look at the second paragraph 19 in that section that starts with "The key to the 20 CRT Method." 21 Do you see that? 22 A. I do. 23 Q. CRT means Cyclic Reversible Termination, 24 correct? 25 A. Correct.</p>

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1 Q. And the CRT method is another name for
2 SBS, correct?
3 A. I would have to read that. It is not a
4 term that I use. In fact, I don't think it is a
5 particularly commonly used term. I'd have to see
6 whether that refers to a specific step of SBS or if
7 it refers to SBS overall, certainly is a step.
8 Q. Please draw your attention to the section
9 that starts with "The use of Dideoxy Nucleotide."
10 Do you see that?
11 A. Yes.
12 Q. Metzker writes "The use of a Dideoxy
13 nucleotide which acts as a chain terminator in
14 Sanger sequencing provided the basis for the
15 initial development of reversible blocking groups
16 attached to the 3' end nucleotides."
17 That is what Metzker wrote, correct?
18 A. That is what is written, yes.
19 Q. And Metzker refers to reference 19 and 20
20 support for that statement, correct?
21 A. Yes.
22 Q. And would you please turn to the
23 references section and look at references 19 and
24 20. And reference 19 is the same Metzker 1994
25 paper that we just looked at, correct?

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1 that a cleavable 3'-O protecting group that works
2 for Sanger sequencing would be a good candidate for
3 development of a blocking group for SBS?
4 A. If it worked for Sanger sequencing, it
5 would satisfy certain requirements that would also
6 be required for sequencing by synthesis, so it
7 would be a piece of data that a person of ordinary
8 skill in the art would look to to form an opinion
9 about sequencing by synthesis, yes.
10 Q. And by the same token, is it fair to say
11 that a POSA understood that 3' protecting group
12 that inhibits polymerase activity in Sanger
13 sequencing would also likely inhibit polymerase
14 activity in SBS?
15 A. I don't know what you mean by the word
16 "inhibit."
17 Q. The way that Metzker uses the word
18 inhibit in his paper.
19 A. No, I do not believe that that would be a
20 necessary fatal flaw to moving forward with an
21 analog.
22 Q. Is it fair to say that a person of
23 ordinary skill in the art understood that the 3'
24 protecting group that is an inefficient terminator
25 in Sanger sequencing would also be expected to be

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1 A. Yes.
2 Q. So in Metzker's 2010 paper, he states
3 that the work he reported in his 1994 paper on
4 terminators for Sanger sequencing provided the
5 basis for development of 3'-O reversible blocking
6 groups for SBS, correct?
7 A. That is what it states.
8 Q. Is it fair to say that a reader of
9 Metzker's 1994 paper understood that the work that
10 it was reported in the 1994 paper on terminators
11 for Sanger sequencing provided the basis for his
12 development of 3'-O reversible blocking groups for
13 SBS?
14 A. If you're asking me if a person of
15 ordinary skill in the art would have read the 1994
16 paper and understood that Metzker was looking to
17 develop reversible terminators for what he
18 called -- he didn't use the term sequencing by
19 synthesis, but for that, then, yes, I think a
20 reader -- I think he states that in the 1994 paper.
21 Q. And is it fair to say the person of
22 ordinary skill in the art -- and, again, whenever I
23 use POSA, I'm referring to POSA that you defined,
24 goes back to October 2000 -- is it fair to say that
25 a person of ordinary skill in the art understand

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1 an inefficient terminator in SBS?
2 A. I want to be careful about how I answer
3 this question, because inefficient is not a
4 particularly useful term here. Inefficient
5 relative to what?
6 Q. Well, you used the word inefficient all
7 the time in what you --
8 A. And I believe I used it very
9 qualitatively, and if you wish for me to define
10 more specifically what I meant, I'm happy to look
11 at any one of them if it's not clear by context,
12 which I hope it would be.
13 But in this case it's really not useful
14 to simply categorize something as interference
15 means inefficient. And I'll tell you why. You can
16 imagine a modification of A to C. The natural
17 triphosphate that polymerases use as natural
18 substrates. C is actually recognized less
19 efficiently than A. So would I call that
20 interference? No, I mean, it's a natural
21 substrate. So I think the question that you're
22 asking is at what point does interference preclude
23 its use in sequencing by synthesis. And that's a
24 slightly hard question to answer without
25 qualitative data, but I think it's certainly safe

<p style="text-align: right;">Page 113</p> <p>1 to say that if it's not accepted as a substrate, 2 then that is not going to be a good candidate for 3 sequencing by synthesis. 4 If it is recognized as well as a natural 5 substrate, that's awesome. People would be really 6 excited, and they would want to move forward in the 7 sequence by synthesis application. But there's a 8 whole range of gray between the two. And at what 9 point it becomes so inefficiently recognized that 10 it could be not be used as a substrate, it's 11 certainly -- there's an area in there where that is 12 going to happen. 13 Q. I think maybe we're getting a little bit 14 too complicated here. Basically, Metzker in 2010 15 pointed to the '94 paper and said that the '94 16 paper provided the basis for his moving forward 17 with protecting groups for SBS, correct? 18 A. Correct. That would be his moving 19 forward with his opinions of what efficiency was 20 required. 21 Q. Okay. And in the 1994 paper he lists 22 some nucleotides as being, for example, inhibitors 23 of the polymerase. And I'm just saying would a 24 person understand that he didn't choose those to 25 move forward with in his SBS studies because they</p>	<p style="text-align: right;">Page 114</p> <p>1 were inhibitors in 1994? 2 A. I think if you looked at the 2010 paper 3 and those compounds that he found inhibited in 1994 4 weren't there, I think that you would have 5 logically assumed that he got rid of them, he 6 didn't pursue them because they were not promising. 7 Q. That is the basis for my question to you, 8 the same for inefficient. Those that he found to 9 be inefficient, he didn't move forward with those. 10 He made that clear in the 2010 paper, correct? 11 A. Are you asking me if this is the only 12 metric that he used to decide to move forward? 13 Q. No, I am not asking you if it is the only 14 metric. 15 A. Certainly the efficiency of which it 16 caused termination as he described it in the '94 17 paper would have been a component of his thought 18 process, of his decision process to decide to what 19 to -- with which -- in his process to decide what 20 he was moving forward with. 21 Q. And those are reasonable decisions that 22 Metzker made. You said his thought process, but 23 that would be is it reasonable for other people to 24 have that thought process? 25 A. Everyone is going to weigh things</p>
<p style="text-align: right;">Page 115</p> <p>1 differently. I don't know exactly what he was 2 thinking. I don't know exactly what motivations he 3 had to choose one or the other, but it was 4 certainly a requirement that you have some 5 recognition. He would have never moved forward 6 with something that has no recognition if he had 7 multiple things that had recognition, he may have 8 chosen one over the other for other reasons. 9 Q. Let's go back to the allyl compound in 10 Metzker, that's compound 3 as you said, right? 11 When I say "Metzker," I should have clarified that 12 Metzker 1994 since there may be several Metzkers on 13 the table. 14 The 3'-O-allyl dATP had no incorporation 15 with seven of the eight polymerases Metzker used in 16 the screening assay, correct? 17 A. That is what it is listed. 18 Q. Based on those results, a POSA understood 19 that the 3'-O-allyl dATP would most likely not work 20 for DNA sequencing with any of those seven 21 polymerases, correct? 22 A. With those polymerases under the 23 condition employed, a POSA would have not been 24 encouraged -- would not have had an expect -- would 25 not have been provided with an expectation for</p>	<p style="text-align: right;">Page 116</p> <p>1 success, correct. 2 Q. For DNA sequencing? 3 A. That is correct. 4 Q. If I refer to Vent (exo-) DNA polymerase, 5 if I refer to that only as "Vent," will you 6 understand that I am referring to the Vent (exo-) 7 DNA polymerase in Metzker '94? 8 A. I will now. 9 Q. Thank you. 10 Metzker reports that the incorporation of 11 the 3'-O-allyl dATP by the Vent polymerase was 12 incomplete at the final concentration of 250 13 micromolar, correct? 14 A. That is what he writes, yes. 15 Q. Please turn to page 4265. Please draw 16 your attention to the second paragraph on the right 17 side of the page that starts with "Some notable 18 correlations." 19 Do you see that? 20 A. I do. 21 Q. And please look at the second sentence in 22 that paragraph that starts with "First, the 23 protecting groups." 24 Do you see that? 25 A. I do.</p>

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1 Q. And Metzker writes "First, the protecting
2 groups containing ether linkages at the 3'
3 position, compounds 1, 3, 4, 7 and 8, were
4 incorporated by some of the polymerases."
5 That is what Metzker wrote, correct?
6 A. That is what he wrote.
7 Q. So when Metzker writes that "Compound 3
8 was incorporated by some of the polymerases," the
9 reader of Metzker understands that the
10 incorporation Metzker refers to is incomplete
11 incorporation with the Vent polymerase at 250
12 micromolar, correct?
13 A. Under the conditions that he employed,
14 yes. I'm sorry. Could you repeat that question?
15 Q. So when Metzker writes that "Compound 3
16 was incorporated by some of the polymerases," the
17 reader of Metzker understands that the
18 incorporation Metzker refers to is incomplete
19 incorporation with the Vent polymerase at 250
20 micromolar, correct?
21 A. Under the conditions that he explored
22 that he is reporting, yes.
23 Q. And earlier we looked at the Tsien
24 publication, and Tsien suggested using nucleotides
25 in the low micromolar range, 1.5 to 30 micromolar.

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1 sentence page -- withdraw the question.
2 Please turn to page 4263 and please draw
3 your attention to the right side of the page where
4 there is a header "3-O Methyl dATP compound 1
5 incorporation."
6 Do you see that?
7 A. I do.
8 Q. And please draw your attention to the
9 last sentence in that section that starts with "All
10 RP-HPLC purified."
11 Do you see that?
12 A. I do.
13 Q. And Metzker writes "All RP-HPLC purified
14 3' modified dATPs, compounds 1 through 7, showed
15 approximately 1 percent dATP contamination, and
16 these trace levels could not be removed by
17 subsequent rp HPLC."
18 That is what Metzker writes, correct?
19 A. That is what he writes.
20 Q. And compound 3, 3'-O-allyl dATP, is one
21 of the compounds included in compounds 1 through 7,
22 correct?
23 A. That is correct.
24 Q. So Metzker is teaching that compound 3,
25 the 3'-O-allyl dATP that is listed in table two

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1 Do you remember that?
2 A. I do.
3 Q. So is it fair to say that a person of
4 ordinary skill would expect that the 3'-O-allyl
5 dATP could show even less incorporation with Vent
6 if it was used at a 10-fold lower concentration
7 that Tsien suggests?
8 A. That is right. But Tsien is suggesting a
9 different reaction than what Metzker is looking at,
10 and so it's very difficult to compare that.
11 Q. I am not asking you to compare it, I'm
12 just saying --
13 A. You just did.
14 Q. I'm saying that -- no, I said that Tsien
15 suggested using lower concentrations of
16 nucleotides.
17 A. And then you asked me to extrapolate onto
18 the Metzker data as to what that would have done.
19 Q. And my question was, at those lower
20 concentrations of nucleotide, would a person of
21 ordinary skill reasonably expect that the
22 incorporation by the allyl nucleotide by Vent could
23 be even less than he reported at 250 micromolars?
24 A. That is a physical law, yes.
25 Q. Please draw your attention to the last

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1 contains approximately percent of the unprotected
2 nucleotide, correct?
3 A. Triphosphate, yes.
4 Q. The unprotected dATP?
5 A. Yes.
6 Q. When Metzker reports that compound 3, the
7 3'-O-allyl dATP, had incomplete termination with
8 Vent at 250 micromolar, it is possible that any
9 incorporation Metzker observed for 3'-O-allyl dATP
10 is actually incorporation of the contaminated dATP,
11 correct?
12 A. I'm sorry. Could you repeat that,
13 please?
14 Q. When Metzker reports that compound 3, the
15 3'-O-allyl dATP, had incomplete termination at 250
16 micromolar with Vent, it's possible that the
17 incorporation Metzker observed is actually
18 incorporation of the contaminated dATP, correct?
19 A. I don't think so.
20 Q. Why not?
21 A. Because you wouldn't get termination if
22 natural dATP were incorporated. There is no
23 terminating group; there is no blocking group. It
24 would, in fact, lead to reduced termination. In
25 fact, that is what almost certainly Metzker is

<p style="text-align: right;">Page 121</p> <p>1 seeing. Some level of the reduced termination, the</p> <p>2 asterisk that he puts there is exactly due to that,</p> <p>3 because there is natural dATP incorporating, and it</p> <p>4 is allowing synthesis to continue.</p> <p>5 Q. I think maybe we're talking past one</p> <p>6 another. When he said the termination is</p> <p>7 incomplete, he's suggesting that there is some?</p> <p>8 A. Termination.</p> <p>9 Q. There is some termination, but that it is</p> <p>10 incomplete, meaning that it continues to go on.</p> <p>11 And I'm saying that is it possible that that is</p> <p>12 because of the contamination of the unprotected</p> <p>13 dATP?</p> <p>14 A. The incomplete termination is because of</p> <p>15 the presence of the contaminating dATP. Yes, I</p> <p>16 think that is certainly correct.</p> <p>17 Q. I am going to put in front of you another</p> <p>18 document.</p> <p>19 MR. SCHWARTZ: This will require a</p> <p>20 marking. 2084.</p> <p>21 (Exhibit 2084 was marked for</p> <p>22 identification.)</p> <p>23 BY MR. SCHWARTZ:</p> <p>24 Q. I am putting in front of you a document</p> <p>25 entitled "The NEB Transcript," dated September 19,</p>	<p style="text-align: right;">Page 122</p> <p>1 1992 that I've marked as Exhibit 2084. Please draw</p> <p>2 your attention to the top far-left side of the</p> <p>3 page, and under the date of September 1992 it reads</p> <p>4 "A scientific newsletter from New England Biolabs."</p> <p>5 Do you see that?</p> <p>6 THE WITNESS: I do.</p> <p>7 MR. ZIMMERMAN: Objection. Lacks</p> <p>8 foundation.</p> <p>9 BY MR. SCHWARTZ:</p> <p>10 Q. New England Biolabs is a supplier of</p> <p>11 biochemical products for the scientific community,</p> <p>12 correct?</p> <p>13 MR. ZIMMERMAN: Same objection.</p> <p>14 BY MR. SCHWARTZ:</p> <p>15 Q. You can answer the question.</p> <p>16 A. NEB is a company that sells such</p> <p>17 reagents, yes.</p> <p>18 Q. And including products for DNA</p> <p>19 sequencing, correct?</p> <p>20 A. I think so.</p> <p>21 Q. Do you recall reading NEB transcripts in</p> <p>22 the course of your own work?</p> <p>23 A. No, I did not.</p> <p>24 Q. On the far right side of the page is an</p> <p>25 index with page numbers.</p>
<p style="text-align: right;">Page 123</p> <p>1 Do you see that?</p> <p>2 A. I do.</p> <p>3 MR. ZIMMERMAN: Objection. Foundation.</p> <p>4 BY MR. SCHWARTZ</p> <p>5 Q. And within the index there is an entry</p> <p>6 entitled "CircumVent Thermal Cycle DNA Sequencing</p> <p>7 Kit."</p> <p>8 Do you see that?</p> <p>9 MR. ZIMMERMAN: Can I have a standing</p> <p>10 objection to this exhibit on foundation, or do you</p> <p>11 want me to make the objection every time?</p> <p>12 MR. SCHWARTZ: You can have a standing</p> <p>13 objection, and the foundation will become clear in</p> <p>14 a minute.</p> <p>15 BY MR. SCHWARTZ:</p> <p>16 Q. Okay. Do you see where there's an entry</p> <p>17 "CircumVent Thermal Cycle DNA Sequencing Kit," in</p> <p>18 the index, page 12?</p> <p>19 A. Yes.</p> <p>20 Q. Please turn to the next page, which is</p> <p>21 page 12. And I will represent that Exhibit 284 --</p> <p>22 2084 is not the complete transcript. It's only the</p> <p>23 portion that refers to the CircumVent Thermal Cycle</p> <p>24 DNA Sequencing Kit.</p> <p>25 Do you see that?</p>	<p style="text-align: right;">Page 124</p> <p>1 A. I do.</p> <p>2 Q. And under that header it reads</p> <p>3 "CircumVent thermal cycle DNA sequencing is a</p> <p>4 simple and rapid method which generates sequence</p> <p>5 information from less template than any other</p> <p>6 protocol. The kit uses the highly thermostable</p> <p>7 Vent (exo-) DNA polymerase."</p> <p>8 That is what it says, right?</p> <p>9 A. That is what it says.</p> <p>10 Q. Now, please go back to Metzker 1994,</p> <p>11 which is Exhibit 10,016 [sic], and go back to table</p> <p>12 two. The Vent polymerase used in Metzker 1994 is</p> <p>13 the Vent (exo-) DNA polymerase, correct?</p> <p>14 A. That is correct.</p> <p>15 Q. Now, please turn to Page 4261 of Metzker.</p> <p>16 And on the right side towards the bottom of page</p> <p>17 4161 is a header entitled "Polymerases."</p> <p>18 Do you see that?</p> <p>19 A. I do.</p> <p>20 Q. And please draw your attention to the</p> <p>21 last sentence in that section. Metzker states that</p> <p>22 he got the Vent (exo-) DNA polymerase from New</p> <p>23 England Biolabs, correct?</p> <p>24 A. That is written, yes.</p> <p>25 Q. So the Vent polymerase in Metzker 1994 is</p>

<p style="text-align: right;">Page 125</p> <p>1 the same Vent polymerase that is being discussed in</p> <p>2 the NEB September 1992 transcript, correct?</p> <p>3 A. I would have to look at this. As I said,</p> <p>4 I haven't looked at this before. This seems to be</p> <p>5 a thermal cycle kit. It seems to use Vent. I</p> <p>6 don't know what else is in the kit.</p> <p>7 Q. I'm just asking you specifically the</p> <p>8 polymerase. It's the same polymerase that Metzker</p> <p>9 says that he used?</p> <p>10 A. It seems to be the same polymerase.</p> <p>11 Q. Please go back to that exhibit, the</p> <p>12 transcript, Exhibit 2084 and turn to the next page,</p> <p>13 which is page 13.</p> <p>14 A. I'm sorry, which? 2084?</p> <p>15 Q. Yes, page 13 is the next page in that.</p> <p>16 Do you see that? And please draw your attention to</p> <p>17 the middle column. And towards the bottom of the</p> <p>18 middle column on page 13, there is a header which</p> <p>19 reads "Can the CircumVent kit be used for</p> <p>20 sequencing templates to be used on automated</p> <p>21 fluorescent sequencers."</p> <p>22 Do you see that?</p> <p>23 A. I do.</p> <p>24 Q. The NEB transcript answers that question</p> <p>25 with a yes, but with a caveat. Now, please draw</p>	<p style="text-align: right;">Page 126</p> <p>1 your attention to the second sentence there which</p> <p>2 starts with "However, when fluorescent tagged."</p> <p>3 Do you see that?</p> <p>4 A. I do.</p> <p>5 Q. And the transcript reads, "However, when</p> <p>6 fluorescent-tagged dideoxy dNTPs are used in the</p> <p>7 sequencing method, the results can be mixed.</p> <p>8 Inefficient incorporation leads to different</p> <p>9 intensities and peak heights on the resulting</p> <p>10 fluorograms, thus, the software has more difficulty</p> <p>11 calling correct bases."</p> <p>12 That is what the transcript states,</p> <p>13 right?</p> <p>14 A. That is what is written, yes.</p> <p>15 Q. So the NEB transcript teaches that adding</p> <p>16 a fluorescent label to a dNTP results in</p> <p>17 inefficient incorporation by Vent polymerase,</p> <p>18 correct?</p> <p>19 A. They don't describe what -- they don't</p> <p>20 describe what the modifications are, but they say</p> <p>21 that inefficient incorporation can lead to</p> <p>22 different intensities, yes.</p> <p>23 Q. When you add a fluorescent tag to the</p> <p>24 dNTP?</p> <p>25 A. Whatever fluorescent tag they are</p>
<p style="text-align: right;">Page 127</p> <p>1 exploring, yes.</p> <p>2 Q. And the transcript states that, that</p> <p>3 inefficient incorporation leads to unreliable</p> <p>4 sequencing. That's what it says, right?</p> <p>5 MR. ZIMMERMAN: Objection.</p> <p>6 Mischaracterizes.</p> <p>7 THE WITNESS: The document says</p> <p>8 inefficient incorporation leads to different</p> <p>9 intensities and peak heights and more difficulty in</p> <p>10 calling correct bases.</p> <p>11 BY MR. SCHWARTZ</p> <p>12 Q. So would you say that that is what</p> <p>13 results in unreliable sequencing?</p> <p>14 A. You have as much information about it as</p> <p>15 I do. It says that difficulty in calling correct</p> <p>16 bases.</p> <p>17 Q. So please go back to Metzker 1994, and go</p> <p>18 back to table two. Metzker reports in table two</p> <p>19 that the unlabeled 3'-O-allyl nucleotide</p> <p>20 incompletely terminated the sequencing reaction</p> <p>21 using Vent (exo-) DNA polymerase at 250 micromolars</p> <p>22 of the nucleotide, correct?</p> <p>23 A. Under the conditions that he is using</p> <p>24 here, that is what the document says.</p> <p>25 Q. And we just looked at the NEB transcript,</p>	<p style="text-align: right;">Page 128</p> <p>1 the September 1992 transcript, and it teaches that</p> <p>2 fluorescently labeled nucleotides are inefficiently</p> <p>3 incorporated by the same Vent polymerases Metzker</p> <p>4 used in those experiments, correct?</p> <p>5 A. The polymerase is the same, so given the</p> <p>6 caveats that we just described, there can be some</p> <p>7 fluorophore link or modifications that reduce</p> <p>8 efficiency and complicate base calling, according</p> <p>9 to NEB.</p> <p>10 Q. Given that Metzker reports that the</p> <p>11 3'-O-allyl dATP without a label is capable of</p> <p>12 incomplete termination even at high nucleotide</p> <p>13 concentrations, a person of ordinary skill in the</p> <p>14 art would expect that adding a fluorescent label to</p> <p>15 that nucleotide could result in even less</p> <p>16 termination activity with a Vent, correct?</p> <p>17 A. No, I disagree with that. He has not</p> <p>18 reported that the 3'-O-allyl is efficiently</p> <p>19 incorporated.</p> <p>20 Q. No, I said incomplete termination.</p> <p>21 A. That's inefficient incorporation. So he</p> <p>22 has not reported that it, on its own, is</p> <p>23 inefficient at termination. As we just discussed,</p> <p>24 there is 1 percent dATP in there.</p> <p>25 Q. But if you add a fluorescent label to</p>

