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

INTELLIGENT BIO-SYSTEMS, INC.

Petitioner,

v.

ILLUMINA CAMBRIDGE LTD.

Patent Owner.

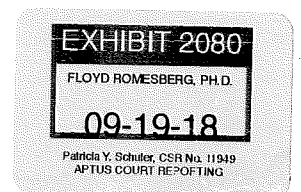
Case No. IPR2013-00128 (LMG)

U.S. Patent 7,057,026

VIDEO DEPOSITION OF FLOYD ROMESBERG, PH.D.

JANUARY 14, 2014

Reported by: Margaret A. Smith, CSR #9733, RPR, CRR



Columbia Exhibit 2080
Illumina, Inc. v. The Trustees
of Columbia University in the
City of New York
IPR2018-00291, 318, 322, 385 & 797

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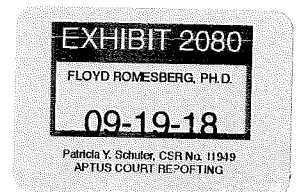
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Intelligent Bio-Systems, Inc.
Exhibit 1033

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1 APPEARANCES

2

3 FOR PETITIONER:

4 BALLARD SPAHR LLP

5 BY: SCOTT D. MARTY, PH.D., ESQUIRE

6 BY: JASON P. GRIER, ESQUIRE

7 999 Peachtree Street, Suite 1000

8 Atlanta, Georgia 30309

9 678.420.9301

10 martys@ballardspahr.com

11 grierj@ballardspahr.com

12

13 FOR PATENT OWNER:

14 KNOBBE MARTENS

15 BY: BRENTON R. BABCOCK, ESQUIRE

16 2040 Main Street, 14 Floor

17 Irvine, California 92614

18 949.760.0404

19 brent.babcock@knobbe.com

20

21

22

23

24

25

1 APPEARANCES continued:

2

3 FOR PATENT OWNER:

4 KNOBBE MARTENS

5 BY: NATHANAEL R. LUMAN, PH.D., J.D., ESQUIRE

6 12790 El Camino Real

7 San Diego, California 92130

8 858.707.4000

9 nate.luman@knobbe.com

10

11 THE VIDEOGRAPHER:

12 JORDAN MEDIA, INC.

13 BY: ALAN PEAK

14 1228 Madison Avenue

15 San Diego, California 92116

16 619.299.5040

17

18 ALSO PRESENT: MARCUS BURCH

19

20 DEPOSITION OF FLOYD ROMESBERG, PH.D., taken on

21 behalf of Petitioner, at 12790 El Camino Real,

22 San Diego, California, commencing on Tuesday,

23 January 14, 2014, at 9:08 a.m., before

24 Margaret A. Smith, Certified Shorthand Reporter,

25 CSR No. 9733, RPR, CRR.

1 San Diego, California; January 14, 2014; 9:08 a.m.

2

3 VIDEOGRAPHER: This is the -- this is the

09:08:12 4 deposition of Dr. Floyd Romesberg, testifying in the

09:08:16 5 matter Intelligent Bio-Systems, Inc., versus Illumina

09:08:20 6 Cambridge in the U.S. Patent Trial and Appeals Board.

09:08:26 7 Case No. IPR2013-00128.

09:08:30 8 This deposition is being held in the offices of

09:08:34 9 Knobbe Martens in San Diego, California, on

09:08:36 10 January 14th, 2014, at 9:08 a.m.

09:08:40 11 My name is Alan Peak, video legal specialist

09:08:44 12 with Jordan Media, Inc., 1228 Madison Avenue in

09:08:48 13 San Diego, California.

09:08:49 14 The certified shorthand reporter is Maggie

09:08:51 15 Smith with Kramm Court Reporting of San Diego.

09:08:52 16 Will counsel please state their appearances for

09:08:54 17 the record.

09:08:55 18 MR. GRIER: My name is Jason Grier from the law

09:08:55 19 firm Ballard Spahr. I'm backup counsel for Petitioner

09:08:55 20 Intelligent Bio-Systems, Inc., in this matter, and with

09:08:55 21 me today is lead counsel, Dr. Scott Marty.

09:08:57 22 MR. BABCOCK: And for the patent owner,

09:08:57 23 Illumina, I'm Brent Babcock with Knobbe Martens. Also

09:08:57 24 with me is Nate Luman, and a representative of Illumina

09:08:57 25 is here, Marcus Burch.

09:09:19 1 VIDEOGRAPHER: And the witness may now be
09:09:20 2 sworn.

09:09:21 3
09:09:21 4 FLOYD ROMESBERG, PH.D.,
09:09:21 5 having been first duly sworn, was examined and testified
09:09:21 6 as follows:

09:09:21 7

09:09:21 8 CROSS-EXAMINATION

09:09:33 9 BY MR. GRIER:

09:09:34 10 Q Good morning, Dr. Romesberg.

09:09:36 11 A Good morning.

09:09:36 12 Q Thank you for your time today. I'll just dive
09:09:40 13 right in here.

09:09:41 14 So could you please state your full name and
09:09:43 15 address for the record.

09:09:45 16 A Floyd Eric Romesberg. I am embarrassed to say
09:09:50 17 that -- my address is on my license. I live in
09:09:55 18 La Jolla, Camino Del Sur Road. I --

09:10:00 19 Q No. I think that --

09:10:03 20 A -- forget my address.

09:10:04 21 Q That's fine.

09:10:05 22 Dr. Romesberg, have you ever been deposed
09:10:08 23 before?

09:10:08 24 A I have not.

09:10:09 25 Q Okay. So this is your first one. We'll try to

09:10:11 1 make it fun for you.

09:10:13 2 So do you understand today that you are under
09:10:15 3 oath, and by that, you are sworn to tell the truth?

09:10:19 4 A I do.

09:10:19 5 Q Okay. And you also understand that even though
09:10:22 6 we're not in a court today, your answers have the same
09:10:25 7 force and effect as if we were in a court before a judge
09:10:27 8 and a jury?

09:10:28 9 A I do.

09:10:29 10 Q Okay. And are you prepared to answer my
09:10:31 11 questions today?

09:10:32 12 A I am.

09:10:33 13 Q Is there anything that will prevent you from
09:10:36 14 giving me your full attention today?

09:10:37 15 A No.

09:10:37 16 Q So you're not taking any medications or
09:10:40 17 suffering from any illnesses that would prevent you from
09:10:42 18 understanding my questions and answering them fully?

09:10:44 19 A No.

09:10:45 20 Q Okay. So throughout the day, I'm going to ask
09:10:47 21 you a series of questions. If at any time you don't
09:10:50 22 understand a question, please feel free to let me know,
09:10:53 23 ask me to clarify it or rephrase it, and I'll be happy
09:10:56 24 to do that as best I can.

09:10:59 25 But can we work under the assumption that if I

09:11:01 1 ask you a question today and you don't tell me that you
09:11:05 2 don't understand it, then we can assume that you
09:11:07 3 understand the question?

09:11:09 4 A Yes.

09:11:09 5 Q Okay. Also, throughout the day, your counsel
09:11:10 6 will likely interpose objections. Unless you're
09:11:13 7 instructed by counsel not to answer the question, just
09:11:16 8 go ahead and answer the question I've asked.

09:11:18 9 Do you understand?

09:11:19 10 A Yes.

09:11:19 11 Q Okay. Also, as you know today, we have a court
09:11:23 12 reporter transcribing the deposition. So throughout the
09:11:25 13 day, as you're answering, I would ask that you try to do
09:11:28 14 so verbally. Avoid hand gestures and "uh-huhs" and
09:11:31 15 things like that. And if that starts to happen, I'll --
09:11:35 16 I'll try to remind you.

09:11:37 17 Do you understand that?

09:11:38 18 A Yes. Thank you.

09:11:40 19 Q And, also, as I ask questions today, please do
09:11:43 20 your best not to talk over me, to let me ask the
09:11:45 21 question fully before responding, and I'll do the same
09:11:48 22 to you. I will try not to interrupt your answers as we
09:11:52 23 go forward today.

09:11:53 24 A Okay.

09:11:54 25 Q And I also try to take regular breaks, but if

09:11:58 1 at any time you need a break, please just let me know,
09:12:01 2 and -- and we can have -- we can take a break. The only
09:12:04 3 thing I would ask is that if there is a question
09:12:06 4 pending, that you answer the outstanding question before
09:12:08 5 we break.

09:12:09 6 Do you understand?

09:12:10 7 A Yes.

09:12:10 8 Q Okay. So, Dr. Romesberg, have you ever served
09:12:14 9 as an expert witness?

09:12:19 10 A Excuse me. I am currently serving as an expert
09:12:22 11 witness for -- in a lawsuit of -- where Roche is being
09:12:28 12 sued.

09:12:28 13 Q Okay.

09:12:30 14 A Excuse me. But before that, no. No.

09:12:36 15 Q And -- and whom do you -- who -- what side are
09:12:38 16 you serving as an expert for in that case?

09:12:40 17 A Roche.

09:12:43 18 Q And who is involved in that case, the parties?

09:12:48 19 I'm sorry.

09:12:48 20 A Roche is being sued by a small company called
09:12:52 21 En- -- Enzo -- Enza -- Enzo.

09:12:58 22 MR. BABCOCK: Water?

09:13:00 23 THE WITNESS: Yeah. Thank you.

09:13:01 24 BY MR. GRIER:

09:13:02 25 Q And is that a patent infringement matter?

09:13:05 1 A It is.

09:13:06 2 Q And when were you retained by Roche in that
09:13:09 3 case?

09:13:10 4 A About a year ago.

09:13:23 5 MR. GRIER: Can I see that declaration, 2009.
09:13:36 6 Start with the original first.

09:13:43 7 BY MR. GRIER:

09:13:44 8 Q Dr. Romesberg, I'll hand you what's been
09:13:48 9 previously marked Illumina Exhibit 2009. This is your
09:13:53 10 original declaration.

09:13:54 11 Do you recognize this document?

09:13:55 12 A I do.

09:13:59 13 Q Is this a copy of the document -- a copy of the
09:14:03 14 declaration you submitted -- the original declaration
09:14:05 15 you submitted in this IPR?

09:14:09 16 A Yes, it appears to be.

09:14:10 17 Q If you look at the last page, page 36 of your
09:14:13 18 declaration, is that your signature?

09:14:15 19 A It is.

09:14:15 20 Q And you signed the declaration October 24th,
09:14:18 21 2013. Is that correct?

09:14:19 22 A Yes. It -- yes, that is correct.

09:14:22 23 Q Okay. So, Dr. Romesberg, turning back to the
09:14:34 24 Roche case, so in your capacity as an expert in that
09:14:37 25 case, have you ever offered any testimony?

09:14:40 1 A No.

09:14:44 2 Q So you've never been deposed in that case?

09:14:46 3 A No.

09:14:49 4 Q So are you serving as a technical expert,

09:14:52 5 then --

09:14:52 6 A Yes.

09:14:52 7 Q -- in that case?

09:14:54 8 A And my understanding is that I will not

09:14:56 9 testify. I will -- I will not be deposed.

09:14:58 10 Q Okay. Dr. Romesberg, have you ever testified

09:15:08 11 in court for any reason?

09:15:09 12 A No, I have not.

09:15:10 13 Q And have you ever offered a declaration to the

09:15:12 14 patent office before?

09:15:16 15 A A -- I'm not sure I understand. Is it -- would

09:15:18 16 a patent be a declaration?

09:15:20 17 Q No. A declaration -- so -- so, like, the

09:15:24 18 declaration that you have signed here, that -- that

09:15:25 19 we've submitted -- that counsel submitted to the PTAB --

09:15:28 20 A No.

09:15:29 21 Q -- have you ever sent a declaration like this

09:15:33 22 to the patent office? Okay.

09:15:35 23 So in the procurement of your patents, you've

09:15:40 24 never submitted a declaration to the patent office?

09:15:44 25 A (Gesturing).

09:15:44 1 Q Okay.

09:15:45 2 THE REPORTER: Verbal answer.

09:15:46 3 THE WITNESS: No.

09:15:47 4 MR. GRIER: Thank you.

09:15:47 5 THE REPORTER: Thank you.

09:15:47 6 BY MR. GRIER:

09:15:47 7 Q Dr. Romesberg, you're being compensated for

09:15:50 8 your role as an expert in this IPR. Correct?

09:15:53 9 A Correct.

09:15:54 10 Q And you're being compensated at a rate of 450

09:15:56 11 an hour. Correct?

09:15:58 12 A That is correct.

09:15:58 13 Q And by whom are you paid for your role in this

09:16:02 14 IPR?

09:16:03 15 A I believe Knobbe Martens.

09:16:06 16 Q And approximately how much time have you spent

09:16:09 17 on your IPR to date?

09:16:17 18 A I would estimate 25 hours, 30 hours. Maybe --

09:16:23 19 maybe 45. Somewhere right in there.

09:16:38 20 Q And how much of that time that you spent to

09:16:40 21 date has been preparing your declaration?

09:16:46 22 A The -- oh, about half.

09:16:52 23 Q So around 22, 23 hours?

09:16:57 24 A Yeah. Twenty-five hours, I guess, something

09:16:59 25 like that.

09:17:06 1 Q And the other 20 hours, has that been preparing
09:17:09 2 for deposition?

09:17:10 3 A That and just reading.

09:17:23 4 Q Dr. Romesberg, does your compensation for your
09:17:25 5 role in this IPR depend on the opinions you render in
09:17:29 6 this case?

09:17:29 7 A No, it does not.

09:17:37 8 Q Is it your understanding that you've been
09:17:38 9 retained by Knobbe Martens in this case?

09:17:40 10 A It is.

09:17:40 11 Q Okay. And by who at Knobbe were you retained?

09:17:44 12 A Well, I was contacted by Nate and Kerry, Nate
09:17:53 13 Luman in this room, originally. I'm not sure if that's
09:17:57 14 who I was retained -- by whom I was retained.

09:18:01 15 Q And when did Nate and Kerry first contact you?

09:18:08 16 A My recollection is maybe early October. Maybe
09:18:21 17 late September.

09:18:21 18 Q Did you have any contact with any lawyers at
09:18:23 19 Knobbe prior to when you were retained in this action?

09:18:27 20 A No, I did not.

09:18:28 21 Q Okay. And presumably you executed an
09:18:34 22 engagement letter. Correct?

09:18:36 23 A I don't know. I -- I assume -- I assume that's
09:18:40 24 correct.

09:18:42 25 Q Do you recall -- do you recall seeing an

09:18:44 1 engagement letter from -- from Knobbe regarding your
09:18:48 2 serving as an expert in this case?

09:18:49 3 A I -- I think so, but to be honest, with that
09:18:52 4 sort of material, my administrative assistant runs
09:18:55 5 things past me that I've agreed on and that I sign. And
09:18:58 6 so I tend not to be as -- I tend to have less of a
09:19:04 7 recollection. I -- I -- I think I -- that was the case.
09:19:07 8 But I don't have a distinct recollection of doing that.

09:19:09 9 Q So in that circumstance, your administrative
09:19:13 10 assistant will say, you know, review this briefly and --
09:19:15 11 and sign off on it? Is that how that would work?

09:19:19 12 A No. She would -- she would take things that I
09:19:21 13 already agreed to that I told her to take care of, and
09:19:24 14 then she would just say, here, make sure you sign this.
09:19:27 15 And I would, I assume, have read that earlier, and she
09:19:30 16 would have then printed it at some later time and given
09:19:33 17 it to me to sign to take care of and send it to the
09:19:36 18 appropriate place.

09:19:43 19 Q So going back, Dr. Romesberg, relating to your
09:19:50 20 compensation in this case, does your compensation -- you
09:19:52 21 testified your compensation does not depend on the
09:19:55 22 opinions rendered in this case. Correct?

09:19:56 23 A Correct.

09:19:57 24 Q Does your compensation depend on the successful
09:20:01 25 outcome for Illumina in this case?

09:20:03 1 A No. No. It -- I was told no.

09:20:08 2 Q And with respect to the engagement letter,

09:20:12 3 again, you testified that you didn't recall seeing it.

09:20:15 4 Correct?

09:20:18 5 A I don't explicitly recall seeing it.

09:20:20 6 Q But that -- it's likely that your

09:20:22 7 administrative assistant saw it and -- and you signed

09:20:24 8 off on it?

09:20:25 9 A Oh, I'm sure I read it, but I don't recall the

09:20:28 10 time that I read it and sat down. I read a lot of that

09:20:31 11 kind of stuff, and I just don't have an explicit memory

09:20:34 12 of that.

09:20:40 13 Q Is that how it worked with your declaration in

09:20:42 14 this IPR?

09:20:43 15 A No. No.

09:20:48 16 Q So you mentioned you were first contacted by

09:20:50 17 Nate and Kerry from Knobbe.

09:20:55 18 How -- how did they contact you?

09:20:57 19 A By email. I believe they asked if I had a

09:21:03 20 moment to talk, and we then spoke by phone.

09:21:06 21 Q And were you contacted by anyone at Illumina

09:21:09 22 about serving as an expert in this IPR?

09:21:12 23 A No. I -- I was not, nor have I -- have I been.

09:21:15 24 Marcus is the first person I've spoken with, and that

09:21:18 25 was only recently.

09:21:24 1 Q And have you ever worked with the Knobbe firm
09:21:28 2 before?
09:21:28 3 A No.
09:21:29 4 Q Did you know of the Knobbe law firm before you
09:21:34 5 were --
09:21:34 6 A No.
09:21:35 7 Q -- retained in this IPR?
09:21:37 8 A And I'm still not sure exactly how to pronounce
09:21:40 9 it.
09:21:40 10 MR. GRIER: Neither am I.
09:21:42 11 MR. BABCOCK: Jason has got it right.
09:21:43 12 MR. GRIER: It's -- it's been a struggle to
09:21:44 13 determine that.
09:21:44 14 MR. BABCOCK: Hard K. Think of Obi Wan Kenobi.
09:21:49 15 MR. GRIER: Ah. That's what I was going with,
09:21:50 16 so --
09:21:51 17 BY MR. GRIER:
09:21:51 18 Q Have you spoken with Scripps -- with anyone at
09:21:53 19 Scripps about your role in this IPR?
09:21:58 20 A I believe my administrative assistant is
09:22:00 21 required to notify -- we have a -- I don't know what
09:22:01 22 it's called -- an extra activities, outside activities
09:22:05 23 obligation through -- I think it's our ethics office or
09:22:10 24 something. And they just have to be aware of the amount
09:22:12 25 of time. Because we're -- my salary is paid by the NIH,

09:22:17 1 I can't -- my outside activities cannot exceed a certain
09:22:21 2 limit. And so there's sort of a standard recording
09:22:24 3 of -- of the sort of amount of outside act- -- time
09:22:28 4 spent on outside activities that we have to keep that
09:22:31 5 office appraised of. And so we did that.

09:22:35 6 Q Other than that, have you spoken with anyone
09:22:37 7 else at -- at Scripps about your role in this IPR?

09:22:42 8 A No.

09:22:45 9 Q And is it your understanding, Dr. Romesberg,
09:22:49 10 that your role in this IPR is to render an opinion as to
09:22:53 11 the validity of the proposed claims of the '026 patent?

09:22:57 12 A Yes.

09:23:01 13 Q And you were told -- were you told by anyone to
09:23:03 14 address the issue of validity?

09:23:08 15 A I don't think so. I think it may have come up
09:23:10 16 indirectly, and -- and I didn't -- I knew very little
09:23:14 17 about language and technical terms. And I think that
09:23:17 18 that probably came up sometime as -- as -- as in just
09:23:22 19 discussion. But I don't recall any event where I was
09:23:25 20 told anything particular.

09:23:27 21 Q And when you say "language and technical
09:23:31 22 terms," what are you referring to by that?

09:23:33 23 A Just like a technical definition of the word
09:23:37 24 "obvious" or "nonobvious" or "novelty." Because I --
09:23:46 25 because I did make statements in my declaration about

09:23:48 1 those.

09:23:49 2 Q Okay.

09:23:49 3 A And so I -- I wanted to make sure that I knew

09:23:52 4 exactly what those terms meant.

09:23:59 5 MR. GRIER: Okay. Can you hand me

09:24:00 6 Exhibit 1001, please.

09:24:02 7 BY MR. GRIER:

09:24:25 8 Q Dr. Romesberg, I will hand you what's been

09:24:27 9 previously marked IBS Exhibit 1001.

09:24:32 10 Do you recognize this document?

09:24:33 11 A I do.

09:24:35 12 Q Okay. And just to be clear, as we go forward

09:24:41 13 today, you see the top of the document on the first page

09:24:46 14 says "U.S. Patent No. 7057026"?

09:24:50 15 A I do.

09:24:50 16 Q Okay. So can we work under the assumption

09:24:52 17 today that when I refer to the "'026 patent," you

09:24:55 18 understand it to mean Exhibit 1001?

09:24:58 19 A Yes.

09:24:59 20 Q Okay. Thank you.

09:25:04 21 So you mentioned you had discussions about

09:25:06 22 language and -- and technical terms.

09:25:08 23 Who -- who did you have those discussions with?

09:25:11 24 A Nate and Kerry.

09:25:13 25 Q Did you discuss those terms with anyone else,

09:25:15 1 other than Nate and Kerry?

09:25:17 2 A No.

09:25:32 3 Q Dr. Romesberg, if we can please turn back to
09:25:35 4 Illumina Exhibit 2009.

09:25:42 5 And you previously testified that you recognize
09:25:45 6 this document. Correct?

09:25:45 7 A Yeah. It -- it appears to be my declaration,
09:25:48 8 yeah.

09:25:49 9 Q And did you draft this declaration,
09:25:52 10 Dr. Romesberg?

09:25:53 11 A I did.

09:25:54 12 Q Can you explain to me the process of how the
09:25:57 13 declaration was drafted.

09:25:59 14 A So after having read a lot of material, I -- I
09:26:04 15 came here to this room. And Kerry and -- and Nate went
09:26:10 16 through this -- had -- had parts of it written and then
09:26:14 17 went through it with me paragraph -- line by line, word
09:26:18 18 by word, sentence by sentence, and were very clear that
09:26:21 19 I had to edit and -- and -- and put my opinion in and
09:26:24 20 make sure that I fully, 100-percent agreed with
09:26:27 21 everything, and if I was at all uncomfortable with
09:26:29 22 any -- even a nuance, to -- to change it and edit it.

09:26:34 23 And I did so. I edited virtually the entire
09:26:37 24 document to try to put it more into my language and to
09:26:39 25 make sure that it was -- that it accurately reflected my

09:26:44 1 opinion.

09:26:45 2 Q Okay. So at that meeting, was there anyone
09:26:48 3 else present other than Nate and Kerry and yourself?

09:26:51 4 A No.

09:27:00 5 Q So you did not discuss, then, the process of
09:27:02 6 preparing the declaration with anyone at Illumina.
09:27:05 7 Correct?

09:27:05 8 A No.

09:27:05 9 Q You did not discuss the process of preparing
09:27:07 10 the declaration with anyone at Scripps. Correct?

09:27:10 11 A No, I did not.

09:27:10 12 Q Okay. So you mentioned, Dr. Romesberg, that
09:27:17 13 during the drafting process, there had been synthesis
09:27:24 14 prepared for you. Is that correct?

09:27:29 15 A Correct.

09:27:30 16 Q So did -- were you provided an outline of what
09:27:38 17 to cover in the declaration?

09:27:39 18 A No.

09:27:39 19 Q Okay. And I assume you communicated with
09:27:40 20 counsel, specifically Nate and Kerry, during the
09:27:44 21 drafting of the declaration. Correct?

09:27:45 22 A Correct.

09:27:45 23 Q And how often did you communicate with counsel
09:27:48 24 while drafting your declaration?

09:27:51 25 A In total, including phone calls and visits

09:27:53 1 here?

09:27:54 2 Q Sure. In total.

09:27:57 3 A Probably four phone calls and two visits, I

09:28:01 4 think. And as well as some exchange by email where I --

09:28:09 5 where I -- when I rewrote sections, I sent them. And

09:28:14 6 they added them to the dec.

09:28:18 7 Q And this -- and this four phone calls, how --

09:28:21 8 how long were those four phone calls, approximately?

09:28:24 9 A None of them long. I think they were mostly --

09:28:31 10 maybe 15 minutes, the longest.

09:28:35 11 Q You said the longest was --

09:28:37 12 A Yeah.

09:28:38 13 Q Okay.

09:28:39 14 A Correct.

09:28:40 15 Q What about the two visits; how long were the

09:28:42 16 two visits?

09:28:46 17 A There might have been three visits. I'm -- I'm

09:28:49 18 not exactly sure. But they would have -- I think -- my

09:28:51 19 recollection is that one was rather short, maybe a few

09:28:54 20 hours, and then the couple others were probably seven

09:28:57 21 hours-ish, eight hours, something like that.

09:29:01 22 Q And those longer visits, the seven to eight

09:29:04 23 hours, during those visits, is that when you -- when you

09:29:06 24 performed the process you described previously where you

09:29:09 25 sat here and edited and worked on the declaration?

09:29:15 1 A I think that's right.

09:29:20 2 Q And, again, you testified that there was no one
09:29:21 3 from Illumina or Scripps present at any one of those
09:29:25 4 meetings. Correct?

09:29:26 5 A That is correct.

09:29:27 6 Q Were there any other individuals present at
09:29:28 7 those meetings?

09:29:31 8 A No.

09:29:36 9 Q So, again, the only folks present there were
09:29:39 10 Nate and Kerry and yourself. Correct?

09:29:42 11 A I believe so, yes.

09:29:54 12 Q During the drafting of your declaration,
09:29:57 13 Dr. Romesberg, were you told by anyone what specifically
09:30:00 14 to assess or analyze in your declaration?

09:30:03 15 A I don't think explicitly. Just there was much
09:30:06 16 conversation about a lot -- I mean, the -- the -- when
09:30:09 17 we were drafting this and we would be talking about a
09:30:12 18 point, I think Nate and Kerry kind of let me talk. And
09:30:16 19 so we wandered over lots of different topics. And so
09:30:18 20 I -- I certainly don't recall -- I was certainly never
09:30:22 21 provided an -- there -- there was very little emphasis
09:30:27 22 on what -- what to talk about, other than -- than the
09:30:31 23 dec itself. And -- and, certainly, questions would come
09:30:36 24 up where they would ask me, well, you know, what do you
09:30:39 25 think about that. And I would give my opinion.

09:30:46 1 Q And since you prepared your declaration, have
09:30:48 2 you been asked to do any additional tasks?

09:30:53 3 A With this -- with this IPR?

09:30:57 4 Q Yes. With this IPR.

09:31:00 5 A No, I don't believe so.

09:31:02 6 Q Have you been asked to do any additional tasks
09:31:04 7 not related to this IPR?

09:31:06 8 A Yeah. I'm working -- yes. I'm working on a
09:31:09 9 second IPR with the same group.

09:31:11 10 Q By "same group," you mean Kerry and Nate. Is
09:31:15 11 that correct?

09:31:16 12 A Yes.

09:31:19 13 Q And it -- what is that second IPR,
09:31:22 14 Dr. Romesberg?

09:31:22 15 A It's a second IPR with IBS.

09:31:26 16 Q Is that the IPR dealing with what we commonly
09:31:32 17 refer to as the '346 patent.

09:31:35 18 A Correct.

09:31:39 19 Q Okay. Are you working on any other IPRs with
09:31:41 20 Kerry and Nate other than the IPR dealing with the '026
09:31:48 21 patent and the IPR dealing with the '346 patent?

09:31:53 22 A No.

09:31:54 23 Q Since preparing your original declaration,
09:31:57 24 Dr. Romesberg, have you had an opportunity to thoroughly
09:31:59 25 review it?

09:32:00 1 A Yes.

09:32:00 2 Q And when you thoroughly reviewed it, did you
09:32:02 3 find any errors in the declaration?

09:32:05 4 A Scientific errors?

09:32:07 5 Q We can start with scientific errors.

09:32:09 6 A No.

09:32:09 7 Q Did you find any other errors in the
09:32:13 8 declaration?

09:32:13 9 A To be honest, my policy, when I write anything,
09:32:14 10 is to try not to reread it, because I'm obsessive about
09:32:18 11 writing, and I always think there would have been a
09:32:21 12 better way to write something. But because of the
09:32:24 13 nature of this, I have reread this and broken that rule.
09:32:26 14 And there are probably parts that I would have written a
09:32:29 15 little bit differently. Not scientific issues but
09:32:32 16 issues of being clear and -- and -- and -- and making it
09:32:36 17 a readable document.

09:32:40 18 Q And what parts specifically would you have
09:32:42 19 written differently?

09:32:48 20 A I think I would have clarified more -- the --
09:32:53 21 the end of the document where -- where I'm discussing
09:32:56 22 the disulfide cleavage and 3' protecting cleavage, I
09:33:07 23 would have separated those more clearly. I think for
09:33:09 24 the reader, it would have clarified things a little bit.
09:33:12 25 There's nothing incorrect in it. I think it would have

09:33:16 1 read a little easier.

09:33:17 2 I might have gone -- in addition, I might have
09:33:19 3 gone into some more opinion about the Odedra patent and
09:33:24 4 why I disagreed with IBS expert witness.

09:33:28 5 Those are two things that jumped in my mind.

09:33:30 6 And maybe thirdly, I would have articulated
09:33:34 7 more of my intuition about the -- the claim, the belief
09:33:42 8 that a person of ordinary schooling in the art would
09:33:48 9 have assumed that cleavage at the 3' group would have
09:33:52 10 not been better than that demonstrated by Ruby and
09:33:56 11 Herman. And I assume we'll talk about all those today.

09:33:59 12 And if you would like me to articulate more on
09:34:02 13 my opinion about that. My opinion has not changed.

09:34:05 14 I -- I did not write it out as -- as -- as -- as -- I
09:34:09 15 did not articulate it as -- as clearly as I maybe should
09:34:12 16 have -- as I would have liked to, in retrospect.

09:34:48 17 Q Dr. Romesberg, I'm going to show you what's
09:34:49 18 been previously marked Illumina Exhibit 2011.

09:35:00 19 Do you recognize this document?

09:35:00 20 A Yeah. It appears to be the list of documents
09:35:02 21 that I -- that I read and thought about when writing the
09:35:06 22 declaration.

09:35:10 23 Q And is this document a complete list of the
09:35:14 24 material that you read and considered when preparing
09:35:17 25 your declaration?

09:35:18 1 A I believe so.

09:35:24 2 Q And are the documents listed in this exhibit
09:35:27 3 the only materials that you relied on in -- in rendering
09:35:30 4 your -- or preparing your declaration?

09:35:33 5 A Other than my knowledge and opinion, the -- the
09:35:38 6 external sources, yes.

09:35:42 7 Q So these are, then -- just to clarify, the
09:35:46 8 documents and materials listed on 2011 are the only
09:35:48 9 documents and materials that you relied on when
09:35:51 10 preparing your declaration. Correct?

09:35:54 11 A Yeah. I mean, I guess the only caveat I'm
09:35:56 12 saying is that I've read a lot of papers about
09:35:59 13 sequencing by synthesis over the past 20 years. And I
09:36:03 14 don't have those or recall them. And those have all led
09:36:06 15 to an opinion, sort of, a belief, an understanding of
09:36:09 16 the field. And so those certainly were important in --
09:36:12 17 but these are the one -- the papers that I read and
09:36:14 18 considered for this declaration.

09:36:15 19 Q The previous sequencing papers that you
09:36:18 20 reviewed, those are not listed in this exhibit.
09:36:21 21 Correct?

09:36:24 22 A I don't even know what they are. They're just
09:36:26 23 things that -- I mean, I have an understanding of the
09:36:28 24 field. And that came from -- everything from textbooks
09:36:31 25 to papers and --

09:36:44 1 Q And how are you provided with the documents
09:36:45 2 listed in this exhibit?

09:36:47 3 A By email. And I printed them, mostly, I
09:36:50 4 believe. It's possible that I might have been given a
09:36:52 5 couple during my visits here. But I -- my recollection
09:36:55 6 is that most were sent to me by email.

09:36:57 7 Q And so your attorneys at Knobbe provided you
09:37:01 8 with the -- with the references in this declaration?

09:37:03 9 A Yes.

09:37:07 10 Q Did you ask for any additional documents from
09:37:10 11 anyone?

09:37:12 12 A No.

09:37:20 13 Q You mentioned that you had done some
09:37:22 14 independent research.

09:37:24 15 Did you -- did you research any additional
09:37:26 16 documents to use in preparing your declaration?

09:37:29 17 A No. Those -- those other documents that I'm
09:37:31 18 referring to are just part of the learning process over
09:37:34 19 the past 30 -- 20 years.

09:37:42 20 Q And did you identify the references listed here
09:37:45 21 in your declaration?

09:37:46 22 A No, I did not.

09:37:47 23 Q Okay. And did your counsel, Knobbe, identify
09:37:54 24 these documents listed in this exhibit?

09:37:56 25 A To me, yes. And I believe some of them were

09:37:58 1 identified to them by others.

09:38:04 2 Q So then the only -- the only materials, then,
09:38:07 3 Dr. Romesberg, that you relied on in preparing your
09:38:10 4 declaration were provided to you by counsel at Knobbe.
09:38:13 5 Is that correct?

09:38:14 6 A The only materials explicitly that I reviewed
09:38:17 7 for this declaration, correct. Yes.

09:38:31 8 Q If you turn to page 2 of this exhibit, you
09:38:36 9 see -- you say you reviewed the file history of the '026
09:38:41 10 patent.

09:38:42 11 A Yes.

09:38:42 12 Q Is that correct?

09:38:48 13 Did you then identi- -- review the information
09:38:51 14 disclosure statements contained within the file history
09:38:54 15 of the '026 patent?

09:38:56 16 A My recollection of that -- of that -- you mean
09:38:59 17 of the file history?

09:39:01 18 Q Of the file history, correct.

09:39:02 19 A My -- my recollection is that it was a long,
09:39:04 20 hard to read document for me. So could I have a look at
09:39:08 21 it, and then -- and then if I can see the part that
09:39:11 22 you're referring to, I'll more easily remember it?

09:39:13 23 Q But you don't recall specifically reviewing
09:39:20 24 information disclosure statements in the file history?

09:39:22 25 A I can't -- at the moment, I can't recall what

09:39:24 1 that is. I mean, I read the entire document, and I
09:39:27 2 recall not reading -- not understanding some of it and
09:39:31 3 focusing on parts that I thought were most relevant for
09:39:33 4 my declaration. If -- if you want me to answer about my
09:39:38 5 recollection of a specific part, could I -- could I see
09:39:40 6 the document, and then maybe I'll be able to give you a
09:39:43 7 more informed answer?

09:39:45 8 Q Sure. We can -- we can use the '026 patent as
09:39:48 9 an example.

09:39:49 10 So if you turn back to IBS Exhibit 1001.

09:39:55 11 So do you see on the face of the patent, there
09:39:57 12 are various references listed. Starting in the
09:40:00 13 left-hand column --

09:40:01 14 A Yes.

09:40:02 15 Q -- you see there's a reference that says "Site
09:40:04 16 Inspection"? Okay.

09:40:06 17 And you see that extends over into the
09:40:08 18 right-hand column?

09:40:09 19 A Yes.

09:40:11 20 Q So what I'm referring to is typically during
09:40:13 21 the patent prosecution, parties will submit to the
09:40:17 22 patent office something called an information disclosure
09:40:19 23 statement, where they list various references.

09:40:21 24 What I'm asking -- and you've testified you
09:40:25 25 didn't recall specifically seeing that. Correct?

09:40:32 1 A No, I do not recall in -- in that particular
09:40:35 2 document, seeing those references.

09:40:38 3 Q Did you review any of the references that are
09:40:40 4 listed on the face of the '026 patent here in these two
09:40:45 5 columns?

09:40:46 6 A I -- I recognize several of them, yes.

09:40:48 7 Q Which ones do you recognize?

09:40:50 8 A Herman, Dower, Ju.

09:40:58 9 Q Do you recognize any of the other ones?

09:41:03 10 A No.

09:41:04 11 Q So if you turn to page 2 of the '026 patent,
09:41:10 12 you see that -- where it says "Other Publications"
09:41:15 13 there?

09:41:15 14 A I do.

09:41:16 15 Q Do you recognize any of those documents?

09:41:26 16 A No, I do not. The only -- the only caveat to
09:41:40 17 that is that several of them are listed with first
09:41:42 18 author, et al. And, often, I remember papers by
09:41:48 19 corresponding author. And so it's possible that one of
09:41:51 20 these I am familiar with and I'm just not recognizing
09:41:55 21 it.

09:41:58 22 Q But as far as you can tell --

09:41:59 23 A As far as I can tell, I don't recognize them.

09:42:02 24 Q Okay. If we can turn back to Exhibit 2011 --
09:42:13 25 I'm sorry. It's the list of the references. Sorry

09:42:16 1 about that.

09:42:16 2 A That's no problem.

09:42:22 3 Q So there are four references -- we can turn to
09:42:24 4 page 2 specifically. There are four references listed
09:42:30 5 here on page 2 -- three on page 2 and one on page 3 --
09:42:36 6 that do not have exhibit numbers. Those references
09:42:40 7 specifically are Meinwald -- do you see where Meinwald
09:42:45 8 is?

09:42:45 9 A Yes.

09:42:45 10 Q And Matsumoto, do you see where that is?

09:42:48 11 A I do.

09:42:48 12 Q And there's a U.S. Patent Publication No.
09:42:51 13 2013/0079232. That's the Kain application.

09:42:55 14 Do you see where that is?

09:42:56 15 A Yes.

09:42:57 16 Q Okay. And then on page 3, if you turn with me,
09:43:00 17 you see there's Rigby there without an exhibit number.

09:43:04 18 Do you see that?

09:43:04 19 A I do.

09:43:05 20 Q Okay. So why did you choose not to reference
09:43:12 21 these particular materials in your declaration?

09:43:14 22 A I thought they were less relevant. The -- the
09:43:17 23 material that was referenced was the material that I
09:43:18 24 thought was the most relevant. I, frankly, found a lot
09:43:22 25 of these references to not be pertinent.

09:43:27 1 Q And how did you make a determination that a
09:43:30 2 reference was less relevant?

09:43:38 3 A A whole variety of criteria, whether or not
09:43:41 4 the -- I mean, I -- I was -- as I read all this, I was
09:43:45 5 asked -- asking the question of how it impacted in terms
09:43:48 6 of prior art, how it impacted the novelty and the
09:43:52 7 nonobviousness. And so anything that discussed things
09:43:55 8 that were of obvious relationship -- that had an obvious
09:43:58 9 relationship to the '026 patent, I would have noticed
09:44:02 10 and immediately found relevant.

09:44:04 11 Some of them, as I read through them, I just
09:44:07 12 couldn't find anything that I thought was related. And
09:44:09 13 so some of the patents, as I read them, became less
09:44:15 14 important and -- some -- sorry. Some of the references
09:44:18 15 and some of the material, and it just didn't stick with
09:44:21 16 me.

09:44:22 17 Q So you note that -- that some of the references
09:44:24 18 you read appeared to you to have an obvious connection
09:44:27 19 to the '026 patent.

09:44:28 20 What --

09:44:30 21 A No. I'm saying that I -- I looked for anything
09:44:32 22 that could be related, because I was considering --
09:44:35 23 because I knew what my job here was to explain to you
09:44:39 24 what I thought was obvious and what -- what would have
09:44:45 25 rendered the Illumina patent obvious or nonobvious and

09:44:48 1 what would have rendered the Illumina patent novel or
09:44:51 2 not novel. So I read -- when I was reading all of these
09:44:55 3 documents, I looked for anything that might inform my
09:44:57 4 opinion about that.

09:44:58 5 Q Right. But, as I understand your testimony,
09:45:02 6 there are certain things about some of the documents in
09:45:05 7 this list that made you feel they were more connected to
09:45:10 8 the obviousness or nonobviousness of the '026 -- claims
09:45:14 9 of the '026 patent. Correct?

09:45:16 10 A Well, for example, if one of them didn't
09:45:18 11 talk -- if it didn't talk anything about any of the
09:45:20 12 material in the Illumina patent, I would have simply not
09:45:22 13 thought much more about it. And some of them were
09:45:31 14 obviously more related, yes.

09:45:33 15 Q So -- so that's my question, then, getting --
09:45:35 16 circling back around, is in your -- in your mind, what
09:45:40 17 made a reference obviously more related to the claims of
09:45:46 18 the '026 patent?

09:45:47 19 A If it discussed structures of triphosphates.
09:45:51 20 If it discussed linkers. If it discussed reversible
09:45:54 21 linkers. Things that were important to the amended
09:45:57 22 claims in the Illumina patent.

09:46:09 23 Q Is there anything else about a reference that
09:46:10 24 made it obviously tied to the material of the -- the
09:46:13 25 '026 patent?

09:46:20 1 A I -- I think that was mostly it, I think.

09:46:31 2 Q So those four references we were just talking
09:46:33 3 about, Dr. Romesberg, Meinwald, Matsumoto, Kain, and
09:46:38 4 Rigby, were you instructed by anyone not to include
09:46:41 5 those references in your -- in your declaration?

09:46:43 6 A No. I wasn't instructed by anyone to include
09:46:52 7 or not to include anything in my declaration.

09:47:07 8 Q So let's turn back to the first reference on
09:47:09 9 this list, and that's Exhibit -- IBS Exhibit 1001. And
09:47:13 10 it's the '026 patent.

09:47:25 11 Dr. Romesberg, when did you first review the
09:47:27 12 '026 patent?

09:47:28 13 A It was the first document Nate sent me.

09:47:30 14 Q Do you recall when that was?

09:47:31 15 A I answered that question earlier. I think it
09:47:33 16 was late September, early October, I believe.

09:47:42 17 Q And that's of 2013. Correct?

09:47:45 18 A Yes.

09:47:50 19 Q Is that the first time that you had ever seen
09:47:52 20 the '026 patent?

09:47:57 21 A That is correct, yes.

09:47:58 22 Q And how many times have you reviewed the '026
09:48:04 23 patent?

09:48:11 24 A Meaning, read it in its entirety page by page?

09:48:14 25 Q Well, how do you -- when I say "review the '026

09:48:17 1 patent," what does that -- what does that mean to you?

09:48:19 2 A Looked at it, flip -- flipped through it, found
09:48:22 3 something, had a question in my mind, wanted to go look
09:48:24 4 at it, see exactly what they said about something. And
09:48:28 5 if that's the way you're counting it, hundreds.

09:48:33 6 Q How many times have you, then, thoroughly
09:48:35 7 reviewed --

09:48:36 8 A Thoroughly read.

09:48:37 9 Q -- the '026 patent?

09:48:39 10 Thoroughly read.

09:48:40 11 A I would say probably three times. Twice.

09:48:48 12 Twice thoroughly, page to page to page --

09:48:48 13 THE REPORTER: Can I hear again, the answer.

09:48:48 14 I'm sorry.

09:48:48 15 THE WITNESS: Twice.

09:48:50 16 BY MR. GRIER:

09:48:51 17 Q And how do you define a -- a thorough review of
09:48:54 18 the '026 patent?

09:48:55 19 A Read it like a book, read the beginning to the
09:48:57 20 end, every -- every word. Just to make sure you're
09:49:01 21 following the logic, following the -- the flow, that you
09:49:07 22 have all the context.

09:49:21 23 Q So if you could turn with me to Column 2 of the
09:49:24 24 '026 patent. And, in particular, I want to look at
09:49:37 25 lines 8 through 19.

09:49:42 1 Do you see those?

09:49:42 2 A I do.

09:49:44 3 Q So do you see there where it describes the uses

09:49:50 4 of the nucleotides?

09:49:54 5 A Can I -- can I go ahead and read it?

09:49:56 6 Q Absolutely.

