UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ILLUMINA, INC.,

Petitioner,

vs.

PATENT OF THE TRUSTEES
OF COLUMBIA UNIVERSITY IN
THE CITY OF NEW YORK

Patent Owner.

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VOLUME II

VIDEOTAPED DEPOSITION OF DR. GEORGE TRAINOR

Wednesday, September 4, 2013

New York, New York

3:56 p.m.

Reported by:
Maureen Ratto, RPR, CCR, CLR
Job No: 31222-B

Illumina Ex. 1098
Illumina v. Columbia
IPR2018-00291, -00318,
-00322, -00385, and -00797

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Videotaped deposition of DR. GEORGE L. TRAINOR, held at the offices of Fitzpatrick Cella Harper & Scinto, LLP, 1290 Avenue of the Americas New York, New York, 10104-3800, pursuant to notice, before Maureen Ratto, Registered Professional Reporter, License No. 817125, and Notary Public.

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A P P E A R A N C E S:

Counsel for the Petitioner:

FOLEY & LARDNER, LLP
777 East Wisconsin Avenue
Milwaukee, WI 53202-5306
414-297-5782
BY: JEFFREY N. COSTAKOS, ESQ.
jcostakos@foley.com

REINHART BOERNER VAN DEUREN, S.C.
22 East Mifflin Street, Suite 600
Madison WI, 53703
608-229-2219
BY: ROBERT A. LAWLER, ESQ.
rlawler@reinhartlaw.com

Counsel for the Patent Owner:

COOPER & DUNHAM, LLP
30 Rockefeller Plaza
New York, New York, 10112
212-278-0400
BY: JOHN P. WHITE, ESQ.
jwhite@cooperdunham.com

A P P E A R A N C E S, continued:

Fitzpatrick Cella Harper & Scinto, LLP
1290 Avenue of the Americas
New York, NY 10104-3800
212-218-2100
BY: ROBERT S. SCHWARTZ, ESQ.
rschwartz@fchs.com
SIEW YEN CHONG, ESQ.
schong@fchs.com

ALSO PRESENT:
Marcus Burch, Esq.
Illumina Senior Patent Counsel
Manuel Abreu, Videographer
Kevin Burgess, Texas A&M University

G E O R G E L. T R A I N O R, having previously sworn, resumes testifying as follows:

CROSS-EXAMINATION BY MR. COSTAKOS:

VIDEOGRAPHER: The time is 3:56 p.m., and we're back on the record.

MR. COSTAKOS: I think we were just going to announce for the record that John White is now sitting in the -- the catbird seat, as it were.

Q. All right. So when we took our break, we were looking at page 27 of Tsien.

Okay. Dr. Trainor, if you look at the bottom of page 27 of Tsien, you see it refers to an embodiment that has a 3'-blocked dNTP, do you see it -- I'm sorry. Let me start over again.

So at the bottom of page 27, the very last line, do you see there is a reference to a "3'-block dNTP analog containing a label, such as a fluorescent group coupled to a remote position such as the base."

TRAINOR

Do you see that?

A. Yes.

Q. Okay. So Tsien discloses a dNTP analog that is 3'-blocked and has a fluorescent label coupled to the base.

A. Yes. In a general sense, yes, in a general notion of that. It's not a chemical structure at that point, yeah.

Q. But it says it in words, and you agree with that?

A. Yes. I'll agree with that.

Q. If you look at page 21 of Tsien, actually beginning at page 20 of Tsien, which is Exhibit 1002, there is a section entitled "Blocking Groups and Methods for Incorporation."

Do you see that?

A. Yes.

Q. Okay. And then on page 21, at line 12, it says, "The most common 3'-hydroxyl blocking groups are esters and ethers."

Do you see that?

TRAINOR

A. Yes.

Q. Okay. And so it expresses esters and ethers blocking groups, right?

A. Yes. In a general sense, yes. Along with other things, yes.

Q. And you agree those are small, right?

A. I don't know. They could be large or small. It doesn't specify.

Q. And allyls are small we already talked about that, right?

A. Yeah, relatively small, right.

Q. Okay. And if you look at page 24, beginning at line 24, there is a reference to "a wide variety of hydroxyl blocking groups." Do you see that?

A. "A wide variety," I don't see those words.

Q. Okay. So at line 24 of page 24 --

A. Of page 24 --

Q. -- it says, "a wide variety of

TRAINOR

hydroxyl blocking groups."

A. Oh, down at the bottom.

Q. Do you see that?

A. Yes.

Q. Okay. And then in the same paragraph it refers to "allyl ethers" at line 29. Do you see that?

A. Among other larger groups as well, so...

Q. Okay. But you agree that it -- it specifically discloses in words, the idea of using allyl ethers as blocking groups?

A. Yes.

Q. And allyl ethers we talked about before are small?

A. A-hum.

Q. Yes?

A. Yes.

Q. Okay.

A. And I should point out that in doing this he's also -- he has not specified the combination of those groups in this section with

TRAINOR

specifically with a base label or cleavable base label. He's simply saying, "blocking groups," with the implication if you put it on the 3' and be blocked there or other -- other options but it's not specific to that context.

MR. COSTAKOS: Move to strike as non-responsive.

Q. Okay. So if we look at page 21 of Tsien, at line 20, you see it refers to "presently preferred embodiments."

Do you see that?

A. Yes.

Q. And it says, "Presently preferred embodiments focus on the ester-blocking groups such as lower (1 to 4 carbon alkalinuric acid), et cetera, et cetera."

Do you see that?

A. Yes.

Q. Okay.

A. It's a long list.

Q. And one to four carbons would be

TRAINOR

small, right?

A. Again, this is --

Q. "Yes" or "no"?

A. -- this is one of a list.

Q. "Yes" or "no"?

A. Yes, but one of a list. I can -- I believe I can answer the questions as I feel. I mean, I --

Q. No, you really can't, actually.

A. -- I don't believe I -- I'm required to give you a "yes" or "no" answer --

Q. Okay.

A. -- but sometimes a qualified yes is the appropriate answer.

Q. No. What I --

MR. WHITE: You can answer the questions the way you think are appropriate.

Q. Well, I -- here -- here is the way it's supposed to work. You answer my questions.

A. A-hum.

Q. And then if he has questions,

TRAINOR

Mr. White has questions for you later, then he can ask you those questions.

A. No.

Q. Okay.

A. That -- it was my -- my understanding --

Q. A-hum.

A. -- that I -- I can give an answer that I believe answers your question.

Q. Okay.

A. Because sometimes a simple "yes" or "no" is not the appropriate answer.

Q. Okay. But my question was: One to four carbon is small?

A. Yes.

Q. Okay. Now, if we go back to page 24, of Tsien, Exhibit 1002, it refers to on line 5, "Removal of ester-blocking groups from the 3'-hydroxyl functions is usually achieved by base hydrolysis."

Do you see that?

A. Yes.

TRAINOR

Q. Okay. And so the blocking groups can be a -- are removable, right?

A. A-hum.

Q. Yes?

A. That's their assertion here.

Q. Okay. And where we were looking down before on line 29, of page 24 it says, "Allyl ethers are cleaved by treatment with Mercury 2 in acetone/water," and it cites to a reference.

Do you see that?

A. Yes, I see that.

Q. Okay. So it discloses that allyl ethers, as blocking groups, can be removable, right?

A. It doesn't specify whether they're removable without other reactions going on that would destroy the ability of the nucleotide to work, which is important to perform this invention.

Q. Okay.

TRAINOR

MR. COSTAKOS: I move to strike as none responsive.

Q. The allyl ethers are disclosed in the reference as being "cleaved by treatment with Mercury 2 and acetone water," on lines 29 and 30?

A. Yes.

Q. Am I right?

A. Those are the words.

THE REPORTER: Those are the --

THE WITNESS: -- words.

Q. Now, if we look at page 28, beginning at line 5, Tsien discusses "a method that uses a fluorescent tag attached to the base moiety."

Do you see that?

A. Yes.

Q. Okay. So in one of the embodiments of Tsien it talks about using a fluorescent tag that is attached on the base. Fair?

A. Yes.

Q. And -- and right after that sentence that I -- I just read it says,

TRAINOR

"the tag may be chemically cleaved."

Do you see that?

A. Yes.

Q. Okay. And if you look at line 27, of page 28, it discloses that "the cleavable linkage can be an allyl ether," agreed?

A. No. It says, "allyls can be cleaved," it doesn't say -- it -- maybe it says it somewhere else but it says, "allyls are cleavable by Mercury."

Q. Okay. Let -- let's just go by point.

A. A-hum.

Q. Okay. Let's look a few lines above that at line 23 and it says, "there are several" -- "several cleavable ethers that permitted removing the fluorescent group before the next successive nucleotide is added."

Do you see that?

A. Yes.

Q. Okay. And then it says, "for

TRAINOR

example," and it lists three possibilities, one of which is allyl ethers, right?

A. Correct.

Q. And it says, "allyl ethers" -- strike that.

So it says that allyl ethers can be cleavable linkers, agreed?

A. That is the implication, yes.

Q. It also says that "a silo ether can be a cleavable linker on are tether," right?

A. It appears to, yes.

Q. I'll hand you what's been previously marked as Exhibit 1008, the Stemple reference.

THE REPORTER: The which reference?

MR. COSTAKOS: The Stemple.

THE REPORTER: Stemple.

MR. COSTAKOS: Yeah.

(Whereupon, the Deponent reviews the document.)

Q. I think it's known to us as the

TRAINOR

Stemple 3 reference even.

MR. COSTAKOS: But for the record, it is Patent No. 7,270,951.

Q. And you're familiar with this reference, right?

A. Yes, I am.

Q. In column 10 of the -- well, strike that.

Stemple discloses a detachable blocking group, doesn't it?

A. I have to take a look.

Q. Okay.

A. I talk about that in my declaration as well.

Q. Well, let -- let's look at column 10?

A. I -- I have to go to my declaration, because there is a lot of material here and a lot of references.

Q. Okay. Well, can you also turn to column 10 while you're looking?

A. Yeah. Yes. I got it open.

Q. Okay. So if you look at column 10 of Stemple, at line 8, it refers to

TRAINOR

"a detachable blocking group is 3'-O2 nitrile benzyl."

Do you see that?

A. Yes, I do.

Q. And if you look, the two lines that are above that, so beginning at line 7, column 10, or excuse me, beginning at line 6, it says, "in a preferred embodiment the detachable labeling group is a label, e.g., a fluorophore linked to the base of the nucleotide" --

A. Sure.

Q. -- "i.e, by a 2-nitrile benzyl group."

Do you see that?

A. Yes.

Q. So that discloses a fluorophore that is attached to the base by a cleavable linker, right?

A. By a photocleavable linker, yes.

Q. Okay. The linker that is in column 10 is cleavable by light?

A. That's correct.

TRAINOR

Q. I'll hand you what's been previously marked as Exhibit 1005. Let's just quickly go off the record, here. Sorry about that.

VIDEOGRAPHER: The time is 4:08 p.m., and we're going off the record.

(Whereupon, a discussion is held off the record.)

VIDEOGRAPHER: The time is 4:09 p.m., and we're back on the record.

Q. So I've handed you what's been marked previously as Exhibit 1005 which is the Dower Patent --

A. Yes.

Q. -- US Patent No. 5,547,839.

A. Yes.

Q. And you're familiar with that reference, right?

A. Yes, I am.

Q. Okay. And so, if you turn to column 25 of Dower, if you look at line 35, beginning at line 35 --

TRAINOR

A. A-hum.

Q. -- it says, "A fluorophore is placed in a position, other than the 3'-OH of the nucleoside and a different group 3'-OH on the dNTPs to function as a chain terminator."

Do you see that?

A. Yes.

Q. Okay. And so, that --

A. So put it somewhere else is what they're saying, you can put it somewhere other than 3'.

Q. Yes. Someplace other than 3', yes.

A. Yes.

Q. And have a blocking group on the OH?

A. Yes.

Q. Okay. And if you look at figure 9 of Dower, figure 9 shows the attachment of FMOC to the base, right?

A. Yes. In a -- in a -- yes. Somehow it would imply it has a B, and I'm guessing that is the base and it's

an FMOC.

Q. And FMOC is a type of fluorophore, isn't it?

A. FMOC is fluorescent. I don't know that it's ever been used as a label. I don't think that's been established.

Q. But it is fluorescent?

A. Yes, it is.

Q. Now, if you look at column 15 of Dower, beginning at line 52, it says that "one important functional property of the monomers is that the label be removable."

Do you see that?

A. A-huh.

Q. Yes?

A. Yes.

Q. Okay. So it does disclose the use of a removable label in Dower?

A. I -- I don't see anywhere where he asserts that the FMOC is removable. It might be but I don't know that he discusses that.

TRAINOR

Q. Okay. But you agree here he talks about in the -- in 52, in line 52 and 53, he refers to the label being removable, do you agree with that?

A. A label, but I don't think that flows from that figure.

Q. Okay.

A. These are two statements they -- it makes.

Q. And if you look at column 18 --

A. A-hum.

Q. -- and down at the bottom there, there is a line 64 and there is a reference to "Figure 9"?

A. A-hum.

Q. Yes?

A. Yup.

Q. And it says, "a suitable nucleotide is labeled with FMOC fluorescently detectible label by reaction," et cetera.

Do you see that?

A. Could you give me the line again, please he is?

TRAINOR

Q. Sure. Beginning at line 64, there is a reference to "Figure 9," and then the very next line --

A. Right.

Q. -- it says, "a suitable nucleotide is labeled with the FMOC fluorescently detectible label."

Do you see that?

A. Yes. Well, actually, that is not a nucleotide. It's incorrect. It's a nucleoside.

Q. It's a nucleoside.

A. It's not a nucleotide. And that's an important distinction because the -- all of the -- all of the nucleotides of interest in Dr. Ju's invention has a phosphorus and this doesn't have a phosphate on it, it has photocapable protecting group on 5', and that's a major distinction.

Q. Okay. So -- but it does say that the molecule that is in Figure 9 is labeled with -- and which you say is a nucleoside, is labeled with the FMOC

TRAINOR

fluorescent -- fluorescently detectible label, right?

A. Well, he claims that it's detectible but I -- I'm struggling to see what that nucleotide has anything to do with the DNA sequencing. It can't be used for DNA sequencing.

Q. Okay. Well, let -- let me --

A. Even a person of ordinary skill in the art would say this has to do with DNA synthesis not with polymerase substratability there is no triphosphate.

Q. Okay.

MR. COSTAKOS: Move to strike as non-responsive.

Q. So my -- this -- the questions I'm asking you here really go to your point that you made earlier as to whether FMOC is is a label.

So isn't it accurate that Dower characterizes FMOC as a fluorescently detectable label?

A. He appears to do that. I'm not

TRAINOR

sure I agree with him, and I -- but I'm not sure a person of ordinary skill in the art reading the literature would see that FMOC was a useful label for the purpose.

Q. FMOC groups are removable by a base. Is that right?

A. A relatively strong base, yes.

Q. Let's turn to paragraph 71 of your declaration as refers to the '698 patent.

A. '697 or '698?

Q. '698, paragraph 71 of '698.

A. Okay.

Q. I'm just waiting for your counsel to get to that page.

A. Yeah.

MR. COSTAKOS: Are you all set?

MR. WHITE: I just wanted to make sure that we got the right one.

A. And -- and '698?

Q. Yeah.

Okay. In paragraph 71 of your declaration as it relates to the '698

patent you are referring to some aspects of original Claim 11.

A. Yes.

Q. And you say here that "Dr. Weinstock testified that he understood that Claim 11, now substitute Claim 25, describes the product of original Claim 5, i.e." --

A. I'll need to see the claims.

Q. Okay.

A. I have a claims' sheet. I don't know if you want to give me one or I -- I have a list of the claims. I can't answer your questions unless I'm --

Q. Well, I -- I'm not done with my questions.

A. Yeah.

Q. Well, why don't we do this --

A. Finish your question and then I -- I'll -- fine.

Q. We -- we'll do it one better, I'll give you the patent then I'll re-ask the question.

A. Excellent.

TRAINOR

Q. Assuming I can find the patent.

A. Okay.

Q. Okay. Here's a copy of it.

A. And this, of course, doesn't have the substitute claim on it, so I will need to -- I believe that might be in the back?

Q. Well, this question really goes to original Claim 11 anyway.

A. Okay.

Q. Let -- let me re-ask the question now.

You say in paragraph 71 of your '698 declaration that Dr. Weinstock "testified that he understood that Claim 11, now substitute Claim 25" -- well, let me start over again.

You say in paragraph 71 of your '698 declaration that, quote, Dr. Weinstock testified that he understood that Claim 11 (now substitute Claim 25) describes the product of original Claim 5; i.e., the product of attaching a plurality of

TRAINOR

different nucleic acid templates to a solid surface, end quote.

A. Right.

Q. Do you see that in your declaration?

A. Yes, I do.

Q. Okay. And you cite there to his transcript, Exhibit 1034, page 79 and 80. Do you see that?

A. Yes, and if you are going to ask me questions about it, then I'll need to see that as well.

Q. My question right now is that is what you cited to, right?

A. Yes. That's correct.

Q. Is -- is that your opinion?

A. Yes. I wrote it.

Q. Okay. And is that -- that an opinion that you came up with on your own?

A. All the opinions were -- were worked on between myself and the attorneys.

Q. Okay.

TRAINOR

A. Because there are certain points of law that I'm -- I'm not qualified to -- that were explained to me and I used them in my judgment of these things.

Q. Is this one of those or is this one of those that you came up with on your own?

A. I don't know about that at all. Certainly, all of this, I was advised by the attorneys, the set of attorneys that I'm working with on all of these the entire declaration.

Q. I -- I guess that the -- the question I'm asking and maybe I'm asking it inartfully is: Is -- is this your opinion as -- as a scientist or were you provided this opinion as sort of a matter of law by your attorneys?

A. The attorneys -- I -- I didn't get into claim construction. The attorneys explained to me what that claim means and how I should interpret that and then I -- I, as an expert witness and as a scientist and applying

sort of the standard of being of ordinary skill in the art, how would I read Dr. Weinstock's testimony in relation to the -- to the claim.

Q. Okay. So the opinion about what -- what Dr. Weinstock testified about, that is your opinion?

A. Yes, it is.

Q. Okay. Now, you understand that original Claim 11 didn't actually have the word "different" in it, right?

A. That's correct.

Q. Okay. But you -- you say that what you characterize as Dr. Weinstock's understanding is consistent with your understanding?

A. Yeah.

Q. Right?

A. So I'd like to --

Q. So you see --

A. -- I would like to see his deposition, if we're going to have a discussion about this point.

Q. We are, but first we're going to

have a discussion just about your -- your conclusion as relates to Claim 11.

A. Okay.

Q. Okay? So, you said that it -- it was consistent with your conclusion that the word "different" --

A. Right.

Q. -- should be part of Claim 11?

A. Right.

Q. So you think that as you read Claim 11, original Claim 11, the word "different" should be in the claim where it says "a plurality of nucleic acid templates," you read that to mean a plurality of different nucleic acid templates?

A. I think that -- that, my understanding, I -- I didn't rewrite the claim, they were represented to me as amended claims.

My understanding was that change was meant to clarify the claim and certainly to broaden the claim, that's for sure.

TRAINOR

And I believe the, and I have to see -- refer to Dr. Weinstock's deposition, but I believe that Dr. Weinstock understood that the original meaning of that claim is as -- as written and unamended was different, you know, different and we said -- said -- and I think the decision of the attorneys must have been to say let's clarify that claim so there is no question as to what we mean.

Q. Sure. My question is: When you read the claim, the original Claim 11, you understood the language "a plurality of nucleic acid templates," to mean a plurality of different nucleic acid templates?

A. Absolutely. The title of the patent is "Massive Parallel Method of Decoding DNA and RNA." There would be no point if you are -- were just sequencing the many copies of the same thing. So the intent of the entire patent is a technology that allows you

to parallel -- to do many different nucleic acids in parallel.

Q. Okay. DNA sequencing wouldn't really make much sense -- strike that.

It wouldn't -- strike that.

It wouldn't make sense to talk about sequencing short DNA segments unless the templates were different?

A. Yeah. And I -- I think that Dr. Weinstock -- and my -- my recollection and I -- I'll be happy to go back to the deposition, but my recollection was he says, "sure," and we all the agree that -- well, I agree with that, and that it -- that these are different.

Q. And the invention in the context of DNA sequencing wouldn't make any sense if the templates were all the same?

A. Well, certainly, there are certain -- in other words, I don't believe the claims restrict to massively parallel sequencing. That's

TRAINOR

-- that is what you like to do commercially but the claims speak to doing it to a single sequencing reaction, which is an element of the larger invention but they're a legitimate -- a legitimate invention.

Q. A-hum.

A. So I mean there is a difference here between what a claim says and what the intent of the larger invention in the commercial realm is, so I think that all along you're looking to do this many times in parallel but you got to do it once --

Q. Right.

A. -- the right way, period, before you can do it many times in parallel.

Q. Right. But I thought you said when you read Claim 11 in its original form where it says, "the plurality of nucleic acid templates," you understood it to mean a plurality because in the context of DNA sequencing it wouldn't really make sense for them all to be

the same?

A. Yes. Yeah. For this particular claim, this -- this speaks to the plurality -- the situation where one is, indeed, sequencing a plural -- a plurality of nucleic acids in parallel.

Q. Of different nucleic acids?

A. Of different nucleic acids, okay. And the other claims that are at issue, for example, claim 1, which is being, you know -- sorry claim 8, reissued -- reworded, these claims speak to a process that -- that restricted to just the process of what you do for any one of those templates, so I think that the -- the -- the intent here is an independent claim that takes into account the fact that you've got plural -- plurality and there is a novel composition created in the process of doing that.

Q. I'm going to hand you a portion of Dr. Weinstock's testimony.

A. Okay.

TRAINOR

Q. I think I'm going to remark it even though it's been submitted already as a huge exhibit.

MR. COSTAKOS: So I'll mark this as Exhibit 1040.

(Exhibit 1040, Excerpt from the document previously submitted as Exhibit 1034, Deposition of Dr. George Weinstock, was received and marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

MR. COSTAKOS: For the record, this is an excerpt from the document that was previously submitted as Exhibit 1034, which is the deposition of George Weinstock, and includes pages 78 through 81.

A. A-hum.

Q. Okay? And you'll see that that includes the section that you refer to in paragraph 71 of your declaration --

A. Okay.

Q. -- right, including the page at

the beginning and the page at the end to give context. Okay?

So in your declaration you say, again, "Dr. Weinstock testified that he understood that Claim 11 describes the product of an original Claim 5, i.e., the product of attaching a plurality of different nucleic acid templates to a solid surface," and you cite his transcript, page 79, line 22 through page 80, line 19.

(Whereupon, the Deponent reviews the document.)

Q. So let's look at that testimony. So if you look at 79, at line 22, it says, there is a question that says:

"QUESTION: So going back to Claim 11" -- and it's referring to -- "a plurality of nucleic acid templates immobilized on a solid support."

And then it has additional language. Do you see that??

A. Yes.

Q. And then you see there is an

answer that begins on 25 and goes through page 80 line 11.

Where in there does he say that he understood the original Claim 11 to describe the product of Claim 5; i.e., the product of attaching the plurality of different nucleic acids templates to a solid substrate?

A. I -- I read his testimony here, going back to Claim 11, the question, line 22, "referring to nucleic acid templates immobilized in a solid support," and then it has additional language.

Then his answer, I mean, if -- if Claim 11 is just referring to product in Claim 5, then that's fine. For some other reason, I don't have the -- he seems to be somewhat confused.

Q. Right.

A. And it says, "if it's meant to series of template primer pairs for each one of the disabled nucleotides it" --

TRAINOR

THE REPORTER: I'm sorry?

THE WITNESS: It says, "if it's meant to mean -- I -- I'll just refer to line 8 through 11, on page 80. It says, "that's" -- "if it's meant to mean a series of template primer pairs, wherein each one of those has a labeled nucleotide on it and the lock" -- "the locking group is still present, that's okay."

And for the question is, in the deposition was: "And that's what you get if you do the method of Claim 5 something of that type?"

And he says, "Yes, that's all right. That would be all right."

Q. He doesn't say anywhere that -- about different template pairs. Do you agree with that?

A. Well, I don't think that the interpretation requires that, you know, he -- the Claim 11 is what you get from Claim 5 if you apply it over and over again.

TRAINOR

Q. Is that what he says?

A. No. He doesn't.

Q. I didn't think so.

A. He didn't say it that way.

Q. Okay.

A. But I think the issue here was how he understood the plural -- the plurality and what he thinks the composition was.

Q. And he never says --

A. And he -- let me finish.

Q. I'm sorry. I'm sorry.

A. He says, "it seems to mean if you mean a number of different primer" -- "of template primer pairs with the nucleotide attached that fits the other description." That's okay. I agree with that.

Q. But he doesn't say that and you agree with that?

A. Where does he say that --

MR. WHITE: Objection.

Q. Well, he -- he says --

A. "If it's meant to mean a series

of template primer pairs wherein each one of those has a labeled nucleotide on it and the blocking group is till presents, that's okay."

Q. He doesn't say different?

MR. WHITE: Objection. Form.

A. I think -- certainly, I think we talk about "different" and in a different section with Dr. -- and whether in -- you might not have pulled that section out. I would have to go back and look at his deposition.

Q. Well, I want you to -- I'm asking you in this section that you just referred to in your declaration, 79, line 22, through 80 line 19 --

A. A-hum.

Q. -- where does he say that Claim 11 requires different -- the plurality of different nucleic acid templates?

A. Let me --

Q. Where does he say it in words or substance?

A. Okay. Let me go back and look

TRAINOR

at my -- I want to get the proper reference, so I'm going to back and look at my --

Q. Sure. It's paragraph 71 on page 39.

(Whereupon, the Deponent reviews the document.)

A. Okay. Yeah. That is not the only discussion, actually.

In this particular statement he obviously doesn't say "different." Okay? But we have, in his deposition -- let me go back because I believe I have it in here but it's just a lot of -- it's a couple hundred pages of testimony here and I have to go back through the...

(Whereupon, the Deponent reviews the document.)

A. My reference on Claim 11 because I know it's in here.

Q. Why don't we do this --

A. Okay.

Q. -- why don't we -- we're

TRAINOR

probably near the end of our two hours anyway.

A. I can find it.

Q. Why don't we take our break for today and if you find it tonight you can point it out to me. I know there are a lot of pages in here.

MR. COSTAKOS: Is that acceptable to stop for today?

Q. I think you know, Dr. Trainor, that you are not allowed to talk to your counsel about substance?

A. A-hum. Okay.

Q. We will come back. Well, that is probably a blessing in disguise, and no criticism intended. I guess, it -- it's hard to avoid that conclusion, though.

MR. COSTAKOS: We're off the record for today.

VIDEOGRAPHER: The time is 4:32 p.m., and we're going off the record.

(Whereupon, the proceedings were

TRAINOR

adjourned at 4:32 p.m.)

J U R A T

I do hereby certify that I have read the foregoing transcript of my deposition.

GEORGE L. TRAINOR

Sworn and subscribed
before me
this 21 day of
Sept, 2013

a Notary Public of
the State of Delaware

JOHN M. DENNIS
NOTARY PUBLIC • DELAWARE
My Commission Expires 3-7-16

C E R T I F I C A T E

I, MAUREEN M. RATTO, a Registered Professional Reporter, do hereby certify that prior to the commencement of the examination, GEORGE L. TRAINOR was sworn by me to testify the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a true and accurate transcript of the proceedings as taken stenographically by and before me at the time, place and on the date hereinbefore set forth.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in this action.

_____

MAUREEN M. RATTO, RPR

License No. 817125

I N D E X

WITNESS:

GEORGE L. TRAINOR 105

CROSS-EXAMINATION BY 105

MR. COSTAKOS

E X H I B I T S

Exhibit 1040, Excerpt from the document previously submitted as Exhibit 1034, Deposition of Dr. George Weinstock, 135

INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.

After doing so, please sign the errata sheet and date it.

You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition.

It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript maybe deemed to be accurate and maybe used in court.

E R R A T A

I wish to make the following changes, for the following reasons:

PAGE LINE

123 13 CHANGE: "substratability" to "substrate ability"
REASON: Mistranscription

130 20 CHANGE: "represented" to "presented"
REASON: Mistranscription

130 24 CHANGE: "to broaden" to "doesn't broaden"
REASON: Mistranscription

138 9 CHANGE: "lock" to "block"
REASON: Mistranscription

138 10 CHANGE: "locking" to "blocking"
REASON: Mistranscription

140 4 CHANGE: "till" to "still"
REASON: Mistranscription

WITNESS' SIGNATURE

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ILLUMINA, INC.,

Petitioner,

vs.