<p style="text-align: right;">Page 129</p> <p>1 that nucleotide, it could result in even less</p> <p>2 termination than Metzker reported at the 250</p> <p>3 micromolar, correct?</p> <p>4 A. That is if -- if the added linker, as was</p> <p>5 the case apparently with the NEB report, if the</p> <p>6 added linker reduced the efficiency, then, yes,</p> <p>7 that would presumably, in an additive way, reduce</p> <p>8 the termination. But, again, that is termination</p> <p>9 in the presence of 1 percent dATP.</p> <p>10 Q. Yeah, I'm just referring to Metzker's</p> <p>11 studies.</p> <p>12 A. As am I, and his Metzker study has</p> <p>13 1 percent dATP in the mixture. No one would</p> <p>14 sequence that way. No one would include dATP that</p> <p>15 you're allowing to compete with your modified dATP</p> <p>16 where you're relying on the modified dATP</p> <p>17 terminate.</p> <p>18 Q. Right. So the fact that there is -- that</p> <p>19 there is unlabeled, unmodified dAPT there would be</p> <p>20 understood to change the way that one would expect</p> <p>21 that nucleotide to behave if that unmodified dATP</p> <p>22 wasn't there, correct?</p> <p>23 A. A POSA would understand that having that</p> <p>24 contaminating dAPT would dramatically change this,</p> <p>25 yes. I guess just to be clear, a POSA would know</p>	<p style="text-align: right;">Page 130</p> <p>1 that the O-allyl modified dAPT at a 100 fold more</p> <p>2 concentration than unmodified dAPT was competing</p> <p>3 with the incorporation of that unmodified dAPT,</p> <p>4 because you are getting some termination.</p> <p>5 Q. Please go back to page 63 of Metzker '94.</p> <p>6 And please look at the header "Terminator Screen"</p> <p>7 on the right side of the page, and please look at</p> <p>8 the last sentence in that section that starts with</p> <p>9 "Compounds 1, 8, 7."</p> <p>10 Do you see that?</p> <p>11 A. I do.</p> <p>12 Q. And Metzker writes "Compounds 1, 8, and 7</p> <p>13 showed specific termination and were further</p> <p>14 evaluated with respect to their</p> <p>15 concentration-dependent effects."</p> <p>16 That is what Metzker writes?</p> <p>17 A. Correct.</p> <p>18 Q. A person of ordinary skill reading</p> <p>19 Metzker understood that Metzker was advancing</p> <p>20 compounds 1, 8, and 7 for further evaluation based</p> <p>21 on the screening tests that were reported -- at</p> <p>22 least based on the screening tests that were</p> <p>23 reported in table two, correct?</p> <p>24 A. At least, but that data was available to</p> <p>25 him when he made the choice to conduct further</p>
<p style="text-align: right;">Page 131</p> <p>1 experiments concentration-dependent effects with 1,</p> <p>2 8, and 7.</p> <p>3 Q. And a person reading -- a person of</p> <p>4 ordinary skill reading Metzker 1994 also understood</p> <p>5 that, based on those screening tests, Metzker did</p> <p>6 not advance compound 3 for further evaluation,</p> <p>7 correct?</p> <p>8 A. No. If you say based on at least those</p> <p>9 screening effects, then I might agree with it.</p> <p>10 Q. Let me change the question then.</p> <p>11 A person of ordinary skill reading</p> <p>12 Metzker 1994 understood that at least based on the</p> <p>13 screening test, Metzker did not advance compound 3</p> <p>14 for further evaluation?</p> <p>15 A. So just to be clear, because I'm not sure</p> <p>16 I understand that turn of the phrase "at least</p> <p>17 based on," he had that information available. He</p> <p>18 certainly had other information available too. And</p> <p>19 he chose to move forward with 1, 8, and 7, and what</p> <p>20 you are getting at, obviously, is that he did not</p> <p>21 move 3 forward, and he had the data from his</p> <p>22 kinetic data that's reported in table two, and he</p> <p>23 had a world of other data as well. And I don't</p> <p>24 know what it was that fed into his choice to not</p> <p>25 move 3 forward.</p>	<p style="text-align: right;">Page 132</p> <p>1 Q. But he didn't move 3 forward?</p> <p>2 A. He did not move 3 forward.</p> <p>3 Q. Metzker 1994 did not describe any</p> <p>4 condition to remove the 3'-O-allyl group, correct?</p> <p>5 A. That is correct.</p> <p>6 Q. He certainly didn't describe any</p> <p>7 condition to remove the 3'-O-allyl group that would</p> <p>8 be compatible with DNA synthesis, right -- or</p> <p>9 DNA -- let me strike that.</p> <p>10 Metzker 1994 did not describe any</p> <p>11 condition to remove the 3'-O-allyl group that is</p> <p>12 compatible with DNA, correct?</p> <p>13 A. That is correct. And in fact, I think</p> <p>14 that's probably related to why he did not move 3</p> <p>15 forward. Because he had the conditions to easily</p> <p>16 deprotect 7. He wasn't the chemist. So he</p> <p>17 probably didn't think about reactions to</p> <p>18 deprotect 3.</p> <p>19 Q. But he didn't describe any conditions?</p> <p>20 A. That is right.</p> <p>21 Q. Six lines down in the abstract, which is</p> <p>22 on page -- we read the first part of the abstract,</p> <p>23 and I'm just going to read the next part of the</p> <p>24 abstract -- there is a sentence that starts with</p> <p>25 "3'-O 2-nitrobenzyl dAPT."</p>

<p style="text-align: right;">Page 133</p> <p>1 Do you see that?</p> <p>2 A. I do.</p> <p>3 Q. And Metzker writes "3'-O- 2-nitrobenzyl</p> <p>4 dAPT is a UV sensitive nucleotide, and was shown to</p> <p>5 be incorporated by several thermostable DNA</p> <p>6 polymerases. Base-specific termination and</p> <p>7 efficient photolytic removal of the 3' protecting</p> <p>8 group was demonstrated. Following deprotection,</p> <p>9 DNA synthesis was reinitiated by the incorporation</p> <p>10 of natural nucleotides into DNA. The</p> <p>11 identification of this labile terminator and the</p> <p>12 demonstration of one-cycle stop/start DNA synthesis</p> <p>13 are initial steps in the development of a novel</p> <p>14 sequencing strategy."</p> <p>15 That is what Metzker writes, correct?</p> <p>16 A. That is correct.</p> <p>17 Q. So Metzker advanced a nitrobenzyl</p> <p>18 nucleotide for further testing and demonstrated it</p> <p>19 was capable of one complete cycle of SBS, correct?</p> <p>20 A. I think that is precisely why he advanced</p> <p>21 it, because it was easy to show it would be capable</p> <p>22 of that complete step.</p> <p>23 Q. And Metzker didn't advance the 3'-O-allyl</p> <p>24 cap nucleotide for SBS testing?</p> <p>25 A. He did not.</p>	<p style="text-align: right;">Page 134</p> <p>1 MR. SCHWARTZ: Do you want to take a</p> <p>2 break for lunch at any particular time? I don't</p> <p>3 know. What are your plans?</p> <p>4 MR. ZIMMERMAN: When are you hungry?</p> <p>5 THE WITNESS: I generally don't eat big</p> <p>6 lunches. So whenever anyone else is hungry.</p> <p>7 MR. SCHWARTZ: Maybe we should break now.</p> <p>8 MR. ZIMMERMAN: If there is a natural</p> <p>9 stopping point or a place, we are not wedded to a</p> <p>10 particular time.</p> <p>11 THE VIDEOGRAPHER: We are off the record</p> <p>12 at 12:16 p.m.</p> <p>13 (Recess taken.)</p> <p>14 THE VIDEOGRAPHER: We are on the record</p> <p>15 at 1:19 p.m.</p> <p>16 BY MR. SCHWARTZ:</p> <p>17 Q. Good afternoon, Dr. Romesberg. I am</p> <p>18 going to put in front of you another exhibit. That</p> <p>19 doesn't require marking. I'm putting in front of</p> <p>20 you Exhibit 107. It is entitled "Termination of</p> <p>21 the DNA Synthesis by N6-Alkylated, Not</p> <p>22 3'-O-Alkylated Photocleavable 2'-Deoxyadenosine</p> <p>23 Triphosphates," by Wu, et al.</p> <p>24 You reviewed this paper in forming your</p> <p>25 opinion in the current IPRs, correct?</p>
<p style="text-align: right;">Page 135</p> <p>1 A. That is correct.</p> <p>2 Q. The corresponding author of this paper is</p> <p>3 Michael Metzker, correct?</p> <p>4 A. Correct.</p> <p>5 Q. And that's the same Michael Metzker who</p> <p>6 is the first author of Metzker 1994, correct?</p> <p>7 A. That is correct.</p> <p>8 Q. Please turn to page 6348 of the paper,</p> <p>9 and please look at the discussion section on the</p> <p>10 left side. Please draw your attention to seven</p> <p>11 lines down in the discussion section where the</p> <p>12 sentence starts with "This is unlike the situation</p> <p>13 for."</p> <p>14 Do you see that?</p> <p>15 A. I do.</p> <p>16 Q. And the author writes "This is unlike the</p> <p>17 situation for 3' modified nucleotides which</p> <p>18 typically act as poor substrates for DNA</p> <p>19 polymerases. For example, screening 3'-O-allyl</p> <p>20 dATP with eight different polymerases revealed</p> <p>21 limited activity at high micromolar concentrations,</p> <p>22 with only Vent (exo-) DNA polymerase."</p> <p>23 That is what the authors wrote, correct?</p> <p>24 MR. ZIMMERMAN: You left out the word</p> <p>25 DNA.</p>	<p style="text-align: right;">Page 136</p> <p>1 BY MR. SCHWARTZ:</p> <p>2 Q. DNA polymerase?</p> <p>3 MR. ZIMMERMAN: Yes.</p> <p>4 MR. SCHWARTZ: I thought I did say DNA.</p> <p>5 THE WITNESS: That is what is written.</p> <p>6 BY MR. SCHWARTZ:</p> <p>7 Q. And the authors cite to reference 8 as</p> <p>8 support for those statements, correct?</p> <p>9 A. They do.</p> <p>10 Q. And can you take a look at the reference</p> <p>11 list. And reference 8 is the Metzker '94 paper</p> <p>12 we've been looking at, correct?</p> <p>13 A. That is correct.</p> <p>14 Q. So the Wu paper which includes Metzker as</p> <p>15 an author refers back to the screening test</p> <p>16 reported in Metzker 1994, correct?</p> <p>17 A. That is correct.</p> <p>18 Q. And the Wu authors which include Metzker</p> <p>19 characterize the screening test in Metzker '94 as</p> <p>20 showing that the allyl capped nucleotide had</p> <p>21 limited activity at high micromolar concentrations</p> <p>22 with only one out of eight polymerases tested,</p> <p>23 correct?</p> <p>24 A. That is what they state, yes.</p> <p>25 Q. And they stated that in 2007, being aware</p>

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1 of the fact that there were contaminants in the
2 1994 studies, correct?
3 A. That is correct.
4 Q. So despite the fact that they were aware
5 of contaminants in the 1994 studies, even years
6 later Metzker concluded that the 3'-O-allyl dAPT
7 had limited activity with Vent at high micromolar
8 concentrations.
9 That is what he says, right?
10 A. He says that. I just, by way of
11 clarification, I think -- I don't know that I would
12 call that a conclusion. He is using sort of
13 justification for what he is doing. He is --
14 decided that he's pursuing a different analog, and
15 he is then saying that the -- that all the old ones
16 were not incorporated efficiently. Which,
17 incidentally, I disagreed with, but that is not
18 your question.
19 Q. And the Wu authors, which include
20 Metzker, characterize the screening test in Metzker
21 '94 as showing that the allyl cap nucleotide had
22 limited activity at high micromolar concentration
23 with only one of the eight polymerases?
24 MR. ZIMMERMAN: Objection. Asked and
25 answered.

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1 author knew that, because I don't think he was in
2 the group at the time that that paper was studied,
3 or that paper was written, Metzker certainly was.
4 I certainly think that that first author would have
5 had access to read the paper. Do I know that he
6 thought about that, no, but ...
7 Q. But the Wu authors do characterize those
8 studies that way, correct?
9 A. I don't know who wrote the paper. Wu is
10 first author on the paper, Metzker is corresponding
11 author.
12 Q. Let's just make it simple. That is what
13 the paper says, right?
14 MR. ZIMMERMAN: Objection.
15 Mischaracterizes the document.
16 BY MR. SCHWARTZ:
17 Q. I disagree that I'm mischaracterizing the
18 document. They say that the 3-O-allyl ATP is a
19 poor substrate for DNA polymerase. They say it.
20 A. I agree with the passages that you read.
21 Q. Okay.
22 And that included Metzker on that paper?
23 A. Metzker is the corresponding author on
24 this paper.
25 Q. Have you been corresponding author on

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1 BY MR. SCHWARTZ:
2 Q. That is what they said, correct?
3 A. They say that, yes.
4 Q. And a person reading Metzker 1994 in
5 October of 2000 understood that the 3-O-allyl ATP
6 had only limited activity at high micromolar
7 concentrations with only one of the eight
8 polymerases?
9 A. I would disagree with that.
10 Q. So you disagree with Metzker's
11 interpretation of his own data?
12 A. I am.
13 Q. But you do agree that Metzker himself
14 stated in 2007 that the O-allyl had limited
15 activity high micromolar concentrations?
16 A. I agreed that he stated what you read.
17 Q. And the Wu authors also stated that "the
18 3-O-allyl dAPT is a poor substrate for DNA
19 polymerase." That's what they said?
20 A. I agree that what you read is out of
21 their paper.
22 Q. And they said that knowing that in their
23 1994 paper they had some contaminate in each of
24 their nucleotides, correct?
25 A. I guess I don't know that the first

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1 papers?
2 A. I have.
3 Q. Is it your practice to read the papers
4 that you are corresponding author on?
5 A. I write the papers that I'm corresponding
6 author on.
7 Q. And is it your practice that, even if
8 there are other authors on the paper where you're a
9 corresponding author, that you would permit
10 information that you did not believe to be accurate
11 to be in that paper?
12 A. No.
13 Q. So would you agree that corresponding
14 authors vouch for the veracity of the information
15 in the papers of which they are corresponding
16 authors?
17 MR. ZIMMERMAN: Objection. Lacks
18 foundation. Calls for speculation.
19 THE WITNESS: So before I accuse Metzker
20 of falsifying data, which I am not going to do, all
21 the statements that we're talking about are
22 qualitative. He's saying that they aren't great
23 substrates. Well, relative to what? Relative to
24 the natural substrate? Sure.
25 I'll tell you what. They're good enough

<p style="text-align: right;">Page 141</p> <p>1 that they compete with natural dAPT for 2 incorporation. Metzker seems to characterize that 3 as "not great." I would characterize that as 4 surprisingly good. I guess it's a matter of 5 perspective or taste, I guess. I don't think he 6 was lying or falsifying anything. There is no 7 quantitative data there that's -- you know, it's he 8 simply says -- he uses a qualitative term that's 9 not wrong. You can buy -- again, I don't 10 particularly like the qualitative way he describes 11 it, but what I'll also say is this is life. 12 People do this. People use qualitative 13 statements to justify where they're at in the 14 program right then. He had chosen, I think, 15 probably because he was seduced into this idea that 16 you could photodeprotect very easily a base 17 protected analog -- sorry, a 3' protected analog. 18 That turned out to be incorrect, as I know you 19 know. 20 And I think he was enticed into that 21 approach because he thought it was so easy to 22 deprotect with light. And so that is why, in fact, 23 I am almost certain moved compound 8 on in 1994, 24 not because it was particularly better as a 25 substrate than O-allyl. I think he made that</p>	<p style="text-align: right;">Page 142</p> <p>1 choice based on the photodeprotection. So I don't 2 think that he's mischaracterizing things. I just 3 wouldn't characterize -- I just wouldn't use the 4 perspective that he -- I would not take the 5 perspective he is taking. 6 BY MR. SCHWARTZ: 7 Q. But you would agree that he did interpret 8 his 1994 data as saying that the 3-O-allyl ATP is a 9 poor substrate for DNA polymerase. 10 A. I would not agree with that. Those are 11 the words he uses. It is attempting to take words 12 so literally. 13 Q. I am only asking you if Metzker is saying 14 that. 15 A. He wrote those words. And that is not 16 how a person of ordinary skill in the art would 17 have written them. 18 Q. Those are the words in his paper? 19 MR. ZIMMERMAN: Objection. Asked and 20 answered. 21 THE WITNESS: Those are the words in his 22 paper. 23 (Exhibit 2025 was previously marked for 24 identification.) 25 ///</p>
<p style="text-align: right;">Page 143</p> <p>1 BY MR. SCHWARTZ: 2 Q. I am going to put in front of you another 3 document. I'm putting in front of you 4 Exhibit 2025, a document entitled "Improved 5 Nucleotide Selectivity and Termination of 3'-OH 6 Unblocked Reversible Terminators by Molecular 7 Tuning of 2-nitrobenzyl Alkylated HOMedU 8 Triphosphate." And, again, the corresponding 9 author of this paper is Michael Metzker, correct? 10 A. That is correct. 11 Q. And this is the same Michael Metzker who 12 is the first author of Metzker '94, correct? 13 A. It is. 14 Q. Please turn to Page 10 of the paper. 15 Please draw your attention to the first full 16 paragraph on the left side of the page that starts 17 with "The Use of HOMedU." 18 Do you see that? 19 A. Yes, I do. 20 Q. Will you please look a little over 21 halfway down that paragraph where there is a 22 sentence that starts "We note 3-O-allyl dAPT is." 23 Do you see that? 24 A. I'm sorry. I'm having a little bit of 25 trouble.</p>	<p style="text-align: right;">Page 144</p> <p>1 Q. It's about halfway down. 2 A. Yes, I found it. 3 Q. You are with me? 4 A. I am. 5 Q. And the Litosh authors write "We note 6 that 3'-O-allyl dAPT is not efficiently 7 incorporated by Vent (exo-) polymerase." 8 That is what the authors wrote, correct? 9 A. That is what they wrote. 10 Q. And they refer to reference 46 to support 11 that statement, right? 12 A. They do. 13 Q. Reference 46 is the Metzker 1994 paper, 14 isn't it? 15 A. It is. 16 Q. So the authors of the Litosh paper, which 17 includes Michael Metzker as the corresponding 18 author, states that the 3'-O-allyl dAPT is not 19 efficiently incorporated by Vent (exo-) polymerase, 20 correct? 21 A. Those are the words -- your reading of 22 those words is correct. 23 Q. And they refer to the Metzker 1994 paper 24 as support for that statement, correct? 25 A. They do.</p>

<p style="text-align: right;">Page 145</p> <p>1 Q. And again, they made that statement in 2 this paper, which was published in 2011, aware of 3 the fact that they had some contamination of the 4 nucleotides that were used in the Metzker 1994 5 studies, correct? 6 A. I assume they were still aware of that. 7 I don't know, maybe he wanted to forget it. It's 8 frankly, it's a mistake on his part, and he may 9 have not been proud of that. 10 Q. So you're putting yourself into Metzker's 11 mind now? 12 A. No, I'm thinking of how I would feel if I 13 had done that, and I'm just feeling how most people 14 would have. He is drawing conclusions that are 15 really not, in my opinion, founded. And I think 16 they wouldn't have been to the person of ordinary 17 skill in the art as well. 18 Q. We looked at two papers, post 1994, where 19 Michael Metzker is the corresponding author, and in 20 both of those papers he is interpreting the 21 experiment in the 1994 paper, correct? 22 A. That is correct. 23 Q. And he is interpreting those experiments 24 to conclude that the 3'-O-allyl dATP was not 25 suitable for his studies as a DNA terminator,</p>	<p style="text-align: right;">Page 146</p> <p>1 correct? 2 A. I don't know that he said that. I would 3 have to look to see that he said that, but the -- 4 Q. He says that it is not efficiently 5 incorporated in 2011. And he says in 2007 that 6 it's a poor substrate for the polymerase, correct? 7 A. So he doesn't refer to sequencing by 8 synthesis as a whole, but, you know, this is why we 9 qualify people's opinions as having to be a person 10 of ordinary skill in the art. A person of ordinary 11 skill in the art, I imagine, would have been 12 confused by these statements. 13 Q. You don't know that though, do you know? 14 A. A person of the ordinary skill in the art 15 would have seen 1 percent contamination. A person 16 of ordinary skill in the art would have understood 17 that dAPT would be very efficiently incorporated at 18 its natural rate, and would therefore be 19 contributing to the lack of termination mediated by 20 the protected analog. It is sophomore organic 21 chemistry. I think that anyone practicing in that 22 field would have been interested in that, and then 23 maybe if they then read these papers been confused 24 by Metzker stepping away from it. 25 And again, I think what they would have</p>
<p style="text-align: right;">Page 147</p> <p>1 concluded is he is interested in these other guys, 2 and he is passing this aside because this is now 3 his direction. 4 Q. This is all speculation on your part, 5 isn't it? 6 A. It is. It is. 7 Q. Do you have any evidence that persons 8 skilled in the art actually believed in what you 9 just said? 10 A. Yes, because what I just said is 11 sophomore chemistry. It's basic chemistry. And 12 that is why we put a certain burden -- my 13 understanding is that's why we put a certain limit 14 on what we define as a person of ordinary skill in 15 the art. And I think a person of ordinary skill in 16 the art would have fully appreciated the natural 17 substrates for polymerase are very efficiently 18 incorporated. 19 Q. But Metzker himself who had even 20 extraordinary skill in the art -- would you agree 21 that he had more than a person of ordinary skill in 22 the art? How would you characterize that? 23 MR. ZIMMERMAN: Objection. Compound. Do 24 you want to pick which one of those questions? 25 ///</p>	<p style="text-align: right;">Page 148</p> <p>1 BY MR. SCHWARTZ: 2 Q. Do you consider Metzker a POSA? 3 A. Yes. 4 Q. You consider Metzker a POSA, and Metzker 5 as a POSA wrote that the 3'-O-allyl dAPT is not 6 efficiently incorporated by a Vent polymerase, 7 right? 8 A. So if you really want to talk about why 9 he said this, I think it's clear. First of all, 10 efficiently is a relative term, and so he's not 11 saying anything wrong, and he is justifying the 12 direction of research that he's going. He's got 13 NIH grants that describe how great his approach is. 14 Unfortunately, everyone in science has to 15 do this. We have to justify what we are doing 16 relative to other things. You're right. This is 17 all speculation. I don't know why he wrote those 18 words, but it is not speculation that there was 19 1 percent dAPT in those reactions and that that 20 1 percent dAPT led to two and a half micromolar of 21 the natural substrate. That's a concentration that 22 is typical of a standard PCR reaction. So it's 23 going in. And so to the extent it goes in, it is 24 going to inhibit the chain termination by the 25 analog. That is not speculation, and that is not</p>