09:49:57 7 A Okay. Thank you.

09:50:25 8 Yes. I -- can you read the question, please.

09:50:27 9 Q Sure. You see in that section you just

09:50:29 10 reviewed, it's describing the various uses for the

09:50:33 11 nucleotides. Correct?

09:50:34 12 A Yes.

09:50:34 13 Q Okay. And you see that one of those uses,

09:50:37 14 specifically in line 10, is sequencing reactions.

09:50:40 15 A I do.

09:50:42 16 Q Do you see that?

09:50:43 17 Would -- would you agree, then, though, there

09:50:46 18 are other uses described here in -- in this section

09:50:50 19 other than sequencing reactions?

09:50:51 20 A There are.

09:51:07 21 Q And can you turn to Column 4 for me, please.

09:51:16 22 Specifically, I'm referring -- I'm going to refer to

09:51:18 23 lines 51 through 58.

09:51:21 24 Do you see that in Column 4?

09:51:22 25 A I do.

09:51:23 1 Q Do you see this is, again, a list of various
09:51:27 2 uses for the nucleotides in the '026 patent.
09:51:30 3 A Yes.
09:51:31 4 Q Correct?
09:51:33 5 And you see, again, it lists sequencing
09:51:35 6 reactions there in line 51?
09:51:41 7 A I do.
09:51:42 8 Q You see it also lists other uses for the
09:51:45 9 nucleotides in the '026 patent. Correct?
09:51:47 10 A Yes. Correct.
09:51:50 11 Q And it provides various examples of those, such
09:51:54 12 as polynucleotide synthesis, nucleic acid hybridization,
09:52:04 13 SNP studies, labeling dNTPs, et cetera.
09:52:09 14 Do you see that?
09:52:09 15 A I do.
09:52:15 16 Q Okay. And can you turn with me to Column 10 of
09:52:21 17 the '026 patent, please. And, specifically, lines 57
09:52:31 18 through 65.
09:52:32 19 Do you see that?
09:52:34 20 A Yes.
09:52:35 21 Q And, again, this is a list --
09:52:39 22 A Can I -- can I take a second to read it?
09:52:41 23 Q Certainly.
09:52:42 24 A Thank you.
09:52:59 25 Yes.

09:53:00 1 Q Okay. And you see there on line -- about 58,
09:53:05 2 it lists DNA sequencing as -- as the use of the
09:53:10 3 nucleotides.

09:53:12 4 Do you see that?

09:53:12 5 A Yes.

09:53:13 6 Q Okay. And it lists other techniques similar to
09:53:16 7 the list we just went over, DNA hybridization assays,
09:53:21 8 SNP studies, et cetera.

09:53:23 9 Do you see those other --

09:53:24 10 A I do.

09:53:24 11 Q Okay. So then you would agree that those other
09:53:27 12 techniques listed are things other than SBS. Correct?

09:53:35 13 A Yes. Correct.

09:54:17 14 Q Dr. Romesberg, I'll hand you what's been
09:54:19 15 previously marked Intelligent Bio-Systems Exhibit 1008.

09:54:31 16 Do you recognize this document?

09:54:32 17 A I do. I -- I refer to it as the Ju patent.

09:54:41 18 Q Okay. So we can go under the assumption today
09:54:44 19 that when we're referring to this document, I'll call it
09:54:46 20 the Ju patent, and -- and you'll understand what -- what
09:54:49 21 I'm referring to?

09:54:50 22 A Yes.

09:54:50 23 Q Okay. When did you first review the Ju patent,
09:55:03 24 Dr. Romesberg?

09:55:06 25 A Shortly after -- it was one of the first --

09:55:09 1 first documents that I read after I started and after I
09:55:15 2 read the '026 patent, the application.

09:55:19 3 Q And do you recall when that was?

09:55:25 4 A I believe it was on a Saturday morning shortly
09:55:28 5 after I started. So I think that would have been
09:55:31 6 early -- a Saturday morning early October.

09:55:35 7 Q Of 2013. Correct?

09:55:37 8 A Correct.

09:55:43 9 Q And was that the first time you had ever
09:55:45 10 reviewed the Ju patent?

09:55:47 11 A Yes.

09:55:51 12 Q And how many times would you estimate you've
09:55:52 13 reviewed the Ju patent?

09:55:57 14 A So similar to our discussion earlier, do you
09:56:00 15 mean an entire read, or --

09:56:02 16 Q We can -- similar --

09:56:04 17 A -- referenced to it, looked to it for
09:56:06 18 something?

09:56:07 19 Q I didn't mean to talk over you. I'm sorry.

09:56:09 20 Similar to our earlier discussion, we'll --
09:56:12 21 we'll do both categories.

09:56:13 22 A Okay.

09:56:13 23 Q We'll start with the first, which is how many
09:56:16 24 times have you reviewed the '079 patent?

09:56:18 25 A I -- I looked to it and read certain parts of

09:56:21 1 it. This is just an estimate. Maybe 30 times, 20, 30
09:56:28 2 times.

09:56:31 3 Q And how many times have you conducted a
09:56:33 4 thorough review of the Ju patent?

09:56:35 5 A I -- I read this patent cover to cover only
09:56:38 6 once.

09:56:50 7 Q And prior to reading the Ju patent, had you
09:56:54 8 ever heard of Dr. Ju?

09:56:56 9 A Yes.

09:56:57 10 Q How -- how have you heard of Dr. Ju?

09:57:00 11 A He works on modified nucleotides. I work on
09:57:02 12 modified nucleotides.

09:57:08 13 Q Is that the only way that you had heard of
09:57:09 14 Dr. Ju?

09:57:10 15 A You mean, professionally?

09:57:13 16 Q We can start with professionally, sure.

09:57:15 17 A Yeah. There's nothing outside of
09:57:16 18 professionally.

09:57:16 19 Q Okay.

09:57:16 20 A And so professionally is the only way I -- I've
09:57:19 21 known him. And it would only -- yes, it would only be
09:57:22 22 through -- I mean, I've been interested in sequencing by
09:57:27 23 synthesis for years, and he works on that. And I've
09:57:29 24 been interested in modified nucleotides, and he works on
09:57:32 25 that. So I believe I've even spoken with him a couple

09:57:36 1 of times at meetings, I think.

09:57:40 2 Q Do you recall how many times you've spoken --

09:57:42 3 A No.

09:57:42 4 Q -- with Dr. Ju?

09:57:44 5 A No. I mean, not five times. Maybe two. Maybe
09:57:47 6 three.

09:57:48 7 Q When was the first time you can remember
09:57:51 8 speaking to Dr. Ju?

09:57:52 9 A I don't -- I don't recall. If -- if I had to
09:57:55 10 guess, I would guess it was around 2004, maybe, 2005,
09:58:00 11 maybe.

09:58:06 12 Q So have you ever met Dr. Ju in person?

09:58:10 13 A I believe so.

09:58:11 14 Q And do you recall when you met Dr. Ju?

09:58:13 15 A No. But I think it's the same time that I
09:58:16 16 spoke to him.

09:58:17 17 Q So that's around 2004. Correct?

09:58:19 18 A I think so, yeah. I don't think I ever spoke
09:58:22 19 to him on the phone. So any recollection I have of
09:58:25 20 talking to him -- I mean, at meetings, you talk to a lot
09:58:27 21 of people. And so I assume I met him at a couple of
09:58:32 22 meetings, because I remember him telling me specifically
09:58:36 23 about something that he was working on. And that's kind
09:58:38 24 of how I remember him.

09:58:40 25 Q And do you remember what specifically you

09:58:43 1 discussed with Dr. Ju?

09:58:45 2 A Funny enough, I do. It was exactly this
09:58:48 3 material. It was -- it was -- it was not so much -- at
09:58:51 4 the time, what I was interested in and I think my -- I
09:58:54 5 think this was after a talk I gave, where I was talking
09:58:57 6 about modified nucleotides. And he was -- he was -- we
09:59:00 7 were talking about modifications that he was interested
09:59:03 8 in, 3' protecting groups. And I -- I think I -- I think
09:59:08 9 I remembered him talking about OLE groups.

09:59:15 10 Q And when you refer to "this material," do you
09:59:16 11 mean the '079 patent?

09:59:18 12 A No, no. I mean, much broader, 30,000 feet
09:59:21 13 modified nucleotides.

09:59:23 14 Q Modified nucleotides in general, or modified
09:59:26 15 nucleotides for use in SBS?

09:59:29 16 A In general.

09:59:33 17 Although, I can't with certainty say that the
09:59:34 18 conversation didn't move around into SBS. I think that
09:59:37 19 we were talking about modified nucleotides and -- and I
09:59:42 20 can't recall. That was 10 years ago. I can't recall
09:59:45 21 much detail about it.

09:59:47 22 Q And have you ever worked with Dr. Ju?

09:59:49 23 A No.

10:00:02 24 We -- we may have spoken of a collaboration.

10:00:05 25 We may have talked about -- I mean, unfortunately, this

10:00:06 1 is very common amongst academics where you say, oh, we
10:00:10 2 should collaborate. But -- but we never did. So I'm
10:00:13 3 not sure what became of that. Maybe neither of us had
10:00:16 4 time or --

10:00:20 5 Q You say you never did. You're referring to
10:00:22 6 collaborating? You --

10:00:24 7 A Correct.

10:00:24 8 Q -- never -- you never did collaborate. Is that
10:00:25 9 correct?

10:00:27 10 A That is correct.

10:00:29 11 Q And do you recall when you had those
10:00:30 12 conversations with Dr. Ju about potential collaboration?

10:00:33 13 A No. I assume it was around the same time. He
10:00:42 14 may have even said he was going to send us something.

10:00:49 15 Q Do you recall if he ever sent you something?

10:00:51 16 A I don't believe so, no.

10:00:52 17 Q By "something," are you referring to modified
10:00:54 18 nucleotides?

10:00:55 19 A My guess, that would have been it. One of the
10:00:58 20 things my group does that's related to sequencing by
10:01:02 21 synthesis is evolve DNA polymerases to better recognize
10:01:07 22 analogs. And I think he might have been interested in
10:01:10 23 having us try to do that for his analogs.

10:01:46 24 Q Dr. Romesberg, I'm going to hand you what's
10:01:48 25 been previously marked IBS Exhibit 1012.

10:02:04 1 Do you recognize this document?

10:02:33 2 A Sorry. Yes. Yeah. Yes, I do. It's -- it's
10:02:36 3 the Chen proposal -- patent.

10:02:40 4 Q So just to keep it straight today, if we refer
10:02:45 5 to this document, Exhibit 1012, by Chen, would you --
10:02:51 6 can we agree that we'd understand what we -- I was
10:02:54 7 talking about?

10:02:54 8 A Yes.

10:02:55 9 Q Okay. When did you first review the Chen
10:03:06 10 patent application?

10:03:07 11 A I think it may have been the same day that I
10:03:09 12 first reviewed the Ju patent application.

10:03:15 13 Probably a Saturday morning, probably early
10:03:18 14 October of 2013.

10:03:22 15 Q And was that the first time that you had ever
10:03:24 16 reviewed the Chen patent application?

10:03:26 17 A Yes, it is. Yes, it was.

10:03:33 18 Q And how many times would you estimate,
10:03:35 19 Dr. Romesberg, you've reviewed the Chen patent
10:03:38 20 application?

10:03:40 21 A Probably about the same as the Ju application.

10:03:43 22 A -- a careful systematic read, one time. And then
10:03:50 23 looking to it -- you know, I -- I just don't know how
10:03:53 24 many times. Something 20 -- it could be 20. It could
10:03:55 25 be 50, because as I -- as I went on over the next month

10:03:58 1 as I was writing the declaration, there were many times
10:04:02 2 when I wanted to consider, well, what does -- what did
10:04:04 3 Chen say about this. And so I would go find that
10:04:07 4 section and reread a few paragraphs or a page or two and
10:04:10 5 maybe even, you know, whatever I needed to get context.
10:04:13 6 So -- but something like that.

10:04:15 7 Q Okay. Prior to reviewing the Chen patent
10:04:20 8 application, had you ever heard of Roger Tsien?

10:04:24 9 A Yes.

10:04:24 10 Q And how had you heard of Roger Tsien?

10:04:27 11 A Well, he's a professor at UCSD. That's very
10:04:30 12 close to my institute. I've -- I know his -- his work.
10:04:35 13 He's a famous -- he won the Nobel Prize, and he's quite
10:04:41 14 a well-known fellow. And I've introduced him several
10:04:45 15 times. And he doesn't like my introductions.

10:04:47 16 Q By "introduced him" --

10:04:48 17 A I've had dinner with him several times. Well,
10:04:50 18 at several meetings, I've been asked to introduce him.
10:04:52 19 And so I've introduced him. I've had dinner with him
10:04:56 20 several times.

10:05:01 21 Q So then you've met Dr. Tsien?

10:05:03 22 A Yes.

10:05:07 23 Q And in the discussions you've had with
10:05:10 24 Dr. Tsien, have you ever discussed modified nucleotides?

10:05:16 25 A Surprisingly, no.

10:05:18 1 Q Have you ever discussed --

10:05:19 2 A It's not really what he works on now. And so,
10:05:22 3 you know, I think that -- that scientists like to talk
10:05:25 4 about what they're interested in at the time. And we
10:05:28 5 wound up talking about various fluorescent things, which
10:05:33 6 is what he's really interested in now, cell labeling,
10:05:36 7 and that kind of thing. So we actually never talked
10:05:39 8 nucleotides. And to tell you the truth, I never really
10:05:43 9 knew that he did this work until I read this patent.

10:05:45 10 Q So you never had discussions with Dr. Tsien
10:05:48 11 about SBS?

10:05:49 12 A No.

10:05:55 13 Q Have you ever worked with Dr. Tsien?

10:05:57 14 A No.

10:06:04 15 Q Similar to Dr. Ju, have you ever had any
10:06:06 16 discussions with Dr. Tsien about possible
10:06:09 17 collaborations?

10:06:13 18 A No.

10:06:47 19 Q Dr. Romesberg, I'll show -- I'm going to show
10:06:49 20 you what's been previously marked IBS Exhibit 1002.

10:06:59 21 Do you recognize this document?

10:07:15 22 A Yes, I do.

10:07:18 23 Q And what is this document?

10:07:20 24 A It's a -- it's what I refer to as the Stemple
10:07:27 25 patent.

10:07:27 1 Q So just to keep things consistent as we've been
10:07:30 2 doing throughout the day, when I -- if I refer to this
10:07:33 3 document as "Stemple," you'll understand what I'm
10:07:35 4 referring to. Correct?

10:07:36 5 A Yes.

10:07:37 6 Q Okay. When was the first time you reviewed
10:07:38 7 Stemple?

10:07:39 8 A I -- it may have been the day after the first
10:07:43 9 time that I reviewed Ju and Chen. I vaguely remember it
10:07:47 10 being on the lower half of the randomly sorted stack of
10:07:53 11 patents that I had. Actually, if you want to know the
10:07:59 12 truth, I think I had flipped through all of them. And I
10:08:01 13 had sort of prioritized them of what I wanted to read
10:08:08 14 first. And it was not on the upward list in terms of a
10:08:10 15 flip through. I think that's how I wound up reading it
10:08:13 16 in that order.

10:08:15 17 Q When you flipped through and made your
10:08:16 18 priority, how did you prioritize what you wanted to read
10:08:20 19 first?

10:08:21 20 A Things that looked -- you know, there's a lot
10:08:22 21 of ways to do that. Things that look easy to read,
10:08:25 22 things that look easy access, because the more you read
10:08:29 23 on a related set of topics, the better you are at it.
10:08:32 24 So I would -- things that are for some reason easier to
10:08:34 25 read for me. It might be bigger font. It may be

10:08:37 1 shorter. Figures that speak to me that I feel like I
10:08:39 2 can sort of already sort of get the feel. You look for
10:08:42 3 any way into -- when you're thinking about something not
10:08:46 4 necessarily new but from a different perspective or you
10:08:49 5 want to say, okay, here's a body of work, I want to
10:08:52 6 think about it. You get a foot in how ever you can. So
10:08:57 7 there's no logic necessarily to it other than just what
10:09:00 8 looked interesting.

10:09:03 9 Q You mentioned that Stemple was at the -- at the
10:09:05 10 bottom of your pile. Correct?

10:09:07 11 A No. It was probably the lower half.

10:09:09 12 Q Okay.

10:09:10 13 A That may have not been fair, but it is what it
10:09:13 14 is.

10:09:14 15 Q Is there anything that you recall about Stemple
10:09:18 16 that led you to -- to place it sort of at the -- the
10:09:21 17 lower part of the stack?

10:09:22 18 A Probably at a first glance, I -- it looked like
10:09:25 19 it was related to a lot of equipment-based aspects,
10:09:30 20 which I think -- I don't -- I don't exactly recall.
10:09:33 21 I -- I vaguely remember this being on the second day
10:09:37 22 of -- of my first bit of reading. And I -- I think it
10:09:42 23 may have been having -- I remember there were several
10:09:43 24 that seemed to bend out that way, and that may have been
10:09:49 25 why.

10:09:49 1 Q So then the first time you reviewed Stemple
10:09:52 2 was, again, early October 2013. Is that correct?
10:09:55 3 A It could have been late November. I'm sorry.
10:09:57 4 It could have been late -- it could have been late
10:09:59 5 September.
10:09:59 6 Q Okay.
10:10:02 7 A But it was somewhere right in there, yes.
10:10:06 8 Q And how many times would you estimate you --
10:10:09 9 you have reviewed Stemple?
10:10:11 10 A About the same as Chen and in exactly the same
10:10:18 11 breakdown.
10:10:21 12 Q So that's -- so that's in -- you testified that
10:10:24 13 Chen was one thorough review. Correct?
10:10:27 14 A One complete review followed by referencing
10:10:29 15 back to it many times as -- as questions might have come
10:10:33 16 up. And I think maybe -- roughly the same.
10:10:39 17 Q Roughly the same as Chen. Correct?
10:10:41 18 A Yeah.
10:10:42 19 Q Okay. So just to be clear, there -- there was
10:10:44 20 one complete review that you made of the -- of the
10:10:47 21 Stemple patent --
10:10:48 22 A Mm-hmm.
10:10:48 23 Q -- application.
10:10:50 24 A Yes.
10:10:51 25 Q Correct?

10:10:52 1 A Yes. One complete read, yeah.

10:10:54 2 Q And had you ever heard of Derek Stemple prior

10:10:57 3 to reviewing this patent application?

10:11:00 4 A No, I had not.

10:11:04 5 Q Have you ever met Derek Stemple?

10:11:06 6 A No.

10:11:06 7 Q So then you've never had any discussions with

10:11:12 8 Derek Stemple about working with him. Correct?

10:11:14 9 A No.

10:11:15 10 Q You never had any discussions with Derek

10:11:17 11 Stemple about potential collaborations. Correct?

10:11:20 12 A I've never had a discussion with him about

10:11:22 13 collaborations, working with or anything. No

10:11:24 14 discussions.

10:11:51 15 Q Dr. Romesberg, I'm going to hand you what's

10:11:53 16 been previously marked IBS Exhibit 24 -- sorry -- 1014.

10:12:01 17 I apologize.

10:12:03 18 Do you recognize this document?

10:12:12 19 A Yes, I do.

10:12:16 20 Q And what is this document, Dr. Romesberg?

10:12:19 21 A I refer to this as the Dower patent.

10:12:25 22 Q And, again, for consistency today, if I refer

10:12:29 23 to this document, Exhibit 1014, as the "Dower patent" or

10:12:33 24 just "Dower," you'll understand what I'm referring to.

10:12:36 25 Correct?

10:12:36 1 A Yes.

10:12:36 2 Q Okay. When did you first review Dower?

10:12:41 3 A I believe day one of my two-day initial read

10:12:48 4 in -- in what was likely early October, late September.

10:12:56 5 Q Again, of 2013. Correct?

10:12:57 6 A Yes. 2013.

10:13:05 7 Q And how many times would you estimate you've

10:13:07 8 reviewed Dower?

10:13:09 9 A Cover to cover, one time. A careful, thorough

10:13:13 10 read to make sure I understood it. And then I

10:13:17 11 referenced back to it many times.

10:13:23 12 Q So is it similar to -- to Chen where 20 to 50

10:13:28 13 times you may have referenced back to Dower?

10:13:39 14 A Yeah. Sure.

10:13:40 15 Q And have you ever heard of William Dower prior

10:13:43 16 to seeing this patent?

10:13:45 17 A I don't believe so, no. I don't -- I don't

10:13:47 18 ever recall having heard of him, no.

10:13:54 19 Q So you never met William Dower, then. Correct?

10:14:01 20 A Not that I recall.

10:14:05 21 Q You've never collaborated with William Dower?

10:14:10 22 A Never.

10:14:46 23 Q Dr. Romesberg, I'm going to hand you what's

10:14:48 24 been previously marked IBS Exhibit 1013.

10:14:55 25 Do you recognize this document?

10:14:57 1 A Yes, I do.

10:15:00 2 Q And what is this document, Dr. Romesberg?

10:15:05 3 A This is a very famous paper that was published
10:15:07 4 in the Journal of Science. It describes
10:15:15 5 dideoxynucleotides for sequencing -- chain-termination
10:15:20 6 sequencing purposes. And I guess it's what I refer to
10:15:22 7 as Prober.

10:15:24 8 Q So throughout the day, Dr. Romesberg, if I
10:15:26 9 refer to this reference, Exhibit 1013, as "Prober,"
10:15:30 10 you'll understand what I'm referring to. Correct?

10:15:31 11 A I will.

10:15:34 12 Q Okay. And when did you first review Prober?

10:15:37 13 A No idea. My guess is that it -- by "review,"
10:15:42 14 you mean read, or for the purposes of this
10:15:45 15 declaration -- or this IPR?

10:15:48 16 Q How about when was the first time you read
10:15:50 17 Prober?

10:15:51 18 A I'm -- I'm going to guess it was probably
10:15:53 19 1997-ish, around 1997.

10:16:09 20 Q And in 1997 when you first read -- reviewed
10:16:12 21 Prober, why did you look at Prober in 1997?

10:16:15 22 A I was interested in -- that's around the time
10:16:18 23 that I was putting together proposals for my own
10:16:22 24 academic job, my own academic job application, and I was
10:16:26 25 interested in nucleotides -- modified nucleotides. And

10:16:32 1 this is a paper that describes that. And so I read this
10:16:35 2 amongst many papers. I probably remember this paper
10:16:38 3 because everyone who did molecular biology and everyone
10:16:42 4 who worked with sequencing then used analogs like this.
10:16:45 5 And so I would have -- would have simply noticed that.
10:16:50 6 And it's a nice piece of work. And you remember a nice
10:16:52 7 piece of work.

10:16:58 8 Q So in your opinion, this -- this was a fairly
10:17:00 9 well-known reference in 1997, then. Correct?

10:17:04 10 A Well known amongst people interested in
10:17:09 11 sequencing, yes. Well known in the broader community,
10:17:12 12 maybe a little less so.

10:17:22 13 Q And in 1997 when you were working on your --
10:17:25 14 your scientific proposals, you were interested in
10:17:30 15 modified nucleotides, you said. Correct?

10:17:31 16 A Correct.

10:17:33 17 Q And what were you using those modified
10:17:34 18 nucleotides for?

10:17:37 19 A The project at the time was and still is trying
10:17:40 20 to develop unnatural base pairs. So you've heard of GC,
10:17:47 21 A, and T?

10:17:48 22 Q I have.

10:17:51 23 A We wanted to develop, and we have developed X
10:17:53 24 and Y.

10:17:55 25 Q And what are -- what are X and Y?

10:17:58 1 A They are unnatural nucleotides, nucleotides
10:18:01 2 bearing nucleic-based analogs, that pair not based on
10:18:06 3 hydrogen bonding but on hydrophobic packing, much like a
10:18:06 4 protein --

10:18:06 5 THE REPORTER: I think I got to get you to back
10:18:06 6 up for me on that little bit, Doctor, and slow down on
10:18:06 7 the technical terms.

10:18:15 8 "That pairs are not based on" --

10:18:16 9 THE WITNESS: Hydrogen bonding but rather
10:18:21 10 hydrophobic packing and are nonetheless stable and
10:18:27 11 selective in duplex DNA, and most importantly,
10:18:33 12 efficiently and with high fidelity recognized by DNA
10:18:37 13 polymerases for the synthesis of DNA containing these
10:18:45 14 modified nucleotides.

10:18:46 15 And I was very interested in beginning to get a
10:18:48 16 look at what sort of modifications would be tolerated by
10:18:51 17 a polymerase and what sort might not be.

10:18:57 18 And so what Prober describes are modifications
10:18:59 19 that are recognized well and that had been highly
10:19:01 20 validated.

10:19:04 21 And another aspect of the project was that if
10:19:07 22 one had an unnatural base pair, one could use it to
10:19:11 23 attach linkers to site specifically modify the DNA or
10:19:17 24 the RNA. And so this, in addition, has validated
10:19:21 25 linkers that I -- that I envisioned might eventually be

10:19:25 1 used to attach to my nucleic-based analogs of my
10:19:30 2 unnatural base pair to site specifically label DNA and
10:19:36 3 RNA.

10:19:36 4 BY MR. GRIER:

10:19:37 5 Q And the linkers that you refer to, can you show
10:19:40 6 me where those linkers are, Dr. Romesberg?

10:19:45 7 A They're illustrated in Figure 2.

10:19:49 8 Q And specifically, which -- which structures are
10:19:51 9 you referring to in Figure 2 as the linkers?

10:19:55 10 A Well -- so what I -- most notably, I guess, and
10:20:00 11 what I would have been most interested in 1997 was the
10:20:04 12 nature and position of linkage of the propargylamine,
10:20:09 13 which is that triple bond and then -- and then a CH₂.

10:20:13 14 Do you -- do you understand the --

10:20:14 15 Q I do.

10:20:15 16 A Okay. And then the NH and the carbonyl. So
10:20:18 17 that -- what an organic comes to is called
10:20:21 18 propargylamine. And there's a large body -- not a large
10:20:26 19 body. There's a nice body of paper -- papers numbering
10:20:30 20 five to ten that sort of identified this type of linker,
10:20:34 21 this propargyl amide linker and its rigidity in
10:20:39 22 particular and its linearity as being important for
10:20:41 23 polymerase recognition and the header atom substitute --
10:20:47 24 sub -- sub -- substit- --

10:20:47 25 THE REPORTER: I'm sorry. We really do have to

10:20:47 1 get you to slow down --

10:20:47 2 THE WITNESS: I'm sorry.

10:20:47 3 THE REPORTER: -- when it comes to the
10:20:47 4 technical terms.

10:20:48 5 THE WITNESS: So there had been a body of work
10:20:51 6 that had validated, sort of identified, explored a lot
10:20:55 7 of different linkers. And what they found to be
10:20:58 8 important was this sort of -- this rigid and linear
10:21:00 9 linker with this header atom substituent at that place.

10:21:08 10 And so that would have been what I was
10:21:09 11 interested in.

10:21:16 12 BY MR. GRIER:

10:21:16 13 Q And if you look in that figure, the last -- the
10:21:21 14 bottom two structures, the one on the left labeled A-512
10:21:24 15 and the one on the right labeled G-505.

10:21:27 16 Do you see those?

10:21:28 17 A I do.

10:21:28 18 Q And in those two structures, the linker is
10:21:31 19 attached to the 7-deaza position. Is that correct?

10:21:40 20 A It is.

10:21:40 21 THE REPORTER: "Is attached to the" -- can I
10:21:40 22 hear again.

10:21:40 23 MR. GRIER: To the 7-deaza position.

10:21:40 24 BY MR. GRIER:

10:21:44 25 Q So, Dr. Romesberg, you mention that your X and

10:21:47 1 Y nucleo base -- that you were working on X and Y
10:21:52 2 nucleo-based analogs. Correct?
10:21:56 3 A Yes. Correct. Sorry.
10:21:58 4 Q And those are modified nucleotides. Is that
10:22:00 5 correct?
10:22:00 6 A They're wholly -- yes. And their nucleo-based
10:22:06 7 portion is wholly unnatural.
10:22:08 8 Q Can you explain to me the structure of -- of
10:22:10 9 those nucleo-based analogs.
10:22:14 10 A We've synthesized over 200 of them. They span
10:22:20 11 a huge range of structures. The whole point of the
10:22:24 12 project was to identify ones that were well replicated.
10:22:28 13 And so I -- that was 10 years of work in my lab. And it
10:22:32 14 was -- the way I usually describe it to other scientists
10:22:36 15 is we moved like as a medicinal chemist would, where we
10:22:42 16 designed analogs that were originally quite simple,
10:22:45 17 several classes of them, and then made lots of
10:22:47 18 modifications and examined how they were -- examined
10:22:50 19 their behavior, their stability in duplex DNA, and most
10:22:54 20 importantly, their recognition by different polymerases.
10:22:58 21 And then when we found ones that were better,
10:23:00 22 we tended to focus on that class and make modifications
10:23:03 23 to it. So I could show you the final structures -- the
10:23:07 24 final sets that we have right now that are -- are
10:23:09 25 optimized pairs. But those are the product of, like I

10:23:15 1 said, a broad exploration.

10:23:17 2 Q Just in general, do those modified nucleotides
10:23:22 3 have cleavable linkers?

10:23:26 4 A In some cases, they do.

10:23:29 5 Q And are any of those cleavable linkers
10:23:32 6 disulfide cleavable linkers?

10:23:36 7 A Yes.

10:23:36 8 Q When did you first design a compound with a
10:23:41 9 disulfide cleavable linker?

10:23:45 10 A So we didn't, per se, design it. What we
10:23:48 11 wanted to do was we wanted to enrich our PCR amplified
10:23:54 12 DNA in pairs that maintained the unnatural base pair.
10:23:57 13 And so the way we did that, rather like Ruby does in the
10:24:02 14 paper I think we're going to discuss, it had a linker on
10:24:05 15 it that we attached a commercially available
10:24:07 16 disulfide-containing moiety to it that linked the DNA to
10:24:13 17 a biotin tag. We then isolated that biotin tag in the
10:24:20 18 DNA that it was now attached to on streptavidin and then
10:24:22 19 released it so that we could -- and the reason we did
10:24:25 20 this is we wanted to characterize how much of the DNA
10:24:27 21 had our unnatural base pair in it.

10:24:31 22 Q And when were you working on those nucleotides?

10:24:34 23 A You mean those particular experiments where we
10:24:36 24 used the disulfide?

10:24:38 25 Q Correct.

10:24:39 1 A 2008, maybe. Around 2008 probably would have
10:24:43 2 been the first time.

10:24:46 3 Q And you mentioned that the -- the disulfide
10:24:49 4 cleavable linkers were commercially available. Is that
10:24:52 5 correct?

10:24:53 6 A Yes. Well, they -- they -- they were just
10:24:56 7 disulfide-containing chains with PEG, with polyethylene
10:25:02 8 glycol, that we conjugated to our unnatural base pair.
10:25:11 9 So they were sold as linkers --

10:25:14 10 THE REPORTER: "That we conjugated" -- can I
10:25:14 11 hear again.

10:25:14 12 THE WITNESS: To the linkers of our unnatural
10:25:14 13 base pair. So they weren't themselves sold with a
10:25:14 14 triphosphate or with a -- a -- with DNA. We attached
10:25:19 15 them to the DNA.

10:25:20 16 BY MR. GRIER:

10:25:23 17 Q And why specifically did you look at disulfide
10:25:26 18 cleavable linkers?

10:25:28 19 A Because they're easy to cleave with small
10:25:30 20 molecules. Convenient.

10:25:37 21 They're convenient to cleave with small
10:25:39 22 molecules. That's what I meant by "easy."

10:25:51 23 Q And the nucleotides you were working on, were
10:25:54 24 those deaza modified nucleotides?

10:25:56 25 A No. That would have no meaning because the

10:25:58 1 deaza refers to a specific position in the puring.

10:26:03 2 These aren't even purings. So there is no analogous

10:26:06 3 position.

10:26:12 4 Q Are they pyrimidines?

10:26:15 5 A No.

10:26:16 6 Q So that's what you meant when you said they

10:26:18 7 were wholly unnatural --

10:26:19 8 A Yes.

10:26:19 9 Q -- nucleo bases. Correct?

10:26:23 10 A Yeah. Yeah.

10:26:27 11 Q Do the nucleotides you were working on have 3'

10:26:28 12 protecting groups?

10:26:30 13 A No.

10:26:35 14 Q Were the nucleotides dideoxynucleotides?

10:26:44 15 A No.

10:26:45 16 Q Did the nucleotides have any substituents

10:26:48 17 substituted on the 2' position?

10:26:50 18 A For a different project, yes. But for a

10:26:54 19 different project. And that project never had linkers

10:26:58 20 or disulfides.

10:27:03 21 Q Do the nucleotides have substituent on the --

10:27:06 22 substituted on the 3' position?

10:27:11 23 A No.

10:27:24 24 Q So how many times, Dr. Romesberg, in your

10:27:27 25 estimation, have you reviewed Prober?

10:27:33 1 A For this IPR, like all the other documents, I
10:27:38 2 carefully read it once and then referred back to it.
10:27:42 3 This one, probably less. Probably referred back to it
10:27:46 4 only three or four or five times, maybe. But, unlike
10:27:54 5 the other documents, this is a document that I had read
10:27:56 6 before. And so I had read it probably -- I think it was
10:28:04 7 a little bit different then. I probably read it
10:28:07 8 straight three times, just cover -- beginning to end
10:28:09 9 three times.

10:28:14 10 Q Just to be clear, beginning to end three
10:28:16 11 times --

10:28:16 12 A 1997.

10:28:17 13 Q Thank you.

10:28:18 14 So not with respect to this IPR?

10:28:21 15 A (Gesturing).

10:28:23 16 THE REPORTER: Verbal answer?

10:28:25 17 THE WITNESS: I'm sorry?

10:28:25 18 MR. GRIER: Verbal answer.

10:28:26 19 THE WITNESS: Oh. That is correct.

10:28:28 20 MR. GRIER: Thank you.

10:28:34 21 BY MR. GRIER:

10:28:34 22 Q As it relates to this IPR, when was the first
10:28:37 23 time that you reviewed Prober?

10:28:39 24 A Shortly after the others. I think not in that
10:28:45 25 first couple of days. So my guess is early October.

10:28:49 1 Q And that's early October of 2013. Correct?

10:28:51 2 A Correct.

10:29:00 3 Q Have you ever met Dr. Prober?

10:29:01 4 A No, I have not.

10:29:06 5 Q Have you ever had discussions about

10:29:12 6 collaborating with Dr. Prober?

10:29:15 7 A No.

10:29:29 8 Q So, Dr. Romesberg, if you can turn back to

10:29:31 9 Exhibit 2012 (sic) for me. That's Chen.

10:29:42 10 When we first started looking at the Chen

10:29:43 11 reference, we were talking about Dr. Tsien, and you

10:29:45 12 mentioned that --

10:29:46 13 A He didn't like my introductions?

10:29:48 14 Q Yes. You mentioned that he did not like your

10:29:50 15 introductions, that's correct.

10:29:51 16 Why does Dr. Tsien not like your introductions?

10:29:54 17 A Are you really asking me that?

10:29:56 18 Q I am asking you that.

10:29:57 19 A Oh. It's because both times I introduced him,

10:30:00 20 he corrected me.

10:30:01 21 Q What did he correct you on?

10:30:03 22 A The first time, we had invited him to Scripps

10:30:05 23 to give a -- a departmental seminar. I had invited him.

10:30:09 24 And I was introducing him to my colleagues. And I

10:30:12 25 mentioned that he had played a seminal role in the

10:30:15 1 development of something called GFP, green fluorescent
10:30:18 2 protein. I was a young assistant professor. I was very
10:30:21 3 impressionable. And I wanted to give him a very
10:30:24 4 favorable introduction.

10:30:26 5 And then he got up and said, "Well, actually,
10:30:28 6 you know, I didn't really do that." And he sort of --
10:30:31 7 he sort of, quite correctly, corrected me.

10:30:34 8 And the second time, we had invited him to what
10:30:36 9 we call a Frontiers symposium, which is something we
10:30:40 10 have at Scripps once a year where there -- only the
10:30:43 11 biggest, sort of Nobel Prize caliber. And so I was
10:30:46 12 very, you know, conscious of putting -- and I was asked
10:30:49 13 to introduce Professor Tsien. So I spent a little time,
10:30:52 14 put together a nice little introduction for him. And I
10:30:55 15 searched around with his name.

10:30:57 16 And I found out, quite surprisingly to me, that
10:31:00 17 he had a Wiki page. So I read his Wiki page. And it
10:31:04 18 said that he was descended from royalty in China.

10:31:10 19 So in my introduction, I said, "We all know
10:31:13 20 that Dr. Tsien is scientific royalty, but I was quite
10:31:16 21 surprised to find out that he's actually also real
10:31:20 22 royalty." And then I reiterated what I had read on his
10:31:23 23 Wiki page.

10:31:26 24 And then he got up and said, "Well, actually,
10:31:28 25 if you do the math and you look at the number of

10:31:31 1 generations and the number of families that descended
10:31:32 2 from that dynasty, then we're all related -- then we're
10:31:35 3 all royalty."

10:31:36 4 And I just remember thinking to myself, you
10:31:38 5 know, if I were you, I would just take a compliment and
10:31:41 6 thank you with it. That's the -- he's a nice guy. But
10:31:44 7 my little story is that he objected to my introduction
10:31:48 8 twice.

10:31:49 9 Q And in the first -- in the first instance, he
10:31:51 10 was there for a seminar.

10:31:52 11 What -- what was Dr. Tsien there to discuss?

10:31:59 12 A You know, I think both of the times he came, he
10:32:05 13 talked about proteases on the cell surface that would --
10:32:13 14 would cleave drugs or drug candidates and activate them
10:32:18 15 locally in the presence of a cancer cell.

10:32:23 16 That was sort of his big thing that he's been
10:32:25 17 really interested in lately.

10:32:27 18 Q So he wasn't there to give seminars on
10:32:30 19 sequencing by synthesis. Correct?

10:32:31 20 A No. As I mentioned earlier, I was not even
10:32:33 21 aware that he had worked on this earlier in his career.

10:32:39 22 MR. GRIER: Okay. I think we're at a natural
10:32:40 23 breaking point if we want to -- we've been going for a
10:32:43 24 while.

10:32:43 25 You want to take a break?

10:32:45 1 THE WITNESS: I would like to take a bathroom
10:32:47 2 break.

10:32:47 3 VIDEOGRAPHER: This concludes Disk 1 of the
10:32:49 4 deposition of Dr. Floyd Romesberg. Off the record
10:32:52 5 at 10:32.

10:49:28 6 (Recess from 10:32 a.m. to 10:50 a.m.)

10:50:43 7 VIDEOGRAPHER: This is Disk 2 of the deposition
10:50:45 8 of Dr. Floyd Romesberg. Back on the record at 10:50.

10:50:50 9 MR. GRIER: All right. Dr. Romesberg, I'm
10:50:51 10 going to hand you what will be marked Intelligent
10:50:57 11 Bio-Systems Exhibit 1029.

10:51:08 12 (Exhibit 1029 was marked for identification.)

10:51:09 13 THE WITNESS: Thank you.

10:51:10 14 THE REPORTER: You're welcome.

10:51:24 15 BY MR. GRIER:

10:51:25 16 Q Dr. Romesberg, before we get going, I just want
10:51:28 17 to ask, did you have any discussions with counsel during
10:51:30 18 the break?

10:51:31 19 A Yes, I did.

10:51:32 20 Q Did you discuss your -- your testimony --

10:51:34 21 A No.

10:51:35 22 Q -- during the break?

10:51:36 23 Did you discuss any questions that might be
10:51:39 24 forthcoming --

10:51:40 25 A No.

10:51:40 1 Q -- during the break?

10:51:44 2 Did you discuss with counsel any -- any

10:51:46 3 questions that you might be asked later in the day,

10:51:48 4 during the break?

10:51:49 5 A No, I did not.

10:51:51 6 Q Okay. So in front of you, you have IBS

10:51:54 7 Exhibit 1029.

10:51:57 8 Do you recognize this document?

10:51:58 9 A Yes, I do.

10:52:00 10 Q And is this your substitute declaration?

10:52:03 11 A It is. It appears to be.

10:52:09 12 Q If you turn to page 37, is that your signature?

10:52:15 13 A It is.

10:52:15 14 Q And signed January 9th, 2014. Is that correct?

10:52:20 15 A It -- that's correct.

10:52:22 16 Q And do you recall reviewing and signing this

10:52:26 17 declaration?

10:52:27 18 A I do.

10:52:29 19 Q Does this substitute declaration reflect your

10:52:33 20 current testimony in this IPR?

10:52:35 21 A It does.

10:52:36 22 Q And have you had a chance to thoroughly

10:52:37 23 review --

10:52:39 24 A I have.

10:52:40 25 Q -- the substitute declaration?

10:52:42 1 A I have.

10:52:43 2 Q And in that thorough review, did you find any
10:52:46 3 additional errors in the substitute declaration?

10:52:49 4 A Errors? No.

10:52:57 5 Q And this document, you drafted to correct
10:53:03 6 errors in your original declaration that we were
10:53:09 7 discussing earlier today. Correct?

10:53:11 8 A Yes.

10:53:11 9 Q And what were the changes you made to this
10:53:14 10 substitute declaration?

10:53:14 11 A They were changes based on the Vermaas
10:53:18 12 declaration that had changed the -- its language, and --
10:53:21 13 and the attempt -- the attempt was to reflect those
10:53:25 14 changes.

10:53:28 15 Q Were those the -- the only changes that you
10:53:31 16 made to the substitute declaration?

10:53:35 17 A Yes, I believe so. I -- I -- there might have
10:53:39 18 been another spot where I found a word or two, but I
10:53:42 19 actually don't think I wound up making that change. So
10:53:45 20 I think, yes, those were the only changes.

10:53:50 21 Q And when you were drafting the substitute
10:53:53 22 declaration, Dr. Romesberg, who told you to make the --
10:53:56 23 the changes that you made?

10:53:57 24 A Well, the -- the Vermaas declaration had
10:54:00 25 changed, and I discussed that with Kerry and -- and Nate

10:54:07 1 and -- and they suggested that -- that the declaration
10:54:09 2 should reflect changes in the Vermaas declaration -- my
10:54:13 3 declaration should reflect the changes made in the
10:54:15 4 Vermaas declaration.

10:54:17 5 Q Did you discuss those changes with anyone other
10:54:20 6 than Kerry and Nate?

10:54:23 7 A No.

10:54:25 8 Q And what is your understanding as to why the
10:54:30 9 changes were made?

10:54:33 10 A My understanding is that they -- for reasons
10:54:36 11 that I'm not -- are you asking what changes were made,
10:54:40 12 or why there were changes made?

10:54:42 13 Q I'll clarify the question, because it was -- I
10:54:44 14 admit, that was sort of confusing.

10:54:47 15 What is your understanding as to why there were
10:54:49 16 changes made to the Vermaas declaration?

10:54:54 17 A My understanding was that he had gone back and
10:55:00 18 found a more correct experiment that -- that either by
10:55:04 19 time or for some reason was -- he preferred including in
10:55:07 20 his -- in his declaration. I guess I'm not absolutely
10:55:11 21 sure as to what his motivations were. I guess you'd
10:55:15 22 have to ask him. But I did notice them and -- and
10:55:19 23 agreed that -- that they -- that required a -- a minor
10:55:22 24 change in my declaration.

10:55:25 25 Q And so can you tell me the circumstances

10:55:27 1 surrounding how you drafted the substitute declaration?

10:55:35 2 A So the substan- -- the substantive aspect of
10:55:39 3 his change was -- was scientifically zero. It was
10:55:43 4 simply -- look. So let me be clear. There were --
10:55:48 5 there were two sort of changes.