PATENT OF THE TRUSTEES
OF COLUMBIA UNIVERSITY IN
THE CITY OF NEW YORK

Patent Owner.

----------x

VOLUME III

VIDEOTAPED DEPOSITION OF DR. GEORGE TRAINOR

Thursday, September 5, 2013

New York, New York

9:00 a.m.

Reported by:
Maureen Ratto, RPR, CCR, CLR
Job No: 31224

* * *

Deposition of DR. GEORGE L. TRAINOR, held at the offices of Fitzpatrick, Cella, Harper & Scinto, LLP, 1290 Avenue of the Americas New York, New York, 10104-3800, pursuant to notice, before Maureen Ratto, Registered Professional Reporter, License No. 817125, and Notary Public.

* * *

A P P E A R A N C E S:

Counsel for the Petitioner:

FOLEY & LARDNER, LLP

777 East Wisconsin Avenue

Milwaukee, WI 53202-5306

414-297-5782

BY: JEFFREY N. COSTAKOS, ESQ.

jcostakos@foley.com

REINHART BOERNER VAN DEUREN, S.C.

22 East Mifflin Street Suite 600

Madison WI, 53703.

608-229-2219

BY: ROBERT A. LAWLER, ESQ.

rlawler@reinhartlaw.com

Counsel for the Patent Owner:

COOPER & DUNHAM, LLP

30 Rockefeller Plaza

New York, New York, 10112

212-278-0400

BY: JOHN P. WHITE, ESQ.

jwhite@cooperdunham.com

A P P E A R A N C E S, continued:

Fitzpatrick, Cella, Harper & Scinto, LLP
1290 Avenue of the Americas
New York, NY 10104-3800
212-218-2100
BY: ROBERT S. SCHWARTZ, ESQ.
rschwartz@fchs.com
SIEW YEN CHONG, ESQ.
schong@fchs.com

ALSO PRESENT:
MARCUS BURCH, ESQ.
Illumina Senior Patent Counsel
Manuel Abreu, Videographer
Kevin Burgess, Texas A&M University

VIDEOGRAPHER: This begins the video deposition of Dr. George Trainor, in the matter of Illumina, Inc., Petitioner, versus Patent Trustees of Columbia University, in the City of New York, patent owner.

This deposition is being held at 1290 Avenue of the Americas, New York, New York, on September 5th, 2013, at approximately 9:03 a.m.

My name is Manuel Abreu, from the firm of David Feldman Worldwide, and I'm the legal video specialist.

The court reporter is Maureen Ratto, in association with David Feldman Worldwide.

Will counsel please introduce themselves.

MR. COSTAKOS: Jeff Costakos, Foley & Lardner, for Illumina. Also, with me is Robert Lawler, Marcus Burch and Kevin Burgess.

MR. WHITE: John White, from Cooper & Dunham for Columbia University, and with me is Robert

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Schwartz, from the Fitzpatrick firm, and Siew Chong also of the Fitzpatrick firm.

* * *

G E O R G E L. T R A I N O R, having been previously sworn according to law by the Officer, resumes:

CROSS-EXAMINATION BY MR. COSTAKOS:

Q. Dr. Trainor, you've used the term "small," a number of times previously in connection with a blocking group.

Do you recall that testimony generally?

A. Yes.

Q. Okay. Well, what does the term "small" mean, in the context of the Ju invention as it relates to blocking groups?

A. I think what he's -- if you read the claims, it is small such that it does not interfere with the recognition by the polymerase.

THE REPORTER: It does not --

TRAINOR

THE WITNESS: -- it does not interfere with the recognition of the polymerase.

Q. Is that the definition of "small"?

A. I have -- "small" can have many definitions, obviously, and I look to the specification of what his intention is and I read the claim. And the -- the intention is that it be sufficiently small that it is now accepted by the polymerase.

Q. Okay. So it's sort of a functional definition, the way you interpret it. Is -- is that fair to say?

A. Well, I think you could ask a chemist: Is this small? And they'd say, Well, relative to what?

And so there's a -- there is a functional definition here. But if you read the claim it simply says, "Does not interfere with recognition by the polymerase." It's a small group, so it

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does not interfere. So I think it's understood that -- that the invention involves a 3'-cap that is removable that is -- is accepted by the polymerase.

Q. Okay. And so that's sort of the cutoff between something that is small and something that is not small as you understand it in the context of the Ju invention?

A. Yes.

Q. As a structural matter, do you have in mind any cutoff between something that is small and not small, in terms of either size or weight or however you'd -- you would measure smallness?

A. No, I -- I don't have a cutoff because I think it's always context dependent.

Q. Okay.

A. So I -- so I can't give you a single -- single criteria to that.

Q. So as long as it works, it --

it's going to be small, in the context of the Ju invention?

A. I think it's -- I can't give you a precise cutoff, I imagine if you give me something with a molecular weight of 1,000 and that was accepted, I would say that wouldn't be small, but I think most chemists would say I would never call that small but it was accepted and perhaps surprising. But I think the notion in this invention is that, is -- is that the insight that Dr. Ju had was that you were going to have to do something relatively small to be accepted by the polymerase. And that was the motivation to look at all the other ways to label -- to look at the base label.

Q. Now, the way you just testified, and I understand that your testimony was somewhat hypothetical, but what you suggested there was that there was some circumstances in which you could envision a molecule that would be

accepted and -- and would not interfere with recognition by the polymerase but would still not be small?

A. Yeah. It was -- it was a hypothetical saying if someone were to show me that, I would -- I guess I would have a hard time saying that was small. If it was a molecular weight of 1,000 than the rest of the nucleotide, for example.

I've never seen an example of such a species and, in fact, I mean the -- what my understanding is certain literature leading up to 2000 that -- that there was relatively little data on groups that any chemist would consider very large, or accepted and the question of where the cutoff is something that has to be experimentally determined and a function of which polymerase you're talking about.

Q. There was literature prior to 2000 that would characterize certain blocking groups as being -- as not

interfering with polymerase. Is that fair to say?

A. There was some literature, some limited success with -- well, with groups in that position, yeah.

Q. And those things would all be considered small as of the date of the Ju invention?

A. Some are considered small and some were getting on the more larger size.

Q. And just to make sure that we -- we have a clear record, and the court reporter made a special point of making this -- this to me this morning, let's try to make sure that you wait until I --

A. I'll give you a beat to let --

Q. Right there, you didn't do it.

A. Yeah.

Q. Okay. So wait until I'm done, and then I'll try to wait until you're done --

A. Right.

TRAINOR

Q. -- as well. You didn't do it again. I know it's hard to do because it's unnatural but that's what we're going to have to do.

Is an acetyl group small?

A. I would think chemists would consider acetyl relatively small. They're a smaller group, so it's a relative term, right.

Q. Well, in -- in the context of a blocking group as it relates to the Ju invention, is an acetyl group small?

A. Yeah. Given -- given that Dr. Ju has given some examples of groups that are of similar size to acetyl and shown those going working I would say that was small.

Q. How about a phosphate group?

A. A phosphate group is a little bit larger because it's a three-dimensional size, but I think you have to understand in the context of this is it -- that it's small and has to be functional with the polymerase,

so there's sort of multiple constraints. It's not just that it's small but it doesn't interfere with the polymerases function.

And I'm not aware of -- of phosphate being accepted and acetyl is -- certainly, Dr. Ju pointed out and the literature suggests that acetyl groups are removed by the polymerase and that was not an acceptable cap for the 3' for that reason.

Q. You've heard of TBOC before, right or BOC?

A. Yeah.

Q. Would that be considered small?

A. No.

Q. Is that because it's large in absolute terms or because it would interfere with the polymerase?

A. No, it -- it's large because I'm speaking as chemist. A chemist would use a TBOC when he wanted to -- to create some space, when he wanted to occupy a lot of space.

TRAINOR

Q. And how about NBOC, would that be considered?

A. N -- excuse me?

Q. NBOC, a nitrogen attached to a BOC?

A. NBOC that would -- okay. That would -- that would not be a cap, that would release 3'-hydroxyl. So I could answer your question but it would not be relevant to sequencing because you can't convert an NBOC to a 3'-hydroxyl.

Q. How about NVOC?

A. NVOC? I'd have to remember -- remind myself what an NVOC is. I think it's a nitroveratryl. I think it would be among the larger size.

Q. Would it be -- it's larger but would it be small in the context of the Ju invention?

A. I think most chemists would say, yeah, that is a small group.

Q. And where do you get your definition of the word "small" in the Ju patent?

TRAINOR

A. Would you like me to look through it?

Q. Well, I'd like you to point it out, I guess. I don't want you to read it?

A. I'd have the look at his patent to do that.

Q. Well, let me do this, can I just hand you the '575 patent --

A. That would be fine.

Q. -- which is one of the patents, yeah.

A. Doctor Ju speaks to the photocleavable cap, in this particular case, photocleavable. Of course, whether it's photocleavable or chemically cleavable, it doesn't matter because the polymerase doesn't know it's the step you do after. So, it would kind of apply to most of the cleavage, obviously.

This is column 3, group -- talking about photocleavable groups and having concerns about the particular

what it considered to be normal photocleavable groups because they're considered to be bulky, polymerase will have difficulty incorporating that 3'. If small chemical moiety could easily cleave to high yield a cap and 3' --

THE REPORTER: Wait. Wait.

Q. Yeah. You need to slow down. Just because you can talk fast doesn't mean --

A. If you want -- if you'd like me to read it I would, or do you want to just refer to it? But I think he -- he doesn't say "I define small by how many atoms." But he clearly indicates that "I define small as 'small enough' that it's accepted by the polymerase."

Q. Okay. And the language you are referring to is in column 3 beginning around line 5?

A. Line 5.

Q. Okay. Now, Ju patent --

A. Can I use the '575 for this?

Q. Yes. Right.

TRAINOR

A. Thank you.

Q. Figure 8 shows a representative scheme for synthesizing the molecule in the patent, right, the nucleotide?

A. I'll take a look.

(Whereupon, the Deponent reviews the document.)

A. Yes. It appears to.

Q. And if you look at column 24 of the '575 patent, beginning at line 44, and extending to around line 52, you see there is a description of Figure 8?

A. A-hum.

Q. Yes? Actually, there are four sentences or so that describe Figure 8 in the Ju patent between --

A. Yes.

Q. Okay.

MR. WHITE: I'm just going to object for the record to the line of questioning since the scope of the deposition is supposed to be limited to the declaration that has been submitted.

TRAINOR

MR. COSTAKOS: Okay.

Q. So I think as we've talked about Figure 8 shows how to make the various constituents of the molecule?

A. Purports to, yes.

Q. Yes. It says that it does at least. And you see at the top of the page on Figure 8, it shows a reaction to attach the fluorescent label to a photocleavable linker, right?

A. That seems to be the case, yes.

Q. And if you look at column 24, you'll see there is one sentence about that where it says, beginning at line 47, "Linker tam is synthesized by coupling the photocleavable linker (Rollaf, 1982) if NHS-tam."

A. Yes.

Q. Do you see that?

A. Yes.

Q. So it cites this Rollaf article for the teaching about how to attach the fluorescent label to the photocleavable linker, right?

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A. I had no opportunities to read that reference but I'll have to take that at face value.

Q. That is at least what the -- the --

A. Yes.

Q. -- the patent is trying to indicate, right?

A. Yes. I presume so. Like I said, I haven't read that reference and it's not -- not part of my declaration, so...

Q. Sure. I'm -- I'm not going to quiz you on the reference. I guess, I'm just asking you about the patents, so that the patent suggests it -- it points to the Rollaf article in connection with the statement about synthesizing the linker tam?

A. Yeah.

Q. Okay. So the first row shows how to make the photocleavable linker and then the second and third rows shows how to attach the photocleavable

linker to the dye, right?

A. That appears to be what he's doing.

Q. Okay. And then after the label is added, an NHS ester is added to one end of the molecule, right?

A. You need to be more specific there.

Q. Sure. If you look at the -- in the third row down --

A. Okay.

Q. -- in Figure 8, and I guess I'm using "rows" to mean this sort of series of molecules. And by the way, I'm counting there are six rows.

Do you understand what I'm talking about?

A. Yes.

Q. So in the third row on the left-hand side of the page it says, "N'" -- "NN' dye succinimide carbonate," and IT points over to the right. Are you with me?

A. Yes.

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Q. And then it has the linker tam molecule and you see over on the left-hand side of that molecule is an NHS ester, right?

A. That's -- that's a carbonate not an ester, technically.

Q. Okay. But it's a -- it's added by NHS technology. Do you agree with that?

A. The -- it's the NHS is leaving --

THE REPORTER: Is a --

THE WITNESS: -- is leaving, is a proposed leaving group.

Q. Okay. And the -- the NHS just so, for us non-chemists, it's the -- the sort of pentagon with the two oxygen attached by double bond that are sticking off like ears on the end? That's a crude description at least of what it kind of looks like in the drawing?

A. Yeah.

MR. WHITE: Objection.

TRAINOR

A. Fair enough.

Q. No, I understand. It's -- it's meant to be just so we'll all know kind of what we're looking at here. Okay. Fair enough.

NHS esters are -- or NHS groups are well-known linkers, aren't they?

A. Yes.

Q. And among the most common linkers in nucleotide chemistry? Would you agree with that?

A. It's not a linker, it's a leaving group, but if you want to be precise. I'm just addressing the question. It is a common -- a common leaving group for coupling complex pieces, yeah.

Q. All right. So for the purpose -- the purposes of the NHS group, is to couple molecules together?

A. It's a leaving group that facilitates the joining of two pieces. Let's put it that way. That's fair.

Q. Okay. And they're commonly used

in nucleotide chemistry because they're versatile. Is that right?

A. I use them myself, in my own work.

Q. Okay. So then in the next row down, after showing how to attach the label to the photocleavable linker, it shows the reaction of how to make the nucleotide molecule itself, so it -- it's sort of a separate reaction from the one we just went through on the first three rows.

Do you see that?

A. Yes.

Q. So that's in the -- by the way I count the fourth and fifth rows in the molecule --

A. Yeah.

Q. -- in the -- in the drawing?

A. Yes.

Q. Okay. And now, if you look at column 24, there's a line about the creation of this particular molecule, so if you look at line 45 and through

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47 --

A. Yes.

Q. -- it says, "7-deaza alkynyl amino, dGTP, is prepared using well-established procedures," and then it cites to Prober, Lee and Hobbs.

Do you see that?

A. Correct.

Q. So the procedure for creating this particular dGTP was well established by 2000. Do you agree with that?

MR. WHITE: Objection. Form.

A. No, I don't.

Q. Even though he says that it was "well established"?

A. Yeah.

Q. And that he points to your article and your patent?

A. Well, my article and my patents don't tell you how to make the oxygen nucleotide particularly with the G -- the G wanting with that linker. And I am presuming that he was -- he might

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have been referring to my -- my disclosure. I was the inventor on the -- the Prober and the Hobbs patent, the co-inventor on the Hobbs patent.

He may have used one of the reactions but the synthetic scheme would have to be completely reworked for it because the guanine is not put in intact. So someone of ordinary skill in the art would look at this and not know how to make the deoxy 3'-cap nucleotide using the direct procedures of Hobbs. They might take one reaction out of there, and that was Hobbs's contribution to -- was the actual coupling of the acetylene to the iodo that was his invention, his contribution to the project.

So he presumably used that chemistry but, Dr. Ju had to do a significant reworking and -- of the chemistry, in my understanding, and I've noticed he's used protecting groups and I didn't, because there is

much incompatibility once you go to the deoxy.

So, you know, he does cite this using methods but he's going to need to do more than that, he had to reinvent the synthesis to get to this species.

Q. Okay. And where is the description of that reinvention of that synthesis?

A. Well, if you go into the -- I don't know. I'd have to -- I'd have to spend time, I haven't gone -- studied my declaration. I'll have to go back and look through the experimental details.

Q. Is there any reference in the Ju patent to how to synthesize this molecule, other than the sentence that says, "It's prepared using well-established procedures," that's citing to your article and your patent?

A. Well, I have to take a look because it wasn't something I was asked to opine on in this -- in the

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declaration.

(Whereupon, the Deponent reviews the document.)

MR. WHITE: While Dr. Trainor is looking at this I'll just reiterate my objection to the line of questioning as outside of the scope of the declaration and prohibited by the rules of the IPR, but I'm not going to tell him not to answer, but -- and I don't think I should have to unless you feel otherwise, and to object every time you ask him a question about this.

MR. COSTAKOS: That's fine.

MR. WHITE: I assume you agree it's sufficiently clear that we've objected to this line of questioning.

MR. COSTAKOS: I understand. Yes. That's fine.

A. I don't see any -- any particular detail that I can refer to at this point. Certainly, he seems to be referring to Hobbs. If you go to line -- column 27, beginning on line

28.

Q. What column are you talking about?

A. 27, line 28.

Q. Yes.

A. And basically talking about doing a propargyl amino GP -- GTP coupling, putting the tag on. I think the best I can do -- and again, I was not asked to evaluate this or even to investigate this as, you know, as part of my declaration -- my understanding this wasn't part of the petition, but I -- from just looking at it in the few minutes that I've had to look at it here I suggested Dr. Ju is referring to the Prober/Hobbs technology for the actual coupling of the linker, which was something there was no way to label a "G" prior to our work, so he was using that, referring to that particular step.

He would have to have some protecting groups, identify suitable

protecting groups and the deazaguanine unlike the other nucleosides is never brought in as a guanine to start it's -- it's prepared by synthesis from a different heterocycle. So the order in which you create, turn the heterocycle into guanine versus the other steps you must carry out is a matter of experimentation. And would probably be somewhat different for a dideoxy and dideoxy guanine in my opinion.

Q. So when you say you suspect he was talking about -- Dr. Ju was talking about the attachment of the linker when he was referring to your article and patent --

A. By attaching, by creating the bond between the acetylene and the 7-carbon, because that was a step -- that was a step for which there was no chemistry previous to our work.

Q. And -- and you don't dispute, obviously that it says that the molecule is prepared using

well-established procedures and points to your article and patent?

A. Well, certainly in the year 2000 that coupling was well established because every company that -- the companies that were selling dye terminators were all using that coupling reaction and there were additional scientists who had -- who were taking our terminators and putting different dyes and they would have to do that work to make those compounds, so that I think that coupling was well, well understood.

Q. The use of ddNTP that were -- that had fluorescent labels attached to the 7-deazapurine position, that was common by the year 2000?

A. For Sanger sequencing, yes.

Q. Applied Bio-Systems was the largest company in the Sanger sequencing market, vaguely -- roughly, you agree with that?

A. Yes. They -- they licensed our

technology.

Q. Right. And the -- the products they were selling had fluorescent dyes attached to the 7-deazapurine position?

A. Of the dideoxy position, yes.

Q. Is it shown in anywhere in the Ju patent how to make a dNTP of a form that is on the left-hand side of the fourth Figure 8 that has an iodine in that position?

A. I don't believe he gives explicit experimental detail for that. Again, he may have been referring to our work and the question is which order do you do the steps in and he doesn't certainly tell you that in here, but I presume that a person skilled in the art would figure out how to do that. It would take sometime and this was a 20-step synthesis in our -- in our work, so -- but that information was available to the person.

Q. So it would have been within the level of skill of one of ordinary skill

in the art to synthesize the molecule that is shown in the left-hand side of the fourth row of Figure 8?

MR. WHITE: Objection to form.

A. With considerable experimentation. I would say it would be a significant project to do that, to rework that synthesis. This was, as I said this was over a year and 20 steps it took us and it would have to be reworked. Some elements of that you could reuse but you would have to reinvestigate it. I think certainly this was in -- this was the toughest synthesis of all the nucleotides.

Q. The "G" is you mean?

A. Yes, the "G."

Q. I'll show you what was previously marked as 1013. I'm also going to show you what's been previously marked as Exhibit 1003.

MR. COSTAKOS: Okay. And for the record, Exhibit 1003 is the Prober reference and Exhibit 1013 is the Hobbs

reference.

Q. So Exhibit 1003 is the Prober reference that is referred to in column 24 as showing how to synthesize this molecule, right?

A. A-hum.

Q. Yes?

A. Yes. That's the reference it describes, yes.

Q. And the Hobbs reference Exhibit 1013 is the reference that's also referred to in column 24 of the Ju patent, right?

A. I believe so.

Q. And you testified before that you were one of the inventors on both of these references. Is that right?

A. I was a co-author on the science papers, not the -- not the patent. I was a co-inventor on the Hobbs patent. My name, it was added later. It was not issued as -- as the others but my inventorship was added later.

Q. Right. And if you look at the

back page you'll see that they --

A. Yeah, it just doesn't appear on the front, but yeah.

Q. Okay. So let's look at the Exhibit 1013. So if you turn to column 17 --

A. A-hum.

Q. -- in the upper left-hand corner there is a molecule with the number 16 below it.

Do you see that?

A. Yes, I do.

Q. Okay. And that is the ddNTP version of the -- the molecule that is shown in Figure 8 of the Ju patent?

A. That is correct.

Q. And then Figure 8, it shows how to add or at least -- strike that.

In Figure 8 it shows the addition of this particular linker to the molecule that is on the left-hand side of row 4 of Figure 8, right?

A. A-hum.

Q. And the molecule with this

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triple bond and then the allyl and then this group starts with an NHC. Do you see that?

A. Let me just go back to Figure 8 to make sure I'm answering it correctly.

Q. Yeah, sure.

(Whereupon, the Deponent reviews the document.)

A. It appears to show that, yes.

Q. And that -- and I'm -- I'm sure I'm going to butcher how I would say this, but that that is a propargyl trifluoroacetamide?

A. Trifluoroacetamide, yes.

Q. That's much better and there is no description of that in the Ju patent it just points to Hobbs and Prober as how to do that?

A. That's correct.

Q. And if you look at example 1A in Hobbs, which is at column 29, example 1A shows how to make the pro -- but I spelled that wrong. Could you say that

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again?

A. Propargyl.

Q. Propargyl? So example 1A is showing how to make the propargyl molecule, right, and that's beginning at 29, line 54 through column --

A. That's how you make the reagent. It was known in the literature that would simply be the procedure. It was a known compound.

Q. Okay. And then in 1C, it shows how to add the propargyl molecule you created to the iodated nucleoside, right?

MR. WHITE: Objection. Form.

A. You would have to be specific. That's adding to the deoxycytidine that particular procedure.

Q. It shows how to add it to --

A. Not a purine but a pyrimidine.

Q. But it shows how to add it to a cytosine nucleoside?

A. For a cytosine, yes.

Q. After that musical interlude --

and I apologize for that.

Would there be any difference in adding the propargyl to an iodated purine?

A. My recollection is that the reactions are probably somewhat different but they -- they ultimately both worked, obviously because we see gave the details and I could go through the procedures and I recall with maybe one was slower than the other, and maybe there were byproducts we had to purify. I can't recall this it was a long time ago and I haven't read this experiment in 30 years.

Q. But the addition of the propargyl to an iodated guanine molecule was well known certainly by 2000?

A. In the dideoxy context only.

Q. But it was well known by 2000?

A. In dideoxy, yes.

Q. Okay. If you look at column 37, I think there is a discussion of the

TRAINOR

preparation of the purine, the dideoxy deazaguanosine?

THE REPORTER: I'm sorry the dideoxy --

MR. COSTAKOS: -- deazaguanosine.

MR. WHITE: Objection. Form.

Q. If you look, beginning at column 37, line 34.

A. Yes. I didn't think there was a question.

Q. Okay.

A. I'm sorry.

Q. I'm sorry. Okay. So getting back to Figure 8 of the Ju patent. So Figure 8 of the Ju patent, after setting forth the molecule on the left-hand side of the fourth row, the iodated DGTP --

MR. WHITE: Objection. Form.

MR. COSTAKOS: What is your objection?

MR. WHITE: Form.

MR. COSTAKOS: What specifically

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is your objection?

MR. WHITE: It would have to be more specific than that. I think for the purpose of this the rules are quite clear about how the objections are to be expressed and I've just expressed it, you know, in accordance with the rules.

MR. COSTAKOS: And you're not going to explain it?

MR. WHITE: I don't have to explain it further than that. You can take my objection or we'll see if we make a motion to exclude evidence later.

MR. COSTAKOS: Okay. I invite you to read the rule on that.

Q. Okay. So, Dr. Trainor, after showing -- after setting forth this molecule and -- and showing the addition of this particular propargyl molecule, you -- you see the sort of intermediate molecule that is in the right-hand side of the fourth row of

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Figure 8?

A. Yes.

Q. And -- and again, that's -- that's all with -- the only explanation of that reaction is by reference to Prober and Hobbs, right?

A. Yes.

Q. And then in the fifth row it shows the addition of the triphosphate group to that molecule, right?

A. Yes.

Q. And then in the bottom row of Figure 8, it shows putting the results of the top portion of Figure 8 together with the sort of middle portion of the Figure 8 to have a completed molecule. Do you agree with that?

A. A-hum.

Q. Yes?

A. Yes.

Q. Okay. So it shows the -- the DGTP with the linker tam dye attached to it, right?

A. It appears to, yeah.

TRAINOR

Q. Okay. And if you look at column 34 -- excuse me, column 24 --

A. In which patent?

Q. -- of the Ju patent, at line 49.

A. Column 34?

Q. I misspoke originally. I'll start over. If you look at column 24 --

A. Thank you.

Q. -- of the Ju patent, the '575 patent at line 49 --

A. Right.

Q. -- the only description of the combination of the linker tam molecule and the -- the deaza dGTP is the sentence that says, "7-deaza alkynyl amino dGTP is then coupled with the linker tam to produce," and then it shows the formula.

Do you see that?

A. I see that.

Q. And -- and it doesn't say how to do it. It just says -- it just shows it, right?

A. A person of ordinary skill in

the art would find that to be a trivial -- a trivial reaction, that coupling.

Q. Okay. And -- and is that because the linker tam was formed with the NHS leaving group and coupling those two things together would be trivial?

A. Yeah. If a person looked at those two and said, "I would not have concerns that if I had those two species I'd be able to couple them." There may be side reactions, the reaction of the -- of another part of the molecule, for example, with the NH on the guanine, but that would just be something you'd have to experimentally work out.

Q. Okay.

A. The expectation of a person with ordinary skill in the art with that reaction would not be one of the more problematic ones, in my opinion --

Q. Okay.

A. -- in my opinion that with --

would be a person of ordinary skill in the art, it would be there.

Q. And is that because the linker tam was created with the -- with this NHS leaving group that facilitated the coupling of that linker tam to the 7-deaza GTP? -

A. Yeah. As I mentioned before, NHS ester carbonate, carbamate couplings are carried out because they're -- they are mild couplings. It can be carried out in aqueous solution and that's why you do it.

Q. Now, if you look back at the Hobbs patent --

A. A-hum.

Q. So at the top of column 9 -- sorry. Let -- let me ask you a question about the coupling of the -- of the dye to the nucleotide through this NHS.

You said that the reaction would be trivial but that you might have to do a little bit of work but that it

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would be within the skill of one of ordinary -- of ordinary skill in the art.

A. A-hum.

Q. Would that be the case whether it was a dNTP that you were attaching it to or the ddNTP?

A. I think if you look a the synthesis as a whole those couplings would certainly be less risky, regardless of what the nucleoside was.

Q. Okay. So whether it was a --

A. There would be other problems with the synthesis that you'd have to cope with but that would not be -- my anticipation would be that that would not be -- that a person of ordinary skill in the art would look at that scheme and say, I probably won't have trouble with that part.

Q. Okay. Whether it was a dNTP or a ddNTP?

A. That is correct. I don't think that it would be -- that any person

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would be -- would reasonably claim those two.

Now, if you had an R group, depending on what the R group is, there could be a problem. Okay. So we've talked about dNTPs free hydroxyl, that's one situation. The dNTP more functional group, the capping group. That person of ordinary skill in the art would have to assess whether the capping group would be stable under the conditions of the coupling and that would -- I'd have to know which capping group and then some will have worked there.

So that's one of those examples of possible side reactions that -- that might require some research to figure it out.

Q. But that is something that one of ordinary skill in the art would be able to cope with?

A. Yeah. Presuming that the simple solutions worked the -- were that a

person of ordinary skill in the art would be able to cope with. There's always the risk that, you know, after a considerable amount of time you can't find a combination of reaction conditions that work with a given cap and you might have to abandon a cap because, Hey, I can't manage to do the couplings in one of the other reactions in the presence of that.

Q. Okay. So if we go back to -- I'm sorry the -- if we go back to the Hobbs patent, which is Exhibit 1013 --

A. Yes.

Q. -- and I was directing you to column 9, at the very top of column 9, so you could look at the bottom of column 8, too, if you need to obviously, but the Hobbs patent sort of shows you the idea of synthesizing the various constituents of the molecules and putting them together to form the -- the label in this instance ddNTP, right?