<p style="text-align: right;">Page 149</p> <p>1 something that would not have been obvious to a</p> <p>2 POSA.</p> <p>3 Q. And when Metzker wrote in the other</p> <p>4 paper, the 2007 paper, that the 3'-O-allyl dAPT is</p> <p>5 a poor substrate for DNA polymerase, that was also</p> <p>6 Metzker as a POSA writing that, correct?</p> <p>7 A. Yeah. And if you want me to speculate</p> <p>8 why I think he might have written that, speculate,</p> <p>9 I'm happy to do so.</p> <p>10 Q. I'm not asking you to speculate. I'm</p> <p>11 only asking you to answer my question.</p> <p>12 A. He wrote that. And I would consider him</p> <p>13 a POSA.</p> <p>14 Q. And earlier we looked at Tsien, and you</p> <p>15 agreed that one of Tsien's specific requirements is</p> <p>16 efficient incorporation of the 3' block nucleotide</p> <p>17 by the polymerase, correct?</p> <p>18 A. Correct.</p> <p>19 Q. You also agree that to be successful for</p> <p>20 SBS, the nucleotide has to be efficiently</p> <p>21 incorporated by the polymerase?</p> <p>22 A. Are you asking my opinion?</p> <p>23 Q. No, you actually said it, I'm just asking</p> <p>24 if you remember that it was your opinion that to be</p> <p>25 successful for SBS, the nucleotide has to be</p>	<p style="text-align: right;">Page 150</p> <p>1 efficiently incorporated by the polymerase?</p> <p>2 A. Just because I would like to understand</p> <p>3 the context in which I said that, where are you</p> <p>4 reading that?</p> <p>5 Q. We can go back. We already have</p> <p>6 testimony on this, but we can go back to your</p> <p>7 deposition transcript in IPR2013-00517. I forget</p> <p>8 what exhibit that is.</p> <p>9 A. I feel like I can answer the question now</p> <p>10 without looking further. That would be in the</p> <p>11 context of a sequencing by synthesis method.</p> <p>12 Q. Let's go back to table two of Metzker</p> <p>13 1994. That is on page 4263 of Metzker.</p> <p>14 A. I am there.</p> <p>15 Q. Compound 1 in table two is a 3'-O-allyl</p> <p>16 dATP, correct?</p> <p>17 A. That is correct.</p> <p>18 Q. And compound 8 in table two is a</p> <p>19 3'-O-Methyl dTTP, correct?</p> <p>20 A. That is correct.</p> <p>21 Q. The only difference between compound 1</p> <p>22 and compound 8 is the base, correct?</p> <p>23 A. That is correct.</p> <p>24 Q. The base in compound 1 is an adenine.</p> <p>25 The base in compound 8 is a thymine, correct?</p>
<p style="text-align: right;">Page 151</p> <p>1 A. That is correct.</p> <p>2 Q. I want to focus on table two's results</p> <p>3 for the AMV RT polymerase, okay?</p> <p>4 A. Okay.</p> <p>5 Q. The AMV RT polymerase was able to</p> <p>6 incorporate the methyl capped adenine nucleotide,</p> <p>7 correct?</p> <p>8 A. That is correct.</p> <p>9 Q. But the same polymerase was unable to</p> <p>10 incorporate the methyl capped thymine nucleotide,</p> <p>11 right?</p> <p>12 A. That is what is reported.</p> <p>13 Q. Again, the only difference between those</p> <p>14 two Methyl capped nucleotides is that one had an</p> <p>15 adenine base and the other had a thymine base,</p> <p>16 correct?</p> <p>17 A. That is correct.</p> <p>18 Q. I want to focus on table two results for</p> <p>19 the last four polymerases, the BST DNA polymerase,</p> <p>20 the AmpliTaq DNA polymerase, the Vent (exo-)</p> <p>21 polymerase, and the RTH DNA polymerase. We'll</p> <p>22 focus just on those, okay?</p> <p>23 A. Yes.</p> <p>24 Q. These four polymerases were capable of</p> <p>25 incorporating the methyl capped thymine nucleotide,</p>	<p style="text-align: right;">Page 152</p> <p>1 right?</p> <p>2 A. That is correct.</p> <p>3 Q. But none of those four polymerases was</p> <p>4 capable of incorporating the methyl capped adenine</p> <p>5 nucleotide, right?</p> <p>6 A. That would seem to be what the table is</p> <p>7 saying.</p> <p>8 Q. You agree none of the polymerases in</p> <p>9 table two were capable of incorporating both the</p> <p>10 methyl capped thymine analog and the methyl capped</p> <p>11 adenine analog, correct?</p> <p>12 A. That would seem to be the case.</p> <p>13 Q. Please turn to page 4266. Look at the</p> <p>14 right column. The second full paragraph that</p> <p>15 starts with "Several unexpected results."</p> <p>16 Do you see that?</p> <p>17 A. Yes.</p> <p>18 Q. And Metzker writes "We have not</p> <p>19 identified a polymerase that will incorporate both</p> <p>20 3'-O-allyl dATP, compound 1, and 3'-O-allyl dTTP,</p> <p>21 compound 8."</p> <p>22 That is what Metzker writes, correct?</p> <p>23 A. That is written there, yes.</p> <p>24 Q. And you agree that the results we just</p> <p>25 looked at show that if a polymerase incorporates a</p>

<p style="text-align: right;">Page 153</p> <p>1 nucleotide analog with one particular base, it may</p> <p>2 or may not incorporate the similar analog</p> <p>3 containing a different base, correct?</p> <p>4 A. That is what is stated there. That is</p> <p>5 the conclusion -- that is obvious in the conclusion</p> <p>6 that is stated there.</p> <p>7 Q. So is it fair to say that a polymerase's</p> <p>8 ability to incorporate a nucleotide analog with one</p> <p>9 base doesn't provide an expectation that that</p> <p>10 polymerase will also incorporate a similar</p> <p>11 nucleotide with a different base?</p> <p>12 A. I would probably have to disagree with</p> <p>13 that. It certainly doesn't prove that it is the</p> <p>14 case, but I think a POSA would have expected it to</p> <p>15 be, because you are making a modification that is</p> <p>16 distant from -- you are talking about the</p> <p>17 modification that change distant from the position</p> <p>18 you are modifying and most people think that a</p> <p>19 Watson-Crick base pair is formed. It doesn't</p> <p>20 particularly matter if it's a GC, AT, TA, CG, so I</p> <p>21 think most people would have dismissed that and</p> <p>22 assumed that it was sort of general.</p> <p>23 I mean it was very common for people to</p> <p>24 simply characterize one analog and sort of expect</p> <p>25 that to transfer, to be transferable to other</p>	<p style="text-align: right;">Page 154</p> <p>1 analogs. I don't think the people would have known</p> <p>2 that is the case. I think they probably would have</p> <p>3 expected it, and I think that is probably why he is</p> <p>4 calling it unexpected. He opens that paragraph by</p> <p>5 saying "several unexpected results." And so I</p> <p>6 think that is a bit of a surprise.</p> <p>7 I would also point out, again, that all</p> <p>8 of those O-methyl ATP reactions have dATP in there.</p> <p>9 So some of those dashes may have been because they</p> <p>10 were being outcompeted by the natural dAPT. So I</p> <p>11 think a POSA would have viewed that conclusion</p> <p>12 cautiously.</p> <p>13 Q. That is your speculation?</p> <p>14 A. That is my speculation. It is not my</p> <p>15 speculation that those reactions had natural dAPT</p> <p>16 in there and those would have officially</p> <p>17 incorporated. Again, each of those reactions had</p> <p>18 1 percent of the natural dAPT in there, and it is</p> <p>19 not my speculation that a POSA would have</p> <p>20 recognized that as an efficient substrate. That is</p> <p>21 my definition of a POSA.</p> <p>22 Q. But you will agree that Metzker's own</p> <p>23 studies demonstrate that just substituting a base</p> <p>24 with the same polymerase can result in completely</p> <p>25 different results in terms of incorporation by the</p>
<p style="text-align: right;">Page 155</p> <p>1 polymerase, correct?</p> <p>2 A. No, I don't agree with that. I agree</p> <p>3 that Metzker states that.</p> <p>4 Q. Yeah, I am asking you, Metzker says that,</p> <p>5 correct?</p> <p>6 A. Yes, I'm sorry. I thought you were</p> <p>7 saying I agree with the result.</p> <p>8 Q. No. I am saying you agree that Metzker</p> <p>9 says that?</p> <p>10 A. Correct.</p> <p>11 Q. And, again, Metzker as a person of</p> <p>12 ordinary skill, he understood his experiments that</p> <p>13 there was no polymerase that he found that could</p> <p>14 incorporate both the 3'-O-allyl dAPT and</p> <p>15 3'-O-methyl dTTP. That is what he says.</p> <p>16 A. That is what he says.</p> <p>17 Q. As a POSA.</p> <p>18 So going back to the allyl capped</p> <p>19 nucleotides, the only allyl capped nucleotide that</p> <p>20 was tested by Metzker is the adenine, correct?</p> <p>21 A. That is correct.</p> <p>22 Q. Metzker didn't test the thymine, did he?</p> <p>23 A. He does not report that.</p> <p>24 Q. So based on Metzker results that we just</p> <p>25 looked at for the methyl capped adenine nucleotide</p>	<p style="text-align: right;">Page 156</p> <p>1 and the methyl capped thymine nucleotide, a POSA</p> <p>2 understood it was possible that for the allyl</p> <p>3 capped nucleotide, changing the base could change</p> <p>4 the way that it would it be incorporated, if at</p> <p>5 all, by a polymerase?</p> <p>6 A. A POSA would have understood that just as</p> <p>7 a matter of his education. I don't think a POSA</p> <p>8 would have interpreted -- I don't think a POSA</p> <p>9 would have been comfortable interpreting the</p> <p>10 results in this manuscript as evidence of that.</p> <p>11 Because I think the POSA would have come into</p> <p>12 the -- would have approached that question from the</p> <p>13 beginning saying, yeah, they're probably going to</p> <p>14 be similar.</p> <p>15 And then he would have seen Metzker's</p> <p>16 conclusion, and he would have said, well, Metzker</p> <p>17 seems to think otherwise, there is 1 percent dAPT</p> <p>18 in these. So I think that a POSA would have</p> <p>19 been -- would have viewed that skeptically.</p> <p>20 (Exhibit 1036 was previously marked for</p> <p>21 identification.)</p> <p>22 BY MR. SCHWARTZ:</p> <p>23 Q. Let's move on to a different exhibit. I</p> <p>24 am putting in front of you Exhibit 1036, entitled</p> <p>25 "Unexpected Enzymatic Fucosylation of the Hindered</p>

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1 Tertiary Alcohol of 3-C-Methyl-N-Acetylactosamine
2 Produces a Novel Analogue of the LeX-Trisaccharide"
3 by Qian that was published in 1998.
4 This is the same Qian paper that you
5 referred to in these IPRs, correct?
6 A. That is correct, Qian.
7 Q. Please turn to Page 2185. Please draw
8 your attention to scheme two. You refer to scheme
9 two to form your opinion that the allyl protecting
10 group is removed quantitatively, correct?
11 A. Yes, that is correct.
12 Q. And the compounds in Qian are not
13 nucleotides or nucleosides, correct?
14 A. That is correct. They are sugars, which
15 is closely related to a -- the sugar of the
16 nucleotide of which the 3'-O-hydroxyl group is part
17 of, meaning that that unit is a sugar. And these
18 are sugars.
19 Q. These are disaccharides, correct?
20 A. They're two sugars attached.
21 Q. Just so that we are understand each
22 other, a nucleotide used for sequencing does not
23 have a disaccharide, does it?
24 A. No, but a nucleotide used for sequencing
25 has a sugar unit. These have sugar units.

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1 that this would have been equivalent in water or in
2 water/methanol mixtures, if not pure water.
3 Q. Earlier we looked at your testimony in
4 IPR2013-00517. It was actually your declaration
5 that was Exhibit 2016. Can you go back to that?
6 A. What is the number?
7 Q. 2007.
8 A. I have it.
9 Q. And if you go back to paragraph 46. You
10 write in paragraph 46: "Furthermore, the conditions
11 used by Loubinoux in table two would not be
12 compatible with Tsien's and Ju's sequencing by
13 synthesis methods. The experiment in table two
14 that achieved 95 percent yield used THF as a
15 solvent, which as with pyrimidine, was a known DNA
16 denaturant," it cites to a Lee paper, "Therefore,
17 one of ordinary skill would not have viewed table
18 two of Loubinoux as teaching that yields vary
19 widely" -- I'm sorry. "Therefore, one of ordinary
20 skill would not only have viewed table two of
21 Loubinoux as teaching that yields vary widely, but
22 would also have considered this method of
23 azido-methyl protecting group removal to be
24 incompatible."
25 MR. ZIMMERMAN: I want to be clear that

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1 Q. Now the scheme that is used to deprotect
2 the allyl in Qian is not performed in aqueous
3 media, correct?
4 A. It is performed in methanol.
5 Q. And you agree that protecting groups for
6 use is SBS must be removable under aqueous
7 conditions, correct?
8 A. That is correct.
9 Q. And you just said this one, instead of
10 aqueous conditions, uses methanol?
11 A. That is what's reported.
12 Q. And you testified earlier that methanol
13 is a DNA denaturation?
14 A. Neat methanol is a DNA denaturation. As
15 long as -- to the extent that it dehydrates DNA, it
16 is a denaturer. There is no reason these reactions
17 could haven't been performed with added water. The
18 reaction scheme they're showing is absolutely
19 compatible with water.
20 Q. So you are suggesting that somebody could
21 modify this reaction scheme, is that what you are
22 suggesting?
23 A. I am suggesting it would have been
24 obvious to a POSA that he would have had the
25 flexibility and had high expectation of success

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1 he skipped several sentences.
2 MR. SCHWARTZ: I did.
3 BY MR. SCHWARTZ:
4 Q. "But would have also considered this
5 method of azido-methyl protecting group removal to
6 be incompatible with Tsien's and Ju's requirements
7 for sequencing by synthesis."
8 Now, your position in those IPRs was that
9 the reaction and conditions in the references that
10 IBS's expert was using for the deprotection of the
11 3' protecting group, the azido-methyl protecting
12 group is not compatible with Tsien's SBS method.
13 You criticized the other expert's use of a method
14 that was not compatible with SBS, correct?
15 A. I appear to be saying that it would not
16 have been compatible.
17 Q. You criticized that paper that the other
18 expert was using because you viewed that paper as
19 being incompatible with SBS, correct?
20 A. Well, I think I was concluding that it
21 was incompatible, but I hope I didn't criticize the
22 expert.
23 Q. I am not saying you criticized the
24 expert. I'm saying you criticized the expert's use
25 of that paper, because it -- in your opinion, it

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1 was not -- did not have compatible 3' protecting
2 group deblocking conditions.
3 A. If the reaction was done in neat
4 pyridine, then I would have said then and I would
5 say now that that is not compatible with any DNA
6 based method.
7 Q. So let's go back to the Qian paper. The
8 Qian paper is using conditions that are not
9 compatible with SBS, correct?
10 A. The difference is that in one case, the
11 transferability to conditions that would be are
12 trivial and well known and commonly practiced. In
13 the other case, they were not.
14 Q. But you agree that the conditions in the
15 paper that you are referring to in your declaration
16 in these cases those conditions are not compatible
17 with SBS?
18 MR. ZIMMERMAN: Objection. Asked and
19 answered.
20 THE WITNESS: A POSA reading the
21 Loubinoux paper would have thought that is
22 unlike -- those conditions are unlike -- there
23 would not have been -- there would not have been
24 high expectation of success of performing a
25 reaction -- of that particular reaction in a way

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1 additive. TruCol is a PEG. Palladium chloride
2 forms polymers, and that precludes it from acting
3 as a catalyst because they precipitate, they become
4 insoluble. What TruCol as a PEG does, is it breaks
5 them up into smaller polymers that are soluble. So
6 it was common knowledge that you could get
7 palladium chloride into water. People wanted to
8 get metallic reactions, metal catalyzed reactions
9 into water to make them green. It was a deal in
10 the '80s. And this was well known. In particular,
11 with palladium chloride, which is part of what drew
12 me to Qian or Qian, I am not sure how to pronounce,
13 but to this reference.
14 Because it is regarding the mild
15 conditions required for compatibility with DNA
16 sequencing by synthesis this really has everything.
17 It is a sugar, which is very close to a nucleotide.
18 It is the O-allyl, it's quantitative, it's less
19 than two hours to room temperature. It's methanol
20 that people understood that that would not be a
21 limitation, that you could -- people would have had
22 expectation this would have worked in water.
23 Q. But this reference that you are relying
24 on to say that there was quantitative cleavage of
25 the allyl protecting group uses conditions that are

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1 that was compatible with DNA. A palladium chloride
2 mediated deprotection of an allyl group -- of an
3 O-allyl would have been known that it could be done
4 in water, and so when you see it done in methanol,
5 you would have had -- a POSA would have had a high
6 expectation that that would be doable in water.
7 MR. SCHWARTZ: Can I just take a minute
8 to ask -- can I go off the record for a second,
9 please?
10 THE VIDEOGRAPHER: This marks the end of
11 media No. 2 of the deposition of Floyd Romesberg
12 Ph.D. We are off the record at 1:57 p.m.
13 (Recess taken.)
14 THE VIDEOGRAPHER: On the record at
15 2:00 p.m. And this marks the beginning media No. 3
16 of the deposition of Floyd Romesberg Ph.D.
17 BY MR. SCHWARTZ:
18 Q. Dr. Romesberg, going back to the
19 reaction, the palladium reaction in Qian.
20 Palladium chloride is only soluble in methanol or
21 an organic solvent, correct? It has to have an
22 organic solvent?
23 A. It is not highly soluble in water, so to
24 solve that problem, people had worked out additives
25 to get it into water. The most common one is a PEG

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1 not themselves compatible with SBS, correct?
2 A. That is correct.
3 Q. Let's go back to the Boss reference that
4 was Exhibit 1035. Please turn to page 558. On the
5 right side of the page you see there is a section
6 entitled "Experimental"?
7 A. I do.
8 Q. And in the experimental section there is
9 an example for compound 7.
10 Do you see that?
11 A. I do.
12 Q. And the reaction -- I'm sorry. Compound
13 7 is a compound that showed a deprotection yield of
14 greater than 95 percent, correct?
15 A. That is correct.
16 Q. And the reaction that is used to
17 deprotect the allyl for compound 7 uses 10 mils of
18 methanol and two mils of water, correct?
19 A. That is correct.
20 Q. We can calculate the concentration of
21 methanol in that mixture, can't we?
22 A. That is possible, correct, yes.
23 Q. I'm going to walk you through a
24 calculation. So I'm going to ask you, may I have
25 another piece of paper?

<p style="text-align: right;">Page 165</p> <p>1 A. I still have the former one you gave me 2 with very little written on it if that saves you 3 the trouble. 4 Q. Did you write anything on that paper? 5 We'll keep that paper, because I will 6 mark it at the end. And so we're going to walk 7 through this calculation for the concentration of 8 methanol in that reaction, okay? And I will 9 provide you with some information which I will 10 represent to you is accurate, and your counsel, if 11 they think it is inaccurate, has a chance to take 12 that up with you on your redirect. 13 So why don't you write down that the 14 molecular weight of methanol is 32 grams per mil. 15 I'm sorry, 32 grams per mole. 16 And the density of methanol is .79 grams 17 per mil. So 10 mils of methanol weighs 7.9 grams, 18 correct? 19 MR. ZIMMERMAN: Do you need a calculator, 20 Dr. Romesberg? 21 THE WITNESS: No. 10 mils would be 22 7.9 grams, that's correct. 23 BY MR. SCHWARTZ: 24 Q. The 7.9 grams, again, the molecular 25 weight of 32 grams per mole is .25 moles, correct?</p>	<p style="text-align: right;">Page 166</p> <p>1 And you can have a calculator. 2 A. Look, as easy as this is, it is 3 surprisingly tricky to do on your feet in front of 4 when 10 people are watching you. If you tell me 5 that is correct, I'll believe it. It sounds about 6 right. If you really want me to sit here and do 7 that freshman chemistry, I'll do it. 8 Q. Yeah, let's do it. 7.9 -- 9 A. All right. I will do it. 10 Q. 7.9 grams, when the molecular weight of 11 32 grams per mole is .25 moles, correct? 12 A. Is 7.9 divided by 32. 13 Q. And it's .25 grams. 14 A. You want me to check that? 15 Q. I do. 16 A. Okay. I will check that. 7.9 divided by 17 32 is 0.25. 18 Q. Moles? 19 A. Moles. 20 Q. The so the molarity of methanol in the 21 mixture of 10 mils of methanol and two mils of 22 water, that is to say you've got a total of .012 23 liters of solution, would be .25 moles over .012 24 liters, correct? 25 A. That sounds right.</p>
<p style="text-align: right;">Page 167</p> <p>1 Q. Would you do that calculation, .25 over 2 0.12? 3 MR. ZIMMERMAN: 0.012. 4 BY MR. SCHWARTZ 5 Q. 0.012. 6 A. 0.012 liters per mole is what you are 7 saying? 8 Q. Mm-hmm. 9 A. So it's not divided by. 10 Q. It's .25 moles over 12 mils, which is 11 0.012 liters, right? 12 A. So you want me to calculate the molarity 13 there? 14 Q. Exactly. 15 MR. ZIMMERMAN: Take your time. 16 THE WITNESS: I calculate 21 molar. 17 BY MR. SCHWARTZ: 18 Q. 20.8 to be exact? 19 A. Okay. 20.8. 20 Q. Do you agree? 21 A. It's what my calculation says, so 22 probably. 23 Q. So the concentration of methanol -- what 24 do you mean probably? It is or it isn't. 25 A. I did the calculation here. I got an A</p>	<p style="text-align: right;">Page 168</p> <p>1 in freshman chemistry in 1984, so I guess I trust 2 my calculation. You got the same result, so I 3 assume it is probably right. But if I were -- if I 4 were you, I would have done this carefully, made 5 sure it is right, and presented me the data. 6 Q. But your calculation -- 7 A. If you want me to go through it and come 8 up with it, I did it, and that is what I got. So 9 you can believe that for what it is. I hope I 10 didn't make a mistake. 11 Q. And you got 20.8 molar? 12 A. I did. 13 Q. So the concentration of methanol in 14 Boss's allyl deprotection reaction is 20.8 molar, 15 correct? 16 A. I believe so. 17 Q. Now, the Boss paper does not provide any 18 details of the deprotection reaction for compounds 19 4 and 5, which also indicates the same 20 methanol/water mixture. Based on the experimental 21 section we looked at, is it reasonable to believe 22 that the same methanol/water mixture was used for 23 those reactions? 24 A. I don't know. If he doesn't tell us, 25 then I guess I don't know.</p>

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1 **Q. It's reasonable though, could he -- he**
2 **could be using that, correct?**
3 A. Could have.
4 MR. SCHWARTZ: I'm going to mark another
5 paper. This is going to require a marking. Court
6 Reporter, this will be Exhibit 2085.
7 (Exhibit 2085 was marked for
8 identification.)
9 BY MR. SCHWARTZ
10 **Q. I'm putting in front of you a document**
11 **entitled "The Relationship of Structure to the**
12 **Effectiveness of Denaturing Agents for**
13 **Deoxyribonucleic Acid" by Levine, et al. published**
14 **in 1973.**
15 **Please turn to page 171 of the paper. On**
16 **the top left side you see there is a table two?**
17 A. I see it.
18 **Q. Table two is a list of reagents that were**
19 **tested for their ability to denature DNA, correct?**
20 A. I see it.
21 **Q. And the DNA being tested here is**
22 **bacteria 5 DNA, correct?**
23 A. That seems to be the case. I have not
24 read this paper. Actually, I have read this paper,
25 surprisingly, but I haven't read it in years, so

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1 **methanol denatures 50 percent of bacteriophage DNA**
2 **under the conditions of the assay, correct?**
3 A. That is correct.
4 **Q. And the conditions of the assay are given**
5 **on page 168.**
6 MR. ZIMMERMAN: To the extent you need
7 time to verify that, please do.
8 BY MR. SCHWARTZ:
9 **Q. The assay conditions for the data**
10 **reported in table two of Levine. Do you see where**
11 **it said denaturation of DNA was determined as**
12 **follows?**
13 A. I do.
14 **Q. And it was 30 minutes under buffered**
15 **aqueous conditions at close to neutral pH at**
16 **73 degrees C.**
17 **Do you see that?**
18 A. I do.
19 **Q. And if you go back to table two it**
20 **indicates that the assay conditions were also done**
21 **at an ionic strength of 0.043.**
22 **Do you see that?**
23 A. I do.
24 **Q. And if you go back to page 169, if you**
25 **look down toward the bottom of the left column on**

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1 that seems to be what it is saying.
2 **Q. You actually relied on this paper in some**
3 **of your IBS IPRs.**
4 A. That's why I said I have read it, but not
5 in years. That is, I believe, 2014.
6 **Q. You testified earlier that DNA primer**
7 **templates that were used in SBS are more**
8 **susceptible to denaturation than large pieces of**
9 **DNA.**
10 **Do you remember that?**
11 A. Yes.
12 **Q. Would you agree that the susceptibility**
13 **of DNA primary templates in an SBS reaction would**
14 **be even more susceptible to denaturation for**
15 **bacteriophage DNA?**
16 A. To the extent that they are smaller, that
17 is correct.
18 **Q. Now, first reagent listed in table two is**
19 **methyl alcohol.**
20 **Do you see that?**
21 A. I do.
22 **Q. And that is the same as methanol,**
23 **correct?**
24 A. It is.
25 **Q. And table two indicates that 3.5 molar**

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1 **page 169, about nine lines up from the bottom,**
2 **there is a sentence that begins with: "At**
3 **73 degrees there is essentially."**
4 **Do you see that?**
5 A. I do.
6 **Q. And the sentence reads: "At 73 degrees**
7 **there is essentially no denaturation of DNA in the**
8 **absence of a denaturing agent."**
9 **That is what Levine wrote, correct?**
10 A. That is correct.
11 **Q. So the condition -- the reaction**
12 **condition used to test the compounds in table two**
13 **of Levine were not themselves denaturing, correct?**
14 A. No, that is not true at all. They
15 basically took the system to the brink of
16 denaturation by heating it up. 73 degrees. That
17 is the point.
18 **Q. But it says "at 73 degrees there is no**
19 **denaturation of DNA"?**
20 A. They took it to the brink of
21 denaturation.
22 **Q. But they say that "at 73 degree there is**
23 **essentially no denaturation in the absence of a**
24 **denaturing agent."**
25 **That is what they say, right?**