10:55:50 6 There was an actual change in the experiment,
10:55:53 7 for example, reflected in Figure 3, is my understanding.
10:55:58 8 And I looked at both -- I was shown both figures because
10:56:02 9 I needed to make a decision as to whether or not the
10:56:04 10 change in the actual experiment reported changed any of
10:56:07 11 my opinions.

10:56:07 12 And so I looked very carefully at both the new
10:56:10 13 Figure 3 and the new Figure 2.

10:56:22 14 Where's Figure 2?

10:57:08 15 Can I ask a question to --

10:57:14 16 Q So is there something that you think is missing
10:57:18 17 from your declaration?

10:57:35 18 A Yeah.

10:57:36 19 Q And what -- what do you think is missing from
10:57:38 20 your substitute declaration?

10:57:46 21 A Figure 2.

10:57:47 22 MR. BABCOCK: I think -- I think he's maybe
10:57:48 23 thinking about the Vermaas declaration.

10:57:50 24 THE WITNESS: Oh, yeah. God. I'm so sorry.

10:57:55 25 Can I make a correction?

10:57:56 1 No, I do not notice anything missing.

10:57:58 2 BY MR. GRIER:

10:57:58 3 Q So if you look at your original declaration,
10:58:01 4 Illumina Exhibit 2009. Can you look at that for me.

10:58:04 5 A Yes. Yes. Yeah. I was -- I was mistaken.
10:58:07 6 There is nothing I see missing in my declaration. And I
10:58:11 7 can answer your question now.

10:58:16 8 Q Okay.

10:58:20 9 A So, for example, there was a new Figure 3, and
10:58:24 10 in order to make sure that I did not -- now -- that I
10:58:26 11 was comfortable that the new -- the new data, the new
10:58:29 12 experiment did not change any of my critiques. The sort
10:58:34 13 of thing is I was shown all of the new figures from the
10:58:37 14 new Vermaas declaration. And that's what I was
10:58:39 15 confusing a second ago. I apologize. And, for example,
10:58:42 16 the new Figure 3 in my dec- -- my declaration. And so I
10:58:48 17 carefully examined them and -- and was -- was convinced
10:58:51 18 there was no difference.

10:58:51 19 And the other change that was made based on the
10:58:54 20 change in the Vermaas dec was the articulation of how
10:58:57 21 the experiment was run. So if you consider a sequencing
10:59:02 22 by synthesis, it -- it's a -- it's cyclic, many rounds
10:59:07 23 of the same cycle over and over again. And the two
10:59:12 24 descriptions start at a different spot in the cycle.

10:59:15 25 And so that makes absolutely no difference to

10:59:18 1 how the experiment runs. It just makes a difference as
10:59:21 2 to the order that you list the things. And my dec- --
10:59:24 3 my declaration was changed to reflect the new
10:59:27 4 description.

10:59:30 5 Q And are those the other changes that you made
10:59:32 6 to your -- in your substitute declaration?

10:59:45 7 A That I recall, yes.

10:59:46 8 Q Did you draft your substitute declaration?

10:59:47 9 A No. It was made -- it was drafted for me from
10:59:48 10 the changes made, and there was a line edit sent to me
10:59:52 11 so I could look exactly what I -- was written before and
10:59:54 12 what it was being changed to. And we went through
10:59:57 13 sentence by sentence and made sure that I was
10:59:59 14 comfortable, that I agreed with -- with the changes.

11:00:02 15 Q And so who drafted your declaration -- your
11:00:04 16 substitute declaration?

11:00:05 17 A That would have been either Nate or Kerry, I
11:00:10 18 think.

11:00:12 19 Q So with your substitute declaration, did you
11:00:16 20 have any of the -- the meetings here that you described
11:00:20 21 earlier where you -- where you sat down with counsel and
11:00:22 22 went through the declaration as part of the drafting
11:00:26 23 exercise?

11:00:30 24 A My recollection is no. It was done by phone.
11:00:34 25 It was sent to me, and -- and I read through it. And

11:00:36 1 then we had a discussion on the phone, going through it
11:00:43 2 again line by line.

11:00:48 3 Q Other than Kerry and Nate and yourself, is
11:00:52 4 there anyone else involved in drafting your substitute
11:00:57 5 declaration?

11:01:00 6 A No.

11:01:01 7 Q Do you know if Mr. Vermaas was involved in
11:01:04 8 drafting your substitute declaration?

11:01:07 9 A I believe not. I was never -- I was -- not to
11:01:10 10 my knowledge. He was not involved, to my knowledge.

11:01:15 11 Q Do you know if anyone at -- anyone other than
11:01:18 12 Mr. Vermaas at Illumina was involved in drafting your
11:01:22 13 substitute declaration?

11:01:22 14 A Not to my knowledge. I believe not.

11:01:27 15 Q Have you had any conversations with anyone from
11:01:30 16 Scripps about your substitute declaration?

11:01:32 17 A No.

11:01:39 18 Q Were you provided an outline for drafting your
11:01:45 19 substitute declaration?

11:01:46 20 A No. Just the strike-through version that I
11:01:50 21 mentioned earlier.

11:01:52 22 Q And other than -- other than that
11:01:54 23 strike-through that you mentioned earlier, were you told
11:01:56 24 to assess or analyze any particular thing in your
11:02:00 25 substitute declaration?

11:02:01 1 A Well, I was told that -- I was warned that --
11:02:04 2 that the Vermaas declaration might change. And so I was
11:02:07 3 sent a version that says here -- here are changes that
11:02:09 4 are made to reflect, please go through this and make
11:02:13 5 sure that you're okay with the changes. So, I guess, in
11:02:15 6 a way, that was directing me to certain parts.

11:02:18 7 Q And who -- who warned you that the Vermaas
11:02:21 8 declaration might be changing?

11:02:24 9 A I believe -- I believe Nate or Kerry -- and/or
11:02:26 10 Kerry.

11:02:30 11 Q And when were you warned that the Vermaas
11:02:32 12 declaration might be changing?

11:02:37 13 A I'm really not sure. Maybe a week or two ahead
11:02:39 14 of time.

11:02:41 15 Q When you say "a week or two ahead of time," a
11:02:43 16 week or two ahead of when you signed the substitute
11:02:45 17 declaration?

11:02:49 18 A Yeah, probably -- I'm not real sure. I just
11:02:54 19 know that by the time it was coming around, I knew that
11:02:59 20 was going to happen. So I think that I was expecting
11:03:01 21 it.

11:03:05 22 Q And since you drafted your substitute
11:03:07 23 declaration, have you been asked to do any additional
11:03:11 24 tasks with respect to the substitute declaration?

11:03:14 25 A No.

11:03:17 1 Q Have you had an opportunity to thoroughly
11:03:18 2 review the substitute declaration?

11:03:21 3 A I have.

11:03:23 4 Q And have you found any additional errors in
11:03:27 5 your substitute declaration?

11:03:28 6 A Errors? Scientific errors? No.

11:03:41 7 Q Dr. Romesberg, what, if anything, did you do to
11:03:46 8 prepare for today's deposition?

11:03:48 9 A I spent two days here in this room going over
11:03:52 10 the -- the declaration and some of the reviews and just
11:03:56 11 discussion.

11:03:57 12 Q And when were those meetings?

11:04:00 13 A Wednesday and Thursday of last week.

11:04:10 14 Q So that's January 8th and January 9th of 2014.
11:04:15 15 Is that correct?

11:04:15 16 A I believe that is correct, yes. Yeah.

11:04:18 17 Q And who attended those meetings?

11:04:25 18 A Both of -- both days were attended by myself,
11:04:28 19 Kerry, and -- and Nate. And on the first day, by phone,
11:04:36 20 Marcus was on the phone occasionally. And the second
11:04:42 21 day -- oh, he may have been only on the phone the second
11:04:46 22 day. Yeah. I think he was only on the phone the second
11:04:55 23 day. And then Brent was down the -- the second day.

11:04:59 24 Q And other than -- than -- than those folks,
11:05:02 25 were there any -- anyone else at those meetings?

11:05:06 1 A I don't think so, no.

11:05:12 2 Q So Marcus was the only attendee from Illumina

11:05:15 3 at those meetings. Correct?

11:05:16 4 A By phone, for part of the meeting.

11:05:20 5 Q But there were no attendees from Illumina in

11:05:23 6 person.

11:05:26 7 A No.

11:05:27 8 Q Is that correct?

11:05:27 9 A Yes, that is correct.

11:05:30 10 Q Have you had any discussions with anyone at

11:05:34 11 Illumina other than Marcus about your deposition today?

11:05:42 12 A I have not.

11:05:43 13 Q Have you had any discussions with anyone at

11:05:45 14 Scripps about your deposition today?

11:05:47 15 A No. Other than mentioning that I had an

11:05:51 16 obligation, to my group, to let them know that I

11:05:54 17 wouldn't be here -- in lab, I mean.

11:05:59 18 Q Did you review any documents to prepare --

11:06:03 19 prepare for today's deposition?

11:06:05 20 A Yeah. All of them in that list.

11:06:08 21 Q By "that list," you're referring to

11:06:11 22 Exhibit 2011. Is that correct?

11:06:16 23 A Yes.

11:06:18 24 Q So you reviewed all of the references listed in

11:06:23 25 this exhibit to prepare for today's deposition.

11:06:27 1 A Oh.

11:06:28 2 Q Is that correct?

11:06:29 3 A You mean, specifically in the last few days for

11:06:31 4 today, or in the -- in the entirety of this IPR?

11:06:34 5 Q Well, I think we've established in the entirety

11:06:36 6 of the IPR. I'm -- I'm just more focused on as you

11:06:40 7 prepared for today's deposition, did you review --

11:06:42 8 A No.

11:06:42 9 Q -- any of the documents?

11:06:44 10 A No. I -- I reviewed what I -- what I came to

11:06:46 11 believe to be the most important documents. And I

11:06:49 12 can -- I can sort of recite most of them off the top of

11:06:52 13 my head if you'd like me to.

11:06:54 14 Q Can you please recite what you believe are the

11:06:56 15 most important documents.

11:06:58 16 A Sure. The actual -- and I -- I might miss

11:07:00 17 something since I'm just reciting this. But the obvious

11:07:06 18 patents, the '026; and the Ju documents; the Prober;

11:07:13 19 the -- the -- what we're going to probably call the Ruby

11:07:17 20 document; the Ruby -- the methods and enzymology paper;

11:07:30 21 the Rabani --

11:07:33 22 THE REPORTER: "The methods" -- can I hear

11:07:33 23 again.

11:07:33 24 THE WITNESS: Methods and enzymology paper.

11:07:30 25 -- Rabani; Herman; Short.

11:07:46 1 Those would probably be --

11:07:51 2 BY MR. GRIER:

11:07:51 3 Q And these would all be documents that you were

11:07:53 4 previously -- previously provided with from -- from

11:07:55 5 Knobbe. Correct?

11:07:57 6 A Correct.

11:07:58 7 Q Did you ask for any additional documents to

11:08:01 8 review before the deposition?

11:08:12 9 A No.

11:08:15 10 Q And how many -- how long would you estimate you

11:08:18 11 prepared for today's deposition?

11:08:24 12 A You mean, time that I spent that was not on the

11:08:27 13 declaration itself?

11:08:28 14 Q Correct?

11:08:28 15 A Oh, you know, I don't know. Twenty-five hours,

11:08:32 16 maybe.

11:08:35 17 Q And that 25 hours was in the course of the

11:08:36 18 two-day meetings that you had?

11:08:38 19 A Plus the extra time that I spent, yeah.

11:09:10 20 Oh, I'm sorry. I should add Chen to that list

11:09:13 21 of documents I thought were important.

11:09:19 22 Q Thank you.

11:09:20 23 I'm going to hand you, Dr. Romesberg, what's

11:09:22 24 been previously marked Illumina Exhibit 2010.

11:09:31 25 Do you recognize this document?

11:09:32 1 A Yeah. Yes, I do.

11:09:34 2 Q And what is this document?

11:09:35 3 A It's a pathetically -- it's a C.V. of a not
11:09:40 4 sufficiently successful academic scientist -- it's my
11:09:44 5 C.V.

11:09:45 6 Q Thank you.

11:09:46 7 And you provided this C.V. in conjunction with
11:09:49 8 your testimony in this IPR. Correct?

11:09:51 9 A Yes, that is correct.

11:09:51 10 Q And in the top right-hand corner, you see where
11:09:54 11 it says "Updated August 2013"?

11:09:59 12 A Yes.

11:09:59 13 Q So is this copy of your C.V., the most current
11:10:02 14 version of your C.V.?

11:10:10 15 A Technically, I think, yes. Yeah. Because I
11:10:12 16 don't think I've sent my C.V. out since this. So I
11:10:15 17 don't think I've made any changes that would -- the --
11:10:18 18 the C.V. lists my publications, which is always
11:10:20 19 changing. And so I don't -- so any time I send out a
11:10:24 20 C.V., I might update it. So there's probably been a
11:10:27 21 couple of papers that have been published since this
11:10:29 22 C.V. was sent here. And so -- but I don't think I've
11:10:33 23 sent out a C.V. since then. So I think this would be
11:10:35 24 the most current C.V.

11:10:36 25 Q Okay. But have you edited your C.V. to include

11:10:39 1 those -- those publications?

11:10:42 2 A No.

11:10:45 3 Q And this C.V. accurately lists your education

11:10:50 4 and work experience. Is that correct?

11:10:51 5 A I believe so.

11:11:03 6 Q So can you turn with me to page 15 of your C.V.

11:11:20 7 Do you see there is a section there, "Current

11:11:23 8 and Past Collaborators"?

11:11:26 9 A I do.

11:11:27 10 Q Okay. Does this section list all of your

11:11:33 11 current and past collaborations?

11:11:39 12 A I believe any -- any collaboration that was

11:11:41 13 substantial that actually, for example, resulted in a

11:11:44 14 publication of a paper.

11:11:48 15 Q So were there collaborations that do not appear

11:11:51 16 on this C.V. -- are there collaborations that do not

11:11:57 17 appear on the C.V.?

11:11:58 18 A Well, I guess it would depend on what you

11:12:00 19 define as collaborator.

11:12:02 20 Q Well, when you were drafting this C.V., how did

11:12:03 21 you define a collaborator?

11:12:05 22 A Just in what I view as being significant. So a

11:12:07 23 C.V. is written to let other people know what you

11:12:10 24 consider your significant accomplishments are. I guess

11:12:13 25 that's somewhat subjective. And so there certainly

11:12:15 1 might have been collaborations that did not make it onto
11:12:17 2 the C.V. because they never went anywhere, I guess. And
11:12:24 3 there are probably also collaborations listed on here
11:12:27 4 that never went anywhere. Probably so -- probably both
11:12:31 5 sides. So there's no criteria one uses to list
11:12:35 6 collaborations. But, certainly, if it resulted -- for
11:12:38 7 example, if it resulted in a paper, it would certainly
11:12:40 8 be considered a collaboration.

11:12:42 9 Q Are you aware of any collaborations that you
11:12:43 10 would consider to be less significant that you did not
11:12:47 11 list on -- in the C.V.?

11:12:51 12 A Am I aware of any collaborations that I
11:12:54 13 consider less significant?

11:12:56 14 Q Right.

11:13:01 15 A Any specific collaborations?

11:13:02 16 Q Any specific collaborations.

11:13:04 17 A I mean, if you gave me five minutes, I might --
11:13:06 18 so -- but, again, I mean, it depends on what you're
11:13:08 19 defining as a collaboration. If you're asking did --
11:13:10 20 did I ever discuss a collaboration with someone that did
11:13:13 21 not make it onto this list because it never went
11:13:15 22 anywhere, there are certainly many of those. And if you
11:13:18 23 gave me time, I can probably think of some.

11:13:22 24 Is that what you're asking me to do?

11:13:24 25 Q I'm -- your testimony is that there are certain

11:13:26 1 collaborations on this C.V. because you felt that they
11:13:29 2 were significant collaborations. Is that correct?

11:13:32 3 A Correct.

11:13:33 4 Q Okay. I'm just trying to understand if there
11:13:34 5 are other collaborations that you did not list on the
11:13:37 6 C.V. because you felt that they were less significant.

11:13:43 7 A That would probably -- I would probably state
11:13:46 8 that -- that I didn't consider them collaborations. I
11:13:49 9 think we're saying the same thing. I think the one --
11:13:51 10 the ones that were significant, I called collaborations,
11:13:54 11 and I listed.

11:13:56 12 To tell you the truth, this -- I haven't really
11:13:58 13 looked carefully at this. This is not something that I
11:14:04 14 rigorously went through and checked to make sure each
11:14:08 15 one of them were or weren't there. It's something that
11:14:10 16 academics do just to show your sort of participation in
11:14:13 17 the community.

11:14:14 18 And so there's not really a -- you know,
11:14:17 19 rigorous definition of what might or might not go on
11:14:21 20 there.

11:14:22 21 Q So then it's -- it's not your practice to
11:14:24 22 rigorously review your C.V. when you send it out?

11:14:28 23 MR. BABCOCK: Objection. Misstates the
11:14:30 24 testimony.

11:14:36 25 MR. GRIER: You can go ahead and answer.

11:14:37 1 MR. BABCOCK: You can answer.

11:14:38 2 THE WITNESS: If there were parts that I
11:14:40 3 thought were irrelevant -- and certainly everything on
11:14:43 4 here is an honest appraisal of my past job environment,
11:14:50 5 my accomplishments and -- and particularly in terms of
11:14:53 6 accomplishments, you'd be careful to list and only list
11:15:00 7 what was accurate.

11:15:01 8 Something like, you know, manuscript reviews,
11:15:03 9 there's -- there's probably manuscript journals that
11:15:06 10 I've reviewed for that I didn't list there because I
11:15:09 11 reviewed one paper for them. So it just really
11:15:11 12 doesn't -- it doesn't -- it's not in line with the --
11:15:13 13 the point of the C.V.

11:15:15 14 In past collaborators, I would put -- I would
11:15:19 15 list people that I had collaborated with that I thought
11:15:24 16 were significant collaborations. And if I came across
11:15:27 17 remembering one of them that was not listed here or
11:15:30 18 seeing one that was listed here that I no longer
11:15:32 19 believed for whatever reason was a significant
11:15:35 20 collaboration, I would probably add it or remove it.

11:15:38 21 BY MR. GRIER:

11:15:38 22 Q And do you recall adding or removing any of
11:15:40 23 those types of collaborations when you were preparing
11:15:43 24 the C.V. for this IPR?

11:15:48 25 A No. Meaning that I did not remove or add

11:15:56 1 anything to the collaboration list for this -- for

11:15:57 2 this -- to the C.V. for this IPR.

11:16:04 3 Q Dr. Romesberg, you've collaborated with

11:16:06 4 Illumina in the past. Haven't you?

11:16:09 5 A Have I collaborated with Illumina in the past?

11:16:16 6 I don't believe so. I gave a talk at Illumina.

11:16:21 7 Q And when did you give that talk at Illumina?

11:16:24 8 A Boy, I -- it's probably on my list of talks.

11:16:27 9 So I imagine that might have been -- I'm guessing 2007

11:16:31 10 or '08. Are my list of talks here? Yes. "Invited

11:16:39 11 Seminars."

11:16:40 12 Do you want me to look and find the Illumina?

11:16:42 13 Q Sure.

11:18:25 14 A I cannot find it. I must have not listed it.

11:18:32 15 Q What was your criteria for choosing which talks

11:18:34 16 to list when you were drafting your C.V.?

11:18:39 17 A So, to be honest, I don't actually do that

11:18:42 18 myself. My administrative assistant puts my talks in

11:18:45 19 invited lectures.

11:18:48 20 So, for example, I just gave a presentation at

11:18:51 21 Sequenom last year, and my guess that it -- in fact, six

11:18:54 22 months ago, maybe. It's not on here either. So maybe

11:18:58 23 she considered it because it was not a scientific

11:19:00 24 meeting or invited from a university. Maybe that's why

11:19:03 25 it didn't go on there. Or it just may have been

11:19:05 1 forgotten. I'm not sure why.

11:19:07 2 Q Are there other components of your C.V. that
11:19:09 3 your administrative assistant is tasked with drafting?

11:19:15 4 A Virtually all of it, except for probably the
11:19:17 5 parts that I paid most attention to was the -- the
11:19:21 6 research interest I think I wrote. And then I probably
11:19:25 7 glanced at it and -- and read through the entire thing
11:19:28 8 to make sure that -- that it was generally correct.

11:19:31 9 But there's a lot of things on here like
11:19:33 10 students, current students, past students, that she just
11:19:35 11 routinely would update as the group moved forward,
11:19:39 12 because there's a lot in my group that changes. And so
11:19:42 13 this would be -- it's not formally one of her things.
11:19:45 14 But every time I would send a new C.V. out, I would say
11:19:48 15 to her please -- please update it and send out a new
11:19:51 16 C.V.

11:19:51 17 Q So did you provide her with the information
11:19:53 18 that she used to draft the portions of the C.V. that she
11:19:55 19 was responsible for?

11:19:56 20 A Not really, because she has access to all that
11:20:00 21 information as part of her position. She arranges all
11:20:03 22 my travel, and obviously, if there's a student in the
11:20:06 23 lab, she has all the information. And when students
11:20:11 24 graduates, the same. And papers that we publish. She
11:20:15 25 has access to all of those.

11:20:16 1 And it will typically be things like do you
11:20:18 2 want -- you know, I -- there's -- there's a lot of cases
11:20:24 3 where you have restricted C.V.s, like they say list five
11:20:28 4 publications or 10 -- and she will typically ask me
11:20:30 5 under those cases, which papers do you want listed and
11:20:33 6 that kind of thing. Which -- which are most relevant.
11:20:36 7 For example, for an NIH application, they -- you're only
11:20:41 8 asked to list a certain number of them. And so I would
11:20:44 9 make calls then. But I've always just assumed that all
11:20:46 10 the rest were in here. And they should be.

11:20:48 11 Q So turning back to the section we were
11:20:51 12 discussing on collaborations, on page 15, did your
11:20:55 13 administrative assistant draft this section?

11:21:02 14 A An administrative assistant. I've had three. So
11:21:05 15 the current one, probably not. My guess is that this is
11:21:08 16 quite old and that she has added to it as time would
11:21:12 17 move on, as -- as -- whatever -- in whatever way she
11:21:15 18 thought was appropriate.

11:21:18 19 Q And these collaborations, then, that appear
11:21:21 20 here, did you provide -- whichever administrative
11:21:25 21 assistant drafted this section, did you provide that
11:21:28 22 administrative assistant with the collaborations to
11:21:30 23 list?

11:21:30 24 A Yeah. I would have either had to have done
11:21:31 25 that, or -- or she would have asked me if there was any

11:21:34 1 updates on this section, or she might have just known it
11:21:38 2 and knew that we were collaborating, and so she might
11:21:42 3 have just put it.

11:21:47 4 Q But it's your testimony that you don't recall
11:21:49 5 working with Illumina in the past. Correct?

11:21:52 6 A On a scientific problem? I -- I think I tried
11:21:55 7 to. I think I suggested that we might evolve
11:21:59 8 polymerases for them. And the -- and I think that was
11:22:03 9 when I went and visited them. And as a result, what
11:22:06 10 they wound up doing was starting their own protein
11:22:09 11 evolution program.

11:22:13 12 Q So you said you went and visited Illumina?

11:22:15 13 A Correct.

11:22:16 14 Q And when did you visit Illumina?

11:22:17 15 A That's what I referred to earlier when I
11:22:19 16 referred to it as a talk. It wasn't -- I guess it
11:22:21 17 wasn't really a talk. Although, I did present. It was
11:22:23 18 to a small group of people. And I -- I don't remember
11:22:25 19 when that was. It might have been 2005-ish. Probably
11:22:30 20 shortly after we published our first few papers on
11:22:34 21 polymerase evolution. So it was probably around then.

11:22:37 22 Q And do you remember who you would have spoken
11:22:39 23 with at Illumina about the possibility of developing
11:22:41 24 polymerases for them?

11:22:42 25 A No. No, I do not.

11:22:46 1 Q But it's your recollection that you never
11:22:48 2 entered into the collaboration with Illumina to do
11:22:51 3 polymerase development. Is that correct?

11:22:57 4 A Not -- no. Not -- not -- no, I don't believe
11:22:59 5 so.

11:23:25 6 MR. GRIER: Dr. Romesberg, I'm going to hand
11:23:27 7 what you will be marked IBS 1030.

11:23:48 8 (Exhibit 1030 was marked and later withdrawn.)

11:23:55 9 MR. GRIER: And I'll note for the record that
11:23:56 10 this document has been marked "highly confidential,
11:24:00 11 attorneys' eyes only."

11:24:09 12 THE REPORTER: And so for the reporter, then,
11:24:09 13 are we entering testimony that would be considered
11:24:09 14 highly confidential, attorneys' eyes only?

11:24:10 15 MR. GRIER: About this document, yes.

11:24:12 16 MR. BABCOCK: Yes. So let's go on the
11:24:15 17 attorneys -- or the confidential transcript at this
11:24:17 18 point.

11:24:23 19 THE WITNESS: So I can look at this?

11:24:24 20 BY MR. GRIER:

11:24:25 21 Q Yes. So if you'll turn to -- you see the
11:24:27 22 numbers at the bottom there, the numbers on the bottom
11:24:29 23 right-hand corner?

11:24:30 24 A Yes.

11:24:30 25 Q If you'll turn to what's marked

11:24:32 1 ILMN_COL2977743. And if you look at this email, you'll
11:24:51 2 see one-third -- one-third down, it says "Original
11:24:54 3 Message" on that page.

11:24:55 4 Do you see that?

11:24:55 5 MR. BABCOCK: Counsel, let me just -- we've
11:24:58 6 not -- I've not seen this before. I just want to make
11:25:02 7 sure we're not violating the protective order.

11:25:06 8 MR. GRIER: Right.

11:25:07 9 MR. BABCOCK: So could you -- I mean, did you
11:25:07 10 address that? These are marked "attorneys' eyes only."
11:25:11 11 They have been produced, it looks like, maybe in
11:25:14 12 litigation?

11:25:15 13 MR. GRIER: Right. And I can -- I can confirm
11:25:17 14 that we are not violating any protective order.

11:25:20 15 MR. BURCH: Actually, I am -- we've entered a
11:25:24 16 protective order and PTO, which is less stringent than
11:25:29 17 the one in the litigation. And the one in the Federal
11:25:32 18 Court litigation specifically says that documents going
11:25:36 19 to be used in the IPR, under the protective order, is as
11:25:39 20 stringent as the one in litigation.

11:25:42 21 So if you're willing to say here on the record
11:25:45 22 that you'll agree to enter into a protective order as
11:25:49 23 stringent as the one in litigation in the IPR, then you
11:25:54 24 can use this document. Otherwise, you can't use this
11:25:56 25 document.

11:25:56 1 MR. GRIER: Well --

11:25:58 2 MR. MARTY: One second. Do we want to stay on

11:25:59 3 the record here? Or do we -- do we want to maybe take a

11:26:02 4 quick break and make sure we can resolve this?

11:26:04 5 MR. BABCOCK: Yeah. We can take a break.

11:26:07 6 VIDEOGRAPHER: Off the record at 11:26.

11:28:16 7 (Discussion off the record.)

11:28:27 8 VIDEOGRAPHER: Back on the record at 11:28.

11:28:32 9 MR. GRIER: So just to confirm what was

11:28:35 10 discussed off the record, IBS at this time is going to

11:28:41 11 withdraw the previously marked Exhibit 1029 --

11:28:47 12 THE REPORTER: 1030, rather.

11:28:48 13 MR. BABCOCK: Or was it 1030?

11:28:49 14 MR. GRIER: 1030. I apologize. Pending

11:28:53 15 further discussions this afternoon, we may -- we may

11:28:57 16 revisit it. But for now, we will withdraw the -- the

11:29:01 17 exhibit.

11:29:01 18 MR. BABCOCK: That's fine.

11:29:14 19 BY MR. GRIER:

11:29:14 20 Q So, Dr. Romesberg, we'll -- we'll turn back to

11:29:16 21 the C.V., Exhibit 2010.

11:29:43 22 So you mentioned that you recalled giving a

11:29:45 23 talk at Illumina. Is that correct?

11:29:48 24 A That is correct. Giving a talk, meaning I

11:29:51 25 presented some -- I think I was interested in trying to

11:29:54 1 get them to collaborate, which means you're trying to
11:29:55 2 get them to give you money. And so I -- I probably
11:30:01 3 presented a subsection of -- of a talk that was focused
11:30:04 4 on what I thought they might be interested in, which I
11:30:06 5 think was polymerase evolution.

11:30:10 6 Q And that talk, is that the only -- the only
11:30:13 7 time you've given a talk at Illumina?

11:30:17 8 A I believe so, yeah.

11:30:27 9 Q And so you were familiar, then, with the
11:30:29 10 scientific -- with the -- with the science at Illumina.
11:30:34 11 Correct?

11:30:39 12 A Am I now, or was I then?

11:30:40 13 Q Well, we'll do both.

11:30:41 14 Were you, in 2005, familiar with the science?

11:30:44 15 A At the time -- that time I went to Illumina?

11:30:46 16 Q Right. Let me -- let me get that question out
11:30:49 17 you answer.

11:30:50 18 Were you familiar then, in 2005, at the time
11:30:52 19 you went to Illumina, with the science being performed
11:30:55 20 and done by Illumina?

11:30:57 21 A Excuse me. Remarkably unfamiliar. I knew that
11:31:01 22 they used modified nucleotides. And I suspected that
11:31:07 23 having polymerases that better recognize them would
11:31:12 24 benefit them. And that was really what I -- what I knew
11:31:15 25 at the time.

11:31:16 1 Q So what about currently, are you familiar
11:31:19 2 with -- were you -- are you familiar with the science
11:31:22 3 and the work being done by Illumina?

11:31:25 4 A Does that include what I learned with -- with
11:31:28 5 working with -- for my declaration in this deposition?

11:31:31 6 Q Sure. Yes.

11:31:33 7 A Then, certainly, rather familiar, yes.

11:31:35 8 Q Are you familiar with the science, other than
11:31:37 9 what you learned in working on this declaration?

11:31:40 10 A Was I familiar with the Illumina technology
11:31:45 11 outside of what I learned for this?

11:31:47 12 Q Correct.

11:31:49 13 A Not as much as I should have been. I was -- I
11:31:53 14 was familiar with the fact that they used fluorescent
11:31:57 15 analogs, but my -- my interest in sequencing by
11:32:00 16 synthesis was largely based from the polymerase side and
11:32:03 17 from the modified nucleotides side. And so there's a
11:32:07 18 lot of technical aspects that I just didn't know. And
11:32:09 19 I'm not sure Illumina released it. I'm not sure what
11:32:12 20 was known. And I never sort of identified that as
11:32:21 21 something I needed to learn and go track down the papers
11:32:24 22 and read.

11:32:24 23 Q In general, what is your -- what is your
11:32:26 24 opinion of Illumina science?

11:32:29 25 A It's great.

11:32:30 1 Q And what do you base that opinion on?

11:32:32 2 A The fact that they've reduced the cost of
11:32:35 3 sequencing and people -- and they facilitate a lot of
11:32:37 4 good science.

11:32:44 5 We've used -- we've published papers using --
11:32:47 6 our core facility at Scripps has one of their
11:32:49 7 instruments, and that's allowed us to do some
11:32:52 8 experiments that we wouldn't have otherwise been able to
11:32:55 9 do.

11:33:00 10 Q So you mentioned that the core at Scripps has a
11:33:03 11 Illumina machine.

11:33:04 12 Is your -- is your group currently
11:33:06 13 collaborating with Illumina?

11:33:08 14 A Well, we -- we use the instrument in our -- in
11:33:10 15 our core. I wouldn't -- I wouldn't call that a
11:33:13 16 collaboration.

11:33:14 17 Q Did you --

11:33:14 18 A Our core bought the instrument.

11:33:18 19 Past that? Is -- are we doing anything with
11:33:20 20 Illumina past that?

11:33:21 21 Q That's right.

11:33:22 22 A No.

11:33:22 23 Q Okay. So you currently don't have any
11:33:29 24 affiliation with Illumina?

11:33:30 25 A No. No.

11:33:35 1 Q Do you own any stock in Illumina?

11:33:37 2 A No. No. Not that I'm aware of. If I did, I'd

11:33:43 3 cash it.

11:33:43 4 Q And do you have any other financial ties to

11:33:45 5 Illumina?

11:33:46 6 A None that I'm aware of, no.

11:33:52 7 Q Let's turn back to page 15 of your C.V.,

11:33:55 8 please.

11:34:09 9 In reviewing these collaborations, Dr. Ju at

11:34:12 10 Columbia University is not listed. Correct?

11:34:14 11 A No, he's not listed.

11:34:19 12 Q You've worked with Dr. Ju in the past. Haven't

11:34:21 13 you?

11:34:22 14 A I -- I alluded to earlier what might have been

11:34:25 15 a potential collaboration, but I would -- no, I would

11:34:29 16 not say that I've worked with Dr. Ju in the past.

11:34:40 17 Q And the potential collaboration that you

11:34:42 18 alluded to earlier, was that for developing polymerases?

11:34:51 19 A Yeah, that would have been.

11:34:52 20 Q And you would have been developing

11:34:53 21 polymerases --

11:34:55 22 A You know, it's entirely --

11:34:56 23 Q Hold on one second.

11:34:57 24 A I'm sorry.

11:34:57 25 Q That's okay.

11:34:58 1 And you would have been developing polymerases
11:35:00 2 in conjunction with Dr. Ju's modified nucleotides. Is
11:35:03 3 that correct?

11:35:04 4 A Yeah. I -- I believe so.

11:35:08 5 Q Okay. But it's your testimony that that
11:35:14 6 collaboration -- that collaboration never actually
11:35:16 7 happened. Is that correct?

11:35:18 8 A Correct. We never ran a single polymerase
11:35:21 9 evolution experiment with an analog that Dr. Ju would
11:35:24 10 have provided, that I recall. I mean, there's lots of
11:35:41 11 experiments that you start and stop. And I -- to the
11:35:43 12 best of my knowledge, we never did anything.

11:35:51 13 Q What do you mean when you say "there's lots of
11:35:53 14 experiments that you stop and start"?

11:35:56 15 A You get materials, you -- you -- polymerase
11:36:00 16 evolution experiments take months. They involve a lot
11:36:03 17 of steps, designing things, getting things in place. Is
11:36:08 18 it possible -- like I -- like I told you, I vaguely do
11:36:12 19 remember that we discussed him maybe sending some
11:36:15 20 materials. Would it be possible that he did send them
11:36:19 21 and that a student took them and put them in the
11:36:21 22 refrigerator and maybe even ran an experiment with them,
11:36:28 23 that's what I'm saying I don't think happened. It --
11:36:31 24 it's something that we talked about. We may have talked
11:36:33 25 about putting a proposal in. We may have actually put a

11:36:40 1 proposal in. Maybe with Steve Quake. But nothing ever
11:36:43 2 came of it. We never ran those experiments.

11:36:47 3 Like I said, I -- I don't recall running those
11:36:49 4 experiments.

11:36:50 5 Q When you say you talked about putting a
11:36:52 6 proposal in, what do you mean by "putting a proposal
11:36:57 7 in"?

11:36:57 8 A I believe -- I -- I did -- I did have a more
11:37:00 9 significant collaboration with Steve Quake, and he -- he
11:37:03 10 is on here, Steve Quake here. He is at Stanford.
11:37:08 11 That's correct.

11:37:10 12 And I think that he asked me to be a
11:37:12 13 participant on a grant, and we got a little bit of --
11:37:16 14 very little bit of money on the side for it. And we ran
11:37:20 15 some experiments with some of his stuff, and it didn't
11:37:23 16 really work. But it's what led to a collaboration that
11:37:25 17 I did have with Helicos. And that's a different story.
11:37:31 18 Helicos is a different sequencing company. And it's
11:37:34 19 just -- I don't really remember. But it's possible that
11:37:38 20 Professor Ju was also in that grant, maybe, and maybe he
11:37:41 21 agreed to send us something. Maybe that's what I'm
11:37:44 22 remembering.

11:37:49 23 Q But you don't recall ever running any tests
11:37:52 24 with -- with Dr. Ju's modified nucleotides. Correct?

11:37:56 25 A You know, I'm not sure I would remember. Did

11:37:58 1 we launch a significant effort? No. That, I would
11:38:01 2 remember. And since I don't remember, I suspect it was
11:38:04 3 nothing. But it could have been, like I said, a student
11:38:07 4 might have done something. I'm not really sure.

11:38:31 5 Q Dr. Romesberg, have you had any discussions
11:38:33 6 with anyone at Scripps about Scripps' relationships with
11:38:36 7 Illumina?

11:38:43 8 A No. No. I mean, I vaguely remember listening
11:38:46 9 in on some conversations with some people in the
11:38:48 10 sequencing facility where they were talking about buying
11:38:51 11 an Illumina instrument, because I think that was sort of
11:38:53 12 a big deal for them, and they were trying to figure out
11:38:55 13 what instrument to buy. And I think they might have
11:38:58 14 asked me my opinion. I think I probably told them I had
11:39:00 15 none because I -- I don't -- I'm not really on the
11:39:03 16 technical side of that. I don't -- I didn't know at the
11:39:05 17 time much about the performance of the instrument, and I
11:39:09 18 wouldn't have had much of an opinion.

11:39:12 19 But, certainly, I've had no conversation
11:39:15 20 about -- about Illumina in any other capacity than that
11:39:19 21 trivial one.

11:39:24 22 Q So you're not aware -- you're not aware, then,
11:39:30 23 of any license agreements that Scripps and Illumina have
11:39:33 24 entered into relating to SBS. Is that correct?

11:39:37 25 A I'm unaware of no such thing, no.

11:39:39 1 Q I'll just clarify that question.

11:39:41 2 So you're not aware of any license agreements

11:39:42 3 entered into between Scripps and Illumina relating to

11:39:46 4 SBS. Correct?

11:39:47 5 A I am not aware, no. That is correct.

11:40:11 6 Q So let's turn, Dr. Romesberg, to Exhibit 1029.

11:40:30 7 THE REPORTER: The number was 1029?

11:40:33 8 MR. GRIER: 1029. Correct. The -- the

11:40:36 9 substitute declaration.

11:40:48 10 BY MR. GRIER:

11:40:49 11 Q Before we go there, Dr. Romesberg, just going

11:40:51 12 back to the -- to Scripps for a second.

11:40:55 13 Did you ask anyone's permission at Scripps

11:40:59 14 before you started working on this IPR?

11:41:05 15 A Ask permission? I don't -- I don't know

11:41:10 16 exactly what was done. What I -- my administrative

11:41:13 17 assistant handled this. And, as I said earlier, what I

11:41:16 18 think that means is they simply informed someone at

11:41:19 19 Scripps that I was doing some sort of an outside

11:41:23 20 activity. I don't know what constitutes asking for

11:41:25 21 permission. That might, I guess. Or --

11:41:31 22 Q Do you recall filling out any forms, for

11:41:33 23 example --

11:41:34 24 A I don't -- no, I don't recall.

11:41:36 25 Q Let me finish the --

11:41:36 1 A Sorry.

11:41:37 2 Q It's okay.

11:41:38 3 So do you recall filling out any forms, for

11:41:39 4 example, where you had to list the fact that you were

11:41:43 5 testifying in support of Illumina, prior to your

11:41:48 6 participation in this IPR?

11:41:50 7 A No.

11:41:51 8 Q Okay. Okay. If we can turn back to

11:42:01 9 Exhibit 1029, it's your substitute declaration. And, in

11:42:09 10 particular, I'd like to look at page 6. And page 6

11:42:18 11 lists the proposed claims.

11:42:21 12 Do you see that?

11:42:21 13 A I do.

11:42:23 14 Q Okay. So I'd like to walk through with you the

11:42:27 15 elements of these -- of these proposed claims. In

11:42:30 16 particular, I'd like to focus on proposed Claim 9.

11:42:33 17 Okay? So proposed Claim 9 is a nucleotide -- first

11:42:41 18 recites a nucleotide triphosphate molecule.

11:42:45 19 Do you see that?

11:42:45 20 A I do.

11:42:45 21 Q Okay. And you would agree with me that as of

11:42:49 22 2002, nucleotide triphosphate molecules were known in

11:42:53 23 the prior art. Correct?

11:42:54 24 A Correct.

11:42:55 25 Q Okay. Let's look now at the next element.

11:43:05 1 It's a 7-deazapurine base linked to a detectable label
11:43:12 2 via a cleavable linker.

11:43:13 3 Do you see that?

11:43:14 4 A I do.

11:43:15 5 Q Would you agree with me that in 2002, the
11:43:20 6 general concept of a base -- a detectable label being
11:43:27 7 linked to a base via cleavable linker was known in the
11:43:32 8 art?

11:43:32 9 A I would agree with that.

11:43:33 10 Q Okay. Let's look at the next element. And
11:43:39 11 there the cleavable linker is attached to the 7-position
11:43:42 12 of the 7-deazapurine base.

11:43:46 13 Do you see that?

11:43:47 14 A I do.

11:43:48 15 Q And would you agree with me that as of 2002,
11:43:50 16 the concept of attaching a linker to a 7-position of a
11:43:55 17 7-deazapurine base was known in the prior art?

11:44:00 18 A I agree.

11:44:01 19 Q And in particular -- and we'll turn back to a
11:44:03 20 reference we were discussing earlier today,
11:44:05 21 Exhibit 1013. If you'll -- if you'll look at that.

11:44:18 22 It's the Prober reference. And I believe it
11:44:24 23 was your testimony that the Prober -- the Prober
11:44:26 24 reference was a famous reference. Is that correct?

11:44:30 25 A Amongst people interested in sequencing, it was

11:44:33 1 a well-known -- it was a well-known cited paper.

11:44:42 2 Q So because of this -- because of the fact that
11:44:45 3 the -- that the Prober reference was well known or
11:44:49 4 famous to those in -- in sequencing, the concept of
11:44:52 5 attaching a -- a linker to the 7-position of a -- of a
11:44:58 6 deazapurine was known in the art in 2002. Is that
11:45:02 7 correct?

11:45:03 8 A Yes.

11:45:06 9 Q And if we look at -- if we look at the next --
11:45:13 10 let's skip down to the next -- "wherein the nucleotide
11:45:17 11 triphosphate molecule has a ribose or deoxyribose sugar
11:45:23 12 moiety comprising a protecting group attached via the 3'
11:45:25 13 oxygen atom."

11:45:27 14 Do you see that limitation?

11:45:31 15 A I do.

11:45:31 16 Q Okay. And would you agree with me that in
11:45:34 17 2002, attaching a protecting group to 3' oxygen atom of
11:45:37 18 a ribose or a deoxyribose sugar moiety was known in the
11:45:43 19 prior art?

11:45:44 20 A I would agree with that.

11:45:45 21 Q If we skip down to the next and final
11:45:48 22 limitation in the claim, you see there that it says the
11:45:52 23 linkage, which is the cleavable linker, and the
11:45:55 24 protecting group are cleavable under identical
11:45:57 25 conditions.

11:45:58 1 Do you see that?

11:45:58 2 A I do.

11:46:00 3 MR. BABCOCK: Objection. Misstates the -- the

11:46:01 4 text.

11:46:01 5 BY MR. GRIER:

11:46:02 6 Q And would you agree with me that in 2002, it

11:46:06 7 was known that you could cleave a linker and a

11:46:10 8 protecting group under identical conditions?

11:46:12 9 A No, I would not agree with that.