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A. A-hum.

Q. Yes?

A. Yes.

Q. And so what -- what it shows here in the very top of column 9 is the five parts of the molecule the triphosphate, the sugar, the heterocyclic base, the linker and the fluorescent label, right?

A. Yes.

Q. And then what Hobbs does is he goes through and shows you how to make each piece of those, right?

A. Specifically, for chain terminators, for irreversible chain terminators, yes.

Q. And shows how to join them together, right?

A. Yes.

Q. Now, if you turn to column 47 of Hobbs, example 8 shows preparation of a deoxy nucleotide, right?

A. Yes.

Q. And in this instance it's a

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dCTP, right?

A. That's correct.

Q. Okay. And if you look at example 9, it also shows an -- an example of how to make a deoxy nucleotide, right?

A. Yes.

Q. And in this instance it's a dUTP, right?

A. A-hum.

Q. Right?

A. Yup. Yes. Both pyrimidines, of course.

Q. We can put Hobbs aside for now.

Sorry. One more question on Hobbs. Both of the deoxy nucleotide the dCTP and the dUTP have alkynyl amino linkers?

A. Let me take a look and go back to that.

Q. Yeah, sure. That was column --

A. That's column --

Q. I'm sorry. Let me just get you there. That's column 47 and 48.

TRAINOR

A. Sorry. I closed it back up when you said you were finished.

Q. Yeah, I apologize.

A. Okay.

Q. Okay. So the question is --

A. Yes. It looks like we take the iodo deoxycytidine and the next step is that heterocyclic coupling -- the plating coupling that -- that Dr. Hobbs pioneered to make that the propargyl linker.

Q. Okay. And so they both have the alkynyl amino linkers, both of these examples is that -- of the nucleotides?

A. Both pyrimidines have that, yes.

Q. Now, when you -- when you were working on your invention that is sort of described in the Hobbs patent and in the Prober reference, one of the hurdles that you alluded to was synthesizing the ddGTP in the first place, right?

A. A-hum.

Q. Right? The 7-deaza ddGTP,

right?

A. Yes.

Q. Okay. And you actually brought in a heterocyclic chemist to do that, correct?

A. That's correct.

Q. And that is Mr. or Dr. -- I don't know -- Kakuza?

A. Yes.

Q. Okay. And he went to work and -- and synthesized that, I think you said, at one point, it wasn't trivial but it was in fairly short order?

A. No. It was about a year.

Q. Okay. And do you remember -- do you recall giving a talk when you said "it was in fairly short order"?

A. Hmm? No, I don't. I may have said it but I don't recall it, no.

Q. Okay. So what you did was you brought in a specialist whose job it was to figure out how to make that synthesis reaction work, right?

A. That's fair.

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Q. Okay. Now, I think I am done at least for now and I'm putting the Hobbs patent aside.

Now, in your declaration in a number of places you talk about something called "a starting point."

Do you recall that terminology, generally?

A. I do.

Q. Okay. And that's kind of the methodology that you used, at least as it relates to the Tsien patent and the Stemple patent, agreed?

A. That's -- that was what was explained to me by the attorneys for the purpose of obviousness.

Q. That was going to be my next question. So that you were instructed to use that method?

A. Yes.

Q. And so, in -- when you use your starting point analysis for the Tsien and the Stemple patent, what you did was you identified a most likely

starting molecule. Is that fair?

A. Fair.

Q. And then you determined whether it would be obvious to modify that starting molecule, right?

A. I -- I determine what a person of ordinary skill in the art would have to do to move from that starting point to the Ju invention.

Q. Okay. And, in fact, and to be fair, you had also alternative starting points for both of those references?

A. Yeah. And I believe in my declaration I talk about if -- if -- even if you felt that one of the other opportunities in one of the other options was the appropriate starting point for a person of ordinary skill in the art then this would be our analysis of that, yeah.

Q. Right.

A. My analysis.

Q. So is it fair to say that your analysis of the obviousness of

modifying Tsien and Stemple is based on the use of the starting point method?

A. Yes.

Q. Okay. Now, let -- let's talk about Tsien first. As it relates to Tsien --

A. Could I have -- do you have a copy of Tsien provided for me?

Q. Yeah. I -- I think we do --

A. Maybe we did it yesterday.

Q. Yeah.

A. Let me just check it and see. I'd like to have that in front of me as we speak. Okay.

Q. Maybe I would just ask you because I don't have the exhibit number down, what is the exhibit number for Tsien?

A. 1002.

Q. So we're all on the same page, Tsien Exhibit 1002, okay, and as we are just alluding to, you had sort of two different starting point analyses that were in Tsien; one, was if you started

with the embodiment where the label was on the 3'-OH and another was if you started with a molecule where the label was on the base, fair?

A. That's fair.

Q. Okay. And you said that you believe the appropriate starting point was the embodiment with the label on the 3'-OH, right?

A. Yes, I believe I -- we went through that, I went through that.

Q. Okay.

A. We -- we talked about it.

Q. And -- and the reason that -- that's your opinion is that if Tsien, as you say, focuses on that as "a preferred embodiment." Is that fair to say?

A. Yeah. I think that's one of the reasons.

Q. So how did you decide whether -- strike that.

How did you decide that Tsien focused on labeling of the 3'-OH as a

preferred embodiment?

A. So I think -- let me just refer to my declaration, so I can just try to give you the right reference.

(Whereupon, the Deponent reviews the document.)

A. I think this is sort of general discussion in Tsien and if I go to talk about -- and I think it's paragraph 75 in my declaration. And I'm using the '698, if that's okay, the '698 declaration right there?

Q. Oh, that's fine.

A. I suspect they're -- they're the same for the purposes of Tsien/Prober.

Q. I -- I understand that you're using it in that example.

A. Okay. And so, if you go through the Tsien in multiple places he discusses the 3'-label and cap and says that that could be "removed in a single step if it could be incorporated."

So person of ordinary skill in the art would be taking that teaching

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and probably would go to the literature and say, Well, you know, where do I go from there? Do I have any guidance in the literature? And they would see that the experts in sequencing-by-synthesis -- and this is in the year 2000, were focusing pretty much exclusively on the label -- the strategy where you had the label and cap together, at 3'. And as far as I know there was no literature describing a strategy that had a label attached to the base, and a 3'-cap. So a person of ordinary skill in the art says, Of all the choices, it looks like I have the best chance of moving forward.

So from one point of view he's looking at the art and how it's advancing, and this is a tough problem as this went on for 12, 15 years, right? And they say, Well, where are people making progress, the experts and this would be the labs of Metzker, Burgess, Welch, people like this, and

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Kinard, Sarfati and trying to figure out how to do this.

The other aspect of this was that we already know -- knew and I think a person of ordinary skill in the art would know having a label on the base was even though it was accepted and it worked, if you look at the concentrations required of the reagents, polymerase is not happy. So meaning they're substrates but you've impaired the ability of the polymerase to work. You need to use higher concentrations.

We knew from the literature and a person of ordinary skill in the art would know, so I would look at it and see that even though there was some progress at the 3' it was clear there were lots of things that didn't work and that was going to be a challenge. But the only place progress had been made was there, so if a person said my choices are, go with the 3'-cap and

label or go with the possibility that a base label and a 3'-cap would both be accepted at the same time, certainly was -- I'm aware of no example of that at that time, up until -- up until the year 2000, certainly until Dr. Ju's work where -- where a person of ordinary skill would say, I think that that strategy has a chance of working.

Now, my understanding of the obviousness is that a person of ordinary skill in the art looking at this reference and looking at other ancillary references needed to have a reasonable expectation of success. So this person has to judge whether the path taken and -- and in this case the starting point means what is he going to see as a teaching, a primary teaching for him, as a guidance and is that going to be a successful approach.

Q. Now, you said that as of 2000, most of the success, most of the activity, at least, in attaching labels

was at the 3'-OH position?

A. As far as I know that was the only in terms that had been successful for -- for sequencing-by-synthesis, people, obviously, were explicitly saying they are working on sequencing-by-synthesis.

Q. So if you could look at -- looking at Stemple which you should also have in front of you from yesterday?

A. Oh, I don't know. Did -- did we get Stemple?

Q. We did.

A. I just got the Dower.

Q. You can have mine if you want it. So it's Exhibit 1008 and if you look at Figure 1?

A. Okay. Let -- let me get to my Stemple section. I would appreciate that. I need the '869 declaration for Stemple.

(Whereupon, the Deponent reviews the document.)

TRAINOR

Q. You see Stemple Figure 1B shows a -- shows a nucleotide that is labeled on the base, right?

A. Yes. And it's -- it's a bit of a cartoon but I think I can accept that.

Q. Okay. And you -- you'll agree that it's attempting to convey the notion of --

A. It's a notion, yes. Conveying a --

Q. It's attempting to convey the notion of labeling on the base, right?

A. Labeling on the base, yes. That's fair.

Q. Okay.

THE REPORTER: Sorry. Labeling --

THE WITNESS: Conveying a notion.

Q. It's attempting to convey the notion of labeling on the base, right?

A. Yes.

Q. Okay. So this at least

definitely shows some activity of somebody --

A. I would not -- I would not agree that it shows activity. You know, anybody can imagine it. I can imagine it, right, write-down a cartoon that says, Let's do it this way. What I think a person of ordinary skill in the art is -- is not looking for a cartoon. They're looking for does somebody actually have some science suggesting that this might actually work and how -- how to do it. And that's not what this car -- this cartoon adds no value to that. It's a concept and it's not -- not teaching.

Q. But it at least shows the idea of attaching it to the base, though, so you agree with that?

A. Yeah. A-hum. Yeah.

Q. And it shows a 3'-cap, right?

A. Yeah. It does.

Q. Okay. Now, getting back to Tsien -- sorry for that little detour

there.

So you agree, though, that Tsien, in addition to disclosing the -- the idea of labeling at the 3'-position, the 3'-OH position also discloses a base labeled embodiment, right.

A. They do. I think I speak to that actually.

Q. So let -- let's take a look at Tsien in a little bit more detail. Do you have Tsien in front of you?

A. I do.

Q. Okay. Good. So the way Tsien is set up, if you see -- if you turn to page 9 of Tsien, you see there is a section that's called "Organization of This Section"?

A. Yes.

Q. And then it describes sort of what the sections are going to be and then it goes ahead and does it on the following pages?

A. Right.

TRAINOR

Q. So right after the "Organization" section there is a section called "Nomenclature," which begins on page 9 and then follows over to page 10.

Do you see that?

A. Right.

Q. And on page 10 it says, "that when there is a blocked 3'-OH it's denoted" -- and then it has a, quote, "3'-blocked DATP," let's say?

A. Yes.

Q. And it says that if they're going to "use the same label, then it would use the terminology or the nomenclature dA'TP or dC'TP, to indicate that the label is the same." Do you see that?

A. Yeah. I also note that in the sentence below it he's saying or he's not implying, of course, that because he's associated the prime or the double prime with the base -- I think he refers to dA as opposed to just A, he

TRAINOR

doesn't imply, and he's very ask explicit about that. It could be anywhere.

Q. Right.

A. It's just the -- the nucleotide is identified by its base as uniquely associated with a given label ', '', et cetera.

Q. And we'll actually get to that in a moment so, but it would be easier if we proceed through question by question then if that will -- we'll --

A. Well, I think sometimes my answer, you're going to ask me an answer, and I need to make sure I have it in the right context because the answers depend on the context sometimes --

Q. Okay.

A. -- to be truthful.

Q. Okay. But the questions I was asking you specifically was in the "Nomenclature" section, when he says, "dA'TP or dC'TP" --

TRAINOR

THE REPORTER: I'm sorry --

MR. COSTAKOS: -- dA'TP or dC'TP.

Q. What he's attempting to indicate is that the label is the same?

A. That's fair, yes.

Q. And then in the next sentence beginning at line 8 through line 10 on page 10 it says, "When there are different fluorescent groups that are represented by dA'TP, dC''TP, dG'''TP and dP''''TP."

Do you see that?

A. Yes.

Q. Okay. And so that -- that's an indication that each of the labels is different in that circumstance?

A. Okay.

Q. I will say he could have thought of a little bit better nomenclature that would be easier for us to read. But, yeah, hey, he won the Nobel Prize so we won't criticize him too harshly.

Okay. And then, the sentence

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you're alluding to is in the next sentence on -- beginning at -- at 10, it says "the indication" -- strike that.

It says, "The fact that the indication of labeling appears associated with the 'nucleoside base part' of these abbreviations does not imply that this is the sole place where the labeling can occur."

Do you see that?

A. Yes.

Q. Okay. And so, what he's saying is if just because I'm putting the prime on the A or the G or the T, doesn't mean that's the only place where a labeling can occur?

A. And I think it -- it suggests that he doesn't quite understand how nucleosides are described, meaning the A in that is not adenine it's the deoxyadenosine, so it's already got the sugar and the base anyway but it -- it's great that he makes it clear

there. But the fact that it's after the T means thy -- thymidine not thymine base, so dA is deoxyadenosine not adenine, deoxyadenine.

Q. Right. So --

A. But I -- I think, his -- we can agree that he -- he means it could be labeled anywhere and it is simply a unique association of a given base nucleotide, nucleotide with a given base with a given dye.

Q. Right. So what he's saying is just because I have the prime on the A or the C or the G, doesn't mean necessarily that the label is on the base, but it's one place that it can be?

A. That's correct. That's correct.

Q. Now, if you look at page 12, page 12 is in -- in the description of figure 2 and if you look to line 14, there is a sentence that describes the "reaction zone accessed by these inlet lines."

TRAINOR

Do you see that?

A. A-hum.

Q. Okay. And then it says, "for four differently labeled blocked dNTPs, that is" -- and I apologize I'm going to read all of these in -- "3'-blocked dA'TP, 3'-blocked dC''TP, 3'-blocked dG'''TP and 3'-blocked dT''''TP."

Do you see that?

A. I do.

Q. So what that means is using his nomenclature, that there is a 3'-blocked OH, right?

A. There is a 3'-blocked that is all I can say, right.

Q. Okay. Which means it's blocked in the 3'-position, right?

A. Which means that there is not a free 3'-hydroxyl. It -- it's blocked by further polymerase action.

Q. The -- it means the material is blocked in their 3'-OH position?

A. Yes.

Q. And this nomenclature or this

passage that we read on page 12 at lines 14 through 18 also means that there are four different labels that are attached, right?

A. Yes, by his nomenclature, yes.

Q. And they could be but are not necessarily attached to the base, agree?

A. He's made that clear. Yeah.

Q. One of skill in the art if they read all of Tsien -- strike that.

We -- we looked at a passage yesterday and I believe we talked about -- we specifically talked about labeling at the OH -- or at the base position.

So if you look at page 27, following over to 28, I think we went through this yesterday, so I won't burden the record on this, but it -- it describes on page 27 the idea of "forming a 3'-blocked dNTP analog containing a label, such as a fluorescent group attached to a remote

position such as a base," right.

A. Correct.

Q. Okay. And then, it goes onto describe in -- on page 28, "a method that involves use of a fluorescent tab attached" -- excuse me -- "a fluorescent tag attached to the base." Right?

A. Yes, it does.

Q. Okay. And so, one of ordinary skill in the art if they were reading all of Tsien would understand that Tsien taught multiple embodiments, right?

A. Yes, I think you would have to -- yes, but you would have to take the teaching as a whole. You would have to look at the entire application to see what the preference for Dr. Tsien was in terms of both how he -- how he describes the invention; what he suggests you should do; whether that is a preferred way to go; does he give more detail for one way or the other or

give experimental instruction on one but not the other and simply express that one might be one way, or another way one could go.

So you have to take the invention as a whole to look at the intent and determine the starting point not a single line reference.

Q. But you agree that he does teach multiple embodiments?

A. He does give the option of a base. Absolutely. Absolutely.

Q. And he taught an embodiment where there's a chemically cleavable cap on the 3'-OH, right?

A. Yes.

Q. Okay.

A. Which may or may not contain a label.

Q. Okay. And he taught an embodiment where the fluorescent label is on the base and there is a 3'-blocked OH, right?

A. A-hum. Which are several --

several of the elements we described in Dr. Ju but not all of the elements.

Q. Well, he also says that the label can be attached by a tether, right?

A. It does.

Q. And he says that the tether can be cleavable?

A. Yes. In -- in his general terms he speaks to the possibility of cleavable tether, but I have seen an example of that, but that's okay, yeah.

Q. But he talks about using chemically cleavable silyl ethers or allyl ether tethers, right?

A. Yes. And I go through the specifications looking for what his chemically cleavable base linker is and I guess I don't see it, a base linker that -- that's cleavable in there.

Q. Well, I --

A. That's explicitly instructed you to put the label on the base, via a cleavable linker. I think he gives a

very nice set of reagents on page 30. It actually doesn't have the same dye but that is okay, that's -- it's not for unique labels but he actually gives you four nucleotides.

And, you know, I was looking at this -- this figure and trying to determine whether this was a figure that was disclosing teaching someone in the art to perform the -- Dr. Ju's invention and, yes, it -- it's base labeled and we can agree on that. Certainly, it's not cleavable, and certainly there is no deaza on this. So, you know, and also the specific example here has no 3' reversible cap and it's certainly implied by a number of people in the field and -- and, in fact, I believe later demonstrated that you don't need a 3'-cap to terminate, okay? That that is one strategy, one of many strategies.

So I think a person of ordinary skill in the art would look at this

figure and say, Okay, I guess I don't need a 3'-cap. I -- I don't -- there would be no -- no reason to look for deaza here, I mean there is no deaza there. I don't know why you would bring one in and then say, I guess, he doesn't tell me exactly how I put a -- you know, he doesn't tell me what the base label to use a cleavable linkage. He certainly talks about a cleavable linkage in the sugar region but his example, which I think is pretty clear, I mean, I like when they give you specific chemical structures and it makes it very clear what he means, and there is no cleavable linker in there.

Q. Okay.

MR. COSTAKOS: I -- I'll move to strike that as non-responsive.

Q. Does the Tsien patent have any embodiment in his process that does not use a 3'-cap?

A. I would not say not in the embodiment but I think this particular

TRAINOR

-- this particular set of nucleotides don't have a cap and I think he's saying here is an example, if we go back.

Q. So this figure -- on -- on page --

A. On --

Q. -- hold on. Just wait until I'm done.

On page 30, is the only example you could find where there was not a 3'-cap?

A. It's the -- you know, well, he gives very few actual embodiments so let's just say that that is an embodiment that shows it without the cap. And so --

Q. And you agree that throughout the rest of the documents he's talking about using a 3'-cap?

A. Well, I'd have to go back and look. I don't think -- certainly he, you know, he brings in the notion of a 3'-cap and brings in the notion of base

labeling. He certainly didn't combine the 3'-cap with the base label in any way that I can see here. And while he may generally refer to that at some point, but his specific example which I think a person of skill in the art would go, Okay, you talked about generalities. Teach me how to do this, which is what is required. Give me a very clear direction on how to put the pieces together and this was -- I was surprised to see that he didn't -- it seemed to indicate that a person of ordinary skill in the art should -- should go and put that cap on there, because he would have put it on there if he thought that's the instruction.

So I guess I was a bit confused by that and it seemed to me to suggest that either he thought you didn't need a cap or, you know, I think the -- the bulk of his work is directing you to go with a 3'-cap label and he provides this as here's is an alternative that

TRAINOR

you might try. And the alternative is missing, by my count, three elements of Dr. Ju's invention.

Q. Okay. If you look at -- and again, we looked at the bottom of 27 through the top of 28, he talked -- talks there about "the formation of a 3' blocked dNTP analog, containing a label such as the fluorescent group attached to a remote position, such as the base," right?

A. A-hum.

Q. And so that's -- and that's describing the idea of base labeling and a 3'-cap, agreed?

MR. WHITE: Objection to form.

A. Yeah. He says there are alternatives. Okay?

Q. Okay.

A. So a person of ordinary skill in the art says, Give me more information, tell me how to do that, give me more direction.

Q. Okay.

TRAINOR

MR. COSTAKOS: Move to strike as non-responsive.

Q. So after that -- after that sentence where he says you could have a 3'-blocked OH and a fluorescent group attached to the base he goes on to describe the attachment of a fluorescent group to the base on page 28, beginning at line 5, right?

MR. WHITE: Objection. Form.

A. Yes.

MR. COSTAKOS: What is the basis for your objection?

MR. WHITE: Because it doesn't say "attached to the base." It says, "to a remote position such as a base."

MR. COSTAKOS: Okay.

Q. And then he says, beginning at line 5, "one method involves the use of a fluorescent tag attached to the base moiety."

Do you agree with that? That's what it says, right, Dr. Trainor?

A. Yes. It does.

TRAINOR

Q. Okay. And then, he describes the labeling on the base through the use of a tether, beginning at line 19 on page 28, right?

A. Line 19? Are you sure it's 19 -- yes, and another remote label, yes.

Q. Okay. So it says, "another remote labeling of the fluorescent moiety or other innocuous label can be attached to the dNTP through a spacer or a tether," right?

A. Yes.

Q. And then he says "the tether can be cleavable," right?

A. He does.

Q. And then he says "there are several cleavable tethers that can be used on that," in the sentence beginning on line 23, correct? Yes?

A. I'll take a look.

(Whereupon, the Deponent reviews the document.)

A. Yes. He says that.

Q. And then he identifies

specifically silyl ethers or allyl ethers on lines 26 and 27. Agreed?

A. Sure.

Q. Let's turn to page 14. So at page 14, if you look beginning at line 12, there is a statement that says, "The labels present in the blocked dNTPs can be incorporated in one of several manners."

Do you see that?

A. Yes.

Q. And then goes on to describe those manners. So it says, "First," beginning at line 13, "they can be incorporated directly and irremovably in the deoxy nucleotide triphosphate unit itself." Right?

A. Yes. It does.

Q. And then in the next paragraph, it says, "Alternatively, and in many cases preferably, the label is incorporated within the blocking group or is otherwise incorporated in a way which allows it to be removed between

each addition."

Do you see that?

A. Yes.

Q. Okay. So what this is doing is this is describing an alternative to irremovable incorporation, right?

A. That's right.

Q. And then it says, "In many cases, that option of removable incorporation, is preferable to the irremovable option," right?

A. Yes. There is some rationale for that, yes.

Q. And as we discussed, it says, "the label is incorporated within the blocking group or is otherwise incorporated," and we described before one of the ways in which it can be incorporated is in the base, right?

A. Yes. And I think it's important to note that there are several ways to, quote, remove the -- the label, per se. When you bleach the label, which effectively removes the label by

limiting its function which would not be a cleavage. So I think he's saying very clear that his concern with -- with not -- not having a removable label is that you accumulate signals and you have trouble as you get that many signals in seeing what you did, but it's clear that, you know, there are several ways to deal with that problem and one of them is a cleavable linker. That is not the only solution to the problem. One can bleach with dye and it certainly has been tried and done.

Q. Okay. So if we take a look at your declaration --

A. And just make sure I'm looking at the right one so we're on the same page here. Which one are you looking at?

Q. Let's look at the '698?

A. Okay.

(Whereupon, the Deponent reviews the document.)

TRAINOR

Q. Are you there?

A. Yes.

Q. So paragraph 74, which is on page 41 of your declaration relating to the '698 patent, in the second sentence you describe that "a person of ordinary skill in the art would have understood that each nucleotide analog includes a removable blocking or capping group at the 3'-OH of the deoxyribonucleotide."

A. Within the context of Tsien's disclosure, right.

Q. Yes. I'm sorry. Of course, this is relating to Tsien. Okay. That's a good point.

And then you say, and that -- and here you are quoting from Tsien and it says, "And that... preferably the label is incorporated within the blocking group... "

Do you see that?

A. Yes.

Q. And what you are trying to say here is that the label is preferably

incorporated within the blocking group. Is that right?

A. I believe so, yes.

Q. But we just went through the actual text of Tsien. And I -- and you just testified, and I think it's inarguable, grammatically, that when Tsien is talking about the preferable, what he's saying is that preferably the blocking group is incorporated in such a way which allows it to be removed between each addition, right?

A. Yeah. But I think you have to go to the entire text. You would have to look at the disclosures as a whole to understand what a person of ordinary skill of in art would take from that reference --

Q. Okay. Well, I'm just --

A. -- to see the whole thing.

Q. -- I'm just focusing on the language that you used in your declaration that you quoted from Tsien?

A. Right.

TRAINOR

Q. And what you quoted from Tsien in paragraph 74 of your declaration is: "Preferably the label is incorporated within the blocking group."

MR. WHITE: Objection. Form.

Q. Agreed?

A. Yes.

Q. And you left out the language that was before and after that quote, right?

A. No, "alternatively and in many cases preferably, the labels incorporated within the blocking group whereas otherwise it would be incorporated without being removed between each addition."

So I, you know, I'm just taking it word for word.

Q. You agree that you the dots, the three dots on the beginning and the end of your quote mean you left language out, right?

A. "In many cases preferably," okay.

TRAINOR

Q. Okay. And we just went through --

A. Yes, the word "preferably" is clear in both cases. "Preferably," says that this is the way I like to do it.

Q. Okay. And we just went through the text in Tsien and what he is saying is he -- he first lays out an irremovable incorporation of the label and then he says, "alternatively and in many cases preferably, the label is incorporated within the blocking group or is otherwise incorporated in a way which allows it to be removed between each addition," right?

A. A-hum.

Q. And what you did in your declaration is you took out that language, which showed that what he was talking about when he used the word "preferably" was that "preferably" meant that the blocking group was removable. Isn't that true?

MR. WHITE: Objection. Form.

TRAINOR

A. I read that sentence preferably, the label -- the labels incorporated within the blocking group or, he's giving a choice, so there is two preferable approaches. He didn't say -- it doesn't -- I think you read that phrase grammatically, if you want to talk to grammar.

The label is incorporated within the blocking group or -- well, that sentence has to stand on its own, so the label is incorporated within the body and I take it as an assertion that -- and if it's prefaced by the word "preferably," yes, okay, now he may have other preferable things as well, but I think you can't deny that he's saying preferably here is a choice.

Q. Let's look at the whole sentence again, I think I might -- I think this is as clear as clear can be, but when you look at the paragraph before, I think we said the labels present in the blocked dNTPs can be incorporated in

one of several manners and then it says, "For one, they can be incorporated directly and irremovably in the deoxyribonucleotide itself." Right?

A. Yes. And he's teaching there distinguished between a reacting group as you post-label it's been -- the intention there is that it already has the label there on the nucleotide.

Q. Okay. And then he says, "Alternatively, and in many cases preferably, the label is incorporated within the blocking group or is otherwise incorporated in a way which allows it to be removed between each addition."

So in contrast to what was in the paragraph before, which was irremovable labeling, the alternative and in many cases preferable option, is to have removable labeling. Agreed?

MR. WHITE: Objection. Form.

A. But I think he's qualified the

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removal by incorporated within the blocking group. He's says -- is saying, Hey, this is a great way to do it. Now, when I remove the blocking group it removes the label. I mean that's very clear to me when I read it, that he's saying, Hey, isn't that great? I can unblock the 3' and remove the label at the same time.

So a person of ordinary skill in the art is looking at all the alternatives, is looking at the whole disclosure, is looking at what he tries to teach you further downstream here and he's saying -- says that's pretty -- that's very, operationally, very simple.

Q. Okay. But you do agree, though, that he says in the language that you left out that the label that is incorporated within the -- the blocking group or is otherwise incorporated?

MR. WHITE: Objection. Asked and answered.

TRAINOR

A. I -- I think we have to grammatically talk to the meaning of the word "or" is -- it says this or that, it doesn't say this, in the case of that. They have to stand on their own. If I say it can be red or blue, it's true that it can be red and it's true that it can be blue. I'm reading that sentence to tell me that the labels is incorporated, preferably the label is incorporated in the blocking group.

And the other thing is the label is prefer label will otherwise incorporated in a way that allows it to be removed and those are two choices. Okay? But he clearly is saying his -- that presently blocking is one of the preferred ways of going.

Q. And both of those ways are preferred incorporating on the 3'-OH or otherwise incorporating it?

A. That's correct. And I think, again, you would have to look at the

disclosure as a whole to see which way he is instructing the person of ordinary skill in the art to go and you can't look at one sentence and say that that is the only sentence that matters to that person in judging what this is teaching and what I should do going forward.

Q. Okay.

MR. COSTAKOS: Let's go ahead and take our break.

VIDEOGRAPHER: The time is 10:26 a.m., and we're going off the record.

(Whereupon, a recess is taken.)

VIDEOGRAPHER: The time is 10:50 a.m., and we're back on the record.