<p style="text-align: right;">Page 173</p> <p>1 A. None of the strands are dissociating, 2 detectably. But they have -- the whole point of 3 elevating the temperature was to give them a regime 4 where they could see changes. 5 Q. What temperature do you think is -- in 6 your opinion, what temperature does denature DNA? 7 A. It depends on the sequence, the sequence 8 length, the sequence context. It's variable. It 9 depends on the conditions. 73 is up there. 10 Q. Would 80 degrees denature DNA? 11 A. PCR reactions, which they have much 12 longer strands of DNA, routinely heat up to 13 90 degrees, 88 degrees, 89 degrees, and assume 14 complete denaturation in no methanol, in just 15 aqueous standard conditions that favor duplex 16 formation. So 73 is a lot closer to 89 or 88 than 17 it is to room temperature of 37. These strands are 18 close to dissociating. 19 Q. I mean it is your point that 73 degrees, 20 even though Levine reports that there is no 21 denaturation of the DNA in the absence of a 22 denaturing agent, your position is that that is 23 close to the level of where DNA would be denatured, 24 if I understood you correctly? 25 MR. ZIMMERMAN: Objection.</p>	<p style="text-align: right;">Page 174</p> <p>1 Mischaracterizes the document. 2 You can answer. 3 MR. SCHWARTZ: No, I'm asking about his 4 testimony. 5 MR. ZIMMERMAN: I know, but the question 6 mischaracterizes the document, so I'm going to make 7 the objection. 8 You can answer. 9 BY MR. SCHWARTZ: 10 Q. The sentence reads: "At 73 degrees there 11 is essentially no denaturation of DNA in the 12 absence of a denaturing agent." That is what it 13 says, right? And then you had a position about 14 that that you said I think that that is close to 15 where DNA denatures. You were making a point, 16 right? 17 A. Yes. The point that I was trying to 18 make -- and it wasn't for this specific strand, 19 because I don't know the temperature at which it 20 would dissociate. 73 degrees -- what -- DNA duplex 21 is susceptible to heating. Heating is a 22 denaturation -- is a denature -- you have a free 23 energy that stabilizes a duplex. When you increase 24 the temperature, the free energy stabilizing the 25 duplex is decreasing, and you can get that to an</p>
<p style="text-align: right;">Page 175</p> <p>1 arbitrarily small value, and it won't dissociate 2 yet. And then a little more denaturation, whether 3 that be provided by further increase in temperature 4 or addition of methanol or whatever sort of 5 denature you are interested in, then makes that 6 free energy increasingly less favorable. And then 7 you will start to see the dissociation of that. 8 So what they are doing is they are taking 9 their system -- my guess is what they did was they 10 wanted to -- within one piece of DNA, they wanted 11 to be able to add different things and be able to 12 see a range -- they wanted everything to be able to 13 cause denaturation so they could compare them. 14 I think a chemist or a scientist would 15 call this increasing your dynamic range so you can 16 see the effects of things. If they would have done 17 this at room temperature, I think a bunch of their 18 things probably wouldn't have shown denaturation. 19 And I think the three molar methanol would not have 20 shown denaturation. I think that is probably true. 21 Q. That is a speculation, correct? 22 A. Based on this data, probably -- I mean, 23 look, if it were 3 molar that caused denaturation 24 at 78 degrees, then certainly not. It would not 25 have caused denaturation at room temperature. That</p>	<p style="text-align: right;">Page 176</p> <p>1 is not speculation. 2 Q. But do you remember relying on this very 3 paper and this very table in your IPRs against IBS? 4 A. I do. 5 Q. And you relied on this paper and this 6 very table to make conclusions about what agents 7 would be DNA denaturing agents. 8 Do you remember that? 9 A. I do. 10 Q. So you -- at one point you relied on this 11 table to make a conclusion about what agents were 12 DNA denaturing agents, correct? 13 A. I made no conclusions about 14 quantitatively at this temperature or any 15 temperature what would cause denaturation. I was 16 simply showing -- I believe -- and I have not read 17 that for a little while -- I believe what I was 18 evoking that table for was that pyridine, I think, 19 was a stronger denaturant than a lot of other 20 things. And so it is certainly true that at any 21 given temperature -- and this is, in fact, why they 22 chose to increase the temperature so they could see 23 denaturation by everything, the concentration at 24 which they caused denaturation they could then 25 compare.</p>

<p style="text-align: right;">Page 177</p> <p>1 So it is not disingenuous, and I would</p> <p>2 still believe this, that if I look at that table,</p> <p>3 you see pyridine is 0.09 molar. That's much less</p> <p>4 than methanol. And I believe my point was, and I</p> <p>5 would have to go look to rethink this if you want</p> <p>6 me to be sure, but I believe my point was that</p> <p>7 pyridine is a relatively strong denaturant. And I</p> <p>8 believe that conclusion is correct.</p> <p>9 Q. But you did rely on this paper and on</p> <p>10 that table to form that conclusion?</p> <p>11 A. In the way I just described it, yes.</p> <p>12 Which is not the same as the way we are looking at</p> <p>13 it now. Just to be clear.</p> <p>14 Q. And in what way is it different?</p> <p>15 A. I was comparing pyridine to other things.</p> <p>16 Q. I haven't even asked you any questions</p> <p>17 about this table yet, so -- all I've asked you is</p> <p>18 what the reaction conditions were.</p> <p>19 A. No, you are asking me about methanol</p> <p>20 being a denaturant, and that is shown there in the</p> <p>21 concentration.</p> <p>22 Q. Yes.</p> <p>23 A. And that is in this table.</p> <p>24 Q. Yes.</p> <p>25 A. The only point that I was making before</p>	<p style="text-align: right;">Page 178</p> <p>1 was that you needed, at any given temperature, less</p> <p>2 pyridine to cause denature than most other things.</p> <p>3 And that is true.</p> <p>4 Q. And going back to the entry for methanol</p> <p>5 that you just brought that up again, 3.5</p> <p>6 methanol -- 3.5 molar methanol is reported in this</p> <p>7 paper to cause 50 percent denaturation of the</p> <p>8 bacteriophage DNA in 30 minutes, correct?</p> <p>9 A. At 73 degrees.</p> <p>10 Q. Which the paper reports there was</p> <p>11 essentially no denaturation of DNA at that</p> <p>12 temperature, the paper reports that, right?</p> <p>13 A. I'm not sure if you don't understand what</p> <p>14 I'm saying or if you just want me to say it again.</p> <p>15 They took this by heating it up to a temperature</p> <p>16 where the free energy stabilizing the duplex was</p> <p>17 almost taken to zero. That allowed them to add</p> <p>18 different denaturants and get dissociation so</p> <p>19 everything they added, they would be able to see</p> <p>20 denaturation. They wanted to do that so they can</p> <p>21 see how they all compared. That is one conclusion</p> <p>22 you can draw from this table.</p> <p>23 That was not the conclusion that I drew</p> <p>24 from the table four years ago in that IPR that you</p> <p>25 evoked. The conclusion I drew at that time was</p>
<p style="text-align: right;">Page 179</p> <p>1 that pyridine under these given conditions is a</p> <p>2 stronger denaturant than methanol. Not that</p> <p>3 pyridine would or wouldn't have denatured it at</p> <p>4 these exact conditions.</p> <p>5 Q. Does this paper report that 3.5 molar</p> <p>6 methanol caused 50 percent denaturation of the</p> <p>7 bacteriophage DNA in 30 minutes? Does the paper</p> <p>8 report that?</p> <p>9 A. At 73 degrees.</p> <p>10 Q. Now, we just did the calculation for the</p> <p>11 concentration of methanol in the allyl protection</p> <p>12 reaction in Boss, correct?</p> <p>13 A. Yes.</p> <p>14 Q. And that was 20.8 molar, correct?</p> <p>15 A. Correct.</p> <p>16 Q. And that is almost six times the</p> <p>17 concentration of methanol that caused 50 percent</p> <p>18 denaturation of bacteriophage DNA in Levine,</p> <p>19 correct?</p> <p>20 A. Are you asking me to calculate that six</p> <p>21 times?</p> <p>22 Q. Sure.</p> <p>23 A. So you want me to take 20.8 and divide it</p> <p>24 by what number?</p> <p>25 Q. 3.5.</p>	<p style="text-align: right;">Page 180</p> <p>1 A. 3.5. Let me get my calculator. 20.8</p> <p>2 divided by 3.5. I get 5.94.</p> <p>3 Q. So that's almost a six fold difference,</p> <p>4 correct?</p> <p>5 A. Yeah, that's almost a six fold.</p> <p>6 Q. So a POSA reading this paper, Levine,</p> <p>7 understood that 20.8 molar would be expected to</p> <p>8 denature DNA?</p> <p>9 MR. ZIMMERMAN: Object as to form.</p> <p>10 THE WITNESS: I don't know how to explain</p> <p>11 this better, because I am not sure if you're simply</p> <p>12 not listening to me, or if I'm not explaining it</p> <p>13 well. I will try to explain this again if you want</p> <p>14 me to, but the conclusion that you just reached is</p> <p>15 wrong. This reaction was performed at room</p> <p>16 temperature. The comparison you just made would be</p> <p>17 at 73 degrees temperature. I'm sure your expert</p> <p>18 witness will help you -- walk you through this if</p> <p>19 you don't believe me.</p> <p>20 20 molar methanol, this paper certainly</p> <p>21 suggests you will get full denaturation. It does</p> <p>22 not tell you what will happen at room temperature.</p> <p>23 BY MR. SCHWARTZ:</p> <p>24 Q. But you expect 20.8 molar methanol to be</p> <p>25 compatible with SBS?</p>

<p style="text-align: right;">Page 181</p> <p>1 A. 20 molar methanol at room temperature?</p> <p>2 Q. 20.8 molar methanol.</p> <p>3 MR. ZIMMERMAN: Objection. Incomplete</p> <p>4 hypothetical.</p> <p>5 THE WITNESS: Are you asking if it would</p> <p>6 denature DNA or if the entire process would be</p> <p>7 compatible with that much methanol?</p> <p>8 BY MR. SCHWARTZ:</p> <p>9 Q. Let's start with the later. Would the</p> <p>10 process be compatible with that much methanol?</p> <p>11 A. Probably. It would probably affect the</p> <p>12 polymerase.</p> <p>13 Q. And at the bottom of table two there is</p> <p>14 an entry for acetonitrile.</p> <p>15 Do you see that?</p> <p>16 A. Bottom of table two.</p> <p>17 Q. Of that Levine paper.</p> <p>18 A. Oh, yes.</p> <p>19 Q. And table two reports --</p> <p>20 A. I'm sorry, acetonitrile? At the bottom?</p> <p>21 Q. At the bottom right.</p> <p>22 A. Oh, yeah, sorry. Yes, I found it.</p> <p>23 Q. And table two reports that 1.2 molar</p> <p>24 acetonitrile causes 50 percent denaturation of</p> <p>25 bacteriophage DNA, correct?</p>	<p style="text-align: right;">Page 182</p> <p>1 A. At 73 degrees.</p> <p>2 Q. Which the paper reports there was no</p> <p>3 denaturation without the denaturant, right?</p> <p>4 A. I know you're making --</p> <p>5 MR. ZIMMERMAN: Objection.</p> <p>6 Mischaracterizes the document again.</p> <p>7 MR. SCHWARTZ: I disagree with your</p> <p>8 saying that it mischaracterizes.</p> <p>9 MR. ZIMMERMAN: You're leaving out the</p> <p>10 word "essentially." Every time you characterize</p> <p>11 you leave out "essentially," so that is a</p> <p>12 mischaracterization of the document.</p> <p>13 MR. SCHWARTZ: The document says that at</p> <p>14 73 degrees there is essentially no denaturation in</p> <p>15 the absence of denaturing agent. That is what the</p> <p>16 document says, correct?</p> <p>17 THE WITNESS: Yes.</p> <p>18 MR. SCHWARTZ: Can we take a break?</p> <p>19 Let's take a break here.</p> <p>20 MR. ZIMMERMAN: Sure --</p> <p>21 THE VIDEOGRAPHER: We are off the record</p> <p>22 at 2:26 p.m.</p> <p>23 (Recess taken.)</p> <p>24 THE VIDEOGRAPHER: We are on the record</p> <p>25 at 2:46 p.m.</p>
<p style="text-align: right;">Page 183</p> <p>1 BY MR. SCHWARTZ:</p> <p>2 Q. Dr. Romesberg, just to step back for a</p> <p>3 moment. We were referring earlier today about</p> <p>4 allyl deprotections with palladium chloride in</p> <p>5 water. Can you point me to any reference prior to</p> <p>6 October of 2000 showing an allyl deprotection with</p> <p>7 palladium chloride in water?</p> <p>8 A. No. I cannot. What I can show you is</p> <p>9 a -- I'm sure I could find papers that talk about</p> <p>10 using palladium chloride in water.</p> <p>11 Q. But can you point me to any paper that</p> <p>12 reports deprotection of an allyl using palladium</p> <p>13 chloride in water?</p> <p>14 A. Not that I know of. In general,</p> <p>15 palladium chloride deprotections of allyl were most</p> <p>16 used in sugar chemistry, and those substrates were</p> <p>17 insoluble in water. People would not have desired</p> <p>18 to run the reactions in water.</p> <p>19 Q. I think I'm ready to go to another</p> <p>20 exhibit.</p> <p>21 MR. SCHWARTZ: Court Reporter, this will</p> <p>22 be marked as Exhibit 2086.</p> <p>23 (Exhibit 2086 was marked for</p> <p>24 identification.)</p> <p>25 ///</p>	<p style="text-align: right;">Page 184</p> <p>1 BY MR. SCHWARTZ</p> <p>2 Q. I am putting in front you, Dr. Romesberg,</p> <p>3 a document entitled "Deoxyribonucleic Acids" by Kit</p> <p>4 that was published in 1963. And this is a paper</p> <p>5 that you relied on in your declarations in the</p> <p>6 IPR2013-00517 case to form opinions about reagents</p> <p>7 that are DNA denaturants, correct?</p> <p>8 A. I believe that is correct, yes.</p> <p>9 Q. And please turn to page 57 of Kit. And</p> <p>10 please draw your attention to the last paragraph on</p> <p>11 the page, and five lines up from the bottom of the</p> <p>12 page there is a sentence that starts with</p> <p>13 "Thiocyanate."</p> <p>14 Do you see that?</p> <p>15 A. I do.</p> <p>16 Q. And Kit writes "Thiocyanate,</p> <p>17 trichloroacetate, and perchlorate are more powerful</p> <p>18 DNA denaturing agents than those prototypical</p> <p>19 hydrogen bond breakers, urea and clonidine</p> <p>20 chloride, and are matched only by certain organic</p> <p>21 solvents such as formaldehyde, dimethylformaldehyde, and</p> <p>22 dimethylsulfoxide."</p> <p>23 That is what Kit writes, correct?</p> <p>24 A. That is what is written.</p> <p>25 Q. And Kit teaches that perchloric acid is a</p>

<p style="text-align: right;">Page 185</p> <p>1 very powerful DNA denaturant, correct?</p> <p>2 A. That is what is written there, yes.</p> <p>3 Q. Please go back to the Boss reference that</p> <p>4 was Exhibit 1035. And please go back to Table 1.</p> <p>5 And if you look at the legend of Table 1, the</p> <p>6 legend indicates that deprotection conditions for</p> <p>7 all of the compounds except compound 8 contained</p> <p>8 perchloric acid, correct?</p> <p>9 A. That is correct.</p> <p>10 Q. And the acid is there because it is</p> <p>11 required for deprotecting an allyl using palladium</p> <p>12 two, correct?</p> <p>13 A. That is not correct.</p> <p>14 Q. There is acid there, correct?</p> <p>15 A. There is acid, yes.</p> <p>16 Q. Okay.</p> <p>17 A. So let me be clear about that, in</p> <p>18 principle, it might have been important. The way</p> <p>19 people run these reactions if you look at the</p> <p>20 mechanism, there is a spot where if you do not have</p> <p>21 a powerful nucleophile, your electrophile has to be</p> <p>22 made a better leaving group. And in those cases it</p> <p>23 might be beneficial to add a proton, very common</p> <p>24 for people if they were not conducting mechanistic</p> <p>25 studies to simply add some acid because they don't</p>	<p style="text-align: right;">Page 186</p> <p>1 really care if it is needed or not. Because</p> <p>2 they're sort of generic conditions.</p> <p>3 And so I imagine that is what they were</p> <p>4 doing here.</p> <p>5 Q. But clearly it indicates that perchloric</p> <p>6 acid is present in these deprotection reactions.</p> <p>7 MR. ZIMMERMAN: Objection. Asked and</p> <p>8 answered.</p> <p>9 BY MR. SCHWARTZ</p> <p>10 Q. And, again, we looked at this before. I</p> <p>11 know that you don't like doing calculations, so I</p> <p>12 won't ask you to do it if you don't want to, but I</p> <p>13 would -- the concentration of perchloric acid</p> <p>14 that's listed there is either 1 millimolar to</p> <p>15 5 millimolar, correct?</p> <p>16 A. I think that I remember reading that.</p> <p>17 Q. It's actually in the paper.</p> <p>18 A. Okay.</p> <p>19 Q. Do you see it? Turn it over and look at</p> <p>20 note a under the table.</p> <p>21 A. Yes.</p> <p>22 Q. And I want to calculate what the</p> <p>23 concentration of perchloric acid is when it's</p> <p>24 1 millimolar -- one millimole per 12 mils. That's</p> <p>25 a simple calculation. I got 83 millimolars. Would</p>
<p style="text-align: right;">Page 187</p> <p>1 you like to confirm that it is 83 millimolars?</p> <p>2 A. No. I'll take your word for it.</p> <p>3 Q. And 5 millimoles of perchloric acid in 12</p> <p>4 mils. I calculated it was 417 millimolars.</p> <p>5 Do you want to confirm that it is 417</p> <p>6 millimolar?</p> <p>7 A. If I bought the first, I bought the</p> <p>8 second.</p> <p>9 Q. I am going to ask you now to do a</p> <p>10 calculation of pHs. And I will provide you with</p> <p>11 some information so use that table -- or use that</p> <p>12 piece of paper. The first piece of information</p> <p>13 I'll provide to you is that the formula for</p> <p>14 determining pH is pH equals minus log of the proton</p> <p>15 concentration. So when the hydrogen -- when the</p> <p>16 proton concentration is .083 molar, pH would be the</p> <p>17 minus log of .083, correct?</p> <p>18 A. That is correct.</p> <p>19 Q. And likewise, when the hydrogen -- the</p> <p>20 proton concentration is .417 molar, the pH will be</p> <p>21 the minus log of .417, correct?</p> <p>22 A. Yes.</p> <p>23 Q. We have a calculator that does logs?</p> <p>24 I won't ask you to do that. I will tell</p> <p>25 you that the pH that I got from .083 molar is pH</p>	<p style="text-align: right;">Page 188</p> <p>1 1.1.</p> <p>2 A. Sounds about right.</p> <p>3 Q. And your counsel will have an opportunity</p> <p>4 to correct me if I am wrong. And the pH for .417</p> <p>5 molar is about .4.</p> <p>6 A. Okay.</p> <p>7 Q. I mean, would you like to do the</p> <p>8 calculation to confirm me?</p> <p>9 A. No. It's a straightforward calculation.</p> <p>10 Q. So maybe you can write that down that the</p> <p>11 pH of .083 molar is about 1.1, and the pH of .417</p> <p>12 molar is about pH of .4.</p> <p>13 A. What was the first number?</p> <p>14 Q. I'm sorry, 1.1.</p> <p>15 A. What was the hydrogen ion concentration?</p> <p>16 Q. .083.</p> <p>17 A. Zero eight?</p> <p>18 Q. .083. I think you may have written that</p> <p>19 down already. There were two concentrations of</p> <p>20 perchloric acid given in that figure.</p> <p>21 A. So it was 0.417 and 0.083 pH of 1.1 and</p> <p>22 0.84?</p> <p>23 Q. Yes. So please go back to the Kit</p> <p>24 reference, Exhibit 2086. Please turn to page 66 of</p> <p>25 Kit. Eight lines down from the top of page 56,</p>

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1 there is a sentence that starts with "DNA is stable
2 over."
3 Do you see that?
4 A. Yes.
5 Q. And Kit writes "DNA is stable over the
6 approximate pH range of 2.7 to 12 --
7 MR. ZIMMERMAN: That's not the same. You
8 said that is the start of the sentence?
9 MR. SCHWARTZ: I said about eight lines
10 down there is a sentence that starts with "DNA is
11 stable over."
12 MR. ZIMMERMAN: There is not a sentence
13 that starts with that.
14 MR. SCHWARTZ: It's in the middle of the
15 sentence. I apologize.
16 BY MR. SCHWARTZ
17 Q. But do you see where I am?
18 A. I do.
19 Q. And it says "DNA is stable over the
20 approximate pH range of 2.7 to 12, but denatures at
21 higher or lower pHs."
22 That is what Kit writes, right?
23 A. That is what's written.
24 Q. So pH 1.1, the pH of perchloric acid at
25 0.83 molar is outside the range of 2.7 to 12 where

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1 IPR, but not all the IPRs, so we're going to mark
2 it to make sure it is in all the IPRs. And it is
3 2057.
4 MR. ZIMMERMAN: So in the case where
5 we're not doing the deposition in that case today,
6 and the case that you refused to do the deposition
7 on that case today, you are marking the exhibits
8 from that case.
9 MR. SCHWARTZ: Not the exhibits from that
10 case. This is only the second exhibit that has
11 been used in that case. There were many exhibits
12 in that case.
13 MR. ZIMMERMAN: This exhibit is outside
14 of the scope of the IPRs that we are here to do the
15 deposition for today.
16 MR. SCHWARTZ: It is not outside the
17 scope, because it deals directly with acid
18 catalyzed denaturation of --
19 MR. ZIMMERMAN: Was it of record in the
20 four that we are doing?
21 MR. SCHWARTZ: It is of record now.
22 MR. ZIMMERMAN: Okay. I am objecting
23 it's outside the scope.
24 MR. SCHWARTZ: Okay.
25 MR. ZIMMERMAN: What number did he mark,

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1 DNA is stable, correct?
2 A. That is correct.
3 Q. And pH of 0.4, the pH of perchloric acid
4 at .417 molar is also outside the range of 2.7 to
5 12 where DNA is stable, correct?
6 A. That is correct.
7 Q. So the concentration of perchloric acid
8 that was used to deprotect the allyl in the Boss
9 deprotection reaction would denature DNA, correct?
10 A. The Kit reference suggests that it would.
11 Q. And that deprotection reaction in Boss
12 would not be considered a mild condition that would
13 not denature DNA, correct?
14 A. That is correct.
15 Q. Let's switch topics for a minute -- for a
16 few minutes, and let's talk about depurination. If
17 it's been known before 2000 that glycosidic
18 linkages and purines are susceptible to acid
19 hydrolysis, correct?
20 A. That is correct.
21 Q. I am going to mark the paper.
22 (Exhibit 2057 was marked for
23 identification.)
24 MR. SCHWARTZ: This is, again, this is
25 one of these papers that was present in only one

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1 this one?
2 MR. SCHWARTZ: This is marked as 2057.
3 BY MR. SCHWARTZ
4 Q. So I'm putting in front of you a paper
5 entitled "Instability and Decay of the Primary
6 Structure of DNA" by Lindahl, which was published
7 in 1993. Now, please draw your attention to the
8 first page of Lindahl. It's Page 709. And on the
9 left side of page 709 is a section entitled "DNA
10 Hydrolysis."
11 Do you see that?
12 A. I do.
13 Q. And please draw your attention to the
14 sentence that begins five lines down. It starts
15 with "The instability of DNA."
16 Do you see that?
17 A. I do.
18 Q. Lindahl writes "The instability of DNA
19 glycosyl bonds under physiological solvent
20 conditions was investigated 20 years ago. It was
21 measured by using DNA with carbon 14-labeled purine
22 or pyrimidine residues and determining the rates of
23 release of free bases as a function of temperature,
24 pH, ionic strength, and nucleic acid secondary
25 structure."