11:46:15 10 Q So if we can turn to -- start Exhibit 1012:

11:46:25 11 That's the Chen reference. And, in particular, if you

11:46:41 12 can turn to page 28 of Chen. And we'll just -- so we'll

11:46:55 13 be clear with each other going forward -- because I know

11:46:57 14 these references are marked in two different ways. So

11:47:00 15 what we'll do is when I refer -- it looks like you're

11:47:03 16 referring to the bottom number. Is that correct? So --

11:47:06 17 A I can refer to either.

11:47:06 18 Q I'll -- I'll -- to make it easy, let's refer to

11:47:09 19 the bottom number.

11:47:10 20 A Okay.

11:47:10 21 Q The exhibit label. So in that case, turn to

11:47:13 22 page 0030. In particular, lines 5 through 8 there.

11:47:23 23 Do you see that?

11:47:27 24 A I do.

11:47:28 25 Q So you see there that Chen says the -- one

11:47:31 1 method involves the use of a tag attached to the base

11:47:35 2 moiety. Correct?

11:47:37 3 A Yes. Correct.

11:47:38 4 Q And that's -- that is a fluorescent label

11:47:40 5 attached to the base of a nucleotide. Correct?

11:47:42 6 A Yes.

11:47:43 7 Q Okay. And then the next sentence says "The tag

11:47:45 8 may be chemically cleaved (either separately or

11:47:49 9 simultaneously with the deblocking step)."

11:47:51 10 Do you see that?

11:47:52 11 A I do.

11:47:52 12 Q And the deblocking step that Chen is referring

11:47:55 13 to there is the 3'OH blocking group. Correct?

11:47:59 14 A Yes.

11:48:00 15 Q So then you would agree that the concept in

11:48:02 16 2002 -- that it was known in the art that you could

11:48:04 17 cleave a base labeled -- a cleavable linker attaching a

11:48:10 18 label to a base and a 3' protecting group?

11:48:16 19 A Just to be clear, I guess what I'm -- I think

11:48:17 20 what we're disagreeing here is whether -- with here is

11:48:19 21 whether the suggestion had been made or whether it was

11:48:22 22 known that you could. I see that Chen is suggesting

11:48:26 23 that. And that was known in -- and that had been

11:48:28 24 suggested in the literature before. I don't believe

11:48:30 25 that Chen provides any data.

11:48:36 1 Q But the prior art did show -- and Chen is an
11:48:38 2 example of that -- that a person of skill in the art
11:48:42 3 could cleave a cleavable linker attaching a label to a
11:48:46 4 base and a 3' protecting group.

11:48:50 5 A I don't --

11:48:51 6 Q Correct?

11:48:51 7 A No. I don't know that Chen provided that. I
11:48:53 8 don't know that anyone -- I don't know that that was
11:48:55 9 known. I'm -- I'm unaware of that.

11:48:57 10 Q But Chen suggests that you could do that.
11:49:00 11 Correct?

11:49:00 12 A Yes. The suggestion was there that one might
11:49:02 13 do that.

11:49:03 14 Q Okay.

11:49:03 15 A And Chen is not the only one that was -- so
11:49:07 16 just to be clear, the difference that we had was whether
11:49:09 17 or not it had been suggested or shown.

11:49:16 18 Q You said others had suggested that.

11:49:18 19 Who else had suggested that you could cleave a
11:49:21 20 label attached to a base and a protecting group under
11:49:25 21 identical conditions?

11:49:31 22 A For example, I believe the Dower proposal, I
11:49:36 23 believe, suggest -- suggests that. I -- that may be --
11:49:42 24 I may have misspoken there. I -- I -- at the moment, a
11:49:47 25 lot of running -- a lot of different reading is running

11:49:51 1 into each other.

11:49:52 2 Q Well, let's turn to the Dower reference. And
11:49:54 3 that's Exhibit 1014. And, in particular, let's turn to
11:50:03 4 page 25 of the Dower reference.

11:50:15 5 You see that?

11:50:15 6 A Yes, I do.

11:50:16 7 Q Okay. And on page 25, we're in Column 25,
11:50:21 8 starting at line 35.

11:50:23 9 Do you see that?

11:50:23 10 A Okay.

11:50:24 11 Q Okay. And there, Dower says that "The
11:50:29 12 fluorophore is placed in a position other than the 3'OH
11:50:33 13 of the nucleoside."

11:50:34 14 Do you see that?

11:50:35 15 A I do.

11:50:35 16 Q Okay. And that a group is placed on the 3'OH
11:50:38 17 to function as a chain terminator.

11:50:40 18 Do you see that?

11:50:40 19 A I do.

11:50:41 20 Q Okay. And then Dower goes on to say "The
11:50:43 21 fluorophore and the 3' blocking group are removed by the
11:50:47 22 same treatment in a single step (preferably)."

11:50:51 23 Do you see that?

11:50:51 24 A Yes.

11:50:52 25 Q Okay.

11:50:52 1 A That's likely -- I'm sorry.

11:50:55 2 Q So then you would agree that in 2002, Dower

11:50:58 3 showed that you could cleave a -- a label attached to a

11:51:03 4 base and a 3' blocking group under identical conditions.

11:51:08 5 Correct?

11:51:09 6 A No. I would disagree with that.

11:51:10 7 Q But you would agree that Dower suggests that

11:51:12 8 you could do that.

11:51:14 9 A Yes.

11:51:15 10 Q Correct?

11:51:15 11 A Correct. And that -- that's what I was

11:51:18 12 remembering.

11:51:30 13 Q Let's turn to Exhibit 1008. IBS Exhibit 1008.

11:51:45 14 And this is the Ju patent. Correct?

11:51:48 15 A Yes.

11:52:11 16 Q In particular, turn to page 38 of Ju. And

11:52:20 17 we're in Column 14 on page 38.

11:52:22 18 Do you see that?

11:52:23 19 A Column 14?

11:52:24 20 Q Column 14, yes.

11:52:26 21 A Yes, I see it.

11:52:28 22 Q Okay. Starting about line 10, there's a

11:52:31 23 paragraph there where Ju lists means by which you could

11:52:35 24 cleave the linker attaching the label to the base.

11:52:39 25 Do you see that?

11:52:39 1 A I do.

11:52:41 2 Q Okay. And then the -- the following paragraph,

11:52:46 3 Ju lists various methods that you could use to cleave

11:52:50 4 the 3' protecting group.

11:52:54 5 Do you see that?

11:52:54 6 A I do.

11:52:55 7 Q Okay. And those are the same methods that Ju

11:52:57 8 lists in both of those paragraphs. Correct?

11:53:01 9 A Yep, they -- yes, they appear to be.

11:53:04 10 Q So then would you agree that in 2002, Ju showed

11:53:09 11 that you could cleave the linker attaching the label to

11:53:12 12 a base and the protecting group, that those were

11:53:17 13 cleavable under identical conditions?

11:53:19 14 A No, I would not agree with that.

11:53:21 15 Q Would you agree that Ju suggests that you could

11:53:25 16 cleave the label from the base and a 3' protecting group

11:53:33 17 under identical conditions?

11:53:40 18 A That might be an inference one draws from that.

11:53:42 19 I can see a logical connection, but I don't see that he

11:53:45 20 states that. He doesn't use the word "simultaneous" or

11:53:48 21 he doesn't say "identical conditions." He just lists a

11:53:50 22 litany of ways that one might cleave something, and if

11:53:53 23 they wound up being the same way, I don't know if that

11:53:56 24 would have been considered intentional or a coincidence.

11:54:01 25 Q But as one of skill in the art, if you read

11:54:03 1 that, then you would understand Ju to be suggesting that
11:54:06 2 you could cleave the cleavable linker and the protecting
11:54:09 3 group under identical conditions.

11:54:10 4 A I --

11:54:12 5 Q Correct?

11:54:12 6 A He has no data. So he's not demonstrating
11:54:14 7 anything. Whether he's suggesting one could, no, I
11:54:22 8 wouldn't -- I wouldn't conclude that.

11:54:23 9 Q You said, though, that a reasonable inference
11:54:25 10 could be drawn that that's what Ju's suggesting.
11:54:27 11 Correct?

11:54:27 12 A Simply because they both have the same lists.
11:54:29 13 But, again, I'm not sure if -- I see no indication, nor
11:54:32 14 do I recall an indication from Ju. I'd have to -- if
11:54:35 15 you want -- I mean, I might have to review in a little
11:54:38 16 more -- to get context. But I -- I have no recollection
11:54:40 17 of him suggesting that that was advantageous. I have no
11:54:52 18 recollection that that was something -- when -- when I
11:54:53 19 read this, I didn't leave thinking that he was
11:54:56 20 suggesting that.

11:54:57 21 Q So I'm not really asking anything about whether
11:54:59 22 it's advantageous. I'm simply asking whether, as one of
11:55:05 23 skill in the art, you could read Ju and see that at the
11:55:10 24 very least, Ju is suggesting that you could cleave the
11:55:13 25 cleavable linker attaching the label to the base and the

11:55:18 1 three-prime protecting group under identical conditions?

11:55:21 2 MR. BABCOCK: Asked and answered.

11:55:24 3 THE WITNESS: I don't see that.

11:55:26 4 So if you want a little clarification on that,
11:55:29 5 he lists chemical means, physical means, heat, and
11:55:36 6 light.

11:55:37 7 BY MR. GRIER:

11:55:36 8 Q Right.

11:55:37 9 A That's everything. I -- I can't -- I don't
11:55:41 10 know of a -- another way to cleave -- to effect a
11:55:45 11 change. And since he's suggesting both for both, I --
11:55:50 12 I -- I don't see that there's any suggestion there that
11:55:54 13 they might be cleaved under -- under the same
11:55:56 14 conditions.

11:55:57 15 Q But you would agree that Ju provides choices
11:55:59 16 for things that you could use to cleave both the
11:56:01 17 cleavable linker and the protecting group. Correct?

11:56:04 18 A But choices that are so broad as to be
11:56:07 19 nonilluminating. I mean, chemical means, physical
11:56:10 20 means, heat, and light.

11:56:14 21 Q As -- as one who is familiar in nucleotide
11:56:17 22 chemistry, when you read "chemical means," you could
11:56:22 23 determine a chemical mean to cleave a cleavable linker.
11:56:25 24 Could you not?

11:56:27 25 A Sure, I could.

11:56:27 1 Q Okay.

11:56:27 2 A But I don't see that Ju is suggesting one.

11:56:29 3 Q That's not what I'm asking.

11:56:30 4 You could, as one of skill in the art,

11:56:33 5 determine a chemical means to cleave a cleavable linker

11:56:36 6 from the base. Correct?

11:56:36 7 A I could.

11:56:37 8 Q Okay. And you, as one of skill in the art,

11:56:40 9 could also determine a chemical means that you could use

11:56:42 10 to cleave the 3' protecting group. Correct?

11:56:49 11 A Those are complicated questions.

11:56:51 12 Do you mean in a way that's compatible with

11:56:54 13 sequencing by synthesis, or just in general?

11:56:57 14 Q I mean in general.

11:56:58 15 A Could I take a nucleotide and find a way to

11:57:00 16 chemically cleave a linker?

11:57:02 17 Q Yes.

11:57:03 18 A Yes.

11:57:04 19 Q Okay.

11:57:05 20 A I, as one skilled in the art, and I imagine

11:57:08 21 others who are skilled in the art could as well.

11:57:11 22 Q So you, as one of skill in the art, you could

11:57:15 23 choose a chemical condition to cleave the cleavable

11:57:17 24 linker and the chemical condition to cleave the 3'

11:57:22 25 protecting group that would be the same conditions.

11:57:24 1 Correct?

11:57:25 2 A If I were motivated to do so, I -- I -- repeat
11:57:31 3 the question, please.

11:57:33 4 MR. GRIER: Could you read back the question,
11:57:33 5 please.

11:57:46 6 (The following was read by the reporter:

11:57:46 7 Q So you, as one of skill in the art, you could
11:57:46 8 choose a chemical condition to cleave the cleavable
11:57:46 9 linker and the chemical condition to cleave the 3'
11:57:46 10 protecting group that would be the same conditions.
11:57:46 11 Correct?)

11:57:48 12 THE WITNESS: No. I'd have to think about
11:57:50 13 that. I mean, so just to clarify to make sure I give
11:57:54 14 you the correct answer, we're not talking about anything
11:57:58 15 related to sequencing by synthesis, but we are talking
11:58:01 16 about a nucleotide?

11:58:03 17 BY MR. GRIER:

11:58:03 18 Q We are talking about a nucleotide right now,
11:58:06 19 that's correct. And a nucleotide that has cleavable
11:58:08 20 moieties at the -- at the -- attaching a label to a base
11:58:13 21 and a cleavable moiety at the 3' group of the
11:58:18 22 nucleotide.

11:58:18 23 A And so with no restrictions on efficiency, no
11:58:21 24 restrictions on compatibility with DNA, could I come up
11:58:24 25 with something that were chemically cleavable at both

11:58:27 1 those sites?

11:58:28 2 Q And that -- and that condition being the same
11:58:30 3 condition, correct, could you come up with that, as one
11:58:33 4 of skill in the art?

11:58:34 5 A Today, yeah.

11:58:39 6 Q Could you have in 2002?

11:58:52 7 A It would -- paying no regard to efficiency and
11:58:57 8 no regard to compatibility with sequencing by synthesis.
11:59:00 9 Correct?

11:59:02 10 Q Correct.

11:59:03 11 A Likely, probably. Not as confidently as today,
11:59:10 12 but probably.

11:59:14 13 Q So if you look back at proposed Claim 9 for a
11:59:17 14 second, in Exhibit 1029, in your substitute declaration,
11:59:24 15 this claim -- nowhere does this claim require that the
11:59:29 16 nucleotide recited is used in sequencing by synthesis.
11:59:32 17 Correct?

11:59:45 18 A In Claim 9, I don't see that.

11:59:48 19 Q Okay. So all this claim requires is that you
11:59:50 20 have a nucleotide triphosphate molecule with the various
11:59:54 21 limitations and that the cleavable linker and the
11:59:57 22 protecting group are cleavable under identical
11:59:59 23 conditions. Correct?

12:00:02 24 A Correct.

12:00:03 25 How -- can I add a slight qualification to my

12:00:06 1 earlier statement, then?

12:00:08 2 Q Which earlier statement are you attempting to
12:00:10 3 qualify?

12:00:12 4 A Would someone skilled in the art be able to
12:00:13 5 come up with conditions that could cleave both a 3' and
12:00:15 6 a linker. And I -- I caveated that -- that --
12:00:20 7 regardless of using sequencing by synthesis. And I'd
12:00:27 8 also like to caveat that by saying that the triphosphate
12:00:30 9 itself is an important issue. So would -- so would
12:00:37 10 someone have been able to come up with a -- a cleavage
12:00:41 11 mechanism that cleaves both groups without damaging
12:00:45 12 the -- the triphosphate back of the -- the
12:00:48 13 triphosphate -- moiety of the triphosphate.

12:01:00 14 Yeah, I'll -- I'll likely keep my same answer.

12:01:03 15 Q And that answer is that yes --

12:01:05 16 A Probably.

12:01:06 17 Q I'm sorry -- I'm sorry. Just let me
12:01:08 18 answer (sic) the question first.

12:01:09 19 And that answer would be, yes, that one of
12:01:12 20 skill in the art could determine conditions by which you
12:01:14 21 could cleave the cleavable linker and the protecting
12:01:16 22 group under identical conditions.

12:01:18 23 A One might -- one would have had a guess as --
12:01:24 24 of -- about conditions that one might have used. It was
12:01:29 25 not demonstrated then. So you would not have known.

12:01:33 1 And it would have been restricted by what was known at
12:01:37 2 the time. But you could have proffered a suggestion
12:01:40 3 of -- of a -- of conditions that might have cleaved
12:01:45 4 both.

12:01:45 5 But, again, it wasn't known. So -- but you're
12:01:49 6 asking me if someone could have suggested conditions.
12:01:51 7 Correct?

12:01:54 8 Q I'm asking -- I think this all started because
12:01:56 9 I'm asking you if, in particular, Ju suggests that you
12:02:00 10 could cleave the cleavable linker and the protecting
12:02:04 11 group under identical conditions.

12:02:09 12 A Could I see where Ju states that?

12:02:10 13 Q Sure. If you turn back to page 38 of Ju, it's
12:02:16 14 Exhibit 1008.

12:02:24 15 A 1008. Okay. Right here. Right.

12:02:34 16 Now, this is -- this is where I'm -- I'm not
12:02:38 17 sure you and I agree as to whether or not he's
12:02:40 18 suggesting that.

12:02:42 19 Q Your previous testimony, though, was as a
12:02:45 20 person of skill in the art, you could look and choose a
12:02:51 21 chemical condition by which you would cleave the
12:02:53 22 cleavable linker and the chemical condition by which you
12:02:58 23 could cleave a 3'OH protecting group, and you could
12:03:03 24 determine chemical conditions that would be identical.

12:03:06 25 A Determine -- you could choose conditions to try

12:03:11 1 that would be identical. But, again, I don't think Ju
12:03:15 2 is suggesting this.

12:03:21 3 Q But you would agree that Chen is suggesting
12:03:24 4 that.

12:03:24 5 A Yes.

12:03:25 6 Q Right?

12:03:39 7 THE WITNESS: I'm sorry. Could I, before you
12:03:43 8 ask a question, run to the bathroom? Could I ask for a
12:03:46 9 break?

12:03:47 10 MR. GRIER: Sure. It's noon. Do you want to
12:03:49 11 take a -- go ahead and go for lunch?

12:03:52 12 MR. BABCOCK: That would be fine.

12:03:52 13 MR. GRIER: Is that okay with you,
12:03:53 14 Dr. Romesberg?

12:03:54 15 THE WITNESS: How ever -- if it involves going
12:03:58 16 to the bathroom, it's fine with me.

12:04:00 17 MR. GRIER: I think we can arrange that.

12:04:02 18 VIDEOGRAPHER: Off the record at 12:03.

13:10:24 19 (Lunch recess from 12:03 p.m. to 1:12 p.m.)

13:12:49 20 VIDEOGRAPHER: Back on the record at 1:12.

13:12:56 21 BY MR. GRIER:

13:12:57 22 Q All right. Dr. Rosenberg -- Romesberg. I
13:13:02 23 apologize.

13:13:03 24 A No problem.

13:13:03 25 Q A named partner in our firm before we merged

13:13:07 1 with Ballard Spahr was Sumner Rosenberg. So just to
13:13:11 2 explain that.

13:13:11 3 Okay. So during the -- the lunch break,
13:13:13 4 Dr. Romesberg, did you have any discussions with
13:13:15 5 counsel?

13:13:18 6 A No -- yes.

13:13:18 7 Q Did you discuss your testimony in today's
13:13:21 8 deposition?

13:13:21 9 A No.

13:13:21 10 Q Did you discuss questions that I might be
13:13:22 11 asking this afternoon?

13:13:23 12 A No.

13:13:24 13 Q Did you discuss any questions that your counsel
13:13:29 14 might be asking you later today when I'm done?

13:13:31 15 A No.

13:13:32 16 Q Okay. So if you'll turn to -- back to IBS
13:13:39 17 Exhibit 1029, which is your substitute declaration.

13:13:46 18 Do you recall before the break we were going
13:13:47 19 through the proposed Claim 9, and that's on page 6 of
13:13:52 20 the exhibit. And we were discussing the elements of
13:13:58 21 proposed Claim 9. So I just want to return back to that
13:14:02 22 claim.

13:14:04 23 You see the third limitation down, "wherein the
13:14:09 24 cleavable linker contains a disulphide linkage."

13:14:12 25 Do you see that?

13:14:13 1 A I do.

13:14:13 2 Q Okay. And would you agree with me that the
13:14:15 3 concept of a disulphide linkage was known in the prior
13:14:19 4 art as of 2002?

13:14:21 5 A Yes. For -- in general, or for a nucleotide?

13:14:27 6 Q In general.

13:14:28 7 A In general, yes.

13:14:29 8 Q Was a disulphide linker for use in a
13:14:33 9 nucleotide, would you agree that that was known in 2002
13:14:36 10 as well?

13:14:36 11 A It was known, yes.

13:14:38 12 Q Okay. Would you also agree that as of 2002, it
13:14:43 13 was known that you could use a disulphide linker and
13:14:48 14 nucleotide for -- for SBS?

13:15:00 15 A No, I would not agree with that.

13:15:10 16 Q Dr. Romesberg, I will hand you what's been
13:15:12 17 previously marked Illumina Exhibit 2015.

13:15:21 18 Do you recognize this document?

13:15:27 19 A Yes. Yes.

13:15:30 20 Q This is the Rabani patent application.
13:15:34 21 Correct?

13:15:36 22 A Yes. Yeah.

13:15:36 23 Q So going forward for the rest of the day, can
13:15:39 24 we just work under the assumption that when I refer to
13:15:42 25 "Rabani," I'm referring to Exhibit 2015?

13:15:50 1 A Yes.

13:15:53 2 Q Okay. Can you look at paragraph 49 of your

13:16:13 3 declaration.

13:16:14 4 A Of my declaration?

13:16:16 5 Q Yes. Of Exhibit 1029, the substitute

13:16:19 6 declaration.

13:16:22 7 A I'm sorry. Page what?

13:16:24 8 Q Paragraph 49.

13:16:26 9 A Paragraph 49. Yes.

13:16:30 10 Q Okay.

13:16:32 11 A I'm sorry. Can I ask for clarification?

13:16:33 12 What was the question?

13:16:34 13 Q The question was so you would agree that as of

13:16:38 14 2002, it was known in the prior art you could use a

13:16:41 15 disulphide linker attached to a nucleotide in the

13:16:45 16 context of SBS?

13:16:46 17 A Okay. No, I -- I -- I -- I would like to keep

13:16:50 18 my answer.

13:16:51 19 Q And -- and that answer was --

13:16:52 20 A No, I -- I don't -- I do not believe that was

13:16:55 21 known.

13:16:55 22 Q Okay. But just -- just for clarification

13:16:57 23 purposes, but you do agree that as of 2002, it was known

13:17:01 24 to attach disulphide linkers to nucleotides.

13:17:06 25 A That was known.

13:17:06 1 Q Correct?

13:17:06 2 A Correct.

13:17:27 3 Q So can you turn with me to page 32 of the

13:17:30 4 Rabani reference.

13:17:32 5 A I'm sorry. Did you want to say something about

13:17:35 6 paragraph 49 of my dec?

13:17:36 7 Q I just -- I want them both sort of --

13:17:39 8 A Okay.

13:17:40 9 Q -- together. Yeah.

13:17:41 10 A Where in the Rabani?

13:17:45 11 Q Page 32.

13:17:51 12 So, then, looking back now at your declaration,

13:17:54 13 paragraph 49, you testified that "Rabani is directed to

13:17:56 14 a device, compounds, algorithms, and methods of

13:18:00 15 molecular characterization and manipulation with

13:18:02 16 molecular parallelism." Is that correct?

13:18:07 17 A Yes.

13:18:08 18 Q Okay. So what do you understand the term

13:18:09 19 "molecular characterization" to mean?

13:18:15 20 A So, first of all, I found a lot of the Rabani

13:18:19 21 patent to be an odd and difficult to read and sort of

13:18:23 22 difficult to follow patent.

13:18:27 23 He's talking a lot about things like molecular

13:18:29 24 recognition. And I -- for -- for the purposes of this

13:18:34 25 IPR, I -- I guess I interpreted that as in terms of

13:18:37 1 sequencing, sort of.

13:18:39 2 Q So just to be clear, you interpreted the term
13:18:42 3 "molecular characterization" in Rabani to mean
13:18:44 4 sequencing?

13:18:45 5 A I didn't put a lot of thought into it. If I --
13:18:48 6 if I thought about it now, I -- to tell you the truth, I
13:18:52 7 don't really know what his title means. It's -- it's an
13:18:56 8 odd title. It's an odd -- so I -- I don't really have a
13:19:03 9 strong opinion about what he means by "molecular
13:19:06 10 characterization" there.

13:19:07 11 Q When you cited to Rabani in paragraph 49 of
13:19:10 12 your substitute declaration and you said in that
13:19:15 13 paragraph that "Rabani was directed to a device,
13:19:18 14 compounds, algorithms, and methods of molecular
13:19:24 15 characterization," when you drafted paragraph 49, what
13:19:27 16 was your understanding of the term "molecular
13:19:29 17 characterization"?

13:19:32 18 MR. BABCOCK: Objection. Mischaracterizes what
13:19:33 19 the text says.

13:19:34 20 THE WITNESS: I guess I was simply stating what
13:19:35 21 he states in his title.

13:19:46 22 BY MR. GRIER:

13:19:47 23 Q Did you understand "molecular characterization"
13:19:48 24 to mean sequencing?

13:19:52 25 A I -- I think so. I mean, I don't think it

13:19:55 1 means only that in the context of his patent. But I
13:19:59 2 think it certainly is -- that is part of what he means
13:20:01 3 by that.

13:20:04 4 Q Okay. So if you turn to page 12 of the Rabani
13:20:18 5 reference.

13:20:30 6 And if you look at line 6 there on page 12, do
13:20:35 7 you see where Rabani is discussing DNA polymerase
13:20:39 8 enzymes?

13:20:40 9 A Yes.

13:20:40 10 Q And he's discussing these in the context of --
13:20:43 11 of using them in sequencing applications.

13:20:46 12 Do you see that?

13:20:46 13 A Yes.

13:20:50 14 Q So Rabani, then, was discussing in this
13:20:52 15 reference, nucleotide sequencing. Correct?

13:20:56 16 A Yes.

13:20:56 17 Q Okay. So then if you turn to page 32 of
13:21:03 18 Rabani, about line 10 on page 32, do you see where it
13:21:12 19 says "cleavable linkers"?

13:21:15 20 A I'm sorry. What line?

13:21:16 21 Q About -- about line 10. So --

13:21:18 22 A Yes.

13:21:19 23 Q Okay. And if you follow down in that same
13:21:22 24 section to line 29, it's -- Rabani states there
13:21:30 25 "Linkages comprising disulfide bonds within their length

13:21:34 1 have been developed to provide for cleavability."

13:21:38 2 Do you see that?

13:21:39 3 A Yes, I do.

13:21:39 4 Q Okay. So then would you agree that Rabani

13:21:44 5 states that you could use a disulfide bond in a

13:21:49 6 nucleotide using sequencing?

13:21:55 7 A I -- again, I believe that he suggests it.

13:21:59 8 Q But the text there on line 29 actually states

13:22:06 9 that. Correct?

13:22:07 10 A Well, it says "Linkages comprising disulfide

13:22:10 11 bonds within their length have been developed to provide

13:22:13 12 for cleavability."

13:22:18 13 Q Right. So Rabani there is discussing disulfide

13:22:21 14 cleavable linkers. Correct?

13:22:27 15 A Yes. Yeah.

13:22:28 16 Q Okay. So then Rabani is an example of prior

13:22:34 17 art that discloses disulfide bonds in nucleotides used

13:22:43 18 for sequencing.

13:22:47 19 Would you agree to that?

13:22:49 20 A Rabani suggests, yes, that you could use -- he

13:22:52 21 teaches that you could use nucleotides with disulfide

13:22:55 22 linkages for sequencing by synthesis.

13:23:18 23 Q But, again, the text there, the text at

13:23:21 24 line 39 -- or line 29 -- I apologize -- the text there

13:23:25 25 actually states it?

13:23:30 1 A It states that they've been developed to
13:23:33 2 provide for cleavability and gives a reference, and in
13:23:36 3 that reference, that's certainly what they're talking
13:23:38 4 about.

13:23:41 5 Q They're talk -- when you say "certainly what
13:23:43 6 they're talking about," they're talking about using
13:23:46 7 disulfide cleavable linkers in nucleotides?

13:23:49 8 A They're talking about cleavage of a linker
13:23:53 9 attached to a nucleotide that -- via cleavage of the
13:23:57 10 disulfide -- of a -- of a disulfide bond. That's --
13:24:05 11 they're -- they're not talking about a triphosphate
13:24:08 12 modified with a disulfide.

13:24:10 13 Q No. And I'm just asking you -- I'm just asking
13:24:13 14 you if you looked at that limitation that we're
13:24:15 15 discussing in Claim -- proposed Claim 9.

13:24:19 16 I'm asking you if, in general, use of disulfide
13:24:22 17 linkers as cleavable linkers in -- in nucleotides for
13:24:28 18 use in sequencing by synthesis was known as of 2002?

13:24:36 19 A Yes. I -- I don't -- so I -- the -- the -- the
13:24:41 20 claim that we're discussing is -- is specific for a
13:24:43 21 triphosphate molecule. Correct?

13:24:47 22 Q That's correct. I'm specifically asking you,
13:24:49 23 though, about the limitation "wherein the cleavable
13:24:53 24 linker contains a disulphide linkage."

13:24:58 25 A Well -- but it says a nucleotide triphosphate

13:25:01 1 molecule "wherein the cleavable linker contains a
13:25:05 2 disulphide linkage."

13:25:06 3 I mean, what I will -- Herman certainly teaches
13:25:09 4 such a triphosphate. Maybe not. I'll just -- I'm
13:25:12 5 sorry. I'll just answer your -- please go on.

13:25:15 6 Q Does Rabani -- does Rabani -- or you would
13:25:21 7 agree with me that Rabani teaches that nucleotide as
13:25:23 8 well? And that is, a nucleotide having a disulfide
13:25:27 9 cleavable linker for use in SBS.

13:25:31 10 A A nucleotide, yes. And, no. No, I can't agree
13:25:35 11 with that for SBS. He -- I -- oh, I'm sorry. You're --
13:25:39 12 you're speaking of Rabani. Yes. Yes.

13:25:41 13 Q Yes, you would agree with me that --

13:25:43 14 A That he --

13:25:44 15 Q -- Rabani --

13:25:46 16 A -- that he --

13:25:48 17 Q Let me. I'm sorry.

13:25:48 18 Yes, you would agree with me that Rabani
13:25:50 19 teaches using a disulfide cleavable linker in a
13:25:53 20 nucleotide for use in SBS?

13:25:55 21 A Yes.

13:25:56 22 Q Okay. Let's turn to paragraph 26 in your
13:26:07 23 substitute declaration. It's Exhibit 1029.

13:26:16 24 So in paragraph 26, you provide your opinion
13:26:21 25 that a person of skill in the art would have understood

13:26:24 1 the one -- the subject matter of the application as
13:26:27 2 early as -- as at least August 23rd, 2002. Is that
13:26:31 3 correct?

13:26:37 4 A Yes.

13:26:39 5 Q And so, in your opinion, August 23rd, 2002 is
13:26:46 6 the earliest filing date for the proposed claims?

13:26:50 7 A That is my understanding.

13:26:52 8 Q So can we agree today, then, when I refer to
13:26:54 9 the "earliest filing date," I'm referring to
13:26:57 10 August 23rd, 2002?

13:26:58 11 A Okay.

13:26:59 12 Q Okay. So if you'll look at paragraphs 27
13:27:03 13 through 31 in your substitute declaration, in these
13:27:19 14 paragraphs, Dr. Romesberg, you explain where you believe
13:27:24 15 support exists for the proposed claims, 9 and 10.

13:27:30 16 Correct?

13:27:31 17 A Correct.

13:27:33 18 Q Okay. So if we look back at page 6, you see
13:27:43 19 proposed Claim 10 there?

13:27:44 20 A Mm-hmm. Yes.

13:27:45 21 Q Okay. And proposed Claim 10 recites that the
13:27:48 22 nuc- -- the nucleotide phosphate molecule of Claim 9,
13:27:52 23 and there's a new limitation "wherein the detectable
13:27:55 24 label is a fluorophore."

13:27:59 25 Do you see that?

13:27:59 1 A I do.

13:28:00 2 Q Would you agree with me that as of the earliest
13:28:02 3 filing date, 2002, using a fluorophore as a detectable
13:28:10 4 label was generally known in the art?

13:28:13 5 A It was.

13:28:14 6 Q So if we turn back to the paragraph --
13:28:17 7 paragraph 27 through 31 of your declaration, in
13:28:22 8 reviewing those paragraphs, Dr. Romesberg, there's not a
13:28:27 9 citation to anywhere in the -- in the specification
13:28:30 10 of -- of the '026 patent or the '131 application that
13:28:37 11 shows the complete structure of the nucleotide recited
13:28:42 12 in proposed Claim 9. Is that correct?

13:29:04 13 A I think there is.

13:29:04 14 Q Can you point me to where that disclosure is?

13:29:14 15 A For example, in -- in paragraph 30? I mean,
13:29:17 16 I'd have to look carefully through that. But I
13:29:21 17 certainly -- sorry. Go ahead.

13:29:23 18 Q But in your declaration --

13:29:25 19 A Mm-hmm.

13:29:26 20 Q -- where you cite for support, the proposed
13:29:31 21 claims, there's not a citation to a place in the '026
13:29:35 22 patent specification or the '131 application that
13:29:39 23 discloses the structure of the proposed Claim 9?

13:29:45 24 A Well, I believe I cite, for example, the
13:29:46 25 figure -- the first four figures. Yeah. That's the

13:29:50 1 very first one. Figures 1 through 4. And I think those
13:29:57 2 contain all of the involved claims.

13:30:09 3 Q Let's look at the '026 patent. That is
13:30:10 4 Exhibit 1001.

13:30:30 5 And you said you believe that the figures
13:30:34 6 provide a structure -- the -- the complete structure of
13:30:38 7 the nucleotide in proposed Claim 9. Correct?

13:30:43 8 A Yeah. Correct.

13:30:45 9 Q Okay. Can you show me where that structure is
13:30:50 10 disclosed in the '026 patent?

13:31:07 11 A So, I mean, are you asking is it -- are -- are
13:31:10 12 all of the aspects of it included in one representation?

13:31:12 13 Q That's what I'm asking you, correct.

13:31:15 14 A What I stated in my declaration and the way
13:31:18 15 I -- I thought about it at the time -- so I'll give you
13:31:20 16 this answer, and then I'll answer your question -- was
13:31:24 17 it's my belief that all aspects of the claim are
13:31:26 18 reflected in -- when you sum up the four figures.

13:31:29 19 Now, if you're asking me is there any one that
13:31:32 20 represents all four, I'm going to ask you for a second
13:31:34 21 to look at them and think about it.

13:31:38 22 Q You can take a second and --

13:31:39 23 A Okay.

13:31:39 24 Q -- and look at it.

13:31:41 25 MR. BABCOCK: Or longer than a second.

13:31:43 1 MR. GRIER: You can take as long as you need,
13:31:45 2 Dr. Romesberg.

13:32:17 3 THE WITNESS: So, simply looking at the
13:32:21 4 figures, technically, your point may be correct. I
13:32:25 5 would argue that -- that it's in practice not, because,
13:32:32 6 for example, in Figure 1 -- sorry -- the compound
13:32:35 7 labeled 1 under the disulfide linker, it shows all the
13:32:39 8 elements except the -- all the sort of artificial
13:32:42 9 elements except the -- the nucleotide. And -- and it's
13:32:45 10 not a 3' block. So I -- I guess that's correct.

13:32:49 11 BY MR. GRIER:

13:32:49 12 Q So then you would agree that nowhere does the
13:32:54 13 '026 specification disclose a structure containing all
13:33:01 14 of the limitations of proposed Claim 9?

13:33:04 15 MR. BABCOCK: Objection. Misstates his
13:33:05 16 testimony. He's looking at the figures.

13:33:09 17 THE WITNESS: I should go ahead and answer now?

13:33:12 18 MR. BABCOCK: You can go ahead and answer.

13:33:15 19 THE WITNESS: Okay. I mean, I guess the
13:33:15 20 problem I'm having is that it's so intuitively clear
13:33:18 21 that that's what they mean, because they show, for
13:33:22 22 example, all of the elements except the linker and the
13:33:24 23 label in Figure 1. And then in Figure 2, the whole
13:33:30 24 thing is -- is linkers -- examples of linkers. And the
13:33:33 25 compound labeled 1 has a dye in it, it has the

13:33:36 1 disulfide. And so I -- I guess, technically, you're
13:33:40 2 right, there's no one structure that shows all of them.
13:33:44 3 But the implication is very -- to me, obvious. And I
13:33:51 4 think it would have been to anyone reading this, trained
13:33:54 5 in the field or otherwise.

13:34:03 6 BY MR. GRIER:

13:34:04 7 Q But, again, just to clarify --

13:34:06 8 A I think I --

13:34:07 9 Q -- there's no disclosure in the specification
13:34:09 10 of the '026 patent that shows a structure containing all
13:34:15 11 of the limitations recited in proposed Claim 9?

13:34:21 12 A In a single structure, I believe that is --
13:34:23 13 that appears to be correct, in the figures.

13:34:27 14 Q Is there anywhere else in the '026 patent that
13:34:31 15 shows a structure that contains all the limitations
13:34:34 16 found in proposed Claim 9?

13:34:36 17 A So when I read this, I didn't look at it that
13:34:40 18 way. It didn't seem to me to be important in one
13:34:43 19 structure to have that. And so, clearly, what -- what I
13:34:46 20 was -- what I intended in my declaration to -- to
13:34:50 21 explain was that each of them individually were
13:34:52 22 supported.

13:34:53 23 Now, if you're asking me in one place, I had
13:34:55 24 never looked at it that way before. And so I would ask
13:34:57 25 you for a minute to go back and look through my

13:34:59 1 statements and -- and see whether that's true or not.

13:35:02 2 Q You can look back through, of course.

13:35:57 3 A So I'm -- in my declaration, I'm referring to

13:36:00 4 the '131 application for actual line numbers and -- so

13:36:03 5 could I have a copy of that? Because I, at one point,

13:36:05 6 went and checked, and every one of them are identical in

13:36:09 7 the two -- in the two applications, in '026 and '131.

13:36:14 8 But the line numbering that I use here is to '131. So

13:36:17 9 to find it, I -- I'd have to have the '131.

13:36:21 10 Q Well, knowing that they're identical and you

13:36:22 11 have the '026 patent --

13:36:24 12 A I just can't find them to confirm what I write

13:36:28 13 here.

13:36:28 14 MR. BABCOCK: The citations are different, is

13:36:29 15 what he's saying.

13:36:31 16 THE WITNESS: Right. So the page numbering

13:36:33 17 winds up being different and the line numbering slightly

13:36:35 18 different.

13:36:38 19 MR. BABCOCK: Exhibit 2008, it looks like.

13:37:06 20 THE WITNESS: Sorry. Am I going to be able to

13:37:08 21 get that, or --

13:37:09 22 MR. BABCOCK: I think they're looking for it.

13:37:20 23 BY MR. GRIER:

13:37:21 24 Q So we'll get you a copy of that.

13:37:23 25 A Thank you.

13:37:24 1 Q It does not look like it was printed for us
13:37:25 2 yesterday. So we will -- we'll work on getting you a
13:37:30 3 copy.

13:37:32 4 A Okay. Thank you.

13:37:32 5 Q But if we just turn back to the -- to the '026
13:37:34 6 patent for a moment. And if you -- and you can take
13:37:48 7 your time to look in the '026 patent.

13:37:50 8 But nowhere in the '026 patent specification,
13:38:00 9 again, is there a structure containing all the
13:38:03 10 limitations in proposed Claim 9. Correct?

13:38:07 11 MR. BABCOCK: Asked and answered.

13:38:17 12 THE WITNESS: Should I answer that?

13:38:19 13 BY MR. GRIER:

13:38:19 14 Q Yes. You can answer that question.

13:38:21 15 A I think I already did answer.

13:38:27 16 Q And your answer was is there is no place in the
13:38:29 17 '026 patent specification --

13:38:31 18 MR. BABCOCK: Objection. Mischaracterizes his
13:38:31 19 testimony.

13:38:32 20 BY MR. GRIER:

13:38:32 21 Q Your answer, Dr. Romesberg, is that there is no
13:38:33 22 place in the -- the specification of the '026 patent
13:38:37 23 that discloses a structure containing all the
13:38:39 24 limitations of the proposed Claim 9?

13:38:42 25 MR. BABCOCK: Same objection.

13:38:43 1 THE WITNESS: I -- what -- what I say is that
13:38:46 2 it's not -- as I explained earlier, I didn't look at it
13:38:48 3 that way. I -- what I looked at was -- was each
13:38:51 4 individual aspect shown. And, again, sometimes it's
13:39:01 5 hard to think on your feet. And so looking at it right
13:39:09 6 now, maybe I'll miss it, but from first glance, I -- I
13:39:10 7 guess I agree with that statement, yes.

13:39:12 8 I don't see one where they're all -- I mean,
13:39:13 9 for example, at the top of Figure 3, where they show a
13:39:16 10 label, a cleavable linker, and a base, and then R1 and
13:39:22 11 R2, which could be any group that can be transformed
13:39:27 12 into an OH could be a protecting group and the cleavable
13:39:29 13 linker, but it's not specified that it's a disulfide.

13:39:34 14 But that -- that certainly -- with the -- with
13:39:37 15 instruction from Figure 2, that's clearly -- contains
13:39:43 16 the possibility of -- of what we're talking about.

13:39:47 17 I would -- I would say that the top drawing in
13:39:51 18 Figure 3 plus cleavable linkers -- actually, there is a
13:39:57 19 disulfide in Figure 3. The label -- and certainly in
13:40:10 20 Figure 3 is cleave -- is a reversible -- is a cleavable
13:40:11 21 blocking group. X triphosphates. So everything is
13:40:15 22 present in Figure 3 if -- if you allow label to be
13:40:20 23 descriptive -- sufficiently descriptive.

13:40:23 24 BY MR. GRIER:

13:40:23 25 Q And I think for proposed Claim 9, the label is

13:40:29 1 sufficiently descriptive.

13:40:31 2 But nowhere in this structure you're discussing
13:40:34 3 in Figure 3 does it show a disulfide linker attached to
13:40:39 4 the 7-position of a deazapurine. Correct?

13:40:45 5 A No. It -- it shows a disulfide attached to the
13:40:51 6 nucleo base of the nucleotide. It doesn't specify the
13:40:54 7 position of attachment. The -- yes, I guess that is
13:40:57 8 correct. The position of attachment is clearly
13:40:58 9 articulated in Figure 1. And I think anyone of any
13:41:03 10 skill in the art at all would catch that. But I -- but
13:41:07 11 you're right, that -- that is missing -- that one aspect
13:41:10 12 is missing the -- the site of attachment of the
13:41:13 13 disulfide to the nucleo base is missing there. But I
13:41:17 14 believe all the other elements are -- are present.

13:41:22 15 Q And would you agree that nowhere in the
13:41:24 16 specification actually provides an example of a
13:41:27 17 disulfide linker attached to the 7-position of a
13:41:31 18 deazapurine?

13:41:39 19 A Does it explicitly write that out? Is that
13:41:42 20 what you're asking?

13:41:43 21 Q I'm asking you if the specification of the '026
13:41:46 22 patent discloses a nucleotide structure having a
13:41:54 23 disulfide cleavable linker attached to the 7-deaza
13:41:56 24 position of the deazapurine?

13:42:04 25 A You know, I'm going to have to go through and

13:42:06 1 look at that. That was certainly my interpretation
13:42:08 2 exactly that they were suggesting that. I mean, to
13:42:12 3 justify that position -- so Figure 3 shows everything
13:42:20 4 that you just described except it doesn't show a
13:42:23 5 deazapur- -- -purine. And it doesn't show attachment
13:42:26 6 at -- at the site within the deazapurine. However,
13:42:31 7 Figure 1 shows a deazapurine with a linker attached to
13:42:35 8 the C7-position of the purine, A, in this case, and it
13:42:39 9 shows the C7-position of a deazaguanosine as well. And,
13:42:46 10 again, Figure 1 plus that -- plus Figure 3 is -- is
13:42:50 11 completely clear.