Q. Let's go back to the Hobbs reference, which is Exhibit 1013 maybe.

A. Yes.

Q. Let's turn first to column 24, 25. So at the bottom of the page that has column 24 in it, there is a

molecule with a 34 next to it. And then, on the top of the next page there are molecules 35, 36 and 37.

Do you see that?

A. Yes.

Q. Okay. Those are the four molecules that are shown in your Prober article as well, right?

A. I believe -- I believe so, yes.

Q. Okay. Now, if we can turn to column 29, at the top of the page there's a molecule that's shown and actually shows two options; one, where R is an H and that's molecule 40; and, one where R is an OH and that's molecule 41. Right?

A. Right.

Q. So molecule 40 where the R is an H, is a deoxy nucleotide, right?

A. That's correct.

Q. Okay. And in this instance it's a 7-deazapurine, agreed?

A. That's correct.

Q. And it's a 7-deaza-adenine in

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this instance, right?

A. Yes.

Q. Okay. And it has attached at the 7 position, it has the same propargyl linker that we talked about before, right?

A. Yeah.

Q. And attached to that linker there's a biotin molecule, right?

A. That's correct.

Q. Okay. So this is a 7-deazapurine, with a biotin labeled attached to the 7-deaza position, right?

A. That's correct. That's fair.

Q. And it's a dNTP?

THE REPORTER: It's a --

MR. COSTAKOS: -- it's a dNTP, right.

A. That's correct.

Q. And if you look at the previous page at column 28, at line 62, it says, "Alternatively, an alkynyl amino" -- I'm going to start over again. I'll

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start over again.

It says at line 62, "Alternatively, an alkynyl amino linker could be used for biotin attachment or, in general, for the attachment of other reporters such as fluorescent dyes."

Did I read that correctly?

A. Yeah. And I think the context of that, of course, is within the Langer technology, and that was our intent of adding this claim. It was to -- we recognized that the Dave Ward chemistry, even though they talked about purines, the chemistry doesn't work and no one has gotten it to work. So we thought that if someone was interested for reasons that I didn't know, but this is a non-sequencing thing, so we just needed to have a DNA for translation labeling of DNA probes that they would be able to use our linker technology, and this was an attempt to get some art in the reference for that.

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But certainly it was clear it was not for DNA sequencing and that we didn't know whether this would work for DNA sequencing. Just that we -- this compound could be made and we asserted it would be a polymerase substrate.

Q. Okay. And so -- but the point of -- was to show that this compound, which is a 7-deaza DATP labeled with biotin or fluorescent label, could be made?

A. Well, yeah, we said a fluorescent, it shows a biotin, of course, but we -- we extrapolated you might be able to -- if you wanted a fluorescent DNA probe.

Q. Okay. And -- and this is meant to show that this particular molecule could be made, right?

A. That's the implication. I don't even know if we made that or if that was just prophetic at that time, but the assertion was that one could imagine the technology into the Dave

Ward space.

Q. And in the -- in the context of this translation the molecule would be incorporated by polymerase, right?

A. Right. Without -- without termination, of course.

Q. Okay. Let's go back to the Tsien reference. If you look at page 20 of Tsien?

A. This is in reference to which declarations, so I know I have my notes for that?

Q. You know, I don't know that I can draw a connection to any particular paragraph.

A. Okay. I'll -- I'll pull out my declaration for that, for Tsien --

Q. I'm not saying it's unconnected but I don't have a --

A. Well, certainly, , you know, the onus is on the reference I'm making or -- are outlined in the declarations, so I'm going to refer to them when I -- I answer your questions.

Q. Right. Right.

A. And so I think that is what I wrote, yeah.

Q. Right. Right. I guess my questions aren't meant to have the answer key associated with them.

So let -- let me -- let me direct you to page 20. If you look at line -- beginning at line 28, and in this section it's talking about "blocking groups and methods for incorporation."

Do you see that?

A. A-hum. Yes.

Q. And at line 28, Dr. Tsien describes "the criteria for successful use of 3'-blocking groups."

Do you see that?

A. Yes. But just give me a chance to read that.

(Whereupon, the Deponent reviews the document.)

A. Okay.

Q. And the first criterion that he

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identifies is "the ability of a polymerase enzyme to accurately and efficiently incorporate the dNTPs carrying the 3'-blocking group into the C-DNA chain." Right?

A. Okay.

Q. So that's one of the criteria that Dr. Tsien identified for selection of the 3'-blocking group, right?

A. Yes.

Q. And if you look at the -- the next two criteria, one is "the availability of mild conditions for rapid and quantitative deblocking," right?

A. Sure.

Q. And then the third criterion that he identifies is "the ability of the polymerase" -- "of a polymerase enzyme to reinitiate the CDNA synthesis subsequent to the deblocking stage," right?

A. Yes.

Q. Okay. So those are the three

parameters of criteria that he gives for selecting which blocking group should be used?

A. A-hum.

Q. Agreed? Yes?

A. Yes.

Q. Okay.

A. That is his criteria, yes.

Q. Okay. Before our break we were talking about 7-deaza deoxy nucleotides and in particular 7-deaza deoxy -- 7-deaza DGTP's, do you recall, generally, that we were talking about that subject?

A. A-hum.

Q. Did you investigate whether anyone had made a 7-deaza deoxy purine prior to 2000?

A. I think I refer to the references that were provided to me in my own experience but I didn't do independent investigation.

Q. Okay. Did you investigate whether anyone had made a 7-deaza DGTP

prior to 2000?

A. Well, I certainly did. I mean 7-deaza DGTP is the Prober work, right, isn't that what you were asking?

Q. Well, that was the -- the -- those are dideoxy?

A. Deoxy, no. I --

Q. Deoxy.

A. -- I actually -- I'm not aware of any reference but I didn't -- I was not asked to and I didn't do a thorough substructural search through the literature --

Q. Okay.

A. -- so I don't know.

Q. So just -- so just so the record is clear, you did not do any investigation into whether someone had made a 7-deaza DGTP prior to 2000?

A. No. I relied exclusively on the references provided and was cited in my own just knowledge of just following nucleosides up to the early 2000s.

Q. Okay. So it's based on your

recollection of what was going on during that time period?

A. Yeah.

Q. And the reference?

A. And the references provided, all the material provided.

Q. The reference --

A. The extensive material provided.

Q. I'm sorry. We need to -- again, we need to try and not talk at the same time. I'm guilty, too, and I'm shaming myself as well.

A. Okay.

Q. So your declarations on the issue of the -- strike that.

Your declarations on this point were based on your recollection and the materials that you were provided and that are identified in your declarations. Is that fair to say.

A. Yes. My experience, recollection and material provided.

Q. Okay. Did you do any investigation as to whether anyone had

made 7-deaza deoxyguanine nucleoside prior to 2000?

A. No. I said I didn't do investigations. This was just material provided. I don't think I was instructed to go to the literature and do a literature search. I think the attorneys certainly had better access to that technology and I can't afford to do that. I'm a consultant. I don't do that kind of search on this kind of job unless somebody provides me with a search tool and asks me to do it, and I wasn't asked to do it.

Q. Okay. So the material you relied on was the materials provided by your attorneys?

A. That's correct.

Q. Okay. Turning to the --

A. But -- and I also have my recollection so, you know, relying on that.

Q. Sure. I'm sorry. And I -- I'm not meaning to exclude your

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recollection or your experience.

A. Okay.

Q. Okay. Turning to the Ju patent is there anyplace in the -- any disclosure in the Ju patent of a 7-deazapurine with a 3'-block actually being used?

MR. WHITE: I'll object to the use of the Ju patent, which was not the subject of his declaration, not discussed in the petitions filed by Illumina and outside the scope of this proceeding.

MR. COSTAKOS: Okay.

Q. Go ahead?

A. I -- I'd have to look. Can you repeat what exactly you are looking for just so --

Q. Sure. Is -- is there any --

A. -- I can --

Q. I'm sorry. Is there anyplace in the Ju patents where there is a disclosure of a 7-deazapurine with a 3'-block actually being used?

TRAINOR

A. Well, certainly Figure 10 shows a 7-deazapurine, which has the hydroxy blocked but doesn't specify exactly how it's blocked. I'm presuming R does not mean hydrogen.

THE REPORTER: R does not mean --

THE WITNESS: -- hydrogen. I'm looking at the '575 patent, Figure 10, so...

Q. Well, I understand that there's a drawing of it. I guess my question is: Is there any evidence that --

A. Okay. So I thought that was what you wanted. I can actually go into the -- into the -- I can look, but while I'm doing that, I have to say that when someone shows me a chemical structure, that is actually more evidence of a description to me than someone describing something vaguely, but I'll go on and if you need me to do that in the text I can, but to me, to a chemist and to a person skilled in the

art who I believe for the purpose of this discussion is a chemist, the description is a chemical structure and not a cartoon but a chemical structure.

And there can be some variability, like an R group which means there are several choices there. But if you want me to go through the text and find that I will try and do that.

(Whereupon, the Deponent reviews the document.)

Q. I guess just to add another condition on top of the question, what I'm really looking for when I say "whether a 7-deazapurine with a 3'-block was actually used," what I mean is incorporated into the molecule and used in -- in a sequencing-by-synthesis reaction?

A. I guess I -- I'd have to go through it because I think my attorney explained that this was -- that my declaration didn't involve anything

other than the claims of Dr. Ju's patent. I was not asked to study the specification or examples, so I'm just going to have to do that.

Q. Did you read the specification of the Ju patent?

A. Yes. I read it, but I mean I didn't read it with the intention to memorize it, so I read it maybe twice in the year and what I needed to read was the claims and -- and only things that related to the claims as they were structured and there was nothing about specific chemical embodiments or, you know, a guanine or how he made a guanine is not part of the claim, so I didn't -- I certainly didn't focus on that in my reading but I did the patent.

Q. And when did you last read the patent?

A. I'd have to guess -- I'm guessing sometime in the last month, probably.

TRAINOR

Q. Okay. Well, I -- I don't think I need to have you read the patent here, but --

A. I -- you know, the best answer to the question is: If someone shows me a chemical structure I'm -- I consider that a disclosure and that -- in fact, that's the best disclosure you can give to a chemist, to a person of ordinary skill in the art.

As to incorporation of that -- that structure, I think he gives a very specific instructions on how to carry out synthesis and whether he shows the data that results from the incorporation, I don't think he had that kind of data in this patent. I didn't know that he needed that kind of data as long as he gives proper instruction on how to do sequencing. So I mean, I don't -- I don't think I can answer your question about where is the G incorporated into DNA.

I mean, I think certainly the

intention is the -- the sequencing. So the assertion that it's useful for sequencing, so one has to presume that he means to imply that -- that it could be incorporated, otherwise you can't sequence.

Q. Right. And certainly that is the goal is to --

A. That is the goal.

Q. -- to incorporate?

A. Right.

Q. And my real question was whether he actually showed whether this molecule could be successfully incorporated in a sequencing-by-synthesis reaction?

A. Yes. Yeah. I don't think he's got any gels here. You know, I would -- there are several ways you can do that and I don't, you know, I don't see that that's in this -- certainly, it's in some -- in some of his publications, subsequently, and I think we all understand that people publish papers

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after patents that usually after patents issue -- publish and certainly gives some indication that compounds are accepted, that G nucleotides are accepted at that point.

And certainly, we know that there is a product here so that the G nucleotides with the 7-deaza are accepted.

THE REPORTER: With --

THE WITNESS: -- the G nucleotides with the 7-deaza feature are accepted by polymerase.

Q. So in -- in the patent you say that there are instructions on how to do sequencing-by-synthesis, right?

A. I believe so. I mean, again, that wasn't -- I was not asked to -- to, you know, to -- to opine on the -- the disclosure and tell me what you think of the disclosure. So I -- I'm not really prepared to do that but if you want me to take the time I would. I would have to -- to read through it

line-by-line and say, Okay, here's the -- here is what you're looking for.

It was not part of the petition, as I understand it. It was not -- there was no element in the petition that talked about whether Dr. Ju had demonstrated a G incorporation or not so I -- that was not something I was asked to deal with.

Q. Okay. So are you -- so you are unaware of whether there are any actual examples in the patent?

A. That's right. I was unaware of that. I was not asked to do that. I could if you wanted me to but that's your choice.

Q. Okay. Just to backtrack a little bit. We -- we were talking a few moments ago about the question of whether you did an investigation on whether anybody had made a 7-deaza DGTP prior to 2000. So do you recall -- let me orient you to that testimony.

A. A-hum.

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Q. And you indicated generally that you relied on your own experience and knowledge and information that was provided by attorneys.

A. A-hum.

Q. Did you ask your attorneys to do a search on whether anybody had made 7-deaza dGTPs or 7-deaza deoxy purines prior to 2000?

A. No. And I wasn't -- in fact, I don't think there was any point where I asked them -- I mean they're coming to me for my opinion. They're saying this is all the material that we have available. This is the -- the references were cited against us and my understanding is the discussion is limited to those for the purposes of this discussion. And I'm not supposed to go outside of that and you are not supposed to go outside of that and that's it.

And they're saying, and here is the material that was provided by

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Illumina as requested and required by the -- in this -- this overall litigation and everything, and this is what we have. And this is what there is.

Q. Okay.

A. And that's it. I mean --

Q. Okay. So just to broaden the question out generally, is it fair to say that you didn't ask your attorneys to do any searching on any topic to try to find additional references?

A. No. Absolutely not.

Q. Fair enough. Let's go back to Tsien. So let's turn to page 29 of Tsien.

A. Okay.

Q. So on page 29 there is a continuation of the discussion that began on the previous page about labeling with a fluorescent label on the base, right?

A. Previous page? Okay.

Q. Have you read that?

A. That's -- that's fine.

Q. And then in the paragraph that begins on page 29, he says, "The C8 position of the purine structure presents an ideal position for the attachment of a label." Right?

A. Yes. It says that.

Q. Yes. And then he cites to two references, a Sarfati reference --

A. Yes.

Q. -- referring -- relating to the purines?

A. Yes.

Q. And then the Prober reference, your reference, that he says has a "quite versatile scheme, based on an approach used by Prober to prepare ddNTPs with fluorescent tags," right?

A. Yes.

Q. Okay. Now, let's take a look at Prober. In your -- in the Prober reference, which you're an author of, if you look to page 2 of the reference, which is page 337?

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A. Okay.

Q. Okay. The first column, second paragraph, third sentence, you see it says, "The linker is attached to the 5 position in the pyrimidines and to the 7 position in the deazapurines." Right?

A. Yes.

Q. So in your reference, your article, the preferred place to attach the label in the purines was at the 7-deaza position, right?

A. Yeah. That was in my article, apparently. Yeah. Dr. Tsien didn't feel the same way.

Q. And then in your article if you look on page 338 there is a figure that's referred to on page 337, Figure 2A, and it actually shows the molecule, ddNTPs with the label at the 5-pyrimidine position and the 7-deazapurine position?

A. Yes. Okay.

Q. Okay. And so, you thought, at

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least, that the 7-deaza position was an ideal location to attach a label, right?

A. Well, I didn't know if it was ideal. I was -- we were one of the first people to ever do this so it was a way to do it that worked, that is fair to say.

Q. But it's the only way that you disclose in this particular article, right?

A. Yes, a-hum.

Q. Okay. So I presume that was your preferred way of doing it?

A. That was our preferred embodiment. It was certainly in our patents, yes.

Q. Right. And, in fact, that was the way that was eventually commercialized by Applied Bio-Systems, right?

A. For Sanger sequencing only, yeah.

Q. Yeah. But that -- that was the

way it was commercialized for Sanger sequencing by Applied Bio-Systems?

A. Yes.

Q. So when they were actually selling the products they were selling a 7-deaza labeled purine?

A. Yeah. No reason to change that for Sanger sequencing.

Q. Okay. And, in fact, in your Prober article, right after the portion I read before on page 337, you explain the reason that the 7-deaza is preferred, right, you say "The 7 deazapurines were used to facilitate stable linker arm attachments at that site," right?

A. Yes. We made that statement.

Q. Now, if we look at the Hobbs reference, and the Hobbs reference, and -- and, again -- again, it's the same inventive group -- well, strike that.

A. Yes.

Q. It -- it's the same group of people that were working on the work

that was in the Prober article, right?

A. Yes.

Q. Including you?

A. Yes.

Q. And provide -- provides lots more detail on how to synthesize other molecules, right?

A. Yes.

Q. Okay. And if you look at column 27, beginning at line 39, you see there is a discussion of the alkynyl -- I keep getting worse. Every time I say this word I say it worst than the time before and I apologize.

A. A-hum.

Q. And so you see in column 27, line 39?

A. Yes.

Q. There is a reference to the alkynyl amino nucleotides linkers, right?

A. Close enough, yeah.

Q. Okay. Close enough. Fair. Not bad for a lawyer, I guess.

TRAINOR

And then, it says, beginning at line 46, it says, "The alkynyl amino" -- can you say that for me?

A. Alkynyl amino.

Q. Okay. "The alkynyl amino linker containing nucleotides of this invention have distinct advantages, such as the small steric bulk of the alkynyl amino linker minimizes perturbation of the nucleotide position in the linker on the 5 position of the pyrimidine nucleotides and the 7 position of the deazapurine nucleotides eventually places its linker and reporter in the major groove when the nucleotide is incorporated into double-stranded DNA."

Do you see that?

A. Yes. That was our explanation why it actually worked in retrospect.

Q. Right. So in the Hobbs patent you explain the advantage of attaching the label at the 7 position of the deazapurine?

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MR. WHITE: Objection. Form.

A. Yeah. That was our rationale for why -- well, certainly we explained why we wanted to have a 7-deaza, but that position we thought was a good one.

Q. Okay.

A. Subsequently, other people have found other positions that on the ionic in the major groove that work.

Q. And --

A. We were very early in this game and so there are -- we, ourselves, published additional ways to get to the minor group of modifying for the nucleotides, so this is just one way and it was just our -- this was our rationalization of why it worked, and nice to put that in there.

Q. Okay. And the reason that you thought it was a good idea to attach the label at the 7 position of the 7-deazapurine was because it places the linker in the reporter in the major

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groove when the nucleotide is incorporated into double-stranded DNA, right?

MR. WHITE: Objection. Form.

A. Yes. We'd -- we had known from Dave Wards work that the linker arm with biotin was accepted at least with some polymerases getting into the major groove and we wanted to do that.

Now, several ways you could have done that. We started with Dave Ward's work and decided we couldn't extend his chemistry to what we needed to do and we created our own chemistry, but, yeah.

Q. And if you turn to column 11 of the Hobbs patent, you see column 11 is just to orient you, it's a discussion of the heterocyclic base and you see that begins on column 10, line 59?

A. Okay.

Q. And then column 11 beginning at line 1 it says, "the unnatural 7 deazapurines can be employed to attach

the linker without adding a net charge to the base portion and thereby destabilizing the glucosidic linkage."

Do you see that?

A. A-hum.

Q. Yes?

A. Yes.

Q. Okay. And so that was an advantage of using the 7 deazapurines and attaching the label at the 7-deaza position?

A. Yeah, those two go hand-in-hand.

Q. Okay. And that was sort of what you were referring to in the Prober article when you say that the 7 deazapurines facilitates stable linker -- linker arm attachment?

A. Yes.

Q. That's right? Okay.

A. Of course, you could do it other ways without having to stabilize, just one -- one of several choices.

Q. And that was your preferred choice, though?

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A. That was our preferred choice, at the time, but that -- that was 13 -- this work that was done 15 years before Dr. Ju's work and that was something to keep in mind. A lot of additional art appeared in between, let's say, 1987 when the paper came out, I forget when the patent was, and 2000, lots of -- including our own, patents of our own, and other ways to do this, but, yeah.

Q. Okay.

A. It might not have been preferred for us 10 years later if we had done this again. I had other things that worked that -- that seemed to me better, perhaps, but I was no longer working commercially in the field so there was no incentive to do that.

Q. But as -- as you mentioned, though, Applied Bio-Systems that was commercializing your technology was still selling products that had the label at the 7-deaza position?

A. Yes. So the -- the landscape

there is they licensed our technology. Because we wrote extremely broad claims to dye terminator functioning, no, it didn't matter how else you labeled, no one else was going to be able to get bite on that claim. And many tried to but they didn't succeed in knocking the patent out so there was no incentive for anyone to look specifically at other ways of making Sanger sequencing terminators because you couldn't use them anyway commercially.

We continued to work on it a little bit for other applications, such as sequencing-by-synthesis and that turned out to be multiple solutions to the problem, including Sarfati and including a number of folks who reported that the -- would put you in the major group.

In our own work we used sugar on the 1' position and we were able to get those accepted, so there were a lot of solutions.

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MR. COSTAKOS: Move to strike as non-responsive.

Q. Is Sarfati sequencing-by-synthesis?

A. Sarfati? Sequencing by -- can I see the reference? Take a look?

Q. I --

A. I do need to see it because I know you're going to ask me questions about it, specifics so I need to see the reference if I could.

Q. Okay.

A. I know roughly what Sarfati is about, and I've written about it but I do need to see the reference to answer your very detailed questions.

Q. Okay. We -- we'll come back to it.

A. Okay.

Q. I'm going to show you what's been previously marked as Exhibit 1030. This is a Rosenblum reference, and you see --

MR. WHITE: Before you continue,

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we objected to the introduction of this exhibit during the deposition of Dr. Weinstock, during the redirect examination. It was obviously not part of the original petition in this matter and we maintain our objections to this exhibit.

MR. COSTAKOS: I -- I understand your position.

Q. Okay. So in this document you see that Dr. Rosenblum, Mr. -- I'm not sure, Ms., could be, I don't -- I don't know, Rosenblum and his group are all from Applied Bio-Systems. Do you see that?

A. Yes. I see that. Well, P -- yeah, Perkin Elmer now, but, yeah, right. The ABI group.

Q. Right. They've undergone a lot of name changes over the years?

A. Yes.

Q. And if you look at Figure 1 which is on the second page, they show the structure of the labeled ddNTPs

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they were using. Do you see that?

A. That appears to be correct.

Q. Okay. And they showed 7-deaza A and G ddNTPs, agreed?

A. These are dideoxy sequencing agents and these are basically versions of our nucleotides that have just been reengineered to change the dyes and linkers for optimizing function on their instrument.

Q. Okay. As we talked before about the largest supplier of Sanger sequencing reagents were supplying ddNTPs where the fluorescent label -- labels were attached to the 7 position of deazapurines?

A. It worked really well for Sanger sequencing.

Q. And if you look at the -- the patent, the Ju patent, so if you have the '575 patent or whichever one you -- you prefer?

A. Right. I -- I have '575.

Q. Okay. So if you look at the

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'575 patent, you see at column 2 --

A. Okay.

Q. -- so column 2 beginning at line 45, you see it says, "On the other hand, it is known that modified DNA polymerases" -- and it identifies two -- "were able to recognize nucleotides with extensive modification with bulky groups, such as energy transfer dyes at the 5 position of the pyrimidines, T and C and at the 7 position of purines, (G and A)," and then it cites Rosenblum and Ju.

Do you see that?

A. Yes.

Q. Okay. And so this Rosenblum reference that we just referred to is actually cited for that very proposition? In other words, that 7 deazapurines were useful for incorporating -- to be incorporated by polymerases with a bulky group such as a dye, right?

MR. WHITE: Objection. Form.

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A. That's a -- that's a caveat and the caveat is that it's only for a dideoxy and it had not been demonstrated with a 3'-cap or anything other than dideoxy at the time.

Q. Right. But my point is that Dr. Ju's group in the Ju patent referred to this Rosenblum reference as background to -- to talk about how 7 deazapurines could be incorporated by polymerases when they had a bulky group attached to the 7 position?

MR. WHITE: Objection. Form.

Q. Right?

A. Clearly he -- he recognizes that in Sanger sequencing we are able to put a bulky dye on the 7 position, yes, but that's all he draws here. That is the only statement he makes. He -- he moves on from there.

(Exhibit 1041, paper by Seela entitled "Oligonucleotide Duplex Stability Controlled by the 7 Substituents of 7-Deaza-Guanine Bases."

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Was received and marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

Q. Okay. I'm going to hand you what I marked as Exhibit 1041 to your deposition.

MR. WHITE: Before you start examining, we'll object for the record to the introduction of a new exhibit at this stage in the proceeding. It's not in the petition that was filed with Illumina and it's not in the declaration of Dr. Trainor.

MR. COSTAKOS: It's called "cross-examination."

MR. WHITE: Cross-examination, this proceeding is limited to the scope of the declaration and the petition.

MR. COSTAKOS: Okay. I -- I think impeachment is fair game. I really don't -- on the record --

MR. WHITE: If you want to show him a document that he wrote like

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Hobbs, that's a different story but this is not documenting.

MR. COSTAKOS: Well, I -- I think I can still impeach his -- his opinions with that document.

Q. So let's look at Exhibit 1041.

(Whereupon, the Deponent reviews the document.)

MR. COSTAKOS: And for the record this is a document, and you see it's authored by Frank Seela and others and it's entitled "Oligonucleotide Duplex Stability Controlled by the 7 Substituents of 7-Deaza-Guanine Bases."

Q. And it's -- it has a date of 1995. Do you see all that?

A. I see the paper, yes. I have never seen this paper, so I'm going to have to read it if you want me to give you any --

Q. Okay.

A. -- any kind of honest answer in any reasonable context.

Q. Okay. If you look at the first

page, the very first sentence says, "Synthetic oligodeoxyribonucleotides targeted to certain segments of M-RNA (anti/syns oligonucleotides) have concerned the center of oligonucleotide research within the last few years."

Do you see that?

A. I see that.

Q. Okay. And -- and just by -- by way of context, you mentioned before that the work you did in Hobbs and Prober articles and patents was back in the mid-'80s, in the early to mid-'80s. Do you agree with that?

A. Yes.

Q. And Dr. Tsien's work was filed in 1989, I think, and was published in 1991, right?

A. I -- I'll take that. I have to go look. Yeah.

Q. Okay. And then the patents here were applied for in October of 2000, right?

A. Correct.

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Q. Okay. So in between the publication of Tsien in 1991, and the invention date of October of 2000, there's nearly a decade, agree?

A. Yes.

Q. Okay. So here in this article that's from 1995, Seela and his group are saying there's been work that's been done within the past few years and I think you alluded to that even in your own answer, right?

A. A-hum.

Q. Okay. And then it says, if you look at the third sentence, "In this respect it has" -- "it was shown that the 5 substituents of pyrimidines which are located in the major groove of B-DNA can stabilize the duplex's structure."

Do you see that?

A. Okay.

Q. And you've talked before about the 5 position of pyrimidine was your preferred attachment point as well,

right?

A. Yes.

Q. Okay. And for exactly the same reason, it would be located within the major groove and it would stabilize the structure, right?

A. Could you repeat that?

Q. Sure.

A. I -- I'm not sure I got that right.

Q. Sure. The reason you preferred 5 pyrimidines was the same reason, in other words, it would fit nicely within the major groove and it would help to stabilize the duplex structure?

A. There was nothing to do with stabilizing duplex structure.

Q. Okay. It would just fit nicely within the groove?

A. It would fit within the groove -- the -- the substituent would stick out in a the major groove such that apparently, we discovered, it does not impair polymerase recognition of the

duplex.

Q. And B-DNA, that's just natural, that's the most common form of DNA, right?

A. Well, it -- it's understood to be the state that DNA is in its -- in sort of the resting state. It can adopt other conformations but most DNA prefers to be B-DNA in under normal salt conditions and temperatures and so on.

Q. Okay. And then in the next sentence it says, "On the contrary, the 8 substituents of purines which are also located in the major groove lead to destabilization."

Do you see that?

A. A-hum.

Q. And it says, "This is a result of steric propulsion which drives the molecule into the syn-confirmation."

Do you see that?

A. Yeah. I could read that. Yes.

Q. Okay. And then in the -- the

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next sentence it discusses its "use of 7 substituted 7-deazapurine nucleosides." Do you see that?

A. I'm reading it sentence by sentence, yes.

Q. Okay. And it says, "On the other hand an anticonfirmation as observed for the common DNA constituents was established for 7 substituted 7-deazapurine nucleosides," and -- and then it has an example of one which I will not try to read.

And then it says, "And furthermore, the 7 substituents do not interfere sterically with the sugar-phosphate backbone and should fit exactly into the major groove of the B-DNA."

Do you see that?

A. Yes.

Q. Okay. So what it's saying is -- what Dr. Seela's group is saying that the use of 7-deazapurines is advantageous because it fits exactly

within the major groove of the B-DNA and that it does not sterically interfere with the sugar-phosphate backbone, right?

MR. WHITE: Objection to form.

