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

Videotaped Deposition of
FLOYD ROMESBERG, PH.D.
October 09, 2018

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

ILLUMINA, INC.,

Plaintiff,

vs.

Case No.: IPR2018-00797
Patent 9,868,985

THE TRUSTEES OF COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Defendant.

VIDEOTAPED DEPOSITION OF FLOYD ROMESBERG, PH.D.
SAN DIEGO, CALIFORNIA
TUESDAY, OCTOBER 9, 2018

Reported by:
Linda E. Marquette
RPR, CLR, CSR No. 11874
Job No. 10048075

UNITED STATES PATENT AND TRADEMARK OFFICE
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ILLUMINA, INC.,

Plaintiff,

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Case No.: IPR2018-00797
Patent 9,868,985

THE TRUSTEES OF COLUMBIA UNIVERSITY
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Defendant.

VIDEOTAPED DEPOSITION of FLOYD ROMESBERG, Ph.D., taken on behalf of Patent Owner, at 12790 El Camino Real, San Diego, California, beginning at 12:31 p.m., and ending at 4:36 p.m., on Tuesday, October 9, 2018, before Linda E. Marquette, RPR, CLR, Certified Shorthand Reporter No. 11874.

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I N D E X

EXHIBITS

EXHIBITS

**(Marked in previous depositions, referenced herein and attached hereto.)

SAN DIEGO, CALIFORNIA; TUESDAY, OCTOBER 9, 2018
12:31 P.M. to 4:36 P.M.

THE VIDEOGRAPHER: We are now on the record. Today's date is October 9, 2018, and the time is 12:31 p.m.

This begins the video-recorded deposition of Floyd Romesberg, Ph.D., being taken on behalf of the plaintiff in the matter of Illumina, Inc. v. Trustees of Columbia University in the City of New York, pending in the United States Patent and Trademark Office before the Patent Trial and Appeal Board, Case No. IPR2018-00797.

We are at the offices of Knobbe Martens, located at 12790 El Camino Real, San Diego, California 92130.

My name is Ryan Asanas, the videographer of Aptus Court Reporting, located at 600 West Broadway, Suite 300, San Diego, California 92101.

Will all counsel present please identify yourselves and state whom you represent, starting with the taking attorney.

MR. SCHWARTZ: I am Robert Schwartz. I represent Columbia University in this matter. With me is my colleague, Zachary Garrett and John Murnane. We're all from the Fitzpatrick Cella Harper & Scinto

firm in New York City. And also with me is Dr. Steven Menchen.

MR. ZIMMERMAN: Bill Zimmerman of Knobbe Martens Olsen & Bear on behalf of Illumina and the witness. With me is my partner Nate Luman and Marcus Birch of Illumina.

THE VIDEOGRAPHER: Thank you.

The court reporter today is Linda Marquette, also with Aptus Court Reporting.

And she may now swear in or affirm the deponent.

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

EXAMINATION

BY MR. SCHWARTZ:

Q. Good afternoon, Dr. Romesberg.

A. Good afternoon.

Q. So we went over the ground rules for a deposition the last time we met, so I won't go over them again, except to say that if there's any reason you can't give truthful testimony today, just -- I'd just prefer that you tell us now.

Page 9

Is there any reason you can't give truthful testimony today?
A. No, there's not.
Q. Okay. Did you meet with your attorneys in preparation for your deposition today?
And I'm only asking for a yes or no answer.
A. Yes.
Q. And what are the names of the attorneys you met with?
A. Nate and Marcus and Bill.
Q. Okay. And how many times did you meet with the attorneys in preparation for your deposition today?
A. One time.
Q. And when did that meeting take place?
A. Yesterday.
Q. And approximately how much time yesterday did you spend preparing for your deposition?
A. Six hours.
Q. Outside of that meeting, did you meet with your attorneys any other time?
A. I did not.
Q. Okay. And did you speak with anybody else other than those attorneys you mentioned about your deposition?
A. I did not.

Page 10

Q. And what did you do to prepare for today's deposition?
A. In addition to meeting with them yesterday?
Q. Uh-huh.
A. I spent a couple of hours this morning rereading, refreshing my memory on -- on selected publications and -- and documents from the IPR.
Q. And you understand that today's deposition is in relationship to IPR2018-00797, correct?
A. I do.
Q. Okay. And you've prepared an expert declaration in that IPR, correct?
A. I did.
Q. And I'm going to put in front of you -- putting in front of you Exhibit 10,000 -- sorry, 1078 entitled Declaration of Floyd Romesberg, Ph.D., In Support of Petition for Inter Partes Review of U.S. Patent No. 9,868,985.
And please turn to the last page of the declaration. Is that your signature on that page?
A. It is.
Q. Okay. The next exhibit I'm going to put in front of you is Exhibit 1075, which is U.S. Patent No. 9,868,985.
///

Page 11

(Exhibit 1075 was previously marked for identification by the Certified Shorthand Reporter.)
BY MR. SCHWARTZ:
Q. The inven- -- the invention claimed in U.S. Patent No. 9,868,985 relates to a method of sequencing of nucleic acid SBS, correct?
A. Correct. Correct.
Q. I'm going to put in front of you Exhibit 2080, which is the deposition transcript in IPR2013-00128.
(Exhibit 2080 was previously marked for identification by the Certified Shorthand Reporter.)
BY MR. SCHWARTZ:
Q. Please turn to page 37. Please draw your attention to line 8. And starting at line 8, the transcript reads:
"QUESTION: You see it also lists other uses for the nucleotides in the '026 patent. Correct?
"ANSWER: Yes, correct.
"QUESTION: And it provides various examples of those, such as polynucleotide synthesis, nucleic acid hybridization, SNP studies,

Page 12

labeling dNTPs, et cetera.
Do you see that?
"ANSWER: I do."
I'm going to ask you to skip ahead to page 38, please. I don't want to read everything into the record.
And please draw your attention to line 11. And certainly feel free to read the testimony in between from where we left off to here if you need to.
A. Yes. Can I do that, please?
Q. Can I ask the question first and just see if you need to? And certainly if you need to, you can. But for now, I'll just read the following testimony that starts at line 11.
"QUESTION: Okay. So then you would agree that those other techniques listed are things other than SBS. Correct?
"ANSWER: Yes. Correct."
That was your testimony, correct?
A. That is what's written.
Q. It is your opinion that polynucleotide synthesis, nucleic acid hybridization, SNP studies, and labeling dNTPs are techniques that are not SBS, correct?
A. Could I take that minute now to read this?

Page 13

Q. Oh, sure.
A. Could I ask for a refresher on what is the '026 patent?
Q. Do you want to see the '026 patent?
A. If you -- I may not need to, if you just tell me who it is.
Q. I can't testify, so I can -- I can put the patent in front of you if you want to see it.
A. Sure.
Q. This is Exhibit 1001. It's the '026 -- oh, I'm sorry. This is not marked yet. I can put it in front of you. I won't mark it, and if you want me to, I'll mark it. But --
A. I don't even -- I'm not sure I know what that means.
Q. Put a number on it.
A. Yeah, I guess I'm not sure why that would -- I don't mind if you don't mark it.
MR. ZIMMERMAN: You don't have to worry about it.
THE WITNESS: Okay.
A. Okay. Could you repeat the question?
BY MR. SCHWARTZ:
Q. So we read your testimony. I won't reread your testimony in the -- in the deposition.

Page 14

My question was: From your testimony you said it was your opinion that polynucleotide synthesis, nucleic acid hybridization, SNP studies, and labeling dNTPs are techniques that are not SBS. That's what you testified, correct?
A. Could you show me where I exactly testified? Because I think what I was being asked was whether or not this patent -- this '026 patent described things other than just sequencing by synthesis. And it goes out of its way to do so in spots where I agreed.
So I don't know that I listed specific things and said whether or not they were sequencing by synthesis. What I was answering there was that this patent was about things in addition to sequencing by synthesis.
So if you could ask me a specific question again.
Q. Okay. Well, let's go back.
A. And if you could clarify whether you're asking me about what this patent says or whether I think a specific technique is sequencing by synthesis.
Q. It was the latter. But we can go back to the transcript at line 8. Do you want to go back and look at the transcript?
A. Which -- which page?

Page 15

Q. Starting at line 8 at page 37. And the question was:
"You see it also lists other uses for the nucleotides in the '026 patent. Correct?"
And your answer was:
"Yes. Correct.
And the question was:
"And it provides various examples of those, such as polynucleotide synthesis, nucleic acid hybridization, SNP studies, labeling dNTPs, et cetera.
"Do you see that?
And your answer was:
"I do."
And I asked you to skip ahead to page 38, line 11, where there was a conclusory question. And the question was:
"Okay. So you would -- so then you would agree that those other techniques listed are things other than SBS. Correct?"
And your answer was:
"Yes. Correct."

Page 16

That was your testimony, correct?
A. That is what's written, yes.
But I do believe that it's referring to what is listed in the patent, not any particular list that may have been part of a question which ends with "et cetera." Because where it ends with "et cetera," the patent does describe other things.
I just want to be clear that I don't want to -- I'd have to rethink the question if it was do I think these are about sequencing by synthesis.
But what I was answering here was whether the patent was -- included things other than sequencing by synthesis, which it clearly does.
Q. Your answer was that you -- you provided an opinion as to whether polynucleotide synthesis, nucleic acid hybridization, SNP studies, labeling dNTPs were things other than sequencing by synthesis, and your answer was "Yes. Correct."
MR. ZIMMERMAN: Objection. Asked and answered.
A. I -- I did not testify -- I believe what I was testifying was whether or not this patent which they're asking about, and they say "and it provides examples of those such as," and it ends with "et cetera." So what the question is referring to is the subject matter in

Page 17

the patent, which I was familiar with at that time, and I was answering questions about that.
BY MR. SCHWARTZ:
Q. Is it your opinion that polynucleotide synthesis is a form of SBS?
A. Polynucleotide synthesis is often involved in SBS. That's the "by synthesis" part. But you can certainly do polynucleotide synthesis without sequencing. So it does not have to involve sequencing.
Q. All right. So when you said that you agree that those other techniques listed are things other than SBS, and you agreed to that, you're withdrawing that testimony?
A. No. I'm -- what that testimony was referring to was the subject matter that I was being asked about in this patent. And I believe that testimony -- I believe I would still answer that the same way.
Q. Well, do you believe that polynucleotide synthesis, nucleic acid hybridization, SNP studies, and labeling dNTPs are things other than SBS?
A. That's not what's asked.
Q. Well, do you believe that? Is that your opinion?
A. So you're now asking me a separate question?
Q. Yes, because -- I am asking you that question.

Page 18

A. Okay. So could you please ask that question again?
Q. Is it your opinion that polynucleotide synthesis, nucleic acid hybridization, SNP studies, labeling dNTPs are things other than SBS?
A. All of those things can involve -- can be related to SBS. They can all be parts of sequencing by synthesis. So I would not say that those are unrelated to sequencing by synthesis, no.
Q. So those are techniques that are SBS; is that your opinion?
A. They can be part of SBS. They can be independent of SBS as well.
Q. I'm putting in front of you Exhibit 2007, which is your expert declaration IPR2013-00517.
(Exhibit 2007 was previously marked for identification by the Certified Shorthand Reporter.)
BY MR. SCHWARTZ:
Q. Please turn to page 10.
A. Can -- can I ask, when did I give this testimony? I'm just drawing -- I've given several of these, so I would like to make sure I know which one I'm talking about. This would have been 2014?
Q. When did you sign this? Is that what you're

Page 19

asking?
A. Yeah, that would be enough --
Q. You signed this May 5th of 2014.
A. Thank you.
Q. I mean, do you agree with that? I shouldn't be testifying so ...
A. It's not written here, but I believe that's correct.
Q. It should be.
A. Oh, it is. Yeah. Then it's correct.
Q. Okay. Please turn to page 10.
On page 10 there is a section entitled Scope and Content of the Prior Art. Do you see that?
A. I do.
Q. And underneath that is a Section A, entitled U.S. Patent No. 6,664,079 to Ju, et al.
Do you see that?
A. I do.
Q. And to make it easier going forward, I'll refer to the U.S. Patent No. 6,664,079 as the '079 patent. Okay?
A. Okay.
Q. Please draw your attention to paragraph 28, which is the first paragraph in Section A. And please look at the last sentence in paragraph 28, which starts

Page 20

with "One of ordinary skill." Do you see that?
A. I do.
Q. You write:
"One of ordinary skill in the art would have understood these teachings of Ju as stating that Ju's invention was nucleotide sequence determination using a DNA polymerase and, in particular, using the method referred to as sequencing by synthesis."
That is what you wrote, correct?
A. That is correct. That is what I wrote.
Q. It is your opinion that a reader of Ju's patent specification understood that the sequencing method in Ju's patent is SBS, correct?
A. That is what is written. I'm not -- I don't have that patent in front of me, but that's certainly what is -- what is written here.
Q. And in support for your opinion, you refer to portions of the '079 patent specification, specifically Column 4, lines 22 to 26, and Column 21, lines 1 through 5, correct?
A. I'm sorry. Where are you getting that?
Q. I'm getting that within the paragraph.

Page 21

Paragraph 28 you cite to in spec- --
A. Oh, in paragraph -- yes.
Q. So as support for your opinion that we just went over, you referred to the portions of the '079 patent specification, specifically Column 4, lines 22 to 26, and Column 21, lines 1 through 5, correct?
A. Correct.
Q. Okay. I'm going to put in front of you U.S. Patent No. 6,664,079 to Ju, et al. And this has been marked as Exhibit 2095.
(Exhibit 2095 was marked for identification by the Certified Shorthand Reporter.)
BY MR. SCHWARTZ:
Q. This is the same patent you referred to in Section 5A of your declaration, correct?
A. It appears to be.
MR. ZIMMERMAN: The copy I have isn't marked. Has it been marked as 2095?
MR. SCHWARTZ: It's been marked.
MR. ZIMMERMAN: Okay.
BY MR. SCHWARTZ:
Q. And again, for convenience going forward, I will refer to this patent as the '079 patent. Okay?
A. That is okay.

Page 22

Q. Okay. Now, go back to your declaration, please, and draw your attention to paragraph 29. In paragraph 29 you write:
"Ju's SBS methods have four 'fundamental requirements.'
(1) "The availability of four nucleotide analogues (aA, aC, aG, aT) each labeled with a unique label and containing a chemical moiety capping the 3'-OH group;
(2) the four nucleotide analogues (aA, aC, aG, aT) need to be efficiently and faithfully incorporated by DNA polymerase as terminators in the polymerase reaction;
(3) the tag and the group capping the 3'-OH need to be removed with high yield to allow the incorporation and detection of the next nucleotide; and,
(4) the growing strand of DNA should survive the washing, detection and cleavage processes to remain annealed to the DNA template."