<p style="text-align: right;">Page 193</p> <p>1 That is what Lindahl writes, correct?</p> <p>2 A. That is what is written.</p> <p>3 Q. And Lindahl cites to references five</p> <p>4 through seven in support for that statement,</p> <p>5 correct?</p> <p>6 A. That is correct.</p> <p>7 Q. And please turn to the references list.</p> <p>8 And reference five is a paper by Lindahl and Nyberg</p> <p>9 published in 1972, correct?</p> <p>10 A. That is correct.</p> <p>11 MR. SCHWARTZ: I am going to mark that</p> <p>12 paper. That is going to be 2087, Court Reporter.</p> <p>13 (Exhibit 2087 was marked for</p> <p>14 identification.)</p> <p>15 MR. ZIMMERMAN: Is this already of record</p> <p>16 in any of the IPRs?</p> <p>17 MR. SCHWARTZ: No.</p> <p>18 BY MR. SCHWARTZ:</p> <p>19 Q. So I am putting in front of you a</p> <p>20 document entitled "Rate of Depurination of Native</p> <p>21 Deoxyribonucleic Acid" by Lindahl and Nyberg,</p> <p>22 published in 1972. This is reference 5 in Lindahl</p> <p>23 1993, correct?</p> <p>24 A. It appears to be.</p> <p>25 Q. Please direct your attention to the</p>	<p style="text-align: right;">Page 194</p> <p>1 abstract. The abstract reads "The rate of</p> <p>2 depurination of double stranded bacillus subtilis</p> <p>3 DNA radio actively labeled in the purine residues</p> <p>4 has been followed as a function of temperature, pH,</p> <p>5 and ionic strength. In the magnesium containing</p> <p>6 buffer of physiological ionic strength, the rate</p> <p>7 constant for depurination of DNA is 4 times 10 to</p> <p>8 the minus ninth per second at 70 degrees and pH</p> <p>9 7.4."</p> <p>10 That's what the authors write, correct?</p> <p>11 A. That is what is written.</p> <p>12 Q. Please turn to page 3616 of the paper,</p> <p>13 and please draw your attention to figure nine at</p> <p>14 the top of the page. Figure nine shows the pH</p> <p>15 dependence of the rate of acid catalyzed</p> <p>16 depurination of DNA, correct?</p> <p>17 A. It does.</p> <p>18 Q. And if you compare figure nine to the</p> <p>19 statement we just read in the abstract, the rate of</p> <p>20 depurination reported in the abstract of four times</p> <p>21 10 to the minus nine per second at pH 7.4 is</p> <p>22 consistent with where the dotted line in figure</p> <p>23 nine intersects the X axis, correct?</p> <p>24 A. Yeah, I guess it is. It's a little hard</p> <p>25 to read, but I guess, yes.</p>
<p style="text-align: right;">Page 195</p> <p>1 Q. And figure nine shows that as the pH</p> <p>2 becomes more the acidic, the rate of acid catalyzed</p> <p>3 depurination greatly increases, correct?</p> <p>4 A. It increases, yes.</p> <p>5 Q. And if you drop from pH 7.4 to about</p> <p>6 pH 4, the rate of acid catalyzed depurination of</p> <p>7 DNA increases about three logs, correct?</p> <p>8 A. That is correct.</p> <p>9 Q. That is an increase of about a thousand</p> <p>10 fold, correct?</p> <p>11 A. Three logs is a thousand fold.</p> <p>12 Q. And if we were to extrapolate figure nine</p> <p>13 to pH 1, the rate of acid catalyzed depurination of</p> <p>14 DNA could increase by about another three logs?</p> <p>15 A. If that same linear relationship holds,</p> <p>16 then that's correct.</p> <p>17 Q. And that would be an increase of about a</p> <p>18 million fold from pH 7.4, right?</p> <p>19 A. That would be correct.</p> <p>20 Q. So Lindahl shows that DNA is rapidly</p> <p>21 depurinated in strong acid, correct?</p> <p>22 A. Well, it shows it down to pH 4.5.</p> <p>23 Q. And he shows that it's rapidly</p> <p>24 depurinated?</p> <p>25 A. Rapidly?</p>	<p style="text-align: right;">Page 196</p> <p>1 Q. We were just talking about the logs. We</p> <p>2 can do the calculation. I know you don't like to</p> <p>3 do calculations, but we're talking about four times</p> <p>4 10 to the minus nine per second at pH 7.4?</p> <p>5 A. So four times 10 to the minus -- it's</p> <p>6 just that rapidly, again, is a relative term. That</p> <p>7 is what it is.</p> <p>8 Q. And go back to Boss, please,</p> <p>9 Exhibit 1035. Let's look at Table 1, and we</p> <p>10 calculated that the pH of the allyl deprotection</p> <p>11 reactions that use perchloric acid is between 1.1</p> <p>12 and 0.4, correct? We put that on that piece of</p> <p>13 paper?</p> <p>14 A. The pHs, yes.</p> <p>15 Q. So let me ask the question again so we</p> <p>16 can get a clean answer.</p> <p>17 We calculated that the pH of the allyl</p> <p>18 deprotection reactions that use perchloric acid in</p> <p>19 Boss is between 1.1 and 0.4, correct?</p> <p>20 A. Yes.</p> <p>21 Q. And Lindahl shows that those conditions</p> <p>22 will lead to rapid DNA depurination all the way</p> <p>23 down to pHs below 1, correct?</p> <p>24 MR. ZIMMERMAN: Objection.</p> <p>25 Mischaracterizes the reference. Assumes facts not</p>

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1 in evidence.
2 THE WITNESS: Lindahl shows rates, I
3 believe, down to pH 4.5, and the pH -- and it shows
4 pH rates for that that vary from four times 10 to
5 the minus nine, and up by about three orders of
6 magnitude as we just discussed.
7 BY MR. SCHWARTZ:
8 **Q. And if we extrapolate from that graph,**
9 **assuming you can extrapolate from the graph.**
10 A. Well, Lindahl does not show that.
11 **Q. I know.**
12 A. If you extrapolate it and it remains
13 linear, then you can multiply that by another
14 thousand.
15 **Q. So it would be a million fold if you did**
16 **that extrapolation?**
17 A. If it's linear over that range, then
18 would that be correct.
19 **Q. And Lindahl shows that in pHs between 1.4**
20 **and 0.4 would be expected to lead to DNA**
21 **depurination, correct?**
22 A. Lindahl does not -- I would have to look
23 at this carefully, but I do not think Lindahl
24 reports stabilities -- experiments under pH of 4.5.
25 **Q. Right.**

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1 suggesting, nor would anyone suggest that pH
2 conditions of 1 -- pH 1 would be stable -- would be
3 useful for a DNA -- would be considered mild for a
4 DNA reaction. As I tried to explain, this Boss
5 reference added perchloric acid, and I was simply
6 including this reference to illustrate that water
7 did not poison the plate and catalyze reaction.
8 The reaction that's much closer to
9 demonstrating mild conditions for DNA is the Qian
10 or Qian, Q-I-A-N, paper which is very -- which is
11 mild. So if you really want to talk about whether
12 or not palladium chloride mediated deprotections of
13 O-allyls are compatible with DNA, we should really
14 be talking -- we shouldn't be calculating pHs for,
15 you know, this Boss paper. If I didn't make this
16 clear, I should have. We should be looking at
17 this -- the Qian paper.
18 **Q. You did put the Boss paper in your**
19 **declaration, didn't you?**
20 A. I did.
21 MR. ZIMMERMAN: Objection. Asked and
22 answered.
23 BY MR. SCHWARTZ:
24 **Q. So you relied on Boss in your**
25 **declaration?**

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1 A. So he doesn't show anything about pH 1,
2 so if you --
3 **Q. He does show that it would be depurinated**
4 **at pH 4.5?**
5 A. Yes.
6 **Q. And if you dropped it down to pH 1.1,**
7 **would you also expect depurination at pH 1.1?**
8 A. I would expect that. My only point was
9 that Lindahl does not actually show that. But I
10 would expect that from the logic we just walked
11 through.
12 **Q. And if you dropped it to pH .4, would you**
13 **expect that there would be depurination?**
14 A. Yes, I would.
15 **Q. And conditions that lead to DNA**
16 **depurination would not be considered mild**
17 **conditions that do not denature DNA, correct?**
18 A. That is correct. I don't know why I'm
19 adding this, but just for the record, I wasn't
20 suggesting that they were. And I know you know
21 that, so why am I saying that.
22 **Q. I am trying to understand what you just**
23 **said. You were not considering that depurination**
24 **conditions to be mild. Is that what you're saying?**
25 A. No. I'm saying that I was not

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1 MR. ZIMMERMAN: Objection. Asked and
2 answered.
3 THE WITNESS: I hope that I clarified
4 what I was relying on it for.
5 BY MR. SCHWARTZ:
6 **Q. You used it in your declaration to say**
7 **that allyl deprotection was a mild condition,**
8 **right?**
9 A. Allyl deprotections can be run under a
10 wide variety of conditions.
11 **Q. But you were relying on that paper?**
12 A. To make that statement, yes. Under a
13 wide variety of conditions, some of which are
14 compatible with -- would be considered mild for
15 DNA, and some of which would not be.
16 **Q. But not under those particular conditions**
17 **in that particular paper?**
18 A. Correct.
19 **Q. Do you recall earlier when we were**
20 **walking through Tsien's requirements for SBS, you**
21 **agree that one of Tsien's requirements is rapid and**
22 **quantitative deprotection of the 3'-OH protecting**
23 **group?**
24 A. I do.
25 **Q. Please go back to the Boss reference.**

<p style="text-align: right;">Page 201</p> <p>1 Again, please look at Table 1. All of the allyl 2 deprotection conditions in Boss are between three 3 hours and six days, correct? 4 A. That is correct. 5 Q. And three hours to six days is not 6 consistent with SBS, is it? 7 A. Three hours, as we went before, depending 8 on what requirements you insisted on, what 9 efficiency meant to you, what applications you were 10 interested in. Maybe six days, very unlikely. 11 Q. You don't remember your testimony when 12 you said that three hours was not consistent with 13 SBS? 14 A. In the context of what I was describing 15 then, that is what I said, and that is what I 16 meant. If you relax one's standards, three hours 17 would not be great. It would take a very long 18 time, but it is not per se inconsistent with 19 running a sequencing by synthesis reaction. 20 Q. But your position in those other IPRs was 21 that three hours was not compatible with SBS. That 22 was your position there, correct? 23 A. I believe I was stating something about 24 whether or not it satisfied the requirements of 25 efficient high-throughput sequencing.</p>	<p style="text-align: right;">Page 202</p> <p>1 Q. Of a protecting group? 2 A. You're not sequencing the protecting 3 group here. 4 Q. Do you want to go back to your testimony? 5 We can go back to it. 6 A. Sure. Let's go back to it. 7 Q. Okay. It was in IPR2013-00517. That was 8 Exhibit 2007, and page 25. 9 A. If I could take a minute to read this. 10 Q. Do you know where I'm directing you to? 11 A. Well, 25 is a pretty short -- very little 12 text on 25, so I assume it's the text. 13 Q. It is where it says "Furthermore, the 14 amount of time required." 15 Do you see that? 16 A. Yes, I do. 17 Q. And you write: "Furthermore, the amount 18 of time required to achieve those yields, three 19 hours to multiple days, would not have been 20 expected to fulfill the rapid deprotection 21 requirement of Tsien's DNA sequencing method." 22 You wrote that, right? 23 A. Yeah, and so just to be very clear with 24 what I just said, and I was correct. I was talking 25 about fulfilling the rapid requirements or the</p>
<p style="text-align: right;">Page 203</p> <p>1 high-throughput, the fast sequence requirements of 2 Tsien. 3 The question you just asked me was 4 sequencing by synthesis compatible with three 5 hours. And the answer I gave then was, yes. Maybe 6 not very efficient, but I wasn't answering whether 7 it fulfilled a requirement for being fast as I read 8 Tsien. 9 Q. It doesn't, but it doesn't -- you agree 10 it doesn't fulfill Tsien's requirement for rapid 11 deprotection? 12 A. That is what I testified here, and, 13 again, it doesn't seem like it -- it does not seem 14 like it would fulfill what Tsien had in mind. But 15 that was not the way -- that was not the question 16 you asked me a moment ago. 17 Q. So none of Boss's reaction conditions 18 satisfied Tsien's requirement for rapid 19 deprotection, correct? 20 A. I would agree with that. 21 MR. SCHWARTZ: I need to ask a question. 22 I'd like to go back to the patents. We 23 have not talked about the patents yet. The patents 24 in this case. Did we circulate those yet? 25 And also I would like to mark that piece</p>	<p style="text-align: right;">Page 204</p> <p>1 of paper where you have your handwritten 2 calculations and notes on. 3 (Exhibit 2090 was marked for 4 identification.) 5 MR. SCHWARTZ: I will start with one 6 patent. I think we all agree that the 7 specifications are the same for the patents. If 8 you would prefer I can put all four patents. 9 MR. ZIMMERMAN: It's up to you. If 10 you're going to ask him about the claims, he needs 11 all four. If you're asking about the spec, one is 12 probably sufficient. 13 MR. SCHWARTZ: Well, let's start with one 14 at a time then. 15 (Exhibit 1001 was marked for 16 identification.) 17 BY MR. SCHWARTZ: 18 Q. So I am putting in front of you 19 Exhibit 1001. This happens to be the U.S. patent 20 9718852 to Ju, et al. This is a patent that is at 21 issue in these IPRs, correct, Dr. Romesberg? 22 A. That is one of them, that is correct. 23 Q. It is a patent that you considered in one 24 of your declarations in these IPRs, correct? 25 A. That is correct.</p>

<p style="text-align: right;">Page 205</p> <p>1 Q. Why don't we turn to the claims.</p> <p>2 A. Do you want to point me to a column.</p> <p>3 Q. I'm just going to start with this. It is</p> <p>4 column 34 of the claims.</p> <p>5 Do you see after the structure it says</p> <p>6 wherein RA represents a small chemically cleavable</p> <p>7 chemical group capping the oxygen at the 3'</p> <p>8 position of the deoxyribose of the</p> <p>9 deoxyribonucleotide analog."</p> <p>10 Do you see that?</p> <p>11 A. I do.</p> <p>12 Q. What is your understanding of what is a</p> <p>13 small group?</p> <p>14 A. Small. A small group. I am okay. I</p> <p>15 accept Dr. Ju's definition, or his use of "small."</p> <p>16 He doesn't define it. He represents it with</p> <p>17 examples, which he uses MOM and allyl. Those are</p> <p>18 both three carbons, so I am okay with that</p> <p>19 definition. I am okay with accepting his</p> <p>20 definition of small.</p> <p>21 Do you want me to talk about small</p> <p>22 outside of this? I'm happy to do so.</p> <p>23 Q. So you understood from reading this what</p> <p>24 a small chemical capping group is?</p> <p>25 A. I understand that Dr. Ju evokes MOM and</p>	<p style="text-align: right;">Page 206</p> <p>1 allyl as small.</p> <p>2 Q. What is your understanding of the</p> <p>3 chemically cleavable chemical group?</p> <p>4 A. That it can be removed by a reaction that</p> <p>5 allows it to -- by a chemical reaction to produce a</p> <p>6 free three-prong hydroxyl group that is compatible</p> <p>7 with continued DNA synthesis.</p> <p>8 Q. Do you see in the structure that is drawn</p> <p>9 for this particular adenine nucleotide that the tag</p> <p>10 is attached to the base via a structure called Y?</p> <p>11 A. A box called Y, yes, I see that.</p> <p>12 Q. What is your understanding of the box</p> <p>13 called y?</p> <p>14 A. It would be a cleavable -- part of a</p> <p>15 cleavable label -- a link or part of a label that</p> <p>16 would attach what he calls the tag.</p> <p>17 Q. So you understand that the tag is not</p> <p>18 directly connected to the base, correct?</p> <p>19 A. Yes. I mean, we'll get a little semantic</p> <p>20 talking about why the tag and why start and stop,</p> <p>21 because they're all going to be chemical bonds, but</p> <p>22 clearly the spirit here is that there is a part</p> <p>23 that is cleavable that will separate the</p> <p>24 fluorophore or the tag from the nuclear base.</p> <p>25 Q. Is it your understanding that the term</p>
<p style="text-align: right;">Page 207</p> <p>1 small in the other patents -- which I can put in</p> <p>2 front of you if you want, but I'll represent it</p> <p>3 uses the same terminology -- would be the same as</p> <p>4 you just described, your understanding of small? I</p> <p>5 guess maybe what I'm trying to say is this is not a</p> <p>6 unique understanding for this particular structure,</p> <p>7 right?</p> <p>8 A. I believe that Dr. Ju uses the same</p> <p>9 description in all five of the patents.</p> <p>10 Q. Again, in terms of understanding what a</p> <p>11 chemical -- cleavable chemical group is, that is</p> <p>12 not unique to this particular adenine nucleotide,</p> <p>13 right?</p> <p>14 A. I believe he represents it equivalently</p> <p>15 in all of the cases we are discussing here.</p> <p>16 Q. Let's go back to Tsien. That was</p> <p>17 Exhibit 1013. Will you please turn to page 24 and</p> <p>18 please draw your attention to the paragraph that</p> <p>19 begins at line 24 and Tsien writes "A wide variety</p> <p>20 of hydroxyl blocking groups are cleaved selectively</p> <p>21 using chemical procedures other than base</p> <p>22 hydrolysis. 24 nitrobenzenesulfonyl groups are</p> <p>23 cleaved rapidly by treatment with nucleophiles such</p> <p>24 as thylphenyl and phenyl sulfate." And he points</p> <p>25 to a Letsinger 1964 paper.</p>	<p style="text-align: right;">Page 208</p> <p>1 Allyl ethers are cleaved by treatment</p> <p>2 with mercury II in acetone water. And he points to</p> <p>3 Gigg and Warren in 1968.</p> <p>4 That is what Tsien writes, right?</p> <p>5 A. That is correct.</p> <p>6 Q. Please go back to Exhibit 1012, which is</p> <p>7 your declaration IPR2018-00291.</p> <p>8 MR. ZIMMERMAN: Which exhibit?</p> <p>9 MR. SCHWARTZ: 1012. It's his</p> <p>10 declaration in IPR2018-00291.</p> <p>11 BY MR. SCHWARTZ:</p> <p>12 Q. Please turn to page 55. Please draw your</p> <p>13 attention to paragraph 98. In paragraph 98 you</p> <p>14 write: "With respect to 3'-O-allyl groups, Tsien</p> <p>15 cites to Gigg, Exhibit 1013, Tsien at 24; 29</p> <p>16 through 30, allyl ethers are cleaved by treatment</p> <p>17 with mercury II acetone water. Gigg and Warren</p> <p>18 1968."</p> <p>19 That is what you wrote, right?</p> <p>20 A. That is correct.</p> <p>21 Q. Tsien's disclosure at page 24, lines 29</p> <p>22 to 30 is of allyl groups, correct? That's what you</p> <p>23 said?</p> <p>24 A. Yes.</p> <p>25 Q. And allyl groups is a genus that includes</p>


<p style="text-align: right;">Page 209</p> <p>1 both unsubstituted allyls as well as substitute 2 allyls, correct? 3 A. No. 4 Q. It's not a genus that includes those? 5 A. You can stretch it to that if you want, 6 but it's certainly not common language. 7 Q. But it is a collection of groups? 8 A. You could stretch it to include that. 9 It's kind of a slang, it's kind of a vernacular. A 10 lot of chemical names have very long complex names, 11 and a lot of times people don't want to write them 12 out. A lot of times people don't even know how to 13 actually name things. So it's very common for 14 people to use sort of a slang. So that's an allyl 15 group. That's an allyl-type group. That's got an 16 allyl in it, so let's call it an allyl protecting 17 group. It's kind of like that's a red car. 18 Q. You yourself use the term 3'-O-allyl 19 groups when you refer to Tsien, right? 20 A. That's right. He wasn't doing single 21 molecule experiments. 22 Q. And you also refer to Tsien saying allyl 23 ethers, correct? 24 A. Again, not single molecule experiments. 25 What I meant was that there are many molecules in</p>	<p style="text-align: right;">Page 210</p> <p>1 his reaction. Just like people would describe 2 templates. That's a very common descriptor. It's 3 not that they were all different, it's just you're 4 sequencing templates. Because there are many of 5 them. In a reaction, there is many molecules. So 6 if that caused confusion, I apologize. I never 7 meant to implicate that there were different allyl 8 groups. If people wanted, like I said, to stretch 9 the definition and to sort of use it as a slang, 10 that's certainly not unheard of. But an allyl 11 group is something, and it's a very specific thing. 12 And it would be what anyone would think of. 13 Q. But you didn't use the term "allyl 14 group," you used the term "allyl groups." That is 15 what you wrote, correct? 16 A. Yeah, just methyl groups. That's a very 17 common expression. If you want to modify methyl 18 groups, you can use this sort of thing. And 19 there's no derivatives of a methyl group. It's 20 sort of like -- it -- the plural is referring to 21 there are many of them. You're deprotecting -- 22 you're not doing a single molecule reaction. 23 You're not modifying one. You're removing a lot of 24 allyl groups, one for every molecule in there. 25 Q. You know how to use the word group if you</p>
<p style="text-align: right;">Page 211</p> <p>1 wanted to; you used the word groups. You know how 2 to use the word ether if you wanted to; you used 3 the word in plural, correct? You chose those 4 words? 5 MR. ZIMMERMAN: Asked and answered. 6 MR. SCHWARTZ: No, that wasn't asked and 7 answered. 8 THE WITNESS: I was using them in plural 9 in the sense that there were many of them. 10 BY MR. SCHWARTZ: 11 Q. Many of them? 12 A. I mean, if there's one molecule in a 13 reaction, you still can use the word molecules to 14 describe the reaction. Doesn't that imply -- 15 Q. I don't understand you said there are 16 many of them. You were referring to Tsien, and 17 Tsien is talking about allyl groups. And you said 18 that Tsien refers to 3'-O-allyl groups. What do 19 you mean many of them? Where in Tsien does it talk 20 about many of them? 21 A. They are not single molecule experiments, 22 so you're not exploring -- you're not doing 23 chemistry on a single molecule. There are many 24 molecules. That doesn't mean there are different 25 molecules. They happen to be many of the same</p>	<p style="text-align: right;">Page 212</p> <p>1 molecule, but still plural. That's all I meant by 2 this. 3 Q. You had meant that Tsien cites to Gigg 4 and Warren for his disclosure of allyl groups, 5 correct? 6 A. He does. 7 Q. Let's look at Gigg and Warren. 8 MR. SCHWARTZ: Can I ask the court 9 reporter for an approximate amount of time on the 10 record right now? Not the court reporter, I'm 11 sorry. I meant the videographer. You know what I 12 meant. 13 THE VIDEOGRAPHER: 4:36. Four hours, 36 14 minutes, around there. 15 (Exhibit 1046 was previously marked for 16 identification.) 17 BY MR. SCHWARTZ: 18 Q. I am putting in front of you Exhibit 1046 19 entitled "The Allyl Ether as a Protecting Group and 20 Carbohydrate Chemistry, Part II," by Gigg and 21 Warren, published in 1968. 22 This is the same Gigg and Warren paper 23 cited in Tsien, correct? 24 A. I believe so. 25 Q. Please turn to Page 1906 of Gigg and</p>

