

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ILLUMINA, INC.,  
Petitioner

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY  
IN THE CITY OF NEW YORK,  
Patent Owner

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Case IPR2018-00291 (Patent 9,718,852 B2)  
Case IPR2018-00318 (Patent 9,719,139 B2)  
Case IPR2018-00322 (Patent 9,708,358 B2)  
Case IPR2018-00385 (Patent 9,725,480 B2)  
Case IPR2018-00797 (Patent 9,868,985 B2)

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Record of Oral Hearing  
Held: March 5, 2019

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Before JAMES A. WORTH, MICHELLE N. ANKENBRAND, and BRIAN  
D. RANGE, *Administrative Patent Judges*.

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The above-entitled matter came on for hearing on Tuesday, March 5, 2019, commencing at 9:01 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia.

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# PROCEEDINGS

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JUDGE ANKENBRAND: Good morning, you may be seated. Just give us a minute here. Is the court reporter ready? All right. Let's go on the record. Good morning, everybody. Today we have our final hearing in IPR numbers 2018-00291, 318, 322, 385 and 797. Between petitioner Illumina Inc., and patent owner, The Trustees of Columbia University in the City of New York.

I'm JUDGE ANKENBRAND. I'm joined today by Judge Worth who is sitting to my left and Judge Range who is appearing remotely from our Dallas hearing room.

Counsel, can you please introduce yourselves and let us know who will be making the arguments today? We will start with petitioner, Illumina.

MR. ZIMMERMAN: Good morning, Your Honor. Bill Zimmerman of Knobbe Martens, Holston and Bear on behalf of petitioner Illumina. I will be making the argument today. With me are my partners Kerry Taylor and Nate Luman, also of Knobbe Martens and Roland Schwillinsky and Marcus Burch of Illumina.

JUDGE ANKENBRAND: All right. Good morning, everyone. And for the patent owner, who do we have today?

MR. WHITE: John White from Cooper and Dunham. Presentation will be made by Mr. John Murnane of Venable and he is sitting right here. And with us are also from Venable, Justin Oliver, Robert Schwartz, and Zachary Garrett. And we have a number of people from Columbia, as well as the inventor, Dr. Ju, present.

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1 JUDGE ANKENBRAND: All right. Good morning, everyone.

2 Thank you, welcome. It is good to have everyone here.

3 We set forth the procedures for today's hearing in our trial order but

4 I'll just remind everyone a little bit about the way this will work today.

5 Each party will have 60 minutes of total time to present their arguments.

6 Petitioner, since you have the burden of showing unpatentability,  
7 you'll go first and then that will be followed by patent owner's presentation.

8 Also both parties may reserve some brief time for rebuttal.

9 One thing I'll say is that one of our goals it to keep the hearing  
10 running smoothly and focused on the merits so we ask that everybody  
11 refrain from objecting during an opposing -- an opponent's presentation. If  
12 you do have an objection you can make that objection during your  
13 presentation time.

14 One more thing before we begin. Judge Range will not be able to  
15 view anything that you project on the screen in the room here. So when you  
16 refer to an exhibit on the screen, please state for the record the exhibit and  
17 page number or if it's a demonstrative, the slide number to which you are  
18 referring so that Judge Range can follow along with us. It is also important  
19 to do so for the clarity and accuracy of our transcript.

20 Also, our microphones do have limitations so Judge Range will be  
21 unable to hear you if you stray too far from the podium. So just keep that in  
22 mind as you are making your arguments. I will try to give each counsel a  
23 warning when you are reaching the end of argument time. Does anyone  
24 have any questions or concerns at this point? Mr. Zimmerman?

25 MR. ZIMMERMAN: No, Your Honor, thank you.

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1 JUDGE ANKENBRAND: Okay. Mr. White?

2 MR. WHITE: No. No, Your Honor.

3 JUDGE ANKENBRAND: All right. So we will start with Mr.

4 Zimmerman. And I guess the first thing I will ask is would you like to

5 reserve any time for rebuttal?

6 MR. ZIMMERMAN: Yes, Your Honor, I would like to reserve 15

7 minutes.

8 JUDGE ANKENBRAND: Okay.

9 MR. ZIMMERMAN: And I have copies of petitioner's

10 demonstratives. I know they were already submitted. If you'd like a bound

11 copy we have them.

12 JUDGE ANKENBRAND: Sure, you can pass them up.

13 JUDGE WORTH: Have you given one to the patent owner?

14 MR. ZIMMERMAN: Yes, patent owner already has a copy. We

15 talked to them earlier.

16 JUDGE ANKENBRAND: Thank you. All right. We are ready to

17 begin whenever you are.

18 MR. ZIMMERMAN: May it please the Board. Illumina has

19 challenged four Columbia patents that claim 3'-O protected labeled

20 nucleotides and one patent that claims a method of sequencing using any of

21 those nucleotides. These patents share the same specification and the same

22 or similar claim limitations to patents that were previously cancelled by the

23 Board in IPR and affirmed by the Federal Circuit.

24 I would like to start with the issues common to all five patents, then

25 address one issue unique to the method patent relating to claim construction,

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1 and then address the judicial estoppel and preclusion issues.

2 If we could go to Slide 2. The party's disputes focus on two claim  
3 limitations. And they relate to R, the 3' capping group. The first that it be  
4 small and chemically cleavable, the second one that it not interfere with  
5 recognition of the analogue as a substrate by DNA polymerase. And that's  
6 basically an incorporation requirement

7 JUDGE WORTH: Does this claim require multiple rounds of  
8 polymerization?

9 MR. ZIMMERMAN: that is the issue unique to the method case and I  
10 will go directly to that. If we could go to slide --

11 JUDGE WORTH: So you're conceding or you're arguing --

12 MR. ZIMMERMAN: It is Illumina's position that none of the claims  
13 require multiple rounds of sequencing. And if we go to the method case,  
14 which is the easiest one to address that, it's Slide 54.

15 The method claim recites a method for sequencing a nucleic acid  
16 which comprises detecting the identity of a nucleotide analogue incorporated  
17 into the end of a growing strand of DNA in a polymerase reaction.

18 The remainder of the claim set forth a full method of detecting so the  
19 preamble doesn't give life and meaning go the claim.

20 And the best way to illustrate that is if we go to Slide 55. The patent  
21 sets out a 9 step process for sequencing. Step 8 is the deprotecting step at  
22 the 3' position and step 9 is repeating the steps. The claim stops at step 5  
23 which is the detecting step.

24 So there is nothing in the claim language that requires repeating the  
25 steps, deprotecting at the 3' position, much less sequencing a particular

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1 number of bases.

2 There is absolutely nothing in the claim language that says 20 bases,  
3 10,000 bases, even though Columbia would like to read that into the claim.

4 There is just no claim language that would support that.

5 And in fact, the patent itself contains no sequencing data showing any  
6 particular number of sequences.

7 JUDGE WORTH: Going back to the product claims.

8 MR. ZIMMERMAN: Yes.

9 JUDGE WORTH: When it says chemically cleavable, why would it  
10 be cleavable if you're not repeating it?

11 MR. ZIMMERMAN: It is cleavable so that it can be used in the  
12 method and you -- the entire SBS process is designed to be repeated but  
13 there is nothing in the claim language that actually requires multiple steps in  
14 the claims as written.

15 And so you need it to be cleavable for an SBS process but in order to  
16 infringe the claim, you don't have to actually cleave it.

17 JUDGE WORTH: So you're saying that the purpose is for repetition  
18 but it's not required.

19 MR. ZIMMERMAN: Exactly. And they could have amended the  
20 claims. They could have written in the steps that require repeating the  
21 process. They knew how to do that in Slide 55 where they set out the full  
22 process but there is nothing in the claim language that actually requires  
23 repeating the process.

24 JUDGE WORTH: I mean, what is unusual about this case is if you  
25 look at the arguments, that there is a lot of arguments about what is mild,

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1 what is aqueous. Where is that in the claim?

2 MR. ZIMMERMAN: The claim itself does not actually recite mild  
3 conditions, aqueous conditions. It recites cleavable and that it be chemically  
4 cleavable.

5 Now if you're using that with a DNA process, both Tsien and the  
6 Columbia patents have the same requirements for their method.

7 And if we go to Slide 17, and so it goes more to motivation, Your  
8 Honor, than an actual claim requirement. The Tsien reference says you need  
9 efficient incorporation for the SBS method. And then it says need mild  
10 conditions for rapid and quantitative deblocking.

11 Those are the conditions you need to run this process multiple times.  
12 and Columbia's patent then gives you four fundamental requirements and  
13 they're the same.

14 And Dr. Menchen, the expert for Columbia, on the next slide, Slide 18  
15 admitted that they're the same requirements in Tsien's method and the  
16 Columbia patents.

17 JUDGE WORTH: Well, in your briefs, do you say anywhere that  
18 SBS is not required and that these thing that are being argued by patent  
19 owner are not required? You know, where is this in your brief?