Page 23

And you cite to the Ju patent specification. That's Column 21, line 3 through 16.
That is what you wrote, correct?
A. That is what is written, yes.
Q. And that is your opinion, correct?
A. I -- I -- do you want me to go back into -- into this '079 patent and refresh my memory on this? It was obviously my opinion then.
Q. No, sir --
A. It probably still is.
Q. Okay. So it is -- it is your opinion that Ju's SBS methods have four fundamental requirements you list in paragraph 29 --
A. Yes.
Q. -- of your declaration, correct?
And as support for your opinion, you cite to Column 21, lines 3 through 16, of the '079 patent, correct?
A. I do.
Q. And please direct your attention to paragraph 30 of your declaration. In paragraph 30 you write:
"Thus, one of ordinary skill in the art would have understood that Ju's sequencing by synthesis methods

Page 24

have the above four fundamental requirements, and if any of these requirements are not satisfied, then Ju's sequencing by synthesis method would not work for its intended purpose."
That is your opinion and that is what you wrote, correct?
A. Yes to both.
Q. Please go to page 12 of your declaration. And draw your attention to paragraph 32. And please draw your attention to the sentence that begins four lines down in paragraph 32, where the sentence starts with "In discussing shortcomings."
Do you see that?
A. I do.
Q. You write:
"In discussing shortcomings of prior art pyrosequencing methods, Ju states that this method 'can only sequence up to 30 base pairs (bps) of nucleotide sequences' Id at Column 2, lines 10 through 25.
"Thus, one of ordinary skill would understand Ju as teaching that

Page 25

a method that can only sequence 30 base pairs is undesirable. Regarding Ju's own method, Ju teaches, 'in the DNA sequencing system disclosed herein, more than 10,000 bases can be identified after each cycle and after 100 cycles, a million base pairs will be generated from one sequencing chip' Id at Column 21, lines 63 through 67. "Thus, a person of ordinary skill in the art would understand that the desired read length of Ju's sequencing method is more than 30 base pairs, and preferably up to a hundred base pairs." That is your opinion and that is what you wrote, correct?

A. I -- I would have to rethink that exactly, but I believe -- this is certainly what I wrote, and I believe it's what I would believe, yes.

Q. If we focused on the last three lines of paragraph 32 -- I'll strike that. Strike that question, please. I'm going to put in front of you your

Page 26

deposition transcript in IPR2013-00517, which has been marked as Exhibit 2035.

(Exhibit 2035 was previously marked for identification by the Certified Shorthand Reporter.)

THE WITNESS: Mine is not marked.

MR. ZIMMERMAN: Down here.

THE WITNESS: Oh, that's a mark?

BY MR. SCHWARTZ:

Q. Please turn to page 87. And please look at line 5. Starting at line 5 --

A. Oh, I'm sorry. Can I ask when this testimony is from? Is this also from 2014? Yes, it is. I see.

Q. Please look at line 5. And starting at line 5 the transcript reads:

"QUESTION: Would you agree with me that a person of ordinary skill would understand that any alleged 30 base pair requirement as a goal?

"ANSWER: I think my reading was that Ju had a much longer -- a goal of being much longer than 30 nucleotides."

That was your testimony, correct?

A. That is what is written.

Page 27

Q. Okay. Please turn to page 88 of that transcript. Please look at line 1. And starting at line 1, the transcript reads:

"ANSWER: I don't read it as 30 nucleotides being a goal of Ju. He actually cites a pyrosequencing method, and he cites the 30 nucleotides as a limitation -- the fact that you can only get a read length of 30 as a limitation. So I think he's -- it's sort of -- it's noted as a limitation, and he then at a later -- at a different spot, talks about much longer reads.

"So my read, I don't think he actually gives a value of what he says is his goal, but it was clearly long -- in my read of it, it was clearly longer than 30 because he is disparaging the pyrosequencing method as only providing 30 nucleotide read lengths."

That was your testimony, correct?

A. That is what is written.

Q. Please go to paragraph 33 on page 13 of your

Page 28

declaration. That's Exhibit 2007 now.

A. The current dec?

Q. Exhibit 2007. It's the -- it's the declaration in that IPR2013-00517.

A. This one? What page?

Q. Page 13, paragraph 33, please.

A. I'm there.

Q. And you write:

[As read]

"In order to achieve a read length of more than 30 base pairs, one of ordinary skill must have understood that Ju's 3'-OH capping group must be removed in nearly quantitative yield through each cycle of sequencing. For example, the removal of efficiency of each cycle must be greater than 95 percent to permit a read length of 30 bases before phasing errors cause the signal-to-noise ratio to decrease beyond detectable limits (i.e., 0.9530 = 21 %).

"One of ordinary skill would have known that, in practice, Ju requires

Page 29

a removal efficiency significantly higher than 95 percent to account for inefficiencies associated with other steps in the sequencing cycle (such as inefficiencies with tag removal and/or polymerase incorporation of unnatural nucleotides)."

And you cite to the Ju patent specification at Column 21, lines 8 through 13.

That is what you wrote and that is your opinion, correct?

A. That is what is written, and I believe that is -- would still be my opinion, yes.

Q. And to support your opinion, you cite to Column 21, lines 8 through 13 of the '079 patent, correct?

A. That is what is written, yes.

Q. And following the portion of paragraph 33 that I just read, you write:

[As read]

"Likewise, one of ordinary skill would have known that the removal efficiency must be greater than 98.5 percent to yield Ju's desired

Page 30

read length of a hundred bases (i.e., 0.85100 = 22%). [sic] Therefore, a person of ordinary skill in the art would have understood that Ju's sequencing method requires nearly quantitative cleavage efficiency for the 3'-OH capping group."

That is your opinion and that is what you wrote, correct?

A. That is what is written, and I believe that would still be my opinion, yes.

Q. Please go to paragraph 34 of that declaration. In paragraph 34 you write:

"Ju also states that 'The success of this [... sequencing by synthesis] system will allow the development of an ultra high-throughput and high fidelity DNA sequencing system for polymorphism pharmacogenetics applications and for whole genome sequencing. This fast and accurate DNA resequencing system is needed in such fields as detection of single

Page 31

nucleotide polymorphisms (SNPs), serial analysis of gene expression (SAGE), identification in forensics and genetic disease association studies."

And you cite to the Ju patent specification at Column 4, lines 10 through 19.

That is what you wrote and that is your opinion, correct?

MR. ZIMMERMAN: Objection. Mischaracterizes the document.

MR. SCHWARTZ: Did I misread something?

MR. ZIMMERMAN: You did. You misread the first sentence of the quote.

BY MR. SCHWARTZ:

Q. Okay. Let me read the beginning again.

"Ju also states that 'The success of this [DNA sequencing by synthesis] system will allow the development of an ultra high-throughput and high fidelity DNA sequencing system for polymorphism, pharmacogenetics applications and for whole genome sequencing."

Page 32

Did I read that correctly this time?

MR. ZIMMERMAN: You did not.

MR. SCHWARTZ: I'll try it again.

BY MR. SCHWARTZ:

Q. Paragraph 34:

"Ju also states that, "The success of this [DNA sequencing" -- Are you -- are you -- are you saying I didn't record the fact that he underlined some words? Is that what you're saying?

MR. ZIMMERMAN: No.

MR. SCHWARTZ: Oh.

MR. ZIMMERMAN: You keep leaving out the word "the" DNA sequencing by the synthesis system.

MR. SCHWARTZ: I thought I had read that.

BY MR. SCHWARTZ:

Q. Let me read it again. Sorry about this.

A. I'm used to it.

Q. [As read.]

"Ju also states that the success of this [sic] [DNA sequencing by the synthesis] system will allow the development of an ultra high-throughput and high fidelity DNA sequencing system for polymorphism

Page 33

pharmacogenetic application -- pharmacogenetics applications and for whole genome sequencing. This fast and accurate DNA resequencing system is needed in such fields as detection of single nucleotide polymorphisms (SNPs) serial analysis of gene expression (SAGE), identification in forensics and genetic disease association studies."

And you cite to the Ju patent specification at Column 4, lines 10 through 19.

That is what you wrote and that is your opinion, correct?

A. That is what is written, and I believe that would still be my opinion, yes.

Q. And I'll note for the record that you underlined the words "ultra high-throughput" and "fast" in what you wrote, correct?

A. That is correct.

Q. Why did you emphasize the word "fast"?

A. At this exact moment, I'm not -- I mean, this was -- I wrote this four years ago. I believe I was emphasizing that the deprotection need to be -- needed to be reasonably efficient. Or I might have been -- I might have been echoing what Ju said.

Page 34

I'm actually not -- I don't -- that was four years ago, and I don't remember.

Q. And why did -- why did you emphasize the word "ultra high-throughput"?

A. Same answer.

Q. Going back to paragraph 34 of your declaration in Exhibit 2007.

A. The same dec?

Q. Yes.

I just read paragraph 34 through the top of page 14. So following what I just read, we are now on the third line from the top of page 14, and you write:

"Ju's characterization of its DNA sequencing system as 'fast'" -- and you put a quotes around fast -- "and 'ultra high-throughput'" -- and you put quotes around ultra high-throughput -- "would have led a person of ordinary skill in the art to understand that speed was an important design consideration for Ju's sequencing system.

"Thus, one of ordinary skill would have considered that each step of Ju's sequencing cycle should proceed as quickly as possible to increase the overall speed of the sequencing method.

Page 35

"Since removal of the 3'-OH capping group is one step in Ju's sequencing cycle,'" and you cite to the Ju patent specification at Column 21, lines 11 through 13, "a person of ordinary skill in the art would understand that rapid removal conditions would be required to develop a 'fast' sequencing system capable of the 'ultra high-throughput' of Ju's sequencing method."

That is your opinion and that is what you wrote, correct?

A. That is what is written, and I believe that would still be my opinion.

Q. I'm going to ask you to go back to your deposition transcript in IPR2013-00517, which was marked as Exhibit 2035. And please turn to page 99, and please look at line 2. Starting at line 2, the transcript reads:

Page 36

[As read.]

"But what I will say is that there are lots of polymerase reactions. There are lots of read lengths that would simply never be useful for sequencing by synthesis.

"A read length of one is just an example. So [sic] you would never be able to do anything with that. So you're going to have to get read lengths of 25 or 30 in -- in a -- with no more than an hour or so between reads to make it -- to -- someone who's reading the Ju material, the Ju patent, and thinking about sequencing by synthesis is going to understand those as restrictions."

That was your testimony and that is your opinion, correct?

A. That is what is written. I would ask to read the context to make sure that I'm -- understand what I'm ask -- what I'm answering, though.

Can I take a moment to read this or --

Q. Sure.

Page 37

A. Okay. Thank you.
Okay. Could you repeat the question, please?
Q. Starting at line transcript -- line 2 of the transcript, you stated:
"But what I will say is that there are lots of polymerase reactions. There are lots of read lengths that would simply never be useful for sequencing by synthesis.
"A read length of one is just an example. So [sic] you would never be able to do anything with that. So you're going to have to get read lengths of 25 or 30 in -- in a -- with no more than an hour or so between reads to make it -- to -- someone who's reading the Ju material, the Ju patent, and thinking about sequencing by synthesis is going to understand those as restrictions."
And my question was, that is your opinion and that is your testimony, correct?
A. That is what is written, but I would like to clarify. What I was -- the 25 to 30 is required for, as

Page 38

I -- as we talked about last time, for genome reassembly. And so for de novo sequencing by synthesis, I should -- probably should have been more clear with this testimony. I was trying to look back to see if that was the subject matter. I'm not sure it was.
The reason -- a reason that you need 25 to 30 nucleotides is that you need to reassemble genomes. And one nucleotide, my point was that you could never -- if you simply had a one nucleotide read, you wouldn't know where in the genome you were.
If you had two, you still don't know because there are too many places where two nucleotides are repeated. You have to get longer to have a unique sequence. And they're on the order of -- depending on the size of how much DNA you have, they're on the order of 15 to 30 nucleotides.
And for the human genome, which is what I was -- in my mind at the time, 25 is about what you need for a unique placement of a sequence.
Q. All right. But you did look back in the transcript, and there's nothing in the transcript where the question specifically was addressing genome sequencing, correct?
A. I could not find it.
Q. Okay. Okay. Please go back to page 14 of

Page 39

your declaration.
A. Same declaration?
Q. Yes, please.
MR. ZIMMERMAN: Just so we have a clear record, can you say which declaration it is?
MR. SCHWARTZ: Exhibit 2007.
BY MR. SCHWARTZ:
Q. Please go to page 14.
A. I'm there.
Q. And draw your attention to about five lines down where you write:
"Thus, one of ordinary skill would have considered that each step of Ju's sequencing" --
A. I'm sorry. I'm in -- I'm in my dec. You said the declaration. I'm sorry. Could you hold on one second?
Q. Sure.
A. Which dec?
Q. Exhibit 2007.
A. Yeah. Page 5?
Q. Yes -- page 14, line 5 -- five lines down.
A. Mm-hmm, yes.
Q. About five lines down you write:
"Thus, one of ordinary skill

Page 40

would have considered that each step of Ju's sequencing cycle should proceed as quickly as possible to increase the overall speed of the sequencing method."
That is what you wrote and that is your opinion, correct?
A. Yes.
Q. Okay. Please go back to paragraph 29 of that declaration. In paragraph 29 of your declaration you refer to the '079 patent specification at Column 29 -- strike that.
In paragraph 29 of your declaration, you refer to the '079 patent specification at Column 21, lines 3 through 16. Do you see that?
A. Yes.
Q. And please go to the '079 patent, which is marked as Exhibit 2095.
A. Column 21?
Q. Yes, please. And lines 3 through 16. I'm just going to ask you to read that section to yourself and let me know when you're done.
A. Lines 3 through 16?
Q. It's what you refer to in your declaration.
A. I read it.

Page 41

Q. Okay. And with the '079 patent still in front of you, please go to U.S. Patent No. 9,868,985, and we're calling that the '985 patent. That's Exhibit 1075. And so now you have in front of you both the '079 patent and the '985 patent, correct?
A. Yes.
Q. And please turn to Column 20 of the '985 patent. And please look at line 65 and continue till Column 21 at line 13. And just read that to yourself and let me know when you're done.
And basically, my question is going to be -- I think you can -- you can understand what I'm doing here is I'm just asking you that the text that you refer to in the '079 patent is identical to the text in the '985; is that correct?
Please compare.
A. Yes, they seem to be identical.
Q. Okay. Please go to paragraph 32 of your declaration, Exhibit 2007, and keep those patents in front of you.
A. Which --
Q. Paragraph 32 of your declaration, Exhibit 2007.
A. Paragraph 32. Yes.
Q. And in paragraph 32 of your declaration, you

Page 42

refer to the '079 patent specification at Column 2, lines 10 through 25, and Column 21, lines 63 through 67, correct?
A. I'm sorry. Could you repeat that? This is in paragraph 32?
Q. Yes.
You refer to Column 2, lines 10 through 25, sort of in the middle of the paragraph, and you refer to Column 21, lines 63 through 67, towards the end, correct?
A. Yes. I see.
Q. Okay. And so please go to the '079 patent, which is Exhibit 2095. And let's start by looking at Column 2, lines 10 through 25. Please read that to yourself and let me know when you're done.
And basically, I'll ask you to do the same thing of the '985 patent.
A. Column 2, I read line 10 through 25.
Q. Okay. Now, please open the '985 patent and go to Column 2 as well, please. And please look at lines 31 through 46. You can read that to yourself and let me know when you're done.
A. You said lines 41 through 46?
Q. 31 through 46.
A. 31.