<p style="text-align: right;">Page 213</p> <p>1 Warren.</p> <p>2 MR. SCHWARTZ: You look like you don't</p> <p>3 agree --</p> <p>4 MR. ZIMMERMAN: Not at all. Did you say</p> <p>5 four hours and 10 minutes. We are almost at five</p> <p>6 hours.</p> <p>7 THE VIDEOGRAPHER: I have to do the math.</p> <p>8 MR. ZIMMERMAN: We are 4:49 right now.</p> <p>9 BY MR. SCHWARTZ:</p> <p>10 Q. All right. So we -- that is the same</p> <p>11 Gigg and Warren that is cited in Tsien, correct?</p> <p>12 A. I believe so, yes.</p> <p>13 Q. And please turn to page 1906 of Gigg and</p> <p>14 Warren, and on the left side towards the bottom of</p> <p>15 the page are shown compounds XL, IX, L, and L2.</p> <p>16 Do you see that?</p> <p>17 A. I do.</p> <p>18 Q. And none of those are three carbon allyl</p> <p>19 ethers, correct?</p> <p>20 A. I think whatever that is, LI is.</p> <p>21 Q. I didn't ask about LI. I said XL, IX, L,</p> <p>22 and L2.</p> <p>23 A. Right. That is correct.</p> <p>24 MR. ZIMMERMAN: He came up with 4:42.</p> <p>25 ///</p>	<p style="text-align: right;">Page 214</p> <p>1 BY MR. SCHWARTZ:</p> <p>2 Q. So none of those are three carbon allyl</p> <p>3 groups, correct?</p> <p>4 A. That is correct.</p> <p>5 Q. And throughout Gigg and Warren there are</p> <p>6 disclosures of allyl ethers that are both</p> <p>7 unsubstituted and substituted, correct?</p> <p>8 A. Apparently, yes.</p> <p>9 Q. And throughout Gigg and Warren there are</p> <p>10 also disclosures of allyl ethers other than a three</p> <p>11 carbon allyl ether, correct?</p> <p>12 A. That is correct. Obviously, from what</p> <p>13 you just pointed out. At least.</p> <p>14 Q. A reader of Tsien -- referring back to</p> <p>15 the Gigg and Warren that Tsien refers to for his</p> <p>16 support of an allyl -- the allyl groups --</p> <p>17 understood that Tsien's reference to allyl ether is</p> <p>18 to a collection of ethers shown by Gigg and Warren,</p> <p>19 correct?</p> <p>20 A. No. People -- as I said, people</p> <p>21 sometimes use the word allyl, and describing this</p> <p>22 as an allyl ether, while technically still a little</p> <p>23 bit weird, is a little less weird than their</p> <p>24 generalizing a group of things. But still, the</p> <p>25 only thing in here that in here strictly properly</p>
<p style="text-align: right;">Page 215</p> <p>1 referred to as an allyl group is the single allyl,</p> <p>2 the three carbon allyl. Other substituted ones</p> <p>3 technically should have different names, like there</p> <p>4 should be like, for example, in -- you're going to</p> <p>5 test my nomenclature. The compound, the first one,</p> <p>6 which really have be called II methyl allyl, but</p> <p>7 like I said, people are a little bit loose with</p> <p>8 those because people don't like to write out things</p> <p>9 like that.</p> <p>10 Q. But do you agree that Tsien refers to</p> <p>11 Gigg and Warren for his disclosure when he</p> <p>12 discloses allyl groups, correct?</p> <p>13 A. That is correct.</p> <p>14 Q. And a POSA reading Gigg and Warren</p> <p>15 understood that Gigg and Warren teaches other than</p> <p>16 the three carbon allyl group, correct?</p> <p>17 A. Yes, that is correct. There is a small</p> <p>18 number of -- I mean, frankly, there just aren't</p> <p>19 that many different sort of allyl groups short of</p> <p>20 making longer -- there are not that many ways to</p> <p>21 substitute allyl per se, only three carbons. You</p> <p>22 can certainly make modifications. They're very</p> <p>23 seldom used allyl groups are typically the common</p> <p>24 C3 one, the namesake of the group.</p> <p>25 Q. Gigg and Warren discloses allyl groups</p>	<p style="text-align: right;">Page 216</p> <p>1 better than that?</p> <p>2 A. As I already said, yes, that is</p> <p>3 correct --</p> <p>4 Q. Let's go back to Exhibit 1001, which was</p> <p>5 the patent the '852 patent.</p> <p>6 A. I'm sorry, where?</p> <p>7 Q. The patent. The '852 patent that is</p> <p>8 Exhibit 1001. Please go to column six, line 23.</p> <p>9 And in column 23 the patent reads "The MOM."</p> <p>10 MR. ZIMMERMAN: Just some confusion, you</p> <p>11 said go to column six, and now you're saying --</p> <p>12 MR. SCHWARTZ: Column 26 -- maybe my --</p> <p>13 MR. ZIMMERMAN: We're both sitting here</p> <p>14 on six.</p> <p>15 MR. SCHWARTZ: Column 26.</p> <p>16 MR. ZIMMERMAN: Thank you.</p> <p>17 MR. SCHWARTZ: Sorry for the confusion.</p> <p>18 MR. ZIMMERMAN: I just wanted to make</p> <p>19 sure we are all at the same place.</p> <p>20 BY MR. SCHWARTZ:</p> <p>21 Q. And line 23. The patent reads "The</p> <p>22 MOM" -- and it draws the structure, CH₂OCH₃, or</p> <p>23 allyl, and it draws a structure CH₂CH-double</p> <p>24 bond-CH₂ -- "is used to cap the 3'-OH group using</p> <p>25 well established synthetic procedures," and refers</p>

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1 to figure 13.
2 So the patent specification, Dr. Ju's
3 patent specification, specifically calls the CH₂CH
4 double bond CH₂ group the allyl group, correct?
5 A. As most people would, yeah. It's the
6 allyl group, and he parenthetically draws it out.
7 Q. And that structure is not disclosed in
8 Tsien, correct?
9 A. It effectively is. Its name is disclosed
10 in Tsien. It's not drawn out in a parenthetical
11 manner like this, but in a way that any POSA would
12 have immediately drawn that conclusion.
13 Q. I'm just saying that the structure is not
14 shown in Tsien, is it?
15 A. The structure is not drawn out.
16 Q. Okay.
17 MR. SCHWARTZ: I would like to go off the
18 record if I could. I have to mark up some
19 exhibits.
20 THE VIDEOGRAPHER: Off the record at
21 3:38 p.m.
22 (Recess taken.)
23 THE VIDEOGRAPHER: On the record at
24 3:48 p.m. This concludes today's deposition of
25 Floyd Romesberg Ph.D. We are off the record at

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1 I, the undersigned, a Certified Shorthand
2 Reporter of the State of California, do hereby
3 certify:
4 That the foregoing proceedings were taken
5 before me at the time and place herein set forth;
6 that any witnesses in the foregoing proceedings,
7 prior to testifying, were duly sworn; that a
8 verbatim record of the proceedings was made by me
9 using machine shorthand which was thereafter
10 transcribed under my direction; that the foregoing
11 transcript is a true record of the testimony given.
12 Further, that if the foregoing pertains to the
13 original transcript of a deposition in a Federal
14 Case, before completion of the proceedings, review
15 of the transcript [X] was [] was not requested.
16 I further certify I am neither financially
17 interested in the action nor a relative or employee
18 of any attorney of party to this action.
19 IN WITNESS WHEREOF, I have this date
20 subscribed my name.
21 Dated: September 21, 2018
22 
23 PATRICIA Y. SCHULER
24 CSR NO. 11949
25

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1 3:48 p.m.
2 (The videotaped deposition of
3 FLOYD ROMESBERG, PH.D., VOLUME I,
4 concluded at 3:48 p.m.)
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1 DECLARATION UNDER PENALTY OF PERJURY
2 Case Name: Illumina, Inc. vs. The Trustees of Columbia
University in the City of New York
3 Date of Deposition: 09/19/2018
4 Job No.: 10047002
5
6 I, FLOYD ROMESBERG, PH.D. hereby certify
7 that I have read the transcript of my deposition and that
8 this transcript accurately states the testimony given by me,
9 with the changes or corrections, if any, as noted on an errata
10 sheet or errata sheets.
11 Executed this ____ day of
12 _____, 2018, at _____.
13
14 _____
15 FLOYD ROMESBERG, PH.D.
16 NOTARIZATION (If Required)
17 State of _____
18 County of _____
19 Subscribed and sworn to (or affirmed) before me on
20 this ____ day of _____, 20____,
21 by _____, proved to me on the
22 basis of satisfactory evidence to be the person
23 who appeared before me.
24 Signature: _____ (Seal)
25

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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: 09/19/2018
Job No.: 10047002

4 Reason Codes: 1. To clarify the record.
2. To conform to the facts.
3. To correct transcription errors.

5

6 Page ____ Line ____ Reason ____
7 From ____ to ____
8 Page ____ Line ____ Reason ____
9 From ____ to ____
10 Page ____ Line ____ Reason ____
11 From ____ to ____
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25 From ____ to ____

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1 DEPOSITION ERRATA SHEET

2 Page ____ Line ____ Reason ____
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15 From ____ to ____
16 Page ____ Line ____ Reason ____
17 From ____ to ____
18 Page ____ Line ____ Reason ____
19 From ____ to ____
20 Page ____ Line ____ Reason ____
21 From ____ to ____
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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**Illumina, Inc. vs. The Trustees of Columbia
University in the City of New York**

**Videotaped Deposition of
FLOYD ROMESBERG, PH.D.
September 20, 2018
Volume II**

Page 223

1 UNITED STATES PATENT AND TRADEMARK OFFICE
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD
3
4 ILLUMINA, INC., Case No. IPR2018-00291
Petitioner, U.S. Patent 9,718,852
5 v. IPR2018-00318
6 THE TRUSTEES OF COLUMBIA U.S. Patent 9,719,139
UNIVERSITY IN THE CITY OF
7 NEW YORK, IPR2018-00322
Patent Owner. U.S. Patent 9,708,358
8 IPR2018-00385
9 U.S. Patent 9,725,480

10
11 VIDEOTAPED DEPOSITION OF FLOYD ROMESBERG, PH.D.
12 VOLUME II
13 SAN DIEGO, CALIFORNIA
14 SEPTEMBER 20, 2018
15
16
17
18
19 Reported By:
PATRICIA Y. SCHULER
20 CSR No. 11949
21 Job No. 10047003
22
23
24
25

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1 APPEARANCES:
2 FOR PETITIONER:
3 KNOBBE MARTENS - SAN DIEGO
4 BY: NATHANAEL R. LUMAN, ESQ.
5 12790 El Camino Real
6 San Diego California 92130
7 (858) 707-4000
8 nate.luman@knobbe.com
9 - and -
10 KNOBBE MARTENS - WASHINGTON DC
11 BY: WILLIAM R. ZIMMERMAN, ESQ.
12 1717 Pennsylvania Avenue, Suite 900
13 Washington, D.C. 20006
14 bill.zimmerman@knobbe.com
15 FOR PATENT OWNER:
16 FITZPATRICK, CELLA, HARPER & SCINTO
17 BY: ROBERT S. SCHWARTZ, ESQ.
18 BY: ZACHARY L. GARRETT, ESQ.
19 1290 Avenue of the Americas
20 New York, New York 10104-3800
21 zgarrett@fchs.com
22 Also Present: Dr. Steven Menchen
John White, Esq.
23 John Murnane, Esq.
Marcus Burch, Illumina
24
25 Videographer: Daniel Bermudez

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5 v. IPR2018-00318
6 THE TRUSTEES OF COLUMBIA U.S. Patent 9,719,139
UNIVERSITY IN THE CITY OF
7 NEW YORK, IPR2018-00322
Patent Owner. U.S. Patent 9,708,358
8 IPR2018-00385
9 U.S. Patent 9,725,480

10
11 Videotaped deposition of Floyd Romesberg, Ph.D.,
12 Volume II, taken on behalf of the Patent Owner at
13 12790 El Camino Real, San Diego, California,
14 beginning at 9:04 a.m. and ending at 10:41 a.m., on
15 September 20, 2018, before PATRICIA Y. SCHULER,
16 Certified Shorthand Reporter No. 11949.
17
18
19
20
21
22
23
24
25

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1 I-N-D-E-X
2 WITNESS: EXAMINATION
3 FLOYD ROMESBERG, PH.D., VOLUME II
4 BY MR. SCHWARTZ 228
5 BY MR. ZIMMERMAN 270
6
7 E-X-H-I-B-I-T-S
8 PATENT OWNER'S PAGE
9 Exhibit 1037 Document entitled "A Mild and 232
Rapid Regeneration of Alcohols
10 from their Allylic Ethers by
Chlorotrimethylsilane/Sodium
11 Iodide" by Kamal et al"
12 Exhibit 2031 Document entitled "DNA polymerase 235
fluorescent substrates with
13 reversible 3' tags"
14 Exhibit 2089 Document entitled 238
"Palladium(II)-Catalyzed
15 Oxidation of Aldehydes and
Ketones. 1. Carbonylation of
16 Ketones with Carbon Monoxide
Catalyzed by Palladium(II)
17 Chloride in Methanol"
18 Exhibit 2094 Document entitled "Interaction of 241
Palladium (II) With DNA"
19
20
21
22
23
24
25

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1 SAN DIEGO, CALIFORNIA; THURSDAY, SEPTEMBER 20, 2018
2 9:04 a.m.
3 THE VIDEOGRAPHER: Good morning. We are
4 now on the record. Today's date is Thursday,
5 September 20, 2018, and the time is 9:04 a.m.
6 This is the video deposition of
7 Floyd Romesberg, Ph.D., Day II, being taken in the
8 matter of Illumina, Inc. versus the Trustees of
9 Columbia University in the City of New York,
10 pending in the United States Patent and Trademark
11 Office before the Patent and Appeal Board, Case
12 Nos. IPR2018-00291, IPR2018-00318, IPR2018-00322,
13 and IPR2018-00385.
14 We are at Knobbe Martens in San Diego,
15 12790 El Camino Real. My name is Daniel Bermudez
16 of Aptus Court Reporting located at 600 West
17 Broadway, Suite 300, San Diego, California 92101.
18 Will counsel please identify yourselves
19 and state whom you represent.
20 MR. SCHWARTZ: I'm Robert S. Schwartz
21 representing Columbia, from Fitzpatrick, Cella,
22 Harper & Scinto. With me is Zack Garrett, also
23 from Fitzpatrick. Sitting next to him is
24 Dr. Steven Menchen. Sitting next to him is
25 John Light from the Cooper and Dunham firm also

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1 A. No, I did not.
2 Q. And did you consult with your attorneys
3 regarding the substance of what you anticipate
4 discussing today?
5 A. No, I did not.
6 Q. I am going to start out by asking you to
7 go back to the Tsien reference. That was
8 Exhibit 1013. Please draw your attention to
9 Page 24, and look at Line 29.
10 And Tsien writes "Allyl ethers are
11 cleaved by treatment with mercury II in acetone
12 water."
13 That is what Tsien writes, correct?
14 A. That is correct.
15 Q. Please go back to Exhibit 2086, which was
16 the Kitt paper we looked at yesterday, 2086. Got
17 it?
18 A. I have it.
19 Q. And please turn to page 59. And please
20 draw your attention to the second full paragraph
21 that starts with "additional evidence."
22 Do you see that?
23 A. I do.
24 Q. And Kitt writes "Additional evidence that
25 partial and reversible denaturation of DNA

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1 representing Columbia. And at the end of the table
2 is John Murnane, also representing Columbia from
3 the Fitzpatrick firm.
4 MR. ZIMMERMAN: Bill Zimmerman of Knobbe
5 Martens Olson & Bear representing Illumina and the
6 witness, Dr. Romesberg. With me is my partner Nate
7 Luman and Marcus Burch of Illumina.
8 THE VIDEOGRAPHER: The court reporter
9 today is Patricia Schuler, and she may now swear in
10 the witness.
11
12 FLOYD ROMESBERG, PH.D.,
13 having been administered an oath, was examined and
14 testified as follows:
15
16 FURTHER EXAMINATION
17 BY MR. SCHWARTZ:
18 Q. Good morning, Dr. Romesberg.
19 A. Good morning.
20 Q. Is there any reason you can't give
21 truthful testimony today?
22 A. No.
23 Q. Did you consult with your attorneys
24 regarding the substance of your testimony
25 yesterday?

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1 molecules may occur has been derived from
2 experiments on the reaction of mercury chloride
3 with DNA."
4 Do you see that Kitt writes that?
5 A. Yes, I do.
6 Q. And mercury II is a DNA denaturant,
7 correct?
8 A. It denatures DNA, yes.
9 Q. Going back to the allyl ethers in Tsien,
10 the cleavage method for the allyl ethers cited by
11 Tsien is based on the Gigg and Warren reference,
12 correct?
13 A. That is correct.
14 Q. And if you wouldn't mind, please, going
15 back to that paper, Exhibit 1046.
16 Do you have it?
17 A. I do.
18 Q. Please draw your attention to Reaction 1
19 on the left side of Page 1904, in Gigg and Warren.
20 A. I'm sorry. Where?
21 Q. Reaction 1 on the left side of 1904.
22 Got it?
23 A. Yes.
24 Q. The first step in that method is for the
25 allyl ethers to be converted to vinyl ethers under

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1 strong basic conditions, and then the vinyl ethers
2 are cleaved by mercury II, correct?
3 A. Yes. I am not reading the first step.
4 If I could take a second to read this?
5 Q. Sure.
6 A. That seems to be the case, yes.
7 Q. The structure of allyl ethers is
8 different from that of vinyl ethers, correct?
9 A. Yes.
10 Q. And the conversion --
11 A. One is an isomer of the other.
12 Q. They are different structures?
13 A. You represent -- we think about them
14 differently as different structures. Technically,
15 if you want to know technically the truth, it's a
16 theoretical description of the two.
17 The connectivities of the atoms are the
18 same. We never know where to draw -- put electrons
19 in reality. And in the two forms, we put the
20 electrons in different places, and they are differen
21 in the two.
22 Q. And so the conversion of allyl ethers to
23 vinyl ethers requires the use of strong basic
24 conditions. We looked at that where he says
25 "potassium t-butoxide."

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1 Have you seen this paper before,
2 Dr. Romesberg?
3 A. I have.
4 Q. Please draw your attention to the last
5 paragraph on the bottom of the first page that
6 starts with "This led us to utilize."
7 Do you see that?
8 A. I do.
9 Q. Kamal writes "This led us to utilize this
10 reagent system for the cleavage of allyl ethers
11 following this procedure. To a solution of allyl
12 ether, one millimole, in acetonitrile, 10 mils,
13 sodium iodide, 1.5 millimoles, was added, and the
14 mixture stirred for two minutes.
15 To this stirred suspension, a solution of
16 chlorotrimethylsilane, 1.5 millimoles, was added,
17 and the stirring continued for another two minutes.
18 For entry seven, 4.5 equivalents of the reagents
19 were used."
20 That is what Kamal writes, correct?
21 A. That is what's written.
22 Q. The scheme that is used to deprotect the
23 allyl group in Kamal is not performed in aqueous
24 medium, correct?
25 A. It is performed in acetonitrile.

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1 You saw that, right?
2 A. Yes.
3 Q. And that denatures DNA, correct? And
4 that cannot be used for SBS, correct?
5 A. Certainly, at high concentrations
6 potassium t-butoxide would denature DNA. I don't
7 know exactly at what concentration that would
8 occur, but that is a base, and, you know, I think
9 at sufficiently basic conditions, DNA is damaged.
10 Q. So a person reading Tsien along with Gigg
11 and Warren would not use Gigg's condition for
12 cleavage of allyl ethers for SBS because there
13 would be no expectation of success using those
14 cleavage conditions, correct?
15 A. I think that is fair.
16 (Exhibit 1037 was previously marked for
17 identification.)
18 BY MR. SCHWARTZ:
19 Q. I am going to put another exhibit in
20 front of you because I know you don't have enough
21 of them already. I am putting in front of you
22 Exhibit 1037, which is a paper entitled "A Mild and
23 Rapid Regeneration of Alcohols from their Allylic
24 Ethers by Chlorotrimethylsilane/Sodium Iodide" by
25 Kamal et al, published in 1999.

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1 Q. And protecting groups for use in SBS must
2 be removable under aqueous conditions. We went
3 over that yesterday, correct?
4 A. Yes, that is correct. Under conditions
5 where the DNA is stable and hybridized, yes.
6 Q. And it has to be done in aqueous
7 conditions?
8 A. Meaning there has to be water there, yes.
9 Q. And as you just mentioned, Kamal's
10 deprotection assay uses acetonitrile, correct?
11 A. That is correct.
12 Q. And acetonitrile is an organic solvent,
13 correct?
14 A. It is an organic solvent, correct.
15 Q. And we talked about this yesterday -- and
16 it is your opinion that deprotection conditions
17 that use organic solvents are not compatible with
18 SBS, correct?
19 A. I don't believe I said that, and I think
20 that you have to say that there can be an organic
21 solvent there, they just can't be sufficient
22 concentrations to denature or damage the DNA.
23 Q. But his reaction takes place in
24 acetonitrile with no water present?
25 A. Yes. And in that case it would denature

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1 the DNA. And you would dehydrate the DNA and cause
2 it to denature.

3 **Q. And Kamal's allyl deprotection method**
4 **uses chlorotrimethylsilane, correct?**

5 A. It does.

6 **Q. And chlorotrimethylsilane is not**
7 **compatible with water, correct?**

8 A. No, it is not.
9 (Exhibit 2031 was previously marked for
10 identification.)

11 BY MR. SCHWARTZ:

12 **Q. I am putting in front of you**
13 **Exhibit 2031, which is a paper entitled "DNA**
14 **Polymerase Fluorescent Substrates with Reversible**
15 **3'-Tags" by Canard and Sarfati, published in 1994.**
16 **Please turn to page 4. You've seen this**
17 **paper before, haven't you, Dr. Romesberg?**

18 A. I have.

19 **Q. Please draw your attention to the right**
20 **side of the page, and please look at the bottom**
21 **where there is a section D.**

22 **Do you see that?**

23 A. I do.

24 **Q. Please draw your attention to the third**
25 **sentence in that section that starts with "We**

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1 cleave.

2 **Q. And in your declarations that you**
3 **submitted in the current IPRs, you don't cite to**
4 **any reference prior to October 2000 that provides**
5 **data showing that a nucleotide with a 3'-O-allyl**
6 **protecting group is cleaved under mild conditions**
7 **compatible with DNA chemical stability, do you?**

8 A. I provided examples of reactions that
9 were very close, that a POSA would have expected,
10 and had high expectation of success that the one
11 difference of methanol versus water would not have
12 been a problem, and that would have provided
13 conditions where a 3'-O-allyl protected nucleoside
14 could have been allyl deprotected. I did not find
15 examples of precisely that reaction in water.

16 **Q. And sitting here today, are you aware of**
17 **any examples of that precise reaction occurring in**
18 **water?**

19 A. No, I did not find any last night.

20 **Q. Did you look for them last night?**

21 A. I did not.

22 MR. SCHWARTZ: I am going to go to
23 another exhibit, please. This one will require a
24 new marking, Court Reporter, 2089.
25 (Exhibit 2089 was marked for

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1 **reasoned that."**

2 **Do you see that?**

3 A. I do.

4 **Q. Canard writes "We reasoned that ether**
5 **bonds would be hard to cleave under mild conditions**
6 **compatible with DNA chemical stability."**
7 **That's what Canard writes, correct?**

8 A. That is what is written.

9 **Q. And the Canard paper was published in**
10 **1994, correct?**

11 A. That is correct.

12 **Q. And the Tsien application was published**
13 **in 1991, correct?**

14 A. That is correct.

15 **Q. So even years after Tsien, it was**
16 **understood that ether bonds are hard to cleave**
17 **under mild conditions compatible with DNA chemical**
18 **stability.**

19 **That is what Canard says, right?**

20 A. Canard says that they reasoned that --
21 that ether bonds would be hard to cleave.

22 **Q. But that reasoning was three years after**
23 **the publication of Tsien?**

24 A. Yes. Canard, in this paper, suggested
25 that they thought that ethers would be difficult to

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1 identification.)