13:42:52 12 Do they show that in one figure? I -- again,
13:42:55 13 I'd have to look more carefully, because I didn't look
13:42:57 14 in that way. It didn't seem to be -- it wasn't
13:43:00 15 important to me. But I -- I guess that might be
13:43:02 16 correct.

13:43:05 17 Without -- without looking through it from that
13:43:07 18 perspective, I'd be a little careful. But I -- I don't
13:43:10 19 see it upon glancing at it here.

13:43:13 20 MR. BABCOCK: Just to clarify, Counsel, you're
13:43:15 21 using specification. He's looking only at the figures.
13:43:17 22 He's -- he's asked to see the document. You haven't
13:43:19 23 shown it to him. I think the record is not clear that
13:43:22 24 you're asking for specification and you led him to the
13:43:29 25 figures. And he should be entitled to see the document.

13:43:33 1 MR. GRIER: Counsel, he led me to the figures,
13:43:35 2 first of all, to be clear. And I've explained my
13:43:38 3 apologies that we seem to have a mix-up. And we're
13:43:42 4 going to get the one --

13:43:43 5 MR. BABCOCK: You -- you said you'd get the
13:43:45 6 document to him, but then you proceed with the
13:43:48 7 questioning without the document after he's asked you
13:43:50 8 twice for the document. So, you know, I have that --
13:43:52 9 that objection over this line of questioning, that if
13:43:55 10 you want -- if you want his true answer, you show him
13:43:57 11 the document. If you want to have him try to figure it
13:44:01 12 out on the fly, as you're trying to do, we'll do the
13:44:04 13 best we can. It's your deposition. But he has asked to
13:44:08 14 see Exhibit 2008.

13:44:12 15 BY MR. GRIER:

13:44:13 16 Q Dr. Romesberg, you testified earlier that you
13:44:15 17 read and understood the '026 patent. Correct?

13:44:18 18 A Correct.

13:44:19 19 Q Okay. And in your review of the '026 patent,
13:44:23 20 you testified that you read it cover to cover. Correct?

13:44:26 21 A I did.

13:44:28 22 Q Okay. And earlier you testified that in your
13:44:31 23 declaration, when you were describing where the support
13:44:34 24 was, you were referring to both the '026 patent and the
13:44:37 25 '131 application. Correct?

13:44:39 1 A Correct.

13:44:40 2 Q But that your specific page cites were to the

13:44:43 3 '131 application. Correct?

13:44:45 4 A Correct.

13:44:45 5 Q But you did review the '026 patent

13:44:47 6 specification, and you did discuss that what was cited

13:44:50 7 in the '026 patent specification in describing what was

13:44:56 8 support for the proposed claims. Correct?

13:44:58 9 A Yes.

13:44:58 10 Q Okay.

13:44:59 11 A And the '026 and '131 applications are

13:45:03 12 identical.

13:45:03 13 Q Okay. So then --

13:45:06 14 A Sorry. They're identical in context. They're

13:45:07 15 unfortunately shifted in terms of being able to find the

13:45:10 16 specific page and line that I'm referring to in the '131

13:45:12 17 patent in the '026 patent.

13:45:14 18 Q Understood. But you could certainly look at

13:45:16 19 the '026 patent specification, because you testified you

13:45:18 20 already have.

13:45:20 21 A Sure. Sure. I'm happy to do that. Sorry.

13:45:23 22 Q And you could -- and you could answer my

13:45:25 23 questions, then, about where support is allegedly

13:45:28 24 contained in the specification of the '026 patent.

13:45:31 25 Correct?

13:45:32 1 A Yes.

13:45:32 2 Q Okay.

13:45:33 3 A The one caveat, though, is that I will have to
13:45:37 4 find the spot in the one thirty -- in the '026 patent
13:45:40 5 from my citation to the '131 patent, and that will take
13:45:43 6 a few moments. And I'll have to find it to -- then read
13:45:46 7 it to answer your question from the perspective you're
13:45:49 8 asking.

13:45:49 9 Q Well, why -- why don't we make it easier for
13:45:51 10 you, then, and let's just look at Figures 1 through 4,
13:45:57 11 since that's where you directed me, okay, Figures 1
13:45:59 12 through 4 of the '026 patent.

13:45:59 13 A Okay. But I also didn't mean to suggest that
13:46:01 14 Figures 1 through 4 were the only origins or maybe not
13:46:04 15 even the best. They were just the first that popped
13:46:06 16 into mind because they're figures and I think it's very
13:46:09 17 clear. But from your -- but, again, you're approaching
13:46:12 18 it from a slightly different perspective than I as a
13:46:16 19 reader or as a scientist approached it from.

13:46:18 20 Q Let's look at the figures, the '026 patent.
13:46:25 21 And, in particular, the three figures that you were
13:46:30 22 referring to. Those are Figures 1, 2, and 3.

13:46:37 23 A I think 1 and 3 are the more central.

13:46:40 24 Q Okay. Then let's look at Figures 1 and 3.

13:46:46 25 Nowhere in Figure 1 of the '026 patent is there

13:46:51 1 a disclosure of a structure containing all of the
13:46:58 2 limitations recited in proposed Claim 9. Correct?
13:47:06 3 A I -- I -- I don't mean to be argumentative.
13:47:09 4 But, no, I disagree with you, because if you look at
13:47:12 5 Figure 1, look at N7 deazaguanosine. Adenosine and the
13:47:18 6 guanosine. So they are the two figures where they
13:47:20 7 show -- would you agree that everything is shown there
13:47:23 8 except the disulfide?

13:47:24 9 Q Dr. Romesberg, while I appreciate your asking
13:47:26 10 me a question, this is your deposition. And I've asked
13:47:29 11 you a question --

13:47:30 12 A Okay.

13:47:30 13 Q -- about Figure 1.

13:47:33 14 A Okay. I apologize.

13:47:35 15 It would -- it -- I -- it would seem to me that
13:47:39 16 the -- the -- the deazaadenosine and guanosine
13:47:46 17 structures there show everything in the proposal,
13:47:48 18 because it says -- in the caption to that figure, it
13:47:52 19 says "Suitable groups for R1 and R2 are described in
13:47:55 20 Figure 3.

13:48:07 21 No. I guess I'm back to what I said before.
13:48:09 22 The disulfide is not included in Figure 1. All elements
13:48:15 23 except the disulfide appear to be included in Figure 1.

13:48:20 24 Q Okay.

13:48:21 25 A And in Figure 3, all elements except the point

13:48:25 1 of attachment, all elements including the disulfide and
13:48:30 2 only missing the point of attachment to the base, which
13:48:32 3 are included in Figure 1. So Figure 1 and Figure 3,
13:48:35 4 yes. Any individual structure, as you're asking me, it
13:48:39 5 would -- I have not found one.

13:48:40 6 Q And just to clarify, in Figure 3, when you say
13:48:43 7 "attachment," you're referring to the attachment at the
13:48:47 8 7-deaza position of the deazapurine. Is that correct?

13:48:51 9 A I am.

13:48:52 10 Q Okay.

13:48:55 11 A But -- but just for the record, other modes of
13:48:57 12 attachment are also shown.

13:48:58 13 Q Okay. But with respect to proposed Claim 9,
13:49:01 14 Figure 3 does not show the disulfide linker attached to
13:49:03 15 the 7-deaza position of a deazapurine. Correct?

13:49:15 16 A I'm -- I'm simply checking the caption to make
13:49:17 17 sure there's no reference back to Figure 1. But that
13:49:21 18 would -- that would appear to be correct.

13:49:28 19 Q So, then, if you look at Figure 1 and Figure 3,
13:49:33 20 would you agree that a person of skill in the art would
13:49:35 21 be able to look at -- at Figure 1 and Figure 3 and
13:49:41 22 synthesize a nucleotide that had a disulfide cleavable
13:49:46 23 linker attached to a 7-deaza position of a deazapurine?

13:49:59 24 A I'm not absolutely sure I understand your
13:50:01 25 question. Would they be able to synthesize -- would --

13:50:04 1 would they take from that, the suggestion that that's
13:50:07 2 what was being proposed.

13:50:09 3 Is that what you're asking?

13:50:11 4 Q Would a person of skill in the art take from
13:50:13 5 those figures, a suggestion that you could attach a
13:50:16 6 disulfide cleavable linker to the 7-deaza position of a
13:50:21 7 deazapurine?

13:50:23 8 A Yeah. Yeah. I think that's what -- that's
13:50:26 9 what they would conclude.

13:50:45 10 Q Dr. Romesberg, can you please turn with me to
13:50:48 11 paragraph 42 of your substitute declaration, which is
13:50:53 12 Exhibit 1029.

13:51:18 13 Okay. You see in -- in Figure -- sorry --
13:51:21 14 paragraph 42, you state that "Proposed Claim 9 recites a
13:51:28 15 nucleotide triphosphate molecule where the disulfide
13:51:33 16 linkage of the cleavable linker and the protecting group
13:51:39 17 are cleavable under identical conditions."

13:51:41 18 Do you see that?

13:51:42 19 A I do.

13:51:43 20 Q What is your understanding of the phrase
13:51:44 21 "cleavable under identical conditions"?

13:51:48 22 A That there's a single set of conditions that
13:51:50 23 result in the cleavage of both moieties, both the
13:51:56 24 protecting group and the linker.

13:52:27 25 Q If we turn back to your -- to paragraph 27 of

13:52:36 1 your substitute declaration, and particularly on page 8.

13:52:51 2 You see the second-from-the-last bullet point
13:52:54 3 there on page 8?

13:52:57 4 A I do.

13:52:58 5 Q Okay. This is the only passage that you cite
13:53:06 6 from the '131 application that provides support for the
13:53:11 7 limitation "cleavable under identical conditions."

13:53:14 8 Correct?

13:53:16 9 A I was not aware of that, but I mean, I didn't
13:53:20 10 count the number of times I cited that.

13:53:23 11 Q Well, looking at those bullet points, is there
13:53:30 12 another citation that you provide for the limitation
13:53:31 13 "cleavable under identical conditions"?

13:53:54 14 A That would appear to be the only place.

13:53:55 15 Q Okay. Can you turn with me back to
13:53:59 16 Exhibit 1001, which is the '026 patent, please. And, in
13:54:06 17 particular, page 12 of the '026 patent. And I'm looking
13:54:17 18 on page 12 at Column 8, line 35.

13:54:22 19 Do you see that?

13:54:22 20 A I do.

13:54:24 21 Q Okay. There, it says "The labile linker may
13:54:29 22 consist of functionally cleavable under identical
13:54:32 23 conditions to the block."

13:54:33 24 Do you see that?

13:54:36 25 A I do.

13:54:38 1 Q Okay. Nowhere in that recitation that I just
13:54:47 2 cited does the specification describe cleaving a
13:54:52 3 disulfide linker under identical conditions. Is that
13:54:55 4 correct?

13:54:56 5 A This particular citation?

13:54:58 6 Q Right.

13:55:00 7 A "The labile linker may consist" -- it does not
13:55:07 8 in that sentence.

13:55:09 9 Q And you testified a moment ago that this was
13:55:12 10 the -- the only citation that you made to the
13:55:16 11 specification that described -- provided support for the
13:55:21 12 limitation "cleavable under identical conditions." Is
13:55:23 13 that correct?

13:55:24 14 A Yes.

13:55:24 15 Q Okay. So, then, you don't cite to a single
13:55:30 16 place in the specification that teaches how to cleave a
13:55:33 17 disulfide cleavable linker and a protecting group under
13:55:37 18 identical conditions. Is that correct?

13:55:38 19 A But I do refer to Figure 3 at the end of that
13:55:42 20 same bullet point. And Figure 3 contains a disulfide.

13:55:48 21 I say specifically, referring to "the
13:55:49 22 functional groups of the linkers of Figure 3." And
13:55:54 23 Figure 3 contains a disulfide.

13:55:55 24 Q Okay. Can we turn to Figure 3, then, for a
13:55:58 25 second?

13:55:59 1 A Sure.

13:56:01 2 Q So looking at Figure 3, though, nothing in
13:56:06 3 Figure 3 teaches that you can cleave a disulfide
13:56:11 4 cleavable linker and a 3' protecting group under
13:56:15 5 identical conditions. Is that correct?

13:56:19 6 A That is correct.

13:56:20 7 Q Okay. So, then, again, this specification of
13:56:30 8 the '026 patent, then, would you agree it does not teach
13:56:36 9 how one would cleave a disulfide cleavable linker and a
13:56:39 10 protecting group under identical conditions?

13:56:42 11 MR. BABCOCK: Objection. Misstates his
13:56:43 12 testimony.

13:56:44 13 BY MR. GRIER:

13:56:44 14 Q You can answer.

13:56:49 15 A I -- really -- okay. Sorry. No, I don't think
13:56:54 16 I would agree with that, because in -- in my statement
13:56:57 17 here, I'm -- I'm citing that -- that -- I'm sorry.

13:57:01 18 Could you repeat the question.

13:57:06 19 MR. GRIER: Could you read back the question,
13:57:07 20 please.

13:57:27 21 (The following was read by the reporter:

13:57:27 22 Q Okay. So, then, again, this specification of
13:57:27 23 the '026 patent, then, would you agree it does not teach
13:57:27 24 how one would cleave a disulfide cleavable linker and a
13:57:27 25 protecting group under identical conditions?)

13:57:28 1 MR. BABCOCK: Same objection.

13:57:31 2 THE WITNESS: Does it teach how you would do

13:57:33 3 it? Is that -- or that you might?

13:57:38 4 MR. GRIER: Can you please read the question

13:57:39 5 again.

13:57:57 6 (The following was read by the reporter:

13:57:57 7 Q Okay. So, then, again, this specification of

13:57:57 8 the '026 patent, then, would you agree it does not teach

13:57:57 9 how one would cleave a disulfide cleavable linker and a

13:57:57 10 protecting group under identical conditions?)

13:57:58 11 THE WITNESS: It does not teach how you would

13:58:00 12 cleave them under identical conditions.

13:58:02 13 BY MR. GRIER:

13:58:03 14 Q Does the specification of the '026 patent teach

13:58:09 15 or disclose cleaving a disulfide cleavable linker and a

13:58:17 16 protecting group under identical conditions?

13:58:20 17 A I don't feel comfortable answering that without

13:58:23 18 going through this again.

13:58:26 19 Q Okay. Well, when -- when we get your copy --

13:58:28 20 A Yeah.

13:58:28 21 Q -- of the --

13:58:29 22 A Can I have a break to -- to look at that?

13:58:32 23 Q Sure. We can do -- we can come -- we can

13:58:34 24 circle back around to it later.

13:58:36 25 VIDEOGRAPHER: I'm going to have to change

13:58:39 1 tape.

13:58:40 2 MR. GRIER: Okay. Okay. There's no question
13:58:43 3 pending. We can -- we can go off the record while --
13:58:45 4 while the videographer changes the tape.

13:58:48 5 VIDEOGRAPHER: This concludes Disk 2 of the
13:58:51 6 deposition of Dr. Floyd Romesberg. Off the record at
13:58:55 7 1:58.

14:15:46 8 (Recess from 1:58 p.m. to 2:16 p.m.)

14:16:18 9 VIDEOGRAPHER: This is Disk 3 of the deposition
14:16:19 10 of Dr. Floyd Romesberg. Back on the record at 2:16.

14:16:24 11 BY MR. GRIER:

14:16:25 12 Q Okay. Dr. Romesberg, I'm going to hand you
14:16:30 13 what was previously marked Illumina Exhibit 2008.

14:16:42 14 Do you recognize this document?

14:16:46 15 A Yes, I do. This is the '131 application.

14:16:56 16 Is it an application, or a filing?

14:16:59 17 Q This is -- an application. That's correct.

14:17:01 18 A Okay. It's the application.

14:17:02 19 Q If you look at paragraph 26 of your substitute
14:17:04 20 declaration, on page 7 --

14:17:09 21 A Page 7.

14:17:12 22 Q -- this is the '131 application referred to in
14:17:15 23 paragraph 26. Correct?

14:17:18 24 A Correct.

14:17:18 25 Q Okay. So going forward, can we work under the

14:17:21 1 assumption that if I call it the "'131 application," you
14:17:24 2 will know that I'm referring to Exhibit 2008?

14:17:29 3 A Yes.

14:17:36 4 Q So, Dr. Romesberg, you recall we were going
14:17:38 5 through paragraphs 27 through 31 of your declaration
14:17:43 6 where you testify as to where support is allegedly found
14:17:49 7 in the -- in the specification for proposed Claims 9
14:17:55 8 and 10. Correct?

14:17:57 9 A Yes.

14:17:58 10 Q Okay. And you testified that you -- in
14:18:03 11 drafting the declaration, you reviewed both the '026
14:18:08 12 patent and the '131 application when determining where
14:18:12 13 support allegedly existed for the proposed claims. Is
14:18:15 14 that correct?

14:18:16 15 A It is.

14:18:21 16 Q Okay. So I'd like to run through, again, some
14:18:23 17 questions, and you can refer to the '131 application now
14:18:26 18 if that is helpful --

14:18:28 19 A Yes.

14:18:28 20 Q -- to your testimony.

14:18:30 21 A Yes. Thank you.

14:18:34 22 Q And I apologize for the mixup.

14:18:38 23 So, Dr. Romesberg, if you look at the '131
14:18:42 24 application, the '131 application does not disclose a
14:18:50 25 structure containing all of the limitations found in

14:18:57 1 proposed Claim 9. Is that correct?

14:19:00 2 A The structures in the Figures 1 through 3 are
14:19:04 3 identical as the '026 application that we just
14:19:07 4 described. So, yes, that is correct.

14:19:09 5 Q Okay. And just for clarification purposes,
14:19:12 6 yes, it is correct that the '131 application does not
14:19:15 7 disclose a structure containing all the limitations of
14:19:21 8 proposed Claim 9. Is that correct?

14:19:22 9 A In one chemical structure, all of the
14:19:24 10 limitations proposed are not included. They are -- they
14:19:28 11 are included by combining two figures. But, yes, that
14:19:33 12 statement is correct.

14:19:33 13 Q So you state that -- you just -- I apologize.
14:19:36 14 I'll start over.

14:19:38 15 Is there anywhere else in the '131 application
14:19:42 16 that discloses all of the limitations -- structure -- I
14:19:47 17 apologize -- with all of the limitations of proposed
14:19:51 18 Claim 9?

14:20:02 19 A A structure, no, there is not a structure with
14:20:07 20 all the proposed -- in -- in one structure.

14:20:15 21 Q Okay. So there's nowhere in the '131
14:20:18 22 application that provides an example of a disulfide
14:20:25 23 linker attached to the 7-deaza position of a
14:20:31 24 deazapurine. Correct?

14:20:34 25 A Repeat that question, please.

14:20:36 1 Q Sure. So nowhere does the '131 application
14:20:39 2 disclose an example or a structure of a disulfide linker
14:20:46 3 attached to 7-deaza position of a deazapurine. Is that
14:20:50 4 correct?

14:20:51 5 A In one structure, that is correct.

14:21:05 6 Q And, again, if we look back to page 8 of your
14:21:11 7 substitute declaration, the bullet point, the second
14:21:14 8 from the bottom -- and this is the only place you cite
14:21:19 9 in the '131 application that allegedly supports the
14:21:25 10 limitation "cleavable under identical conditions." Is
14:21:28 11 that correct?

14:21:29 12 A That is the only place that I cite that, that
14:21:31 13 is correct.

14:21:33 14 Q Okay. Is there anywhere else in the '131
14:21:37 15 application that supports the limitation that a
14:21:41 16 protecting group and the cleavable linker are cleavable
14:21:45 17 under identical conditions?

14:21:47 18 MR. BABCOCK: Objection. The document speaks
14:21:47 19 for itself.

14:21:48 20 You can answer.

14:21:49 21 THE WITNESS: I would have to look through it.
14:21:51 22 I -- I -- the one I cited was -- I -- I did not -- when
14:21:57 23 I cited it, I did not check to see whether or not it was
14:22:00 24 the only place that it was cited. I would have to read
14:22:02 25 back through it to see if that's the only place that it

14:22:06 1 cited.

14:22:07 2 BY MR. GRIER:

14:22:07 3 Q But you testified that you read and understood

14:22:09 4 the '131 application. Correct?

14:22:11 5 A That is correct.

14:22:12 6 Q Okay. In drafting your declaration, you cite

14:22:15 7 to various places in the '131 application where the

14:22:20 8 limitations of the proposed Claim 9 are supported. Is

14:22:24 9 that correct?

14:22:25 10 A That is correct.

14:22:26 11 Q Okay.

14:22:26 12 A But I didn't -- I didn't --

14:22:29 13 Q Let me finish --

14:22:31 14 A I --

14:22:31 15 Q -- the -- okay.

14:22:33 16 So, then, if you look at -- specifically in

14:22:36 17 paragraph 27, you lay out, in bullet point form, places

14:22:48 18 in the '131 application that allegedly support each

14:22:51 19 limitation of the proposed claims. Correct?

14:22:53 20 A Correct.

14:22:53 21 Q Okay. And when you -- in doing so, you only

14:22:59 22 cite to one place in the '131 application that allegedly

14:23:04 23 supports the limitation "cleavable under identical

14:23:06 24 conditions." Is that correct?

14:23:08 25 A That is correct.

14:23:20 1 Q And isn't that because there's nowhere else in
14:23:26 2 the '131 application except for what's cited on page 8
14:23:29 3 that allegedly supports the limitation "cleavable
14:23:33 4 under identical conditions"?

14:23:34 5 MR. BABCOCK: Objection. The document speaks
14:23:35 6 for itself. The declaration is clear. It's exemplary.

14:23:39 7 You can answer.

14:23:40 8 THE WITNESS: I don't recall. When I listed
14:23:41 9 these in -- in paragraph -- in -- in my declaration in
14:23:44 10 paragraph 27, in no place did I say they were the only
14:23:47 11 places that these things were evidenced. They were
14:23:50 12 simply places that I -- when I was reading it, I found
14:23:53 13 and I thought that's a good place to cite it. And so I
14:23:54 14 did. And I then didn't look -- I may not have looked
14:23:57 15 strongly elsewhere.

14:23:58 16 So I can't -- I'd have to go back and look
14:24:01 17 through the document. Yes, I did read it. But there's
14:24:03 18 a lot there, and I read a lot of documents. And so
14:24:06 19 to -- to tell you whether or not it was the only place
14:24:08 20 that was cited, I'd have to -- I'd have to take half an
14:24:12 21 hour and read the document.

14:24:13 22 BY MR. GRIER:

14:24:14 23 Q If you look at the bullet points in
14:24:17 24 paragraph 27, nowhere do you cite for support in the
14:24:24 25 '131 application for the limitation where a disulfide

14:24:28 1 cleavable linker is cleavable under identical conditions
14:24:32 2 in a protecting group. Is that correct?

14:24:39 3 MR. BABCOCK: Objection. Asked and answered.

14:24:40 4 BY MR. GRIER:

14:24:41 5 Q You can answer the question.

14:24:42 6 A Where -- where -- where -- under identical
14:24:44 7 conditions to a disulfide cleavage.

14:24:47 8 Is that what your question was?

14:24:50 9 Q Right. The question was nowhere in your
14:24:52 10 declaration do you cite to anywhere in the '026 patent
14:24:55 11 specification or the '131 application that teaches how
14:24:59 12 to cleave a disulfide cleavable linker and a protecting
14:25:03 13 group under identical conditions. Is that correct?

14:25:07 14 MR. BABCOCK: Objection. Lacks foundation.

14:25:08 15 THE WITNESS: So can I -- can I -- can I --
14:25:11 16 what -- what I cited here in this bullet point, I
14:25:17 17 thought that's what I was providing evidence for.
14:25:19 18 It's -- so what I'm referring to is in the '131
14:25:24 19 application, where it says "The linker may contain
14:25:26 20 function groups as described in Figure 3." Figure 3
14:25:29 21 shows a hydroxyl group, and it says -- it -- the
14:25:33 22 paragraph opens by saying "The labile -- the labile
14:25:37 23 linker may contain functionality cleavable under
14:25:40 24 identical conditions to the block." To -- the following
14:25:45 25 sentence, it just gives motivation for why one would do

14:25:49 1 that.

14:25:50 2 Then it says, "Thus, the linker may contain
14:25:52 3 functional groups as described in Figure 3," which
14:25:54 4 clearly shows a disulfide.

14:25:58 5 So when I was citing this, I -- I believe this
14:26:00 6 is exactly -- this is the exact -- the point that I
14:26:03 7 was -- that I was -- that I took as evidence for that.

14:26:06 8 BY MR. GRIER:

14:26:08 9 Q But the specification, the text of the
14:26:10 10 document, the '026 patent and the '131 application, does
14:26:16 11 not state or teach how to cleave a disulfide cleavable
14:26:20 12 linker and a protecting group under identical
14:26:22 13 conditions. Correct?

14:26:24 14 MR. BABCOCK: Objection. Asked and answered.

14:26:28 15 THE WITNESS: I don't understand the question.

14:26:28 16 By -- by -- do you mean does it show conditions under
14:26:32 17 which you could achieve that, or does it suggest that
14:26:34 18 you could use a disulfide that's in the linker that you
14:26:39 19 could cleave under identical conditions with a 3'
14:26:42 20 protect group? The former, you're right, it does not.
14:26:46 21 It does not provide conditions. The latter, I think it
14:26:51 22 does.

14:26:51 23 In this paragraph, it says that "The linker may
14:26:53 24 contain function groups as described in Figure 3."
14:26:55 25 Figure 3 clearly shows a disulfide. And it says that

14:26:58 1 they could be cleaved under conditions identical to the
14:27:00 2 block.

14:27:00 3 So I think that's saying that the disulfide,
14:27:03 4 amongst about a handful of other ones, not an infinite
14:27:08 5 number, but a finite number, drawn out carefully,
14:27:13 6 four -- it's one of only four shown. Disulfide is one
14:27:17 7 of those. And I believe that paragraph is suggesting
14:27:19 8 that it could be cleaved simultaneously with a 3'
14:27:22 9 protecting group.

14:27:24 10 So I believe they are stating that.

14:27:30 11 BY MR. GRIER:

14:27:33 12 Q In your review of the specification, the '026
14:27:36 13 patent and the '131 application, there's nothing in the
14:27:39 14 specification that describes a novel way of cleaving
14:27:42 15 disulfide linkers. Correct?

14:27:46 16 A That is correct.

14:27:49 17 Q And there's nothing in the proposed claims that
14:27:51 18 recites a new way to cleave disulfide linkers. Is that
14:27:55 19 correct?

14:27:56 20 A That is correct.

14:28:00 21 Q And, in fact, doesn't the example section of
14:28:02 22 the '026 patent specification and the '131 application
14:28:06 23 teach using DTT as the cleaving agent for the disulfide
14:28:09 24 linker?

14:28:09 25 A I think it uses that as an example, yes.

14:28:12 1 Q And DTT, is that the same cleaving agent that
14:28:15 2 was used in the Rabani reference?

14:28:19 3 A It is -- well, the Rabani -- Rabani doesn't
14:28:22 4 actually disclose that. Rabani cite -- I believe --
14:28:25 5 I -- at least in the part I'm thinking of, Rabani cites
14:28:28 6 to Ruby.

14:28:29 7 Q But you would agree that DTT as a cleaving
14:28:31 8 agent for disulfide linkers was known in the prior
14:28:34 9 art --

14:28:35 10 A Sure.

14:28:36 11 Q -- as of 2002?

14:28:36 12 A Yes.

14:29:10 13 Q I want to turn, Dr. Romesberg, back to page 18
14:29:13 14 of your substitute declaration, which is, again,
14:29:15 15 Exhibit 1029.

14:29:19 16 A It's --

14:29:20 17 Q I'm sorry. Page 18.

14:29:22 18 A Page 18.

14:29:23 19 Q Yeah. Specifically, again, paragraph 42. And
14:29:31 20 I believe you testified earlier that "cleavable under
14:29:33 21 identical conditions" to you meant single set of
14:29:36 22 conditions that result in the cleavage of both the
14:29:39 23 protecting group and the cleavable linker. Is that
14:29:44 24 correct?

14:29:51 25 A So they are -- they are cleaved in the same

14:29:53 1 reaction, yes. They -- yeah, I guess -- that's what I
14:30:02 2 mean, they're cleaved in the same reaction.

14:30:04 3 Q So is it your testimony that "cleavable under
14:30:06 4 identical conditions" requires a cleavage reaction?

14:30:12 5 A "Cleavable under identical conditions" requires
14:30:16 6 a cleavage reaction? No. I mean -- I mean, if -- if --
14:30:28 7 dem- -- demonstrating cleavage, they have to be
14:30:33 8 conditions that you feel demonstrate cleavage. If you
14:30:34 9 can demonstrate that cleavage under -- under the
14:30:40 10 conditions -- if you can demonstrate that they would
14:30:42 11 cleave under the conditions that you're suggesting,
14:30:45 12 then, yes, they -- they would -- so if two things that
14:30:51 13 we're -- we're talking about here are cleaving and we're
14:30:55 14 talking about cleaving both of them, do I think that you
14:30:57 15 would have to show simultaneous cleavage of both? Is
14:31:00 16 that what you're asking? To suggest that there are
14:31:02 17 conditions where both would cleave?

14:31:06 18 Q I'm really trying just to understand when you
14:31:09 19 said that single set of conditions was how you
14:31:11 20 understood "cleavable under identical conditions." I'm
14:31:15 21 really trying to understand if you understand "cleavable
14:31:18 22 under identical -- under identical conditions" to
14:31:20 23 require a cleavage reaction?

14:31:22 24 A Sure. I think that's in the English. I think
14:31:24 25 that's in the words.

14:31:28 1 Q So, then, is it your testimony that "cleavable
14:31:32 2 under identical conditions" requires actual cleavage of
14:31:34 3 the protecting group and the cleavable linker?

14:31:42 4 A It requires conditions that are demonstrated to
14:31:43 5 do that.

14:31:45 6 Q What do you mean by "demonstrated to do that"?

14:31:46 7 A Well, for example, in the -- I'll just use the
14:31:48 8 case at hand as an example. The -- the Vermaas dec- --
14:31:54 9 declaration does not actually demonstrate cleavage of
14:31:58 10 both simultaneously. And that's obviously where you're
14:32:02 11 going with this.

14:32:03 12 But what they do demonstrate is condition --
14:32:06 13 they -- they -- they cleave under -- they demonstrate
14:32:09 14 conditions where you would get cleavage -- where you
14:32:12 15 know you would get cleavage of both.

14:32:16 16 Q Honestly, Dr. Romesberg, I'm really just trying
14:32:18 17 to understand how you interpret the phrase "cleavable
14:32:23 18 under identical conditions." And I'm trying to
14:32:24 19 understand if it's your testimony that "cleavable under
14:32:27 20 identical conditions" requires actual cleavage of the
14:32:30 21 protecting group and the cleavable linker.

14:32:34 22 MR. BABCOCK: Asked and answered.

14:32:35 23 THE WITNESS: Could you repeat the question.

14:32:37 24 MR. GRIER: Could you read it back, please.

14:32:39 25

14:32:56 1 (The following was read by the reporter:
14:32:56 2 Q Honestly, Dr. Romesberg, I'm really just trying
14:32:56 3 to understand how you interpret the phrase "cleavable
14:32:56 4 under identical conditions." And I'm trying to
14:32:56 5 understand if it's your testimony that "cleavable under
14:32:56 6 identical conditions" requires actual cleavage of the
14:32:56 7 protecting group and the cleavable linker.)
14:32:57 8 MR. BABCOCK: Same objection.
14:33:06 9 THE WITNESS: In the end, of course, it will
14:33:07 10 require cleavage of both. I guess I'm just being
14:33:11 11 careful not to say something that is not what I mean.
14:33:23 12 BY MR. GRIER:
14:33:24 13 Q And I'm just trying to understand exactly --
14:33:25 14 exactly what you mean.
14:33:27 15 So, again, I'll ask is it your testimony that
14:33:28 16 "cleavable under identical conditions" requires actual
14:33:33 17 cleavage of the cleavable linker and the protecting
14:33:37 18 group.
14:33:37 19 A Yes.
14:33:45 20 Q And if you turn with me to -- back to the '026
14:33:48 21 patent, which is Exhibit 1001, specifically page 12 of
14:33:52 22 that exhibit. And Column 8. Line 35. It says "The
14:34:04 23 labile linker may consist of functionally cleavable
14:34:09 24 under identical conditions to the block."
14:34:11 25 Do you see that?

14:34:11 1 A I do.

14:34:12 2 Q And the following sentence says "This will make
14:34:14 3 the deprotection process more efficient as only a single
14:34:18 4 treatment will be required to cleave both the label and
14:34:21 5 the block."

14:34:21 6 Do you see that?

14:34:22 7 A I do.

14:34:22 8 Q So as one of skill in the art, is there
14:34:26 9 anything about an SBS work flow that makes it
14:34:30 10 advantageous to cleave a linker and a protecting group
14:34:33 11 under identical conditions?

14:34:35 12 A Sure. As it -- as it -- as it states right
14:34:38 13 here, it would -- it would make it more efficient
14:34:40 14 because only a single treatment would be required.

14:34:46 15 Q And why would making it more efficient be more
14:34:49 16 advantageous?

14:34:50 17 A Fewer steps.

14:35:00 18 Q Is there anything else?

14:35:05 19 A That would seem to be the big -- the largest
14:35:08 20 advantage, fewer steps.

14:35:29 21 Q So, then, in your opinion, it's better to
14:35:33 22 cleave the linker and the protecting group under
14:35:35 23 identical conditions because, for example, it's more
14:35:39 24 efficient. Is that correct?

14:35:40 25 A It -- there could be -- it would -- it would be

14:35:43 1 more efficient from one -- I can understand the
14:35:47 2 perspective where it would be more efficient because
14:35:49 3 it's fewer steps. I'm -- there are other constraints
14:35:52 4 when running sequencing by synthesis. And all other
14:35:55 5 being equal, it -- I think it's reasonable to say that
14:35:58 6 you would prefer to cleave with a single step. If that
14:36:01 7 brought with it any issues, then that might not be true.

14:36:04 8 Q But all things being equal, as you say, it's
14:36:07 9 your testimony that you would prefer to cleave under
14:36:10 10 identical conditions because of efficiency. Is that
14:36:11 11 correct?

14:36:15 12 A I guess I don't see what my preference matters.
14:36:18 13 Are -- are you asking me if I think that it
14:36:21 14 would be a better sequence -- an SBS method if you could
14:36:27 15 do it with one step, or if it's novel?

14:36:28 16 Q No. I'm really just trying to ask you as a
14:36:32 17 person of skill in the art, you test- -- you testified,
14:36:35 18 I believe, that it's advantageous to cleave the
14:36:38 19 protecting group and the cleavable linker in one step
14:36:42 20 under identical conditions.

14:36:43 21 So I'm just asking you to confirm or explain to
14:36:48 22 me why, as one of skill in the art, you would think
14:36:51 23 that's preferable.

14:36:54 24 A Because -- well, you -- you would use fewer
14:36:56 25 steps. But -- but, again, I -- could you point to where

14:37:00 1 I said that it's -- it's advantageous -- that it's my
14:37:03 2 opinion that it's advantageous?

14:37:05 3 Q I believe that when we began discussing
14:37:08 4 Column 8 here in the '026 patent, and specifically where
14:37:16 5 the specification says cleavage under identical
14:37:21 6 conditions will "make the deprotection process more
14:37:24 7 efficient as only a single treatment will be required to
14:37:28 8 cleave both the label and the block."

14:37:30 9 And I asked you if, as one of skill in the art,
14:37:35 10 there was any particular advantage to cleaving the
14:37:37 11 protecting group and the cleavable linker under
14:37:40 12 identical conditions.

14:37:42 13 And I -- as I recall, your testimony was there
14:37:44 14 was an advantage and -- and that advantage was it was
14:37:47 15 more efficient.

14:37:49 16 So I'm just asking is that your testimony?

14:37:52 17 A Sure. But I don't believe anywhere in there
14:37:54 18 I've said that it's better. Illumina is saying it's
14:37:57 19 better. And if you ask me why might it be better, I
14:38:02 20 think it's a likely possibility that it might be better
14:38:06 21 because you're using fewer steps.

14:38:08 22 I don't believe I have an opinion about why --
14:38:10 23 whether one would want to cleave in two or not. I
14:38:16 24 have -- I can offer you an opinion about whether I think
14:38:18 25 that was novel or -- or -- or prior art or not. But

14:38:22 1 I -- I -- I -- I don't have a strong opinion as to
14:38:25 2 whether I think it's better or not, I guess, is what I'm
14:38:30 3 saying.

14:38:30 4 Q So as a person of skill in the art,
14:38:31 5 Dr. Romesberg, you're familiar with SBS. Correct?

14:38:33 6 A I am.

14:38:34 7 Q And you're familiar with modified nucleotides
14:38:37 8 for use in SBS. Correct?

14:38:39 9 A Sure. But there's also lots of SBS -- sorry.
14:38:41 10 I don't --

14:38:42 11 Q So you're familiar with work flows in which
14:38:49 12 sequencing by synthesis is conducted. Correct?

14:38:51 13 A Yes.

14:38:52 14 Q Okay. And as a person of skill in the art with
14:38:57 15 that experience, do you believe it's advantageous to
14:39:03 16 cleave the protecting group and the cleavable linker
14:39:06 17 under identical conditions?

14:39:08 18 A I don't think there's a simple general answer
14:39:10 19 to that. There's lots of different sequencing by
14:39:12 20 synthesis methods. There's lots of different sequencing
14:39:15 21 by synthesis work flows. I think it's completely
14:39:19 22 reasonable that it might be, because it might make
14:39:21 23 things streamlined and a more -- and -- and fewer steps.

14:39:25 24 I'd have to see a specific work flow and -- and
14:39:28 25 I'm not even sure I have enough practical familiarity

14:39:33 1 with the overall -- what -- the other aspects that
14:39:36 2 might -- that -- that -- that might be involved to -- to
14:39:39 3 say whether I think that's -- to have an opinion on
14:39:42 4 that.

14:39:43 5 Q Well, let's take it out into a more -- more
14:39:46 6 general matter, then.

14:39:47 7 As a person of skill in the art familiar with
14:39:50 8 nucleotide chemistry, would you agree that making a
14:39:54 9 reaction proceed in a more efficient manner is a basic
14:39:58 10 goal of a synthetic chemist?

14:40:02 11 A Generally, yes.

14:40:03 12 Q Okay. Dr. Romesberg, I would like to turn now
14:40:18 13 to page 15 of your substitute declaration, which is
14:40:21 14 Exhibit 1029. Specifically, paragraphs 34 and 35.

14:40:38 15 In your declaration, you offer an opinion as to
14:40:40 16 the obviousness of Illumina's proposed claims. Is that
14:40:45 17 correct?

14:40:45 18 A It is.

14:40:47 19 Q And what is your understanding for what it
14:40:48 20 means for a claim to be obvious?

14:40:52 21 A If all aspects of the claim are present in --
14:40:55 22 in -- in something else that was previously available, a
14:40:58 23 publication or a patent.

14:41:08 24 Q And what is your basis for your understanding
14:41:11 25 of "obviousness"?

14:41:13 1 A My discussions with Kerry and Nate.

14:41:18 2 Q Did you have discussions with anyone other than

14:41:19 3 Kerry and Nate about obviousness?

14:41:22 4 A No, I did not.

14:41:28 5 Q Did you do any independent investigation as to

14:41:31 6 what it means for a claim to be obvious?

14:41:33 7 A No, I did not.

14:41:40 8 Q And if you turn to paragraph 37 of your

14:41:47 9 declaration, you state there that in making an

14:41:57 10 obviousness determination, one must always consider

14:42:00 11 objective evidence of nonobviousness.

14:42:02 12 Do you see that?

14:42:03 13 A I do.

14:42:03 14 Q Okay. And what is your understanding of what

14:42:05 15 "objective evidence of nonobviousness" means?

14:42:11 16 A For example, other papers that address the

14:42:14 17 issue that would lead you to think one thing or another.

14:42:17 18 Other people's work or publications that would lead

14:42:20 19 someone of skill in the art to have a bias or a

14:42:23 20 prejudice or a -- or an opinion.

14:42:26 21 Q And you further state you understand such

14:42:28 22 evidence includes unexpected results. Is that correct?

14:42:31 23 A Yes.

14:42:33 24 Q What is your understanding of what constitutes

14:42:35 25 an unexpected result in the context of an obviousness

14:42:39 1 analysis?

14:42:40 2 A If you -- if two modifications are -- are -- if
14:42:42 3 a modification is made and -- and the -- the yield or
14:42:48 4 the efficiency of that modification is -- is anticipated
14:42:51 5 to be something and it's then found to be sig- --
14:42:55 6 significantly different, that -- that would be
14:43:01 7 nonobvious.

14:43:19 8 Q And what is your basis for that understanding?

14:43:22 9 A My discussions with Kerry and Nate.

14:43:28 10 Q And did you -- did you discuss the -- the
14:43:32 11 unexpected results analysis with anyone other than Kerry
14:43:36 12 and Nate in forming your understanding?

14:43:40 13 A No, I did not.

14:43:57 14 Q So, Dr. Romesberg, can we turn to -- in your
14:44:02 15 substitute -- substitute declaration -- I'm sorry --
14:44:05 16 that's Exhibit 1029. Can we turn to paragraph 49. So,
14:44:22 17 in general here, I just want to understand at a higher
14:44:28 18 level the opinions that you provided in the declaration.

14:44:34 19 Is it fair to say that your opinions in the
14:44:40 20 declaration depend on the fact that there is nothing in
14:44:42 21 the prior art that showed a cleavage efficiency of a
14:44:46 22 disulfide linker greater than 90 percent?

14:44:53 23 A Yes.

14:44:54 24 THE REPORTER: And can I hear again. "Greater
14:44:54 25 than" --

14:44:56 1 MR. GRIER: Than 90 percent.

14:44:58 2 THE REPORTER: Thank you.

14:44:59 3 BY MR. GRIER:

14:45:00 4 Q So, then, is it also fair to say --

14:45:02 5 A I'm sorry. Can I add something to that?

14:45:04 6 MR. BABCOCK: Sure.

14:45:07 7 BY MR. GRIER:

14:45:07 8 Q Sure.

14:45:08 9 A In -- that there's nothing in a sequencing by

14:45:11 10 synthesis compatible framework that suggests cleavage

14:45:15 11 would be greater than 90 percent.

14:45:25 12 Q And what do you mean when you say a

14:45:29 13 synthesis -- SBS compatible framework?

14:45:32 14 A So it's a bit of a relative term because the

14:45:35 15 exact thing is not -- in the -- in the absence of the

14:45:37 16 exact thing being in the literature, one has to say how

14:45:40 17 close is it and -- in order to be how predictive -- to

14:45:43 18 judge how predictive it might be. So it could be on a

14:45:46 19 nucleotide. It could be on a nucleoside. It could be

14:45:50 20 on a DNA fragment. You know, it -- the closer to the --

14:45:56 21 to the actual sequencing by synthesis application, the

14:46:01 22 better the evidence would be.

14:46:02 23 Q And the evidence you speak of, you're talking

14:46:05 24 about the cleavage efficiency of the disulfide linker?

14:46:08 25 A Yes.

14:46:24 1 Q So, Dr. Romesberg, would it also be fair to say
14:46:27 2 that because you claim that nothing in the prior art
14:46:33 3 taught disulfide cleavage efficiency at greater than
14:46:37 4 90 percent, that one of skill in the art would not have
14:46:40 5 been motivated to try to use the disulfide linkers in
14:46:43 6 the context of SBS?