Page 43

I have read them.
Q. So the text of the '079 patent specification at Column 2, lines 10 through 25, is found word for word in the '985 patent specification, correct?
A. It is.
Q. Please go to Column 21, lines 63 through 67 of the '079. Column 21, lines 63 through 67.
A. So 2095. What -- what column?
Q. Of the '079 patent, Column 21, lines 63 through 67.
A. 63 through 67.
Q. Please read that to yourself and let me know when you're done.
A. Yes.
Q. Okay. Now, please look at the '985 patent, Column 21, and look at lines 60 through 64. Please read that to yourself and let me know when you're done.
A. Column 21, line 60.
Q. Through 64.
A. I have read them.
Q. The text of the '079 patent specification at Column 21, lines 63 through 67, is found word for word in the '985 patent specification, correct?
A. They are not identical.
Q. And in what way are they different?

Page 44

A. In the 2095, the '079 patent, the reference "Schena et al. 1995 et al." has a period, whereas in the '985 patent that we're discussing, now there's a comma.
Q. Okay. Otherwise they are identical?
A. Otherwise --
MR. ZIMMERMAN: Objection. Mischaracterizes the document.
BY MR. SCHWARTZ:
Q. Otherwise the portions that we read are identical?
A. Otherwise the portion that you asked me to read seems to be identical.
MR. ZIMMERMAN: Is now a good time for a break?
MR. SCHWARTZ: Do you really need a break right now? Because I'm going through --
THE WITNESS: It will only take me a second. I'll be -- I'll right back.
MR. SCHWARTZ: Sure.
MR. ZIMMERMAN: Can I just step out?
THE VIDEOGRAPHER: Going off the record at 1:28 p.m.
(Recess taken from 1:28 p.m. to 1:31 p.m.)
THE VIDEOGRAPHER: We are back on the record

Page 45

at 1:31 p.m.
BY MR. SCHWARTZ:
Q. Dr. Romesberg, during your break did you discuss today's deposition with your attorney?
A. No, I did not.
Q. Please go to paragraph 33 of your declaration, Exhibit 2007.
A. Where?
Q. Paragraph 33.
A. Yes.
Q. In paragraph 33 of your declaration you referred to the '079 patent specification at Column 21, lines 8 through 13. Do you see that?
A. Where is this? 8 through 13?
Q. 21, 8 through 13.
A. Yes, I see it.
Q. And please go to the '079 patent, which is Exhibit 2095 and look at Column 21, lines 8 through 13. Please read that to yourself and let me know when you are done.
A. I have read it.
Q. Please turn to the '985 patent and look at Column 21 of that patent. And please look at lines 5 through 10 of the '985 patent at Column 21. And please read that to yourself and let me know when you're done.

Page 46

A. I have read it.
Q. The text of the '079 patent specification at Column 21, lines 8 through 13, is found word for word in the '985 patent specification, correct?
A. The specification in the '079 patent is found word for word in the '985, the parts that you just asked me to read, yes.
Q. Okay. Please go to paragraph 34 of your declaration, which is Exhibit 2007. In paragraph 34 of your declaration you refer to the '079 patent specification at Column 4, lines 10 through 19, and at Column 21, lines 11 through 13, correct?
A. Correct.
Q. Okay. Please go to the '079 patent, Exhibit 2095, and look at, starting with Column 4, lines 10 through 19.
A. The '079?
Q. Yes. Column 4, lines 10 through 19. And read that to yourself and let me know when you're done.
A. I am complete.
Q. Please go back to the '985 patent and look at Column 4 and draw -- Column 4. And draw your attention to lines 31 through 41. And please read that section to yourself and let me know when you're done.
A. I'm done.

Page 47

Q. The text of the '079 patent specification at Column 4, lines 10 through 19, are found word for word in the '985 patent specification, correct?
A. Yes, they are.
Q. And now please go to the '079 patent and look at Column 21, lines 11 through 13.
A. Yes.
Q. And please read that to yourself and let me know when you're done.
A. 11 through 14?
Q. 11 through 13.
A. 13. I'm done.
Q. And please go back to the '985 patent and turn to Column 21 and look at lines 8 through 10. Please read that to yourself and let me know when you're done.
A. I'm done.
Q. The text of the '079 patent specification at Column 21, lines 11 through 13, is found word for word in the '985 patent specification, correct?
A. It is not identical.
Q. Okay. And the difference being what?
A. I believe it's called a superstrike. It's a longer hyphen between the 3' and the OH versus a dash, which the '985 patent has.
Q. Do you understand both of them to mean the 3'-OH group?

Page 48

A. I understand them both to mean the identical thing.
Q. Okay. And other than that difference, the specifications are the same in that section, correct?
A. Correct.
MR. SCHWARTZ: Would this be a good time for you to take a break? It's been about an hour.
MR. ZIMMERMAN: Sure.
THE VIDEOGRAPHER: Going off the record at 1:37 p.m.
(Recess taken from 1:37 p.m. to 1:55 p.m.)
THE VIDEOGRAPHER: We are back on the record at 1:55 p.m.
BY MR. SCHWARTZ:
Q. Okay. Dr. Romesberg, during the break did you have any conversations with your attorneys relating to this case?
A. No, I did not.
Q. Please go back to the declaration in the present IPR, which is Exhibit 10,000 -- 1078. It's the declaration in IPR2018-00797. And please turn to page 49. Please draw your attention to the first two lines on page 49.

Page 49

You rely on the Qian 1998 paper to support your statement on page 49, and also elsewhere in your declaration, that in O-O-allyl ether is removed using palladium chloride in quantitative yield, correct?

A. That is what is written, yes.

Q. I'm going to put in front of you Exhibit 1036, which is the Qian 1998 paper, correct?

(Exhibit 1036 was previously marked for identification by the Certified Shorthand Reporter.)

A. Yes. It is.

BY MR. SCHWARTZ:

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

(Exhibit 2102 was marked for identification by the Certified Shorthand Reporter.)

BY MR. SCHWARTZ:

Q. This is marked as Exhibit 2102.

A. Are you marking this now or it's been previously?

Q. It's been premarked [sic]. And please look at the second page of the document. And it's entitled Enzymatic and Chemical Synthesis of Oligosaccharide Analogs by Xiangping Qian.

Page 50

Do you see that?

A. I do.

Q. And please turn to the fourth page of that exhibit, the page that is entitled Library Release Form. Do you see that?

A. I do.

Q. At the bottom of the page there's a signature, it appears to be by Qian, that was signed on January 25th, 2000. Do you see that?

A. I do.

Q. Okay. So please go back to the Qian 1998 paper, which was Exhibit 1036. And Xiangping Qian, who was the first author of Exhibit 1036, is the same Xiangping Qian who was the author of Exhibit 2102, correct?

A. Well, they have the same name, so yeah, I would assume there's the same name and the same affiliation, so it would seem likely.

Q. Please turn to page 2185 of the Qian 1998 paper. And please draw your attention to Scheme 2. And you rely on Scheme 2 in the Qian 1998 paper to support your opinion that an O-allyl ether is removed using palladium chloride in quantitative yield in a two-hour reaction at room temperature, correct?

A. Yes. I cite that.

Page 51

Q. Okay. Please keep that paper in front of you and go back to the thesis. When I say "thesis," I'm referring to Qian Ph.D. thesis, Exhibit 2102. And please turn to page 42. And please draw your attention to compound 65.

Compound 65 in Qian's Ph.D. thesis is the same O-allyl protected compound as compound 7 in the Scheme 2 in Qian 1998, correct?

A. He explicitly writes out what R must be in compound 65 in the thesis, where he leaves it as an R in compound 7.

Q. I believe if you look a little bit to the right, you'll see O -- you'll see R is O-octyl in the thesis.

A. It is written as octyl in the thesis, but it's written as R in the text -- in the manuscript, in the paper. My guess is that --

Q. And look -- please look at the paper again, and right under compound 6, do you see R octyl?

A. Yes, that's correct. Yep.

Q. So they are the same compound?

A. They would appear to be the same compound.

Q. Okay. Now, look at compound 66 in the thesis, Qian's Ph.D. thesis. And that is the same allyl deprotected compound as compound 8 in Qian 1998,

Page 52

correct?

A. Yes. It would seem to be, yes.

Q. And please turn to page 77 of Qian's thesis.

A. I'm there.

Q. Page 77 of Qian's Ph.D thesis provides experimental details for the allyl deprotection of compound 65, correct?

A. It would appear to.

Q. And Qian writes --

A. I haven't read it carefully, but that would appear to be the case.

Q. Qian writes on that page:

"Compound 65 (220 mg, 0.23 mmol) was treated with palladium chloride in the same fashion as described for 17."

That's what Qian writes, correct?

A. That is what is written.

Q. And please turn to page 54 of Qian's thesis. You might want to keep your finger where you were.

A. I'm there.

Q. And please draw your attention to the bottom of the page where you see there are experimental details provided for compound 17. Do you see that?

A. At the bottom of page 54?

Page 53

Q. At the bottom of page 54 there's experimental details for compound 17. Do you see that?
A. Yeah. I don't know what the details are for, but, yeah --
Q. Okay.
A. -- I see some details.
Q. And Qian writes:
"To a solution of 16 (400 mg, 0.39 mmol) in methanol (15 ml) was added palladium chloride (34 mg, 0.19 mmol). The mixture was stirred at room temperature for four hours."
Qian writes that, right?
A. That is written, yes.
Q. Okay. The Qian Ph.D. thesis discloses that the O-allyl deprotection of compound 65 to compound 66 using palladium chloride in methanol at room temperature proceeds for four hours, correct?
A. No, it doesn't report that. The text says "two hours," and I have no reason to believe that's incorrect -- the manuscript from --
Q. I'm asking you about the thesis.
A. Oh, the thesis does not define a time. Not -- I mean, I can look and search more carefully, but I don't see a time.

Page 54

Q. We're -- we're looking at -- maybe we're -- we're on page 54 of this thesis, right? We were looking at compound 17.
A. Oh, I'm sorry. You were referring to compound 17?
Q. Yes.
A. He describes that it was treated in a solution with methanol and palladium chloride that was stirred for four hours.
Q. Okay. So the Qian Ph.D. thesis discloses that the O-allyl deprotection of compound 65 to compound 66 using palladium chloride in methanol at room temperature proceeds for four hours, correct?
MR. ZIMMERMAN: Objection. Mischaracterizes the document.
MR. SCHWARTZ: It doesn't mischaracterize the document.
A. It doesn't say that it was run for four hours. As I said a minute ago, I don't see a time. If you want me to look to see if --
BY MR. SCHWARTZ:
Q. Well, can I just -- we looked at this before. We were -- we were on page 77 of Qian, right, of his thesis?
A. Yes.

Page 55

Q. On page 77 he said "Compound 65" -- and I won't read what's in parens -- "was treated with palladium chloride in the same fashion as described for 17," correct?
A. Yes, that is what is written.
Q. Okay. And for compound 17, the reaction took place at four hours, correct?
A. There is -- there is a time given for reaction 17. There's not a time given for reaction 65.
Q. Right. It says -- it says "in the same fashion as described for 17," correct?
A. He says it was treated with palladium chloride in the same fashion.
Q. Uh-huh.
A. There's no time dependence to treatment with palladium chloride in that sentence.
Q. But he does indicate that it was treated with palladium chloride in the same fashion as described for 17?
MR. ZIMMERMAN: Objection. Asked and answered.
BY MR. SCHWARTZ:
Q. And in 17 he described using palladium chloride for four hours, correct?
MR. ZIMMERMAN: Objection. Asked and

Page 56

answered.
A. In -- he -- he explicitly says four hours for compound 16 to 17 -- sorry, 15 to 16 -- no, wait.
On page 40 -- on page 54 he describes treatment of compound 16 to yield 17 with palladium chloride in methanol. And he then in a separate sentence says it was stirred for four hours.
In a single sentence on page 77, he says, "Compound 65 was treated with palladium chloride in the same fashion as described for 17." I take that to be the concentrations in the methanol. And in the text of the paper where he reports this, it says two hours, and I have no reason to think that that was not the time that he used.
Q. In the thesis he says that he treated with palladium chloride for four hours for 17, which was the same fashion as compound 65, correct?
A. Where you and I are having problems communicating is whether the statement refers to the conditions of the reaction, the mixture of the reagents present, or whether it implies a time. You are reading it as it applies a time; I am not. So that's --
Q. So you're saying that "in the same fashion" to you means everything but the time?
A. It -- to tell you the truth, it's ambiguous.

Page 57

Someone should have edited this and told him to put in the time.

Q. Okay. So again, I want to get your testimony correct. So you're reading this thesis as saying that when Qian said that he did it, the reaction for compound 17, the same way as compound 65, your interpretation of that is that he means everything except for the four hours that he explicitly states for 17, correct?

MR. ZIMMERMAN: Objection. Mischaracterizes the document.

A. What I read that as is his treatment with palladium chloride refers to the -- the -- the amount of the palladium chloride and the -- and the methanol and the temperature. Those are all things that chemists would refer to conditions.

Could they refer to time as a condition? Sure. Maybe. It -- it -- it just leaves it ambiguous.

BY MR. SCHWARTZ:

Q. So a person of ordinary skill reading that thesis could understand that he treated it for four hours, correct?

A. I think a person of ordinary skill in the art would not have known, because it's simply not stated.

Q. But they could have understood it to mean four hours?

Page 58

MR. ZIMMERMAN: Objection. Asked and answered.

A. I think they would not have known. I see no -- I see no reason to assume the time of the treatment was the same. I mean, it's just ambiguous. I don't know -- I can't interpret how someone would have interpreted something that's ambiguous.

BY MR. SCHWARTZ:

Q. So "in the same fashion" to you means it is ambiguous?

A. No. "In the same fashion" describes the treatment, the -- so when a chemist talks about reaction conditions, what they're talking about is the catalyst added, the solvent, the ligands that are added. You let that reaction go, and you monitor it for time typically, and then find -- when the reaction is complete, you would -- you would quench it and purify it. It is -- it's ambiguous and a little odd that he didn't put the time.

Q. That he didn't put the time?

A. That he seems to not to have -- I mean, I haven't read this carefully, but he seems not to have included the time.

Q. He did for compound 17, correct?

A. Yeah. That's not what I was talking about.

Page 59

Q. Okay. For compound 17, he says four hours?

A. That is -- that is correct.

Q. And then for compound 65, he says it was treated in the same fashion as described for 17, correct?

MR. ZIMMERMAN: Objection. Asked and answered, twice.

BY MR. SCHWARTZ:

Q. Does he say that?

A. He says that he describes the reaction conditions for the solution. And he gives how much methanol and how much palladium chloride was used, the molar equivalents and their weights. And then he says that that mixture was stirred at room temperature for four hours.