A. Yeah. Yeah. You have to -- yeah, it's talking about nucleotide stability and not polymerase utilization, right? So that -- so at no point do we discuss a -- in -- either in my work or anyone else's the effect of the modification we make on duplex stability. And I -- I guess I need to know why that would be thought to be particularly relevant?

As long as you can incorporate the nucleoside and even once that's all that matters and, in fact, for Sanger sequencing that was all that mattered.

So I -- I read this and I understand the words but I -- I, personally I see this as totally irrelevant to how you design a nucleotide triphosphate for a single

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incorporation at a time.

Q. But he is explaining that the reason you -- you attach at the 7 -- using a 7-deazapurine is because it fits within the major groove of the --

A. If you want --

Q. -- of the DNA?

A. -- to make a DNA probe he says that. He didn't say if you want to make a DNA polymerase substrate.

Q. But the reason --

A. It's very different. It's a completely different art, I mean, prior art.

Q. Yeah, I understand your point.

A. Okay.

Q. Okay. But I guess, the point I'm making is that the reason he's using 7-deazapurines is exactly the same reason that you were using 7-deazapurines?

MR. WHITE: Objection to form.

A. No. He didn't talk about a stability problem here. He's talking

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not so much -- because that was our choice. I preferred not to have the modified nucleotide. I -- I had to do it if I wanted the nucleotide to be establish stable. He's simply saying that -- that in the observation, that in the context -- in the context of the -- of an oligonucleotide -- and if you look at his data, he's making -- he's substituting all the nucleotides and so this oligonucleotide in No. 9, in this -- in this modification and examining this effect on Delta -- on Delta S for stability, that's the assessment of stability.

And he's speculating as to in the context of a duplex structure where you've got many of these, is it favorable or unfavorable and to me, in my mind, what he is trying to say is, you know, if -- is this going to help me in making an oligonucleotide or if I wanted to make an oligo with something hanging off it in the middle like DNA

probes, and people do that all the time.

Q. A-hum.

A. And it was Dave Word's invention, should I go with an 8 or 7 and I guess that the person who is interested in making DNA probes would interpret this paragraph to say, Hmm, well, maybe for the purpose of labeling an oligonucleotide synthetically or any other way but in -- in labeling it inside a nucleotide with something, I might want to look at -- I might prefer a 7 over an 8 for that indication. But interestingly he doesn't talk about -- he doesn't talk about the DNA sequencing terminating function and he doesn't talk about sequencing-by-synthesis and whether it's better or worse for that, and which I remind you that you're, you know, putting one in, and that Dr. Ju's claim is that he adds one nucleotide.

So this effect of stabilizing or

deestablizing an oligonucleotide is completely irrelevant.

Q. Okay. That's all well and good. I guess, my -- my point is that, the point that -- that Seela and his group are making is that using a 7 substituted, a 7-deazapurine is advantageous in this context --

A. In this very different context.

Q. -- in this -- okay. Because it fits exactly within the major groove of the B-DNA, right? That -- that's his point?

A. He doesn't say that the 8 doesn't fit in the major groove. What he says is it -- it alters the nucleotide base confirmation, okay? The 8 is still in the major groove, it's just that it does so -- there is some bumping apparently that occurs is what he's implying with the nucleotide which prefers so that the nucleotide instead of preferring to be that and instead is spending more time this way.

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And that -- and it spends some time there, because if it doesn't spend any time there it would have no affinity, and he doesn't say that.

He simply says it's somewhat reduced. Well, that's okay. It works fine -- fine enough. He's just saying that if you are going to pick one or the other for an oligo stability, pick the 7 that's all he's saying.

Q. Right.

A. They both go in the major groove.

Q. Right. And -- and he points -- and if you look at the next sentence he specifically points to your article as -- for -- for the notion that 7 substituted 7-deazapurine nucleosides had already been used in, as chain terminators in Sanger dideoxy sequencing, right?

MR. WHITE: Objection. Form.

A. Yeah. Right. So I think the implication here is since he's not

talking about specifically, you know, doing sequencing, he's saying, I guess 7 fits, period. I mean if it didn't fit period, I couldn't do sequencing, right? If it didn't fit within some DNA structure and he's simply saying, Hey, people have used that.

I don't think he said that -- at no point here does he say that this -- that this insight as to 8 versus 7 on an oligo stability has anything to do with, you know, sort of improving a DNA -- or, you know, redesigning a DNA sequencing agent.

I mean, I'll remind you this is oligonucleotide stability. This is not DNA sequencing. DNA probes is an entirely different art and it's, you know, a different art than DNA sequencing.

Q. But he does draw the parallel between --

A. Well, he does. I -- I don't see that it's relevant to DNA sequencing,

in any way whatsoever, personally. And I don't think any person skilled in the art would read this and say, What is he talking about, oligos? He's not talking about -- I don't see -- I don't see where he talks about the relative rates of polymerase incorporation.

Q. Is syn-confirmation of a nucleotide important to polymerase incorporation of nucleotides?

A. Yes. If it can adopt a -- if it cannot at all adopt the right confirmation, it can't be incorporated. Okay? We already know that modifications that we make for purposes of sequencing take -- make it hard to -- to recognize. So just removing the 3'-hydroxy, a big impact for most polymerases on acceptance. And anything on the base that could influence the -- what's called syn-anti-equilibrium could affect it.

Now, for DNA sequencing we already -- we already established and

spoke to, you can use large concentrations and you could overcome small differences in stability.

So, for example, he's saying, Well, gee, there is a little -- there's a difference here in stability in melting. Well, it -- but in this-- even for oligonucleotides it doesn't say it can't work. It simply says, I -- you know, it's a little more stable if I go with the 7, but again, that doesn't tell you whether 7 or 8 would be preferred in DNA sequencing. I don't know that.

Does -- does the 8 confirmation affect polymerase? Sure, it does. But I believe the -- the work of Sarfati, which is pretty much contemporary with this one, says I made the nucleotide and it works, it gets incorporated. And that would be surprising to me because all it has to spend is a couple percent of the time in the confirmation and it would be incorporated at some

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rate, and apparently at a useful rate.

Q. So sequencing-by-synthesis relies on stable double-stranded DNA primers, right?

A. Yes. The --

THE REPORTER: Sorry. The double-stranded DNA --

MR. COSTAKOS: -- primers.

THE WITNESS: A-hum.

(Exhibit 1042, paper by Ms. Ramzaeva and others, entitled "7-Deaza-Guanine DNA Oligonucleotide with Hydrophobic or Cap Ionic Side Chains", was received and marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

A. Again, I haven't seen this reference before and I never read it.

Q. Okay. Hold on.

MR. WHITE: I object to this exhibit on the same grounds as the last one, which is it's not referred to in the petition or in the declarations,

either of Dr. Weinstock or Dr. Trainor, and it's outside the scope of the IPR trial.

MR. COSTAKOS: I understand. Let me just identify it for the record so we know what it is.

So I've marked as Exhibit 1042 for your deposition, a document by a Ms. Ramzaeva and others, entitled "7-Deaza-Guanine DNA Oligonucleotide with Hydrophobic or Cap Ionic Side Chains," from 1997.

A. Okay.

Q. Now, if you look at page, the second page of this exhibit, the first full paragraph, the first sentence of that it says, "One of the outstanding features of the 7 position of guanine residues is its deepest electrostatic potential minimum, as well as its highest steric accessibility within the major groove of the DNA."

Do you see that?

A. Yes, I do.

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Q. Okay. And then, again, this is making the point that I -- and I understand in the context of oligonucleotides that an outstanding position feature of 7 substituted guanine residues is that the electrostatic advantage and the steric accessibility within the nature or groove of B-DNA --

A. I have no idea what he means when he says "in its deepest electrostatic potential minimum." I, you know, I would have to read this paper and the references cited by it because I have no idea what he's talking about, frankly.

Q. Okay.

A. But the accessibility I do understand, and that's fine.

Q. Okay. And that's the same point we saw earlier about fitting within the major groove?

A. Yes.

MR. WHITE: Objection. Form.

TRAINOR

A. I do want to point out actually thinking about it that on both of these references, "accessibility" means that it's in the major groove and it means you could form a duplex with it and it's still nothing about whether you can actually recognize such a piece of DNA with a polymerase as a primer even, in any way.

Q. Okay.

A. So, you know, in all of this he's saying, Gee, this works really well if you want to put two oligos together --

Q. Okay.

A. -- that's not sequencing, that's the initial step in sequencing. So, you know, again, I -- I'm not sure what the relevance is, but go ahead.

Q. And you -- you would use polymerase as a part of that process, you would agree with that, right?

MR. WHITE: Objection. Form.

Q. Yes?

TRAINOR

A. Well, yes, sure.

Q. Of course.

A. But I don't know that I would use a polymerase with, you know -- I -- I don't know if I would make an oligonucleotide as a primer with these intact within it and then go ahead and try to use it as a primer. I don't know.

And I think if you look at Dr. Ju's claims he simply says that "the incorporation of a nuclear method whereby a nucleotide is incorporated into a primer template and a number of specific limitations and it's detected for its identity."

So I -- you know, I'm really struggling to see how this has any relevance to that single incorporation because, in fact, we're not -- in fact, you could imagine sequencing where the -- that terminal residue -- when the polymerase falls off it's very destabilized but that is not what the

claim is, the claim claims that it has to go in once and be identified.

Q. Yeah.

A. That's it.

(Exhibit 1043, document entitled "7 Substituted 7-Deaza D'Deoxy-Guanosines", authored by Ramsayva and Seela, was received and marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

Q. I'm handing you what I marked as Exhibit 1043 for your deposition.

A. Another one?

MR. WHITE: Again --

MR. COSTAKOS: Wait. Wait. Let me make your -- a comment and I'll -- let me just identify it and then you can go for it.

MR. WHITE: Okay.

MR. COSTAKOS: So for the record, Exhibit 1043 is a document entitled "7 Substituted 7-Deaza

TRAINOR

D'Deoxy-Guanosines" -- and there are some more, authored by a Ramsayva and Seela, the same people that we saw previously, dated 1995.

Go ahead, Mr. White.

MR. WHITE: Okay. So once again, I'm going to object to the introduction of this exhibit at this time. It is not included in the Illumina petition or the declaration of Dr. Weinstock and it is not discussed in the declaration of Dr. Trainor. It's outside the scope of the IPR trial.

Q. Okay. So if you look at this article, you see just in the title itself it talks about 7-deaza -- 7 substituted 7-deaza deoxy-guanosines, right?

A. Okay.

Q. If you look at the second page of the document, first full paragraph, last sentence, it says, "These compounds are of high importance as

TRAINOR

they allow not only stabilization of DNA duplex structures but can be further transformed to derivatives by side chains carrying reporter groups at this sterically favorable position."

Do you see that?

A. Yes. So I guess what I interpret that to mean, since this is making oligomers, which enhance stability means, Oh, this is a good way to make a DNA probe and we can stick fluorophores on it for the purposes of DNA probes. But, again, there is no mention of the effect of these modifications on the polymerase incorporation, the function as a substrate polymerase, for the -- say, for the purpose of sequencing.

So -- so I mean, I keep coming back to you're talking about oligonucleotide stability which is of great importance for DNA probes and is -- yeah, I don't understand the relevance to the Dr. Ju claims.

TRAINOR

Q. So if you look at page 1087, there is a paragraph about halfway down, that says, "The 7 position of 7 substituted 7-deazapurines is ideal for the labeling of DNA with reporter groups not showing the drawback of the destabilizing effects of purines, with substituents located at C8, at least from the stereochemical behavior of B-DNA."

A. Yeah.

Q. Do you see that?

A. Yes, I see that.

Q. Okay. So again, here it's pointing, in this context at least, to the to the advantageous use of the 7 substituted 7-deazapurine, right?

A. For DNA probe, that you might want to label.

Q. Right.

A. And that you wouldn't destabilize by putting a linker there or label there.

Q. And they contrast that with the

TRAINOR

--

A. With the --

Q. -- hold on. It contrasts that with the destabilizing effects of purines with substituents located at the C8 position, right?

A. Yes. For the purposes of DNA probes, apparently -- and, I guess I -- I was not even aware of this literature. Obviously, I haven't seen these papers and if I was interested in DNA probes, which I was and I probably would have found this and it would have been really useful information but I don't think it tells me anything about how to design a DNA polymerase substrate even particularly for the DNA -- the sequencing-by-synthesis, which has got all sorts of issues you got to cope with. I wasn't aware this was one.

And, you know, even the -- even Dr. Ju's invention adding one nucleotide and I don't believe he

TRAINOR

discusses the effect of adding a single nucleotide at the end of the chain to the primer stability, so I don't know.

That might -- that might -- might have been a useful piece of information but, again, this is addressing a completely different art.

(Exhibit 1044, paper entitled "Nucleotide Stability of Oligonucleotides Containing 7 substituted, 7-deaza and 8-aza, 7-deazapurine nucleosides" by Seela, was received and marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

Q. I'll hand you what I marked as Exhibit 1044 to your deposition.

MR. COSTAKOS: Let me identify it for the record. So Exhibit 1044 is entitled "Nucleotide Stability of Oligonucleotides Containing 7 substituted, 7-deaza and 8-aza, 7-deazapurine nucleosides," by Seela

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and others, dated 1997.

MR. WHITE: Objection. Form. And That's actually not the title.

MR. COSTAKOS: Excuse me?

MR. WHITE: You didn't read the title correctly.

MR. COSTAKOS: Didn't I? What -- what did I miss.

MR. WHITE: I -- I don't mean by pronunciation you started by saying the first word in the title was "nucleotide," and the first word is "duplex."

MR. COSTAKOS: Oh, yeah. I -- I'm sorry. Okay. Well, let me -- I -- I'll start over again. I wasn't expecting that objection, but I have no doubt it's true.

Okay. So let me just for the record, identify Exhibit 1044 is a document entitled "Duplex Stability of Oligonucleotides Containing 7 substituted 7-deaza and 8 aza, 7-deazapurine nucleosides," by Seela

TRAINOR

and others from 1997.

A. Yeah.

MR. WHITE: So, again, I'll still object to the introduction of this exhibit in this deposition at this time. It is not referred to in the -- in Illumina's petition or Dr. Weinstock's initial declaration or in Dr. Trainor's declaration.

Q. Okay. So let me refer you to the third page of the document, page 965. And in the last paragraph there it says, "Table 1 indicates that substituents in the 7 position of 7-deazapurines have considerable steric freedom within the major groove of DNA and may carry bulky substituents without significantly interfering overall finding. Therefore, the 7 position of 7-deazapurines is an ideal position for the functionalization of DNA with reporter groups."

Do you see that?

A. Yes. Yes. So my comments are

TRAINOR

exactly the same as the other. If you go to page 1 -- and because I'm seeing this the first time, I'm kind of winging. All right? So these are phosphoramidites, this is -- these are being -- not polymerase substrates they -- they're functioning very well as phosphoramidites to make oligos, which have these modifications. And he's looking at these relatively simple oligonucleotides and saying, Well, if I have these things, they do not seem to stabilize the duplex structure of the synthetic oligonucleotide.

And again, I think that may be true and, in fact, that -- that's pretty neat science, and I -- I like the work. I -- I like that he used my chemistry and that's great, but I'm -- not clear to me that this is relevant to Dr. Ju's invention, because at no point did we discuss the effect of a TM, melting temperatures, that -- that didn't -- that certainly didn't come

TRAINOR

into the Sanger sequencing in my -- in my calculations and certainly in my, you know, in my design and I'm not sure that came into Dr. Ju's design, what Dr. Ju was concerned about was the polymerase recognized this and incorporated -- and the claims at issue, say, you incorporated a nucleotide by a polymerase with the following characteristics and you do so in such a way and -- and it's all about incorporating nucleotide or the nucleotide itself or the product of incorporation of a nucleotide.

This is talking about duplex stability and I think anybody with any minimal skill in the art of DNA field would recognize that this person was talking about DNA probes and not DNA sequencing. And one of the reasons why I didn't see these papers and I had no interest in DNA probes and I had great interest in DNA sequencing, but I wouldn't have found these because I

still don't see the relevance and I probably wouldn't have seen the relevance then. I think it was neat that they used my chemistry but that's about it.

Q. Okay. You do see the point that Seela is making here that the 7 position of 7-deazapurines is an ideal position for the functionalization of DNA with reporter groups in this context?

A. Well, he's saying you can have anything there and without the reporter. You can put the reporter on later and it didn't make a difference, so the linker that -- and he showed earlier that simple organic groups that are big work and he's saying, Gee, if you what to put a big dye out there you can probably do that.

Q. Right.

A. But we kind of already knew that, I mean this is '97. We had Prober. We had a slew of Applied

TRAINOR

Bio-Systems showing the -- that the 7 position of deazapurine for the Sanger sequencing at least was just fine. And it didn't need Seela to tell him that that was going to work. It worked. And, in fact, this is somewhat -- this is a little bit redundant, although it's a different field but fair enough.

He's looking at DNA probe function but certainly Dr. Ju coming in is -- he's got nothing here is telling him whether a nucleotide he might design is going to work very well for sequencing-by-synthesis and he already knows that if he wants to -- that if he chooses to use the 7 position to put a linker, he has to have a deaza there because of the stability issue. He could choose other ways and there are other ways to do it, but that is the one way he chose to do, and guess what, it worked. You know, okay, great. There are other ways to do it and I -- I'm sure other people will find other

ways to do it over time.

Q. So if -- if you attach the -- in sequencing-by-synthesis, or in any context, if you were going to attach the label to the 7 position of a purine you know it has to be deaza?

MR. WHITE: Objection. Form.

Q. Right?

A. There are -- you could attach, if -- if the 7 position probably will have to be a deaza, okay, but you have other choices. But you could say I'll go with the deaza and all the synthetic grief that's required and many, many steps or I could go with the Sarfati on 8 for sequencing because he -- he says it's incorporated or you could go with labeling on the bases on the -- the collection for some of the nucleotides and you could take that strategy.

So there are a couple of strategies one could use here and been suggested and certainly throughout the references that are cited in the

petition and in my declaration, there are certainly lots of choices and there are things that people are working on. It's an active field.

Q. Okay. And -- and I think you -- the point you made was by the time this work was done, the -- the Seela and Ramsayva and -- and these others that we've looked at in the 1996, '97 time period it was well known for Sanger sequencing to attach the fluorescent label at the 7-deaza position?

A. That's for Sanger, yes, but interestingly that was known for 13 years before Dr. Ju parlayed that into a sequencing-by-synthesis system. So I've got -- I always found it interesting that we've got a whole, you know, family of experts in DNA labeling and I, you know, I did this work in the '80s and continued somewhat in the '90s, but throughout the '90s, it was a very active field because everyone understood there was this

sequencing-by-synthesis that might really be the breakthrough. And all the experts were working on this but I -- I didn't see any papers. I don't recall and certainly nothing has been provided to me that suggested that prior to Dr. Ju anyone ever thought that -- that -- and -- and said here is how to turn Prober into a reagent, a reagent of my invention to actually demonstrate sequencing-by-synthesis with a Prober 7 linkage.

Q. But everybody -- it was well known to use in the context of Sanger sequencing --

A. In Sanger sequencing.

Q. -- in Sanger sequencing the attachment of the fluorescent label at the 7-deaza position?

A. Yes. And it's also --

Q. And -- and the reason for that was, as you explained in your paper and in your patent, because it increased the stability of the linker on it?

TRAINOR

A. Right. To the extent it's not increased. It -- it's completely unstable. If you alkylate or proteinate that -- that 7, you -- you've got a problem and you wouldn't be able to isolate those. So you could -- you could go with that synthetic complexity or take some of the other choices that you could go forward with.

Q. Okay. So if you are incorporating -- would a polymerase be -- strike that.

Would a polymerase be more or less likely or inclined to form double-stranded DNA if the double-stranded DNA created is stabilized versus destabilized?

MR. WHITE: Objection. Form.

A. I guess I don't know the answer to that question. What I do know is, it's interesting, is that we've got, you know, the notion is how are we changing, perturbing, the ability to recognize it. I know that in my own

TRAINOR

work, in my patent and I published is that an acyclic nucleotide that has no sugar whatsoever, is accepted perfectly well for Sanger sequencing. And in there, there is not even a discussion of syn/anti or stabilization and there is no stabilization whatsoever, and yet it's incorporated.

Q. If the -- if the double-stranded DNA is destabilized, isn't it less likely to be incorporated by DNA?

A. No. I would say the acyclic nucleoside, I -- I'd say no.

Q. Let me ask the question again, because I -- I said the wrong thing at the end and you answered right at the very same time.

A. Sorry.

Q. Isn't it true that destabilized double-stranded DNA is less likely to be incorporated by polymerase than a stabilized DNA?

MR. WHITE: Objection. Form.

A. I guess I don't have an answer

TRAINOR

to that because I don't have any data that you presented or that I'm aware of that -- that tells me what the effect of a single modification on the end in -- to the end of a primer does to the stability of that DNA.

I do know as I just cited that an acyclic nucleoside which really gives no stabilization whatsoever can't -- can't because it doesn't have any confirmational constriction works perfectly fine as a Sanger sequencing terminator. And that tells me that the -- that the newly added nucleotide needs to somehow look like something after it's done, is not important to the incorporation in a single step by a nucleotide, by a polymerase.

I was pretty surprised by that, actually, so I guess my answer would be no, because my -- I was shocked that the acyclos worked.

MR. WHITE: Jeff, if we're going to keep on, just I think we said we

TRAINOR

would stop around 12?

MR. COSTAKOS: Oh, okay. Yeah.

MR. WHITE: And it's two minutes after 12.

MR. COSTAKOS: Oh, okay. I -- I was having so much fun, I was losing track of time. Now is a fine time for a break.

VIDEOGRAPHER: The time is 12:03 p.m., and we're going off the record.

(Whereupon, a lunch recess is taken.)

VIDEOGRAPHER: The time is 1:11 p.m., and we're back on the record.

Q. Dr. Trainor, you mentioned earlier that -- we talked earlier about the fact that Applied Bio-Systems had acquired the technology that you developed. Do you remember that generally?

A. Yes.

Q. And they eventually

commercialized products for Sanger sequencing for capillary electrophoresis sequencing that used your technology?

A. I believe so. I was never privy to the composition of their products, obviously. But my understanding is they did, yes.

Q. Okay. And you know that they used 7 substituted 7-deazapurines?

A. I actually don't know that for a fact. They certainly published on that but -- in other words, since I was not a practicing sequencer, I never looked at their product brochures and said, Gee, what's the -- looked at the structure of their products.

Q. Okay.

A. The license that they really required was the terminator license not specifically nucleotides or dyes, per se --

Q. Okay.

A. -- but they got that, too.

TRAINOR

Q. But you understood, based on what you read in the literature, that they were using --

A. I presumed that they were using my linkers and the 7-deaza, yes.

Q. When did their technology -- strike that.

When did the Applied Bio-Systems technology come out that used your technology, as far as you know?

A. I don't understand the question. Can you repeat that?

Q. At some point Applied Bio-Systems introduced products that had the technology that was developed by your group at DuPont, right?

A. Yes.

Q. And approximately when was that, that that technology --

A. Yeah. All right. I'm not sure I can give you a specific year. The sequence of events was that Applied Bio-Systems commercialized the dye label primers in slab gel

electrophoresis format, as their first instrument and that came out before our instrument. We actually commercialized our instrument with the terminators with the slab gel with the actual four dyes you see in Prober.

That happened -- I'm guessing it happened -- I think it happened right around the time when we published the science paper, I just don't remember the commercial timing, but by probably '89 or so, it was clear that DuPont was not going to be -- didn't want to compete in this business and they didn't want to have a support group and they didn't want to have to do the next generation machines and things like that.

And so -- so they did a deal with -- with Applied Bio-Systems who was very interested in the terminator licensing because they understood they could not practice dye terminator sequencing without that license.

TRAINOR

DuPont was happy to get some return for that technology and I -- I'll guess that they were working on it knowing that this was going to go this way sometime before. And I'm guessing that their dye terminator chemistry came out in the very early '90s, but I don't know. You'd probably look at product brochures and know that. I stopped worrying about it. A week after this happened I was pretty sad about it and then I moved on and I did other things.

Q. Okay. But in -- the -- the general timeframe was, you think, the early '90s that Applied Bio-Systems was introduced?

A. Yeah. I -- I think it -- I wouldn't be surprised if that was the date. I just don't know what year.

Q. Okay. But that's consistent with your recollection?

A. Yeah. That's correct.

Q. Now, polymerase extension reactions required double-stranded DNA

templates, right?

A. The template primer, I -- I think it's fair to say that, I mean, I don't -- I have not -- I can't recall a study in which someone said what form of DNA needs to be, but I think it's likely. My understanding is that DNA polymerase recognizes B-DNA in the primer helix portion and then adds to the next nucleotide.

Q. Okay. And so it starts with at least a double-stranded portion for the template?

A. Yeah.

Q. And the double-stranded portion I think you just said tends to be B-DNA, right?

A. I think so. I mean, that wasn't my expertise in measuring DNA structure, per se, so I don't know for sure and I can't recall reading something about that but my presumption would be that a B-DNA recognized it.

Q. And that is the most common form

TRAINOR

of DNA?

A. Well, that is the form that seemed to -- well, I guess my understanding is that that's the form that most DNA adopts unless it has unusual sequences where you might get higher order structures and so on.

Q. Okay. And so that double-stranded DNA that's used in polymerase extension reactions tends to be helical, right?

A. Yes. That's helical.

Q. Okay. And so the structure that is recognized by the polymerases in the extension reaction is also helical, agreed?

A. In the primer portion, yes.

Q. Yes. Okay. So if the DNA -- excuse me -- if the double-stranded DNA primer were not helical it would be less likely to be recognized, agree?

A. If it could not be helical. Certainly, you know, I think you have to recognize, as a matter of degree,

TRAINOR

that something may be -- may have a preference to unwind or melt but in the present polymerase might actually be stabilized and that's not uncommon, that -- that binding to a protein, stabilizes it, a given confirmation.

So actually given that it recognizes B-DNA I would not at all be surprised to see the DNA polymerase stabilized to some extent because that would be consistent thermodynamically to draw the cycle.

THE REPORTER: And that would be --

MR. COSTAKOS: -- consistent thermodynamically.

Q. The polymerase is -- strike that.

In the polymerase extension reaction the polymerase recognizes the helical structure of the double-stranded DNA?

A. I think crystal structures that, you know, they're likely because we've

got crystal structures of -- and this is what I worked -- work done long ago and I remember reading, but I haven't followed up on, you know, nicely shows a helical DNA and there is an end, and what you are doing is propping something on the ends.

Q. Right. And as a sequencing-by-synthesis reaction continues, the double-stranded portion of the template gets longer, right?

A. Is what? Excuse me.

Q. Gets longer?

A. Yes, it does.

Q. Okay. Now, in the process of extending the double-stranded DNA primer in sequencing-by-synthesis, the dye groups are cleaved and removed, right?

A. That's the way -- some methodology suggests you simply bleach them, but I think Dr. Ju's technology, and as I understand it, other technologies, cleave it --

TRAINOR

Q. Okay.

A. -- and leave a piece left.

Q. Okay. So as the -- in the process of extending the double-stranded DNA primer, in sequencing-by-synthesis there are going to be linker groups that remain on the bases of the double-stranded DNA after cleaving the --

A. After -- after multiple steps but not after a single step.

Q. Right. But as the chain grows, there are going to be these sort of residual linker arms that are or linkers that remain after the cleavage of the dyes, right?

A. Yes. I'd have to guess so. I didn't think about it too hard because the claims of ester involved the addition of a single nucleotide.

Q. But you understand that sequencing-by-synthesis sequencing by -- strike that.

You understand that

TRAINOR

sequencing-by-synthesis involves multiple steps, right?

A. That would sort of be the next step in the process so you might say I've got to work really hard to get one of them in and I can stop and it stops anyhow and see did it go in and can I deprotect it. And I think the -- the standards, and if you read the way people have developed the technology, that is the first thing that they look for.

And then you got to ask the question: Well, how well does it go for sequencing? How well does it go multiple times? But if, for example, you are going to use your invention to determine sequence of a single sight, like a single nucleotide -- a single nucleotide polymorphism, which sequence-by-synthesis is great for and that -- that's a great way to do that, to sequence a single nucleotide polymorphism.

TRAINOR

Q. Okay. You need to slow down.

THE REPORTER: I --

THE WITNESS: Sorry.

MR. COSTAKOS: You're going very fast.

THE WITNESS: It might not be on your list, I'm sorry, but it -- it's relevant -- and then you would only have to put it in once.

So, you know, if I was considering the reason of -- I guess your questioning is sort of outside my declaration because I was asked to consider the requirements to perform Dr. Ju's invention which -- which speaks to a single step.