20 MR. ZIMMERMAN: These conditions, Your Honor?

21 JUDGE WORTH: What we just talked about. I'm --

22 MR. ZIMMERMAN: The --

23 JUDGE WORTH: -- incorporating the whole prior discussion we just  
24 had about --

25 MR. ZIMMERMAN: Okay.



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1 JUDGE WORTH: -- is SBS required by any of the five claims and --

2 MR. ZIMMERMAN: There is no dispute among the parties that both  
3 Tsien, Dower and the Columbia patents are all directed to SBS. And a  
4 person of skill in the art would have known that these are the requirements if  
5 you're going to make a commercial SBS system.

6 But if you look at the claims as written, none of the nucleotide claims  
7 actually require a step of deprotecting the 3'-OH. And none of the method  
8 claims say you have to deprotect the 3'-OH or repeat the cycles for any  
9 number of sequences.

10 JUDGE WORTH: Did you say that in your brief?

11 MR. ZIMMERMAN: Which part?

12 JUDGE WORTH: What you just said?

13 MR. ZIMMERMAN: We did.

14 JUDGE WORTH: You did. And where is that?

15 MR. ZIMMERMAN: In the petitioner reply, we made clear, there's a  
16 section on claim construction relating to the method claims. And it is  
17 specifically at let me see, the reply at page 4.

18 Now the interesting piece of this is you have the Tsien patent, which  
19 has no data, no actual sequencing data. And the Columbia patents none of  
20 which contain any actual sequencing data.

21 And so I think it is important that you understand the timeframe we  
22 are dealing with. When Tsien's method comes out in '91, his patent says  
23 here is the method but there is no data. And he tells the skilled artisan use  
24 allyl, allyl has advantages. And if we look at slide --

25 JUDGE WORTH: Sorry, before we move on so you were just

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1 referring to the reply brief in the 797 case.

2 MR. ZIMMERMAN: Yes.

3 JUDGE WORTH: So in the product claim cases, did you put in a  
4 claim construction that multiple rounds of SBS are not required for this  
5 product?

6 MR. ZIMMERMAN: We did not argue that in the petitions and there  
7 was no argument in the nucleotide cases from patent owner that multiple  
8 rounds were required. That issue only came up in the context of the method  
9 claim in the 797 IPR.

10 JUDGE WORTH: Okay. Please proceed.

11 MR. ZIMMERMAN: Okay. So we are in a state of the art where  
12 Tsien is in '91. It sets forth an SBS method but it has no data. And so it  
13 directs you to the allyl capping group.

14 And if we look at Slide 4, it specifically discloses allyl ethers as the 3'  
15 blocking group. But Tsien does more than that. It gives you a reason to use  
16 the allyl ethers along with the other specified ones that these capping groups  
17 are stable during the sequencing steps and they have some advantages.

18 And the advantage is that deblocking occurs only when specific  
19 reagents are present and premature deblocking during incorporation is  
20 minimized. You then have --

21 JUDGE WORTH: Well, --

22 MR. ZIMMERMAN: Go ahead, Your Honor

23 JUDGE WORTH: Please proceed.

24 MR. ZIMMERMAN: Okay. Dr. Menchen, Columbia's expert, agrees  
25 if we look at Slide 5 that a person of ordinary skill in the art would have

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1 recognized the advantages of Tsien's allyl.

2 JUDGE WORTH: What do you make of the argument that mercury  
3 denatures DNA?

4 MR. ZIMMERMAN: Mercury would denature DNA and I think what  
5 you have to do is look at Tsien's reaction conditions which is the mercury 2  
6 and then you have to look at what is actually in the patent and that is at Slide  
7 32.

8 In the patent, they tell you that it is known that MOM and allyl groups  
9 can be used to cap an OH group and can be cleaved chemically with high  
10 yield, cites to Kamal.

11 Then if we go to Slide 32 --

12 JUDGE WORTH: Isn't that hindsight

13 MR. ZIMMERMAN: No. The patent itself is telling you use  
14 Kamal's conditions. And it tells you on Slide 32 that Kamal is mild, doesn't  
15 denature the DNA, rapid 3 minutes, and 93 percent.

16 Kamal is in the prior art and now Columbia says Tsien's conditions  
17 don't work. Kamal's conditions don't work. They've admitted in their  
18 specification that Kamal provides cleavage conditions. And now they're  
19 denigrating those conditions.

20 And what we really have is, I don't think the cite in the patent to  
21 Kamal is saying use Kamal exactly. And I don't think Tsien is saying use  
22 Gigg and Warren's method exactly. I think they're pointing out represented  
23 -- representative chemistries and that a person of skill in the art would have  
24 known how to adjust these chemistries to work with SBS systems.

25 JUDGE WORTH: So your first argument is that the chemistries don't

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1 matter because you don't need multiple rounds of SBS. That's your first  
2 argument.

3 MR. ZIMMERMAN: Yes.

4 JUDGE WORTH: And then your second argument is that Kamal is  
5 mentioned and that a person of ordinary skill would know how to adapt  
6 Kamal so that it would work with multiple rounds?

7 MR. ZIMMERMAN: Let me be very clear because I don't want there  
8 to be any confusion and I might not have been clear. The patent says Kamal  
9 provides cleavage conditions.

10 And there are no other cleavage conditions in the Columbia patents.  
11 The only cleavage conditions are the cite to Kamal. And so they're now in  
12 this strange position of saying we cited Kamal in our patent, it is the only  
13 cleavage conditions but those don't work. And I don't think that can be  
14 right.

15 I think we have to take the patent at its face value that Kamal provides  
16 conditions. But I think what they were really trying to teach is the skilled  
17 artisan knew of other conditions that would work.

18 And in our petition, Dr. Romesberg, if we go to Slide 35, he explained  
19 that it was known in the art that the allyl group could be removed chemically  
20 with high yield using palladium chemistry. And he said this could be done  
21 in aqueous conditions and that's at Exhibit 1012 at paragraph 64.

22 And so the state of the art he cites the Qian reference, the Boss  
23 reference. He cites to Kamal which comes out of the patent. And so you  
24 have this situation of this palladium chemistry was known in the art.

25 Columbia comes back and says individually Tsien doesn't work. The

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1 Kamal conditions in our patent don't work by themselves. Qian's conditions  
2 don't work individually. Boss doesn't work individually.

3 But they miss the collective state of the art that this palladium  
4 chemistry was known to people of skill in the art and they would have been  
5 able to use that in an SBS compatible way.

6 And when they raise this challenge based on each one individually  
7 rather than the whole of the art we came back and said okay, look at Exhibits  
8 1094, 1114, 1115. These are papers by Genet.

9 And if we bring up Slide 38, Genet shows palladium based chemistry  
10 in aqueous media that's rapid. And the title even says aqueous media.

11 JUDGE WORTH: Are these the esters -- you're -- this is the where  
12 you're relying on esters for ether chemistry?

13 MR. ZIMMERMAN: This is alloc is what is shown in the Genet  
14 papers.

15 JUDGE WORTH: Okay. And so patent owner's argument is that  
16 alloc is different than an allyl group?

17 MR. ZIMMERMAN: Yes. And I will address that directly. If we go  
18 to Slide 39, Columbia's expert admitted that the chemistry of Genet, this  
19 palladium chemistry was well known.

20 Then if we go to Slide 41, Ju's lab, one of his thesis advisees publishes  
21 a paper in 2006 and I know that's not prior art, but he says in the paper in the  
22 past decades.

23 So going back into the prior art, chemists have developed efficient  
24 catalysts to cleave groups from allyl ethers. And he cites to Genet. So their  
25 own lab, Dr. Ju's own lab, makes clear that the Genet chemistry isn't limited

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1 to allyl alloc. It covers allyl ethers as well.

2 He goes on to say that the -- it happens in aqueous media, its rapid, it's  
3 efficient and the conditions were mild and complete in 15 minutes. That's at  
4 Exhibit 116 page 164.

5 JUDGE WORTH: So what you're saying is that you're relying on  
6 that reference not for a claim limitation but for the knowledge of -- to inform  
7 what the knowledge of a person of ordinary skill would have been before the  
8 critical date?

9 MR. ZIMMERMAN: Yes. And if you look at the claims, I believe  
10 they just claim the nucleotide. Now whether that 3' group is cleavable is a  
11 latent property of allyl. So you shouldn't have to demonstrate cleavage  
12 conditions.

13 The allyl group is cleavable, that's just a property that's inseparable  
14 from the compound. But to the extent you need to show cleavage  
15 conditions, because that is our burden, the prior art has palladium based allyl  
16 cleavage conditions that are rapid, aqueous, efficient and meet all the  
17 requirements.

18 And the real question is if Kamal which is cited in the patents doesn't  
19 work, and their position is that the skilled artisan wouldn't have known, then  
20 what are they relying on for disclosure in the patents? What supports this  
21 cleavability if it's not Kamal, which is the only thing cited?

22 So they would have a real problem if that's truly their position. I  
23 don't believe it is. I believe although they're attacking each reference  
24 individually, that they will admit that palladium based chemistry of Genet  
25 was known in the art and would cleave allyl, especially in view of Dr. Ju's

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1 own lab admitting it.

2 JUDGE WORTH: Are you relying only on an allyl group?

3 MR. ZIMMERMAN: So --

4 JUDGE WORTH: From the 3' blocking group or are you relying in  
5 your petition or somewhere else for something other than an allyl group?