I do -- that is not -- implicit in the statement of the conditions being the same is not how long the reaction was stirred.

Q. Okay. We've already established that compound 65 and 66 in Qian's thesis are the same as compound 7 and 8 in Qian's 1998 paper, correct?

A. That is correct.

Q. Okay. Please turn to page 77 of Qian's thesis.

A. Page 77?

Page 60

Q. Yes, please.

A. I'm there.

Q. And starting at the third line Qian writes:

"Compound 65 (220 mg" --

A. I'm sorry. Page 77? On the third line? Oh, compound -- sorry. Could you start again?

Q. All right.

"Compound 65 (220 mg, 0.23 mmol) was treated with palladium chloride in the same fashion as described for 17. Purification by column chromatography (4:1 hexanes/EtOAc) gave 66 (202 mg, 96%) pass a whit solid."

And I believe "white" may have a typo. It doesn't have the E at the end.

A. That is correct.

Q. That's what Qian writes, correct?

A. That's correct.

Q. Qian is reporting that the allyl deprotection that results in compound 66 occurs at a 96 percent yield, correct?

A. No.

Q. Why?

A. He reports that it was purified at 9 -- that

Page 61

after purification he recovered 96 percent. There's inevitably loss during the recovery process.

Q. Okay. I would like to mark another paper.

A. Are we done with this one? We're just building up a lot of open documents.

Q. I think so, yes.

I'm putting in front of you a document entitled --

A. I'm sorry. One second.

Q. Let me just say that this was marked as Exhibit 2097.

(Exhibit 2097 marked for identification by the Certified Shorthand Reporter.)

A. Okay. Sorry. What?

BY MR. SCHWARTZ:

Q. So I just put in front of you a document that was marked as Exhibit 2097, and it's a paper entitled Chemoenzymatic Synthesis of alpha 1 - 3 Gal(NAc) Terminating Glycosides of Complex Tertiary Sugar Alcohols by Qian, et al. that was published in 1999.

Both the Qian 1998 and the Qian 1999 papers list Xiangping Qian as the first author, correct?

A. They do.

Q. In fact, three of the four authors of Qian

Page 62

1998 are also authors of Qian 1999, correct?

A. There are names -- I'm having trouble reading the names. There are four authors on the '98 paper, and let's see. This one is on it. Monica Palcic. Three of the four in the '98 paper seem to be on the '99 paper.

Q. Please go to page 12065 of Qian 1999. And please draw your attention to Scheme 2 on the top of the page. Scheme 2 shows an allyl deprotection in reaction E, correct?

A. That's correct.

Q. And Qian 1999 reports that the allyl deprotection in Scheme 2 of Qian 1999 used palladium chloride in methanol, correct?

A. Sorry. Could you repeat that question?

Q. Qian 1999 reports that the allyl deprotection in Scheme 2 of that paper used palladium chloride in methanol, correct?

A. Can you give me a minute to look at this? I haven't read this paper.

Q. I think if you look at the legend of Scheme 2.

A. Yeah, that's where I'm looking. That is correct.

Q. And please turn to page 12069 of Qian 1999. And draw your attention to the right side of the page where there's an entry for -- and I won't read the whole

Page 63

thing. It starts with "Octyl 2,4, 6 Tri-O-benzyl."

Do you see that on the top right?

A. They actually all start that way on the right.

Q. Sorry. It's the first full one, "Octyl 2, 4, 6 Tri-O-benzyl beta D" --

A. The one that ends with compound 9?

Q. Correct.

A. Yeah, I see it.

Q. The allyl deprotection reaction in Scheme 2 is done at room temperature, correct?

A. In the 1999 paper?

Q. Yes.

A. I don't see a temperature.

Q. Well, in that section we just read, I didn't read the whole thing, but the one that ended in compound 9, if you continue reading it -- I won't read it into the record -- do you see where it says "at room temperature for four hours"?

A. Yes.

Q. So that that reaction was done at room temperature, correct?

A. That is what is written.

Q. Okay. So please go back to the Qian 1998 paper. And again, draw your attention to Scheme 2. And the allyl deprotection reaction in Scheme 2 in Qian 1998

Page 64

is also done using palladium chloride in methanol at room temperature, correct?

A. That's correct.

Q. All right. So going back to the Qian 1999 paper, and looking again at Scheme 2, step E, Qian reports that the allyl deprotection yield is 83 percent after four hours, correct?

A. In the 1999 paper, the deprotection of allyl is listed palladium chloride in methanol for four hours, 83 percent.

(Court reporter clarification.)

A. In methanol for four hours, 83 percent.

Q. So POSA in October 2000, having read Qian 1998 and Qian 1999, understood that the allyl deprotection using Qian's deprotection chemistry varies between 96 percent and 83 percent?

A. No. That's not what I said.

I would have -- between 83 percent and 96 percent isolated yield. If you want to use the 96 percent, the isolated yield was 96 percent, that is correct.

Q. Okay. So it varies between 96 percent isolated yield and 83 percent?

A. Yeah. I'm not sure of the 83 percent, whether it was an isolated yield or an in situ yield. I'm not

Page 65

sure. I haven't read the paper.
Q. Okay. But it reports it as 83 percent?
A. Yes. In the figure caption, it reports it as 83 percent.
Q. And the reaction -- the allyl deprotection Scheme 2 in Qian's allyl deprotection in Qian 1999 takes place for four hours, correct?
A. That is what it says, yes.
MR. SCHWARTZ: I guess it's just been pointed out to me that, at least in LiveNote, there's a mistake at line 14 -- or time 14:18:33. It says: You want to use Ju's to 96 percent. And I think it was "if you want to use." If you want to use. So you have "Ju" when he said "use," I believe.
Do we agree?
MR. ZIMMERMAN: Yes. Thank you.
THE WITNESS: There's no action item there for me, right?
MR. ZIMMERMAN: No.
BY MR. SCHWARTZ:
Q. I'm going to put in front of you an exhibit that's been marked as Exhibit 2054.
(Exhibit 2054 marked for identification by the Certified Shorthand Reporter.)

Page 66

BY MR. SCHWARTZ:
Q. Which is a paper entitled A Sequencing Method Based on Real-Time Pyrophosphate by Ronaghi, et al. It was published in 1998.
Please draw your attention to the second paragraph on the first page of the paper, which is page 363. And the authors write:
"Sequencing-by-synthesis is based on the detecting of nucleotide incorporation, using a primer-directed polymerase extension. The sequence can be deduced iteratively. During the last decade, many researchers, including the groups of Rosenthal, Gibbs and Jones, described various protocols based on fluorescently labeled nucleotides."
That's what the authors write, correct?
A. Yeah, that is what's written.
Q. And so -- and then they continue to write, the authors continue to write:
"The level of incorporation of these fluorescent nucleotides is low. However, as shown by Metzker,

Page 67

et al." -- citing to reference 7 -- "and therefore, the protocols only permit detection of a few bases."
MR. ZIMMERMAN: I just want to object that it mischaracterizes the document. I don't know if your version is different, but mine has boxes and never an F.
MR. SCHWARTZ: I agree. It does have a box there, but --
MR. ZIMMERMAN: Throughout the document. Everything you're reading as an F is a box.
BY MR. SCHWARTZ:
Q. Okay. Would one understand that to be for the word "fluorescent"?
A. Is that a question for me?
Q. Yes.
A. Yes.
Q. Okay. And would you take a look at reference 7. And reference 7 is the Metzker 1994 paper, correct?
A. Correct.
Q. The Ronaghi authors state that Metzker's 1994 nucleotides have low levels of incorporation. That's what they say, right?
A. That is what is written.
Q. And the Ronaghi 1998 authors do not say anything in their paper -- and you can read it, the

Page 68

whole thing if you want -- that they believe that Metzker's 1994 experiments were flawed. They don't say that, do they?
A. I have -- I have -- I have read this paper. It has been a while. And I did not read it from that perspective. I would be very sur- -- let me put it this way. If they would have called that out, I would have remembered it, so I don't think they do.
Q. So despite the fact that Metzker 1994 reported in that paper that there was a small amount of contaminating dATP in each of the 3' O protected amine nucleotides, the authors of Ronaghi 1998 still relied on that paper to draw conclusions about what the prior art taught, correct?
A. It's -- it's a little difficult to answer that question, because they are not writing this in a legal document. They're writing this in a paper where they're trying to promote their technique. This is common in science. You try to highlight your work as being superior to others.
It is certainly true that any 3' protected nucleotide is not going to go in as efficiently as an unprotected natural nucleotide. No doubt about that.
They're -- and what they are trying to emphasize in that statement is that they're using

Page 69

natural triphosphates. That's what anyone who would have read this would have read, that, boy, that's neat because they don't have to use modified nucleotides.

Q. They do state expressly that the level of incorporation of the nucleotides is low when they refer to the Metzker 1994 paper, correct?

MR. ZIMMERMAN: Objection. Asked and answered.

A. No one would read that with any knowledge of what low meant. It's not wild type. Everyone would have read that knowing that it wasn't as efficient as a natural. Everyone would have read this. And this is no doubt what the authors expect -- were intending, to emphasize the use of their unmodified triphosphates, which are incorporated faster. No doubt.

BY MR. SCHWARTZ:

Q. Okay. And so the authors of the Ronaghi paper were able to make those interpretations of the Metzker 1994 paper despite the fact that it had small amounts of contaminating dATP, correct?

A. They made these statements. The paper that Metzker published, the experiments reported had those contaminating amounts of ATP. So what you're stating is factually true. It's written there. And that doesn't change the fact that the Metzker experiments had the

Page 70

contaminating dATP. So what you're saying is by definition true.

Q. I think my question was, is that the authors of Ronaghi 1998 made statements about Metzker 1994, including the fact that the incorporation of the nucleotides was low, but didn't say anything about the fact that those -- those results were skewed by contaminating dATP, correct?

A. That is factually correct. They write that, and they do not cite the contaminating dATP.

Q. And Michael Metzker is not one of the authors of Ronaghi 1998, correct?

A. He is not.

Q. And none of the authors of Ronaghi 1998 indicate any affiliation with Dr. Metzker's lab, correct?

A. Not that I know of.

Q. And are you aware that Dr. Ronaghi is the chief technology officer and senior vice president of Illumina?

A. I was not aware of that.

Q. I'm going to switch subjects now. And I'm going to ask you some questions about allyl ether deprotection and palladium.

Before I hand out the article -- that's okay.

Page 71

It's all right that you have it.

I just wanted to ask the -- the question. It is your opinion that the allyl deprotection scheme that's reported in Qian 1998, which was Exhibit 1036, which uses palladium chloride in methanol, could be modified so that it would work the same under aqueous conditions as reported in Qian 1998, correct?

A. I don't exactly recall saying that, and that seems like a little bit of an aggressive statement to say. I think that a person of ordinary skill in the art would have known that there were standard methods to get a palladium chloride reaction of any sort into aqueous environments that would have been compatible with DNA stability and all the requirements for sequencing by synthesis. They would have had the expectation, based on the literature, that the yields might have been quantitative, but they would not have known that.

So just to be clear, I didn't mean to testify that they would have known that the reaction would have been the same as reported in the 1998 paper in a different environment. That would have required checking.

Q. So if I understand your testimony, a skilled artist in October 2000 wouldn't have known from the Qian 1998 paper that they would get quantitative yield of

Page 72

allyl deprotection using Qian's conditions except under aqueous conditions; is that --

A. Because they were modifying the conditions, they would have had an expectation of success based on the Qian report. But would they have known? No one can predict the future. So they would have had to run the experiment.

I don't mean to be trite by that. Small differences can have impact. So they would have -- they would have run the experiment.

Q. Okay. I'm going to put in front of you a paper that's been marked Exhibit 2105.

(Exhibit 2105 marked for identification by the Certified Shorthand Reporter.)

BY MR. SCHWARTZ:

Q. And it's a paper entitled Isomerization and Cleavage of Allyl Ethers of Carbohydrates By Trans-[Pd(NH3) 2 Cl2] by Bieg and Szeja. That was published in 1985.

And please go to the first page of Bieg, page 441. And Bieg writes:

"Allyl ethers are widely used for the 'temporary' protection of hydroxy groups in carbohydrates.

Page 73

The allyl group is conveniently removed by isomerization and subsequent cleavage of the labile prop-1-enyl group."
That's what Bieg writes, correct?
A. That's correct, yes.
Q. And a POSA reading Bieg understood that the deprotection of allyl ethers occurs in two steps where the first step converts the allyl ether to an enyl ether followed by a second step that converts the enyl ether to the alcohol, correct?
A. I don't know if that's correct. These reactions are complex. There are different variants of them. One's called Tsuji-Trost, for example.
(Court reporter clarification.)
A. Tsuji-Trost. I think T-S-U-G-I [sic] dash T-R-O-A-S-T [sic], I think.
If you want to make statements about the mechanism of these reactions, you -- and people do this all the time, and they are in papers where people study the mechanisms, so that is a viable mechanism. It is one of a variety -- one of a couple that are -- that these reactions can precede through.
Q. Okay. But just focusing on this paper, this paper specifically teaches that the -- "the allyl group

Page 74

is removed by isomerization of subsequent cleavage of the labile prop-1-enyl group?
A. It does say that.
Q. Okay. So that in this paper, the authors of this paper teach that the deprotection occurs in two steps, first, conversion to an enyl ether, followed by conversion of the enyl ether to alcohol. That's what they teach in this paper, right?
A. That is what it says.
Q. And please look down from where we were reading in Bieg to the middle of the first page where there is a sentence that starts with "Prop-1-enyl ethers." Do you see that?
A. I do.
Q. And Bieg writes:
"Prop-1-enyl ethers are readily cleaved under acidic conditions ..."
Do you see that?
A. I do.
Q. And a POSA in 2000 reading Bieg understood that an enyl ether produced under acidic conditions would cleave to produce an alcohol in a carbonyl compound, correct?
A. That's a hard question. If there's -- I would have to read this and see exactly what he's talking

Page 75

about, but enyl ethers are stable, in general. In acid they may not -- I mean, they are certainly going to isomerize. I would have to think this mechanism through carefully to make sure that I didn't misspeak.
Q. But a person reading this paper -- so my question was, a person reading this paper in 2000 would understand that Bieg is teaching that an enyl ether produced under acidic conditions would cleave to produce an alcohol in a carbonyl compound, correct?
A. Where does he say that? I see where he says propine 1 -- prop-1-enyl ether are -- ethers are readily cleaved under acidic conditions, ozonolysis followed by alkaline hydrolysis, reaction with alkaline, permanganate solution, or treatment with chloride ... is that what you're talking about?
Q. I'm talking about he says earlier when we read isomerization and subsequent cleavage. So the isomerization would result in the carbonyl, correct?
A. No. The isomerization results in the enyl ether, I think. And that then hydrolyzed -- I mean, these mechanisms are complex. I would have to sit down and, you know, draw out exactly what he's thinking about here.
I mean, the way it usually happens is a palladium chelates to the double bond of the enyl

Page 76

ether -- of the allyl and then isomerizes to where the palladium is palladium on the internal -- where a water or a nucleophile attacks the least hindered carbon and then you eliminate, and what's that produce? That produces -- can I write that down?
Q. Yes.
A. Let's see. I don't think it produces a carbonyl group. I might be missing something, but -- despite what he's talking about, just an allyl group deprotection by isomerization and cleavage. I don't think there's a carbonyl group that ever appears there.
You're asking me a bit on the spot, and so I hope I'm getting this right, but I think I am. It produces an alcohol.
Q. Is a --
MR. SCHWARTZ: Just give me a second here.
BY MR. SCHWARTZ:
Q. So what happens to enyl ethers in water and acid?
A. An enyl ether will -- it will tautomerize to a ketone. It's an enyl ether -- yeah.
Q. Okay. I'm going to put another paper in front of you.
///
///

Page 77

(Exhibit 2098 marked for identification by the Certified Shorthand Reporter.)