14:46:45 7 A It's not so much that. It's more that data was
14:46:50 8 there in the literature that suggested that you would
14:46:54 9 not get nine -- greater than 90 percent. So it wasn't
14:46:57 10 just the absence of data; it was the presence of data
14:47:00 11 that was less than 90 percent efficient. Someone had
14:47:03 12 already sort of run the play, and that taught something.
14:47:08 13 And so it -- it's not so much the absence of greater
14:47:13 14 than 90 percent; it's the demonstration of less than
14:47:18 15 90 percent.

14:47:18 16 Q And when you say "someone had run the play,"
14:47:22 17 you're referring to Ruby and Herman. Is that correct?

14:47:26 18 A That is correct.

14:47:42 19 Q So, then, is it also fair to say that because
14:47:45 20 nothing in -- no one in the prior art had been able to
14:47:49 21 achieve greater than 90-percent cleavage efficiency of a
14:47:54 22 disulfide linker, that the fact that Illumina was able
14:47:57 23 to achieve, as you testify, essentially 100-percent
14:48:02 24 cleavage, that that was a significant and unexpected
14:48:05 25 result over the prior art?

14:48:07 1 A Given that, plus the time scale that Illumina
14:48:10 2 achieves that cleavage in, something like -- I think
14:48:13 3 it's, like, 23 seconds or something -- it's in my dec --
14:48:18 4 is -- it's certainly less than the, you know, hours that
14:48:20 5 the 90 -- that the 86 and 87 from Ruby and -- and Herman
14:48:25 6 were -- were achieved. Yes, that's the -- that's the
14:48:30 7 unexpected result.

14:48:31 8 Q And it's unexpected because Illumina was able
14:48:33 9 to achieve that -- that cleavage efficiency in 2012. Is
14:48:41 10 that correct?

14:48:47 11 A I don't know when Illumina achieved that. I --
14:48:49 12 I read it in the Vermaas declaration. That's -- that's
14:48:54 13 the only data that I have.

14:49:23 14 Q So earlier in the day, Dr. Romesberg, we were
14:49:26 15 talking about the '026 patent. And if we can get the
14:49:30 16 '026 patent back out, Exhibit 1001. I have to find it.

14:50:05 17 So, earlier, if you recall, we looked at
14:50:10 18 page -- we looked at page 9 of the '026 patent in
14:50:20 19 Column 2.

14:50:21 20 Can you turn there, please.

14:50:29 21 And do you recall you testified that the '026
14:50:35 22 patent taught that you could use the nucleotides for
14:50:39 23 things other than SBS. Is that correct?

14:50:41 24 A Yes.

14:50:45 25 Q And we went over those other uses, and they're

14:50:47 1 shown here in Column 2, labeling of nucleotides,
14:50:51 2 polynucleotide synthesis, hybridization assays, for
14:50:56 3 example.

14:50:57 4 Do you see that?

14:50:58 5 A (Gesturing).

14:51:00 6 Q So in those --

14:51:01 7 A Yes.

14:51:03 8 Q I'm sorry to talk over you.

14:51:04 9 So in those uses, Dr. Romesberg, it wouldn't
14:51:06 10 matter if you were able to achieve disulfide cleavage
14:51:09 11 efficiency of greater than 90 percent. Isn't that
14:51:13 12 correct?

14:51:14 13 A I'm not sure. I'd have to think about the
14:51:15 14 application, because the other listed applications are
14:51:17 15 very broad and general, and I think it would depend on
14:51:19 16 if you were -- if you were labeling oligonucleotides and
14:51:22 17 you needed 99.9 percent of them labeled, then that
14:51:25 18 particular application would need a
14:51:27 19 greater-than-90-percent yield or efficiency.

14:51:30 20 So it would be a case-by-case thing. I'd have
14:51:33 21 to know exactly what you're wanting to do, and that will
14:51:35 22 determine what cleavage efficiency you -- you need.

14:51:39 23 As -- as I describe in my dec, the specific
14:51:43 24 cleavage efficiency that you need for sequencing by
14:51:45 25 synthesis, the value I think I use in my dec is

14:51:47 1 90 percent, which, in reality, is not a -- a
14:51:51 2 particularly good value. You'd want it higher.

14:51:54 3 But that's sort -- sort of a cutoff, because --
14:51:58 4 I chose that because it was slightly above what Ruby and
14:52:01 5 Herman demonstrated to sort of prove -- to make my
14:52:04 6 point.

14:52:04 7 But for these other applications, I think it
14:52:07 8 would depend on what the -- on what the application was.

14:52:09 9 Q But you could agree that for some of these
14:52:12 10 other applications, it's certainly possible that you
14:52:14 11 would need to achieve disulfide cleavage efficiency of
14:52:17 12 greater than 90 percent. Correct?

14:52:19 13 A Is it possible? Is that what you're asking?

14:52:22 14 Q Right. I mean, looking at these other uses on
14:52:25 15 Column 2, would you agree that you wouldn't necessarily
14:52:30 16 need disulfide cleavage efficiency of greater than
14:52:34 17 90 percent?

14:52:36 18 A So I just want to make sure I don't say
14:52:39 19 something that I -- that I don't mean. There's likely
14:52:43 20 applications for all of these. There's likely specific
14:52:47 21 applications for all of these more broader categories
14:52:49 22 that would require very high efficiency and some that
14:52:54 23 might be somewhat less demanding.

14:52:56 24 So to the extent there are some that are less
14:52:59 25 demanding, then, yeah, there -- there -- it's possible

14:53:01 1 that there would be some that would require less
14:53:04 2 efficient cleavage.

14:53:05 3 Q "Less efficient," meaning less than 90 percent
14:53:09 4 cleavage. Is that correct?

14:53:10 5 A Maybe some that would require even less than
14:53:12 6 that.

14:53:28 7 Q And if you could turn to Exhibit -- Illumina
14:53:31 8 Exhibit 2015. It's the Rabani reference.

14:53:40 9 A 2015. Mm-hmm. It's this one here. Yeah.
14:53:51 10 Yeah.

14:53:51 11 Q Okay. And, specifically, on page 3 of Rabani,
14:53:54 12 at lines 5 through 8.

14:54:04 13 Do you see that?

14:54:10 14 A I do.

14:54:12 15 Q Okay. Is this recitation of Rabani here on
14:54:18 16 page 3, is this where -- is this where you come up with
14:54:22 17 your number relating to cleavage efficiency being
14:54:28 18 90 percent?

14:54:30 19 A Yeah. Yeah.

14:54:32 20 Q And it's because Rabani makes that assertion
14:54:36 21 that 90-percent cleavage efficiency is required in SBS.

14:54:42 22 Is that -- is that your testimony?

14:54:45 23 A Actually, it's kind of a coincidence. I think
14:54:47 24 I -- I don't think that I used that 90 percent because
14:54:49 25 of this. I think I chose the 90 percent because it was

14:54:52 1 a round number above what Ruby and Rabani -- sorry --
14:54:55 2 what Ruby and Herman report.

14:55:01 3 But -- but I'm also aware that in my dec, I
14:55:03 4 also cite this number. And I think I sort of
14:55:06 5 coincidentally came across those numbers independently
14:55:09 6 from two different directions. And I think I -- I think
14:55:12 7 it occurred to me, and I was fine with that.

14:55:14 8 I guess the only thing I'm saying -- and I
14:55:16 9 think this is probably trivial -- is that I chose the
14:55:20 10 number originally because it was just larger.

14:55:23 11 Q Larger than --

14:55:24 12 A Ruby and Herman.

14:55:25 13 Q Large than what Ruby and Herman --

14:55:28 14 A Report.

14:55:28 15 Q -- report? Okay.

14:55:29 16 Had you reviewed the Ruby and Herman references
14:55:31 17 prior to reviewing Rabani?

14:55:34 18 A No. I read Rabani and then read Ruby
14:55:39 19 immediately after it. In fact, I print -- I think I may
14:55:42 20 have read Ruby during it.

14:55:49 21 Q So prior to reading Ruby, you had not
14:55:54 22 established that 90-percent cleavage efficiency was
14:55:58 23 required. Is that correct?

14:56:00 24 A Are you asking if I knew that high efficiency
14:56:02 25 would be required? I certainly knew that.

14:56:06 1 Are -- are you asking if I would have chosen
14:56:07 2 the value of 90 before I read this? Probably -- I mean,
14:56:18 3 I guess it would be a bit context-dependent. The
14:56:21 4 context of why I chose the 90 percent initially was
14:56:24 5 because Ruby and -- and Herman report something slightly
14:56:27 6 under that, and I rounded above that. I've had
14:56:30 7 experience with sequencing by synthesis, and the
14:56:31 8 question really comes down to -- I apologize for getting
14:56:34 9 technical. But the question comes down to what read
14:56:37 10 length do you want. And if you need -- and -- and this
14:56:40 11 depends on what your apparatus is, what your -- how
14:56:44 12 your -- your instrumentation works.

14:56:46 13 You may be okay with 20 nucleotide reads, which
14:56:50 14 I think is -- my personal opinion is not great. You may
14:56:54 15 go after 100 nucleotide reads. To go after 100
14:57:02 16 nucleotide reads, you're going to need a much higher
14:57:06 17 efficiency, obviously.

14:57:06 18 So it -- it sort of depends on the read length
14:57:08 19 that you have and -- and -- or what you expect and how
14:57:13 20 that might be limited by other things.

14:57:15 21 Ninety percent, as I -- as I described in my
14:57:18 22 dec, will get you a very moderate read length that you
14:57:21 23 would probably want better than. But it's a value that
14:57:25 24 was slightly larger than those reported by Herman and --
14:57:27 25 and Ruby. And I wanted to make my point that way.

14:57:37 1 Q Can you turn in your declaration to the
14:57:38 2 proposed claims. And, again, that's on page 6.

14:57:49 3 And looking there at proposed Claim 9, proposed
14:57:53 4 Claim 9 doesn't recite a limitation requiring a certain
14:57:57 5 read length. Correct?

14:57:58 6 A That's correct.

14:58:00 7 Q Okay. So back to Rabani and back to page 3 of
14:58:13 8 Rabani, in particular.

14:58:18 9 The 90 percent that Rabani recites there, he's
14:58:23 10 not talking about cleavage efficiency of the cleavable
14:58:28 11 linker attached to a base. Is that correct?

14:58:31 12 A That is correct.

14:58:31 13 Q He's talking about cleavage efficiency of the
14:58:35 14 3' protecting group. Is that right?

14:58:38 15 A That is correct.

14:58:38 16 Q Okay. Is there anywhere in Rabani where he --
14:58:45 17 he reports that it would be required to cleave a
14:58:50 18 cleavable linker at 90-percent efficiency?

14:58:55 19 A Again, I would have to go look and check for
14:58:57 20 that, but I don't believe so. I don't recall. I don't
14:59:01 21 recall him saying that, and I probably would recall it
14:59:04 22 if he did. So I don't think it's there.

14:59:11 23 Q But when you look at the 90-percent cleavage
14:59:14 24 efficiency, that's in relation to the disulfide linker
14:59:16 25 attached to the base. Is that correct?

14:59:21 1 A Could you repeat the question.

14:59:22 2 Q Sure. When you are looking at cleavage
14:59:25 3 efficiency, the disulfide bond, in your declaration,
14:59:31 4 that is the disulfide bond and the cleavable linker
14:59:34 5 attached to the base. Correct?

14:59:35 6 A Well, that's certainly where I start, and
14:59:37 7 that's what I cite Ruby and Herman for, yes.

14:59:40 8 Q Okay. But Rabani doesn't teach that you need
14:59:45 9 to be able to cleave a cleavable linker attached to a
14:59:49 10 base with greater than 90-percent efficiency. Correct?

14:59:54 11 A That's correct.

15:00:07 12 Q Okay. Dr. Romesberg, I will show you what's
15:00:20 13 been previously marked Illumina Exhibit 2016.

15:00:33 14 Do you recognize this document?

15:00:34 15 A I do.

15:00:40 16 Q And this is the Ruby reference that we've
15:00:42 17 referred to periodically throughout the day. Is that
15:00:43 18 correct?

15:00:44 19 A That is correct.

15:00:44 20 Q Okay. And can we operate under the assumption
15:00:46 21 that if I refer to 'Ruby,' you'll understand that I'm
15:00:51 22 referring to Illumina Exhibit 2016?

15:00:56 23 A Yes.

15:00:56 24 Q Okay. The nucleotides taught by Ruby are not
15:01:02 25 used in an SBS reaction. Correct?

15:01:04 1 A That is correct.

15:01:09 2 Q In fact, what Ruby describes are biotinylated
15:01:12 3 nucleotides for use in affinity chromatography. Is that
15:01:16 4 correct?

15:01:17 5 A What Ruby describes are linker-modified
15:01:23 6 triphosphates that are incorporated into RNA, that then
15:01:29 7 are then, after incorporation into RNA, modified with
15:01:32 8 linkers that attach a biotin tag via a di- -- a
15:01:37 9 disulfide bond.

15:01:49 10 Q So the nucleotides are modified after
15:01:51 11 incorporation. Correct?

15:01:53 12 A With a disulfide bond, yes. They are modified
15:01:56 13 before incorporation with a linker that allows for
15:01:59 14 site-specific attachment of that -- of that
15:02:02 15 disulfide-containing moiety. So they're not natural
15:02:06 16 RNTPs. They're not natural ribo triphosphates. They
15:02:12 17 have a linker, and, you know, they have a very similar
15:02:15 18 linker to the linker everyone else uses, in this case,
15:02:21 19 this trans CH olefin with an amine functionality, and
15:02:25 20 that amine functionally allows you to hook -- to connect
15:02:28 21 to the disulfide-containing moiety.

15:02:32 22 Q Can you point to me where in -- in Ruby, the
15:02:34 23 structure that you were just looking at?

15:02:36 24 A Sure. It's Figure 2B.

15:02:40 25 Q Figure 2B. And what -- I'm sorry.

15:02:47 1 What structure were you specifically referring
15:02:49 2 to?

15:02:49 3 A So you see the -- the -- the -- what he's
15:02:52 4 calling biotinylation?

15:02:56 5 Q I do.

15:02:58 6 A You see the U. It has a CH double bond CH CH2
15:02:58 7 NH2 --

15:02:58 8 THE REPORTER: Could I get that again.

15:02:58 9 THE WITNESS: There is a U illustrated that's
15:02:58 10 bound to a CH double bonded -- double bond CH CH2 NH2.
15:02:58 11 And that's a linker. And that's an unnat- -- and so --
15:02:58 12 so the -- the ribo triphosphate is already modified.
15:02:58 13 It's not modified with the disulfide. It's modified in
15:02:58 14 a way that allows you to post RNA synthesis modified
15:02:58 15 with the disulfide.

15:02:58 16 BY MR. GRIER:

15:03:01 17 Q Okay. So post -- that's just what I was
15:03:31 18 wanting to make clear.

15:03:32 19 So post-incorporation, the nucleotide analog is
15:03:36 20 modified with a disulfide linker, and that disulfide
15:03:40 21 linker has attached a biotin. Is that correct?

15:03:45 22 A That is correct.

15:03:46 23 Q Okay. And that's done so that you can attach
15:03:48 24 your molecule of interest to the affinity column. Is
15:03:52 25 that correct?

15:03:53 1 A Yes.

15:03:54 2 Q Okay. And you said, Dr. Romesberg, that

15:04:04 3 everyone else was using that molecule in 2B.

15:04:07 4 What do you mean by everyone else was using

15:04:10 5 that?

15:04:12 6 A I don't recall saying that everyone else was

15:04:14 7 using that.

15:04:14 8 Could you remind me of what context I said

15:04:16 9 that?

15:04:17 10 Q Sure. You said -- we were discussing Ruby,

15:04:22 11 and, in particular, you were leading me through the

15:04:25 12 compounds in Figure 2B. And you referred to this

15:04:29 13 NHS-SS-biotin, I believe, and said that they were using

15:04:34 14 a compound that everyone was using. I'm just trying to

15:04:37 15 understand what you meant by that statement.

15:04:42 16 A I don't recall saying that. And I don't know

15:04:43 17 what I meant by it. I don't know what I -- what I -- I

15:04:46 18 apologize. I don't know what I would have meant by

15:04:48 19 saying that. I -- I don't know whether that was a

15:04:55 20 comment you said or not.

15:04:56 21 Can I ask to hear my response?

15:04:58 22 MR. GRIER: Yeah. Could you -- 167, line 17, I

15:05:02 23 think.

15:05:07 24 THE REPORTER: I'm sorry?

15:05:07 25 MR. GRIER: Does that help you?

15:05:07 1 THE REPORTER: Oh, that doesn't, because I'm
15:05:07 2 different from where you are. But you're looking for --
15:05:18 3 MR. GRIER: I'm looking for --
15:05:19 4 THE WITNESS: I do know what I was referring
15:05:22 5 to.
15:05:22 6 BY MR. GRIER:
15:05:23 7 Q Okay. So -- so the question was "So the
15:05:25 8 nucleotides are modified after incorporation. Correct?"
15:05:28 9 And your answer was "With the disulfide bond,
15:05:30 10 yes. They're modified before incorporation with the
15:05:34 11 linker that allows for site-specific attachment of
15:05:36 12 that -- of that disulfide-containing moiety. So they're
15:05:39 13 not natural RNTPs. They're not natural ribo
15:05:43 14 triphosphates. They have a linker, and they have a very
15:05:47 15 similar linker to the linker everyone else uses."
15:05:50 16 A Yes.
15:05:50 17 Q So --
15:05:50 18 A Yeah.
15:05:50 19 Q -- what were you referring to when you said
15:05:52 20 "they have a linker that's similar to the linker that
15:05:54 21 everyone else uses"?
15:05:55 22 A The linker. Not the NHS-SS-biotin.
15:06:00 23 Q And going back to Figure 2B, then, can you
15:06:06 24 point me to what linker you are referring to?
15:06:08 25 A I'm pointing to the -- to where the U comes off

15:06:14 1 with the CH double bond CH --

15:06:14 2 THE REPORTER: Slower again for me.

15:06:14 3 THE WITNESS: The -- the U is attached to a CH,
15:06:17 4 double bond, CH, CH₂, NH₂.

15:06:22 5 This is one of two linkers that has received
15:06:26 6 broad use, and it's kind of been supplanted by one
15:06:30 7 that's very close. But it's one of two that kind of
15:06:32 8 work. So when I said that's what everyone uses,
15:06:35 9 that's -- I was referring to the -- to this and not to
15:06:38 10 the NHS-SS-biotin.

15:06:38 11 BY MR. GRIER:

15:06:47 12 Q Okay. Thank you.

15:06:48 13 So then when -- when Ruby attaches the modified
15:06:50 14 nucleotide to the column, it's later eluted with DTT.
15:06:57 15 Correct?

15:06:58 16 A That is correct.

15:07:01 17 Q Okay. And that's done by using DTT to cleave
15:07:04 18 the disulfide bond in the linker. Correct?

15:07:06 19 A At varying PHs, yes.

15:07:11 20 Q And it's your testimony that when Ruby cleaves
15:07:15 21 the disulfide bond, he is able to recover 86 percent of
15:07:24 22 the nucleotide. Correct?

15:07:27 23 A I believe that's correct.

15:07:31 24 Q In this method, if -- if Ruby wanted to
15:07:36 25 increase the percent recovery, couldn't Ruby just alter

15:07:42 1 the cleavage conditions?

15:07:43 2 A Probably not.

15:07:46 3 Q And why is that?

15:07:47 4 A Well, because he's already at something of an

15:07:49 5 optimal pH. And the most obvious thing to do would be

15:07:54 6 to increase the concentration of the DTT. But the

15:07:56 7 concentration of the DTT is already -- he's already

15:08:01 8 looked at 150 millimolar. And so what you would do is

15:08:07 9 you would double the concentration, and you would expect

15:08:10 10 a doubling in the rate.

15:08:13 11 But you're already so high that you sort of

15:08:14 12 have a pretty small amount of room to go. You could

15:08:19 13 maybe increase it fivefold before you're getting into

15:08:21 14 concentrations where the DNA is going to denature

15:08:24 15 because you can't put it into DTT. DNA wants to be in

15:08:28 16 water. So you're already -- 150 millimolar is already

15:08:32 17 very high. And to go higher -- I mean, to approach a

15:08:36 18 molar concentration of DTT is silly. It's -- it --

15:08:41 19 no one would do that. DNA wouldn't be stable under

15:08:45 20 those --

15:08:45 21 So maybe you could eke out another twofold,

15:08:47 22 maybe another threefold, if you want to -- you know,

15:08:51 23 really high concentrations. But that would give you a

15:08:54 24 threefold increase in rate. And what's that going to do

15:08:57 25 when you're only getting an 85-percent cleavage over two

15:09:00 1 hours anyway.

15:09:01 2 So the -- so, yeah, I thought about that.

15:09:04 3 And -- and the -- the -- the -- what occurred to me is
15:09:08 4 that the cleavage is surprisingly -- well, the cleavage
15:09:11 5 is inefficient. It is what it is. And getting another
15:09:14 6 threefold to -- which you probably couldn't even get.

15:09:18 7 Maybe -- I mean -- again, it's 150 millimolar in DTT
15:09:22 8 already.

15:09:23 9 Q Is --

15:09:25 10 A Sorry?

15:09:26 11 Q I just -- I was just waiting for you --

15:09:28 12 A It's already -- it's already very high in DTT.
15:09:31 13 So if you double the concentration, would a doubling in
15:09:33 14 the rate bring you into that efficiency sufficient for
15:09:37 15 sequencing by synthesis, no.

15:09:39 16 If you were at a nanomolar, then I'd say, boy,
15:09:44 17 you could juice this up a thousand fold, that -- that
15:09:46 18 would be a different story. But you're starting at 150
15:09:50 19 millimolar. You're starting at a significant fraction
15:09:54 20 of your solution already being DTT.

15:09:56 21 Q What about altering the pH? Did Ruby alter the
15:09:59 22 pH and change cleavage efficiency?

15:10:03 23 A Well, he already explored 7.6 and 9. I don't
15:10:06 24 recall him saying that he explored others. But 9 is --
15:10:10 25 you don't want to go a lot higher for a variety of

15:10:14 1 reasons for sequencing by synthesis.

15:10:19 2 But 9 is -- is -- 9 might even be optimal
15:10:23 3 for -- for cleavage of a disulfide. And it -- it
15:10:27 4 certainly is uncommon to cleave disulfides at higher
15:10:31 5 pHs, to my -- to my knowledge.

15:10:35 6 Q But if you wouldn't want to go higher than 9
15:10:38 7 for SBS, Ruby wouldn't be concerned with that, right,
15:10:40 8 because this is not an SBS reaction?

15:10:42 9 A Right. So he may have gone higher and found
15:10:45 10 no -- no advantage. I don't know that he didn't try to
15:10:47 11 optimize further on that. I -- I only have the data
15:10:50 12 that he presented.

15:10:51 13 Q But is it your testimony that Ruby could have
15:10:53 14 optimized the cleavage efficiency by altering parameters
15:10:56 15 such as pH?

15:10:58 16 A Probably not. And I'll -- I'll just guess -- I
15:11:00 17 don't know -- I don't know that. But -- but I think
15:11:02 18 there's a significant chance that it's not, because he's
15:11:05 19 already probably depro- -- fully deprotonated the --
15:11:15 20 substrate. And so there's not going to -- I don't
15:11:18 21 think -- unless there's -- I'm not -- in the mechanism
15:11:20 22 of di- -- disulfide cleavage, is there a role for a
15:11:24 23 hydroxide group? I don't think so. I think that what
15:11:30 24 you need is the deprotonation of the thiol, which around
15:11:40 25 pH 9, you should be pretty much there.

15:11:42 1 So just sitting here spontaneously thinking,
15:11:45 2 I -- I don't think it's likely -- so if you're pH 12 and
15:11:48 3 you've got your thi- -- so the mechanism of disulfide
15:11:50 4 cleavage, you have to have a thiol come back and
15:11:54 5 displace at the disulfide so that you put the electron
15:11:58 6 pair on the leaving group thiol, which is then
15:12:06 7 oxidized.

15:12:09 8 THE REPORTER: "Put the electron pair on
15:12:09 9 the" -- can I hear again.

15:12:09 10 THE WITNESS: Leaving group sulfur.

15:12:09 11 THE REPORTER: "Leaving"?

15:12:09 12 THE WITNESS: Yeah. Leaving group sulfur. And
15:12:09 13 that's oxidation. So you have to have the nucleophilic
15:12:16 14 one that comes back in deprotonated. If it's already
15:12:19 15 deprotonated, going to increasingly basic conditions
15:12:23 16 isn't going to get you anything. I mean, so if you
15:12:24 17 think of a PKA curve, just an equilibrium curve, it --
15:12:30 18 it -- it's exponential at the deprotonation end, or at
15:12:30 19 the protonation end, it's exponential at both --

15:12:35 20 THE REPORTER: You've got to slow down for me
15:12:35 21 some.

15:12:35 22 THE WITNESS: It's sigmoidal. And when you're
15:12:37 23 in the tail of a sigmoid, you're getting very little
15:12:40 24 increase in the concentration of the active species.

15:12:48 25 Is that clear? Did I get that all in?

15:12:49 1 THE REPORTER: We do need to slow down some.

15:12:54 2 THE WITNESS: I'm sorry.

15:12:54 3 THE REPORTER: Yeah. Thank you.

15:12:54 4 BY MR. GRIER:

15:12:57 5 Q But if you look at page 118 of Ruby, the

15:13:03 6 paragraph at the top of the page there --

15:13:07 7 A That's exactly what I just said.

15:13:09 8 Q So do you see where Ruby says "By increasing

15:13:11 9 the pH and DTT concentration of the elution buffer

15:13:18 10 slightly, one can effectively elute the RNA during

15:13:23 11 longer incubation times"? Do you see that?

15:13:25 12 A I'm sorry. No. I'm sorry. Where?

15:13:28 13 Q Page 118 --

15:13:31 14 A Yep.

15:13:32 15 Q -- of Ruby. Top paragraph. One, two, three,

15:13:35 16 four -- five lines down, it starts "By increasing." "By

15:13:39 17 increasing the pH and DTT concentration of the

15:13:42 18 elution" --

15:13:44 19 A Correct.

15:13:44 20 Q -- "buffer slightly, one can effectively elute

15:13:47 21 the RNA during longer incubation times."

15:13:50 22 Do you see that?

15:13:51 23 A I do.

15:13:54 24 Q So doesn't that suggest that Ruby was able to

15:13:57 25 optimize cleavage efficiency by altering parameters such

15:14:01 1 as pH and DTT concentration?

15:14:04 2 A Yes. That's what he did. That's exactly what
15:14:07 3 he's showing in his -- in his figure. He's showing
15:14:09 4 cleavage -- what he's referring to is the fact that you
15:14:11 5 get more efficient cleavage at -- at the higher pH than
15:14:15 6 you get at the lower pH. And that's shown in the
15:14:18 7 figure. And the values of 86 that I use, 86 percent,
15:14:23 8 are his most efficient cleavage conditions after having
15:14:30 9 optimized that.

15:14:31 10 THE REPORTER: "Are his most efficient
15:14:31 11 cleavage" -- slow down.

15:14:31 12 THE WITNESS: -- conditions after having
15:14:31 13 optimized the pH.

15:14:35 14 And more importantly, what I -- the sentence
15:14:37 15 before that, what Ruby says is "The pH dependence is
15:14:41 16 probably due to the pKa of the thiol group." So that's
15:14:47 17 what I just described, suggesting that a further
15:14:49 18 increase in pH will buy you nothing, because you've
15:14:52 19 already deprotonated the thiol. You can't deprotonate
15:14:58 20 it twice.

15:14:59 21 Q But Ruby was able to optimize cleavage
15:15:01 22 efficiency by increasing the pH in the DTT
15:15:04 23 concentration.

15:15:05 24 A He went from a --

15:15:07 25 Q Correct?

15:15:07 1 A Correct. He went from a pH where it was
15:15:10 2 predominantly mostly protonated. As he describes, he
15:15:14 3 went through its pKa to where it was predominantly
15:15:17 4 deprotonated. And you will not get -- you will not get
15:15:20 5 much of an acceleration after that.

15:15:22 6 Q But just to be clear, Ruby was able to optimize
15:15:25 7 the disulfide cleavage conditions by increasing the pH
15:15:30 8 and DTT concentration. Correct?

15:15:32 9 MR. BABCOCK: Asked and answered.

15:15:33 10 THE WITNESS: Correct. That's what he shows in
15:15:34 11 this figure.

15:15:43 12 MR. GRIER: Would it be all right if we took a
15:15:45 13 break --

15:15:45 14 MR. BABCOCK: Sure.

15:15:45 15 MR. GRIER: -- at this point?

15:15:46 16 VIDEOGRAPHER: Off the record at 3:15.

15:35:55 17 (Recess from 3:15 p.m. to 3:36 p.m.)

15:36:49 18 VIDEOGRAPHER: Back on the record at 3:36.

15:37:08 19 BY MR. GRIER:

15:37:10 20 Q Dr. Romesberg, I'm going to show you what's
15:37:14 21 been previously marked Illumina Exhibit 2017.

15:37:27 22 First, Dr. Romesberg, while we were on break,
15:37:29 23 did you have any discussions with counsel?

15:37:30 24 A No, I did not.

15:37:31 25 Q So you did not discuss the testimony you

15:37:32 1 provided today in this deposition?

15:37:34 2 A No.

15:37:35 3 Q Or questions I might ask the rest of the day?

15:37:38 4 A No.

15:37:38 5 Q Okay. You didn't discuss questions that your
15:37:40 6 counsel might ask you --

15:37:41 7 A No.

15:37:41 8 Q -- at the end of the day?

15:37:47 9 Do you recognize Exhibit 2017?

15:37:49 10 A I do. It's the proposal from Herman we've
15:37:54 11 already referred to. Sorry. The patent.

15:38:01 12 Q That's fine.

15:38:09 13 Please turn to your substitute declaration,
15:38:14 14 Exhibit 1029, paragraph 56. This is the Herman that you
15:38:20 15 discuss in your -- in your declaration. Is that
15:38:23 16 correct?

15:38:23 17 A That is correct.

15:38:25 18 Q Okay. And like we've been doing, can we just
15:38:29 19 go under the assumption that if I say "Herman," then you
15:38:32 20 understand I'm referring to Exhibit 2017?

15:38:34 21 A Yes.

15:38:34 22 Q Okay. The nucleotides taught by Herman, again,
15:38:50 23 are biotinylated nucleotides for use in affinity
15:38:54 24 chromatography. Is that correct?

15:38:57 25 A That is correct.

15:38:58 1 Q Okay. So the nucleotides taught by Herman are
15:39:00 2 not used in SBS. Correct?

15:39:04 3 A No.

15:39:13 4 Q And what Herman was measuring here was elution
15:39:19 5 of his molecules of interest from the affinity column.
15:39:23 6 Correct?

15:39:23 7 A Upon treatment with DTT, yes.

15:39:25 8 Q Okay. And because Herman wasn't -- wasn't
15:39:30 9 conducting sequencing by synthesis but, rather, just
15:39:35 10 eluting molecules, Herman wouldn't be necessarily
15:39:39 11 concerned with cleavage efficiency of greater than
15:39:42 12 90 percent. Would he?

15:39:44 13 A It depends on what his -- what his goal was.
15:39:51 14 In general, people want to recover fully their material.
15:39:54 15 I suspect he was, because he ran it five times. And if
15:39:58 16 he was just trying to get a little bit and didn't care
15:40:01 17 how much, he probably would have taken one and run. But
15:40:04 18 he did take care to do it five times.

15:40:12 19 Q But, in general, the method described in
15:40:14 20 Herman, eluting from affinity chromatography, there's
15:40:17 21 something about that method in particular that would
15:40:18 22 require greater than 90 percent cleavage efficiency.
15:40:21 23 Correct?

15:40:22 24 A Again, it's not really a -- a method in and of
15:40:25 25 itself. It's a purification step. So it would really

15:40:27 1 depend on what you were doing with it, what the
15:40:29 2 application was. And that would sort of tend to
15:40:32 3 like- -- likely set what the efficiency required was.

15:40:36 4 In the elution step, you can elute with
15:40:39 5 1 percent. You can elute with 50 percent. It's just
15:40:42 6 a -- it's just a purification step. It doesn't care
15:40:44 7 about anything. You could be satisfied with -- it
15:40:46 8 doesn't -- there's -- there's not really a -- it's just
15:40:51 9 a single step that you can optimize how ever you want
15:40:54 10 depending on what level of a -- of a -- of cleavage
15:40:57 11 you -- you wanted for the actual application that you
15:40:59 12 were using the DNA, I guess is my answer.

15:41:08 13 Q So then, again, there's nothing in that Herman
15:41:17 14 reference that would require cleavage efficiency of the
15:41:20 15 disulfide linker of greater than --

15:41:23 16 THE REPORTER: I'm sorry. Can I get --

15:41:23 17 MR. GRIER: Sure.

15:41:23 18 THE REPORTER: -- hear that again, please.

15:41:23 19 BY MR. GRIER:

15:41:23 20 Q So there's nothing, Dr. Romesberg, in the
15:41:23 21 Herman reference that would require cleavage efficiency
15:41:23 22 of the disulfide linker greater than 90 percent?

15:41:24 23 MR. BABCOCK: Asked and answered.

15:41:24 24 BY MR. GRIER:

15:41:25 25 Q Is that correct?

15:41:26 1 MR. BABCOCK: Same answer -- objection.

15:41:27 2 THE WITNESS: I -- I find it impossible -- I
15:41:29 3 find it a difficult question to address, because it --
15:41:34 4 it's a single step. It's -- it's not an application.
15:41:38 5 It's not an application of a labeled nucleotide. It's
15:41:41 6 the purification step. So it would set a limit on what
15:41:44 7 cleavage efficiency you've got and could purify. But it
15:41:47 8 doesn't really -- you don't really have -- you want
15:41:50 9 those steps to be as efficient as possible. But, again,
15:41:53 10 the downstream application may be more forgiving or it
15:41:56 11 may not be. And that's really what would depend -- set
15:42:00 12 the -- the -- the -- the requirement of a certain
15:42:02 13 efficiency.

15:42:04 14 My -- my guess is that Herman wanted it to be
15:42:08 15 as efficient as possible because he wants people to use
15:42:11 16 his Nick translation and purification system --

15:42:17 17 THE REPORTER: "Because he wants people to use
15:42:17 18 his" --

15:42:17 19 THE WITNESS: Nick translation and purification
15:42:17 20 system as scientists always do. They want people to use
15:42:20 21 their stuff.

15:42:21 22 He -- he exposed it five times to washes with
15:42:24 23 DTT, which is unusual, which suggests to me that he was
15:42:29 24 very concerned about cleavage efficiency.

25

15:42:36 1 BY MR. GRIER:

15:42:38 2 Q Sir, if you could turn with me to Column 11 on
15:42:41 3 page 8 at the bottom of the Herman reference.

15:42:51 4 And in particular, if you look at line 14 --
15:42:56 5 right around line 14, here, Herman is describing elution
15:43:01 6 of a Bio-SS-DNA, with a buffer containing 50 millimolar
15:43:07 7 DTT. Is that correct?

15:43:08 8 A Yes.

15:43:08 9 Q Okay. And the Bio-SS-DNA that Herman is
15:43:15 10 referring to, is that shown -- is that shown in
15:43:24 11 columns 5 and 6 of Herman?

15:43:34 12 A No. No. The -- the nucleotide triphosphate
15:43:38 13 synthesis is shown there. The DNA is -- is not shown.

15:43:43 14 Q So the structure at the bottom of columns 5 and
15:43:46 15 6, do you see where the Bio-12-SS-dUTP?

15:43:52 16 A Mm-hmm.

15:43:53 17 Q So -- so what is that structure?

15:43:55 18 A That's the dUTP. That's the U triphosphate.

15:44:00 19 Q And why was Herman using that structure?

15:44:05 20 A Because he wanted that to be incorporated
15:44:11 21 during Nick translation into a fragment of DNA that
15:44:15 22 would result in the incorporation of biotin.

15:44:18 23 Q And then when that was incorporated, was that,
15:44:20 24 then, referred to as Bio-SS-DNA by Herman?

15:44:24 25 A Yeah. Once it's incorporated in the DNA.

15:44:27 1 Q Okay. And so the disulfide bond there in the
15:44:31 2 figure at the bottom of columns 5 and 6, that's the
15:44:36 3 disulfide bond that Herman is cleaving with the DTT. Is
15:44:39 4 that correct?

15:44:40 5 A That's correct.

15:44:41 6 Q All right.

15:44:41 7 A With -- the -- the exception being that it's
15:44:43 8 not in a triphosphate. It's after the triphosphate --
15:44:46 9 as we just discussed, after the triphosphate has been
15:44:50 10 put into DNA.

15:44:51 11 Q Right. So like Ruby, after the incorporation
15:44:54 12 of the triphosphate, the disulfide linker is added so
15:44:59 13 that the DNA is in biotinylated. Is that correct?

15:45:05 14 THE REPORTER: "So that the DNA" --

15:45:05 15 BY MR. GRIER:

15:45:05 16 Q Is in biotinylated. Is that correct?

15:45:06 17 A Not quite. In this case, the biotin is already
15:45:09 18 attached. The disulfide is already intact. So Ruby has
15:45:14 19 only that amine that he then used to couple on the
15:45:18 20 disulfide after the incorporation. They both cleave
15:45:21 21 after incorporation. Ruby and -- and -- and Herman do
15:45:25 22 it -- Herman does it more directly. Ruby does it in two
15:45:30 23 steps.

15:45:32 24 Q So if we look at Column 11 in Herman.

15:45:36 25 A Mm-hmm.

15:45:37 1 Q Line 15, Herman says after eluting with the 50
15:45:41 2 millimolar DTT resulted in a recovery of a total of
15:45:46 3 87 percent of the DNA from the affinity column.

15:45:49 4 Do you see that?

15:45:50 5 A I do.

15:45:50 6 Q And the next line there, he says "Only
15:45:52 7 7.3 percent of the Bio-SS-DNA remained bound to the
15:45:57 8 resin." Is that correct?

15:46:03 9 A Yes. Yes, that's right.

15:46:05 10 Q Okay. And so the 87 percent that Herman was
15:46:10 11 measuring there, is the 87 percent the total starting
15:46:14 12 material?

15:46:16 13 A That's how I read that.

15:46:19 14 Q So then after cleavage, there's 7.3 percent
15:46:25 15 remaining bound to the resin. Correct?

15:46:30 16 A That's how I read that.

15:46:32 17 Q Okay. So that means that when Herman ran his
15:46:36 18 elution reaction, then, he actually only had
15:46:39 19 94.3 percent of his starting material bound to the
15:46:43 20 column. Correct?

15:46:47 21 A That would be one explanation.

15:46:52 22 Q So if we take that explanation that only
15:46:54 23 94.3 percent was bound to the column and Ruby was able
15:47:00 24 to elute 87 percent, isn't the calculation, then, the
15:47:04 25 87 percent over the 94.3 percent that was bound to the

15:47:08 1 column? Isn't that how you would calculate disulfide
15:47:11 2 cleavage efficiency?

15:47:16 3 A If only 7.3 percent were bound. So give me a
15:47:20 4 second to think about this.

15:47:24 5 Q Sure.

15:47:51 6 A It -- it is a bit of an odd description. I --
15:47:55 7 there are several possibilities. What you described
15:47:57 8 certainly is one of them. He -- his masses -- his
15:48:01 9 yields don't add up. And so I -- I can't really speak
15:48:05 10 to that, other -- other than saying that when he labeled
15:48:09 11 the DNA and then he cleaved it, he got 87 percent.

15:48:13 12 Where that other 6 percent went, it could still be stuck
15:48:17 13 to the column and just have lost the phosphate and so he
15:48:20 14 can't detect it. It could have flowed through and not
15:48:24 15 been detected. Or it could have been from inefficient
15:48:33 16 labeling. I really don't know.

15:48:35 17 But -- but his masses don't add up, that's
15:48:37 18 correct.

15:48:38 19 Q So then in the scenario I was describing where
15:48:42 20 the 94.3 percent was what actually was loaded to the
15:48:49 21 column, if you did that math and you calculated
15:48:51 22 87 percent over the 94.3, you get something more like
15:48:54 23 95-percent cleavage efficiency. Correct?

15:48:57 24 A In that case, that would be correct.

15:48:59 25 Q And that, you would agree, is greater than the

15:49:02 1 90 percent that you testified was required by Rabani.

15:49:04 2 Correct?

15:49:05 3 A Ninety-five is greater than 90, correct.

15:49:14 4 MR. BABCOCK: And just --

15:49:15 5 MR. GRIER: That -- yeah, I -- I see that.

15:49:17 6 BY MR. GRIER:

15:49:17 7 Q Just to clarify, Dr. Romesberg, that 87 over --

15:49:21 8 over 94.3 is 92.2 percent.

15:49:25 9 A Okay.

15:49:26 10 Q Correct?

15:49:27 11 A Ninety-two is still greater than 90, if that

15:49:29 12 was your point.

15:49:30 13 Q That was my point. Thank you.

15:49:32 14 A Yeah. Can I -- can I add something to that?

15:49:37 15 MR. BABCOCK: Yeah.

15:49:38 16 THE WITNESS: I -- I don't think 92 percent is

15:49:40 17 good enough for sequencing by synthesis. And it would

15:49:44 18 not change my opinion that the greater than -- that the

15:49:46 19 virtual complete cleavage demonstrated by Illumina were

15:49:49 20 in any less way novel or un- -- or -- or not obvious.

15:49:55 21 BY MR. GRIER:

15:49:56 22 Q But, Dr. Romesberg, you've testified that

15:49:59 23 90-percent cleavage efficiency was what is required --

15:50:04 24 A No. I'm sorry. I didn't mean to interrupt.

15:50:13 25 Q Earlier today, I asked you is it fair to say

15:50:15 1 that your opinion depends on the fact that there was
15:50:18 2 nothing in the prior art that taught greater than
15:50:21 3 90-percent cleavage efficiency. And to that, you
15:50:26 4 answered yes.

15:50:27 5 MR. BABCOCK: Objection. Misstates the record.

15:50:28 6 THE WITNESS: I don't believe that's what I
15:50:29 7 said. What I meant to say was that my opinion was based
15:50:33 8 on the demonstration that it was 86 and 87 percent. I
15:50:37 9 chose 90 as a number to illustrate my point in my
15:50:41 10 declaration simply -- like I said, simply because it was
15:50:44 11 greater than 87 and 86 percent. I could have chosen 93,
15:50:48 12 and that would have been -- or it 94, and that would
15:50:51 13 have been greater than 93 percent. And the numbers
15:50:53 14 would have been slightly more favorable but still not
15:50:56 15 good enough and still -- in my opinion, not good enough.
15:51:00 16 But more importantly, still significantly less than the
15:51:03 17 virtually complete demonstrated by -- by Illumina.

15:51:07 18 I would have no problem saying that 86 and 87
15:51:11 19 was substantially similar to 86 and 92 and not similar
15:51:17 20 to -- to virtually complete.

15:51:22 21 BY MR. GRIER:

15:51:23 22 Q On page -- paragraph 58 of your substitute
15:51:25 23 declaration, on page 26, is your testimony there that
15:51:30 24 "Since Herman's cleavage efficiency under disulfide
15:51:33 25 cleavage conditions is less than 90 percent, Herman does

15:51:36 1 not provide an expectation that disulfide

15:51:41 2 cleavage conditions would cleave" --

15:51:46 3 THE REPORTER: I didn't quite hear.

15:51:46 4 BY MR. GRIER:

15:51:46 5 Q "Since Herman's cleavage efficiency under
15:51:48 6 disulfide cleavage conditions is less than 90 percent,
15:51:52 7 Herman does not provide an expectation that disulfide
15:51:57 8 cleavage conditions would cleave a 3'-OH protecting
15:52:02 9 group with greater than 90 percent efficiency."

15:52:06 10 That's your testimony. Correct?