Q. You can't --

A. The claim does.

Q. -- you can't detect single nucleotides polymorphisms by doing one step of sequencing-by-synthesis, can you?

A. Sure you can.

Q. How is that?

TRAINOR

A. You go in and you -- you put a primer that butts right up against that polymorphic site and you give it four nucleotides and see which one goes in.

Q. Okay. So as long as you know where the polymorphic -- where the single nucleotide polymorph is?

A. You generally do. In fact, that's the -- in my field it's the pharmaceuticals, and that is what you are doing. The polymorphisms that --

Q. You need to slow down.

A. Okay. In my field, pharmaceuticals, not uncommon in projects of mine to be concerned about single nucleotide polymorphisms in drug targets.

Q. Okay.

A. If you do that you need to know what base is present in a given patient to be able to make sure that -- that they are going to respond to your drug and there are certainly many drugs where that wasn't done and it was

TRAINOR

disastrous. So there is a major application for how do you detect in a patient sample one nucleotide at a position that's well known, you know the flanking sequence -- sequence and then, you know, you just ask the question what is that next nucleotide.

Q. Okay. So you if you are going to sequence one step there is no difference between using a reversible terminator and irreversible terminator?

A. You could use either one of those that's true. You could.

Q. Let's get back to the -- the situation where you are talking about sequencing-by-synthesis using multiple rounds of a base addition.

So in there are linker arms that -- that remain after the repeated cleavage of the fluorescent dye, if those destabilize the double-stranded DNA template, from the shape that's recognized by a polymerase then cycles, additional cycles of

sequencing-by-synthesis are less likely to be successful, agreed?

A. Well, I would say, particularly in reading the references you presented me, that it's an amount of degree of destabilization. The polymerase only recognizes a couple of bases of the template primer and, actually, it's only contact may be three or four bases, my understanding and I -- I've done the work on it and -- but I don't know. I can't give you the exact number. It -- it's a small number that is in -- in intimate contact with and I think the key there to my thinking, when you were designing a sequencing-by-synthesis you want to make sure that with the piece that's left, does it interfere with the polymerase binding.

But you -- if you still got a lot of DNA that is on the tail, the primer, it's streaming out anyway. You only have to maintain the helix for

three or four bases for the polymerase to recognize it.

So you are talking a matter of degrees with me here, I guess, or how -- how much destabilization is -- is it possible to hybridize. I agree that is going to be a real problem. But if you are saying it's a little less stable, well, we already know that AT regions are considerably less stable than GC but yet we have no problem sequencing AT-rich regions. So some degree of destabilization would be acceptable and would work just fine and if they were not the true, the AT regions would not be sequencing.

Q. So if there is some destabilization it would be acceptable, but you would agree it wouldn't be as good as if -- if you had a stable molecule?

A. Well -- well, the only thing I would worry about there since you remember you are doing a single step

and you are not asking the nucleotide to compete, except with the other bases, you either put one in or not and I think something like that if you found that maybe it was a little less stable so it didn't work as well, you would probably lengthen the incubation time to make sure it had plenty of time because basically I'm in the right confirmation or wrong confirmation, right/wrong. Maybe you have to wait until it gets in the right, which means going a little -- just waiting a little longer.

Now, where it would be problematic is if you misincorporated and I see no evidence that the next nucleotide would misincorporate as a result of -- of, for example, I'm not aware that misincorporation occur after AT-rich regions and, in fact, in practice the sequencing-by-synthesis was a remarkable performance with respect to fidelity. So I'm guessing

that it's not that big a problem.

Q. So one effect of having a destabilized helix is that you might need to increase the length of time that the reaction takes?

A. Yes. That's hypothetical. I'd have no idea. I -- I don't know actually how long they do incubate and I don't know if -- if that's a problem or if they notice that it goes slower in certain regions, that, I don't know.

Q. Okay. But in any event, you need to maintain the helical shape of the double-stranded portion of the molecule?

A. For about three -- three or four bases is enough for the polymerase to see.

THE REPORTER: To see?

THE WITNESS: To see, yeah.

Q. Okay. I'll hand you what's been previously marked as Exhibit 1032. This is the Ward patent, Patent No. 5,449,767, and I believe you used David

TRAINOR

Ward's name a number of times in this deposition?

A. Yes.

Q. This is the same David Ward you referred to?

A. Yes, it is.

Q. Okay. Now, if you turn to --

MR. WHITE: Just for the record, this is an exhibit that we objected to and that was present to do Dr. Weinstock during his redirect examination and it was not initially identified in either his declaration or Illumina's petition, so we reserve our right to move to exclude this exhibit.

Q. So if you turn to page -- excuse me -- column 7. Actually let's look at column 6 first.

You see in column 6 there is a section entitled, "Detailed description of the invention."

(Whereupon, the Deponent reviews the document.)

A. I see that's there.

TRAINOR

Q. And at the beginning at around line 48 it says, "Substitution at ring positions that alter the normal anti-nucleoside confirmation also must be avoided since such confirmational changes usually render nucleotide derivatives unacceptable as polymerase substrates."

Do you see that?

A. Yes.

Q. And then it says --

A. And that is a true statement.

Q. -- it says, "and normally such considerations limit substitution positions to the 5 position of a pyrimidine and the 7 position of a purine or a 7-deazapurine."

Do you see that?

A. Yes. I see that was the statement he made back in -- well, whatever original filing date that was back in around 2000, I believe, or earlier. In '81. Yes.

Q. Well, it's a little unclear when

that statement was in?

A. Yes. But '80s, probably.

Q. Okay. And then if you look at column 7, beginning at line 59, you see it says, "Thus, although purines, pyrimidines and 7-deazapurines are in principal, useful pyrimidines and 7-deazapurines are preferred, since purine substitution at the 8 position tends to render the nucleotides ineffective as polymerase substrates. Thus, although modified purines are useful in certain respects, they are not as generally useful as pyrimidines and 7-deazapurines."

Do you see that? You see that?

A. Yes, I do.

Q. Okay. And he's saying in the context of incorporation of nucleotides by using polymerase, that 7-deazapurines are more useful than other options, right?

A. Yes. I think that's his implication.

TRAINOR

Q. And he specifically criticizes substitution at the 8 position?

A. Well, he doesn't specifically say it that way, but I understand what he's saying, positions that alter the normal anti-nucleoside confirmation, I suspect that might be a function of size, obviously.

So -- and, you know, it was certainly -- I -- I think people at some point because of the chemistry looking at bromonucleotide, so bromine might not have worked there, but I don't know that anyone knew if the linker would work there. And certainly and subsequently people reported that it did work.

So I think he's sort of -- you know, I don't see him referencing these statements. Maybe he's such an expert he didn't have to probably reference this but I -- I don't know what the basis for that is. You'd have to -- and, you know, I certainly didn't

research this topic.

Q. Right.

A. But I do recognize and -- and one thing I did notice because this was brought in and I would say, you know, I had to look at it, as a result of being brought in at Dr. Weinstock's deposition. But he really didn't give any -- he likes to talk about the 7-deazapurine base, but it's not clear if he ever made one or he even told you he had made one or knew whether it was -- ever was really, truly accepted. I don't know. There is nothing in here, as I recall. And I could go back and look more carefully.

So I guess, if I were a reader, as a person of ordinary skill in the art I would say that's a nice idea but I'm not sure if he's told me how to do it, in the particular chemistry from doing it as well as, you know, as example that he actually tried it and it -- it worked so it's a big leap from

TRAINOR

a pyrimidine to a purine.

Q. Certainly, he says 7-deazapurine is preferred?

A. Yes. That's -- that's certainly the statement he makes and I just don't see the support for it but I understand he's -- he's allowed to say those things in there but --

Q. And he's a famous scientist?

A. Yes, he is.

THE REPORTER: He's a --

MR. COSTAKOS: -- a famous scientist.

A. Yes, he is.

Q. And he even says that substitution at the 8 position tends to render the nucleotide ineffective as a polymerase substrate?

A. Yeah. I don't know the reference for that. I mean, again, I -- I'll have to accept it and I think a person of ordinary skill in the art would take that statement and -- and do a further look at that, do their own

research.

Q. If you look at the drawing that is in column 7, the top drawing, so it's between lines roughly 12 and 20?

A. Yes.

Q. Of -- I'm talking about the Ward patent?

A. I got it. I got it.

Q. You'll see that there are a number of groups that can be added on here. I see there is a B and an A, for example.

A. A-hum.

Q. And then, it identifies beginning at line 27, it says, "A represents a moiety consisting of at least three carbon atoms."

Do you see that?

A. Yes.

Q. So this shows attachment of something that is at least three carbon atoms long to a purine, deazapurine or pyrimidine, right?

A. I believe so, yes.

TRAINOR

Q. Okay. And if you look at column 10 of Ward --

A. You know, I -- and just to comment, which is pertinent to your question about what he does disclose, and that it's notable that he discloses that X, Y and Z can be things like hydrogen, hydroxy phosphate and asserts that these are widely useful as probes. And I think everyone would recognize, including anyone normally skilled in the art that X, Y and Z can't all be hydrogen and that's not a polymerase substrate. And certainly having multiple phosphates on the Y and Z would not be a polymerase substrate.

And so, I think he's taking considerable license here and I think that a person of ordinary skill in the art would say that's an awfully broad structure, and maybe I better check in to see what actually works and what the literature shows. And he is entitled to draw as broad of a structure as he

wants in this case and hope that he's given that scope in the claim.

But certainly a person of ordinary skill in the art who is not looking at this in -- from a patentability standpoint, but is saying what does this teach me? He's probably saying, Boy, he's just -- this is, you know, he's laundry-listing this and putting everything that he could imagine would work but yet doesn't tell me much about it. He doesn't tell me how to make it and he doesn't tell me how to use them, except for the limited case that he actually did do and when he commercialized the reagents which was the Bio dUTP agents.

Q. I'm sorry. So we were going to look at column 10 of Ward. And line 49 you see it says, "Because of the ease of preparation it has been found preferable to use NHS esters for probe addition." Do you see that?

A. Yes.

TRAINOR

Q. All right. And that's sort of along the lines of what you testified about earlier about the use of NHS esters as a lead-in group for coupling molecules together?

A. Yes. I think that's pretty standard in the art and certainly was to me.

Q. Okay.

(Exhibit 1045, article entitled "Synthesis of nucleosides designed for combinatorial DNA sequencing", was received and marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

Q. Dr. Trainor, I've handed you what's been marked as Exhibit 1045 for your deposition.

A. Right.

Q. You testified earlier about --

MR. WHITE: I'm going to object, again -- once again that this is an exhibit that was not previously

introduced in the proceedings by Illumina with its petition or in Dr. Weinstock's deposition and it is not discussed in Dr. Trainor's declaration and is outside the scope of the direct testimony.

Q. So you've testified earlier about some of the work by the Welch Group and I think you mentioned Welch and -- and Gibbs and Burgess as -- as having published some articles and that sort of thing relating to DNA sequencing.

Do you remember that testimony generally?

A. I do.

Q. Okay. And so you were talking about some of the -- the work they had done during the -- had been doing during the '90s to try and develop massively parallel sequencing?

A. Yes.

Q. Okay. And I think the -- strike that.

TRAINOR

You testified earlier that Welch's group had focused on attaching fluorescent labels at the 3'-OH position. Do you recall that testimony generally?

A. Yes. And I think this -- well, I think I had testified that they were one of the groups that was working on this. There were certainly like Metzker who was also working on this and I know there was -- is that some relationship between those folks a while ago but I don't remember. But certainly, there were multiple publications with different first authors and groups and I didn't worry about who did what, but certainly, yeah, multiple papers.

Q. Right. But the point of your testimony was that, that the Welch group, or however you describe it, was focused on attaching the fluorescent dye at the 3'-OH?

A. Yes. They were certainly -- yes, that was a focus.

TRAINOR

Q. If you turn to page 956 of this article?

A. I'll have to take a moment to look at this. You asked me a question and I didn't review this in preparation for this, so -- but go ahead.

Q. Okay. Let's back up a little bit. You see that these -- the title of the article is "Synthesis of nucleosides designed for combinatorial DNA sequencing." Do you see that?

A. Yes. I do.

Q. And the article has a 1999 date on the bottom of that. Do you see that?

A. I see that.

Q. And you are aware this particular group, again, however you describe them, Welch and others were involved in attempting to develop a massively parallel DNA sequencing scheme?

A. I think that's fair, yes.

Q. Okay.

TRAINOR

A. Just intending to develop a sequencing-by-synthesis that would a how you to do mass parallel but it would also let you work in -- in a low throughput mode, so I just want to be clear about that.

THE REPORTER: In a low --

THE WITNESS: -- throughput mode. I mean, this -- it -- anyone to demonstrate doing it once would have been great with the understanding it would facilitate doing massive parallel sequencing.

Q. Right. But the -- the point of their developing sequencing-by-synthesis technology was to do massively parallel sequencing?

A. Correct.

Q. And the idea of massively parallel sequencing compared to the Sanger sequencing is that you have small -- relatively small fragments of DNA that you sequence in parallel?

MR. WHITE: Objection. Lacks

foundation.

A. I don't know. I wouldn't characterize the fragments as small I think the focus here was that you could have large arrangements of different templates. They could be large, small, whatever. And the limitation of capillary gels is you had to have the one capillary for every template so how many do you want to put in the machine, so maybe you put 100 capillaries. And I don't know what the biggest that was ever done was but it was in that order of hundreds and now you are able to do maybe thousands or more, you know, with the grid on the matrix surface.

Q. Okay. In that context, if we turn to page 956, which is about halfway through the article but it's right -- so the last paragraph before the experimental section.

A. Yeah.

Q. You see there is a paragraph that's entitled "Conclusions"?

TRAINOR

A. Yeah.

Q. Okay. And it says in the first sentence it says, "3'-O blocked nucleoside triphosphates wherein the 3' protecting group is both photolabile and fluorescent are synthetically accessible."

Do you see that?

A. A-hum.

MR. WHITE: Objection. That is misquoted. You misread what it said.

MR. COSTAKOS: I'm sorry. What did I say?

MR. WHITE: You said, "3'-OH protected."

MR. COSTAKOS: Oh, I thought I said "O blocked," but I'll just read it over again. Fine.

Q. So it says, "3'-O blocked nucleoside triphosphates wherein the 3'-protecting group is both photolabile and fluorescent, are synthetically accessible."

Do you see that?

TRAINOR

A. Yes, I do.

Q. And next -- the next one says, "However, they tend to be too big to fit into the active site of DNA polymerases as evidenced by the data from the activity screens and the molecular simulation experiments."

Do you see that?

A. I do.

Q. Okay. So what this group was concluding in 1999, when they were publishing their work was that there are drawbacks to attempting to attach labels at the 3'-OH position, agree?

A. Yes.

Q. And specifically, what they say is that those labels tend to be too big to fit within the active site of DNA polymerases, right?

A. Yes. So they conclude that what we're going to have to do to make this word is to go to modern --

Q. Just stop, can you just give that answer again more slowly?

TRAINOR

A. Okay. If you go to the next sentence, it says, "it seems clear that modifications to the polymerase enzyme as well as to the nucleotide triphosphate required this to be developed into a viable sequencing scheme."

So it didn't say 3'-block nucleosides aren't going to work, they said, well, what we see have presented and, of course, I'm reading this conclusion I would never read a conclusion and draw something from it without reading the paper. If you really want me to give an honest answer, I really have to read the whole paper because I might not agree with this conclusions, but that's okay. There is data in here, but even if I were to agree with his conclusions, I don't think they said that. If they're talking about modifying the polymerase, as well as the nucleotide triphosphates it suggests to me we might have to open

TRAINOR

a little space at the 3' by changing the polymerase but it doesn't say we're going to have to go to a strategy, other than the 3' block labeled that is my take on this answer because I think you read to me the first two sentences but you didn't read the next two, which gave the direction the authors thought should go.

Q. I understand your point but the sentence that I read identifies the problem that they found, right?

A. Yeah. There are lots of problems, obviously.

Q. And the problems they identified here and the reason they are having difficulty was that the labels tend to be too big to fit in the active site of the DNA polymerases?

A. Yes. So it's one of the things I might have done, had I been, you know, reading this and working with these folks the conclusion is let's try linking the dye differently. Right?

TRAINOR

Q. Okay. I'll just stop you. I'm really not interested in the rest.

A. You're asking me to endorse a conclusion from a paper I haven't read. I don't think that's acceptable.

Q. So my question is, that what Welch and his group concluded was that labels tend to be too big to fit in the active site of DNA polymerases, yes?

A. That is a statement they made. I don't know if the paper supports that or the data supports that. Okay?

Q. Certainly, that is a statement that is in the paper?

A. That is a statement they make but I reserve the right to say maybe it's an incorrect conclusion because I didn't read the paper.

Q. Okay. Let's go back to Exhibit 1037, which we looked at yesterday. So as we talked about yesterday, this Exhibit 1037 --

MR. WHITE: Can you tell me what exhibit -- what this is, please?

TRAINOR

MR. COSTAKOS: It looks like this.

MR. WHITE: Was this something that was done in the confidential part?

MR. COSTAKOS: Yes, right.

MR. WHITE: I do not have a copy.

MR. COSTAKOS: This is not confidential. Maybe we can take a break and see if we can rectify that.

VIDEOGRAPHER: The time is 1:43 p.m., and we're going off the record.

(Whereupon, a discussion is held off the record.)

VIDEOGRAPHER: The time is 1:49 p.m., and we're back on the record.

Q. So we were looking at Exhibit 1037.

MR. COSTAKOS: Which for the record is patent application filed by Barnes, dated December 4th, 2001.

Q. So if I can refer you to page 2

TRAINOR

of the application, which is about four or five pages into the document. Are you there?

(Whereupon, the Deponent reviews the document.)

A. A-hum.

Q. Okay. So in this Barnes application, it says, beginning at line 5, "Welch" -- and then it cites that article we just looked at -- "describe the synthesis of nucleotide triphosphates modified with a 3'-O blocking group that is photolabile and fluorescent. The modified nucleotides are intended for use in DNA sequencing experiments. However, these nucleotides prove to be difficult to incorporate into an existing polynucleotide due to an inability to fit into the polymerase enzyme active site."

Do you see that?

A. Yes.

Q. So they were making the --

TRAINOR

drawing on the conclusion that Welch set forth in that conclusion paragraph that we just read a few minutes ago, right?

MR. WHITE: Objection. Lacks of foundation.

A. I'll comment that it says "proved to be difficult to incorporate," because he didn't say impossible to incorporate or this approach will not work. It's saying we have some alternatives and this one was proving to be difficult. The other alternatives I don't think they've got any citation for. So I mean, it's not much to go on.

I also want to point out that this is a person of ordinary skill in the art in 2003, so I don't think it's pertinent to the discussion of what a person of ordinary skill in the art would know with respect to the Ju invention which was filed in 2000.

MR. COSTAKOS: I move to strike

all of that after the word "yes." I don't really think that has anything to do with my question.

A. I think I'm the one who has to determine what the answer is. That's my understanding. You can -- you can ask me the question again or you can ask me a different question again if you don't think that I answered it but I can answer it as I see fit based on your answer -- question, and as I was instructed by my attorney's and I'll continue to do that.

Q. No. Okay. That's just not the way it works. Sorry.

So in the next line after what we just read it cites to Zhu and it says, "that discloses the use of fluorescent labels attached the a nucleotide via the base group."

Do you see that?

A. Yes.

Q. And then as we talked about yesterday --

TRAINOR

A. You should finish the -- the paragraph it does say in -- in areas of hybridization, which is different than sequencing, and the requirements are different.

Q. You know, Dr. Trainor, I appreciate whose side you're on. I appreciate you have points you want to get out, I really do, but -- and you may think that all of those points are helpful but if they are, your counsel can ask you later. I'm just going to ask the questions I have and then you have to answer my questions and that's -- I'm sorry but that's just the way the deposition works.

A. And that's -- that is my answer and that's what I've been instructed to answer.

Q. So you are going to stick to my questions. That is just the way it has to work. I am sorry.

A. Yeah. But I decide what the answer is.

TRAINOR

Q. No. No. You can only answer the question. You don't get to editorialize after that with gratuitous comments. That's just not the way it goes. Okay?

I mean, it will be -- it's just a lot more productive to do it that way.

MR. WHITE: Okay.

MR. COSTAKOS: That -- that is just the way depositions work and you obviously know that, and that is the way -- I mean this is a trial. And so in a trial, you don't get to just say whatever you want to say. It's not the way it goes you answer my question. And if he has stuff that he wants you to get out then he'll make the point. Okay? All right. So let's move on.

Q. And we talked about yesterday the fact that this particular reference, the Barnes reference, shows that attachment of a label at a 7-deaza position on a guanine nucleotide,

right?

A. I have to go back. I vaguely recall that. We can just go back and look at the structure again.

Q. So you -- if you look at Figure 1 which is towards the back.

A. Okay. 1B, 1C, yes. To a pyrimidine, yes.

Q. There is also to a purine?

A. Figure 1, Compound 1. Figure 1 is different. I see Figure 1, yes.

Q. Okay. So Figure 1, the second molecule on the right shows attachment at the 7-deaza position of a purine, right?

A. Yeah.

Q. Okay. Now, let's look at the Ju patent, J-U, not Z-H-U, the '575. Okay? So if you turn to column 2, are you there?

A. I am now.

Q. If you look beginning at line 35, you see it talks about more recent work in DNA sequencing and it refers to

attaching a fluorescent dye to the 3'-OH. Do you see that in the first four lines there?

A. Yes, I do.

Q. Okay. And it cites to a Welch article. Do you see that, Welch's group?

A. Yes.

Q. And then it says after that, this is in the Ju spec, it says, "limited success for the incorporation of the 3' modified nucleotide by DNA polymerase is reported. The reason is that the 3' position on the deoxyribose is very close to the amino acid residues in the active site of the polymerase and the polymerase is therefore sensitive to modification in this area of the deoxyribose ring."

Do you see that?

A. Yes.

Q. And this is the same problem that was reported in Welch that it tends to be difficult to incorporate

DNA nucleotides that are labeled at the 3'-OH position?

A. That was their conclusion, yes.

Q. And so let's take a look then at the Stemple reference which is Exhibit 1008. So the Stemple reference you see was -- I'm sorry it's Exhibit 1008. Okay. I've got the right one.

Okay. So the Stemple reference, if you turn to column 22, and looking, beginning at line 53, it refers to "an alternative configuration in which a photolabile group" -- "group is attached to the 3'-OH."

Do you see that?

A. Yup. I see that.

Q. And then you see beginning at line 57, it says, "The 3' attached photolabile group will serve as a reversible chain terminator," and it -- it's citing to Metzker.

And then it says, "the base attached fluorochrome labile linker will serve as a removable label," so it

describes an alternative configuration in which the label is attached at the base, right?

A. That's correct.

Q. All right. And then it says, "such a configuration may be preferred if it is found that a steric hindrance of large fluorochrome groups attached to the 3'-OH of the nucleotides prevent the nucleotide from entering the polymerase."

Do you see that?

A. Yes.

Q. So Stemple is identifying the same problem that was identified both in Welch and --

A. He's still -- he's saying if -- if there was a problem then I would do this.

Q. Okay. Just let me finish my question.

Okay. So Stemple is identifying the same potential problem that was identified by Welch in the Barnes

application and in Ju of the problem of steric hindrance of large fluoroform groups if they're attached to the 3'-OH, right?

A. He's discussing what he would do in that -- in the event of that contingency.

Q. And -- and that was a known issue as evidenced by the Welch reference, right?

A. Let me look at the date.

Q. Sure. The Welch was --

A. Certainly -- certainly, that was reported in '99, and that one attempt was not successful, correct.

Q. Let's just stay with -- now with Stemple, the focus of the Stemple reference is on cleavage of the label by light, agreed?

THE REPORTER: I'm sorry. The focus of the Stemple reference is on --

MR. COSTAKOS: Sorry. The focus of the Stemple reference is on the cleavage of the label by light.

TRAINOR

THE REPORTER: Thank you.

A. I agree.

Q. But Stemple also says you could cleave by chemical means, doesn't it?

A. He -- without any detail, he says it's a possibility one could do, yes.

Q. So if you turn to column 3 of the Stemple reference, beginning at line 33 -- let me just go up further so beginning at line 31, it says, "in another preferred embodiment the labeling group is attached to the base of each nucleotide with a detachable linker, rather than to the detachable 3'-blocking group." Right?

A. So that is his second choice, yes.

Q. Well, it is another preferred embodiment?

A. Yes, presented second, yes.

Q. Second in order, right?

A. I'm telling you how -- you are asking me how I interpret this and I'm

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just telling you how I interpret it, yes.

Q. Okay.

A. That's fine. Second in order.

Q. Okay. Another preferred child of mine.

A. Fine.

Q. Okay. So 33, the labeling group of the -- strike that.

At line 33 it says, "the labeling group and the 3'-blocking group can be removed enzymatically, chemically or photolytically?"

A. Yes.

Q. So Stemple does disclose that you can remove the label chemically?

A. It shows that concept, yes.

Q. So you agree that's an adequate disclosure of a chemically cleavable label?

A. I'm not sure that's adequate if a person of ordinary skill in the art would want to now what kind of blocking groups, how do you make them, you know,

what -- is that compatible with the way I linked my dye to the base, if that is the route you're taking.

So I think the person of ordinary skill in the art would read this to say, okay, it's giving me some choices here and I have to look at the whole document and what does he teach me how to do? Does that give me direction? And that, I think, if you look at it from that point of view the direction is towards having the label on the 3' cap.

Q. Is there --

A. Except if -- if all that doesn't work at the end of the day, then I go to this base label and then I refer to Anazawa.

Q. All right. And he talks about using a photolabile -- a photocleavable linker, right?

A. Yes. Most of this is photocleavable.

Q. And then, he has the statement

TRAINOR

also that you can remove the label chemically?

A. Yes. He does.

Q. Okay. And so isn't that sufficient to disclose the notion of cleaving in a way, other than by light?

MR. WHITE: Objection. Lack of foundation.

A. I would -- I would expect a little more disclosure than that, and some teaching.

Q. What else would you like to see?

A. I would like to see hypothetical examples or listings of what groups and how you might cleave them. What he does do, a person of ordinary skill in the art would say what actually -- and because I need to know would he teaches me and what direction he gives me and he's showing me a photolabile groups. So I said, Well, he didn't teach me how to do the other stuff, so that's got to be -- that's what I have to take from this, that's got to be my starting

point, the photolabile approach.

Q. So the single sentence in this document that says you can cleave the label chemically is not sufficient to you to disclose that concept?

A. Disclose the concept, but it doesn't teach -- teaches you how to do it. It won't give you any more specifics that -- and I agree, would not have to give you the full final compound but he's got to give you see more than that, in my opinion. It's -- it's a list of things that one might do, just simply one might try without any -- there is no references there about what chemical linkers that would be cleavable might be and how would I go about putting them in and reference to that, maybe, or how do I cleave it or what is a good cleaving condition that might be compatible with a nucleotide and so on.

I'd need -- I think a person of ordinary skill in the art is looking

TRAINOR

for that and absent that, he's going to go with what he does tell you how to do.

Q. Now, if you turn to column 10, in column 10, Stemple discloses a fluorophore linked -- I should tell you exactly where I'm pointing to and I apologize.

Okay. So in column 10, if you look, beginning at line 4.

A. Okay.

Q. You see it says, "an alternative set of useful set of nucleotides."

Do you see that?

A. I do.

Q. And then it says -- it refers in the second sentence to, "in a preferred embodiment the detachable labeling group is a label, e.g., is a fluorophore linked to the base of the nucleotide by a 2-nitrile benzyl group and the detachable blocking group is a 3'-O2 nitrile benzyl group."

Do you see that?

TRAINOR

A. I see that.

Q. What he's disclosing there is a compound where there is a fluorophore that is attached to the base of a nucleotide by a photocleavable group, right?

A. A-hum.

Q. Yes?

A. Yes.

Q. Okay.

A. He does.

Q. Okay. And then he discloses a detachable blocking group at the 3' position?

A. Yes. And I think we understood those are photocleavable.

Q. Yes.

A. And that's what he -- he's giving the information about. And that would be direction to a person of ordinary skill in the art, using the nitrile benzyl cap. That is pretty actionable and that's direction.

Q. You would expect to see some --

some statement at least in the document that would say use a chemically cleavable linker, for example, X?

A. I would like to see a more complete disclosure, yes.

Q. And one of ordinary skill in the art at the time wouldn't have been able to select a chemically cleavable linker that would work based on the single statement in Stemple to use a chemically cleavable linker. Is that your opinion?

A. It's giving no direction, and certainly the person is looking for the elements of Dr. Ju's claim that he can find in this disclosure then he has to figure outer what else do I need? And I've got to have the motivation to go look in a certain place with some expectation of success. So I think the person here is saying, clearly, I don't have all the elements of Dr. Ju's invention in this single reference so what can I take from this? What is my

preferred way of embodiment?