MR. SCHWARTZ: This has been marked as Exhibit 2098.

MR. ZIMMERMAN: Marked as what number?

MR. SCHWARTZ: 2098.

BY MR. SCHWARTZ:

Q. And I've just put in front of you a paper entitled Complete Reverse Regioselection in Wacker Oxidation of Acetonides and Cyclic Carbonates of Allylic Diols by Kang, et al., published in 1995.

And please refer to footnote 6 on the first page of the paper. And are you looking at footnote 6?

A. I am.

Q. Looking at the reaction there as drawn. The compound on the left side of the equation in footnote 6 where R is OBn or O-MOM is an allyl ether, correct?

A. Yeah. It's a substituted allyl ether, yes.

Q. The catalyst used in the first reaction in that footnote is palladium chloride, correct?

A. Yes.

Q. And the solvent used in that first reaction in footnote 6 contains water, correct?

A. It is DMF water, yes.

Page 78

Q. And the reaction produced two products, one of which is an alpha alkoxy ketone, correct?

A. Alpha alkoxy -- alpha alkoxy, yep.

Q. And the other product is a beta alkoxy aldehyde, correct?

A. Yep.

Q. And so a person of ordinary skill in 2000 reading Kang, et al. in 1995, which is Exhibit 2098, understood that when Kang used water and palladium chloride with allyl ethers, they got oxidized products and not enyl ethers or alcohols, correct?

MR. ZIMMERMAN: Objection. Mischaracterizes.

A. I haven't read this. What you're showing me is a Wack -- I believe is a Wacker oxidation, and you are -- they are showing the production of -- of an alpha ketone and a beta aldehyde.

BY MR. SCHWARTZ:

Q. But not enyl ethers or alcohols, correct?

A. That's right. I mean, this is kind of what I meant where the mechanisms can be complex. This is a different mechanism than -- all palladium mechanisms are not the same.

MR. SCHWARTZ: Again, it's being pointed out to me, for the court reporter, that in my question which was: A person of ordinary skill in 2000, it reads 2003.

Page 79

I'm sure I didn't ask you a person of ordinary skill in 2003.

Do we agree that I meant 2000? It should have said 2000?

MR. ZIMMERMAN: Yes.

That doesn't change your answer, does it?

THE WITNESS: No.

BY MR. SCHWARTZ:

Q. Okay. I'm putting in front of you a new exhibit. And it's Exhibit 1023, which is a paper entitled Syntheses of Nucleosides Designed for Combinatorial DNA Sequencing by Welch, et al. that was published in 1999.

(Exhibit 1023 marked for identification by the Certified Shorthand Reporter.)

BY MR. SCHWARTZ:

Q. Please turn to page 952. And please draw your attention to the left side of the page and, in particular, to the first full paragraph that starts with "Our group and others."

Do you see that?

A. I do.

Q. And the authors write:

"Our group and others have been exploring another way to facilitate parallel analyses of multiple samples in an array without gel electrophoresis."

And they refer to references 38 to 43.

"We call this the Base Addition Sequencing ... or BASS."

That's what the authors write, correct?

A. They call it the Base Additional Sequencing Scheme or BASS, yes.

Q. And the authors cite to reference 38 to 43 to support their statement, correct?

A. In the preceding sentence they cite -- reference 38 to 43, yes.

Q. And please turn to the references page. And I just want to confirm with you that reference 38 is the Metzker 1994 paper.

A. It appears to be, yes.

Q. Okay. Now, please turn to page 956 of the Welch paper. And please draw your attention to the left side of the page where on the top of the page there's a section entitled Conclusions.

Do you see that?

A. I do.

Q. Please draw your attention to line -- to six

Page 81

lines down in the "Conclusions" section where there is a sentence that starts with "It seems clear that modifications." Do you see that?

A. I do.

Q. And the authors write:

[As read.]

"It seems clear that modifications to the polymerase enzyme, as well as to the nucleotide [sic] triphosphate are required if BASS is to be developed into a viable sequencing scheme."

MR. ZIMMERMAN: Objection. Mischaracterizes the document.

MR. SCHWARTZ: How does it mischaracterize the document?

MR. ZIMMERMAN: You didn't read the sentence correctly.

MR. SCHWARTZ: Let me read it again.

BY MR. SCHWARTZ:

Q. "It seems clear that modifications to the polymerase enzyme as well as to the nucleoside triphosphate are required if BASS is to be developed into a viable sequencing scheme."

Page 82

Is that correct? That's what the authors, write, correct?

A. That is what the authors write, yes.

Q. And the BASS sequencing scheme is what was later called SBS, correct?

A. I don't know whether it was also concurrently called SBS or not, but it is certainly today, as I understand BASS, it is -- I believe that is sequencing by synthesis. I mean, it's obviously very early.

Q. So a person of ordinary skill in October 2000, reading the Welch 1999 paper, understood that modifications to the polymerase enzyme as well as to the nucleoside triphosphate are required if BASS is to be developed into a viable sequencing scheme, correct?

A. That is not how I would read that sentence. Nor do I think a person of ordinary skill in the art would. Look, this is a conclusion. They're speculating. It seems clear as code for hey, maybe.

Q. It actually directly states what I read, though, right?

A. I'm telling you how a person of ordinary skill in the art would have read that. Science is just not like law like this. Just every sentence, every word doesn't mean some legal thing.

I'm telling you in the "Conclusions" section,

Page 83

what that sentence reads is they're speculating about what future progress would have to be accomplished, speculating, to -- to achieve that goal.

Q. Okay. So -- and you're suggesting that a person of ordinary skill in 2000, reading those "Conclusions," would speculate that modifications to the polymerase enzyme as well as to the nucleoside triphosphate are required if BASS is to be developed into a viable sequencing scheme. Is that what you're saying?

A. No. I'm saying -- I'm saying this paper is speculating about that.

Q. So when it says "it seems clear that," you're saying that a POSA would read that as pure speculation?

A. I would have to read this whole paper. In a conclusion section like this, a statement that -- that -- I mean, it's such a forward-looking statement that -- if you want me to read it more carefully and -- if this -- if this paper is about polymerase mutants, maybe, but it just -- it -- it is much more typical a sentence like that in the position that it's located in this "Conclusion" is just a forward-looking speculative statement.

Q. But the reader would see that it says "it seems clear that," correct? The authors are saying "it

Page 84

seems clear that." That's what they're saying, isn't it?

MR. ZIMMERMAN: Objection. Compound.

A. No. No, that's not what they're saying. I mean, those are the words written there, yes. Those words are written there.

BY MR. SCHWARTZ:

Q. And those authors wrote those words five years after the Metzker 1994 paper was published, correct?

A. This paper was written in 1999. The Metzker paper was -- that you're referring to was written in 1994.

Q. Okay. I'm going to put in front of you -- I'm just looking at the time. I'm putting in front of you a document that carries Exhibit No. 2099.

(Exhibit 2099 marked for identification by the Certified Shorthand Reporter.)

MR. ZIMMERMAN: Have these been previously marked? Because, again, my copy isn't marked.

MR. SCHWARTZ: We just marked one copy.

MR. ZIMMERMAN: Okay.

BY MR. SCHWARTZ:

Q. I'm putting in front of you U.S. Patent No. 5,858,671 to Jones. Please turn to Column 2.

Page 85

A. Have I read this? Have I seen this before?
Q. Have you?
A. I don't recall seeing this before.
Q. Okay.
A. Have I testified from this? Have I cited this in any of my writings?
Q. I'm really not here to be asked questions, so you have to -- these are things that you need to be thinking about.
MR. ZIMMERMAN: If it's not something you've seen, take as much time as you need to review it.
THE WITNESS: Yeah. Thanks.
BY MR. SCHWARTZ:
Q. Please turn to Column 2. And please look at line 21 where there is a paragraph that starts with "The base addition DNA sequencing scheme." Do you see that?
A. I do.
Q. And Jones writes:
"The base addition DNA sequencing scheme uses fluorescently labeled reversible terminators of polymerase extension, with a distinct and removable fluorescent label for each of the four ... analogs."
And there's a citation to Metzker 1994.

Page 86

Correct?
MR. ZIMMERMAN: Objection. Mischaracterizes the document.
MR. SCHWARTZ: You left out the word "nucleotide" in front of "analogs."
BY MR. SCHWARTZ:
Q. Okay. With the word "nucleotide" in front of the word "analogs," that's what Jones writes, and he refers to Metzker, et al. 1994, correct?
A. That seems to be what's written.
Q. And the Metzker, et al. 1994 paper cited by Jones is the same Metzker 1994 paper that's in your declaration, correct?
A. It would seem to be.
Q. And please look down a few lines to line 37. There's a sentence that starts with "A fundamental." Do you see that?
A. I do.
Q. And Jones writes:
"A fundamental limitation to this approach is inherent in iterative methods that sequence consecutive nucleotides. That is, in order to sequence more than a handful of nucleotides, each cycle of analog

Page 87

incorporation and deprotection must approach 100 percent efficiency. Even if the base addition sequencing scheme is refined so that each cycle occurs at 95 percent efficiency, one will have less than 75 percent of the product of interest after only six cycles (0.956 = 0.735). This will severely limit the ability of this method to sequence anything but very short DNA sequences. Only one cycle of template-directed analog incorporation and deprotection appears to have been demonstrated so far."
And there is a citation to Metzker 1994.
Do you see that?
A. I do.
Q. And again, the Metzker 1994 paper cited by Jones is the same to Metzker 1994 paper as in your declaration, correct?
A. It seems to be.
Q. And the approach that Jones is referring to when he states that there is a fundamental limitation to this approach, that's SBS he's referring to, correct?

Page 88

A. It would seem to be. I -- I don't recall reading this document, so I'm not 100 percent certain, but it would seem to be. He opens the paragraph by saying "The base addition DNA sequencing scheme." That sounds like sequencing by synthesis.
Q. So a POSA in 2000 reading Jones understood that, as Jones teaches, "In order to sequence more than a handful of nucleotides using the SBS method, each cycle of analog incorporation and deprotection must approach 100 percent efficiency," correct?
A. Sequence more than a handful, is that what you said?
Q. In order -- I'm just reading from what Jones is saying. So a person of ordinary skill reading Jones in October of 2000 understood that in order to sequence more than a handful of nucleotides using the SBS method --
A. That is what Jones writes. That is what's written there.
Q. And a POSA in 2000 reading Jones understood that if each cycle of SBS occurs at 95 percent efficiency, one will have less than 75 percent of the product of interest after only six cycles, correct?
A. That is what is written, and I believe that is correct.

Page 89

Q. And Jones writes that that "will severely limit the ability of this method to sequence anything but very short DNA sequences." A POSA understood that from reading Jones as well, correct?
A. That is certainly what is written.
Q. And if you'd turn to the front page of the Jones patent and you look at the top right corner where there's a date of patent, the patent issued in January 1999, correct?
A. That is correct.
Q. And so a POSA in 2000 reading Jones understood that at least as of January 1999, when Jones issued as a patent, there had been only one cycle of template-directed analog incorporation and deprotection actually demonstrated for SBS, correct?
MR. ZIMMERMAN: Objection. Mischaracterizes.
A. I think they would have read that Jones says something like there appears to have been.
BY MR. SCHWARTZ:
Q. And as support for that statement, Jones refers to the Metzker 1994 paper, correct?
A. Again, I don't recall reading this, but he must be referring -- that must be what he's referring to as the demonstration of a single nucleotide incorporation.

Page 90

Q. And the demonstration of a single nucleotide incorporation in Metzker 1994 was for the two nitrobenzyl capped nucleotide, correct?
A. Again, I don't know for sure that that's what he's referring to here, but that is -- if he's referring to Metzker for the demonstration of a single nucleotide incorporation, then that I believe would be referring to the nitrobenzyl case.
Q. Metzker 1994 did not demonstrate one cycle of template-directed analog incorporation and deprotection using an allyl capped nucleotide, correct?
A. That is correct.
Q. And Jones did not say anything, when he refers to the Metzker 1994 paper, he didn't say anything about Metzker's experiments being tainted by the presence of a small amount of contaminating dATP, correct?
A. I haven't -- don't recall reading his patent, so I can't --
Q. In the portion we read.
A. In the portion --
Q. Is it fair to say in the portion we read he doesn't say anything about the Metzker 1994 experiments being tainted by the presence of a small amount of contaminating dATP?
A. In the portion we read, I did not see that.

Page 91

Q. And there's no indication on the face of the Jones patent that Jones had any affiliation with Michael Metzker or the Metzker lab, correct?
A. I have no idea.
Q. I'm just saying on the face of the patent.
A. Do you want me to read the entire front page?
Q. Well, just -- you can read the title, the inventor, and the assignee. Do you see anything in there that suggests that there's any relationship to Michael Metzker or his lab?
A. Not that I see.
Q. Okay.
MR. ZIMMERMAN: Is now a good time for a break? We've been going about an hour.
MR. SCHWARTZ: Sure.
THE VIDEOGRAPHER: Going off the record at 2:56 p.m.
(Recess taken from 2:56 p.m. to 3:17 p.m.)
THE VIDEOGRAPHER: We are back on the record at 3:17 p.m.
BY MR. SCHWARTZ:
Q. And, Dr. Romesberg, thank you very much for the cup of coffee.
Did you speak to your attorneys during your

Page 92

break about anything relating to this deposition?
A. No.
Q. I'm going to put a new document in front of you. It's going to be marked as a new exhibit, 2100.
(Exhibit 2100 marked for identification by the Certified Shorthand Reporter.)
BY MR. SCHWARTZ:
Q. I just put in front of you U.S. Patent No. 6,013,445, to Albrecht, et al. And please turn to Column 1. And please look at line 40.
Do you see there's a sentence that starts with "As an alternative to the Sanger-based approaches"? Do you see that, where it starts?
A. Sorry. Column 1?
Q. Column 1, around line 40. Do you see where it starts out --
A. Yes.
Q. -- "As an alternative"?
Albrecht writes:
"As an alternative to the Sanger-based approaches to DNA sequencing, several so-called 'base-by-base' or 'single base' sequencing approaches have been

Page 93

explored ..."
And if you follow that sentence down a few lines, there's a citation to Metzker, et al. 1994.
Do you see that?
A. I do.
Q. And the Metzker, et al. 1994 paper cited by Albrecht here is the same Metzker 1994 paper that is in your declaration, correct?
A. It is Metzker 1994. I -- I don't have a reference list with any more information. I don't know of any other paper he published, so it would seem to be, yeah.
Q. Please go to line 57 of Column 1. And there's a paragraph that begins with "unfortunately."
Do you see that?
A. I do.
Q. Albrecht writes:
"Unfortunately, 'base-by-base' sequencing schemes have not had widespread application because of numerous problems, such as inefficient chemistries which prevent determination of any more than a few nucleotides in a complete sequencing operation."