15:52:07 11 A That's what I wrote, yes.

15:52:09 12 Q Right. And 90 percent there is the number that
15:52:11 13 you are using as a hallmark of efficiency. Correct?

15:52:15 14 MR. BABCOCK: Objection. Misstates the
15:52:16 15 testimony.

15:52:17 16 THE WITNESS: No, that's not correct. As I --
15:52:19 17 as I said before, what I intended by 90 was simply
15:52:23 18 picking a number, a round number that was greater than
15:52:26 19 the numbers published by Herman and -- and Ruby.

15:52:31 20 And if you come back and if your explanation is
15:52:34 21 right and Herman's 87 percent is incorrect, I simply
15:52:40 22 took it for what he wrote.

15:52:42 23 If your explanation is -- is correct, then that
15:52:45 24 number should be adjusted up to 92, and I would be
15:52:48 25 perfectly happy writing this all having chosen 95 as a

15:52:52 1 round number above what Herman and Ruby report.

15:52:55 2 BY MR. GRIER:

15:52:55 3 Q And assume for a moment I came back and I said
15:52:57 4 that the Herman calculations were 96 percent, would then
15:53:00 5 your testimony be that it needed to be 97 percent
15:53:03 6 efficient?

15:53:04 7 A No. At -- at some point, it would get to be
15:53:06 8 close enough that I would say, look, that's no longer a
15:53:09 9 big surprise. But I -- at 86 and 92, I'm still
15:53:15 10 confident -- I'm still comfortable saying virtually
15:53:18 11 complete is a big surprise. Of course, that's a --
15:53:20 12 there is a line there someplace. And you -- at some
15:53:23 13 point, you will approach it, at 98 percent, 97 percent,
15:53:26 14 something like that, sure. And I -- I'd have to think
15:53:29 15 about that. But at 92 percent, I would -- I would still
15:53:36 16 say it's a surprise.

15:53:36 17 And also, functionally, it's rather important
15:53:38 18 because if you look at the sequencing reads that
15:53:41 19 Illumina gets in -- in the declaration that you saw
15:53:43 20 yesterday, they're really outstanding. They're out to
15:53:46 21 110. And if you -- if you look at 95-percent cleavage
15:53:50 22 efficiency and if you -- if you assume that's the upper
15:53:53 23 end that you would have gotten for deprotection at a 3'
15:53:57 24 site, then you're not going to get anywhere near that.

15:54:00 25 Q But, again, I'm not talking about the

15:54:02 1 declaration yesterday. I'm talking about the Herman
15:54:04 2 reference, and your testimony that because Herman showed
15:54:08 3 disulfide cleavage conditions less than 90 percent, it
15:54:11 4 didn't provide an expectation that you could cleave a
15:54:15 5 protecting group with greater than 90-percent
15:54:17 6 efficiency. That's what I'm talking about.

15:54:19 7 And you -- you testify that 90 percent here is
15:54:21 8 the number that's required. Correct?

15:54:23 9 MR. BABCOCK: Objection. Misstates the
15:54:24 10 testimony. Asked and answered.

15:54:26 11 THE WITNESS: So let me be clear about the
15:54:27 12 90 percent. I apologize if it's not clear. But I think
15:54:30 13 this is, like, the fourth time I've said this. There's
15:54:33 14 nothing magic about my having chosen the number 90. I,
15:54:36 15 in fact, didn't choose it because Rabani cited it. I
15:54:40 16 chose it because it was a round number slightly above
15:54:42 17 the values reported by Ruby and Herman. And those are
15:54:45 18 the numbers that Ruby reported.

15:54:47 19 Now that you've pointed out this other
15:54:49 20 possibility that maybe the number that I should have
15:54:50 21 used for Herman -- excuse me -- was 92 percent, I would
15:54:53 22 be happy setting my value at 95. And I think in my only
15:54:58 23 vocation of the -- of the data that you saw yesterday
15:55:01 24 was that my -- my indication -- I'm trying to articulate
15:55:06 25 to you why I would still find it a surprising and

15:55:09 1 unexpected result, because going up to virtually
15:55:12 2 complete is a significantly different thing than sitting
15:55:15 3 under -- and let -- let me also emphasize, Herman washed
15:55:21 4 his column five times. That means five times, he
15:55:23 5 provide new reagent. Five washes are significantly
15:55:31 6 harsher conditions than one wash at the same amount of
15:55:35 7 time.

15:55:35 8 BY MR. GRIER:

15:55:35 9 Q Dr. Romesberg, I don't recall asking you a
15:55:37 10 question about harsh conditions. What I'm trying to
15:55:40 11 understand is your testimony that seems to indicate here
15:55:44 12 in paragraph 58 that because Herman's cleavage
15:55:49 13 efficiency was less than 90 percent, it does not provide
15:55:54 14 an expectation that disulfide cleavage conditions cleave
15:55:57 15 a protecting group with greater than a 90-percent
15:56:01 16 efficiency.

15:56:02 17 And that is your testimony. Correct?

15:56:03 18 A Yes.

15:56:03 19 Q Okay. Now, under our scenario that we are
15:56:07 20 discussing with Herman and the calculations, it's
15:56:09 21 92 percent. Correct? We went through those
15:56:13 22 calculations.

15:56:14 23 Do you recall that?

15:56:14 24 A Yes.

15:56:15 25 Q And it's your testimony that 92 percent is

15:56:19 1 greater than 90 percent. Correct?

15:56:21 2 A I believe that is an arithmetic fact.

15:56:25 3 Q Okay. And it's greater than the 90 percent
15:56:27 4 that you cite here in paragraph 58 as the disulfide
15:56:32 5 cleavage conditions that would provide an expectation
15:56:37 6 that the disulfide cleavage conditions could get
15:56:40 7 cleavage of a 3'-OH protecting group with greater than
15:56:44 8 90-percent efficiency.

15:56:47 9 MR. BABCOCK: Objection. Misstates the
15:56:48 10 testimony. Asked and answered.

15:56:49 11 THE WITNESS: Do I still answer?

15:56:51 12 MR. BABCOCK: Yeah. At some point, we'll stop
15:56:51 13 it, but --

15:56:52 14 THE WITNESS: I never suggested that greater
15:56:53 15 than 90 percent was sufficient. It's certainly
15:56:59 16 necessary. But necessary is not necessarily sufficient.
15:57:01 17 And 91 percent is greater than 90, but that would not be
15:57:04 18 sufficient. Ninety-five percent would not be
15:57:06 19 sufficient. Sufficiency is really something approaching
15:57:08 20 100.

15:57:09 21 BY MR. GRIER:

15:57:09 22 Q Okay. So --

15:57:10 23 A I'm sorry. I was simply trying to explain why
15:57:13 24 I still thought that ninety -- 87 versus 92 made no
15:57:18 25 difference to any of my positions in my declaration.

15:57:22 1 Q So what is, then, in your opinion, the
15:57:25 2 number -- the percent cleavage that you would need to
15:57:28 3 see to make it efficient cleavage conditions?

15:57:34 4 A That would -- so are you asking what would have
15:57:38 5 made me less surprised that a -- that Illumina was able
15:57:41 6 to achieve virtually complete cleavage, or are you
15:57:43 7 asking what would be necessary in my opinion for
15:57:45 8 sequencing by synthesis?

15:57:46 9 Q I'm asking you -- I'm not asking you about
15:57:48 10 surprise.

15:57:48 11 I'm asking you what would be necessary -- what
15:57:52 12 would be a necessary cleavage efficiency for sequencing
15:57:57 13 by synthesis?

15:57:57 14 A As we discussed earlier, it would depend on the
15:58:00 15 read length that you needed. I'd have to do the math.
15:58:03 16 But 95 percent would probably get you something like --
15:58:08 17 I'm not doing the math in my head right now. But I'm
15:58:11 18 guessing 20 nucleotides before you're -- before you're
15:58:15 19 wildly dephased.

15:58:17 20 It would probably not get you a read length
15:58:20 21 sufficient to assemble the human genome. So depending
15:58:25 22 on your application, this might not be correct. You
15:58:27 23 might have lower-hanging fruit that's easier. But I
15:58:30 24 think that anyone who -- who -- was interested in
15:58:33 25 sequencing by synthesis, that's a reasonable sort of

15:58:35 1 metric, and you would not achieve that, is my guess, in

15:58:38 2 95. But I'd have to do the math to check that, but --

15:58:41 3 Q So then why in your declaration did you not

15:58:43 4 state that 95-percent cleavage efficiency is what's

15:58:47 5 required?

15:58:48 6 MR. BABCOCK: Asked and answered.

15:58:48 7 THE WITNESS: I could have. I chose --

15:58:50 8 BY MR. GRIER:

15:58:50 9 Q But you --

15:58:51 10 A I didn't, no. That's right.

15:58:53 11 Q And, in fact, you -- you stated that 90 percent

15:58:55 12 was efficient enough. Correct?

15:58:58 13 A No.

15:58:59 14 MR. BABCOCK: Objection. Misstates testimony.

15:59:01 15 Asked and answered.

15:59:02 16 THE WITNESS: No, I didn't --

15:59:03 17 THE REPORTER: Wait. I'm sorry. Hold on.

15:59:04 18 MR. BABCOCK: Misstates the testimony. Asked

15:59:05 19 and answered.

15:59:05 20 THE WITNESS: I don't -- can I say something?

15:59:07 21 MR. BABCOCK: Of course.

15:59:08 22 THE WITNESS: I don't believe I anywhere stated

15:59:09 23 90 percent was sufficient. If I stated that, it's

15:59:12 24 incorrect. I probably said, look, let's take 90 and --

15:59:16 25 and show that that's clearly not sufficient. And

15:59:20 1 they're -- and they're below that. So it's -- it's
15:59:23 2 nowhere near the efficiency needed.

15:59:26 3 If you want to tell me the number I should have
15:59:28 4 used is 95, I'd have no problem with that.

15:59:31 5 Now, if you tell me the number is 99, that's
15:59:33 6 getting to be a -- that -- that would have been a -- a
15:59:37 7 bigger issue, I guess. At some point -- you're right.
15:59:40 8 At some point, the -- the literature values would
15:59:43 9 approach the values demonstrated by Illumina or the
15:59:47 10 values needed for sequencing by synthesis. And at some
15:59:49 11 point, I would have to say, yeah, that's getting fuzzy.
15:59:53 12 But we're not there. Ninety-two is not there.

15:59:58 13 BY MR. GRIER:

15:59:58 14 Q So is it your testimony, then, that 95-percent
16:00:02 15 cleavage efficiency is required for sequencing by
16:00:04 16 synthesis?

16:00:05 17 A There's not a value that's required. It
16:00:08 18 depends on the read length that you need. If you had
16:00:11 19 for some reason some sequencing by synthesis approach
16:00:14 20 where you were okay with a five nucleotide read length,
16:00:17 21 I can't imagine one, but then you could probably get by
16:00:21 22 with a 95-percent efficiency -- cleavage efficiency.

16:00:27 23 I think that any legitimate sequencing effort
16:00:30 24 where you're going to be commercially viable, you're
16:00:33 25 going to need read lengths -- I mean, this is getting to

16:00:37 1 a technical aspect that -- that -- that -- that maybe
16:00:39 2 I'm not such an -- so qualified to talk about other
16:00:43 3 people's -- in terms of what other people's needs are
16:00:47 4 for read length.

16:00:48 5 But I -- my opinion would be something like 30,
16:00:50 6 as a minimum.

16:00:53 7 Q If you turn to page 6 of your substitute
16:00:55 8 declaration. Proposed Claim 9.

16:01:05 9 Can you show me where in proposed Claim 9
16:01:08 10 there's a requirement that you achieve a certain read
16:01:10 11 length?

16:01:11 12 A There isn't --

16:01:12 13 Q Okay.

16:01:12 14 A -- a claim.

16:01:17 15 Q And you testified a moment ago that virtually
16:01:21 16 complete would be good enough.

16:01:24 17 Do you recall that?

16:01:27 18 A Yeah. I -- yes, I recall that.

16:01:31 19 Q What do you mean by "virtually complete"?

16:01:33 20 A It's probably a poor choice of words, because
16:01:35 21 it's not very specific. What you need is -- what you
16:01:37 22 would want is -- what you would need is an efficiency of
16:01:42 23 cleavage that does not contribute to an error rate.
16:01:47 24 That's what you -- that's what you would want, that
16:01:50 25 your -- because your error rate is going to come from

16:01:53 1 other things eventually. And if you don't -- if you're
16:01:56 2 substantially adding to that error with a modification
16:02:01 3 you have that's required for your nucleotide, then
16:02:03 4 that's a problem.

16:02:57 5 Q Dr. Romesberg, is it fair to say that the only
16:02:59 6 references that you relied on when making your
16:03:05 7 determination that a person of skill in the art would
16:03:09 8 not have expected to obtain greater than 90-percent
16:03:14 9 cleavage efficiency, the only two references you relied
16:03:17 10 on for that were Ruby and Herman. Is that correct?

16:03:20 11 A Yes.

16:03:22 12 Q And you also relied on Rabani, is that correct,
16:03:26 13 but through the citation of Ruby?

16:03:28 14 A Yes.

16:03:30 15 Q Did you consider any other references that
16:03:33 16 taught cleavage of disulfide linkers?

16:03:35 17 A No, I did not.

16:03:48 18 Q So assume for a moment that there were other
16:03:52 19 prior art references that showed you were able to cleave
16:03:55 20 a disulfide cleavable linker with greater than
16:03:58 21 90-percent efficiency.

16:04:00 22 Would that change your opinion as to whether a
16:04:03 23 person skilled in the art would have expected that you
16:04:05 24 could cleave a disulfide linker with greater than
16:04:07 25 90-percent efficiency?

16:04:11 1 MR. BABCOCK: Hypothetical.

16:04:14 2 THE REPORTER: Can I hear again.

16:04:14 3 MR. BABCOCK: Hypothetical. Objection.

16:04:15 4 THE REPORTER: Thank you.

16:04:16 5 THE WITNESS: Do I --

16:04:17 6 BY MR. GRIER:

16:04:17 7 Q You can answer the question, yes.

16:04:19 8 A That would depend. So I -- I assume this would

16:04:21 9 be on a nucleotide triphosphate, if it were -- as I said

16:04:27 10 earlier, the closer the disulfide context was to the

16:04:31 11 sequencing by synthesis context, the better evidence

16:04:34 12 that would be. And, of course, as we just went over, I

16:04:37 13 would not use greater than 90 percent as any sort of a

16:04:40 14 magic cutoff. It's not. It would depend on the

16:04:44 15 cleavage efficiency and whether that efficiency was

16:04:47 16 sufficient for your sequencing by synthesis application.

16:04:49 17 Q But, again, just to be clear, in your

16:04:51 18 declaration, you did use 90 percent as the cutoff.

16:04:56 19 MR. BABCOCK: Objection.

16:04:56 20 BY MR. GRIER:

16:04:56 21 Q Correct?

16:04:57 22 MR. BABCOCK: Objection. Misstates the

16:04:59 23 testimony.

16:04:59 24 THE WITNESS: No, I did not use that as a

16:05:01 25 cutoff. I simply used that as a value that was greater

16:05:05 1 than the values reported by Ruby and by Herman and to
16:05:07 2 just simply show that that value wasn't sufficient
16:05:09 3 enough. I thought I was picking one with a little
16:05:11 4 headroom. I didn't go in and pick 88 because that's
16:05:14 5 slightly above 87. I thought I was picking a round
16:05:16 6 number that was greater than -- than what Herman had
16:05:19 7 suggested and -- and showing that it was woefully
16:05:22 8 inadequate.

16:05:23 9 So my point was to show that if you're waking
16:05:26 10 up in St. Louis, you're probably not in New York.

16:05:52 11 MR. GRIER: Dr. Romesberg, I'm going to show
16:05:53 12 you what we'll mark as IBS Exhibit 1030.

11:23:48 13 (Exhibit 1030 was marked for identification.)

16:06:11 14 THE WITNESS: Thank you.

16:06:12 15 THE REPORTER: You're welcome.

16:06:19 16 BY MR. GRIER:

16:06:20 17 Q Have you ever seen this document --

16:06:21 18 A No.

16:06:21 19 Q -- Dr. Romesberg?

16:06:22 20 A No, I have not.

16:06:23 21 Q And if you look at the authors of this
16:06:26 22 document, you see the second author is Tim Herman.

16:06:28 23 Do you see that?

16:06:29 24 A I do.

16:06:32 25 Q And that Tim Herman listed there is from the

16:06:35 1 Medical College of Wisconsin.

16:06:36 2 Do you see that? Right below his name there on
16:06:42 3 the first page.

16:06:43 4 A Right. It looks like they're all from --

16:06:45 5 Q Okay.

16:06:45 6 A -- that same place.

16:06:47 7 Q Is this the same Herman who is the named
16:06:50 8 inventor of the Herman patent, Exhibit 2017?

16:07:00 9 A It looks like it. They're the same name in
16:07:01 10 the -- in the same institute. So I would say that's a
16:07:03 11 likely conclusion.

16:07:05 12 Q If you turn to page 12832 of Exhibit 1030, in
16:07:15 13 the second paragraph, you see here Herman is describing
16:07:20 14 an affinity isolation technique.

16:07:23 15 Do you see that?

16:07:23 16 A Can I just take a second to read the paragraph?

16:07:25 17 Q Certainly.

16:07:26 18 A Okay.

16:08:20 19 Okay. I -- I read the paragraph.

16:08:23 20 Q Okay. And in this paragraph, the final step
16:08:27 21 of -- of this Herman method is biotinylated DNA that was
16:08:31 22 bound to the affinity column was recovered by cleavage
16:08:34 23 of the disulfide bond in the linker arm joining the
16:08:36 24 biotin to the DNA.

16:08:38 25 Do you see that?

16:08:48 1 A I'm sorry. Where in the paragraph are you?

16:08:50 2 Q I'm in the paragraph about three-quarters of

16:08:53 3 the way down. It starts "Finally." "Finally,

16:08:56 4 biotinylated DNA bound" --

16:09:00 5 A Is this the second full paragraph?

16:09:05 6 Q I'm sorry. The second paragraph, first full

16:09:09 7 paragraph on that page.

16:09:10 8 A Oh. I'm sorry.

16:09:11 9 Q I apologize --

16:09:11 10 A I read --

16:09:11 11 Q No. I apologize for that.

16:09:14 12 A Can I --

16:09:14 13 Q Absolutely.

16:09:15 14 A I'm sorry. Can I spend a second to read this?

16:09:17 15 Q Certainly.

16:09:21 16 MR. BABCOCK: Take your time to read as much as

16:09:23 17 you need.

16:10:16 18 THE WITNESS: Okay.

16:10:18 19 BY MR. GRIER:

16:10:18 20 Q Okay. So, now, do you see the sentence that

16:10:19 21 starts "Finally, biotinylated DNA bound to the resin is

16:10:23 22 recovered by cleavage of the disulfide bond in the

16:10:25 23 linker arm joining biotin to the DNA"?

16:10:29 24 A I do.

16:10:30 25 Q Do you see that?

16:10:31 1 And this elution step here, this is the same
16:10:33 2 method that was used in the Herman patent. Correct?

16:10:40 3 A It doesn't give much detail. I'd have to -- it
16:10:43 4 looks like it, but I'd have to try to track down to make
16:10:45 5 sure that that was precisely identical.

16:10:47 6 Q Well, let's just speak in -- in terms of
16:10:49 7 general cleavage.

16:10:51 8 A Yeah.

16:10:52 9 Q The -- you would agree, then, that the -- the
16:10:55 10 biotinylated DNA that's bound to the affinity column in
16:10:59 11 Exhibit 1030 is recovered through the cleavage of the
16:11:03 12 disulfide bond, like it was in Exhibit 2017?

16:11:08 13 A To the extent that it's from the cleavage of
16:11:11 14 the disulfide bond, sure, yeah.

16:11:15 15 Q So can you turn back to the first page of
16:11:17 16 Exhibit twenty -- or 1030 -- I apologize.

16:11:23 17 So if you look in the abstract there, about
16:11:26 18 three-quarters of the way down, the sentence that says
16:11:28 19 "Cleavage of the disulfide bond in the linker arm of the
16:11:32 20 biotinylated nucleotide resulted in elution of virtually
16:11:35 21 all of the affinity isolated sequences."

16:11:39 22 Do you see that?

16:11:41 23 A I'm sorry. No. Could you -- what did the
16:11:44 24 sentence begin with again?

16:11:45 25 Q The sentence begins with the word "Cleavage."

16:11:48 1 It's about three-quarters of the way down in the
16:11:50 2 abstract.

16:11:51 3 A "Cleavage." Yeah. I found it.

16:11:52 4 Q It says "Cleavage of the disulfide bond in the
16:11:55 5 linker arm of the biotinylated nucleotide resulted in
16:11:59 6 elution of virtually all of the affinity isolated
16:12:04 7 sequences."

16:12:05 8 Do you see that?

16:12:09 9 A I do.

16:12:13 10 Q So then you would agree that in this
16:12:15 11 experiment, Herman was able to show virtually complete
16:12:18 12 cleavage of a disulfide bond. Correct?

16:12:20 13 MR. BABCOCK: Objection. The document speaks
16:12:21 14 for itself. And I don't think the witness has had
16:12:23 15 nearly an opportunity to -- to evaluate what this
16:12:26 16 experiment shows. It's multiple pages, and he's read a
16:12:29 17 couple paragraphs. So --

16:12:31 18 THE WITNESS: Also, I've not seen any data.
16:12:33 19 The author states that.

16:12:41 20 BY MR. GRIER:

16:12:41 21 Q But you would agree the author does state --
16:12:43 22 Herman states that cleavage of the disulfide bond
16:12:45 23 resulted in elution of virtually all of the Affinity
16:12:49 24 isolated sequences.

16:12:52 25 MR. BABCOCK: Same --

16:12:52 1 BY MR. GRIER:

16:12:53 2 Q Correct?

16:12:56 3 MR. BABCOCK: Same objections.

16:12:57 4 THE WITNESS: That -- that is what it says.

16:12:57 5 BY MR. GRIER:

16:12:57 6 Q And as a person skilled in the art, the term

16:13:01 7 "virtually all," does that imply to you greater than

16:13:05 8 90-percent cleavage efficiency?

16:13:08 9 MR. BABCOCK: Objection. Same objections.

16:13:12 10 THE WITNESS: I -- should I still answer that?

16:13:14 11 BY MR. GRIER:

16:13:15 12 Q Yes, please.

16:13:17 13 A To me, yes, it would.

16:13:23 14 Q So then you would agree, then, that a person of

16:13:27 15 skill in the art looking at this reference and seeing

16:13:31 16 virtually all of the affinity isolated sequencing

16:13:34 17 recovered after the cleavage of the disulfide bond, that

16:13:36 18 person -- that person skilled in the art would have an

16:13:38 19 expectation that disulfide cleavage conditions could

16:13:41 20 cleave greater than 90-percent efficiency?

16:13:44 21 A From that one sentence, if I had to make a

16:13:46 22 call, I would suggest that -- that that's what that

16:13:49 23 would suggest. But I -- I haven't read this document.

16:13:51 24 If you want me to spend five minutes, I can try to

16:13:54 25 assimilate as quickly as I can to try to have an -- a

16:13:56 1 slightly more informative opinion on it.

16:14:16 2 Q Dr. Romesberg, are you familiar with George
16:14:18 3 Church?

16:14:19 4 MR. BABCOCK: So you're not going to let him
16:14:21 5 finish?

16:14:21 6 MR. GRIER: No. We can -- we can move on. I
16:14:23 7 apologize. I thought I answered that.

16:14:25 8 MR. BABCOCK: So just so the record is clear,
16:14:26 9 Dr. Romesberg has not had a chance to review the
16:14:29 10 document in much other than the couple paragraphs that
16:14:31 11 he was --

16:14:32 12 THE WITNESS: I've essentially reviewed a
16:14:33 13 couple sentences, yeah, in a paragraph.

16:14:35 14 BY MR. GRIER:

16:14:35 15 Q Dr. Romesberg, would it help your testimony if
16:14:37 16 you had the opportunity to review the document?

16:14:39 17 A It depends if you want me to have a more
16:14:41 18 informed opinion on it and -- and if you want -- if you
16:14:44 19 want a five-minute more informed opinion, I would be
16:14:46 20 happy to give that to you.

16:14:48 21 Q I would -- I would -- that would be great.

16:14:51 22 THE WITNESS: Okay. Can I have -- I'm going to
16:14:53 23 try to -- can I --

16:14:55 24 MR. BABCOCK: Do you want a pen?

16:14:56 25 THE WITNESS: Yeah. Can I have a pen?

16:14:57 1 MR. GRIER: Keeping in mind that whatever is
16:14:59 2 marked on that exhibit --

16:15:00 3 MR. BABCOCK: Stays part of the exhibit.

16:15:01 4 MR. GRIER: -- stays as part of the exhibit.

16:15:02 5 MR. BABCOCK: Would you like him to -- you'd
16:15:04 6 like him to mark it. Right?

16:15:06 7 MR. GRIER: That's up to him. If he wants to
16:15:08 8 mark the exhibit, he can. I just want to make clear
16:15:11 9 that whatever markings are made on the exhibit remain
16:15:13 10 part of the exhibit.

16:15:18 11 THE REPORTER: Did you mean to go off the
16:15:19 12 record for a moment, or --

16:15:20 13 MR. BABCOCK: No.

16:15:21 14 MR. GRIER: No.

16:19:27 15 THE WITNESS: Okay. I've read what is sort of
16:19:30 16 a first -- a first read. It's certainly not a complete
16:19:32 17 read. But, you know, in seven minutes, you get what you
16:19:35 18 pay for.

16:19:36 19 What I -- what I went to is that without going
16:19:38 20 through the details, it looks like he reports -- he
16:19:41 21 claims virtually complete cleavage.

16:19:43 22 And what I would point to is that he -- he gave
16:19:45 23 it two washes with high concentrations of 30 and 15
16:19:50 24 minutes each at an optimal pH. So the question, then,
16:19:54 25 would -- so -- correct. Given -- given those

16:19:58 1 conditions, then, yes, I agree with you, that he reports
16:20:01 2 virtually complete cleavage.

16:20:02 3 BY MR. GRIER:

16:20:14 4 Q Okay. And then because Herman then reports
16:20:17 5 virtually complete cleavage, you would also agree with
16:20:21 6 me, then, a person skilled in the art, looking at
16:20:24 7 Herman, would have an expectation that you could cleave
16:20:27 8 a disulfide linker under conditions that would result in
16:20:29 9 greater than 90-percent cleavage efficiency. Correct?

16:20:32 10 A Correct.

16:20:40 11 Q Dr. Romesberg, are you familiar with George
16:20:43 12 Church?

16:20:44 13 A I am.

16:20:45 14 Q And how are you familiar with George Church?

16:20:50 15 A Through the literature, he's sort of a big
16:20:53 16 name. We also both consulted for a sequencing company
16:20:59 17 called Helicos. And he called me out of the blue and
16:21:03 18 wanted some of my nucleotides. So I sent them to him.
16:21:06 19 That was probably a year ago.

16:21:09 20 Q So then you are -- you obviously know
16:21:12 21 Dr. Church. Correct?

16:21:16 22 A I know of him, yes.

16:21:18 23 Q Have you collaborated with -- with Dr. Church?

16:21:21 24 A Other than sending him those nucleotides, no.

16:21:26 25 Q What is your opinion of Dr. Church's work?

16:21:33 1 A This is being recorded? It's mixed. Some of
16:21:36 2 his stuff is super creative and really interesting. My
16:21:40 3 opinion has always been some of his stuff is a little
16:21:42 4 bit whacky. But, certainly, he does -- he's a very
16:21:46 5 smart, very creative, very broad thinker.

16:21:51 6 Q And are you familiar with sort of his
16:21:54 7 reputation in -- in the field, generally?

16:21:59 8 A In my opinion, my opinion probably represents
16:22:06 9 the opinion in the field. My opinion is probably pretty
16:22:08 10 average with the field in that I -- I think there's some
16:22:11 11 stuff that he does that the field has been curious
16:22:14 12 about. But he's also done some really neat stuff.

16:22:31 13 MR. GRIER: Are we at 1031 on the exhibit
16:22:33 14 numbers? 1031?

16:22:34 15 THE REPORTER: Yes.

16:22:34 16 MR. GRIER: Okay.

16:22:35 17 BY MR. GRIER:

16:22:35 18 Q Dr. Romesberg, I'm going to show you what will
16:22:36 19 be marked as IBS Exhibit 1031.

16:22:44 20 And while the court reporter is marking that,
16:22:47 21 so the "neat stuff" that you referred to in discussing
16:22:49 22 Dr. Church's work, what exactly do you mean by "neat
16:22:52 23 stuff"?

16:22:57 24 A Stuff that I found neat. Stuff that I -- in my
16:23:01 25 opinion was interesting or important or -- if you want

16:23:04 1 to know the truth, he does some stuff that other people
16:23:07 2 can't do because he's got tons of money.

16:23:13 3 Q What types of things are those?

16:23:16 4 A He lately took all the stop -- amber stop
16:23:19 5 codons out of a genome with a massive, you know, hands
16:23:23 6 effort that took a lot of people. It's just my personal
16:23:29 7 bias. I tend to really respect sort of people who
16:23:35 8 publish a paper that's super creative and novel and sort
16:23:39 9 of -- you know, they didn't -- they didn't rely on force
16:23:43 10 of, you know, manpower. I mean, Alexander won at -- at
16:23:50 11 Per- -- no. Wait. Alexander won the famous battle in
16:23:54 12 the north because of the -- the pincer movement as
16:23:59 13 opposed to being outnumbered by the Persians. And
16:24:03 14 that's impressive, as opposed to just winning by brut
16:24:06 15 force. Gaugamela.

16:24:21 16 (Exhibit 1031 was marked for identification.)

16:24:23 17 BY MR. GRIER:

16:24:23 18 Q Dr. Romesberg, have you ever seen this
16:24:25 19 document?

16:24:26 20 A No.

16:24:31 21 Q Do you see that this is a -- a published patent
16:24:33 22 application listing as the inventor -- -ventors, George
16:24:40 23 Church and Robi Mitra?

16:24:47 24 A I -- I see George Church. I -- I --

16:24:49 25 Q If you follow the --

16:24:50 1 A Oh, yeah. Yeah. I guess, Robi -- Robi --
16:24:54 2 yeah. Robi Mitra.

16:25:01 3 Q If turn to page 86 of this document. And in
16:25:17 4 particular, if you look at lines 9 to 11.

16:25:21 5 Church describes using a dCTP label with the
16:25:27 6 fluorophore Cy5 with either a noncleavable linkage or
16:25:32 7 with a disulfide-containing cleavable linkage.

16:25:40 8 Do you see that?

16:25:41 9 A I do.

16:25:41 10 Q Okay. And if you turn back to -- to page 85,
16:25:53 11 you see where Church states, in particular lines 14
16:25:55 12 through 16, that he demonstrated a method of sequencing
16:26:02 13 nucleic acid molecules using what he calls "Fluorescent
16:26:07 14 In Situ Sequencing Extension Quantification."

16:26:11 15 Do you see that?

16:26:11 16 A I do.

16:26:16 17 Q And in the nucleotides that we were
16:26:18 18 specifically referring to on page 86 a moment ago, those
16:26:21 19 are the nucleotides that Church used in this method.
16:26:24 20 Correct?

16:26:34 21 A I -- I can't tell for sure. But it looks --
16:26:38 22 looks -- just on proximity, it looks like they likely
16:26:41 23 are. But I haven't read it.

16:26:42 24 Q Would -- would it help your testimony to read
16:26:44 25 pages 85 and -- and 86?

16:26:47 1 A Well, that depends on what you want me to say.

16:26:50 2 I mean, I haven't seen this before. If you want me to
16:26:53 3 read it, I'm happy to read it.

16:26:56 4 Q Yeah. Let's -- let's do that. How about you
16:26:58 5 read -- do you see on page 85 where it says "Example
16:27:01 6 17" --

16:27:02 7 A Mm-hmm.

16:27:02 8 Q -- how about you read through the end of that
16:27:04 9 example, which ends at the top of page 87.

16:27:07 10 A Okay.

16:27:08 11 MR. BABCOCK: And, of course, you're free to
16:27:09 12 read whatever else you want to read.

16:27:11 13 MR. GRIER: Of course.

16:27:12 14 MR. BABCOCK: Background, beginning, end,
16:27:14 15 whatever.

16:29:51 16 VIDEOGRAPHER: Counsel, we've got eight minutes
16:29:55 17 to change tape.

16:29:56 18 MR. BABCOCK: How long have we been going on
16:29:57 19 this tape?

16:30:08 20 VIDEOGRAPHER: Almost two hours.

16:30:08 21 MR. GRIER: With eight minutes, yeah -- yeah,
16:30:09 22 let's go ahead and switch the tapes out.

16:30:12 23 MR. BABCOCK: You want to just take a break
16:30:12 24 then while we're --

16:30:13 25 VIDEOGRAPHER: This concludes Tape 3 of the

16:30:17 1 deposition of Dr. Romesberg. Off the record at 4:30.

16:41:03 2 (Recess from 4:30 p.m. to 4:42 p.m.)

16:42:19 3 VIDEOGRAPHER: This is Disk 4 of the deposition

16:42:21 4 of Dr. Floyd Romesberg. Back on the record at 4:42.

16:42:29 5 BY MR. GRIER:

16:42:29 6 Q Okay. Dr. Romesberg, before we took a break,

16:42:32 7 you were looking at IBS Exhibit 1031. Correct?

16:42:41 8 A Correct.

16:42:42 9 Q In particular, you were reading through

16:42:44 10 Example 17.

16:42:46 11 Have you had a chance to read Example 17?

16:42:47 12 A Yes, I did.

16:42:48 13 Q Okay. So looking at that example, Dr. Church

16:42:53 14 here is describing a method for sequencing by synthesis.

16:42:56 15 Correct?

16:42:59 16 A The section I read wasn't really on that.

16:43:03 17 My -- my impression is is that is correct. But

16:43:05 18 Example 17 does not make that clear. But it looks like

16:43:11 19 it. It is a step of that process.

16:43:22 20 Q If you turn to page 6 of Church, in particular,

16:43:32 21 starting at line 9 of page 6. Can you just read through

16:43:45 22 line 28.

16:44:16 23 A Yes.

16:44:17 24 Q Okay. And would you agree, then, after reading

16:44:19 25 this in combination with Example 17, Dr. Church is

16:44:22 1 describing a method here for sequencing by synthesis?

16:44:24 2 Is that correct?

16:44:26 3 A It appears to be, yes.

16:44:28 4 Q So if we can turn back to page 86, back into

16:44:36 5 Example 17. Again, I direct your attention to lines 9

16:44:46 6 through 11.

16:44:48 7 Do you see where Dr. Church describes the

16:44:51 8 nucleotides used in this experiment?

16:44:53 9 A I do.

16:44:53 10 Q And one nucleotide that he describes is dCTP

16:44:56 11 labeled with the fluorophore Cy5. And that -- that

16:45:00 12 nucleotide is -- is -- contains either a noncleavable

16:45:06 13 linkage or contains a disulfide-containing cleavable

16:45:14 14 linkage.

16:45:15 15 Do you see that?

16:45:15 16 A I do.

16:45:16 17 Q Okay. Can you turn to page 5 of Church.

16:45:25 18 And is this the nucleotide that is being

16:45:27 19 referred to on lines 9 through 11 of page 86?

16:45:34 20 A It is consistent with what he calls it, yes.

16:45:37 21 Q Okay. And this -- this is the nucleotide that

16:45:39 22 shows the disulfide-containing cleavable linkage. Is

16:45:43 23 that correct?

16:45:44 24 A Yes.

16:45:44 25 Q Okay. So can you turn back with me to page 86

16:45:53 1 of Church, in particular, line 20.

16:45:59 2 Do you see where Church says "Cleavage of the
16:46:01 3 cleavable disulfide linkages was performed by incubation
16:46:05 4 with the reduce -- reducing agent dithiothreitol (DTT)."

16:46:11 5 Do you see that?

16:46:12 6 A I do.

16:46:13 7 Q Okay. And this is the same DTT cleavage
16:46:15 8 reagent that we've been discussing throughout the day,
16:46:17 9 the same one utilized by Ruby and Herman. Is that
16:46:19 10 correct?

16:46:21 11 A Yes.

16:46:22 12 Q Okay. And starting at line 23 on page 86, do
16:46:26 13 you see where Church describes the results in the
16:46:30 14 experiment?

16:46:31 15 A On line 23?

16:46:34 16 Q Right. Of page 86. It says -- starts with the
16:46:40 17 sentence "Figure 6 shows the results of this
16:46:42 18 experiment."

16:46:45 19 A Line 24.

16:46:47 20 Q Okay. Line 24 of page 86.

16:46:52 21 A It says "Figure 6 shows the results of this
16:46:55 22 experiment."

16:46:55 23 Q Right. Okay.

16:46:56 24 And so continuing on there, describes the
16:47:00 25 in- -- the incorporation of both the cleavable and the

16:47:03 1 noncleavable fluorescent labeled nucleotide. And then
16:47:08 2 in line 26, it shows the DTT wash, Church says, then
16:47:12 3 removed the fluorescent signal from the samples extended
16:47:15 4 with the disulfide modified nucleotide.

16:47:23 5 Do you see that?

16:47:23 6 A Yes.

16:47:24 7 Q But Dr. Church says that cleavage -- or the DTT
16:47:29 8 wash did not -- did not cleave -- result in cleavage of
16:47:37 9 the noncleavably linked fluorophore.

16:47:41 10 Do you see that?

16:47:41 11 A Yes.

16:47:41 12 Q Okay. So Dr. Church concludes, then, that that
16:47:43 13 demonstrates that cleavable linkages could be cleaved
16:47:46 14 from the disulfide nucleotide extended samples with the
16:47:46 15 DTT --

16:47:50 16 THE REPORTER: I'm sorry. Can I get you to
16:47:50 17 back up on that one.

16:47:50 18 MR. GRIER: Sure.

16:47:50 19 BY MR. GRIER:

16:47:50 20 Q So then Dr. Church concludes there that the
16:47:56 21 fluorophore could be cleaved from the
16:47:59 22 disulfide-containing modified nucleotides but not from
16:48:05 23 the -- from the modified nucleotides that did not
16:48:08 24 contain the disulfide linkage.

16:48:10 25 Do you see that?

16:48:11 1 A Yes.

16:48:11 2 Q Okay. And you would agree that -- that those
16:48:14 3 are the results that Dr. Church demonstrated in this
16:48:17 4 experiment. Correct?

16:48:18 5 A Yes.

16:48:20 6 Q Let's look at Figure 6. And in Figure 6, let's
16:48:38 7 focus on the -- the top row in Figure 6.

16:48:43 8 Do you see the fluorescence measured before the
16:48:47 9 DTT wash there?

16:48:48 10 MR. BABCOCK: Counsel, is this the best copy
16:48:50 11 you guys have?

16:48:52 12 MR. GRIER: This is the best copy we have.

16:48:53 13 MR. BABCOCK: Okay. So I'll just object to the
16:48:54 14 quality of the copying when you're looking at visual
16:48:58 15 results that are photocopied in black and white that are
16:49:01 16 poor quality. But do the best you can.

16:49:03 17 BY MR. GRIER:

16:49:05 18 Q Do you see, Dr. Romesberg, the fluorescence
16:49:07 19 before the DTT wash --

16:49:09 20 MR. BABCOCK: Same objections.

16:49:10 21 BY MR. GRIER:

16:49:10 22 Q -- in the top row?

16:49:12 23 MR. BABCOCK: Same objections.

16:49:13 24 THE WITNESS: I -- I see signal that would be
16:49:15 25 associated with -- yes.

16:49:17 1 BY MR. GRIER:

16:49:17 2 Q And the signal you see, then, would be

16:49:19 3 associated with the fluorescence. Correct?

16:49:22 4 MR. BABCOCK: Same objections.

16:49:23 5 THE WITNESS: Without having read this, I --

16:49:25 6 I -- that would be the most likely thing that he is

16:49:28 7 showing here, yeah.

16:49:29 8 BY MR. GRIER:

16:49:29 9 Q But you read Example 17.

16:49:31 10 A Yeah.

16:49:31 11 Q Correct?

16:49:32 12 A But, I mean, I'm not reading the citation

16:49:35 13 wavelength. I mean, he knows what he's doing. So I

16:49:38 14 assume this is correct.

16:49:39 15 Q And then the second row, you see after the DTT

16:49:42 16 wash.

16:49:43 17 MR. BABCOCK: Same objection.

16:49:44 18 BY MR. GRIER:

16:49:45 19 Q And do you see on the left-hand side, the

16:49:47 20 nondisulfide-containing modified nucleotide, the

16:49:51 21 fluorescence is still there. Correct?

16:49:53 22 MR. BABCOCK: Same objection.

16:49:59 23 THE WITNESS: Yes. I mean -- not -- not having

16:50:03 24 had time to think or -- or to read this or think about

16:50:06 25 this, yeah, there is signal there. It -- it is -- yes,

16:50:11 1 there is signal there.

16:50:12 2 BY MR. GRIER:

16:50:12 3 Q And then in the -- in the figure next to that,
16:50:15 4 after DTT wash, there's no signal in the
16:50:20 5 disulfide-containing nucleotide. Is that correct?

16:50:25 6 MR. BABCOCK: Same objection.

16:50:25 7 THE WITNESS: That would appear to be the case.

16:50:30 8 BY MR. GRIER:

16:50:30 9 Q So then if you go back to page 86, line 26, and
16:50:45 10 Figure 6 supports Dr. Church's conclusion that the DTT
16:50:48 11 wash removed the fluorescent signals extended with the
16:50:53 12 disulfide-containing modified nucleotide. Correct?

16:50:56 13 MR. BABCOCK: Same objection.

16:50:56 14 THE WITNESS: That certainly would seem to be
16:50:57 15 what he's saying. I -- I -- up from 30,000 feet from
16:51:01 16 the time that I've had to look at this, I would -- it
16:51:04 17 would seem that I agree -- I would seem -- I think I
16:51:07 18 would agree with that.

16:51:08 19 BY MR. GRIER:

16:51:08 20 Q And would you also agree, looking back at -- at
16:51:12 21 Figure 6, that Dr. Church was able to demonstrate
16:51:16 22 complete cleavage of the fluorophore after the DTT wash?

16:51:20 23 MR. BABCOCK: Same objection.

16:51:20 24 THE WITNESS: That would be a harder thing for
16:51:22 25 me to say to use the word "complete" without having more

16:51:29 1 time to look at it and -- I mean, for example, there
16:51:32 2 seems -- there seems to be something of a decrease in
16:51:35 3 intensity in the Cy5 dCTP labeled as well. I can't
16:51:42 4 quite tell. But this is all somewhat minor. It looks
16:51:45 5 like there is significantly more cleavage in the Cy5-SS
16:51:50 6 with the disulfide linker.

16:51:54 7 BY MR. GRIER:

16:51:54 8 Q And do you see any fluorescence left after the
16:51:56 9 DTT wash in the Cy5 --

16:52:02 10 THE REPORTER: I'm sorry. Can I hear again.

16:52:03 11 BY MR. GRIER:

16:52:03 12 Q Dr. Romesberg, do you see any fluorescence left
16:52:05 13 after DTT cleavage in the column with the Cyfi -- Cy5
16:52:12 14 label disulfide nucleotide?

16:52:14 15 MR. BABCOCK: Same objection.

16:52:15 16 THE WITNESS: From the quality, it -- it --
16:52:17 17 given the quality, as a caveat, but, no, I don't see
16:52:21 18 any.