6 MR. ZIMMERMAN: The petition was based on the allyl group of  
7 Tsien and the Dower based ground using the allyl group of Metzger 94. So  
8 both Ground 1 and Ground 2 rely on an allyl group.

9 And the patent owner admitted during prosecution that allyl was small  
10 so there is no need for a claim construction of small. There is no dispute that  
11 allyl is small and satisfies that requirement.

12 JUDGE WORTH: Can you walk us through the argument and the  
13 evidence and specifically where is this in your briefs about Dr. Menchen's  
14 patents? It seems like you're relying on maybe deposition testimony but  
15 then you're talking about Dr. Menchen's own patents.

16 MR. ZIMMERMAN: Yes. So there was an argument raised by  
17 Columbia that you have the Tsien article, Tsien patent, and then Metzger  
18 which discloses specific data with allyl and that nobody then did it until  
19 Columbia. That allyl was essentially abandoned as a capping group.

20 And Dr. Menchen's patents respond directly to that argument. If we  
21 look at Slide 12, Dr. Menchen has a 1998 patent that talks about capping at  
22 the 2' or 3' position and he uses allyloxy, which everybody has admitted in  
23 this proceeding is the 3'-O allyl.

24 So the idea that nobody used allyl as a 3' blocking group is undercut  
25 by their own expert.

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1 JUDGE WORTH: So you're talking about Exhibit 1119?

2 MR. ZIMMERMAN: Exhibit 1091 is the mentioned patent. Exhibit  
3 1119 is Dr. Romesberg's testimony that 3'-O allyl is the same as 3' allyloxy.

4 JUDGE WORTH: Okay. And then there is a notation here. Is this in  
5 your -- what exactly is in your reply brief? And which case is this in?

6 MR. ZIMMERMAN: This is in the reply brief in all five cases. And  
7 this simply responds to the argument that nobody used allyl as a capping  
8 group. And the suggestion seems to be that Metzger's data would have  
9 pushed people away from allyl as a capping group. Then if we go to Slide  
10 13 --

11 JUDGE RANGE: This is Judge Range in Dallas. Isn't Menchen's  
12 patent, is that an SBS process?

13 MR. ZIMMERMAN: It is not an SBS process but it's still in the  
14 DNA polymerase context.

15 JUDGE RANGE: Okay.

16 MR. ZIMMERMAN: And the cap, the use of a capping group it  
17 spans more than just SBS, Your Honor.

18 And then if we look at Slide 13 Dr. Menchen in his 1999 patent again  
19 cites to allyloxy as a capping group but this time he specifically cites the '94  
20 Metzger article for reversible nucleotide terminators.

21 So it's the exact article that discloses the data for the 3' allyl group as a  
22 capping group.

23 And then on Slide 15, Dr. Menchen was asked well, why did you still  
24 identify the allyl group and he says because that's what Metzger calls it. He  
25 cites Metzger in his patent and admits that his disclosure of the allyl is based



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1 on Metzger so it's to refute this idea that nobody looked at allyl from the  
2 time of Metzger to the time of the Columbia patents.

3 JUDGE WORTH: So you may have a claim presentation but I did  
4 want to take you to a different tack right now, which is and I, you know, you  
5 can tell me if this is in your briefing. But let's say according to your first  
6 argument that we discussed that there is no multiple rounds required.

7 Does that change the lens through which we would look at the  
8 effectiveness of let's say the completeness of the termination? So in the  
9 primary Metzger reference, it's with an asterisk and that means its  
10 incomplete termination at a certain concentration.

11 And let's just say hypothetically that you don't have to have multiple  
12 rounds of polymerization. Does that affect the way you look at whether it is  
13 desirable to have complete termination or not? Or not desirable and is this  
14 briefed?

15 MR. ZIMMERMAN: Your Honor, it -- the -- what Metzger shows  
16 and teaches with respect to incorporation is briefed. But I think the better  
17 way for me to explain it is in context of what happened in the actual world.

18 So Tsien has this method and says use allyl, it has advantages but  
19 there is no data. Then Metzger in '94 tests eight different nucleotides,  
20 different 3' capping groups, one of which is allyl. And in that he says there  
21 is incorporation.

22 And I know it's termination star but Metzger's actual conclusion in  
23 that article and its Exhibit 1016 at page 4265. The protecting groups  
24 containing ether linkages of the 3' position, compounds 1, 3, 4, 7 and 8 were  
25 incorporated by some of the polymerases.

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1           And that's his conclusion and compound 3 is the allyl. So he says it is  
2 incorporated. And so you have this period where Tsien gives you a method,  
3 says use allyl, it has advantages and then Metzger comes along with data  
4 that shows incorporation. And we can debate whether it's full incorporation  
5 or partial incorporation but incorporation of some nucleotides.

6           So five nucleotides that show actual incorporation and then you get to  
7 the Columbia patents in 2000, there's no other data. The parties agree that  
8 there is no other data on allyl and that the patents in suit have no sequencing  
9 data on allyl.

10          So Metzger's data would have been promising to a skilled artisan  
11 because Tsien says use allyl, then Metzger comes along and gives you actual  
12 incorporation data whether its partial or incomplete versus totally complete.  
13 That would have told a skilled artisan you're at a good starting point. Go  
14 ahead.

15          JUDGE WORTH: I would like to try the hypothetical one more time.

16          MR. ZIMMERMAN: Okay.

17          JUDGE WORTH: And it sounds like you're pursuing the argument  
18 that at a higher concentration a person of ordinary skill would have believed  
19 that there was either complete incorporation or complete enough  
20 incorporation.

21          And that's based on multiple rounds of polymerization and you might  
22 be arguing that based on Tsien because that's when Tsien is talking about.  
23 So this is a hypothetical. So let's say hypothetically that the claim does not  
24 require multiple rounds of polymerization.

25          MR. ZIMMERMAN: Okay.

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1 JUDGE WORTH: And let's just say that at that concentration,  
2 hypothetically, that that star means that it's incomplete at that concentration.

3 Is there anything in your briefing or evidence about whether that  
4 might actually be desirable if you're not doing multiple rounds of?

5 MR. ZIMMERMAN: It wasn't briefed separately of not doing  
6 multiple rounds still being appealing. What you do have is Dr. Romesberg  
7 explained that even if it was incomplete termination, a person of skill in the  
8 art would have still found the data favorable.

9 But I think under your hypothetical, our case only gets better.  
10 Because if you don't need multiple rounds of sequencing, you just ended one  
11 incorporation, Metzger showed you some incorporation.

12 Like there is no dispute that Metzger showed incorporation. The  
13 question is whether it was complete and absolute.

14 JUDGE WORTH: And I guess what I'm asking you is where you  
15 think is, you can show me some testimony or if this is in your briefing?  
16 Because, you know, we are not going to build that part of the case out of  
17 here.

18 MR. ZIMMERMAN: No, you -- the case was really addressed as to  
19 whether a person of skill in the art would have been motivated by Metzger's  
20 data as it stood. Not in the context of whether the claim required one round  
21 or multiple rounds. It wasn't addressed at that level of granularity.

22 JUDGE WORTH: Well it --

23 JUDGE RANGE: This is -- can I jump in? This is Judge Range in  
24 Dallas. I think that maybe this is the way patent owner is looking at is that  
25 even if the claims don't require multiple rounds as we are discussing, the

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1 two primary references, Tsien and Dower, are both SBS references.

2 So we still have this issue of would you reach this nucleotide analogue  
3 without having a reason to think it works for SBS. Isn't having a reason to  
4 think it works for SBS sort of essential to your case? I guess that's the  
5 question.

6 MR. ZIMMERMAN: I think showing some incorporation is an  
7 essential piece because you have the prophetic Tsien method and then once  
8 you got actual data that showed some level of incorporation, you would have  
9 been motivated to move it forward.

10 There were only five nucleotides in Metzger that showed -- five  
11 capping groups that showed activity. Those would have all been good  
12 choices to move forward and the skilled artisan would have looked at them.

13 But I would like to look at the patent itself. If we go to Slide 19 --

14 JUDGE WORTH: Well, but before we move on and I do want to let  
15 you answer however you want to, but before we move on, it does sound like  
16 your case is built on Tsien and accordingly multiple rounds of  
17 polymerization because you are relying on the Tsien reference.

18 And that's -- you're looking at the Metzger data through the lens of  
19 the prophetic discussion in Tsien.

20 MR. ZIMMERMAN: The claims at issue don't require multiple  
21 rounds. But the skilled artisan was looking at Tsien's method which says we  
22 are doing an SBS method, there would be multiple rounds.

23 Use allyl in this method because it's advantageous and then actual data  
24 that shows incorporation, which would have encouraged the use of it in that  
25 method.

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1 JUDGE WORTH: And when you are saying Tsien is prophetic, is  
2 Tsien enabling? Is Tsien an enabling reference?

3 MR. ZIMMERMAN: Tsien is an enabling reference and if Tsien is  
4 not enabled, the patents in suit aren't enabled. There is no sequencing data  
5 in the patents, there is no unique chemistry different from Tsien. There are  
6 no special cleavage conditions. There are no special polymerases. There are  
7 no experiments showing incorporation.