Page 94

That's what's written in Albrecht, right?
A. That is correct.
Q. And again, another name for the base-by-base sequencing scheme referred to by Albrecht would be SBS, correct?
A. I suspect so. I don't see a definition exactly, but it probably is. My -- I would guess that it is.
Q. Okay. And if you'd turn to the front page of Albrecht and you look at the top right corner, there's an issue date of the patent of January 11th, 2000.
Do you see that?
A. I do.
Q. So a POSA in 2000 reading Albrecht understood that, at least as of January 2000 when the Albrecht patent issued, SBS has problems such as inefficient chemistries which prevent determination of any more than a few nucleotides in a complete sequencing operation, correct?
A. That is what this patent reads.
Q. And one of the papers that Albrecht cites in reaching that conclusion is Metzker 1994, correct?
A. I'd have to reexamine that. He -- he doesn't seem to cite Metzker on the spot where he says "Unfortunately, base-by-base sequencing schemes have not

Page 95

received widespread application." That part that I think you're referring to, he doesn't cite Metzker there. He cites it above where he's just introducing so-called base-by-base or single base sequencing approaches have been explored. And then he lists several of which we're pretty all familiar with, including Tsien and Metzker.
Q. Right.
And then he goes on to say, talking still about base-by-base sequencing schemes, and the reference is that he relies on for base-by-base sequencing schemes are above, and that includes Metzker, correct?
A. It -- Metzker is included in the group of citations that are general to the base-by-base. The -- "unfortunately, the base-by-base sequencing schemes have not received widespread application" is a bit narrower of a statement. He doesn't provide any other reference.
So the only thing -- the only references that anyone would have up to this point for sequencing by synthesis were the ones at the introductory level.
Q. Okay. Please go back to Column 1, and just after the portion of the spec that we just read at line 61, there's a sentence that begins with "Moreover, in base-by-base." Do you see that?
A. I do.

Page 96

Q. Albrecht writes:
"Moreover, in base-by-base approaches that requires enzymatic manipulations, further problems arise with instrumentation used for automated processing."
And I'm going to ask you to skip to Column 2 at line 1. And in the first full sentence on line 1 Albrecht writes:
"The accumulation of protein" -- excuse me. [As read.]
"The accumulation of protein also affects molecular reporter systems, particularly those employing fluorescent labels, and renders the interpretation of measurements based on such systems difficult and inconvenient. These and other [sic] difficulties have significantly slowed the application of 'base-by-base' sequencing schemes to parallel sequencing efforts."
And it's been pointed out to me that I should have said:
"These and similar difficulties

Page 97

have significantly slowed the application of 'base-by-base' sequencing schemes to parallel sequencing efforts."

A. That's what it says.

Q. And so a POSA in 2000, reading the portions of the Albrecht patent specification that we just looked at, understood that in addition to inefficient chemistries which prevent determination of any more than a few nucleotides in a complete sequencing operation, there were additional technical hurdles to successfully practice SBS that had yet to be solved as of January 2000 when the Albrecht patent issued, correct?

A. That is what it says.

Q. And of these technical issues that Albrecht teaches was yet to be solved as of January 2000 is the accumulation of protein, which renders interpretation of the SBS output difficult, particularly when the nucleotides have fluorescent labels.

That's what he teaches, correct?

A. That is what's written.

Q. And if you would go back to the '985 patent, the patent at issue in this case, it was marked as Exhibit 1075. You may not need to look at it. If you -- I'm just going to ask you that the SBS method

Page 98

claimed in the '985 patent uses nucleotides with fluorescent labels, correct?

A. Yes.

MR. SCHWARTZ: I'm going to mark another exhibit. This is being marked as Exhibit 2103.

(Exhibit 2103 marked for identification by the Certified Shorthand Reporter.)

BY MR. SCHWARTZ:

Q. I'm putting in front of you -- excuse me for a second. I'm putting in front of you a document entitled Project Information 1R21HG003977-01.

Exhibit 2103 relates to a grant proposal you submitted to the National Human Genome Research Institute that was awarded to you in 2006, correct?

A. Ah, yeah, I think so.

Q. And if you look at the top left of Exhibit 2103, it indicates that the title of your grant is Evolving Novel Polymerases for Genome Sequencing; is that correct?

A. Yes, that is correct.

Q. That's what it says?

A. Just to be clear, I'm not sure that this grant was funded. I don't remember. Are you saying that it was? In fact, I think it was not.

Page 99

Q. It says that the award notice date was the 18th of May 2006. So you received an award notice?

A. I think this was not funded. Special Emphasis Panel. Yeah, I'm virtually certain this was not funded. Yeah, an award notice, I think, is just a generic name. I'm not sure, but I guess I should -- it might have been funded. To be honest, I'm not sure.

I certainly wrote this grant.

Q. Okay. It does state that it was -- you received an award notice on 18th of May 2006, and it gives a project start and end date, correct?

A. Yeah, I think -- I think this must have been funded.

Q. Okay. I'm going to mark another exhibit.

(Exhibit 2104 marked for identification by the Certified Shorthand Reporter.)

BY MR. SCHWARTZ:

Q. This exhibit is going to carry the number 2104.

A. Yeah, I think it must have been not funded and then funded, because it gives a project history.

Q. So it's your recollection that this project information sheet refers to a funded project?

A. I'm not 100 percent certain, but I think so.

Page 100

I apologize. I've had a lot of grants come and go.

Q. Me too.

So I just put in front of you Exhibit 2104 -- oh, I'm putting in front of you another exhibit.

Did I give it to you? I'm sorry. You've got me confused now about where we were. Exhibit 2104, and that's a document entitled Helicos and Columbia to Test Scripps' Improved Polymerases for Next Generation Sequencing. And it was published in Genome Web News on October 3rd, 2006.

And you're the same Floyd Romesberg as is being quoted in Exhibit 2104, correct?

A. Yeah. I -- I do not recall this at all, but, yeah, this would appear to be me.

Q. And please go to the second-to-last paragraph on the first page that begins with "Romesberg, this spring." Do you see that?

A. I do.

Q. And it says -- the article reads:

"Romesberg, this spring, won a two-year grant from the National Human Genome Research Institute entitled 'Evolving Novel Polymerases for Genome Sequencing,' he will work with Helicos, Ju's group, and

Page 101

Scripps' sequencing facility to test polymerases with novel properties in actual sequencing settings."

And again, you're the Romesberg that's being referred to in this exhibit, correct?

A. Yeah, that's right.

Q. And does this refresh your recollection that that patent was funded?

A. That -- the proposal, yeah.

Q. Okay.

A. It wasn't --

Q. It -- I'm sorry. Strike that.

Does that refresh your recollection that that proposal was funded -- was a funded patent -- funded grant?

A. Well, it doesn't so much spark my recollection as tell me that it was.

Q. And the grant that is being referred to in Exhibit 2104 is the same one that was -- the same grant as in Exhibit 2103, correct?

A. I believe that is the case, yes.

Q. And Dr. Ju was a collaborator with you on that grant, correct?

A. Yes, I believe that's correct. That was a long time ago. And I only vaguely remember that. But

Page 102

yeah, I think that -- I think that -- I think that he wanted -- I think we -- we spoke briefly at a meeting, and he was going to supply us with O-allyl nucleotides, I think. And he never did. I think we never actually ran those experiments.

Q. And the grant relates to SBS, correct?

A. Yep. Yes.

Q. And continuing in the Genome Web news article where we left off in the article, it reads:

"It's no secret that nucleotides labeled with a fluorescent dye are poor substrates for natural polymerases."

So when the Genome Web News article was written, it was understood that nucleotides labeled with a fluorescent dye are poor substrates for natural polymerases, correct?

A. I'm not sure I'd take Genome Web to be a definitive source of science. I don't even remember this article. I have -- don't -- I don't know who wrote this. I don't know.

Again, this is not so different than a lot of other things we've talked about. There's no doubt that fluorescent labeling -- nucleoside triphosphates with linkers that attach fluorophores tend to reduce their

Page 103

recognition by polymerases. So certainly what they are saying is not far off.

Q. Okay. And they say that "nucleotides labeled with a fluorescent dye are poor substrates for natural polymerases." That's what they say, right?

A. That is what it says.

Q. So please go back to Exhibit 2103, which is the Project Information sheet. And please draw your attention to the section entitled Abstract Text. The abstract starts with a description and it says that it is "provided by the applicant." Do you see that?

A. I do.

Q. That means that you wrote the text that is in the description of this exhibit, right?

A. I did.

Q. And the description reads:

"There is great incentive for developing low cost technologies for sequencing genomes. While significant advances have been made in conventional sequencing methods, the reductions in cost and time required to make genome sequencing more feasible require the development of new methodologies.

Page 104

Indeed, many new and promising methods are under development. However, these new approaches are generally limited by the inability of DNA polymerases to synthesize DNA with modified deoxynucleotide triphosphate (dNTPs)."

That's what you wrote, correct?

A. That is correct.

Q. And when you refer to "new approaches," you're including in those approaches SBS, correct?

A. Yes.

Q. And so it was your opinion in the 2005 -- 2000 time -- 2005-2006 time frame, when you submitted this grant proposal, that new approaches, including those of -- including SBS "are generally limited by the inability of DNA polymerases to synthesize DNA with modified deoxynucleotide triphosphates," correct?

A. That is what is written, but I mean -- but I guess I would ask you to clarify what you think I meant by "limited."

Q. Again, Dr. Romesberg, respectfully, I can't testify. But those are --

A. Sure.

Q. -- your words.

Page 105

A. Just to clarify, "limited" means would be improved by optimizing.
Q. So there were improvements that needed to be made in methods, including SBS, as of the 2005-2006 time frame when you used modified deoxynucleotide triphosphates?
A. Yeah. And so I was specifically collaborate -- trying to collaborate with industry, because I wanted to be -- to be involved in a polymerase that could help commercialize these ideas. So I wasn't interested in -- in -- in reactions or people showing sequencing of 10 or 20 or whatever nucleotide sequences people could do.
I -- I -- by, I think 2005 it was beginning to come clear -- become clear that people were going to do things like human genomes, and that's why I actually am talking about genome sequencing. And so that was still challenging then and that sort of like big scale commercialization. And certainly anything that optimized polymerase recognition, polymerase selectivity, the triphosphates, all of it, you know, all hands on board, anything that makes things better.
Q. Okay. But these new approaches, which include SBS, are generally limited by the inability of the polymerases to synthesize DNA with modified dNTPs;

Page 106

that's what you wrote?
A. "Limited" meaning that -- that they needed -- that I was -- that I was asking the NIH to fund me to optimize that.
Q. And would you agree that if you understood in the 2005-2006 time frame that new approaches, including SBS, are generally limited by the inability of DNA polymerases to synthesize DNA with modified dNTPs, that that was also true in 2000?
A. Again, it depends on how you define "limited." I mean, for example, Metzker showed with two analogs in principle that you could. No one had -- no one had sequenced a human genome -- well, no one had sequenced a human genome with the cost that people would soon be able to. So people weren't sequencing like they were today. So it hadn't sort of been commercialized or to that point where it had become this notion that you could get a genome for a grand, which the NIH had already announced.
So that was kind of like the big incentive. In fact, that was one of the big incentives of going to the NIH, because the NIH had announced this program because people around this time knew you could sequence. But what the NIH wanted to do was to do -- to reduce the cost. So when you think -- say things like "limited by"

Page 107

whatever, a part of that is that you want to reduce costs to the point to make progress towards that $1,000 genome, because that's what the NIH was going to fund. So any application to the NIH was going to try to reflect.
Q. These are your words, though, right?
A. And I was -- and that's what I was trying to do.
Q. Okay. So it was your -- in your words, these new approaches, which included SBS, were generally limited by the inability of DNA polymerases to synthesize DNA with modified deoxynucleotide triphosphates. Those are your words, correct?
MR. ZIMMERMAN: Objection. Asked and answered, literally four times now.
A. They were my words. And since they were my words, I can -- I can tell you what I meant by "limited." I was talking about reducing the cost, increasing the efficiency, making progress towards, frankly, what Illumina eventually did.
BY MR. SCHWARTZ:
Q. Okay. And let's -- why don't we look down a little bit further in the "Abstract Text" section and look down at Specific Aim 2. Do you see Specific Aim 2?
A. I do.

Page 108

Q. And Specific Aim 2 reads:
"Evolve polymerases that efficiently incorporate reversibly fluorophore tagged dNTPs with 3'-O-allyl protecting groups and then continue synthesis after double deprotection."
That's what you wrote, correct?
A. Yep, that is correct.
Q. So one of the goals of your grant proposal that was submitted in the 2005-2006 time frame, as funded in 2006, was to "evolve polymerases that efficiently incorporate reversibly fluorophore tagged dNTPs with 3'-O-allyl protecting groups," correct?
A. That is what I wrote.
Q. That was one of your Specific Aims, right?
A. That is listed under Specific Aim 2, yes.
Q. And that was -- so that was one of the goals of the grant at that time?
A. That is listed as Specific Aim 2, yes.
Q. And the Specific Aim represents a goal of the grant, right?
A. Yes.
Q. So if, as you contend in your declaration, in IPR2018-00797, which is the declaration in this case,

Page 109

that a POSA would have been motivated by Metzker in 1994 to use the 3'-O-allyl capped nucleotide for SBS because it was efficiently incorporated by Vent (exo-) DNA polymerase, then why are you asking the National Human Genome Research Institute in the 2005-2000 time -- 2006 time frame to give you research money to discover new polymerases that will efficiently incorporate fluorophore tagged 3'-O-allyl protected nucleotides by a polymerase?

A. Several reasons. One, "efficient" is a relative term. And so the question is efficiency relative to what. In my dec that we're discussing now, if I used the word "efficient," I don't remember using it, but I might have, and if you say I did, I believe you, but I can tell that you that what it would have been about, the subject matter of the declaration was sequencing by synthesis. So it would have been relative to that required for sequencing by synthesis.

And in my estimation, what Metzker demonstrated was enough to give a POSA optimism, expectation of success that the O-allyl protected group would have been accepted. The modified analog with an O-allyl protecting group would have been accepted sufficiently for sequencing by synthesis.

That is not to say that they accepted as well

Page 110

as a natural triphosphate. That is certainly true. And that was very much the goal in the grant I wrote. Because I wanted to help of all polymerases that would synthesize genomes and have relengths of just -- they -- they would synthesize DNA as efficiently with the modified analogs as they did with unmodified of the sort that pyroseq- -- that only pyrosequencing could do.