16:52:21 19 BY MR. GRIER:

16:52:21 20 Q So, then, again, you would agree that that
16:52:23 21 would suggest that there is complete cleavage of the
16:52:26 22 disulfide linker after the wash with DTT?

16:52:31 23 MR. BABCOCK: Same objection.

16:52:31 24 THE WITNESS: I would have a problem using the
16:52:32 25 word "complete" just because I'm not familiar with this.

16:52:35 1 I -- I -- I'm not familiar with the experiment. I don't
16:52:38 2 know how valid of an experiment -- how rigorous and how
16:52:41 3 sensitive an experiment this is. And I'm not -- I'm
16:52:43 4 not -- I'm not just bickering over those -- those words.
16:52:47 5 I mean, to compare this with the Vermaas data -- can I
16:52:50 6 compare this to that?

16:52:51 7 BY MR. GRIER:

16:52:51 8 Q Well, I'm not asking you to compare this with
16:52:54 9 Vermaas right now. I'm just asking you if you look at
16:52:56 10 the figure -- if you look at what's shown in Figure 6 of
16:52:59 11 Church, I'm asking would you agree that after the DTT
16:53:02 12 wash, it shows no fluorescence in the nucleotide
16:53:08 13 containing the disulfide cleavable linker?

16:53:09 14 A Yeah, I don't --

16:53:10 15 MR. BABCOCK: Same objection. Same objection
16:53:11 16 after his question.

16:53:13 17 Slow down.

16:53:14 18 Now you can answer.

16:53:15 19 THE WITNESS: I don't see any signal in the
16:53:17 20 bottom right panel. So qualitatively, that supports
16:53:23 21 what you're saying. The -- the issue I have with it is
16:53:25 22 I, at this point, would have a little bit of a problem
16:53:29 23 saying it's complete or whatever, because I'm -- I'm not
16:53:31 24 familiar with the sensitivity of the experiment, I don't
16:53:33 25 know what one -- 95-percent cleavage would have looked

16:53:38 1 like. But there is no signal that I can tell, given
16:53:40 2 the -- with the caveat being that it's not a very
16:53:43 3 high-quality image. But -- but there seems to be
16:53:47 4 significant cleavage.

16:53:54 5 BY MR. GRIER:

16:53:55 6 Q So, Dr. Romesberg, would you agree, then, this
16:53:57 7 is another example of prior art in combination with the
16:54:02 8 Herman reference we just discussed, Exhibit 1030, that
16:54:06 9 shows cleavage efficiency of a disulfide linker that's
16:54:09 10 greater than 90 percent?

16:54:11 11 MR. BABCOCK: Same objection.

16:54:16 12 THE WITNESS: That -- that's hard for me to
16:54:18 13 answer, because I don't know if 10-percent residual
16:54:22 14 uncleaved product, what it would have looked like here.
16:54:25 15 And, also, in the Herman -- the second paper -- again, I
16:54:28 16 haven't read either of these papers. I'm going
16:54:30 17 completely on the word "virtually" -- the word
16:54:32 18 "virtual," "virtually." And I'm -- I'm not exactly sure
16:54:35 19 what that -- that's sort of a comparative term. He
16:54:38 20 might have been describing it relative to the 87 that he
16:54:43 21 presented earlier and maybe -- so I -- I would rather
16:54:47 22 see an -- if you really want me to judge this and -- and
16:54:51 23 whether or not it -- it -- it -- how -- how the cleavage
16:54:57 24 event occurred, I -- I would like to see more data here.

16:55:02 25 I don't see any data in the -- in the Herman

16:55:04 1 paper. So we -- we can go by his word "virtual" --
16:55:06 2 "virtually." I -- I -- and you can interpret that in --
16:55:13 3 that certainly could be consistent with high cleavage.
16:55:15 4 But it's just -- it's just a descriptor. It's an
16:55:19 5 adjective.

16:55:21 6 And in the -- in the -- in the -- in the Church
16:55:23 7 paper, I don't know what 10 percent -- I don't know what
16:55:27 8 90 percent would have looked like here.

16:55:37 9 BY MR. GRIER:

16:55:37 10 Q Would you agree that after the DTT wash in
16:55:42 11 Church, he's showing virtually complete cleavage of the
16:55:45 12 disulfide-labeled nucleotide?

16:55:48 13 MR. BABCOCK: Same objection. Asked and
16:55:49 14 answered.

16:55:49 15 THE WITNESS: Same answer. I -- I -- I -- that
16:55:53 16 would be hard for me to judge. I just -- I can't --
16:55:56 17 judging the completeness of the reaction would require
16:55:59 18 an estimation of the signal-to-noise in the reaction.
16:56:02 19 If the signal-to-noise were, you know, 10 percent,
16:56:06 20 then -- then I would say no. But if it were 1 percent,
16:56:09 21 then I would -- then I would say much more likely. It's
16:56:13 22 just a little -- without any -- any sort of -- more
16:56:17 23 understanding of the experiment. I -- I will certainly
16:56:21 24 say that there is significant cleavage there. I will
16:56:24 25 not -- I would not be comfortable qualifying it in any

16:56:31 1 sort of quantitative --

16:56:35 2 BY MR. GRIER:

16:56:35 3 Q And to be clear, though, you would -- you would

16:56:38 4 agree that after the DTT wash, there's no fluorescence

16:56:44 5 shown in Figure 6?

16:56:46 6 MR. BABCOCK: Same objections.

16:56:47 7 THE WITNESS: Yes. Yes, as I said before, I

16:56:49 8 would -- I would agree with that.

16:57:03 9 MR. GRIER: Dr. Romesberg, I'm going to hand

16:57:05 10 you what will be marked IBS 1032.

16:57:27 11 (Exhibit 1032 was marked for identification.)

16:57:31 12 BY MR. GRIER:

16:57:32 13 Q Dr. Romesberg, have you ever seen this

16:57:34 14 document?

16:57:35 15 A No, I have not.

16:57:36 16 Q Do you see in the authors, on the first page,

16:57:41 17 George Church is listed as the corresponding author?

16:57:46 18 A I do.

16:57:47 19 Q Okay. And do you see the first author of this

16:57:50 20 paper is Robi Mitra?

16:57:58 21 A I do.

16:57:59 22 Q And you recall we were discussing on the face

16:58:00 23 of the -- Exhibit 1031, the Church patent application,

16:58:03 24 Robi Mitra is listed as one of the inventors. Correct?

16:58:08 25 A Correct.

16:58:09 1 Q So would you agree that Exhibit 1032 contains
16:58:15 2 Robi Mitra and George Church, who are the same inventors
16:58:19 3 listed in the 1031 patent -- Exhibit 1031. Correct?

16:58:24 4 A Yes.

16:58:24 5 Q So in Exhibit 1032, can you please turn to
16:58:29 6 page 61.

16:58:45 7 In particular, the Figure 4 on the top left of
16:58:48 8 page 61.

16:58:53 9 A Yes.

16:58:54 10 Q Okay. Do you see the nucleotide structure
16:58:56 11 there?

16:58:56 12 A I do.

16:58:57 13 Q And is this nucleotide structure, Cy5 disulfide
16:59:05 14 dCTP analog?

16:59:07 15 A It is.

16:59:08 16 Q Can you turn to Figure 5 of Exhibit 1031, the
16:59:12 17 Church reference.

16:59:15 18 Are these two structures, the structure in
16:59:18 19 Figure 4A of Exhibit 1032 and the structure in Figure 5
16:59:24 20 of Exhibit 1031, the same modified nucleotide?

16:59:27 21 A It -- they are the -- it is the same, yes.

16:59:31 22 Q Can you look at Figure 4D. And if you read the
16:59:42 23 legend of the figure, stepping through from A to D, the
16:59:49 24 Mitra paper says that the structure of the -- of the Cy5
16:59:53 25 molecule is extended in the primer, and the yellow

16:59:59 1 polonies in Figure B.

17:00:03 2 Do you see those?

17:00:03 3 A I do.

17:00:04 4 Q And that indicates that the DNA polymerase

17:00:06 5 recognizes the nucleotide analog, and so the

17:00:09 6 fluorescence was achieved.

17:00:11 7 Do you see that?

17:00:11 8 A I do.

17:00:11 9 Q Okay. And then Figure C, Mitra goes on to say

17:00:15 10 "After a wash in buffer containing

17:00:18 11 beta-mercaptoethanol" --

17:00:24 12 THE REPORTER: "After a wash containing" --

17:00:24 13 BY MR. GRIER:

17:00:24 14 Q -- "beta-mercaptoethanol, the fluorescence can

17:00:27 15 be removed from the slide."

17:00:29 16 Do you see that?

17:00:29 17 A I do.

17:00:29 18 Q Okay. Does beta-mercaptoethanol cleave the

17:00:44 19 disulfide cleavable linker in the molecule of A?

17:00:45 20 A It should do so.

17:00:47 21 Q If you look in D, Mitra says "The signal decays

17:00:52 22 exponentially with a time constant of 7 seconds."

17:00:57 23 Do you see that?

17:00:57 24 A Yes.

17:00:58 25 Q And if you look there, would you agree that

17:01:02 1 Figure 4D shows complete cleavage of the disulfide
17:01:08 2 linker?

17:01:12 3 A Again, I haven't read this. It -- the only
17:01:15 4 thing that's a little bit troubling -- troubling --
17:01:18 5 technically, it doesn't show that because it's
17:01:20 6 normalized fluorescence. So if there were fluorescence
17:01:23 7 still at the end, that would be normalized out. I -- I
17:01:29 8 have to -- let me think about this.

17:01:34 9 No. It's -- it's -- what you said is, I think,
17:01:37 10 correct.

17:01:38 11 Q So then you would agree, just to be clear, that
17:01:43 12 Figure 4D shows complete cleavage of the disulfide
17:01:47 13 linker. Correct?

17:01:49 14 A It shows that -- again, I'm not reading this,
17:01:54 15 but I assume that what this is -- is showing, a time
17:01:57 16 course of fluorescence from -- I don't quite know what.
17:02:02 17 I assume it's the modified nucleotide. I don't know
17:02:05 18 whether it's in DNA or in solution, I'm -- I'm -- or
17:02:08 19 whether I guess it's in the col- -- in the polony. But
17:02:14 20 whatever the source of the fluorescence is, it would
17:02:16 21 appear to be completely cleaved with the time constant
17:02:19 22 of seven seconds, with a half life of -- I think it's a
17:02:23 23 half life of seven seconds.

17:02:26 24 Q And if you look at the X axis on the graph in
17:02:29 25 4D, would you agree that the fluorescence reaches zero

17:02:35 1 in approximately 30 seconds?

17:02:42 2 A Well, if half life is seven seconds, yes.

17:02:44 3 Thirty -- yeah, that would be about right.

17:02:49 4 Q So, then, would you agree that Mitra,

17:02:54 5 Exhibit 1032, supports the conclusion that the disulfide

17:02:58 6 linker shown in the Church reference, Exhibit 1031, is

17:03:01 7 capable of being cleaved at a greater than 90-percent

17:03:06 8 efficiency?

17:03:08 9 A Given the caveat that I don't know the

17:03:09 10 conditions in which this is being used and -- given that

17:03:16 11 caveat, because I haven't read it, yes.

17:03:34 12 Q All right. Dr. Romesberg, let's go back to

17:03:38 13 your substitute declaration. It's Exhibit 1029. And in

17:03:50 14 particular, let's turn to page 27, paragraph 61. And in

17:04:06 15 paragraph 61, it's your testimony that "Illumina has

17:04:11 16 evaluated the incorporation of nucleotides having

17:04:14 17 disulfide linkers and the cleavage efficiency of such

17:04:18 18 linkers." Is that correct?

17:04:21 19 A I'm sorry. I didn't hear the question.

17:04:25 20 That -- that's what I wrote.

17:04:26 21 Q Okay. So that's your testimony. Correct?

17:04:28 22 A Yeah.

17:04:29 23 Q Okay. And for support, you cite to the Vermaas

17:04:32 24 declaration. Correct?

17:04:32 25 A Mm-hmm. Yes.

17:04:39 1 Q Are you aware that Mr. Vermaas drafted a
17:04:42 2 substitute declaration in this case?

17:04:46 3 A You mean, the one that changed slightly before
17:04:48 4 Christmas?

17:04:49 5 Q That's -- that's the one.

17:04:51 6 A Yes.

17:04:51 7 Q And you have seen that substitute declaration.
17:04:53 8 Correct?

17:04:54 9 A I have.

17:04:56 10 Q Okay. Are you aware that the substitute
17:04:59 11 declaration submitted by Mr. Vermaas in this case
17:05:03 12 describes a different sequencing experiment than the
17:05:06 13 experiment that was described in the original
17:05:08 14 declaration?

17:05:09 15 A Yes.

17:05:11 16 Q And did counsel provide you with that
17:05:14 17 information?

17:05:15 18 A Yes.

17:05:26 19 Q And is it your understanding that Illumina
17:05:29 20 conducted the experiment described in the Vermaas
17:05:32 21 declaration for the purposes of evaluating the cleavage
17:05:35 22 efficiency of disulfide linkers?

17:05:39 23 A I am -- I am not -- I'm -- I'm not sure. I'm
17:05:43 24 not sure that's the case. I'm not -- I think it was
17:05:47 25 just a sequencing reaction. I'm not sure if it was run

17:05:53 1 specifically to demonstrate disulfide cleavage
17:05:56 2 efficiency, which -- which it does. I'm not sure if it
17:05:59 3 was run for that purpose.

17:06:05 4 Q And you testify in paragraph 61 that Illumina
17:06:06 5 has evaluated the cleavage efficiency of disulfide
17:06:09 6 linkers. Correct?

17:06:09 7 A Correct.

17:06:10 8 Q And you cite to the Vermaas declaration for
17:06:13 9 support of that testimony. Correct?

17:06:14 10 A Correct.

17:06:17 11 Q Okay.

17:06:18 12 A The only thing I meant to say was I don't
17:06:20 13 know -- I mean, they are certainly -- they can certainly
17:06:21 14 use that sequencing data to support that -- my
17:06:24 15 statement. I don't know if they ran the experiment
17:06:28 16 expressly for that purpose or not.

17:06:48 17 Q Dr. Romesberg, when you were preparing your
17:06:51 18 declaration, in particular, the section that we're
17:06:54 19 discussing now where you cite to the Vermaas
17:06:56 20 declaration, did you talk to Mr. Vermaas at all about
17:07:02 21 his data?

17:07:02 22 A No, I did not.

17:07:05 23 Q Did you discuss the experiment with -- with
17:07:06 24 anyone at Illumina?

17:07:08 25 A No, I did not.

17:07:12 1 Q Did you review any lab notebooks describing
17:07:15 2 this experiment?

17:07:15 3 A No, I did not. I relied on the data presented
17:07:18 4 in the Vermaas declaration.

17:07:26 5 Q Did you review any materials other than the
17:07:30 6 Vermaas declaration in drafting this section of your
17:07:33 7 declaration?

17:07:36 8 A No. For the -- the data that describes -- the
17:07:39 9 section that describes the Vermaas data?

17:07:42 10 Q Correct.

17:07:42 11 A No. I relied only on the Vermaas declaration
17:07:45 12 for that data.

17:07:53 13 Q And you are -- are you aware, Dr. Romesberg,
17:07:56 14 that Mr. Vermaas was deposed in this case yesterday?

17:07:59 15 A I am.

17:08:00 16 Q Have you read Mr. Vermaas' testimony --

17:08:03 17 A I have not.

17:08:03 18 Q -- or deposition?

17:08:15 19 Can you turn, Dr. Romesberg, in your substitute
17:08:20 20 declaration to paragraph 40.

17:08:37 21 In this paragraph, Dr. Romesberg, you
17:08:39 22 describe -- or you opine as to -- as to a person of
17:08:42 23 ordinary skill in the art and what qualifications that
17:08:44 24 person has. Correct?

17:08:45 25 A Correct.

17:08:47 1 Q And is your opinion that a person of ordinary
17:08:50 2 skill in the art would have a doctoral degree in
17:08:56 3 chemistry. Is that correct?

17:08:57 4 A Or a related field.

17:08:58 5 Q Or a related field.

17:08:59 6 But that a person skilled in the art would need
17:09:02 7 to have a doctoral degree. Is that correct?

17:09:04 8 A That is what I wrote. That is what I defined
17:09:06 9 this as.

17:09:08 10 Q Is that your opinion of what a person
17:09:11 11 skilled -- skilled in the art would be?

17:09:14 12 A Sure. I mean, that's sort of a relative term.
17:09:17 13 And so this is set. You -- so -- that is -- that is the
17:09:20 14 definition that I'm using for this particular
17:09:23 15 declaration. I guess it will all come down to what
17:09:29 16 level -- what "skilled" means.

17:09:31 17 Q Well, what is your understanding of a person of
17:09:33 18 ordinary skill in the art, what that term means?

17:09:37 19 A For this declaration, what I used in
17:09:40 20 establishment of my opinion was someone who had a degree
17:09:43 21 in chemistry or closely related field, such as molecular
17:09:47 22 biology, and five years of practical academic or
17:09:48 23 industrial experience.

17:09:53 24 Q And are you aware that Mr. Vermaas does not fit
17:09:57 25 your description of a person of ordinary skill in the

17:10:00 1 art?

17:10:01 2 A I was not aware of that.

17:10:14 3 Q Would that change your opinion of -- of

17:10:18 4 Mr. Vermaas' data to know that?

17:10:21 5 A No.

17:11:13 6 Q So, Dr. Romesberg, we've gone through some

17:11:15 7 prior art today, and in particular, we've discussed

17:11:22 8 Exhibit 1030, which is the second Herman reference.

17:11:28 9 We've discussed Exhibit 1031, which is the Church

17:11:34 10 reference. We discussed Exhibit 1032, which was the

17:11:41 11 Mitra reference. Correct?

17:11:44 12 A The Church patent and the Mitra paper.

17:11:47 13 Q Yeah.

17:11:48 14 A Yeah.

17:11:49 15 Q Would you agree that those three references all

17:11:54 16 show that in the year surrounding the filing of the '026

17:11:59 17 patent, back in 2002, that there were other groups that

17:12:02 18 were developing disulfide linkers for use in SBS and

17:12:06 19 that -- that those groups were able to cleave that

17:12:09 20 disulfide linkers with greater than 90-percent

17:12:13 21 efficiency?

17:12:14 22 MR. BABCOCK: Objection to the extent -- you

17:12:17 23 used the word "surrounding," so it was not prior art.

17:12:20 24 Objection to form, and compound.

17:12:22 25 Go ahead.

17:12:22 1 THE WITNESS: So I think the only paper I would
17:12:23 2 feel comfortable saying -- the only material here that I
17:12:26 3 would feel comfortable saying that complete sentence
17:12:29 4 would be the -- the analytical biochemistry paper,
17:12:32 5 because it actually shows, as you pointed out, the
17:12:36 6 efficient cleavage that's -- that's greater than
17:12:38 7 90 percent.

17:12:39 8 The -- we went over multiple times my issues
17:12:42 9 with the -- the patent, the -- Exhibit 1031. That
17:12:50 10 might, but it's hard -- it's hard to say, given -- given
17:12:54 11 the quality of the repres- -- of the pictures. And,
17:12:58 12 also, more importantly, just not knowing what the
17:13:01 13 signal-to-noise is on the experiment.

17:13:08 14 So I -- I don't feel comfortable, myself,
17:13:10 15 placing a value on what the efficiency of that cleavage
17:13:13 16 was. You know, it was -- I think -- I think the
17:13:16 17 conditions were overnight. I -- and I don't know what
17:13:21 18 conditions that -- I mean, just comparing the data
17:13:23 19 presented in that patent to the analytical biochemistry
17:13:27 20 paper, I think it's clear why I would feel more
17:13:30 21 comfortable with it than the data here.

17:13:32 22 BY MR. GRIER:

17:13:33 23 Q Right. And as -- as I believe you testified,
17:13:35 24 the data in the -- in Exhibit 1032 showed that one
17:13:48 25 skilled in the art around the time of the filing date of

17:13:52 1 the patent was able to achieve greater than 90-percent
17:13:55 2 cleavage of a disulfide linker. Correct?

17:13:59 3 MR. BABCOCK: Same objection. Around the time
17:14:00 4 of the patent. That's not the test. It's not prior
17:14:02 5 art.

17:14:02 6 You can answer.

17:14:03 7 THE WITNESS: Reading this paper, I would -- I
17:14:05 8 would conclude that the -- that the cleavage would have
17:14:08 9 a half life of about seven seconds, under the conditions
17:14:11 10 reported here. Without knowing what those are. But
17:14:14 11 whatever those are, they're at least compatible with
17:14:19 12 polony sequencing. And that would -- I would call seven
17:14:24 13 seconds efficient, yes.

17:14:26 14 BY MR. GRIER:

17:14:26 15 Q And the cleavage that was demonstrated in that
17:14:28 16 paper is cleavage of the same structure that was shown
17:14:31 17 in Figure 5 of Church. Correct?

17:14:36 18 MR. BABCOCK: Same objections.

17:14:36 19 THE WITNESS: It is -- which brings up the sort
17:14:38 20 of curious question as to why they ran it overnight.

17:14:44 21 But -- but it is the same structure. I
17:14:46 22 don't -- having read them to the extent -- having been
17:14:50 23 able to give -- give the attention to them that I was
17:14:53 24 able to give, I have no idea if they were cleaved under
17:14:56 25 the same conditions, or if the setup was similar, or if

17:14:59 1 one was on a solid support, one was in a --

17:15:05 2 THE REPORTER: "One was on a" -- can I hear

17:15:05 3 again.

17:15:05 4 THE WITNESS: Solid support, or if one was in

17:15:06 5 solution, or if one was -- it's -- it's -- it's

17:15:08 6 difficult to gauge why they're different, why they would

17:15:11 7 appear to be different.

17:15:18 8 BY MR. GRIER:

17:15:18 9 Q But my question, Dr. Romesberg, is that the

17:15:21 10 structures are the same.

17:15:23 11 MR. BABCOCK: Same objections.

17:15:23 12 THE WITNESS: The structures are iden- --

17:15:27 13 MR. BABCOCK: Give me a chance to --

17:15:29 14 THE REPORTER: Can I hear the rest of the

17:15:31 15 answer.

17:15:31 16 THE WITNESS: Yes.

17:15:32 17 BY MR. GRIER:

17:15:32 18 Q "Yes," the structures are the same. Right?

17:15:34 19 A Yes.

17:15:35 20 MR. BABCOCK: Same objections.

17:15:39 21 MR. GRIER: At this point, can we take a quick

17:15:41 22 break? I think -- I think we might be wrapped up here.

17:15:44 23 VIDEOGRAPHER: Off the record at 5:15.

18:04:33 24 (Recess from 5:15 p.m. to 6:04 p.m.)

18:04:49 25 VIDEOGRAPHER: Back on the record at 6:04.

18:04:56 1 BY MR. GRIER:

18:04:56 2 Q Dr. Romesberg, during the break, did you have

18:04:57 3 any discussions with counsel?

18:04:58 4 A No, I did not.

18:04:59 5 Q So you did not discuss your counsel -- your

18:05:02 6 testimony that you've given today in this deposition.

18:05:04 7 Is that correct?

18:05:04 8 A That is correct.

18:05:05 9 Q You did not discuss any questions that your

18:05:06 10 counsel might ask you on redirect. Is that correct?

18:05:11 11 A That is correct.

18:05:12 12 MR. GRIER: Okay. Dr. Romesberg, thank you for

18:05:14 13 your time today. We have no further questions.

18:05:16 14 THE WITNESS: Thank you.

18:05:18 15 MR. BABCOCK: All right. I guess it's good

18:05:20 16 evening now, Dr. Romesberg.

18:05:21 17

18:05:21 18 REDIRECT EXAMINATION

18:05:22 19 BY MR. BABCOCK:

18:05:23 20 Q As you know, I'm Brent Babcock. I represent

18:05:26 21 Illumina. And I have the opportunity now to ask you a

18:05:31 22 few clarification questions based upon your testimony

18:05:35 23 earlier today.

18:05:35 24 Is that okay?

18:05:36 25 A Yes.

18:05:36 1 Q And you understand you're still under oath?

18:05:38 2 A I do.

18:05:39 3 Q I want to focus our conversation a little bit.

18:05:41 4 You testified at the beginning of the day that in your

18:05:44 5 20 years of experience, you've read a lot of textbooks

18:05:47 6 relating to nucleotides and modifications of

18:05:51 7 nucleotides. Is that correct?

18:05:52 8 A Yes. Yeah.

18:05:54 9 Q And papers --

18:05:55 10 A I'm not sure there are a lot of textbooks on

18:05:57 11 that, but --

18:05:58 12 Q And papers and --

18:05:59 13 A Yes.

18:05:59 14 Q -- and other periodicals?

18:06:00 15 A Yes. And -- and other people's research and at

18:06:03 16 meetings and -- yes.

18:06:04 17 Q All right. And papers and -- and other kinds

18:06:06 18 of journal articles?

18:06:08 19 A Yes.

18:06:08 20 Q All right. With respect to the issues

18:06:11 21 presented in this IPR, are you aware of any of those

18:06:14 22 papers or references or periodicals or textbooks that

18:06:18 23 jump to mind or come to mind as being more relevant than

18:06:21 24 the references that you identified in your declaration?

18:06:26 25 A Could you repeat the question.

18:06:27 1 Q Sure. With respect to all of your review of
18:06:32 2 materials throughout your career, papers, journals,
18:06:36 3 articles, are -- does anything come to mind as being
18:06:39 4 more relevant to the issues presented in this IPR than
18:06:41 5 the ones that you specifically identified in your
18:06:45 6 declaration?

18:06:45 7 A More relevant?

18:06:46 8 Q Yes.

18:06:47 9 A No.

18:06:48 10 Q So in your -- in your -- your testimony is that
18:06:50 11 you've identified in your list of references the most
18:06:55 12 relevant references that you're aware of?

18:07:01 13 A I -- I would have to say that these two -- two
18:07:03 14 of the references brought to me here were also relevant.

18:07:06 15 Q But you weren't aware of those prior to today?

18:07:09 16 A That's correct.

18:07:09 17 Q So as of the time of your declaration, you
18:07:11 18 identified the most relevant references of which you
18:07:14 19 were aware?

18:07:14 20 A Correct.

18:07:16 21 Q Okay. Now, I want to turn your attention back
18:07:19 22 to the patent at issue, the '026 patent, Exhibit 1001.
18:07:24 23 You spent a fair amount of discussing the figures in
18:07:30 24 Exhibit 1001.

18:07:32 25 Do you recall that?

18:07:33 1 A Yes, I do.

18:07:38 2 Why can't I find it?

18:07:39 3 MR. BABCOCK: Oh, maybe the reporter organized

18:07:50 4 them for you.

18:07:52 5 THE REPORTER: Actually, I did organize the

18:07:52 6 exhibits, and I notice that that particular exhibit was

18:07:52 7 not in front of the witness.

18:07:54 8 MR. BABCOCK: Do I have yours? I don't think

18:07:56 9 that's my copy. So you can --

18:07:58 10 THE WITNESS: Yeah, I don't -- I don't -- I'm

18:07:59 11 not sure where mine went.

18:08:02 12 MR. BABCOCK: It was possibly -- it was -- it

18:08:17 13 was in the middle. I've got a copy here. So that one,

18:08:19 14 you can use.

18:08:20 15 THE WITNESS: Okay.

18:08:21 16 MR. BABCOCK: And leave that one here.

18:08:23 17 BY MR. BABCOCK:

18:08:23 18 Q Turning to Figure 1, Dr. Romesberg.

18:08:32 19 In Figure 1, is the linker drawn just

18:08:37 20 generically?

18:08:38 21 A It is.

18:08:42 22 THE REPORTER: "Is the linker" -- can I hear

18:08:42 23 again.

18:08:42 24 MR. BABCOCK: Drawn generically.

18:08:44 25 THE WITNESS: It is.

18:08:44 1 BY MR. BABCOCK:

18:08:44 2 Q And in Figure 3, is there any disclosure that
18:08:49 3 excludes deazapurines?

18:08:51 4 A No, it is not.

18:08:53 5 Q Is the base just shown generically?

18:08:55 6 A It is.

18:08:56 7 Q Okay. If you'd look at a portion of this text
18:08:59 8 of the specification, I'm going to point you to
18:09:02 9 Column 6, lines 47 to 61. If you would take a moment to
18:09:10 10 read through that to refresh your recollection.

18:09:53 11 A I read it.

18:09:54 12 Q Okay. And you understand that paragraph?

18:09:59 13 A I'm sorry?

18:10:00 14 Q You understand what it's teaching?

18:10:01 15 A I do.

18:10:02 16 Q And what does that figure say about Figure 1
18:10:04 17 regarding the structures for that paragraph with respect
18:10:08 18 to Figure 1?

18:10:11 19 A It says that "Suitable nucleotide structures
18:10:13 20 are shown in Figure 1."

18:10:14 21 Q Okay. And what does it say about looking at
18:10:19 22 Figure 3 regarding teaching the structures for that
18:10:21 23 paragraph?

18:10:23 24 A Some suitable functional groups for R1 and R2
18:10:26 25 are in Figure 3 -- are included in the structures in

18:10:32 1 Figure 3.

18:10:37 2 I think that's the only spot that Figure 3 is
18:10:52 3 mentioned.

18:10:53 4 Q Okay. So that paragraph references both
18:10:54 5 Figures 1 and Figures 3?

18:10:56 6 A Yes.

18:10:56 7 Q And identifies both those figures as -- as
18:10:59 8 structures for what's disclosed in that paragraph?

18:11:03 9 A Yes.

18:11:05 10 Q And if you look at the next paragraph, starting
18:11:09 11 at line 62, does that paragraph have any indication
18:11:17 12 regarding -- with regards to Figure 2?

18:11:20 13 A Yes.

18:11:20 14 Q What does it say?

18:11:21 15 A It says that the linkers can include disulfide
18:11:26 16 linkers. "Suitable linkers are shown in Figure 2," and
18:11:29 17 it draws one's attention to the disulfide linkers, 1,
18:11:32 18 and the -- the -- the other linkers, the acid labile and
18:11:36 19 the other -- the other linker as well.

18:11:39 20 Q So with respect to the structure of the claimed
18:11:42 21 compound with respect to that structure and the
18:11:46 22 teachings of the patent, are the teachings of the
18:11:48 23 patent, do they disclose that -- that whole structure?

18:11:51 24 A I believe they do.

18:11:52 25 Q And -- and explain just why they do, why the

18:11:54 1 patent disclosures that structure.

18:11:56 2 A Explain why?

18:11:57 3 Q Yeah.

18:11:58 4 A For the reasons that we talked earlier,
18:12:00 5 looking -- basically, this paragraph says what I said
18:12:04 6 earlier, the -- the linkers are clarified in one spot,
18:12:08 7 and the -- the site of the -- the D -- the -- the types
18:12:14 8 of nucleic bases, including the naturals and the
18:12:18 9 deazapurines are disclosed in the other figure, and the
18:12:22 10 sites of attachment, and this -- that's what that
18:12:25 11 paragraph says. It says that those are all suitable for
18:12:29 12 the compound disclosed.

18:12:30 13 Q All right. And does that paragraph, does it
18:12:32 14 discuss disulfide with deaza -- deaza nucleotides?

18:12:40 15 A Yes.

18:12:44 16 Q And looking at Figure 3, are there any blocking
18:12:47 17 groups in that figure that cleave under identical
18:12:50 18 conditions as the disulfide linkers?

18:12:59 19 A Yes. Yes, there are.

18:13:00 20 Q And which are those?

18:13:01 21 A Well, they're the alkylazido and -- at least,
18:13:08 22 and -- and there are several -- I believe several
18:13:12 23 representations of alkylazidos. Well, they're
18:13:23 24 generically represented by R4 and R5. And -- yes.

18:13:31 25 Q Okay. And sticking with the patent, could you

18:13:39 1 turn to Column 8, lines 28 to 30 and read that in a
18:13:44 2 minute.

18:14:00 3 A Okay.

18:14:01 4 Q And do you recognize the reference to Green and
18:14:03 5 Wuts?

18:14:05 6 A I do.

18:14:05 7 Q Are you familiar with Green and Wuts?

18:14:07 8 A I am.

18:14:08 9 Q And can you explain what Green and Wuts is and
18:14:09 10 what it discloses?

18:14:11 11 A It is the standard book that people use for
18:14:14 12 protecting groups, including the sorts of protecting
18:14:19 13 groups that we're talking about here. But it's sort of
18:14:22 14 a compendium of all possible protecting groups. Every
18:14:32 15 synthetic chemistry lab has it.

18:14:33 16 Q And does that -- does that particular
18:14:35 17 discussion link the -- the blocking groups of Figure 3
18:14:38 18 with the -- the -- with the protecting groups that are
18:14:47 19 identified in Green and Wuts?

18:14:49 20 A Yes. I -- I think that's its whole point.

18:14:57 21 Q With regards to an SBS system, is phasing the
18:15:00 22 only source of errors?

18:15:03 23 A No.

18:15:03 24 Q What other kinds of errors are there?

18:15:08 25 A In this particular case, there would be errors

18:15:11 1 associated with the cleavage of the disulfide bond. And
18:15:15 2 that would lead to one particular type of error in this
18:15:17 3 case.

18:15:20 4 There are errors just with inherent polymerase
18:15:22 5 fidelity.

18:15:24 6 Q If more than half the strands were out of phase
18:15:26 7 after a given number of cycles, would that be sufficient
18:15:29 8 for SBS?

18:15:31 9 A No. No.

18:15:36 10 Q All right. You discussed with -- with
18:15:38 11 Mr. Grier the -- the language of the claim as -- I think
18:15:42 12 he pointed primarily to your declaration, which is
18:15:50 13 Exhibit 1029 on page 6. And the last limitation, it
18:16:05 14 says "The disulfide linkage of the cleavable linker and
18:16:09 15 the protecting group are cleavable under identical
18:16:11 16 conditions."

18:16:12 17 Do you see that?

18:16:13 18 A Yes.

18:16:14 19 Q Does the claim require that the 3' blocking
18:16:20 20 group and linker be actually cleaved?

18:16:22 21 A No. It just says they're cleavable -- I mean,
18:16:26 22 I'm just reading the language. It says "are cleavable
18:16:29 23 under identical conditions." Cleavable. Not cleaved.

18:16:32 24 Q So do you actually have to cleave in order to
18:16:34 25 be covered by what the claim calls out?

18:16:36 1 A No. In fact, in -- in -- the -- the -- in my
18:16:39 2 disclosure -- I -- I hope I made that clear. The
18:16:45 3 Vermaas dec- -- declaration clearly supports that there
18:16:48 4 are -- the conditions that cleaved the alkylazido would
18:16:54 5 cleave the disulfide as well. In their particular
18:16:56 6 implementation, they had already done so, had already
18:16:58 7 cleaved that disulfide. But those conditions would
18:17:00 8 clearly cleave both.

18:17:01 9 Q Okay. And the claim is directed to a molecule.
18:17:05 10 Right?

18:17:05 11 A It is.

18:17:06 12 MR. GRIER: Objection. Calls for a legal
18:17:06 13 conclusion.

18:17:07 14 BY MR. BABCOCK:

18:17:07 15 Q So there's no requirement that you perform the
18:17:11 16 cleavage in order to -- to perform -- in order to fall
18:17:16 17 within the scope of what the claim covers.

18:17:17 18 A No. I would -- no. I'm not a lawyer. But
18:17:22 19 that would not seem -- that would not seem to be the
18:17:24 20 case to me.

18:17:33 21 Q Mr. Grier provided you with some new exhibits
18:17:35 22 you hadn't seen before. I want to point you to 1031
18:17:38 23 and 1032. 1031 is the Church patent application. 1032
18:17:48 24 was the paper.

18:18:03 25 If you first start with Exhibit 1031, the

18:18:08 1 Church patent application -- and I turn you back to
18:18:13 2 Exhibit (sic) 17 to what Mr. Grier had you look at.

18:18:17 3 A Example 17. Yeah.

18:18:20 4 Q Example 17. Thank you.

18:18:21 5 Can you identify what reagent was used to
18:18:23 6 cleave the disulfide?

18:18:30 7 A DTT, dithiothreitol.

18:18:37 8 Q Okay. And then if you turn to Exhibit 1032,
18:18:39 9 the -- the Mitra paper, which also Church was on that.

18:18:45 10 And could you also help identify the -- the cleaving
18:18:48 11 agent that was used. You may focus on page 60 for
18:18:56 12 some --

18:19:07 13 A My recollection was that it was
18:19:08 14 beta-mercaptoethanol. But I'm trying to find where it
18:19:12 15 said that.

18:19:13 16 Q The top of that column, the second column.

18:19:15 17 A Beta-mercaptoethanol, that's correct.

18:19:18 18 Q Thank you.

18:19:18 19 So were the cleaving agents the same in these
18:19:20 20 two experiments?

18:19:21 21 A They were not.

18:19:21 22 Q So were these two experiments the same?

18:19:23 23 A No, they were not.

18:19:29 24 Q And are the conditions of the experiments in
18:19:32 25 these two references the same?

18:19:33 1 A They are -- the -- the disulfide is cleaved by
18:19:36 2 two different reagents.

18:19:37 3 Q So is the -- are the conditions the same, or
18:19:40 4 different?

18:19:41 5 A They are different.

18:19:42 6 Q And what year was the -- the 1032 Mitra paper
18:19:48 7 published?

18:19:49 8 A In 2003.

18:19:59 9 MR. BABCOCK: Can you give us a couple more
18:20:00 10 minutes, if we can take a break? I think we may be --
18:20:03 11 may be close to finishing.

18:20:04 12 MR. GRIER: Sure.

18:20:05 13 VIDEOGRAPHER: Off the record at 6:20.

18:36:40 14 (Recess from 6:20 p.m. to 6:36 p.m.)

18:36:52 15 VIDEOGRAPHER: Back on the record at 6:36.

18:36:56 16 MR. BABCOCK: All right. Dr. Romesberg, I
18:36:59 17 don't have any further questions. So I appreciate you
18:37:02 18 taking the time today to talk with us and to spend the
18:37:05 19 day here.

18:37:05 20

18:37:05 21 RECROSS-EXAMINATION

18:37:05 22 BY MR. GRIER:

18:37:06 23 Q Okay. Dr. Romesberg, I literally just have one
18:37:08 24 housekeeping question, just for clarification of the --
18:37:10 25 of the record.

18:37:14 1 During the redirect examination, Mr. Babcock
18:37:18 2 asked you if you -- you said -- in your testimony, you
18:37:24 3 identified in your list of references the most relevant
18:37:27 4 references that you're aware of.

18:37:29 5 Do you recall that question?

18:37:29 6 A (Gesturing).

18:37:30 7 Q And in response, you answered "I would have to
18:37:32 8 say that these two -- two of the references brought to
18:37:34 9 me here were also relevant."

18:37:37 10 So just for clarification purposes, for the
18:37:39 11 record, you were referring to Church reference,
18:37:42 12 Exhibit 1031, and the Mitra reference, Exhibit 1032.
18:37:48 13 Correct?

18:37:51 14 A No. I was referring to 1030 and 1031.

18:38:00 15 Q And ten -- Exhibit 1030, that is the -- that is
18:38:03 16 the Herman paper. Correct?

18:38:06 17 A Herman is the middle author on it, yes.

18:38:13 18 MR. GRIER: Okay. Dr. Romesberg, thank you for
18:38:14 19 your time today. I appreciate it. We have no further
18:38:17 20 questions.

18:38:18 21 MR. BABCOCK: All right. That's it. Thanks,
18:38:22 22 Doctor.

18:38:23 23 THE REPORTER: And no designation of
18:38:25 24 confidentiality?

18:38:27 25 MR. BABCOCK: Did we have anything today?

18:38:30 1 MR. LUMAN: I don't think so.

18:38:30 2 MR. GRIER: I don't think so.

18:38:31 3 MR. LUMAN: Because we -- we didn't touch on

18:38:32 4 all the --

18:38:33 5 MR. BABCOCK: We started to.

18:38:34 6 MR. GRIER: We started to but we --

18:38:35 7 MR. BABCOCK: So, no, I don't think the

18:38:37 8 transcript is not confidential, and none of the exhibits

18:38:39 9 are confidential.

18:38:40 10 MR. GRIER: Good question. Off the record.

18:38:41 11 VIDEOGRAPHER: This -- this concludes the

18:38:44 12 deposition of Dr. Floyd Romesberg. Off the record at

18:38:48 13 6:38.

18:38:49 14 (The proceedings concluded at 6:38 p.m.)

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1 DECLARATION UNDER PENALTY OF PERJURY

2
3 I, FLOYD ROMESBERG, PH.D., the witness herein,
4 declare under penalty of perjury that I have read the
5 foregoing in its entirety; and that the testimony
6 contained herein is a true and accurate transcription of
7 my testimony elicited at said time and place.

8 Executed this _____ day of _____, 2014.
9

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11 _____
12 FLOYD ROMESBERG, PH.D.
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1 I, Margaret A. Smith, Certified Shorthand
2 Reporter licensed in the State of California,
3 License No. 9733, hereby certify that the foregoing is a
4 true and accurate transcript of the deposition of said
5 witness, who was first duly sworn by me on the date,
6 time and place hereinbefore set forth. I certify that
7 the list of appearances on the foregoing pages
8 accurately indicates the individuals that were present
9 during the deposition of said witness.

10 I further certify that I am neither attorney
11 nor counsel, nor related to or employed by any of the
12 parties to the action in which this deposition was
13 taken, and further that I am not a relative or employee
14 of any attorney or counsel in this action, nor am I
15 financially interested in this case. Dated this 20th,
16 day of January, 2014.

17
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21 _____
Margaret A. Smith, CSR No. 9733, CRR
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Executed this 23rd day of February, 2014.

FLOYD ROMESBERG, PH.D.

Errata Sheet

Job No. 54646

Re: Deposition of Floyd Romesberg

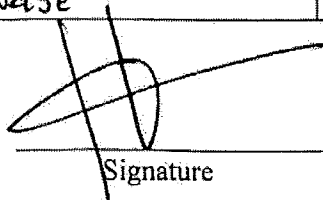
Date: 1-14-2014

Caption: Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd - IPR2013-00128

Page	Line	Correction/Change	Reason
42	9	OLE → O-allyl	error
48	24	bend → bin	error
54	2	nucleic-based → nucleobase	error
55	1	nucleic-based → nucleobase	error
55	17	what an organic comes to → to what an organic chemist	error
55	23	header → hetero	error
56	9	header → hetero	error
54	2	nucleic-based → nucleobase	error
57	1	nucleo base → nucleobase	error
57	2	nucleo-based → nucleobase	error
57	6	nucleo-based → nucleobase	error
58	17	tag in the → tag and the	error
60	1	purine → Purine	error
60	2	purings → purines	error
60	9	nucleo bases → nucleobases	error
64	6	you with it → you for it	error
76	24	enzymology → Enzymology	Proper Name
132	6	nucleo base → nucleobase	Error

Feb 23, 2014

Date


Signature

Errata Sheet

Job No. 54646

Re: Deposition of Floyd Romesberg

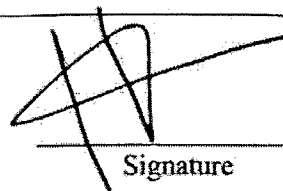
Date: 1-14-2014

Caption: Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd – IPR2013-00128

Page	Line	Correction/Change	Reason
132	13	nucleo base → nucleobase	error
150	20	function → functional	error
174	16	RNTPs → rNTPs	convention
175	14	modified → modify	error
177	13	RNTPs → rNTPs	convention
182	17	PKA → pKa	convention
198	23	Vocation → evocation	error
217	7	respect sort → respect the sort	error
225	12	citation → excitation	error
227	13	cyfi → cy5	error

Feb 23, 2014

Date


Signature