And I think a person of ordinary skill in the art would say, Look, he's really -- he's coming back to this nitrile benzyl and seems, that was the first choice he gave me in this concept and he comes back and is telling me how to make them, and that's my starting point.

Q. So a person of ordinary skill in the art in 2000, would not have been able to select a particular chemical -- chemically cleavable linker based on this single statement to use a chemically cleavable group?

A. Yeah. I think the problem he has is that there is no example given and, you know, a person of ordinary skill in the art knows you're working with a very complex structure and I can't go to linker references from other tech fields because they're not done in the presence of DNA. So I'm going to have to -- I need some

TRAINOR

understanding and there is just no teaching here of how to do anything but photochemicals.

Q. Now, if you look at column 9 the portion of column 9 that bridges columns 9 and 10, you see there is a reference to Metzker?

A. A-hum?

Q. Yes. And you already referred to Metzker, Metzker and his group were attempting to develop sequencing-by-synthesis techniques that could be used for massively parallel sequencing?

A. That is my understanding, yes.

Q. Okay. If we look back at the Ju specification, Exhibit 1001, the '575 patent. If you turn to column 2. Are you there?

(Whereupon, the Deponent reviews the document.)

Q. So at column 2, at line 16, you see it says, "Consequently several groups have investigated such a system

with the aim to construct an ultrahigh throughput sequencing system," and it refers to Metzker and Cheeseman, correct?

A. Yes.

Q. Unfortunately named. Unless you're in the dairy business, I suppose.

So I'm going to show you Exhibit 2015. This is a copy of the Metzker reference.

A. Okay.

Q. You reviewed this before, right? I'll tell you that you referred to it in your declaration. Do you remember this one?

A. I believe so, yes.

Q. So Metzker describes the concept as we've talked about before of doing essentially sequencing-by-synthesis although he doesn't use those words, he calls it Base Addition Sequencing Scheme, BASS.

Do you see that?

A. Yes.

Q. I don't know if it's "BASS" or "BASE." I suppose base makes a lot more sense then bass. Okay. I'll go with "base" then. And you see that in the second column, second sentence, it says, "We and others have independently conceived a radically different gel free alternative to Sanger scheme for DNA sequencing."

A. Yes.

Q. Okay. And the concept is, as we said before, to have massively parallel sequencing, and that is the ultimate goal, right?

A. Yes.

Q. Okay. And the -- the idea is to do massively parallel sequencing of DNA templates, right?

A. Yes.

Q. As replacement for traditional Sanger sequencing or adjunct to traditional --

A. Yes.

TRAINOR

Q. Okay. And then the -- the sentence that I read to you that says, "we and others," it cites references 15 through 18. And if you look at the back you'll see that reference No. 15 is the Tsien reference that we've talked about before. Do you see that?

A. I see that.

Q. So he cites to Tsien as somebody who has previously developed technique for massively parallel DNA sequencing?

A. I would -- yeah, I mean, it's a citation. I -- since there is no working instructions in Tsien, I -- a person of ordinary skill in the art would look at Tsien and say, He's mapped out the idea, but hasn't told me how to do it. So, you know, it's a fine distinction but probably an important one.

Q. But the point of these at least is Metzker identified Tsien as somebody who at least wrote about the idea of --

A. Fair.

TRAINOR

Q. -- doing massively parallel DNA sequencing?

A. Fair.

Q. Okay. You can put that aside.

I'll hand you what's previously been marked as Exhibit 1006. This is the Rabani reference, right?

A. All right.

Q. And you've looked at this reference before?

A. I believe so, yes.

Q. So if you look at the very first page of the Rabani text, so it's the third page of the exhibit.

A. I deal with Rabani in my declaration and I'd like to make sure I have it with me. I'd like to recall what I said on Rabani.

Q. Then, we were going to look at the very next paragraph of the text which has the text, "Field of the invention."

Do you see that?

A. Yes.

TRAINOR

Q. Okay. And the first sentence says, "the invention relates to massively parallel single molecule examination," et cetera, et cetera.

Do you see that?

A. Yes.

Q. And this is again talking about the same overall concept of doing massively parallel sequencing. Do you agree with that?

A. Yes.

Q. And if you turn to page 6 of the Rabani patent or patent application, on line 14 --

A. Okay.

Q. -- you see it says there, "Sequencing of polynucleotide molecules may be affected by the (MY) immobilization of a library of such molecules to a surface at a density convenient for detection which will vary according to the detection methodology availed. Several methods capable of affecting such

immobilization will be obvious to those skilled in the arts of recombinant DNA technology and molecular biology, among others."

Do you see that?

A. Okay.

Q. Okay. So Rabani, in connection with his massively parallel sequencing scheme, discloses the immobilization of molecules on a surface, agree?

A. Yes. He's talking about immobilization, yes.

Q. And he's talking about an immobilization of a library of such molecules, rights?

A. It appears to be, yes.

Q. So that means that there is a collection of different polynucleotide molecules, right?

A. That's correct.

Q. Okay. And they're immobilized on the surface and we already discussed that, right?

A. A-hum.

TRAINOR

Q. Yes? Yes they're immobilized on the surface?

A. Yeah, they are.

Q. And they're at a density that is convenient for detection.

A. That's fine.

Q. Okay. So Rabani discloses an array of different polynucleotide molecules?

A. It does.

Q. Okay. At a density that is convenient for detection?

A. Apparently.

Q. And so that would be considered to be a microarray? Do you agree with that?

A. I don't think he's giving you the density. I -- I think it's reasonable -- that would be a microarray of templates, yeah. I would think so. I don't know where to draw the line between a microarray and something larger and I don't think he specifies how many, but it could be a

TRAINOR

microarray.

Q. But the time the Ju patents were filed in the 2000 time period, microarrays were common in the field, weren't they?

A. They were.

Q. It was common knowledge or -- strike that.

It was routine to immobilize high-density, single-stranded DNA on a chip in a microarray form, right.

A. So --

Q. Yes? Yes?

A. Yeah. He didn't actually call it a microarray which leads me to believe whether he meant this to be -- this to be a microarray because he doesn't actually use that. I don't think he actually uses the term "array" in the context of DNA here. The term "microarray," in terms of DNA.

Q. What is the definition of a "microarray"?

A. A microarray is a something that

is spatially separated in some orderly fashion or some addressable fashion on a microscale. But I think in terms of -- he didn't, I guess he didn't choose to use that but perhaps he didn't want to limit this to a microarray. It could be any -- it could be a larger array or something even smaller than what could be considered a microarray at the time.

Q. So if you have DNA templates that are immobilized on a surface, that would not by itself constitute a microarray?

A. I think you'd have to know what the density was and I don't think he's giving any guidance as to what the proposed density is but that's probably a fine point, but...

Q. But he does -- he -- strike that.

He does say it has to be in a density convenient for detection, right?

TRAINOR

A. It -- that doesn't mean it has to be super small, okay, but okay.

Q. They need to be packed together at least closely enough that you can detect them, you would agree with that?

A. Well, we can detect -- to be honest you can detect by having them packed super close, I mean, that's -- that is one way of doing it, yes.

Q. Well, what is the dividing line between density level that would qualify as a microarray and something that would not qualify as a microarray?

A. I don't know what that would be. I honestly don't know what that would be. I just know that he didn't necessarily use the term "microarray" with respect to DNA.

Q. But it could be a microarray, you don't have an opinion on that?

A. He hasn't specified that.

MR. COSTAKOS: Let's take a break.

VIDEOGRAPHER: The time is

TRAINOR

2:23 p.m., and we're going off the record.

(Whereupon, a recess is taken.)

VIDEOGRAPHER: The time is 2:47 p.m., and we're back on the record.

Q. Dr. Trainor, before our break we were talking about the Stemple reference and you testified and your -- you say in your declaration as well, that Stemple does not disclose a chemically cleavable linker, fair?

A. I don't think he discloses a specific chemical linker, no.

Q. Did you consider whether any other references, when combined with Stemple, would teach a chemically cleavable linker?

MR. WHITE: Objection. Lack of foundation.

A. I was not asked to. I was only asked to consider whether the -- the Anazawa in combination with the -- the Ju claim.

TRAINOR

Q. Okay. Did consider any other prior references in connection with any of the amended claims?

A. No.

Q. You only looked at the ones that were --

A. I was responding to the petition.

Q. So you were looking at the ones that were applied against the claims even the amended claims?

A. That's correct. And the comments applied to the amended claims as well as the original claims. That was understood.

Q. I'm handing you a document that was previously marked as Exhibit 1029. This is the Herman reference.

A. Yes.

MR. WHITE: This is a reference that was brought up in the -- for the first time on redirect of Dr. Weinstock and is not included in either the Illumina petition or the original

TRAINOR

Weinstock declaration. We've maintained our objection to referring to it.

Q. Okay. So the Herman reference, Exhibit 1029, is entitled Chemically Cleavable Linkers -- excuse me. It's entitled Chemically Cleavable Nucleotides. Do you see that?

A. That's correct.

Q. And if you turn to column 5 and 6, you see that in the figure, the reaction figure that is shown in columns 5 and 6 here that Herman discloses attaching a biotin molecule to the amine group of a linker as attached to the base of a nucleotide using a linker?

A. I believe so, yes.

Q. And you see by looking at the Herman, the molecule that is shown there, that it shows a disulfide linkage?

A. I believe so.

Q. Okay. And if you look at column

TRAINOR

7, under the section called "Materials and Methods." Do you see that?

A. This page is upside down. I got get it.

Q. Sorry about that. If you look where it says, "Materials and Methods," are you with me?

A. Yes, I am.

Q. At line 57, beginning at line 57, it describes that "the disulfide linkage was added using NHS coupling."

A. Yes.

Q. And that disulfide linkage in this sort of NHS package was something that was commercially available at that time period, you remember that, right?

A. Likely. I -- I didn't investigate that. I wasn't presented information on that.

Q. Disulfide linkages were well known?

A. Yes.

Q. And they're known to be cleavable, right?

TRAINOR

A. That's correct. And it's also known to be somewhat unstable.

Q. But the reason for using a disulfide linkage, one reason for using a disulfide linkage, is because it's cleavable?

A. Yes. I might add these are not polymerase substrates to the extent to which you need to have a cleavable linkage in a polymerase substrate you need to have a different insuring configuration but you would hope someone would figure that out.

Q. Actually, let's go back to that. So let's go back to Exhibit 1029?

A. Go back to --

Q. -- Herman Exhibit 1029.

(Whereupon, the Deponent reviews the document.)

Q. So you see at column 10, at lines 20 and 21.

A. Yes, I do.

Q. It refers to this being a "substrate for polymerization"?

TRAINOR

A. It says, a "Bio dUTP as a substrate."

Q. Okay.

A. The figure is not a Bio UTP. It's not a uridine.

Q. Okay.

A. It's an L sugar.

Q. Okay. The UTP version is a substrate for polymerase, you would agree with that?

A. Yes. If you would correctly show that would -- I'm taking it at face value it would be a substrate, yes.

Q. And likewise, if you look at column 8, there's at beginning at line 44, there's a paragraph which has the heading "Nick Translation Reactions."

Do you see that?

A. Yes.

Q. And there it also shows that it can be -- that the molecule that's described -- described in this paragraph can be incorporated by a --

let me -- in this paragraph at -- it begins at line 44 of column 8 that's entitled "Nick Translation Reactions," it shows that the molecules that are described in this paragraph can be incorporated by a polymerase.

A. That's correct. It's suggesting that the -- yes, the UTP and it could be incorporated, yes.

Q. Okay. If you look at column 26 Herman, in the portion that spans lines 10 through 15, roughly, there is a figure. You see that?

A. A-hum. Yes.

Q. And the B that's in the figure is the base, right?

A. That's correct.

Q. Okay. And it says, "the base can be a deazapurine." Do you see that line 18?

A. Yes. It does.

Q. And at line I hope it's 19, roughly, at 19, it says, "it can be a 7-deazapurine"?

TRAINOR

A. Correct. It says it can be on the list and I -- they don't tell you how to make those, so I don't know. You know, I think its intent at its broadest conception and I'll include those, but it doesn't tell you how to make the double-bonded linker to any of the purines.

There is actually no information, so a person of ordinary skill in the art who would draw on this reference would say he might be telling me how to make a cleavable linker for the purine but I don't know how to put that linker on the purines.

MR. COSTAKOS: Okay. Move to strike as non-responsive.

Q. Going back to column 10, if you look at that paragraph that began at line 20 you -- you'll see that in the second sentence it actually in the context of the dUTP, which you identified, describes an experiment that determined -- to determine whether

TRAINOR

this particular molecule could serve as a substrate for e-Coli DNA polymerase 1, right?

A. Yes.

Q. Let's go back to the Hobbs reference for a moment, which I think is Exhibit 1013.

MR. COSTAKOS: Just to stop you John while you're looking there, I have the wrong Hobbs. I have a different Hobbs I'm going to give him in just a second, so you can stop searching.

MR. WHITE: Thank you.

MR. COSTAKOS: Sure.

(Exhibit 1046, Hobbs patent bearing Patent No. 5,151,507, was received and marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

Q. So I've marked as Exhibit 1046 the Hobbs patent bearing Patent No. 5,151,507. This is a patent on which you're a named inventor, right?

TRAINOR

A. It appears so.

Q. And you can see if you look in the very front of it, it says -- it's a continuation in part of the previous Hobbs patent that we just looked at?

A. Yes.

Q. The '519 patent.

MR. WHITE: And before you continue, just for the record, I'm going to make an objection to the introduction of this exhibit at this time as it wasn't previously identified in the Illumina petition or in Dr. Trainor's declaration nor was it the subject of Dr. Trainor's declaration. And to the extent that you want to ask him questions to elicit some inconsistency, I accept that possibility, but other than that I think it's a problem.

Q. Okay. So if you can look at column 30, beginning at around line 60.

A. Okay.

Q. Where it has the language

TRAINOR

"Nucleic acid polymerases." Do you see that?

A. Yes.

Q. And it says, "nucleic acid polymerases which have been used to incorporate labeled alkynyl amino nucleotides include," and then it lists a whole bunch of polymerases, right?

A. Yes.

Q. Okay. And so it actually lists actual polymerases that were successfully used to incorporate nucleotides with alkynyl amino linkers?

A. Yes.

Q. And you see at the very last line in column 30, and bridging over to column 31, it says, "dyes which have been successfully incorporated include fluoresceins, protamines, cumarins and benzofurans" -- if I said that correctly.

A. A-hum.

Q. So it actually identifies various labels that had, in fact, been

TRAINOR

successfully incorporated?

A. Yes.

Q. Right?

A. Yes.

Q. And then at beginning at column 31, at line 2, it says, "given the likelihood that all nucleic acid polymerases are evolutionary derived from the same ancestral polymerase, it is believed that given alkynyl amino nucleotides can be substrates for any useful nucleic acid polymerase."

Do you see that?

A. I think that statement is clearly in reference to these deoxy nucleotides.

Q. So it's stating that it will be generally successful with other polymerases and with other alkynyl --

A. Alkynyl --

Q. Hold -- hold on, wait until I'm done.

So it's saying it would be generally successful with other

TRAINOR

polymerases and with other alkynyl amino nucleotides?

A. Yes. Be it a ribonucleotide or 3'-deoxynucleotide, but nothing beyond that with respect to caps or anything like that.

Q. Let's take a look at the '575 patent again.

(Whereupon, the Deponent reviews the document.)

Q. The focus of the Ju patent is on cleavage of the label by light, agreed?

A. I think that's one example given.

Q. Well, isn't light what's used in every actual example in the Ju patent?

A. I'd have to go back. As I said, I'll have to go through it and take a look. I was not asked to look at the specs for purposes of what the disclosure was or what the particular embodiments were. I was asked to look at the claims and the only reason to refer to the specifications was to

TRAINOR

define what the terms of the claims were that's all that I -- but I have not looked at this patent for that fact.

Q. So you didn't look at the patent to determine whether it disclosed the cleavage of the label by any means, other than light?

A. No. I wasn't asked to. I wasn't defending the disclosure in the specs, I was defending the claims versus the cited references in the petition.

Q. So if you look at column 24 of the '575 patent at line 38, there's a reference to a "photocleavable 2-nitrile benzyl moiety."

Do you see that?

A. Yes.

Q. That's the only specific example of a cleavable linker in the Ju patent, isn't it?

MR. WHITE: Objection. Lack of foundation.

TRAINOR

A. I'll have to check that. I certainly see chemically cleavable caps. I haven't gone through -- as I said, I didn't -- if you want me to look through it to answer you honestly, I mean, I can't agree to something I haven't actually gone through and established. So if you want me to answer if this is the only example, I'm going to have to read it.

Q. Okay. Is there any disclosure in the Ju patent of cleavage of the label by physical means?

A. I don't know.

Q. What -- what does that mean, "physical means"?

A. I don't know the meaning. I wasn't asked to determine that.

Q. I'm sorry. My -- my question was: When it says, "cleavage of the linker by physical means," what does that mean?

A. That could be, for example, ultrasound or something like that.

TRAINOR

Q. Would that be selectable?

A. What?

Q. Would that be selectable?

A. Selectable?

Q. In other words, if you try to cleave by ultrasound, as in your example, would it cleave where you wanted it to cleave?

A. If it was assigned properly it might. I have no idea. I'm not an expert. I -- again, I didn't look up physical means. I didn't come up with any specific variations of that. That wasn't what I was asked to do.

Q. All right. Is there any disclosure in the patent of cleavage of the label by heat?

A. Heat? I don't know.

Q. Would that work?

A. I don't know.

(SOTTO VOCE Discussion.)

Q. You don't know if heat would work?

A. I don't know.

TRAINOR

Q. Okay.

MR. COSTAKOS: You know there is something called a mute button on this phone.

MR. WHITE: It's Dr. Ju calling to answer.

MR. COSTAKOS: Yeah, right. It could be.

Q. Is there any disclosure of cleavage of the label by physical chemical means?

A. I don't know.

Q. What does that mean, "physical chemical means"?

A. Physical chemical means, is something that's not a chemical reagent added, something that is not light added but it might be mechanical. I -- I cited that it -- it might be ultrasound, which form of mechanical stimulation, perhaps. Micro -- microwave, the radiation, could generate extreme heat and you might be able to design a particularly labile

bond, I don't know. I mean, I wasn't asked -- you're asking me things I was not asked to weigh-in on, and I don't have any experience with cleaving linkers with any of those methods, nor was I presented with any documents to talk about that.

Q. So you have no idea what whether cleavage by physical chemical means would even work?

A. No.

Q. And you don't really know what "physical chemical means" is?

A. No, I don't know whether it could or not work. I mean, I know that it -- I have an idea what physical means, it means applying some physical process, some physical force. So I would consider ultrasound to be a physical means but I don't know.

Q. Right. But my question was physical chemical means, as opposed to physical or chemical means?

A. Physical chemical means?

TRAINOR

Q. Yeah. Does that make any sense to you?

A. It makes more sense than physical and it makes more sense than chemical to me, so perhaps there is some combination that I don't know about. I don't know.

Q. As you sit here, you don't know what "physical chemical means" means?

A. No. Perhaps some combination of chemistry and a physical stimulation, and maybe a reagent that goes in and renders it now sensitive to physical -- to a physical cleavage. I don't know.

Q. Okay.

A. Again, I wasn't asked to look at that.

Q. So as far as you know -- well, strike that.

You don't know whether there are any specific examples in the Ju patent of chemically cleavable linkers for attaching the label where the cleavage is done by chemical, physical, physical

chemical or heat means?

A. No, I don't know. I could find out. I could go through it and read it but I don't know because that wasn't the subject of the declaration. There was nothing in the petition that suggested I needed to look at that.

Q. Okay. So you didn't try to figure that out?

A. No.

(Exhibit 1047, Odedra Patent No. 7,078,499, was received and marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

Q. I'll hand you what's been marked as Exhibit 1048 (sic). This is a patent to Odedra it's Patent No. 7,078,499.

MR. WHITE: I'll reiterate that we object to the introduction of exhibits like this 1048, which are not the subject of the direct testimony in Dr. Trainor's declaration and were not

TRAINOR

included in the petition or in the declaration submitted by Dr. Weinstock to commence this trial.

MR. COSTAKOS: Let me just say, I misidentified the exhibit. It's actually 1047, but I won't make you repeat your objection and I'll take it as applying to Exhibit 1047.

MR. WHITE: Thank you.

Q. So if you look at column 2 of this patent --

A. Of course, I haven't seen this before, so go ahead.

Q. Okay. So column 2, line 1, it says, "Firstly, by attaching the bulky reporter moiety in the 3' position of the nucleotide the ability of the DNA polymerase to recognize or tolerate the nucleotide is reduced."

Do you see that?

A. I see that.

Q. Okay. And so, that's mentioning the same sorts of problems that we've talked about before, when a reporter

group such as a label is attached at the 3' position of the nucleotide, right?

MR. WHITE: Objection. Lack of foundation.

A. I guess that's what he means. He goes on to say in the next sentence, "Currently known nucleotide terminators are incorporated by polymerases with an efficiency that fails to approach 97%."

Q. Hold on.

A. It seems like he's talking about -- well, I'm trying to understand the context. I can't answer a statement about -- you can't point to a sentence and say, Give me your opinion on that without letting me see the context.

Q. I -- I am actually not trying to prevent you from answering it. I'm just trying to get you to slow down for the benefit of the court reporter. That is all I was trying to do.

A. All right.

MR. WHITE: Why don't you start

over.

A. It goes on to say "Currently known" -- "currently known nucleotide terminators are incorporated by polymerases with an efficiency that fails to approach 97%. In addition to being poorly incorporated modified nucleotides may be enacted."

Q. Please slow down.

A. I believe that "currently known" refers to all terminators, I guess. I have no idea what he's talking about, to tell you the truth, and why 97 is the magic number.

Q. All right.

A. So I guess I don't understand the context of that statement.

Q. If you turn to Figure 2 of this patent, Figure 2 is at the front?

A. I've got the patent. I want to make sure I know what the reference to Figure 2 is because I can't interpret Figure 2 without knowing what they're saying it is, but I'll get there in a

moment.

Q. Okay. So you see in the bottom two examples in Figure 2, in the bottom two rows, it shows attachment at the 7-deaza position of a purine, agreed?

A. Yes. I believe so.

Q. Okay. So it shows a -- strike that.

It shows a purine nucleotide analogs, agreed?

A. Yeah. I believe so.

Q. Okay. That have a 7-deazapurine base?

A. I believe so.

Q. Okay. And there's a label attached to the 7 position?

A. Yes. It seems to be attached via a double bond, I guess, yeah.

Q. Okay. And if you look at column 3, line 43, it refers to "these groups being cleavable." Do you see that?

A. Yes. I see that general structure, the general statement, yes.

Q. And if you go back to Figure 2

TRAINOR

you see that there's a 3' -- strike that.

If you go to Figure 2, you see that there's a blocking group at the 3' position?

A. It's a blocking group that I think is well known not to be useful in this application but they -- they're asserting it's a blocking group.

Q. And it is small, you agree with that?

A. It is small but unstable.

Q. So in this patent, there's a disclosure of attachment of a cleavable label at the 7-deaza position of a purine, and a --

A. Where is the cleavable part? I guess, they are claiming that the ester in the linkage and is cleavable part?

Q. Well, we looked at --

A. Is that it?

Q. -- I'm sorry. We looked at column 3, beginning of line 43, and that talks about groups X and Y being

cleavable.

A. Okay.

Q. So there's a cleavable label and a cleavable linker that's disclosed here. You agree?

A. I think that's their intent --

Q. Okay.

A. -- but again, I haven't read this patent so I'm trying to -- struggling here to get through and see what it is they really mean.

Q. Okay. And there's a small 3'-blocking group that is the intent?

A. That would be small.

Q. And it's at the 3' position?

A. That's correct. I'm trying to see where they -- where this came from. I -- I think it's pertinent to my answer, so if you want to ask me questions about these structures.

Q. Those concepts that we went through were the same basic concepts that were invented by Dr. Ju and Dr. Barnes, right?

TRAINOR

A. I'd have to go through the claim step-by-step.

Q. Well, certainly, you would agree that it has the same disclosure of a blocking group at the 3' and a base attached to the 7-deaza position of a purine, right?

A. Well, I think Dr. Ju -- I think that what's pertinent to your question is that Dr. Ju would argue and did argue in his application that acetyl is not competent to be a -- to be 3' block for a polymerase. So if this was known not to work then this would not be a disclosure of the invention. And I believe since many people have suggested acetyl and beginning from the first days of polymerase studies, people have recognized that acetyl was unique and it actually could be removed by an active site to a nucleophile --

THE REPORTER: Could be actually --

THE WITNESS: -- could be

removed by an active site to a nucleophile and that would render it inoperable for sequencing-by-synthesis because it would deblock prior to when you wanted to.

So I think that would -- and, again, I'm giving you my opinion and without having had a chance to read all of this to know what information is provided, and what he cited. So, you know, I can't tell you -- I can't answer the question as to whether this is -- reads on anything, let alone the Ju invention without reading the whole thing.

Q. Okay. I'm going to hand you what I marked as Exhibit 1048 in your deposition.

(Exhibit 1048, copy of Odedra Patent No. 7,078,499, was received and marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

TRAINOR

MR. COSTAKOS: Exhibit 1048, just for the record, is a PCT or GB patent application to Odedra.

A. Yeah, I haven't -- I haven't seen this before, as you know.

Q. Well, I'll just represent to you without going through it word for word that this is the same document, and it has the same substance, the same text as the document that we just marked as Exhibit 1047. So let's just take a quick look.

MR. WHITE: Before we go he forward I'll object to the use of this document, once again, because it's a document that was not the subject of Dr. Trainor's deposition -- declaration, and therefore it's outside the scope of the declaration and the direct testimony and also not raised by Illumina in its petition or by Dr. Weinstock in his declaration and also, your characterization as a PCT application is incorrect.

TRAINOR

MR. COSTAKOS: I think it's a GB, Great Britain application.

Q. So if we turn to page 2 of the text, at line 20, you see it has the same language that you looked at before that begins with "Firstly, by attaching the bulky reporter moiety."

Do you see that?

A. I do.

Q. And then if you look at Figure 2, which is the second page from the end, you see it has the same figure that we just looked at in the US Patent. Do you see that?

A. A-hum.

Q. And it has those same two drawings of the 7-deazapurine with a cleavable label and a cleavable linker attached to it. Do you see that?

A. I see that. But my reaction to that is I'm not aware that anyone has ever made a guanine with a deaza with a double bond and whether there is any chemistry to do that. So I would

really be interested in reading through the experimental to see if anyone has ever made that species, because it would be very important if he doesn't teach how and it's never been made, then I don't think this is a disclosure that's truthful or is actionable or -- or can be used as a reference if there is -- if he's made it up out of thin air.

It's possible to draw a chemical structure that you would like to have made but I don't know whether he did. And the reason we went to acetylene is -- was because we couldn't make double bonds work, and I can't -- I've not seen anyone do that in the intervening years, and certainly not before 2000.

MR. WHITE: Also, did I understand you to represent these documents -- that the 1047 and 1048 were the same?

MR. COSTAKOS: It's my understanding.

TRAINOR

MR. WHITE: Well, there are two figures in 1048 and 12 figures in 1047.

MR. COSTAKOS: Well, I guess I'm wrong. My point was that I -- I'm sorry, I didn't mean to say it that way because that's what I understood. I mean that the pertinent disclosure is the same.

MR. WHITE: That, I don't know. You just handed it to me.

MR. COSTAKOS: Yeah. I -- I take your point. I take your point.

Q. Okay. The disclosures we went through -- during your testimony we went through and saw that they were the same in both documents, right?

So let's look at -- let's go back to Exhibit 1037, which is the Barnes application.

A. Okay.

Q. If you look at page 10 of the document, it describes the addition of the -- the nucleotides generally. Do you see that in the first paragraph?

A. Okay.

Q. Okay. And it says that the nucleotides -- strike that.

It says at the beginning line 2, "the nucleotides may be added sequentially, i.e., a separate addition of each nucleotide type, A, T, G or C, or added together."

Do you see that?

A. That's true. Nucleotides could be added together, yes. I agree with that.

Q. Okay. So it discloses the addition of four nucleotides at one time?

A. The nucleotides at one time, yes.

Q. And it also discloses, if you look at lines 4 and 5, four different labels?

A. I believe so.

Q. And it says, "it's preferable in each nucleotide type is labeled with a different label"?

TRAINOR

A. Yes.

Q. So it discloses unique labels?

THE REPORTER: It discloses unique --

MR. COSTAKOS: -- unique labels.