So I was not -- when I say "efficiently" here, I don't mean to say that they -- that -- that there was anything that wasn't efficient enough for some application already. I just believed, and I still believe, that the -- the proposal was meritorious. And we're still sort of working on this to make polymerases better for different things because your applications change. What you want to use them for changes.

And so now what people want isn't sequencing 30 nucleotides. It isn't sequencing 35 nucleotides. It's getting increasing long read lengths that will continue to drive down costs of sequencing. And they want to continue to get analogs that are cheaper and more affordable and brighter. And there's all sorts of applications that are still optimization, that are still increasing the efficiency of different recognitions.

Has that clarified it?

Q. Dr. Romesberg, if you believed in 2005 and

Page 111

2006 that the 3'-O-allyl capped nucleotide was efficiently incorporated, as taught by Metzker, then why are you asking the NIH in one of your goals of your grant to give you money to find an enzyme that efficiently incorporates exactly that capped nucleotide?

MR. ZIMMERMAN: He just answered that very question. Objection. Asked and answered.

BY MR. SCHWARTZ:

Q. All right.

A. I will try to answer it again if you want me to.

MR. SCHWARTZ: Well, first off, I don't like -- I don't appreciate the coaching. So you've been coaching for a while now, and I'm going to ask you to stop coaching. You can object.

MR. ZIMMERMAN: Objection. Asked and answered, because you're repeating the same question over and over to him.

MR. SCHWARTZ: Dr. Romesberg isn't answering my question.

MR. ZIMMERMAN: So you admit that you're asking the same question again --

MR. SCHWARTZ: No.

MR. ZIMMERMAN: -- and he's answered it.

You can go ahead and answer his question,

Page 112

again.

A. I will try to answer this question.

"Efficiency" is a relative term. If you're asking were the 3' O-allyl protecting -- were nucleotides with 3' O-allyl protecting groups accepted by polymerases efficiently enough for them to perform any application that people would have wanted to use them for, and the answer is no. And that's what I was asking for funding to help do.

For example, we were evolving them in a thermostable polymerase so that you would have been able to heat cycle it, and there's certain advantages that might have come with that. And so there's all sorts of applications that people might want to rec- -- be able to recognize these analogs to perform, to partici- -- to help with.

As a -- as a basic sequencing by synthesis platform, O-allyls had been demonstrated to be recognized by polymerases reasonably well. And so I -- I wasn't saying that they weren't recognized by polymerases at all and that you can't perform any sequencing by synthesis. I was talking about pushing forward and participating in what was coming, genome sequencing, the ability to sequence genomes for a thousand dollars, which I actually think this grant was

Page 113

in response to, the call for the 1K genome.
And that may not be true, but it was around the same time. And like I said, this was 12 years ago, but I think that's actually true. It was in response to the 1K genome or shortly thereafter.
So that kind of goal -- let me be clear about that. O-allyls were not recognized well enough for that goal. But that goal was unimaginable in 2000. No one knew what was coming.
Q. You're not denying that you told the NI -- the granting agency in Specific Aim 2 that you wanted to "evolve polymerases that efficiently incorporate reversibly fluorophore tagged dNTPs with 3'-O-allyl protecting groups? You're not denying that, are you?
A. It is --
MR. ZIMMERMAN: Objection. Asked and answered.
A. It is written there.
BY MR. SCHWARTZ:
Q. Okay. You can put that away.
I'm going to put the -- I'm going to ask you to look at the '985 patent. That's Exhibit 1075. And please go to the claims, which start at Column 34. And I want to focus on the Y element in Claim 1. So please turn to column -- you can keep your finger on the claim,

Page 114

but please turn to Column 36. Are we -- 36 is the claim. Please turn to 36, Column 36 in the claim. At line 6 the claim reads:
"... wherein in Y represents a chemically cleavable, chemical linker ..." Do you see that?
A. I do.
Q. And I asked you for your understanding of what Y meant in your deposition on September 19th, and it was your -- your testimony that Y represented a cleavable -- part of a cleavable label, a link or part of a label that would attach what he calls the tag.
Do you remember that testimony?
A. No. That sounds correct, but I do not explicitly remember it.
Q. Well, let's -- we'll look at it, then. I was just trying to save -- avoid having to mark another exhibit, but we will.
I'm going to be marking an exhibit as 2096.
(Exhibit 2096 marked for identification by the Certified Shorthand Reporter.)
BY MR. SCHWARTZ:
Q. And this is your deposition transcript in the four previous IPRs in this case, correct?
A. I have not seen this before, but it would --

Page 115

it is labeled as such.
Q. Okay. And just so -- for your information, this is the Min-U-Script version of it, so it means that there's multiple pages on a single page. I don't know if you've seen them like this before --
A. I have.
Q. -- but it has multiple pages. I'm sure your counsel has seen something like this.
Please turn to page 206. It will be on your top right corner. Do you see 206?
A. I do.
Q. And starting at line 8 of the transcript, it reads:
"QUESTION: Do you see in the structure that is drawn for this particular adenine nucleotide that the tag is attached to the base via a structure called Y?
"ANSWER: A box called Y, yes, I see that.
"QUESTION: What is your understanding of the box called Y?
"ANSWER: It would be a cleavable -- part of a cleavable label -- a link or part of a label

Page 116

that would attach what he calls the tag.
"QUESTION: So you understand that the tag is not directly connected to the base, correct?
"ANSWER: Yes. I mean, we'll get a little semantic talking about why the tag and why start and stop, because they're all going to be chemical bonds, but clearly the spirit here is that there is a part that is cleavable that will separate the fluorophore or the tag from the nuclear base."
That was your testimony, correct?
A. There's a variety of typographical errors there. I have not edited this yet. But that seems to be what I said and certainly consistent with what I would say, but there are typographical errors.
Q. Did the typographical errors change the substance of your answer?
A. I don't know. I mean, they get -- it just gets a little confusing. Like where it says "we'll get a little semantic talking about why the tag" -- it's almost certainly I said about where the tag starts and

Page 117

stops, because they are going to be chemical bonds. But clearly the spirit here is that there is part -- there is a part that is cleavable that will separate the fluorophore from the tag -- or the tag -- of the tag from the nucleobase, not nuclear base.

Q. Okay. So --

A. It's just a little hard to read.

Q. Okay. But your testimony was that Y represents a component that is between the fluorophore and the base that is cleavable, correct? It's not directly attached, the fluorophore to the base?

A. Yeah. Yeah. That's certainly the spirit of what I was saying.

Q. And the chemically cleavable chemical linker that is denoted as Y in Claim 1 must be cleavable under conditions that are suitable for SBS, correct?

A. If you're asking under the criteria of -- in general, no, but could you ask me -- I'm sure you're asking this from a specific criteria. If you're going to use it for sequencing by synthesis, then -- then yeah, sure.

Q. So the conditions must be mild so as to allow continued DNA synthesis to occur after chemical cleavage, correct?

A. For most applications you're going to have to

Page 118

we reinitiate DNA synthesis, so you would have to reinitiate DNA synthesis. So if cleaving the linker did something that prevented that, then -- the reason I'm being a little hesitant here is because this is a specific requirement, I think, of some of the patents that we're talking about. And so it would be easier to sort of answer the question in their context as opposed to a vacuum.

Q. Well, let's do that in the context of Claim 1 of the '985 patent. The cleavage of the cleavable -- chemically cleavable chemical linker must take place under conditions that would be compatible with SBS, correct?

A. Correct.

Q. Please go back to your declaration in IPR2018-00797. That's this case. That was marked as Exhibit 1078. So it's your declaration in this case. Exhibit 1078.

MR. ZIMMERMAN: It's going to be a thick one with a binder clip.

THE WITNESS: It must be this, right?

MR. ZIMMERMAN: 1078, yes.

THE WITNESS: 1078, yeah, I have it.

BY MR. SCHWARTZ:

Q. Okay. Please turn to page 130.

Page 119

A. 130?

Q. Yes, please.

On page 130, towards the bottom of the page, there is a section entitled Section IX.A.9, "Limitation 'wherein Y represents a chemically cleavable, chemical linker.'"

Do you see that?

A. I do.

Q. Please keep your finger on that page, but I would ask that you turn to page 108 of that declaration. And Section IX relates to ground 3 in which you contend that the '985 claims are obvious over Dower, Prober, and Metzker, correct?

A. Section IX, ground 3, that's right.

Q. And please go back to page 131 of your declaration.

A. 131?

Q. Yes.

And page 131 is part of paragraph 183, which is within the Section IX.A.9 that relates to your ground 3 challenge, correct?

A. Yes.

Q. And please draw your attention to the sentence on the bottom of page 131 where three lines up from the bottom of the page you refer to Figure 9.

Page 120

Do you see that?

A. I do.

Q. And if you would, please, turn to page 132 of your declaration. Starting at the top of the page you draw the structure depicted in Figure 9.

Do you see that?

A. I do.

Q. I'm going to put in front of you the Dower reference. Just keep all of that in front of you. And here's the -- it's not easy. I understand.

I'm putting in front of you Exhibit 1015, which is U.S. Patent No. 5,547,839, and that's the Dower reference in your declaration, correct?

A. Yes, it is.

Q. Please turn to Figure 9 in Dower. On the top right side of Figure 9 in Dower, that's the same structure you drew in your declaration, correct?

A. That is right.

Q. And the B in Figure 9 of Dower represents the nucleotide base, correct?

A. That is correct.

Q. And the FMOC in Figure 9 is what you are calling the label, correct?

A. Where -- where do I -- probably, but could I ask you where I describe that as a label, to make sure

Page 121

I'm on the same page?
Q. Do you consider that to be the label?
A. The FMOC?
Q. Yes.
A. It has the fluorophore and the linker in it. I -- I -- did I -- the label. So I think the label sort of generically refers to both the linker and the fluorophore. Is that right?
I can't ask questions. Sorry.
Yeah, that is -- the FMOC provides the label. Sure.
Q. And the reaction scheme on top of Figure 9 in Dower for attachment of FMOC to the base results in direct attachment of FMOC to the base via a carbamate linkage, correct?
(Court reporter clarification.)
A. A carbamate will form from the amine of the base.
Q. According to the Figure 9 teachings in Dower, correct?
A. Well, it doesn't expressly say that, but it certainly is the only -- it's the only likely thing from as he's drawn it.
Q. Okay. So FMOC is directly attached to the nucleotide base in Dower Figure 9, correct?

Page 122

A. The FMOC is directly attached to the base in Figure 9, that's correct. It's -- the FMOC -- the fluorinenal -- fluorophore of the FMOC is attached to the base via the built-in FMOC linker. That's the carbamate that you mentioned.
Q. Is directly attached by a covalent bond to the base? There isn't a Y structure in between, correct?
A. No, there is.
Q. There's not a chemically cleavable Y structure that's compatible with SBS, correct?
A. No, there is. If you take FMOC and treat it with mild base, it eliminates.
Q. You're saying you can take F -- you can take the Figure 9 FMOC carbamate linkage and treat it with a condition that would be compatible with SBS?
A. Before I answer that, let me make sure.
Yes.
Q. And via what reaction?
A. Would you like me to draw it for you or -- it's a little hard to explain. So the FMOC forms carbamate, as you mentioned. In the FMOC there is a acidic proton that's on the other side of the oxygen. It's acidic so you can add mild base. It's often like a -- like a -- just a mild base like mor- -- like a -- just like an aniline -- no. Like an aromatic amine,

Page 123

like pyridine or something, some weak base.
And that eliminates. It blows off CO2, and that leaves an amine. So you would regenerate the amine that you used to form the carbamate.
FMOCs are used in peptide protection all the time, of -- of primary amines, of alkylamines. And they are cleaved off that way.
MR. SCHWARTZ: I'd like to take a quick break. Thank you.
THE VIDEOGRAPHER: Going off the record at 3:57 p.m.
(Recess taken from 3:57 p.m. to 4:09 p.m.)
THE VIDEOGRAPHER: We are back on the record at 4:09 p.m.
BY MR. SCHWARTZ:
Q. Dr. Romesberg, I'm going to put in front of you what's been marked as Exhibit 1014. And that's the Prober reference site that you rely on in your declaration. That's the same Prober reference you rely on, correct?
A. It is.
Q. And please go to page 338 of Prober. And please draw your attention to Figure 2(A), which shows the structures of Prober's base labeled nucleotides.

Page 124

The labels are attached to the base in Prober's nucleotides by an acetylenic linker, correct?
A. A propargylamine, correct. Yes.
Q. And a POSA in October -- a POSA in October 2000 understood that that linker is not cleavable under conditions that are suitable for SBS, correct?
A. No one -- so that part of any linker would not be cleavable, that is correct. The propargylamine part. The amine is a part that you would use to attach the cleavable part.
Q. And a POSA in October 2000 understood that Prober does not disclose the use of the chemically cleavable chemical linker to attach the label to the base of a nucleotide, correct?
A. Prober does not. That is correct.
Q. And a POSA in October of 2000 understood that Prober's fluorescently labeled nucleotides are ddNTPs, correct?
A. They are dideoxy, that is correct. DdNTPs, yes.
Q. And a POSA in October 2000 understood that Prober's fluorescently labeled ddNTPs are permanent terminators and cannot be used for SBS, correct?
A. They cannot restart synthesis. They are incorporated in much the same way, but because they're

Page 125

missing the 3' hydroxyl group as opposed to it being protected, they by definition cannot restart synthesis. So that step of sequencing synthesis, they would have failed it, yes.

Q. So in October of 2000, a POSA understood that it was not possible to convert a ddNTP into a dNTP by any chemical procedure that would not severely damage the nucleotide, correct?

A. I would have to think about that, but almost certainly I would -- I would be very prone to agree with that. Yeah, I can't imagine doing that selectively, but I haven't thought about it.

Q. And I don't know that I'm going to necessarily need to mark this exhibit. I just want to ask you one last question about Metzker 1994.

Do you recall that Metzker 1994 does not disclose any nucleotides with labels attached to the base?

A. Metzker does not. His -- the 1994 paper is focused on 3' blocking groups.

Q. Okay. I'm going to put in front of you a document that -- let me -- this is going to be marked as 2101.

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Page 126

(Exhibit 2101 marked for identification by the Certified Shorthand Reporter.)

BY MR. SCHWARTZ:

Q. Putting in front of you a document entitled Regioselective Oxidation of Internal Olefins Bearing Neighboring Oxygen Function by Means of -- by Means of Palladium Catalysts. Preparation of ß-Alkoxy or Acetoxy Ketones from Allyl and Homoallyl Ethers or Esters by Tsuji, et al. as published in 1982.

Please turn to page 2680. And please direct your attention to the first paragraph. And the authors write:

"As shown in Table 1, the oxidation of various allyl ethers and acetates with palladium chloride, copper chloride, oxygen, or palladium chloride P, benzoquinone catalyst system gave the corresponding Beta alkoxy ketones regioselectively."

That's what the authors write, correct?