8 The entirety of the data in the Ju patents is the reference to Metzger's  
9 data and Kamal for cleavage conditions.

10 JUDGE WORTH: Well, we are only talking about obviousness here.

11 MR. ZIMMERMAN: Yes.

12 JUDGE WORTH: And so when we talk about enabling we are  
13 talking about whether a reference relied upon for obviousness is enabling for  
14 what it teaches. So that's why we are discussing it.

15 And we've already talked about how mercury is known to denature  
16 DNA and so is -- I'll just ask it one more time. Is Tsien enabling at that  
17 point?

18 MR. ZIMMERMAN: There may have been a question as to in 1991  
19 whether Tsien fully enabled cleavage. There is no doubt by the priority date  
20 we are talking about here, 1999, that there was data and the chemical  
21 cleavage conditions using palladium were known to a skilled artisan.

22 So as of the priority date that we are talking about, 1999, there is no  
23 doubt that Tsien's method was enabling.

24 JUDGE WORTH: Okay. And in your -- to make that -- to --  
25 complete the circle there, you're -- the keystone for you is Genet. You're

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1 saying that the Genet chemistry is what enables --

2 MR. ZIMMERMAN: It is but it's not just Gent. The work builds on  
3 each other so you have Qian, Boss, and Genet, which are all the same  
4 palladium chemistry altered in slightly different ways with respect to being  
5 aqueous, not denaturing DNA.

6 That universe of chemistry builds on each other to ultimately get to  
7 Genet. Which Ju's lab admitted was rapid, mild, complete in 15 minutes  
8 and fully aqueous and applied to allyl ethers.

9 JUDGE WORTH: I mean, we at the end of the day have to be able to  
10 articulate something with rational underpinning. And so therefore it's  
11 petitioner's burden to articulate how you stitch it together. So this is your  
12 chance.

13 MR. ZIMMERMAN: And I would say that the chemistry builds from  
14 Boss and Qian to Genet and the Genet chemistry as taught in Exhibits 1094,  
15 1114, 1115 is SBS compatible.

16 It's rapid, it's mild, it's efficient, it happens in less than 15 minutes.  
17 It's an aqueous media and I don't think you will get a challenge from  
18 Columbia given their labs admission that it applies to allyl ethers that that  
19 chemistry does work.

20 JUDGE ANKENBRAND: And the same analysis applies in the 322  
21 case where even though Tsien teaches all of the limitations of the claims at  
22 issue in that case? Is that why it's an obviousness case and not an  
23 anticipation case?

24 I was a little confused when I read it because it's obviousness over  
25 Tsien, but then everything is disclosed in Tsien and it doesn't look like

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1 you're making any modifications the disclosure.

2 MR. ZIMMERMAN: You do need Prober for the location of the  
3 nucleotide labels at the 5 and the 7 position.

4 JUDGE ANKENBRAND: But that's not part of your ground, at least  
5 for one of the claims. Your first ground is just over I believe just Tsien  
6 alone.

7 MR. ZIMMERMAN: If you give me one second, Your Honor

8 JUDGE ANKENBRAND: Sure.

9 MR. ZIMMERMAN: Yes, okay. So the, I'm sorry, the 322 case is  
10 the one unique case.

11 JUDGE ANKENBRAND: Right.

12 MR. ZIMMERMAN: In that the reason its obviousness is you're  
13 moving around the reference. There isn't a single embodiment that gives  
14 you anticipation. You have different pieces of the reference that teach  
15 different things. So it's a single reference.

16 JUDGE ANKENBRAND: Okay. Can you walk me through that just  
17 for a minute? You're -- just walk me through the case on claim 1 just on  
18 obvious over Tsien alone.

19 MR. ZIMMERMAN: Yes. If I could get --

20 JUDGE ANKENBRAND: And it just was confusing to me because  
21 that's what the petition says but then when you get to the reply, it seems like  
22 all of the arguments are addressed to a combination of Tsien and Prober. So  
23 it seemed like the 322 case was a little bit left out.

24 MR. ZIMMERMAN: Give me one second, let me grab the patent.

25 JUDGE ANKENBRAND: Um-hum.

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1 MR. ZIMMERMAN: Okay. Are you looking for the side by side  
2 matching up, Your Honor? Or --

3 JUDGE ANKENBRAND: No I guess just what the -- what is the  
4 obviousness case? Because you said you were picking and choosing  
5 different I guess different embodiments from Tsien?

6 MR. ZIMMERMAN: Yes. So Tsien teaches the cytosine nucleotide.  
7 In a separate place it teaches the allyl capping group. And then it goes on in  
8 different places to talk about it in the context of the method with respect to  
9 cleavability, incorporation, and the various labels.

10 But it isn't that what we have here is an anticipatory picture or an  
11 anticipatory disclosure of one nucleotide. You have a section on tethers, you  
12 have a section on allyl capping groups, you have a section on the nucleotides  
13 and so you have to put them all together and that's why we ran it as an  
14 obviousness challenge. Not the anticipation based challenge.

15 JUDGE ANKENBRAND: Okay. And then the arguments are  
16 exactly the same, you would have put those together because of all the  
17 things you've been talking to Judge Worth about?

18 MR. ZIMMERMAN: Yes.

19 JUDGE ANKENBRAND: Okay. I just wasn't quite sure how that  
20 worked and why it really wasn't an anticipation case.

21 JUDGE RANGE: I had one I guess important logistical question,  
22 which I think everyone is in agreement that the priority for all five of the  
23 patents goes to. Is it October 6, 2000?

24 MR. ZIMMERMAN: Yes, Your Honor.

25 JUDGE RANGE: Okay, thank you.



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1 MR. ZIMMERMAN: If I could go back to the incorporation issue for  
2 one moment, Your Honor. If we go to Slide 19, the Ju patents admit that  
3 Metzger showed incorporation. And it's an unqualified statement that  
4 Metzger showed incorporation by Ventr(exo-) DNA polymerase of the allyl  
5 group.

6 That admission is binding here. It's also consistent with Metzger's  
7 own conclusion that allyl was incorporated. It's only after the fact that there  
8 is any issue as to what Metzger's data shows and their basis for saying  
9 Metzger shows unacceptable levels of incorporation are a 2007 and a 2011  
10 Metzger paper. Both of which are long after the priority date and they don't  
11 reflect the state of the art at the relevant time. It's important to know that --

12 JUDGE ANKENBRAND: So are you saying that maybe over time  
13 people went away from these methods because they might have been shown  
14 not to work as well as other methods?

15 MR. ZIMMERMAN: No.

16 JUDGE ANKENBRAND: That's in 2007 or 2010?

17 MR. ZIMMERMAN: I'm saying exactly the opposite, Your Honor.

18 JUDGE ANKENBRAND: Okay.

19 MR. ZIMMERMAN: And the reason it is so in pre 2000, you have  
20 Tsien which has no data, Dower which has no data, and then you have  
21 Metzger's '94 paper saying five nucleotides are good including allyl.

22 And then you get the Ju patents and they have no data in them either.  
23 And so nothing changes. Then you get to 2001.

24 And if we go to Slide 30 in 2001, you get the fully sequenced human  
25 genome and in 2004, NIH starts giving out grant money for SBS and to

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1 move toward \$1,000 genome.

2 So you go from this period where there was limited data, everybody  
3 had an SBS method but they were prophetic, very little data. 2001 hits and  
4 there is a fully sequenced human genome and then the race is on for the  
5 \$1,000 human genome.

6 And so rather than abandon these methods, people are ramping up  
7 looking at nucleotides, they're ramping up looking at SBS. By 2006  
8 Illumina has commercial product placed and they're doing actual sequencing  
9 in the market.

10 If you look at Metzger's 2007 and 2011 papers, he admits that the race  
11 for the \$1,000 genome is on. He is looking at things like altering  
12 polymerases, optimizing reaction times. So you go from hey, this is  
13 something we are looking at generally to we are really going to hone this in.  
14 We have got funding and now we are trying to find a \$1,000 genome.

15 And what is acceptable as you are moving to a \$1,000 genome, is very  
16 different than what was acceptable when these methods were prophetic and  
17 in the early stages.

18 And so they're trying to time shift a POSA by nearly 13, 14 years with  
19 these Metzger articles. And they don't accurately reflect what the state of  
20 the art was in 1999.

21 JUDGE ANKENBRAND: So if the state of the art was prophetic in  
22 1999, why would a skilled artisan have -- I guess have had a reason to create  
23 what is in the claimed subject matter?

24 MR. ZIMMERMAN: Because the Tsien method is the exact same  
25 method as what Ju teaches. It's the same SBS method.

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1 Well, Ju teaches use allyl and they would have been led to allyl even  
2 more when Metzger's promising 94 data came out and showed  
3 incorporation. And so --

4 JUDGE ANKENBRAND: But Ju is a -- Ju is the -- are the patents in  
5 suit, right. You can't use them for the teaching --

6 MR. ZIMMERMAN: I'm sorry. Did I say Ju? So Tsien's method  
7 shows SBS and a reason to use allyl. Then Metzger come out with  
8 promising data that confirms Ju's teaching to -- I'm sorry, Tsien's teaching.