2 BY MR. SCHWARTZ:

3 **Q. I'm putting in front of you a paper**
4 **entitled "Palladium(II)-Catalyzed Oxidation of**
5 **Aldehydes and Ketones. 1. Carbonylation of Ketones**
6 **with Carbon Monoxide Catalyzed by Palladium(II)**
7 **Chloride in Methanol" by Hamed et al, which was**
8 **published in 2001.**

9 **Please turn to page 182. And please draw**
10 **your attention to the left side of the page towards**
11 **the top of the page where there is a reaction**
12 **scheme entitled "Alkoxy Palladium Root."**

13 **Do you see that?**

14 A. I do.

15 **Q. The reaction scheme showing**
16 **palladium (II) reacting with an olefin plus an**
17 **alcohol to generate a palladium (II) complex with**
18 **the olefin with the generation of acid."**

19 **That is what is the reaction scheme**
20 **shows, correct?**

21 A. It does show that.

22 **Q. An allyl protecting group is an example**
23 **of an olefin, correct?**

24 A. Yes.

25 **Q. So a POSA reading -- I'm sorry, strike**

<p style="text-align: right;">Page 239</p> <p>1 that.</p> <p>2 A POSA understood that reacting in allyl</p> <p>3 protecting group with palladium (II) will generate</p> <p>4 acid, correct?</p> <p>5 A. Yes.</p> <p>6 MR. ZIMMERMAN: Object to the form of the</p> <p>7 question. And just so you know my objection, you</p> <p>8 made clear yesterday that a POSA was in 2002 --</p> <p>9 THE WITNESS: 2000.</p> <p>10 MR. ZIMMERMAN: 2000. And you are asking</p> <p>11 him about something dated after that and assuming a</p> <p>12 POSA would know.</p> <p>13 So the timing in your question is</p> <p>14 nonsensical. So I am objecting as to form.</p> <p>15 MR. SCHWARTZ: Okay.</p> <p>16 BY MR. SCHWARTZ:</p> <p>17 Q. A POSA understood that reacting in allyl</p> <p>18 protecting group, palladium (II) generates acid,</p> <p>19 correct?</p> <p>20 A. Yes.</p> <p>21 Q. So please --</p> <p>22 A. Stoichiometric acid, yeah.</p> <p>23 Q. Please go back to the first page of</p> <p>24 Hamed -- strike that.</p> <p>25 Yesterday we looked at some papers by</p>	<p style="text-align: right;">Page 240</p> <p>1 Lindahl.</p> <p>2 Do you recall that?</p> <p>3 There were two papers, Lindahl 1993 and</p> <p>4 Lindahl and Nyberg 1972, and those papers reported</p> <p>5 that acid catalyzes depurination of nucleotides.</p> <p>6 Do you remember that?</p> <p>7 A. Yes.</p> <p>8 Q. And conditions that result in</p> <p>9 depurination of nucleotides are not compatible with</p> <p>10 SBS, correct?</p> <p>11 A. If you're depurinating during sequencing</p> <p>12 reaction, that would not be compatible with</p> <p>13 sequencing by synthesis.</p> <p>14 Q. And please go back to the Qian reference</p> <p>15 we looked at yesterday, Exhibit 1036, and go back</p> <p>16 to Page 2185 where there was Scheme 2. And please</p> <p>17 look again at the figure legend. The deprotection</p> <p>18 of the allyl takes place with palladium (II) and</p> <p>19 methanol, correct?</p> <p>20 A. It does.</p> <p>21 Q. And that reaction would be expected to</p> <p>22 produce acid, correct?</p> <p>23 A. It would produce stoichiometric amounts,</p> <p>24 very small amounts of acid compared to a solvent --</p> <p>25 compared to the adding solvent at millimolar</p>
<p style="text-align: right;">Page 241</p> <p>1 concentrations of the sort that we talked about</p> <p>2 yesterday, and of the sort that Lindahl talked</p> <p>3 about, this would generate the amounts of acid</p> <p>4 that -- one proton for every time you deprotected</p> <p>5 an allyl. And that's common, and that would be</p> <p>6 handled under sequencing by synthesis methods,</p> <p>7 because I assume that is what we are interested in.</p> <p>8 And that would be handled by buffering the system.</p> <p>9 That would be well within the buffer power and</p> <p>10 standard for any POSA to deal with.</p> <p>11 Q. But I'm not talking about a different</p> <p>12 reaction condition. I'm talking specifically about</p> <p>13 Qian's reaction condition.</p> <p>14 So in Qian's reaction condition that would</p> <p>15 be expected to produce acid, there is not a buffer</p> <p>16 there, correct?</p> <p>17 A. It would produce stoichiometric acid.</p> <p>18 MR. SCHWARTZ: I am going to mark a new</p> <p>19 exhibit. Court reporter, this will require a new</p> <p>20 number, 2094.</p> <p>21 (Exhibit 2094 was marked for</p> <p>22 identification.)</p> <p>23 BY MR. SCHWARTZ:</p> <p>24 Q. I'd like to direct you to a document</p> <p>25 entitled "Interaction of Palladium (II) with DNA"</p>	<p style="text-align: right;">Page 242</p> <p>1 that was published in 1977 by Pillai and Nandi. Go</p> <p>2 to the abstract. And the abstract reads -- I'm not</p> <p>3 going to read the whole thing. I am going to ask</p> <p>4 you to look at the second sentence that starts with</p> <p>5 "The results."</p> <p>6 Do you see that?</p> <p>7 "The results indicate that palladium (II)</p> <p>8 interacts with both the phosphate and bases of</p> <p>9 DNA."</p> <p>10 That is what the authors write, correct?</p> <p>11 A. That is correct.</p> <p>12 Q. And the palladium (II) referred to by</p> <p>13 Pillai is palladium chloride as indicated in the</p> <p>14 last paragraph of Page 11, correct?</p> <p>15 A. That is correct. That seems to be</p> <p>16 correct. They cite palladium chloride, and in the</p> <p>17 intro they're talking about palladium II, and the</p> <p>18 palladium in palladium chloride is palladium II. I</p> <p>19 haven't read this reference to know if that is all</p> <p>20 they are talking about, but that would seem to be</p> <p>21 consistent with that.</p> <p>22 Q. And please go to Page 16 of Pillai, and</p> <p>23 draw your attention to the top of the page. And it</p> <p>24 reads "The ORD and CD curves of DNA were also</p> <p>25 altered considerably on addition of palladium</p>

<p style="text-align: right;">Page 243</p> <p>1 chloride, figure 4."</p> <p>2 And I'm not going to read the whole thing</p> <p>3 into the record, but let me just ask you to go to th</p> <p>4 next paragraph that starts with "The ultraviolet."</p> <p>5 Do you see that?</p> <p>6 A. I do.</p> <p>7 Q. It reads "The ultraviolet spectrum</p> <p>8 (figure 1), indicates binding of palladium (II) to</p> <p>9 the bases of DNA. This is expected to modify the</p> <p>10 electronic state of the bases, and will be</p> <p>11 reflected in the interaction of their dipoles in</p> <p>12 the polymer, thus affecting the shape and magnitude</p> <p>13 of the cotton effects." Cites a reference.</p> <p>14 "Unstacking of the bases of</p> <p>15 polynucleotides is thought to result in diminished</p> <p>16 magnitudes of cotton effects." And it cites a</p> <p>17 reference. "Similarly disruption of hydrogen bonds</p> <p>18 between the base pairs of double-stranded</p> <p>19 polynucleotides may give rise to a red shift in the</p> <p>20 position of the maxima." And it cites a reference.</p> <p>21 "Figure 4A and 4B show that binding of</p> <p>22 palladium (II) to DNA results in reduction of ORD</p> <p>23 and CD bands accompanied by red shifts. These</p> <p>24 results suggest that stacking interactions are</p> <p>25 reduced considerably, and the Watson and Crick</p>	<p style="text-align: right;">Page 244</p> <p>1 hydrogen bonded double helical system has been</p> <p>2 disturbed at least in the regions where binding of</p> <p>3 palladium (II) takes place."</p> <p>4 MR. ZIMMERMAN: Object to norm.</p> <p>5 BY MR. SCHWARTZ:</p> <p>6 Q. That is what the authors write, correct?</p> <p>7 A. That is what is written.</p> <p>8 Q. A POSA understood from Pillai that</p> <p>9 palladium chloride cannot be used in a reaction</p> <p>10 with DNA, because palladium chloride disturbs the</p> <p>11 Watson Crick hydrogen bonded double helical system,</p> <p>12 and the fidelity of the Watson Crick hydrogen</p> <p>13 bonded double helical system is essential for DNA</p> <p>14 sequencing, including SBS.</p> <p>15 Do you agree?</p> <p>16 A. No.</p> <p>17 Q. And why don't you agree?</p> <p>18 A. There's no evidence that the duplex is</p> <p>19 disrupted in any manner that would prevent</p> <p>20 sequencing by synthesis here.</p> <p>21 If you want me to explain a little bit about</p> <p>22 ORD, ORD stands for optical rotatory dispersion. CD</p> <p>23 stands for circular dichroism.</p> <p>24 Chiral molecules, when you polarize light,</p> <p>25 interact differently with the two-plane polarized</p>
<p style="text-align: right;">Page 245</p> <p>1 lights, left and right polarized. DNA duplex is</p> <p>2 chiral. Anything that relaxes that chirality at all</p> <p>3 leads to changes.</p> <p>4 So if you simply relax the duplex slightly,</p> <p>5 you get differences in the ORD and CD signals.</p> <p>6 People don't understand the origins of</p> <p>7 ORD and CD. It's -- the only way that we use these</p> <p>8 signals is by model systems. We say, okay, an</p> <p>9 alpha helix is like this, and a protein and beta</p> <p>10 sheet's like this. DNA duplex A form is like this;</p> <p>11 B form is like this.</p> <p>12 Little small changes happen all the time,</p> <p>13 and they are only understandable in the context of a</p> <p>14 model system. And so if there is no model system to</p> <p>15 show that, you can't say that it's denatured</p> <p>16 anything.</p> <p>17 Slight relaxations of the DNA is common,</p> <p>18 it doesn't in any way show that the hydrogen bonds</p> <p>19 are disrupted. It just shows that the duplex is</p> <p>20 slightly relaxed. Its chirality is not identical.</p> <p>21 There is nothing in that to me -- there is</p> <p>22 nothing that you read here that to me would suggest</p> <p>23 that it would no longer be able to be substrate for</p> <p>24 sequencing by synthesis.</p> <p>25 I mean, sodium sort of does the same</p>	<p style="text-align: right;">Page 246</p> <p>1 thing, and sodium is perfectly compatible.</p> <p>2 Palladium (II) is simply interacting with the</p> <p>3 nitrogens of the bases in the waters and the</p> <p>4 phosphates. There's nothing -- it's just -- in</p> <p>5 some respects it's -- there's no evidence here that</p> <p>6 palladium (II) is acting as anything other than a</p> <p>7 counterion in the same way that sodium, which is a</p> <p>8 cation, would be interacting.</p> <p>9 But there is nothing in the change in the</p> <p>10 CRD and the ORD that suggests to me that the DNA is</p> <p>11 denatured.</p> <p>12 In fact, in all cases, it still has a CD an</p> <p>13 an ORD signal, suggesting that it is still chiral,</p> <p>14 suggesting there is still duplex.</p> <p>15 Q. The authors themselves, however,</p> <p>16 interpret their own results by suggesting that the</p> <p>17 stacking interactions are reduced considerably.</p> <p>18 That is what they say, correct?</p> <p>19 A. If they interpret the CD and ORD specter</p> <p>20 that way, that's fine, but they're certainly not</p> <p>21 ablated because -- they're certainly not gone,</p> <p>22 because there is still ORD and CD signal there.</p> <p>23 Q. But they do interpret this data as</p> <p>24 suggesting that their stacking interactions are</p> <p>25 reduced considerably. That is what the authors</p>

<p style="text-align: right;">Page 247</p> <p>1 say, correct?</p> <p>2 A. I don't see that they relate that to</p> <p>3 recognition by a polymerase in any manner.</p> <p>4 Q. They are simply saying that the presence</p> <p>5 of palladium results in stacking interactions</p> <p>6 reduced considerably -- they use the word</p> <p>7 "considerably" -- and that the Watson Crick</p> <p>8 hydrogen bonded double helical system is disturbed</p> <p>9 where the regions of palladium binding are. That</p> <p>10 is what they say. That is what they teach, right?</p> <p>11 A. Could you, again, point me to exactly</p> <p>12 where they say that?</p> <p>13 Q. At the end of the paragraph: "These</p> <p>14 results suggest that stacking interactions are</p> <p>15 reduced considerably." Those are their words.</p> <p>16 "And the Watson and Crick hydrogen bonded double</p> <p>17 helical system has been disturbed, at least in the</p> <p>18 regions where binding of palladium takes place."</p> <p>19 That was the authors' interpretation of</p> <p>20 their own data, correct?</p> <p>21 MR. ZIMMERMAN: Objection.</p> <p>22 Mischaracterizes the document. And you read it</p> <p>23 incorrectly.</p> <p>24 MR. SCHWARTZ: Where did I read it</p> <p>25 incorrectly?</p>	<p style="text-align: right;">Page 248</p> <p>1 MR. ZIMMERMAN: You said palladium not</p> <p>2 palladium II.</p> <p>3 MR. SCHWARTZ: Okay. I will correct it</p> <p>4 by saying palladium II.</p> <p>5 THE WITNESS: That is what they say. And</p> <p>6 I think a POSA would have understood that those</p> <p>7 changes that -- number one, that there was no link</p> <p>8 to any sequencing by synthesis to any polymerase</p> <p>9 recognition for that matter at all. And a POSA</p> <p>10 certainly would have still understood that there</p> <p>11 was still a helical structure there.</p> <p>12 So there still had to be pattern. So to</p> <p>13 whatever extent they're reduced considerably, they</p> <p>14 are not gone.</p> <p>15 Q. But a POSA reading this would understand</p> <p>16 that the authors interpret this data as showing</p> <p>17 that the palladium causes stacking interactions to</p> <p>18 be reduced considerably?</p> <p>19 MR. ZIMMERMAN: Objection. Asked and</p> <p>20 answered.</p> <p>21 THE WITNESS: Those are the words there.</p> <p>22 BY MR. SCHWARTZ:</p> <p>23 Q. What you were talking about before when</p> <p>24 you gave your long explanation of the ORD and the</p> <p>25 CD, that was speculation on your part on whether or</p>
<p style="text-align: right;">Page 249</p> <p>1 not these were reduced considerably, correct?</p> <p>2 A. I don't understand the question. What</p> <p>3 part are you asking me if it was speculation?</p> <p>4 Q. Well, you gave a very long explanation of</p> <p>5 ORD and CD, okay, but you didn't find anything --</p> <p>6 let's strike that. Let's just let's stick --</p> <p>7 A. I'm happy to try to answer.</p> <p>8 Q. Let's strike it.</p> <p>9 MR. ZIMMERMAN: He doesn't have a</p> <p>10 question.</p> <p>11 BY MR. SCHWARTZ:</p> <p>12 Q. Let's just stick with what the paper</p> <p>13 teaches.</p> <p>14 I'm going to ask you to go back to</p> <p>15 Exhibit 2035.</p> <p>16 A. Which is what?</p> <p>17 Q. Your deposition transcript in</p> <p>18 IPR2013-00517. And please turn to Page 63. Please</p> <p>19 draw your attention to Line 19. And starting at</p> <p>20 Line 19, the transcript reads:</p> <p>21 "Question: Now, back in 2002 would one</p> <p>22 with skill in the art have been able to modify or</p> <p>23 engineer polymerases to improve their ability to</p> <p>24 incorporate nucleotides?</p> <p>25 "Answer: In 2002?"</p>	<p style="text-align: right;">Page 250</p> <p>1 And then there is a partial attorney</p> <p>2 statement, and the question continues with</p> <p>3 3'-oxygen protecting groups. The question that was</p> <p>4 asked of you was, "Back in 2002, would one with</p> <p>5 skill in the art have been able to modify or</p> <p>6 engineer polymerases to improve their ability to</p> <p>7 incorporate nucleotides with 3'-oxygen protecting</p> <p>8 groups," correct?</p> <p>9 A. That's what it says, yes.</p> <p>10 Q. And I won't read everything into the</p> <p>11 record that came after that question, and certainly</p> <p>12 feel free to review the transcript if you need to</p> <p>13 to follow along with me, but for now I'm going to</p> <p>14 ask you to skip ahead to Page 65.</p> <p>15 A. I'm there.</p> <p>16 Q. And please look at Line 3. And starting</p> <p>17 at Line 3 the transcript reads:</p> <p>18 "Question: Whether one of ordinary skill</p> <p>19 would believe that they would be able to do that?</p> <p>20 "Answer: Judging from the response of my</p> <p>21 reviews on grants that I submitted that it was not</p> <p>22 common, then the answer would be, no. People did</p> <p>23 not believe that you could."</p> <p>24 So the portions of your testimony that I</p> <p>25 read is what you testified, correct?</p>

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1 MR. ZIMMERMAN: Objection. Incomplete.
2 BY MR. SCHWARTZ:
3 Q. I said the portions that I read were what
4 you testified, correct?
5 A. Those are the words written, yes.
6 Q. And you testified that as of 2002, people
7 did not believe that they could modify or engineer
8 polymerases to improve their ability to incorporate
9 nucleotides with 3'-O protecting groups, correct?
10 MR. ZIMMERMAN: Objection.
11 Mischaracterizes.
12 THE WITNESS: Could you repeat the
13 question?
14 BY MR. SCHWARTZ:
15 Q. You testified that as of 2002 people did
16 not believe that they could modify or engineer
17 polymerases to improve their ability to incorporate
18 nucleotides with 3'-O protecting groups?
19 MR. ZIMMERMAN: Objection.
20 Mischaracterizes.
21 BY MR. SCHWARTZ:
22 Q. That is what you testified, correct?
23 A. I would like to read this.
24 Q. Sure.
25 A. One second please.

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1 difficult, correct?
2 A. There are no significant differences
3 between 2000 and 2002, in my opinion, in my
4 recollection. I don't know of anything that would
5 have changed my answer for 2000.
6 Q. But again, in the testimony that we read,
7 your response to the question at that deposition
8 was, no, people did not believe that you could.
9 A. No, I believe I tried to clarify that and
10 explain that people would have thought it was very
11 difficult. But there were groups working on it.
12 So if there were groups working on it,
13 people -- some people believed that you could,
14 including my group. So I believed we could.
15 But what I was trying to say then is that -
16 and this certainly is still the case today, is that
17 it's not easy.
18 Q. I am going to ask you to turn back to
19 Exhibit 2080, which is your deposition transcript
20 in IPR2013-00128. Please turn to Page 45.
21 A. I am there.
22 Q. Please draw your attention to Line 21,
23 and starting at Line 21 the transcript reads:
24 "Question: So then you've met
25 Dr. Tsien?

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1 Q. Take your time.
2 A. Okay. Could you repeat the question?
3 Q. Sure. So my question was you testified
4 that as of 2002 people did not believe that they
5 could modify or engineer polymerases to improve
6 their ability to incorporate nucleotides with 3'-O
7 protecting groups?
8 A. I think that's too general of a
9 statement. That is certainly not what I intended
10 to say in this declaration. What I intended to say
11 was that it would have been viewed by -- in
12 general, as being very difficult.
13 Q. But you didn't actually say that. You
14 said that people would not believe that you could?
15 A. No, I did say that. If you read on, I
16 said people would not have considered that a likely
17 possibility. A handful of groups including --
18 people were starting to make progress. In 2002,
19 people were starting to make progress. A handful
20 of groups, including mine, sure. No one thought it
21 was easy. To this day it is not easy.
22 So I certainly meant that it was difficult
23 and that people would have viewed it as difficult, n
24 doubt.
25 Q. And in 2000, it would have been even more

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1 "Answer: Yes.
2 "Question: And in the discussions you've
3 had with Dr. Tsien, have you ever discussed
4 modified nucleotides?
5 "Answer: Surprisingly, no."
6 I'm not going to read the whole
7 transcript into the record, but -- and of course
8 you can look at any part that you want. I'm going
9 to ask that you skip ahead to Page 46 and draw your
10 attention to Line 8. Starting at Line 8, the
11 transcript reads:
12 "Answer: And to tell you the truth, I
13 never really knew that he did this work until I
14 read this patent."
15 And the portions of the transcript I read
16 is what you testified, correct?
17 A. That is what is written, yes.
18 Q. And the patent which you were referring
19 to in your testimony is the Tsien patent
20 application, which is marked as Exhibit 1013,
21 correct?
22 A. It is the Tsien patent. It is marked as
23 1013.
24 Q. And you've been doing scientific research
25 on modified nucleotides for over 25 years; is that

<p style="text-align: right;">Page 255</p> <p>1 right?</p> <p>2 A. No. I've been doing work on modified</p> <p>3 nucleotides since 19 -- the end of 1998, so...</p> <p>4 Q. About 20 years?</p> <p>5 A. About 20 years.</p> <p>6 Q. And you've published many research papers</p> <p>7 on modified nucleotides during that time, right?</p> <p>8 A. I have published a number of papers on</p> <p>9 that topic, yes.</p> <p>10 Q. Did you ever cite to Tsien's patent</p> <p>11 application in any of your papers?</p> <p>12 A. No.</p> <p>13 Q. Do you recall ever citing to Tsien's</p> <p>14 patent application in any of your review articles?</p> <p>15 A. No.</p> <p>16 Q. Do you ever recall citing to Tsien's</p> <p>17 patent application in any of your grant</p> <p>18 applications?</p> <p>19 A. No, I did not.</p> <p>20 Q. Do you ever recall citing to Tsien's</p> <p>21 patent application in any presentations that you've</p> <p>22 made?</p> <p>23 A. No.</p> <p>24 Q. I'm talking about scientific</p> <p>25 presentations.</p>	<p style="text-align: right;">Page 256</p> <p>1 A. No.</p> <p>2 Q. And you testified in 2014 in the</p> <p>3 transcript that we just looked at that you never</p> <p>4 even knew that Tsien did any work on modified</p> <p>5 nucleotides until you became involved as an expert</p> <p>6 for Illumina in the 2013 time frame, correct?</p> <p>7 A. I guess I'm not positive I said that. I</p> <p>8 certainly was unaware that he had worked on the</p> <p>9 sequencing aspect of modified nucleotides. I mean,</p> <p>10 he did lots of work on RNA and DNA, and there were,</p> <p>11 for example, linkers in that. And I would have to</p> <p>12 rethink that carefully as to -- I've never cited</p> <p>13 it, but I am sort of peripherally aware that he did</p> <p>14 that work, but I believe what would be a factual</p> <p>15 statement -- and I would have to read this to make</p> <p>16 sure that this is what I said, but the content of</p> <p>17 the patent that is under discussion, I was unaware</p> <p>18 that he had been interested in that.</p> <p>19 MR. SCHWARTZ: I'm just looking at the</p> <p>20 record.</p> <p>21 THE WITNESS: While you do that, could I</p> <p>22 request a bathroom break?</p> <p>23 MR. SCHWARTZ: Sure.</p> <p>24 THE VIDEOGRAPHER: We're off the record</p> <p>25 at 9:46 a.m.</p>
<p style="text-align: right;">Page 257</p> <p>1 (Recess taken.)</p> <p>2 THE VIDEOGRAPHER: We are on the record</p> <p>3 at 9:49 a.m.</p> <p>4 BY MR. SCHWARTZ:</p> <p>5 Q. I asked you this yesterday,</p> <p>6 Dr. Romesberg, and I think you agree that Tsien</p> <p>7 doesn't provide any data showing that any 3' block</p> <p>8 nucleotide works for DNA sequencing, correct?</p> <p>9 MR. ZIMMERMAN: Objection. Asked and</p> <p>10 answered by your own admission.</p> <p>11 THE WITNESS: Yes. I believe we had that</p> <p>12 discussion. And I believe I agreed with that.</p> <p>13 BY MR. SCHWARTZ:</p> <p>14 Q. And Tsien's application is entirely</p> <p>15 prophetic, right?</p> <p>16 A. On this subject, yes. I'd have to go</p> <p>17 back and -- I did not have that in mind as I read</p> <p>18 it, so it is possible that there were spots that</p> <p>19 had data. I did look at the patent in regards to</p> <p>20 this particular issue, and there is no data.</p> <p>21 Q. And in contrast to Tsien's prophetic</p> <p>22 patent application, Metzker 1994 does provide data</p> <p>23 for a number of 3' block nucleotides for use in DNA</p> <p>24 sequencing, right?</p> <p>25 A. Metzker provides data for, I think, eight</p>	<p style="text-align: right;">Page 258</p> <p>1 O-modified nucleotides.</p> <p>2 Q. So a person of ordinary skill who is</p> <p>3 developing nucleotides for use in SBS in the 2000</p> <p>4 time frame, it's fair to say that they would give</p> <p>5 more weight to Metzker's paper that does provide</p> <p>6 data than Tsien's prophetic application that is</p> <p>7 completely devoid of data, correct?</p> <p>8 A. On certain issues that -- data certainly</p> <p>9 is important. And I think that there are -- people</p> <p>10 would have weighted that data differently and</p> <p>11 certainly more impactfully. They would have --</p> <p>12 seeing is believing.</p> <p>13 So I just don't want to say in any way that</p> <p>14 they would have then dismissed a good idea, whether</p> <p>15 you viewed Tsien's idea as good or not.</p> <p>16 The downside of data is that it is a</p> <p>17 specific question, and you can only get answers to</p> <p>18 specific questions.</p> <p>19 So it is difficult to interpret data that i</p> <p>20 negative as being -- it is difficult to know how</p> <p>21 general a negative result is.</p> <p>22 Q. I think my question may have been a</p> <p>23 little bit different, which is, given that Metzker</p> <p>24 actually provided data for 3'-O protecting groups</p> <p>25 for use in DNA sequencing, is it fair to say that a</p>

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1 skilled artisan would give more weight to a paper
2 with data in terms of understanding how those 3'-O
3 protecting groups would work for DNA sequencing
4 than another application that is entirely
5 prophetic?
6 A. I mean, I understand what you are saying,
7 and in one perspective I agree with that because,
8 like I said, data speaks louder than suggestions.
9 Seeing is believing. But at the same time, there
10 is always the caveat -- because, as I said,
11 experimental data always is a specific experiment.
12 It answers a specific question.
13 And you may look at that and say, well, tha
14 is not the question exactly I wanted, or I think tha
15 I could optimize this. There are a variety of
16 responses.
17 In general, certainly seeing is
18 believing, and you want to see data. That is
19 always good.
20 So, yeah, what you're saying is certainly
21 sort of true, but at the same time, a good idea is a
22 good idea. And sometimes people want to pursue it
23 more than someone else might.
24 **Q. I think -- again, I'm not sure that you**
25 **are responding directly to my question, which is,**

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1 specific questions and only those specific
2 questions, then you might not want to dismiss an
3 entire idea based on one particular set of data.
4 **Q. Please go back to Exhibit 2035, your**
5 **deposition transcript in IPR2013-00517.**
6 A. I'm there.
7 **Q. And please turn to Page 99, and starting**
8 **with the first full sentence, halfway through it**
9 **states -- the transcript reads -- I'm sorry, the**
10 **transcript reads "There are lots of read lengths**
11 **that would simply never be useful for sequencing by**
12 **synthesis. A read length of one is just an**
13 **example. You would never be able to do anything**
14 **with that."**
15 That is what you said, right?
16 A. That is what is written.
17 **Q. So your testimony is there are lots of**
18 **read lengths that would simply never be useful for**
19 **sequencing by synthesis, and a read length of one**
20 **is an example.**
21 A. For sequencing by synthesis, I believe
22 that is what I was saying, yes.
23 **Q. Please go back to Exhibit 2007. That is**
24 **your declaration in IPR2013-00517.**
25 A. I'm sorry, what declaration?