A. That is what is written.

Q. And please direct your attention to Table 1 on page 2681. Compounds A, B, C, D, and E in Table 1 are

Page 127

referred to as allyl ethers, correct?

A. Those are allyl ethers. There's a substitute allyl ethers, yes.

Q. So -- so allyl ethers in Table 1 -- strike that.

The Tsuji 1982 paper refers to allyl ethers as a genus that includes substituted allyl ethers, correct?

A. I haven't read this, but it appears to, and that would not surprise me.

Q. Okay. And some of the com- -- the com- -- some of the compounds contain four carbon atoms, six carbon atoms, seven, eight. They vary in size, correct?

A. That is -- that is -- again, I have not read this, but it is not unusual to describe to that -- to describe that group as allyl ethers. And there are certainly analogs with the number of carbons you described.

Q. Okay. You can put that away. I'm going to mark another exhibit.

(Exhibit 2106 marked for identification by the Certified Shorthand Reporter.)

BY MR. SCHWARTZ:

Q. This is going to be marked as 2106.

A. By the way, this was the Tsuji of the

Page 128

Tsuji-Trost reaction that I brought up a few minutes ago.

Q. I'm putting in front of you a document entitled Hypervalent (tert-Butylperoxy) Iodanes Generate Iodine-Centered Radicals at Room Temperature in Solution: Oxidation and Deprotection of Benzyl and Allyl Ethers, and Evidence for Generation of Alpha-Oxy Carbon Radicals by Ochiai, et al. that was published in 1996.

Please turn to page 7719 and draw your attention to Table 3. And Table 3 is entitled Allylic Oxidation of Allyl Ethers with Peroxyiodane 1a, correct?

A. It is.

Q. And Table 3 discloses compounds 1 to 13, which are referred to in that paper as allyl ethers, correct?

A. I have not read this, but the table heading would appear to suggest that's the case, yes.

Q. Okay. And included in that group of allyl ethers are allyl ethers that contain anywhere from three to nine carbon atoms, and they are both substituted and unsubstituted, correct?

A. There are both substituted and unsubstituted there, yes.

Q. And there's -- and there's multiple carbon atoms, more than three?

A. Yes.

Page 129

Q. Okay. I'm going to put another paper in front of you. This is going to be marked as 2107.

(Exhibit 2107 marked for identification by the Certified Shorthand Reporter.)

BY MR. SCHWARTZ:

Q. And I won't even read the title of this paper. It's self-evident.

I'm going to ask you to turn to page 1319. And please draw your attention to the right column on page 1319 where there's a heading entitled Preparation of Allyl Ethers.

Do you see that?

A. I'm sorry. 1319?

Q. 1319.

Has "Preparation of Allyl Ethers."

A. A paragraph heading, yes.

Q. Yes.

And if you look down in the section, you see "Scheme 4." Do you see that?

A. I do.

Q. And please draw your attention to the three compounds shown in the middle of Scheme 4 labeled 20a, b, and c. Do you see those?

A. I do.

Page 130

Q. And compounds 20a through c are referred to as allyl ethers by these authors, correct?

A. I have not read this paper, but they --

MR. ZIMMERMAN: Take your time to read whatever you need to read.

BY MR. SCHWARTZ:

Q. Are they referred to as allyl ethers by these authors?

A. Allyl ethers, 20a through c, so yes, those are -- the compounds labeled 20a through c are being referred to as allyl ethers.

Q. Okay. And compound 20a contains 12 carbon atoms and 20b contains 10 and 20c contains 12.

Do you agree with that?

A. Do you want me to count them?

Q. Well, I just -- maybe the better question is to say the compounds 20a and b -- a, b, and c are not three carbon allyl ethers, correct?

A. They are not.

Q. Okay. And so the authors -- the authors of this paper referred to allyl ethers as ethers containing more than three carbon atoms, correct?

A. As is common, people can loosely refer to the group of -- of compounds as allyl ethers, and people would know what they meant, yes.

Page 131

Q. Okay.

MR. SCHWARTZ: How much time do I have?

THE VIDEOGRAPHER: Seven minutes.

BY MR. SCHWARTZ:

Q. All right. I'm going to put one last exhibit in front of you. And I'm putting in front of you what's been marked previously as Exhibit 1013, which is the Tsien patent application.

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

BY MR. SCHWARTZ:

Q. This is the same Tsien patent application that you refer to in your declaration, correct?

A. It appears to be.

Q. Please direct your attention to pages 20 through 23 of Tsien. And there's pages 20 through 23, and there's a section entitled Blocking Groups and Methods for Incorporation.

Do you see that section?

A. I do.

Q. In this section Tsien addresses criteria for the selection of 3-O [sic] capping groups to block the 3'-OH group of a nucleotide for incorporation by a polymerase for SBS, correct?

Page 132

A. I'm sorry. Did you say that he discusses three blocking groups?

Q. 3'-O capping groups.

A. 3'-O capping, yes.

Q. To block the 3'-OH group of a nucleotide for incorporation by a polymerase for SBS. That's what he discloses here, correct?

A. Yes.

Q. And in this -- in this section, Tsien never expressly states that the 3'-O capping group needs to be small, correct?

A. I don't think -- I don't think Tsien ever evoked small.

Q. And nowhere in this section does Tsien mention the use of allyl ethers to cap the 3'-OH of the nucleotide, correct?

A. I would have to check that -- I would have to read this because Tsien talks about -- Tsien teaches O-allyl ethers as blocking groups. So if he doesn't, I would have to read this section to see if it's not in here in particular.

Q. No. I'm asking in this particular section. So he never mentions in this section anything about allyl ethers?

A. So again, in the section "Blocking Groups and

Page 133

Methods for Incorporation", right?
I'm going to take a second to read them.
Q. Uh-huh.
A. I'm just skimming the end of it.
He does not appear. So where he goes through this litany of different ones, he says:
"The most common 3'-hydroxyl blocking groups are esters and ethers. Other blocking modifications ...." then he goes on for this very long list.
And I assume that what he was baking into "other ethers" were the allyl ethers, because that's -- they are ethers, and they are discussed in -- specifically called out in other parts of this same application. So I would assume that's where they're embedded, but he does -- you're correct, he does not call out at any spot then in this section.
Q. Nowhere in this section does Tsien disclose an allyl group CH^2-CH double bond CH^2 containing three carbons and five hydrogens to cap the 3'-OH of the nucleotide, correct?
A. I did not see it in this section.
Q. All right. And I want to just quickly look at pages 23 to 25.

Page 134

MR. SCHWARTZ: How much time?
THE VIDEOGRAPHER: Two.
BY MR. SCHWARTZ:
Q. And in this section, Tsien addresses the criteria for the selection of the 3'-O capping group to block the 3'-OH group of the nucleotide for incorporation for -- by polymerase for SBS, correct?
A. It's labeled deblocking methods. I mean, if you want me to read -- I mean, it's been -- I've read a lot of these. Do you want me to -- I would like to read it quickly.
Q. While you're reading it, I guess I'll just pose my question, since we're running out of time. And nowhere in this section does Tsien expressly disclose the specific allyl group CH2-CH double bond CH2 containing three carbon atoms and five hydrogen atoms to cap the 3'-OH of the nucleotide, correct?
A. He includes the allyl ethers. And the one that you just described is the parent allyl ether, and that would have been the first one anyone would have thought of. But no, he does not expressly say "the parent allyl ether compound."
Q. Okay.
MR. SCHWARTZ: I have no further questions for this part of the deposition. Thank you.

Page 135

EXAMINATION
BY MR. ZIMMERMAN:
Q. Dr. Romesberg, I have just a few questions for you. If you could pull up the Ju '985 patent, Exhibit 1075.
A. Not the '985?
Q. I'm sorry. The '985. It's Exhibit 1075.
A. Yes. Yes, I have it.
Q. And we'll wait for them to get the copy.
MR. SCHWARTZ: Okay.
BY MR. ZIMMERMAN:
Q. And to save you the headache of later questions, did we have any discussions at the break regarding the substance of your testimony?
A. We did not.
Q. And did we have any discussions at any of the breaks about questions I might ask you in today's deposition?
A. We did not.
Q. Okay. Looking at the Ju '985 patent, Exhibit 1075, if you could turn to Column 21, lines 57 to approximately 64.
A. Starting with "It is a routine"?
Q. Yes. You'll see that there's reference to "10,000 bases can be identified after each cycle ..."

Page 136

Do you see that?
A. It does -- that is what it says.
Q. Okay. Does this suggest that the method of Ju can sequence 10,000 base pairs?
A. It says:
"Thus, in the DNA sequencing system disclosed herein, more than 10,000 base cycles can be identified after -- more than 10,000 bases can be identified after each cycle, and after 100 cycles, a million base pairs will be generated from one sequencing chip."
Q. Okay. Is there any data in Tsien showing sequencing of a million base pairs?
A. No.
Q. I'm sorry. Is there any data in the Ju patent, Exhibit 1075, showing the sequencing of a million base pairs?
A. That would still be no.
Q. Okay. Is there any data in the Ju patent, Exhibit 1075, showing 10,000 base pairs?
A. No.
Q. Is there any data in the Ju patent showing sequencing of a hundred base pairs?

Page 137

A. No, there is not.
Q. Is there any data in the Ju patent, Exhibit 1075, showing 25 base pairs being sequenced?
A. No, there is not.
Q. Is there any actual sequencing data at all in the Ju patent, Exhibit 1075?
A. I believe not.
Q. Okay. Now, if you could turn to Claim 1, which starts on paragraph -- I'm sorry -- Column 34 of the Ju patent, Exhibit 1075. You'll see it recites, "A method for sequencing a nucleic acid" and then continues.
A. Yes, I see that.
Q. Okay. In all of Claim 1 does it refer to sequencing by synthesis?
A. No, it would appear not to. I believe it just talks about the incorporation of one of these nucleotide of analogs.
Q. Okay. And does Claim 1 expressly state that you have to sequence 25 to 30 base pairs?
A. No.
Q. Does Claim 1 of the '985 patent put any limitation on the number of base pairs that must be sequenced?
A. There is no limitation, high or low.

Page 138

Q. If you do one base, does that qualify under Claim 1 of the '985 patent?
A. I -- as I read it, yes.
Q. Now, there was some discussion earlier and reference back to a prior deposition where you indicated or appeared to indicate that SBS wouldn't be useful for sequencing one nucleotide, correct?
A. I don't recall that exact testimony. Sequencing -- sequencing a single nucleotide, if you're using a polymerase and you're incorporating a fluorophore, that is sequencing by synthesis, and that could be of interest.
I think what I was trying to discuss then was, as we talked about earlier, was sequencing like a human genome, in which case you would need much longer sequences. But that's because you have to place them in -- you have to construct the genome from fragments, and you need enough overlap to be able to do that.
There are certainly applications where one would want a smaller number of sequence information.
Q. Are -- are there any real world practical applications where sequencing three base pairs is of value or use?
A. No, absolutely. In the end, what most people care about is amino acid sequence in a protein, because

Page 139

lots of cancer states are caused by proteins with changes at the amino acid level. That's the only spot where differences are actually made and felt in nature to the cell.
And nucleotide -- amino acids are coated in triplets of nucleotides. So three nucleotides correspond to one amino acid. So to identify what an amino acid is, you need three nucleotides. So -- and this is just off the top of my head, but it would seem very common and very reasonable to want a primer to lay down before a codon, read what the codon is. That would require three nucleotides. And then you would know the amino acid.
So that what I imagine, off the top of my head, would be the most useful.
MR. ZIMMERMAN: If you'll give me one quick second.
I have no further questions for Dr. Romesberg.
But I do want to make an objection on the record to Exhibits 2102, 2103, and 2104 as outside the scope and because they are not prior art, just to make sure that that's preserved.
I also want to make clear for the record that this deposition is solely for the purposes of IPR2018-00797. And we will object to its use in any of

Page 140

the other four IPR proceedings.
MR. SCHWARTZ: Okay. Can you give us a break --
MR. ZIMMERMAN: Sure.
MR. SCHWARTZ: -- for just a few minutes?
THE VIDEOGRAPHER: Going off the record at 4:30 p.m.
(Recess taken from 4:30 p.m. to 4:35 p.m.)
THE VIDEOGRAPHER: We are back on the record at 4:35 p.m.
BY MR. SCHWARTZ:
Q. Dr. Romesberg, just one last question about the Claim 1 of the '985 patent that we just looked at.
A. Yes. I have it.
Q. Claim 1 is "A method for sequencing a nucleic acid," correct?
A. That is what it says, yes.
Q. A nucleic acid is a polymer of nucleotides; is that correct?
A. A nucleic acid is a polymer of nucleotides made up of individual nucleotides, that's correct.
MR. SCHWARTZ: I have no further questions.
MR. ZIMMERMAN: I have no further questions either.

Page 141

THE VIDEOGRAPHER: This concludes the video-recorded deposition of Dr. Floyd Romesberg, Ph.D. Going off the record at 4:36 p.m.

(Deposition concludes at 4:36 p.m.)

Page 142

STATE OF CALIFORNIA)
)
COUNTY OF SAN DIEGO)

I, Linda E. Marquette, a Certified Shorthand Reporter, do hereby certify:

That prior to being examined, the witness in the foregoing proceedings was by me duly sworn to testify to the truth, the whole truth, and nothing but the truth;

That said proceedings were taken before me at the time and place therein set forth and were taken down by me in shorthand and thereafter transcribed into typewriting under my direction and supervision;

I further certify that I am neither counsel for, nor related to, any party to said proceedings, nor in anywise interested in the outcome thereof.

Further, that if the foregoing pertains to the original transcript of a deposition in a federal case, before completion of the proceedings, review of the transcript [X] was [ ] was not requested.

In witness whereof, I have hereunto subscribed my name.

Dated: October 15, 2018

Linda E. Marquette
RPR, CLR, CSR No. 11874,

Page 143

DECLARATION UNDER PENALTY OF PERJURY

Case Name: Illumina, Inc. vs. The Trustees of Columbia University in the City of New York
Date of Deposition: 10/09/2018
Job No.: 10048075

I, FLOYD ROMESBERG, PH.D., hereby certify that I have read the transcript of my deposition and that this transcript accurately states the testimony given by me, with the changes or corrections, if any, as noted on an errata sheet or errata sheets.

Executed this _____ day of _____, 2018, at _____.

_____
FLOYD ROMESBERG, PH.D.

NOTARIZATION (If Required)
State of _____
County of _____
Subscribed and sworn to (or affirmed) before me on this _____ day of _____, 20__, by_____, proved to me on the basis of satisfactory evidence to be the person who appeared before me.
Signature: _____ (Seal)

Page 144

DEPOSITION ERRATA SHEET

Case Name: Illumina, Inc. vs. The Trustees of Columbia University in the City of New York
Name of Witness: Floyd Romesberg, Ph.D.
Date of Deposition: 10/09/2018
Job No.: 10048075
Reason Codes: 1. To clarify the record.
2. To conform to the facts.
3. To correct transcription errors.

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FLOYD ROMESBERG, PH.D.

T