9 JUDGE ANKENBRAND: Okay.

10 MR. ZIMMERMAN: To use allyl.

11 JUDGE ANKENBRAND: That's when you said Ju and I was  
12 thinking --

13 MR. ZIMMERMAN: I'm sorry. It's Tsien teaching.

14 JUDGE ANKENBRAND: Okay.

15 MR. ZIMMERMAN: So Tsien gives you a list of nucleotides and  
16 says 2-nitrobenzyl is good, allyl is good and here is why. So it gives you a  
17 limited grouping, but then Metzger comes out and says here is data and it  
18 shows that allyl is incorporated.

19 JUDGE WORTH: With the asterisk.

20 MR. ZIMMERMAN: With the asterisk. And I would like to come  
21 back to the asterisk. If we go to Slide 19, Columbia's own patents say  
22 Metzger showed incorporation. Full stop. No qualification, no inefficient  
23 termination.

24 The representation they make to the world in their patents is Metzger  
25 shows incorporation. It's the only incorporation data in their entire patent.

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1 And so clearly they believe there was incorporation. That's consistent with  
2 Metzger's own conclusion that allyls showed incorporation and that is the  
3 only data that existed at the relevant time.

4 JUDGE WORTH: So why would it have been desirable to use the  
5 blocking group with an asterisk?

6 MR. ZIMMERMAN: Because at the time, you had no data on  
7 available blocking groups. Metzger shows incorporation even if in the  
8 asterisk and that would have been positive data.

9 I would like to make three points --

10 JUDGE ANKENBRAND: So are you just saying in the absence of  
11 data it was some data that got you from point A to point B? Because the  
12 prior art before it did not have any data? So you would take even the  
13 asterisk because it was some data moving in that direction?

14 MR. ZIMMERMAN: Exactly.

15 JUDGE ANKENBRAND: Okay.

16 MR. ZIMMERMAN: It was the only data. But Metzger teaches more  
17 than that.

18 JUDGE ANKENBRAND: You have about two minutes left before  
19 you start cutting into your rebuttal time.

20 MR. ZIMMERMAN: Okay. I would like to speak a little bit about  
21 what else Metzger teaches. Metzger wasn't just termination star end of  
22 story.

23 If we go to Slide 22, Metzger said termination was incomplete at 250  
24 microliters for 10 minutes. And the reaction was arbitrarily stopped. But  
25 Metzger teaches that his products contain 1 percent natural dATP

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1 contaminate.

2       The fact that you've got any incorporation over the natural nucleotide  
3 would have taught that that was a good substrate and that's at Exhibit 1119,  
4 paragraph 65 and 66.

5       But then Metzger also notes that the nucleotides behaved in a  
6 concentration dependent manner. It's Exhibit 116 at paragraph -- at page  
7 4263.

8       JUDGE ANKENBRAND: You mean 1016?

9       MR. ZIMMERMAN: 1116.

10       JUDGE ANKENBRAND: Okay. I think you said 116.

11       MR. ZIMMERMAN: I'm sorry its, you're right. Its 1016.

12       JUDGE ANKENBRAND: Okay.

13       MR. ZIMMERMAN: My mistake, Your Honor. And then if we go to  
14 Slide 25, Metzger expressly taught that by increasing concentration, you can  
15 drive to complete termination. And he does it in figure 4B.

16       It's shown that if you look where the termination line is with A, the  
17 line below it, the G, in the seven lanes shows dark bands and they go away  
18 by lane 9. So raising concentration makes the missing incorporation or the  
19 stopping of the incorporation go away and this isn't just our interpretation.

20       Dr. Menchen, their expert, admitted that that's exactly what that  
21 shows at Exhibit 1112, page 203 lines 16 through 204 line 14.

22       JUDGE WORTH: So this is an experiment using methoxy which is  
23 disclaimed.

24       MR. ZIMMERMAN: It is, but what does this teach the skilled  
25 artisan? When you have issues with incomplete incorporation, you increase

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1 concentration and information gets better. That's what Metzger's own work  
2 taught the skilled artisan.

3 JUDGE WORTH: You mean would that --

4 JUDGE ANKENBRAND: Does that apply broadly to anything or  
5 only if it's being used with a methoxy?

6 MR. ZIMMERMAN: It applies in methoxy, but he also talks about  
7 the nucleotides behaving in a concentration dependent manner. So it would  
8 have -- a skilled artisan would have thought that this applied across.

9 JUDGE ANKENBRAND: And is that your argument or did your  
10 expert make that argument?

11 MR. ZIMMERMAN: Our expert explained --

12 JUDGE ANKENBRAND: And so where?

13 MR. ZIMMERMAN: Dr. Romesberg explained that the fact that you  
14 saw incorporation with natural ATP present, and that's at 1119 paragraph 65  
15 and 66, he talks about raising concentration at paragraph 91 of Exhibit 1119.

16 JUDGE ANKENBRAND: Okay.

17 MR. ZIMMERMAN: And then the admission from their expert that  
18 that's what Figure 4 shows is Exhibit 1112 page 203 and 204.

19 JUDGE WORTH: I have one question about, at least one question  
20 about Ground 2. Does Dower teach the wrong position on the nucleotide  
21 base for a chemical linker?

22 MR. ZIMMERMAN: Okay. So Dower teaches attaching FMOC  
23 directly to the nucleotide. He doesn't teach the 5 and the 7 positions. Prober  
24 teaches the 5 and the 7 positions.

25 JUDGE WORTH: So what's your affirmative case for Ground 2

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1 then?

2 MR. ZIMMERMAN: Okay. So the affirmative case is the  
3 combination of Dower and Prober gets you a linker from the correct  
4 positions to the 5 and 7 positions to a fluorescent label combining the  
5 teachings of Dower and Prober.

6 JUDGE WORTH: So you are using Prober as a location and what  
7 linker are you using?

8 MR. ZIMMERMAN: There are two separate arguments in the  
9 petition, Your Honor. If we go to Slide 48, the first one is Dower discusses  
10 a propargyl amine at the 5 or the 7 position and then attaching a label to that  
11 using a cleavable linker. And this is directly from the petition.

12 And so if we go to Slide 49, Dower, I'm sorry, Prober shows the  
13 propargyl amine and another linker and the florinal group. So the  
14 combination is you take Prober's position, Prober's propargyl amine, the  
15 methoxy carbonyl linker of Fmoc from Dower and the florinal from the  
16 Fmoc of Dower. So you basically put the Fmoc on the propargyl amine  
17 at the right point as taught by the combination of Dower and Prober.

18 There is also a single linker theory in the petition and that's on Slide  
19 50. And the argument here was you would combine Prober and Dower, and  
20 Columbia has admitted that there is nothing patentable about the labels.  
21 There is no disclosure in their patent of a particular linker that's chemically  
22 cleavable. And so combining Dower and Prober gives you the same level of  
23 detail.

24 If we look at the next slide, Slide 51. The function descriptions in the  
25 Columbia patent that you have a linker that's cleavable by chemical means

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1 matches up with Dower and a person of skill in the art would have been able  
2 to combine Dower and Prober for a single linker. Because they say the 2  
3 linker is excluded. I see that I'm into my rebuttal. If the panel has other  
4 questions?

5 JUDGE ANKENBRAND: I think we are good. And we will us the  
6 rest of your time for rebuttal.

7 MR. ZIMMERMAN: Thank you.

8 JUDGE ANKENBRAND: Mr. Murnane, I think you are up.

9 MR. MURNANE: Thank you, Your Honor.

10 JUDGE ANKENBRAND: Did you want to reserve any time for  
11 rebuttal?

12 MR. MURNANE: I would like to reserve, Your Honor, five minutes  
13 please.

14 JUDGE ANKENBRAND: Sure.

15 MR. MURNANE: Your Honor, if I may, we have the bound versions  
16 of the slides that we have sent in. May I?

17 JUDGE ANKENBRAND: Sure.

18 MR. MURNANE: Thank you.

19 JUDGE ANKENBRAND: You can pass them up. Thank you.  
20 Whenever you are ready, you may begin.

21 MR. MURNANE: Thank you, Your Honors. Good morning, Your  
22 Honors, and may it please the Board.

23 Illumina has told you that Columbia's SBS invention, which no one  
24 was able to achieve prior to Colombia, would have been obvious to solve  
25 through the selection of the 3'-O-2-propylene capping group, which for



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1 brevity I'll refer to as the allyl capping group.

2 The argument suffers from a lack of motivation and a lack of  
3 expectation of success. In that regard, there are three main categories that I  
4 would like to discuss today.

5 One, the Board invited briefing on whether the Metzger reference  
6 discouraged use of the ally capping group for SBS and I will explain today it  
7 did. Two, the Board invited briefing on whether the cited references taught  
8 SBS compatible cleavage conditions for the allyl capping group. The record  
9 now shows that none of the Illumina references teach such cleavage  
10 conditions.

11 And three, with the foundation of the petition failing, Illumina now  
12 attests to distract with new theories and misdirection concerning enablement  
13 and incorrect technical arguments concerning contamination and high  
14 concentrations.

15 Now with your permission, before discussing the Metzger and other  
16 prior art, I would like to first focus on Columbia's claimed invention and the  
17 prior art.