A. Yes.

Q. If you look at line, beginning on line 11, it talks about detection. Do you see that?

A. I do.

Q. Okay. And it discloses there a detection in order to identify the base?

A. Yes.

Q. It also, in line 2, says, "the label can be fluorescent." Do you see that?

A. Line 2?

Q. I'm sorry. In line 12, it says, "the label can be fluorescent"?

A. Yes.

Q. If you look at page 8, line 24, it says, the sequencing methods are

preferably carried out with the target polynucleotide arrayed on a solid support." Do you see that?"

A. Page 8, line 24? I don't know if I can read exactly what you said. Can you give me the line, please, and repeat that again.

Q. At page 8, line 24, it says --

A. Wrong page, I'm sorry. I'm on page 9. My mistake. Go ahead.

Q. Okay. It says, "the sequencing methods are preferably carried out with the target nucleotides arrayed on a solid support." Do you see that?

A. I see that.

Q. Okay. So it discloses attachments of the templates to a solid support?

A. Apparently, yes.

Q. And it discloses an array of nucleotides?

A. Either the nucleotides are arrayed so I guess that constitutes some sort of array, yeah.

TRAINOR

Q. If you look at page 9, at line 20, it says, "to carryout the polymerase reaction it would usually be necessary to first anile a primer sequence to the target polynucleotide."

Do you see that?

A. I do.

Q. So it discloses hybridizing the primer to the template?

A. It appears to.

Q. Sorry. Going back to page 8, at line 13, it says, "the method makes use of polymerization whereby a polymerase enzyme extends the complementary strand by incorporating the correct nucleotide complementary to that on the target."

Do you see that?

A. I do.

Q. Okay. So it's disclosing there incorporation of the nucleotide by polymerase?

A. Yes, I do.

Q. If you look at page 7, beginning at line 17, it says, "the ribose ring

may also be modified to include a protecting group at the 3' position or a group that can be transformed or modified to form a 3'-OH group. The protecting group is intended to prevent nucleotide incorporation into a nascent polynucleotide strand and maybe removed under defined conditions to allow polymerization to occur."

Do you see that?

A. Yes. I do.

Q. So it's disclosing there a removable 3'-cap to allow incorporation in the next nucleotide?

A. Yeah. I believe so.

Q. And you see that it says in the next line, "in contrast to the prior art, there is no detectible label attached to the ribose 3'-position."

Do you see that?

A. Yes, I do.

Q. Now if you look at page 8 again, line 20, it refers to "preferred enzymes." Do you see that?

TRAINOR

A. A-hum. I do.

Q. Okay. And among those enzymes are "T7." Do you see that?

A. I believe so.

Q. Okay. And Taq polymerase as well?

A. Yes.

Q. And Vent polymerase?

A. It's there.

Q. You can put that aside.

A. A-hum.

Q. Okay. We talked a little bit yesterday about your experience with next generation sequencing. Do you recall that discussion generally?

A. Yes, I do.

Q. Okay. And I think you testified that you hadn't seen, at least to your knowledge, an Illumina next generation sequencing instrument or any of the competitive next-generation sequencing instruments?

A. I didn't go into sequencing labs and I don't go into biology labs.

TRAINOR

Q. Okay. So you have no knowledge for the next-generation sequencing, I take it?

A. Only what's been provided to me, that information, yes. I know it's very large, very lucrative and big.

Q. And the information that is provided to you is all the information that is identified in your declarations, right?

A. Yes.

Q. Have you ever spoken to any customers about the market for next-generation sequencing?

A. No.

Q. Have you ever spoken to any customers about the reasons for success of the Illumina products?

A. No.

Q. Do you have any personal knowledge -- strike that.

I take it, you have no personal knowledge about why Illumina's instruments are better than any of its

competitors, right?

A. I don't know anything about the instrument. I know something about the chemistry.

Q. You don't have any knowledge of how the competitors' products work, do you?

A. No.

Q. You don't have any knowledge what technology the competitors' products are based on, do you?

A. I've read reviews, so I don't know the exact details but there is no need for me to do that. I was asked to evaluate the Illumina material presented to me. That's all.

Q. Okay. Now, I know that your technology for Sanger sequencing was transferred to Applied Bio-Systems. Applied Bio-Systems or Life now, has a next-generation sequencing platform or one or more? Are you aware of that?

A. I've heard of something of that. I don't know how it works. I haven't

paid attention to that.

Q. Do you have any idea or knowledge whether Applied Bio-Systems uses SBS chemistry?

A. No, I don't.

Q. You don't know whether Illumina could have been successful in the market using the same technology that Applied Bio-Systems or Life is currently using, right?

A. No, I don't.

Q. You don't have any knowledge of how the cost of Illumina's instruments compare to its competitors, right?

A. None of that information was provided to me.

Q. You don't have any information about whether Illumina's instruments are more cost effective than competitors' instruments?

A. No, I do not.

Q. And you have no idea why, if at all, Illumina's products are more cost-effective than their competitors?

TRAINOR

A. No. I would just know that the chemistry must work pretty well or you wouldn't be able to defend it or the marketing or anything else or your pricing, actually, but I know the chemistry must work extraordinarily well.

Q. But that's just sort of an assumption you're making?

A. I think that's -- I don't think you can deny that. I think that if the chemistry didn't work well you can have the world's best instrument and it wouldn't give you the performance.

So I would agree that all those factors contribute, but at the bottom of that chemistry has to work as well. Otherwise, the information is not there to capture.

Q. And that's just an -- that is just sort of an assumption that you're making, that you're taking as a given?

A. No. As -- as an expert, okay, that is said as an expert. And I think

TRAINOR

this is speaking to, as I understand it, the other secondary considerations. I believe this is where we've talked about this material. And I -- I -- as an expert, I know that the chemistry has to work well or the instrument it -- it doesn't matter. If you have a fuzzy picture and no matter how good a copy you have, it's still fuzzy.

MR. COSTAKOS: Let's take another break and we'll try to wrap up.

VIDEOGRAPHER: The time is 3:35 p.m., and we're going off the record.

(Whereupon, a recess is taken.)

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VIDEOGRAPHER: The time is 4:11 p.m., and we're back on the record.

Q. Dr. Trainor, return to your declaration relating to the '698 patent?

A. Okay.

Q. Turn to paragraph 205, which is

TRAINOR

at page 95.

(Whereupon, the Deponent reviews the document.)

Q. Are you there?

A. Yes.

Q. Okay. So you see --

MR. WHITE: You are doing objective indicia, now you're --

MR. COSTAKOS: Huh?

MR. WHITE: -- you are not doing something confidential there?

MR. COSTAKOS: No. No. Don't worry. Don't worry.

MR. WHITE: If you do, as far as I'm concerned, it's not confidential anymore.

MR. COSTAKOS: Yeah, I -- I understand your point. This was in the non-confidential part of the declaration.

MR. WHITE: I just want -- I'm just looking at something, at this section and see that it's --

MR. COSTAKOS: No. This was

TRAINOR

filed publicly. I'm confident of that.

MR. WHITE: Okay.

MR. COSTAKOS: And my question has nothing to do with the technology anyway.

Q. So in the paragraph that bridges page 95 and 96, on page 96, the last sentence of paragraph 205 you say, you make a reference to the Ju 2006 article and then you say that "it provides comparison of the results of SBS with the results obtained using pyrosequencing."

Do you see that?

A. Yes.

Q. Okay. What is pyrosequencing?

A. Pyrosequencing is a technique whereby, as -- as certainly as practiced there, you release a pyrophosphate, which is a byproduct of the polymerization reaction. And you have some methodology that detects the release of pyrophosphate.

Q. And does anyone in the

TRAINOR

marketplace using pyrophosphate in the market now to your knowledge?

A. I don't believe so. It might have been but I don't believe so now, so it is a form of sequencing-by-synthesis because you are -- you are detecting the fact that something incorporated.

Q. And the reason that Dr. Ju's method worked better in this instance was because it had reversible terminators, right?

A. Yes. That was probably -- certainly, that's a key element of that function, yes.

Q. Let's go back to this Odedra reference, which is Exhibit 1048. Right there.

A. Okay.

(SOTTO VOCE Discussion.)

Q. Okay. So if you turn to page 7, with the 7 in the lower right-hand corner?

MR. WHITE: So we'll continue to

TRAINOR

object to questioning about this document.

MR. COSTAKOS: I understand.

Q. At line 12 --

A. Okay.

Q. -- it refers to "having more than one base being incorporated and detected in a single sequencing reaction." Do you see there?

A. I just would like to very quickly figure out what the context is. This wasn't what I studied before you flashed it in front of me a little while ago. I just want to make sure I'm answering your question correctly. Okay?

(Whereupon, the Deponent reviews the document.)

Q. Okay. And beginning at line 13, at the very next sentence, in other words says, "in a particularly preferred embodiment each base will be labeled with a different reporter moiety, so that all four bases can be

TRAINOR

used at the same time in a sequencing reaction."

Do you see that?

A. Yes. I do.

Q. And that talks about using four nucleotides at once, right?

A. It appears to, yeah.

Q. Okay. And having different unique labels on each base?

A. That's what they seem to be implying, yeah.

Q. Okay. And then if you look at the very next sentence it says, "the different reporter moieties will enable the different bases to be distinguishable by a fluorescent spectroscopy or other optical means."

So that discloses detecting the labels in order to identify the base, right?

A. Yeah, I think so. Let me take a quick look.

Q. If you look at -- if you'll look at page 6, at line 16, it says, "In a

TRAINOR

preferred embodiment the reporter moiety has fluorescent properties and can be detected using a sensitive fluorescence detector."

Do you see that?

A. Yes.

Q. And then, it says, "it may be a fluorophore." Do you see that?

A. Yes, I do. I just want to make sure I understand what the -- what the embodiment is, actually, so...

I guess, I'm having trouble understanding how the substrates that the -- the subject of this invention is polymerase substrate. So this -- this invention describes a compound that has no 5'-carbon on the sugar and has a phosphate directly attached to the 4' and just -- and I'm quite sure this is not a polymerase substrate.

Also, a hydroxyl Z' hydroxy at the 4' position, will render that sugar unstable on opening.

So I read your words, I can --

but I don't really understand that this is any kind of description of something that could be used by a polymerase, as given the structure.

This says, "W is a phosphate." It's not even a triphosphate, it's a phosphate. So, you know, I can't say this is an example of anything having to do with sequencing, even though I can agree with the words -- read the words with you.

Q. Even though it says that is the point?

A. But the structure they're giving is not a -- it can't be used, in any way, and that would be obvious to not -- not just the expert but to someone skilled in the art.

Q. Okay. So if you turn to page 9, at line 17, there is a description of an "immobilizing" --

A. Right.

Q. -- "immobilizing a complex primer template to a solid phase." Do

you see that?

A. I see that.

Q. So that discloses attaching to a solid support?

A. I got that.

Q. Okay. If you go -- if you go to page 4?

A. Yup. Okay.

Q. Okay. And you refer to "W being an a phosphate," before, and do you remember that?

A. That's correct. That's what it says.

Q. And then, at line 16, it says, "it can be a triphosphate"?

A. Sure. It doesn't matter if it's a triphosphate. As I said, there is a carbon missing in the ribose so it won't be recognized. So the step on page 9B, "incubating the polymerization is present as a comp in Formula 1" --

Q. You need to slow down. You can give your answer, just more slowly. Okay?

TRAINOR

A. Okay. It says it can be a triphosphate. Okay? So let's make it a triphosphate. It's still not a polymerase substrate because it's missing a carbon that would be recognized as such.

Q. If you look at page 10, lines 4 through 6, it refers to using this in "array-based sequencing." Do you see that?

A. I see the words, yes.

Q. And it says, "it can be used in array-based sequencing, such as BASS or BASE." Do you see that?

A. Yes.

Q. And that is the methodology that we looked at before, that was described in Metzker and other articles, right?

A. I would disagree with the statement that these -- that if he's referring to the compounds of Formula 1, I disagree that they should be used or not.

Q. But you agree that is what it

says?

A. That's what it says and even a person of ordinary skill in the art would realize this was a mistake.

Q. Okay. If you look at Figure 2, which is the second to the last page, you see that there's a carbon for the triphosphate, right?

A. In that one maybe. In Figure 2? Yeah, in Figure 2 it has the different structure.

Q. So that one shows a carbon for the triphosphate?

A. That one does.

Q. So it doesn't have the same problem that you identified for --

A. Yeah. I'm just reacting to the statement that the substance of Figure 1, which is what the statement says and that statement is not true.

Q. Okay.

A. Now, if you want to show me a statement that says the structures of Figure 1, then, that would be

different.

Q. Okay. So the structure that is in Figure 2, does not have the same problem that you identified for the compound of Formula 1. Is that right?

A. It's also not the subject of the invention because I think it says the subject of the invention is the compounds of Formula 1.

Q. Okay. Why --

A. So I -- I have a problem with the disclosure.

Q. Let -- let's just stick to the questions here, for just one second.

So the compound that is in Figure 2 has a carbon on the triphosphate, right?

A. Has the 5'-carbon, that's correct.

Q. Okay. And so it does not have the problem that you identified with respect to the compound that is shown in Formula 1, correct?

A. If these were the subjects of

the invention, yes.

Q. Okay.

A. It should not have that problem.

Q. Okay. So let's then turn to page 9, beginning at line 20, you see there is a reference to "a complex of a primer and a template that can be formed by incubation under appropriate hybridization conditions before immobilizing the complex onto a solid base."

Do you see that?

A. I can read those words, yes.

Q. Okay. So it describes hybridizing a primer to a template?

A. It appears to describe a complex and a primer and a template then taking the complex and putting it onto a solid phase, yeah, that particular sentence.

Q. If you look at page 9, line 29, it identifies particular polymerases that can be used to incorporate the molecule?

A. I do.

TRAINOR

Q. Okay. And he identifies, among other things, T7. Do you see that?

A. I believe so, yes.

Q. And on the -- if you can turn to the next page, he refers to a Vent polymerase. Do you see that?

A. Yes. I believe that's all in reference to the structure of compounded Formula 1, yes. So actually I don't believe it matters which polymerase you try. It -- it's not going to work with Formula 1.

Q. If you turn to page 8, so at line 12, it says, "that the blocking group does not also act as a reporter molecule." Do you see that?

A. Yes.

Q. Okay. So it's saying that the blocking group is not also a label, right?

A. Yeah. And the -- the reason I know that actually in the prior paragraph, in line -- I believe starting at line 30 on page 7 it says,

"preferred embodiment of the blocking group is a methyl group."

So clearly the methyl group doesn't have a reporter, but unfortunately a methyl group is not removable under any chemistry that is compatible with DNA.

Q. On page 7 right above where you were just identifying, at line 26, it says, "in particular a blocking group is any chemical group, which can be attached to a nucleotide and which will allow the 5' end of the modified nucleotide to attach to a 3' end of another nucleotide in a DNA chain, but will not allow attachment of a nucleotide to the 3'-hydroxyl group of the modified nucleotide." Do you see that?

A. Yes. So that's a description of what a blocking group is in this context but then it says, "particularly preferred is a methyl group."

Q. So -- but you would agree that

he describes the features of a blocking group in a functional way --

A. That's right.

Q. -- in the -- in the lines that I read, which are on page 7, lines 26 through 30, right?

A. That's correct.

Q. Okay. Now, if you look at page 8, at line 15, you see there's a reference to -- it says, "procedures for selecting suitable nucleotide and polymerase combinations will be readably adapted from Metzker," and then it cites -- it has a cite for Metzker.

Do you see that?

A. I see that.

Q. And we looked at Metzker before. Let's just go back to Metzker for a moment. It's Exhibit 2015 and it looks like so (indicating).

A. Sorry. It's a big stack here. Let me get it out. There we go. It's 2015?

TRAINOR

Q. That's the exhibit number, yeah.

A. Got it.

Q. Okay. If you turn to page 4263, do you see there's a Table 2?

A. I see that.

Q. And Table 2 shows combinations of blocking groups with particular polymerases, right?

A. Correct.

Q. Okay. And it shows the combination of an allyl blocking group with Vent polymerase, right?

A. Yes.

Q. And if you look at the Ju patent?

A. '575, I presume?

Q. That's fine. At line -- at column 3, line 15?

A. Okay. And I'll remind you, I may have to look at the context because I didn't read this for this particular topic, but that's okay. We'll walk through it.

Q. Column 3, line 15?

TRAINOR

MR. WHITE: Yes, objection. This is beyond the scope of the direct testimony of this witness.

Q. It says, "3'-O allyl dATP was also shown to be incorporated by Vent DNA polymerase in the growing strand of DNA," and it cites to Metzker. Do you see that?

A. I just want to make sure that's a correct citation in terms of what he said it was.

(Whereupon, the Deponent reviews the document.)

A. Yes. He says that.

Q. So the notion of using an allyl as a blocking group and the -- the polymerase to incorporate it, the citation for that is Metzker, right?

A. That's correct. I will note that of real importance is he does cite the termination has a star after it, saying "activity is incomplete."

So I think the intent of the author, Metzker was to say, it -- it

TRAINOR

works, but possibly not that well. So that's just an important to note that and I don't think Dr. Ju noticed that, but that's certainly the -- one skilled in the art would look at this and say, How? Just how incomplete was it," because, you know -- because as you know, from sequencing-by-synthesis you could have any significant incompletion in any step you have a problem.

Q. Okay. If you turn to column 25 of the Ju patent. Sorry.

Hold on a second. I think I have my reference from the wrong patent so let me just orient myself here.

Sorry. Just bear with me. I apologize.

(Pause in the proceedings.)

MR. COSTAKOS: Sorry about that. Column 22. No wonder.

Q. So if you turn to column 22 of the '575 patent at lines 8 through 10, it describes possible DNA polymerases. Do you see that?

TRAINOR

MR. WHITE: Objection. Outside the scope of the direct testimony of this witness.

A. Yes, I see that.

Q. Okay. And the polymerases that are identified there are all polymerases that were well known in the prior art, right?

A. I -- I am not an expert in that. I -- I've seen all of those before, so let's say that's true. I'm not a expert on that part of the polymerase story.

THE REPORTER: I'm sorry. I'm not --

THE WITNESS: -- I'm not a expert on that part of the polymerase story, but I believe I've seen most of those.

Q. Okay. Let's go back to the Tsien reference. All right?

A. A-hum.

Q. So if you look at Figure 2 --

A. Yes.

TRAINOR

Q. -- you remember our discussion long ago now, about the nomenclature that was used in Tsien.

So if you look in the sort of top of Figure 2, the right-hand side, depending how you look at it.

A. Right.

Q. All of those inputs there are 3' blocks. Do you see that?

A. Correct.

Q. Likewise, if you look at Figure 3, all of these are 3' blocked or Hs, right?

A. And the label position is unspecified.

Q. Yes, right. And we -- and we've been through that. I'm not going to re-do that.

A. I just want to make it clear, so, yeah. So my -- as I understand it, yes. Go ahead.

Q. And the point I was making just -- was just that they are 3' blocked OH. You -- you agree with that, right?

TRAINOR

A. Yes.

Q. And if you turn to page 12 -- sorry.

Okay. Let's turn to page 7. So on page 7 beginning at line 17, it says that "there are many different configurations that he's going to explain as he goes along." Do you see that?

A. I got it.

Q. And then at line 19 it says, "a key to all of them, however, is the fact that the DNA sequence is determined not by generating a series of nested fragments, which must be separated according to size but rather by direct identification of the dNTPs as they are incorporated into the growing complementary DNA chain." Do you see that?

A. Yes, I do.

Q. And that's a general -- a description of the general concept of sequencing-by-synthesis, agreed?

A. I agree.

Q. Turn to page 28, and beginning at line 2, right after that he talked about attaching the fluorescent group to a remote position, such as the base, he says, "This dNTP can be incorporated in the fluorescence measured and removed according to the methods described below."

Do you see that?

A. Okay.

Q. And then, he goes on and he describes some methods for incorporating the dNTP and measuring and removing the fluorescence. Do you see that?

A. Okay.

Q. Do you agree with that?

A. Okay.

Q. If you look at page 29, you see at line 16 it says, "the synthetic routes have great flexibility and that the linker can be varied with respect to length or functionality." Do you

TRAINOR

see that?

A. Yes. And I see that that refers to structures A, B, C, D, on the subsequent page.

Q. And it also says, "The terminal fluorescent moiety can be varied according to need." Right?

A. I understand that, yes.

Q. You can put Tsien aside.

MR. COSTAKOS: If we can take one second, we can fix this exhibit and then we'll be done.

VIDEOGRAPHER: The time is 4:42 p.m., and we're going off the record.

(Whereupon, a discussion is held off the record.)

VIDEOGRAPHER: The time is 4:49 p.m., and we're back on the record.

Q. I'm going to hand you what I've marked as 1049 for your deposition.

(Exhibit 1049, Declaration of Dr. Bruce Branchaud, was received and

TRAINOR

marked on this date for identification.)

(Whereupon, the Deponent reviews the document.)

MR. COSTAKOS: And just for the record, this is entitled the "Declaration of Dr. Bruce Branchaud" -- and I don't know if that's how you say his name -- "in support for US Patent No. 7,057,026."

Q. Do you see that?

MR. WHITE: Again, I'm going to object. I'll object to using this exhibit, again, because it's certainly not the subject of any testimony by anyone in this case -- in this trial. But also, is this not the exhibit that the Board actually expunged from the record? There was a declaration of Dr. Branchaud that was submitted by Illumina, which the Board determined should be expunged from the record.

MR. COSTAKOS: I think that was for a procedural reason and has nothing

TRAINOR

to do with the --

MR. WHITE: No, no, no. It was because it was improperly filed.

MR. COSTAKOS: Well --

MR. WHITE: And it's been expunged from the record and so I think any attempt to examine this witness on the basis of a document that the Board has expunged is totally inappropriate.

MR. COSTAKOS: Well, we will move to -- we will address that at --

MR. WHITE: I'll instruct the witness not to answer questions about this exhibit.

MR. COSTAKOS: I don't think you're allowed to do that.

MR. WHITE: Well, I -- I think you're not allowed to take an exhibit that the Board has expunged from the record and ask this witness questions about it.

MR. COSTAKOS: No, I think it was expunged for procedural reasons and it has nothing to do with substance.

TRAINOR

MR. WHITE: I -- I do not agree with you.

MR. COSTAKOS: I -- I read the decision.

MR. WHITE: Well --

MR. COSTAKOS: And I'm not going to ask any substantive questions anyway. So let me -- let me ask you this --

MR. WHITE: I'm going to caution him not to answer until I have an opportunity -- an opportunity to hear the full question.

MR. COSTAKOS: That's fine. That's a good caution regardless.

THE WITNESS: Okay. So I've learned.

MR. COSTAKOS: Okay. So we -- we'll take this slowly. Okay?

Q. Okay. First of all, let me ask you this question: Have you ever heard of or do you know Dr. Branchaud?

A. I know him.

Q. Okay. Have you had any contact

TRAINOR

with him in the context of this IPR or the -- the work that you're doing?

A. No.

Q. Okay. You've had no contact with him in the context of the work that you're doing for Columbia?

A. We were graduate students together.

Q. Okay. Good. Now, you see in the first paragraph it says that he was "retained relating to Intelligent Bio-Systems' petition." Do you see that?

A. I see that, but I don't know anything about that.

Q. Okay. And then, if you look at the second paragraph, it refers to a US Patent, and then it says, "I understand that the '026 patent issued from U.S. Patent Application No.," et cetera and it claims priority to this GB patent that has this filing date of December 4, 2001.

Do you see that?

TRAINOR

MR. WHITE: I don't understand what you're asking him.

MR. COSTAKOS: I'm just asking what it says.

MR. WHITE: You're reading him the document. The document says what it says.

MR. COSTAKOS: I know.

MR. WHITE: And like I told you, he's never seen the document. He has no knowledge of any of this. He's not communicated with Dr. Branchaud about anything involved in this IPR that was commenced by IBS.

MR. COSTAKOS: Okay.

MR. WHITE: He -- he's not involved in it.

MR. COSTAKOS: But I'm not going to ask him the --

MR. WHITE: And the reason is --

MR. COSTAKOS: I'm just going to ask him -- I'm just going to ask him the --

MR. WHITE: The reason it was

TRAINOR

struck was -- it was to do with a procedural reason, it was because this has nothing to do with this case.

MR. COSTAKOS: No. I can -- I disagree. I disagree.

MR. WHITE: The reason the Board struck it -- well, you can disagree but we're the one that asked for it expunged and it was at our request that it was granted.

MR. COSTAKOS: Things have a way of cropping back up again.

MR. WHITE: Well, not -- not today. Not today.

MR. COSTAKOS: Okay.

Q. And my only question was, I was just orienting you to this particular language right here that refers to this GB patent application.

And my next question was going to be: Have you ever seen this declaration before?

THE WITNESS: Can I answer that?

A. No.

TRAINOR

MR. COSTAKOS: Well, then, I don't have any questions about it. So that solves everyone a lot of heartache, doesn't it?

I have no further questions of you today. Thank you very much for your time.

THE WITNESS: Thank you.

VIDEOGRAPHER: The time is 4:53 p.m., and we're going off the record.

(Whereupon, the proceedings were adjourned at 4:53 p.m.)

J U R A T

I do hereby certify that I have read the foregoing transcript of my deposition.

GEORGE L. TRAINOR

Sworn and subscribed
before me
this 21 day of
Sept, 2013

a Notary Public of
the State of Delaware

JOHN M. DENNIS
NOTARY PUBLIC • DELAWARE
My Commission Expires 3-7-16

C E R T I F I C A T E

I, MAUREEN M. RATTO, a Registered Professional Reporter, do hereby certify that prior to the commencement of the examination, GEORGE L. TRAINOR was sworn by me to testify the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a true and accurate transcript of the proceedings as taken stenographically by and before me at the time, place and on the date hereinbefore set forth.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in this action.

_____

MAUREEN M. RATTO, RPR

License No. 817125

I N D E X

WITNESS:

GEORGE L. TRAINOR 154

DIRECT EXAMINATION BY

MR. COSTAKOS 154

E X H I B I T S

Exhibit 1041, paper by Seela 276
entitled "Oligonucleotide
Duplex Stability Controlled
by the 7 Substituents of
7-Deaza-Guanine Bases."
Exhibit 1042, paper by 293
Ms. Ramzaeva and others,
entitled "7-Deaza-Guanine DNA
Oligonucleotide with
Hydrophobic or Cap Ionic Side
Chains",
Exhibit 1043, document 298
entitled "7 Substituted
7-Deaza D'Deoxy-Guanosines",
authored by Ramsayva and
Seela,
Exhibit 1044, paper entitled 303
"Nucleotide Stability of

Oligonucleotides Containing 7 substituted, 7-deaza and 8-aza, 7-deazapurine nucleosides" by Seela, Exhibit 1045, article 343
entitled "Synthesis of nucleosides designed for combinatorial DNA sequencing", Exhibit 1046, Hobbs patent 393
bearing Patent No. 5,151,507, Exhibit 1047, Odedra Patent 404
No. 7,078,499, Exhibit 1048, copy of Odedra 412
Patent No. 7,078,499, Exhibit 1049, Declaration of 450
Dr. Bruce Branchaud,

INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.

After doing so, please sign the errata sheet and date it.

You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition.

It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript maybe deemed to be accurate and maybe used in court.

E R R A T A

I wish to make the following changes, for the following reasons:

PAGE	LINE		
158	10		"1,000" to "1,000 greater"
172	22		"oxygen" to"deoxy-"
172	24	CHANGE:	"G wanting" to "guanine"
197	10		"plating" to "palladium"

REASON: Mistranscription

205	2		"Kinard" to "Canard"
238	15		"prefer label will" to "preferably"
243	25	CHANGE:	"into" to "working in"
254	19		"did" to "did read"
267	10		"on the ionic" to "project into"

REASON: Mistranscription

267	11		"in" to " "
271	7		"bite on" to "by you"
271	15	CHANGE:	"bit" to "bit. And"
297	13		"nuclear method" to "nucleotide"
313	5		"proteinate" to "protonate"

REASON: Mistranscription

315	23		"acyclos" to "acyclics"
323	4		"present" to "presence of"
323	13	CHANGE:	"to" to "if you"
324	7		"propping" to "popping"

REASON: Mistranscription

326	19		"sight" to "site"
331	17		"sequencing" to "sequencable"
371	23	CHANGE:	"nitrile benzyl" to "nitrobenzyl"
373	6		"nitrile benzyl" to "nitrobenzyl"

REASON: Mistranscription

389	12		"insuring" to "sugar"
412	2		"to a" to " "
427	10	CHANGE:	"copy" to "copier"
433	24		"on" to "to"

REASON: Mistranscription

9/21/13

WITNESS' SIGNATURE DATE

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