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1 if you have a situation where you have a paper and
2 suppose that you are interested in developing 3'-O
3 protecting groups for DNA sequencing, you have a
4 paper that actually tests 3'-O protecting groups?
5 A. See, that is the problem. So you can
6 make the suggestion that you could use 3'-O
7 protecting groups, and you cannot address that
8 question in a single paper. You cannot fully
9 address that question.
10 So you can look at the results from any
11 one paper and you can look at the specific
12 experiments that were run, and you get data there.
13 And if you believe the data, then that is the
14 answer. But a question is often much broader than
15 an experimental result.
16 So you would not necessarily dismiss an
17 entire idea based on one piece of data, or two piece
18 of data. You might have optimism that you could
19 optimize the experiment or that it could be run
20 differently or in the case that we are talking about
21 you could use different polymerases or whatever, but
22 my point is that on any experimental result where
23 there is a result, you would believe that data more
24 than you would believe a suggestion, obviously.
25 But to the extent that data answers

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1 **Q. The IPR2013-00517. It is Exhibit 2007.**
2 A. Yes.
3 **Q. Please turn to Page 23. Please look at**
4 **the first full sentence. And the sentence reads**
5 **"This reaction was performed in methanol, which was**
6 **known to denature DNA. See infer at paragraph 55.**
7 **Required two hours and resulted in only 75 to**
8 **91 percent yield." And you cite to the Loubinoux**
9 **paper. "Further, stannous chloride, SnCl₂, was**
10 **known to damage DNA by causing nicks in DNA**
11 **strands." And you cite to a Dontis 1999 paper.**
12 And you write "Any one of these
13 considerations would have led one of ordinary skill
14 to have expected stannous chloride to be
15 incompatible with Tsien's and Ju's requirements for
16 sequencing by synthesis."
17 That is what you wrote, correct?
18 A. That is correct. That is what is
19 written.
20 **Q. And it is your opinion that a**
21 **deprotection reaction that requires two hours is**
22 **incompatible with Tsien's SBS methods, correct?**
23 A. That is not exactly correct, no.
24 **Q. That is what you wrote.**
25 MR. ZIMMERMAN: Objection.

<p style="text-align: right;">Page 263</p> <p>1 Mischaracterizes.</p> <p>2 THE WITNESS: That is not what I intended</p> <p>3 to write.</p> <p>4 BY MR. SCHWARTZ:</p> <p>5 Q. Did you write it?</p> <p>6 MR. ZIMMERMAN: Objection.</p> <p>7 Mischaracterizes.</p> <p>8 THE WITNESS: I wrote the words that are</p> <p>9 there. You are interpreting it differently than I</p> <p>10 intended.</p> <p>11 BY MR. SCHWARTZ:</p> <p>12 Q. Do you not say that any one of these</p> <p>13 considerations would have led one of ordinary skill</p> <p>14 to have expected stannous chloride to be</p> <p>15 incompatible with Tsien's and Ju's requirements for</p> <p>16 sequencing by synthesis?</p> <p>17 A. That is what I wrote. And that is what I</p> <p>18 meant.</p> <p>19 Q. And any one of those requirements</p> <p>20 included the two hours?</p> <p>21 A. Can I explain it?</p> <p>22 Q. Did you write that?</p> <p>23 A. I would like to explain it.</p> <p>24 Q. Can you answer my question first?</p> <p>25 A. You can read it. That is correct.</p>	<p style="text-align: right;">Page 264</p> <p>1 Q. And so you wrote it?</p> <p>2 A. It's written. Two hours with 80 percent</p> <p>3 yield is very different than two hours</p> <p>4 quantitative.</p> <p>5 So the time is inseparable from the yield.</p> <p>6 Those are related things. So -- because I know wher</p> <p>7 you are going with this, just be clear that my</p> <p>8 criteria for two hours, that is influenced by the</p> <p>9 fact that it is 90 percent yield. So just to be</p> <p>10 clear.</p> <p>11 Q. So if the yield is not satisfactory, two</p> <p>12 hours is certainly not satisfactory with that</p> <p>13 yield. Is that what you are saying?</p> <p>14 A. I'm sorry. Could you repeat that?</p> <p>15 Q. If the deprotection yield is not</p> <p>16 satisfactory, then certainly two hours with that</p> <p>17 deprotection yield is not satisfactory?</p> <p>18 A. Certainly.</p> <p>19 Q. And that would not be compatible with</p> <p>20 Tsien's method?</p> <p>21 A. For any efficiency component of that. As</p> <p>22 we talked about yesterday, you can still do</p> <p>23 sequencing by synthesis, just not in any sort of</p> <p>24 efficient way that I believe Tsien required.</p> <p>25 Q. And that's true for SBS methods in</p>
<p style="text-align: right;">Page 265</p> <p>1 general. It's not just for Tsien, correct?</p> <p>2 A. For anything to be efficient, if you have</p> <p>3 a deprotection time that's part of the procedure</p> <p>4 then, yes, that would add time and make it</p> <p>5 effectively unrealistic to perform.</p> <p>6 Q. I am going to ask you to go back to the</p> <p>7 Metzker paper. The Metzker 1994 paper, I should</p> <p>8 say. It is Exhibit 1016.</p> <p>9 A. I have it.</p> <p>10 Q. And please go back to Table 2 on</p> <p>11 Page 4263. Yesterday we discussed how Table 2</p> <p>12 reports termination asterisk for the 3'-O-allyl</p> <p>13 dAPT with the Vent polymerase.</p> <p>14 Do you remember that?</p> <p>15 A. I remember the discussion.</p> <p>16 Q. And the asterisk indicates that there was</p> <p>17 incomplete termination, correct?</p> <p>18 A. That is what is written.</p> <p>19 Q. And if I understand your position from</p> <p>20 yesterday, the incomplete termination is the result</p> <p>21 of the natural dAPT contaminate being incorporated,</p> <p>22 which allows synthesis to continue.</p> <p>23 Is that your position?</p> <p>24 A. I think that would have been the likely</p> <p>25 suspicion of a POSA.</p>	<p style="text-align: right;">Page 266</p> <p>1 Q. And because of the natural dAPT</p> <p>2 contaminant you would end up with read through; is</p> <p>3 that correct?</p> <p>4 A. It would prevent termination.</p> <p>5 Q. And that would result in read through?</p> <p>6 A. It would prevent termination. So I think</p> <p>7 we're using -- I think we're saying the same thing.</p> <p>8 Q. So please turn to Page 4263, right</p> <p>9 column, second full paragraph. Halfway through</p> <p>10 that paragraph Metzker says in Figure 3B -- do you</p> <p>11 see that?</p> <p>12 A. I do.</p> <p>13 Q. Metzker writes in Figure 3B "The O-allyl</p> <p>14 template gel also shows the incorporation of 3'-O</p> <p>15 methyl dAPT, compound one, by AMV RT.</p> <p>16 In addition to termination, some read</p> <p>17 through was also observed due to the presence of</p> <p>18 contaminating dATP."</p> <p>19 That is what Metzker writes, correct?</p> <p>20 A. That is what is written.</p> <p>21 Q. So the read through reported for the 3'-O</p> <p>22 methyl dATP for AMV indicates that there was</p> <p>23 incomplete termination, correct?</p> <p>24 A. The read through indicates there was</p> <p>25 incomplete termination. I think those are the same</p>

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1 thing.

2 **Q. And so let's look at Table 2 and focus on**

3 **the 3'-O methyl dAPT with the AMV reverse**

4 **transcript, please.**

5 **Do you see that?**

6 A. Yes.

7 **Q. And Metzker reports that there was**

8 **complete termination, correct?**

9 A. That is correct.

10 **Q. And Metzker reports that there was**

11 **complete termination even though there was read**

12 **through, correct?**

13 A. Some read through he reports.

14 **Q. So the presence of read through caused by**

15 **the natural dAPT contaminant did not lead Metzker**

16 **to report incomplete termination for the 3'-O**

17 **methyl dAPT with that polymerase, correct?**

18 A. That is what is written. And what that

19 would mean is that the O-methyl is even better

20 incorporated.

21 **Q. But despite the presence of the read**

22 **through, Metzker reports that as complete**

23 **termination?**

24 A. I don't know how much read through was

25 there, but it might have been such a small amount

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1 cross-examination.

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1 that you still have -- I believe what termination

2 means here is that you produced a banding pattern

3 the same as the dideoxy.

4 Now, if there was a little bit of read

5 through but effectively you produced exactly that

6 same banding pattern, I believe that Metzker would

7 have called that complete termination. And that's

8 simply because the contaminating 1 percent dAPT just

9 didn't effectively prevent all those bands from bein

10 formed due to termination.

11 And I assume that's because the 3'-O methyl

12 is very competitive with the dAPT. And the 3' allyl

13 would have been less competitive with the dAPT.

14 So I think that's consistent with the

15 O-methyl being more competitive.

16 MR. SCHWARTZ: I would like to take a

17 break now and discuss whether I have any further

18 questions.

19 THE VIDEOGRAPHER: We are off the record

20 at 10:04 a.m.

21 (Recess taken.)

22 THE VIDEOGRAPHER: We are on the record

23 at 10:25 a.m.

24 MR. SCHWARTZ: Thank you, Dr. Romesberg.

25 I have no further questions on this

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1 EXAMINATION

2 BY MR. ZIMMERMAN:

3 **Q. Dr. Romesberg, I appreciate you being**

4 **here today and yesterday. I have a short series of**

5 **questions that I would like to run through with you**

6 **just to make sure we have a clear record.**

7 **If you could look at Exhibit 1001.**

8 MR. SCHWARTZ: Would you just give me a

9 chance to get a pad?

10 MR. ZIMMERMAN: Sure.

11 THE WITNESS: What is Exhibit 1001?

12 MR. ZIMMERMAN: Give me just a second.

13 BY MR. ZIMMERMAN:

14 **Q. So it's the '852 Ju patent.**

15 A. Yes.

16 **Q. Do you recall yesterday you were asked**

17 **some questions about what small means in the**

18 **context of Ju?**

19 A. I do.

20 **Q. And you cited to Ju's teaching of MOM and**

21 **allyl?**

22 A. I did.

23 **Q. I went back and looked at that testimony,**

24 **and you indicated that both MOM and allyl have**

25 **three carbons; is that correct?**

<p style="text-align: right;">Page 271</p> <p>1 A. Yes.</p> <p>2 Q. If you look at Column 8 of Ju at Line 26.</p> <p>3 A. Yes.</p> <p>4 Q. Do you see there is preference to, quote,</p> <p>5 "A small chemical moiety such as."</p> <p>6 A. I'm sorry. Where are you?</p> <p>7 Q. Line 25.</p> <p>8 A. Yes.</p> <p>9 Q. Column 8. You will see it reads "A small</p> <p>10 chemical moiety such as CH₂OCH₃ or CH₂CH-double</p> <p>11 bond-CH₂?</p> <p>12 A. Yes.</p> <p>13 Q. What is the second compound there?</p> <p>14 A. That is the allyl.</p> <p>15 Q. And what is the first compound?</p> <p>16 A. That is the MOM.</p> <p>17 Q. And does that show MOM as having three</p> <p>18 carbons?</p> <p>19 A. Did I say three carbons? I apologize. I</p> <p>20 meant three atoms.</p> <p>21 Q. So let me ask you the question again. Do</p> <p>22 MOM and allyl both have three carbons?</p> <p>23 A. No, I'm sorry.</p> <p>24 Q. How many carbons does allyl have?</p> <p>25 A. Allyl has three carbons.</p>	<p style="text-align: right;">Page 272</p> <p>1 Q. And how many carbons does MOM have?</p> <p>2 A. It has two carbons.</p> <p>3 Q. Leaving aside hydrogen, how many atoms</p> <p>4 does MOM have?</p> <p>5 A. Three.</p> <p>6 Q. And leaving aside hydrogen, how many</p> <p>7 atoms does allyl have?</p> <p>8 A. Three.</p> <p>9 Q. If we could turn to the Tsien patent,</p> <p>10 which is Exhibit 1013.</p> <p>11 A. Yes.</p> <p>12 Q. Do you have that in front of you?</p> <p>13 A. Yes.</p> <p>14 Q. Do you recall there was some discussion</p> <p>15 during your examination of Example 2?</p> <p>16 A. Could you direct me to that?</p> <p>17 Q. Yes. It is on Page 36 and spans over to</p> <p>18 Page 37.</p> <p>19 A. Yes, I do.</p> <p>20 Q. And there was some discussion, if you</p> <p>21 will recall, about the concentrations in that</p> <p>22 example, correct?</p> <p>23 A. Yes. On Page 35, Example 2?</p> <p>24 Q. Yes.</p> <p>25 A. Yes, I think I remember.</p>
<p style="text-align: right;">Page 273</p> <p>1 Q. And then there was comparisons of those</p> <p>2 concentrations to other references?</p> <p>3 MR. SCHWARTZ: I just want to make an</p> <p>4 objection. I don't believe that there was any</p> <p>5 testimony about Example 2.</p> <p>6 MR. ZIMMERMAN: Okay.</p> <p>7 BY MR. ZIMMERMAN:</p> <p>8 Q. I may have misspoken. If you will turn</p> <p>9 to Page 38.</p> <p>10 A. Yes. Correct.</p> <p>11 Q. Do you see Example 4?</p> <p>12 A. Yes.</p> <p>13 Q. Do you recall some discussion about the</p> <p>14 concentrations in Example 4?</p> <p>15 A. Yes.</p> <p>16 Q. Was that the only example of Tsien that</p> <p>17 you were pointed to with respect to concentrations</p> <p>18 during your examination?</p> <p>19 A. I believe it was.</p> <p>20 Q. Does Tsien have other examples?</p> <p>21 A. Yes. He has six examples, I believe.</p> <p>22 Q. And does Tsien in its teaching have any</p> <p>23 requirements with respect to concentrations?</p> <p>24 A. No.</p> <p>25 Q. You can put that aside.</p>	<p style="text-align: right;">Page 274</p> <p>1 Do you recall a number of discussions</p> <p>2 during your examination about a POSA?</p> <p>3 A. Yes, I do.</p> <p>4 Q. And you were asked to assume that a POSA</p> <p>5 was a person -- in October of 2000?</p> <p>6 A. That is correct.</p> <p>7 Q. Is it safe to say that a person of</p> <p>8 ordinary skill in the art, if we assume October of</p> <p>9 2000, wouldn't have had knowledge of articles that</p> <p>10 were published after that?</p> <p>11 A. That is correct.</p> <p>12 Q. Can we agree that the Metzker 2011</p> <p>13 article, Exhibit 2025, was published after</p> <p>14 October 2000?</p> <p>15 A. Yes.</p> <p>16 Q. And can we agree that the Metzker 2007</p> <p>17 article, Exhibit 1017, was published after</p> <p>18 October 2000?</p> <p>19 A. Yes.</p> <p>20 Q. And the new one that was marked today,</p> <p>21 Exhibit 1089, by Hamed, which was published in</p> <p>22 2001, can we agree that was after October 2000?</p> <p>23 A. Yes.</p> <p>24 Q. So would a person of ordinary skill in</p> <p>25 the art as you've defined them have access to those</p>

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1 articles?
2 A. No.
3 Q. I would like you to look at the Metzker
4 '94 article, which is Exhibit 1016.
5 Do you have that?
6 A. I do.
7 Q. So between the publication of this paper
8 and October of 2000, did Dr. Metzker publish any
9 retraction or correction of this paper, to your
10 knowledge?
11 A. Not to my knowledge.
12 Q. And are you aware of any publication by
13 Metzker or anyone in his group or anyone who
14 reviewed this, that indicated the data in this
15 publication was incorrect between '94 and
16 October 2000?
17 A. No, I do not believe there were any such
18 publications.
19 Q. Now, if you look at Table 2 on Page 4263.
20 A. Yes, I'm there.
21 Q. Entry No. 3.
22 A. Yes.
23 Q. 3'-O-allyl modified dATP?
24 A. That is correct.
25 Q. Can you tell me if that is a single


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1 THE VIDEOGRAPHER: We're on the record at
2 10:41 a.m.
3 MR. SCHWARTZ: Dr. Romesberg, we don't
4 have any recross. Thank you for your time today.
5 THE WITNESS: You are welcome.
6 MR. ZIMMERMAN: Thank you.
7 THE VIDEOGRAPHER: This concludes today's
8 deposition of Floyd Romesberg, Ph.D. We are off
9 the record at 10:41 a.m.
10 (The videotaped deposition of
11 FLOYD ROMESBERG, PH.D., VOLUME II,
12 concluded at 10:41 a.m.)
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1 compound or multiple compounds?
2 A. That should be a single compound as he
3 has shown it here. He shows the structure of that
4 compound in Figure 2.
5 Q. And is that a substituted allyl?
6 A. No, that is just the canonical allyl
7 group.
8 Q. Are there any other 3'-O allyls in the
9 Metzker '94 paper?
10 A. No, there's not.
11 Q. Does he describe a genus of 3'-O allyls?
12 A. No, he does not.
13 Q. Does he describe a substituted
14 3'-O allyl?
15 A. Not to my knowledge, no.
16 Q. So the only 3'-O allyl in Metzker,
17 Table 2, is the one there?
18 A. Yes, that is correct.
19 MR. ZIMMERMAN: I have no further
20 questions at this time.
21 MR. SCHWARTZ: We can go off the record
22 and take a break.
23 THE VIDEOGRAPHER: Going off the record
24 at 10:35 a.m.
25 (Recess taken.)

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1 I, the undersigned, a Certified Shorthand
2 Reporter of the State of California, do hereby
3 certify:
4 That the foregoing proceedings were taken
5 before me at the time and place herein set forth;
6 that any witnesses in the foregoing proceedings,
7 prior to testifying, were duly sworn; that a
8 verbatim record of the proceedings was made by me
9 using machine shorthand which was thereafter
10 transcribed under my direction; that the foregoing
11 transcript is a true record of the testimony given.
12 Further, that if the foregoing pertains to the
13 original transcript of a deposition in a Federal
14 Case, before completion of the proceedings, review
15 of the transcript [X] was [] was not requested.
16 I further certify I am neither financially
17 interested in the action nor a relative or employee
18 of any attorney of party to this action.
19 IN WITNESS WHEREOF, I have this date
20 subscribed my name.
21 Dated: September 21, 2018
22
23 
24 PATRICIA Y. SCHULER
25 CSR NO. 11949

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1 DECLARATION UNDER PENALTY OF PERJURY

2 Case Name: Illumina, Inc. vs. The Trustees of Columbia
University in the City of New York

3 Date of Deposition: 09/20/2018

4 Job No.: 10047003

5

6 I, FLOYD ROMESBERG, PH.D., hereby certify

7 that I have read the transcript of my deposition and that

8 this transcript accurately states the testimony given by me,

9 with the changes or corrections, if any, as noted on an errata

10 sheet or errata sheets.

11 Executed this _____ day of

12 _____, 2018, at _____.

13

14 _____

15 FLOYD ROMESBERG, PH.D.

16 NOTARIZATION (If Required)

17 State of _____

18 County of _____

19 Subscribed and sworn to (or affirmed) before me on

20 this _____ day of _____, 20____,

21 by _____, proved to me on the

22 basis of satisfactory evidence to be the person

23 who appeared before me.

24 Signature: _____ (Seal)

25

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1 DEPOSITION ERRATA SHEET

2 Page _____ Line _____ Reason _____

3 From _____ to _____

4 Page _____ Line _____ Reason _____

5 From _____ to _____

6 Page _____ Line _____ Reason _____

7 From _____ to _____

8 Page _____ Line _____ Reason _____

9 From _____ to _____

10 Page _____ Line _____ Reason _____

11 From _____ to _____

12 Page _____ Line _____ Reason _____

13 From _____ to _____

14 Page _____ Line _____ Reason _____

15 From _____ to _____

16 Page _____ Line _____ Reason _____

17 From _____ to _____

18 Page _____ Line _____ Reason _____

19 From _____ to _____

20 Page _____ Line _____ Reason _____

21 From _____ to _____

22 _____ Subject to the above changes, I certify that the

23 transcript is true and correct

24 _____ No changes have been made. I certify that the

25 transcript is true and correct.

FLOYD ROMESBERG, PH.D.

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1 DEPOSITION ERRATA SHEET

2 Case Name: Illumina, Inc. vs. The Trustees of Columbia
University in the City of New York

3 Name of Witness: Floyd Romesberg, Ph.D.

4 Date of Deposition: 09/20/2018

5 Job No.: 10047003

6 Reason Codes: 1. To clarify the record.

7 2. To conform to the facts.

8 3. To correct transcription errors.

9

10 Page _____ Line _____ Reason _____

11 From _____ to _____

12 Page _____ Line _____ Reason _____

13 From _____ to _____

14 Page _____ Line _____ Reason _____

15 From _____ to _____

16 Page _____ Line _____ Reason _____

17 From _____ to _____

18 Page _____ Line _____ Reason _____

19 From _____ to _____

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25 From _____ to _____

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