18 If we look at Columbia Slide 6, we see Claim 1 in the '852 patent and  
19 how it differs from Claim 16 in Columbia's previously adjudicated '869  
20 patent. The briefing that you have read focuses a lot on this R cap if I may.

21 With this screen, the laser doesn't show. We all know it's the R cap,  
22 forgive me, Your Honors. On the 3' oxygen substituent shown on the sugar  
23 element of the adenine analogue. This R is small, chemically cleavable, and  
24 does not contain a ketone. The oxygen plus the R, the OR, is not a methoxy  
25 or an ester group.

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1       The claim also says, as we see on the right, that the nucleotide  
2 analogue is recognized as a substrate by a DNA polymerase and is  
3 incorporated at the end of a growing strand of DNA during a DNA  
4 polymerase reaction.

5       Now why does the capping group have those characteristics of being  
6 small, not a ketone, an ester, or a methoxy?

7       Let's look at Columbia Slide 4. The capping group has those  
8 characteristics because Columbia's Dr. Ju, who is here with us today, he and  
9 his colleagues, the inventors at Columbia, recognized the problem that had  
10 plagued the sequencing by synthesis, SBS, effort in the 1990's.

11       The problem they recognized was that in order for the capped portion  
12 of the nucleotide to fit into the pocket of the DNA polymerase resection, it  
13 had to be small. Indeed, as Dr. Ju explained to the examiners in his  
14 declaration during prosecution, the maximum size of the capping group is  
15 3.7 angstroms because the area in the polymerase nucleotide complex  
16 surrounding the 3' position of the sugar is very crowded.

17       We know the claims are construed in light of the prosecution history.  
18 So the inventors recognize that there were spatial constraints that had to be  
19 taken into account in SBS. Those particular constraints had not been  
20 appreciated by others before.

21       Dr. Ju and his colleagues also recognized that there were chemical  
22 constraints introduced by the polymerase itself that rendered the use of  
23 ketone, ether and methoxy groups incompatible with SBS. Based on these  
24 insights, the inventors discovered and patented nucleotide analogues having  
25 small, chemically cleavable capping groups that were not ketone, ester or

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1 methoxy.

2 JUDGE WORTH: Mr. Murnane.

3 MR. MURNANE: Yes, Your Honor.

4 JUDGE WORTH: But where is the multiple rounds of  
5 polymerization in the product claim or the method claim?

6 MR. MURNANE: Thank you, Your Honor. If we take a look at the,  
7 any of the product claims that we have in suit, we will see that the product  
8 claims refer to the R being stable during a DNA polymerase reaction, that Y  
9 is stable during a polymerase reaction.

10 We see in the incorporation portion at the end of the claim wherein  
11 the analogue is incorporated at the end of a growing strand of DNA during a  
12 DNA polymerase reaction. And we see that it as we end the claim, it no  
13 longer includes a tag upon base -- a tag upon the base upon cleavage of the  
14 Y.

15 Now we know because this is a compound claim and under *In re*  
16 *Papesch*, compounds and their nature are something we have to take into  
17 account. These claims were challenged by Illumina based on references  
18 which cite capping groups. And those references have SBS conditions. And  
19 they said that it would have -- Illumina said it would have been obvious to  
20 use these references to achieve these SBS results.

21 The patent specification is all about, the Columbia patent specification  
22 is all about SBS. If you read the claim in light of the specification, you  
23 know that those nucleotide analogues have been made and I have given you  
24 some of the characteristics in the claim language of the nucleotides, have  
25 been made for use in these SBS processes.

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1           And the challenging in fact, I think earlier counsel said that there is no  
2   dispute that Tsien, Dower, and Columbia are all SBS. They're all SBS. So  
3   these were SBS teachings.

4           The method claim refers to a, Zach, can you put the method claim up?  
5   One moment, Your Honor. 54, I think Slide 54. Illumina Slide 54. Thank  
6   you.

7           That's a method for sequencing a nucleic acid. Dr. Romesberg agreed  
8   that a nucleic acid is a polymer of nucleotides. Each cycle of SBS only  
9   sequences a single nucleotide so there should be no dispute that you must  
10   conduct multiple cycles of SBS to sequence a polymer of nucleotides.

11          Moreover, as I said the specification for all the patents makes clear  
12   that the purpose of the claimed invention is SBS. And we just saw that  
13   Illumina has conceded that requires sequencing of at least 20 bases.

14          And lastly, Columbia argued that the method patent requires multiple  
15   cycles and a POSA would not have had a reasonable expectation that the  
16   allyl capping group would achieve that limitation. Beyond that simple --  
17   that single argument, Columbia's argument have not depended upon the  
18   Columbia patents requiring multiple cycles.

19          Illumina argues that a POSA would be motivated to use the allyl  
20   capping group for Tsien and Dowers SBS methods and those methods  
21   indisputably require multiple cycles.

22          A POSA would therefore only be motivated to use the allyl capping  
23   group for Tsien, Dowers, SBS methods if it was believed to be capable of  
24   achieving multiple cycles, that is efficient incorporation SBS compatible  
25   cleavage conditions.

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1       So whether Columbia's claims require multiple cycles is really,  
2 respectfully, irrelevant to the response we have made to the challenges  
3 they've made based on Tsien and Dower.

4       JUDGE WORTH: So if we disagree that the product may require  
5 multiple rounds it would be based on the case that petitioner has built and  
6 their prior art references. Their prior art references are requiring multiple  
7 rounds, Tsien, Dower. Would you agree with that?

8       MR. MURNANE: If I understand it, Your Honor, I want to make  
9 sure that I understand your question. Is Your Honor's question that the  
10 references require multiple rounds and therefore they wouldn't be pertinent  
11 to our product claims?

12       JUDGE WORTH: Well, let's put it this way. And this was  
13 something that Judge Ankenbrand asked petitioner. Would a person of  
14 ordinary skill have combined the references to arrive at the claimed  
15 invention?

16       MR. MURNANE: No. Emphatically no, Your Honor.

17       JUDGE WORTH: And is that based on, in part on teachings in the art  
18 to use, to create an SBS system?

19       MR. MURNANE: Indeed, Your Honor. The prior art and Tsien is  
20 the first one. Tsien has been cited and Tsien has, although it's a prophetic  
21 patent, it has categories of things that one must consider for SBS  
22 sequencing, proper SBS sequencing. And you -- we have spent a lot of time  
23 in our papers going over those conditions of, for the cleavage conditions.

24       And so they are now saying in these proceedings that the particular  
25 allyl ether that they've invited attention to, they said that that would have

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1 suggested to a person of ordinary skill in the art Columbia's claimed

2 nucleotide inventions. That's what they've said.

3 And we have said no it would not have because the allyl ether that is  
4 taught in Tsien, you have to go see Gigg and Warren, and in fact the  
5 advantages that Your Honors noted in your petition institution decision don't  
6 exist because it is base hydrolysis, and they said the advantages are not base  
7 hydrolysis.

8 So in other words, they're saying look at Tsien, you will see there is an  
9 allyl ether which could be used for SBS and therefore your claims, all of  
10 them, are invalid. And we are saying no, because you wouldn't get the  
11 result that they say you would have gotten. And you wouldn't have gotten  
12 that result. In fact, nobody got that result as we will point out.

13 JUDGE WORTH: Well, we haven't talked about Gigg and Warren  
14 today. Can you expand on that?

15 MR. MURNANE: Sure.

16 JUDGE WORTH: On those references.

17 MR. MURNANE: Thank you very much, Your Honor. Very simply.  
18 Zach, could we have the slide that refers to Tsien? Thank you. It's the  
19 Tsien slide which refers to allyl ethers and Gigg and Warren.

20 JUDGE ANKENBRAND: And can you just --

21 MR. MURNANE: Sorry, yes, Your Honor.

22 JUDGE ANKENBRAND: -- for the record state which slide you are  
23 going to now?

24 MR. MURNANE: Thank you very much, Your Honor, I apologize.

25 JUDGE ANKENBRAND: Yes.

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1 MR. MURNANE: The prior one --

2 JUDGE ANKENBRAND: Just for Judge Range.

3 MR. MURNANE: The prior one, Judge Range, was Illumina Slide  
4 54, the prior one. I apologize. Now we are --

5 JUDGE RANGE: Thank you.

6 MR. MURNANE: Now we are looking at Columbia Slide 44. So we  
7 see here that what they have pointed to is this paragraph in the box at the top  
8 and the sentence in the bottom of the box, allyl ethers are cleaved by  
9 treatment with mercury to an acetone water, Gigg and Warren 1968.

10 And the advantages that they had talked about up above, that a wide  
11 variety of hydroxyl blocking groups are cleaved selectively using chemical  
12 procedures other than base hydrolysis. That's a key there, okay. They say  
13 these are advantages they're talking about.

14 And then they say allyl ethers and they go see Gigg and Warren. But  
15 when you read Gigg and Warren, the allyl was converted to a vinyl by base  
16 hydrolysis. And then the vinyl was cleaved. Okay.

17 So when -- and in fact, later on if I'm -- Zach, put the slide please  
18 which talks about the change of position for Illumina. Illumina now says  
19 and this is now Slide 47.

20 So in the petition, the non-base hydrolysis advantage was alleged but  
21 we now know it doesn't exist because in the petition you will see we've  
22 highlighted in the top the, in violet, other than base hydrolysis in the top box,  
23 Judge Range, and then in the middle box the institution decision based on  
24 the advantageous blocking group and the advantage was supposed to be  
25 based on the other than base hydrolysis.

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1 And in the reply we see in the bottom box the statement Tsien cites to  
2 the pioneering 1968 Gigg and Warren article, which discloses that allyl ether  
3 is cleavable by base hydrolysis. So it's gone. The rationale for choosing  
4 Tsien as asserted in the petition is gone. That's my answer to your Gigg and  
5 Warren question.

6 JUDGE WORTH: Okay. And what about Genet?

7 MR. MURNANE: Oh, Genet. Thank you, Your Honor. There  
8 firstly, I would like to very, very briefly and then we will go to -- Illumina's  
9 slides please.

10 A comment made in the opening that this report from Dr. Ju's lab  
11 after the issuance or, excuse me, after -- well after the filing date and relying  
12 on Genet. We will talk about alloc in just a moment and Genet.

13 But if one looks at, this is Exhibit, Illumina Exhibit 1116. And it was  
14 submitted by Quinlan-Mang at Columbia University and there is some  
15 historical information in there about Genet. But guess what. They chose a  
16 different method.

17 If we look at page 165, the bottom of the page to 166, considering  
18 reaction conditions solvents, conversion efficiency and reaction time,  
19 Milton's method which is not Genet, Milton's method employing sodium  
20 tetrachloropalladate --

21 JUDGE ANKENBRAND: Can you slow down just a little bit?

22 MR. MURNANE: I'm sorry.

23 JUDGE ANKENBRAND: For the court reporter.

24 MR. MURNANE: Forgive me, Your Honor, I'm sorry.

25 JUDGE ANKENBRAND: That's okay. I do the same thing when



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1 I'm reading. I think we all tend to speed up but just to make sure they're  
2 getting the record --

3 MR. MURNANE: I understand, Your Honor. Especially when I'm  
4 reading on the clock.

5 JUDGE ANKENBRAND: -- clear and correct.

6 MR. MURNANE: I understand. Thank you again, Your Honor.

7 JUDGE ANKENBRAND: Um-hum

8 MR. MURNANE: So the tetrachloropalladate and TPPTS appear to  
9 be the most promising for a DNA sequencing system. Therefore, a series of  
10 experiments based on Milton's method were performed. They didn't go the  
11 Genet way. If we could, thank you, Zach, for --

12 JUDGE WORTH: So who didn't go the Genet way?

13 MR. MURNANE: Columbia in 2006. There and in that paper that  
14 was referenced by Illumina, there is historical information about Genet but  
15 they went the Milton way which the exhibit shows.

16 JUDGE ANKENBRAND: But is that the --

17 JUDGE WORTH: So --

18 JUDGE ANKENBRAND: -- point that petitioner is making? Aren't  
19 they just saying that Genet's method cleaved these allyl groups using this  
20 palladium chemistry and that was known not only in 2006, but also prior to  
21 the priority date of the patents that are challenged?

22 MR. MURNANE: Well, thank you very much, Your Honor. There is  
23 no evidence prior to the priority date. The -- we have here and thank you,  
24 Judge Range, this is Slide 40 from Columbia's slides.

25 And we see here that Illumina's new reference relate to alloc and as

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1 Judge Worth noted earlier, it's different and that's in the bottom part of the  
2 slide. You've got an oxy carbonyl there. Columbia's capping group, we  
3 have the ether there and they're different.

4 And the next slide please, Zach? Our next slide is Columbia Slide 41.  
5 Illumina concedes that the prior art taught that ethers are difficult to cleave.  
6 In Canard we see that ether bonds would be hard to cleave.

7 In the Illumina Exhibit 2033, we have Illumina's statement Dr.  
8 Metzger testified that it was not known that ether -- excuse me. That it was  
9 not known that ether bonds were hard to cleave under DNA comparable  
10 conditions, but the art did teach this.

11 Then we have Illumina's bottom box, the oral hearing, Exhibit 2032.  
12 Canard's '94 paper, Exhibit 2043, expressly states we reasoned that ether  
13 bonds would be hard to cleave.

14 And we note at the bottom of our slide Illumina in this, in these  
15 proceedings failed to provide evidence that alloc references teach allyl ether  
16 cleavage under SBS compatible conditions. There is no evidence.

17 JUDGE RANGE: So in the -- I think petitioner argued that Genet was  
18 known prior to 2000, so I think you agree with that. Right?

19 MR. MURNANE: Yes, Your Honor.

20 JUDGE RANGE: And I think they also argued that Genet taught SBS  
21 compatible cleavage conditions prior to 2000. Do you disagree with that?

22 MR. MURNANE: I wouldn't -- thank you very much, Your Honor. I  
23 invite attention to our slide 42. Illumina's current position that SBS  
24 compatible allyl ether cleavage conditions were known prior to 2000 in fact  
25 contradicts its prior positions. Now it says that the prior art discloses SBS

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1 compatible cleavage conditions.

2 In Exhibit 2015, which is related to the '444 Illumina patents -- patent,  
3 they said, in other words, it has not been possible hitherto to conduct DNA  
4 sequencing using 3'-OH allyl block nucleotides.

5 Up above that, they note that the 3' allyl group under DNA compatible  
6 conditions, that is conditions under which the integrity of the DNA is not  
7 wholly or partially destroyed.

8 So they said that and this is the '444 patent, which is 2002, it's a 2002  
9 patent. Priority date of 2002. After our priority date. So we submit that  
10 there wasn't evidence before that.

11 JUDGE WORTH: So just to circle back, you're saying that they  
12 haven't -- that there is a gap, they haven't shown that Genet was usable in  
13 this context and then there is mixed evidence on that point about whether  
14 Genet was usable in this context?

15 MR. MURNANE: We are saying, Your Honor, thus far there has  
16 been no prior art evidence adduced that shows that it is workable in this  
17 context.

18 JUDGE ANKENBRAND: What about their slide 19, which cites  
19 your patent that says 3'-O allyl dATP was also shown to be incorporated by  
20 DNA polymerase in the growing strand of DNA?

21 Because I thought you said there was no evidence anywhere about the  
22 allyl capping group. What about that admission in your patent?

23 MR. MURNANE: Well, Your Honor, I would respectfully say it's  
24 not admission. I think it's about to go up on the screen. One moment, Your  
25 Honor.

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1 JUDGE ANKENBRAND: We have it up on our screen, so you can  
2 talk about it now.

3 MR. MURNANE: Okay, all right.

4 JUDGE ANKENBRAND: We are --- I looking at slide 19 from  
5 Illumina's demonstrative exhibits. And it refers to Exhibit 1001 at 3, lines  
6 22 through 30. In the background of the invention section.

7 MR. MURNANE: Oh, yes, thank you, Your Honor. Okay. Thank  
8 you, I appreciate that. All that Dr. Ju and his colleagues did here is say what  
9 is said in the Metzger publication.

10 The Metzger publication, if we take a look at our Columbia slide 16,  
11 and what Your Honor is pointing to is in the middle box there in that slide.  
12 That's the same language that Your Honor just pointed to.

13 So if we look at the bottom box, the bottom box is from Metzger and  
14 as counsel read during the Illumina opening argument, first the protecting  
15 groups containing ether linkages at the 3' position compounds 1, 3, 4, 7, and  
16 8 were incorporated by some of these polymerases. That's what it says.

17 And Dr. Ju and his colleagues wrote exactly what Your Honor said.  
18 Next slide please.

19 JUDGE ANKENBRAND: So then why aren't they telling the  
20 ordinary artisan that Metzger shows that the 3' allyl was incorporated by  
21 DNA polymerase in the growing strand of DNA?

22 MR. MURNANE: And here's my point, Your Honor. The next slide,  
23 our slide 15. Metzger -- we -- of course we know we are looking at the prior  
24 art as a whole and we are reading our entire patent, including the  
25 specification. And we will get to that as well Your Honor.

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1        So here is the Metzger also said. Metzger says and we have in the top  
2 two boxes, three components. Compound 1, the 3'-O-methyl-dATP.  
3 Compound 8, the 3'-O-methyl-dTTP and compound , the 3, excuse me, the  
4 3'-O<sub>2</sub> dintro benzyl proved to be interesting DNA terminators. They're  
5 terminators.

6        The next box says compounds 1, 8 and 7 show a specific termination  
7 and were further evaluated with respect to their concentration dependent  
8 effects. They're terminators, specific terminators. It didn't say that about  
9 compound 3.

10       In Tsien, --

11       JUDGE ANKENBRAND: I know. I guess my question is a little  
12 different though. I'm asking what Columbia itself told the world about what  
13 was known in the art.

14       MR. MURNANE: I will tell --

15       JUDGE ANKENBRAND: And I'm reading it that statement from the  
16 background of the invention and it doesn't say but Metzger didn't move  
17 forward with a 3' allyl. It just says that Metzger showed that it was  
18 incorporated into the growing strand of DNA.

19       MR. MURNANE: Correct, Your Honor. And then lower down,  
20 Zach, we will be in column 3 of the patent. Lower down in that same  
21 column. So up where Your Honor has been focusing in column 3 of the  
22 patent, he is giving the history there about --

23       JUDGE ANKENBRAND: Correct.

24       MR. MURNANE: -- what Metzger did and what others did. And  
25 then he says beginning at line 44 in column, I'm looking at the '139 patent

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1 but what do you have up there, Zach? That's the 85 -- we have the '852 up  
2 on the board.

3 If we look at line 44, it says "The approach disclosed in the present  
4 application is to incorporate nucleotide analogues, which are labeled with  
5 cleavable unique labels such as the florescent dyes to mass tags and where  
6 the 3'-OH is capped with a cleavable chemical moiety such as either a MOM  
7 group ( $\text{---CH}_2\text{OCH}_3$ ) or an allyl group ( $\text{---CH}_2\text{CH=CH}_2$ ) into the growing  
8 strand DNA as terminators."

9 And if we go back to Ju, which is I think it is page 21, Zach, in Ju if  
10 you can. We will see it in a moment up on the screen. Ju says incorporation  
11 and termination. So the fact that Metzger shows that and he says later on in  
12 the papers, which we will come to.

13 The fact that Metzger says you have terminated asterisk, which meant  
14 it was incomplete and, therefore, as we see in our papers and as we have  
15 seen in the subsequent Metzger publications, it was inefficient.

16 Could you put Ju up? Did you put Ju up? Page 20, I'm sorry, Tsien,  
17 page 21. Tsien, page 21. Sorry, excuse me.

18 JUDGE ANKENBRAND: Do the claims require incorporation as  
19 terminators?

20 MR. MURNANE: The claims that we have here are the nucleotides.

21 JUDGE ANKENBRAND: Right.

22 MR. MURNANE: In these particular cases, in four of them. The  
23 other one is the method.

24 JUDGE ANKENBRAND: Right.

25 MR. MURNANE: And these are in the context of SBS. This is all

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1 written for SBS. When you are talking about --

2 JUDGE ANKENBRAND: Well where --

3 MR. MURNANE: -- the characteristics I mentioned before -

4 JUDGE ANKENBRAND: -- is the claim requiring incorporation as a  
5 terminator? I see it is incorporated at the end of a growing strand of DNA  
6 during a DNA polymerase reaction, which seems to be what you told the  
7 world that Metzger showed. I guess where is the -- where does the claim  
8 require incorporation as a terminator?

9 MR. MURNANE: Thank you, Your Honor. See if I may just, since it  
10 took a little while to get on this screen, so Tsien page 21 you see at I think it  
11 is line 17, line 17. Yes.

12 Incorporation and chain termination have been demonstrated. You  
13 need both of them there, okay, according to Tsien according to --

14 JUDGE ANKENBRAND: What is this?

15 MR. MURNANE: I'm sorry.

16 JUDGE ANKENBRAND: I know, but where does the claim require  
17 termination?

18 MR. MURNANE: Okay. I'm getting to it Your Honor.

19 JUDGE ANKENBRAND: Okay.

20 MR. MURNANE: But it took us a while to get that up, I wanted Your  
21 Honor to see I'm sorry. Thank you.

22 So the claim is the specification says this is for SBS. And if you look  
23 at let's see Stemple --

24 JUDGE ANKENBRAND: All right. But the claim isn't a method of  
25 SBS. Right.

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1 MR. MURNANE: Right.

2 JUDGE ANKENBRAND: It's just a nucleotide.

3 MR. MURNANE: I'm about to tell Your Honor very completely the  
4 answer.

5 JUDGE ANKENBRAND: Okay. All right.

6 MR. MURNANE: But you have to see, forgive me, Your Honor. But  
7 you are going to need to see couple of antecedents first. Stemple, the bottom  
8 of page 2.

9 Stemple, which was filed and published shortly before our filing date,  
10 which focuses on Metzger, Stemple spends a lot of time on Metzger and  
11 talks only about the two nitrobenzyl.

12 If we see at the bottom of page 2, talking about SBS, moreover this  
13 technique is plagued by any inefficiencies of interpretation and deprotection  
14 because incorporation and 3'-OH regeneration are not completely efficient.  
15 We talked about inefficient information before.

16 A pool of initially identical extending strands are wrapped -- can  
17 rapidly become a synchronized and sequencing cannot be resolved beyond a  
18 few limited initial additions.

19 Now let's look at those, the slides with the colored slides. Okay.  
20 Okay. Now here, Your Honor, this is efficient incorporation. This is where  
21 you have termination as well as incorporation. This isn't incorporation  
22 asterisk, this is -- or termination asterisk, this is efficient incorporation. You  
23 see the T's, they're --

24 JUDGE ANKENBRAND: So are you saying then that incorporation  
25 necessarily includes termination?



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1 MR. MURNANE: And not --

2 JUDGE ANKENBRAND: Is that where you are going?

3 MR. MURNANE: One more slide. The next slide, Your Honor.

4 This is what happens when it's inefficient. This is what happens when you  
5 have termination asterisk. It's out of phase which Stemple says at the  
6 bottom of page 2, the top of page 3, this is what you get if you don't have  
7 efficient incorporation.

8 JUDGE RANGE: Which slide is that?

9 MR. MURNANE: I'm sorry. Please forgive me, Your Honor. We  
10 were just looking at now its 73, and before that it was Columbia's 72. And  
11 before that we were looking at Stemple, the bottom of two and the top of  
12 three.

13 JUDGE WORTH: So if we disagree with you about what the claim  
14 requires, it sounded before like you had a secondary argument that a person  
15 of ordinary skill would not have combined the references to arrive at the  
16 claimed invention because Tsien is calling for certain conditions and then on  
17 top of it you have got other references, Stemple that aren't calling for similar  
18 conditions.

19 MR. MURNANE: That's correct, Your Honor. That -- again if we go  
20 back to the petition that we are responding to, we are responding to a  
21 petition where the petitioner said your nucleotide claims are obvious in  
22 view of Tsien, Dower, Metzger, Prober. And those references, Tsien to  
23 begin with says that there are conditions, there are SBS conditions.

24 We are saying well, to answer what they're saying, we are saying no.  
25 The conditions -- and they have secondary references. We are going to talk

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1 about them right now. Boss, Qian, and so forth and we will see, I can go  
2 into those right now.

3 JUDGE WORTH: Before we move on to the cleavage or go back to  
4 the cleavage, can you talk about -- can you respond to petitioner's arguments  
5 about upping the, increasing the concentration of the nucleotide or getting  
6 rid of the competing natural nucleotides as a way of correcting the asterisk?  
7 And also, you know, and the other arguments that petitioner was making on  
8 that point?

9 MR. MURNANE: Yes, Your Honor, we will do that, thank you.  
10 Now they're talking about high nucleotide concentrations and we are  
11 looking at slide 21, Judge Range, slide 21 of Columbia.

12 High nucleotide concentrations are incompatible with SBS. We have  
13 here Exhibit 2081, paragraph 17 from Romesberg declaration, Dr.  
14 Romesberg declaration.

15 A person of ordinary skill in the art seeking to develop sequencing by  
16 synthesis methods would recognize the need to use a nucleotide with a 3'  
17 protecting group that could be incorporated by a polymerase with high  
18 fidelity at moderate to low concentrations.

19 The lower box again this is from the same paragraph. Polymerases  
20 lose the ability to accurately replicate a DNA strand at high nucleotide  
21 concentrations because the seal activity of polymerases is hindered at high  
22 nucleotide concentrations.

23 Next slide please, Zach. Now we will look if we may please at slide -  
24 - Columbia's slide 22. And we see that on the left we have Tsien's example  
25 30 micromolar, okay. In his deposition testimony, Dr. Romesberg said that

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1 would be okay.

2 The next we have -- so that's low. Okay. Then we have moderate,  
3 200 micromolar. Dr. Romesberg said that's certainly not in the low range,  
4 probably in the moderate range.

5 We have the 250 micromolar which Metzger used for compound 3  
6 and it's at, in table 2 in the concentration. And that's characterized as high  
7 micromolar concentrations at 50,000 fold excess.

8 Then you have Metzger's 3-O methyl experiments for Sanger  
9 sequencing at 500 micromolars. All the way over on the right you have  
10 Illumina's current position that 10 milli micromolar is okay. But if you go  
11 back, Dr. Romesberg has said previously that one tenth of that, one milli  
12 micromolar is too high for SBS.

13 JUDGE WORTH: Can you talk about the methoxy experiment? Is  
14 that relevant? Does that --

15 MR. MURNANE: The concentration, Your Honor?

16 JUDGE WORTH: Does that remedy the deficiency?

17 MR. MURNANE: We say no, Your Honor. All that shows, firstly, as  
18 Your Honor pointed out, it's not in the claim and you're right. The methoxy  
19 as shown in Metzger is a terminator. So to increase the concentration of a  
20 terminator, for a terminator, is not apposite to our situation.

21 There is no evidence that if you increase the concentration of  
22 something that is not a terminator, you're going to get a terminator

23 JUDGE ANKENBRAND: So are you saying --

24 MR. MURNANE: No evidence of that.

25 JUDGE ANKENBRAND: -- that the methoxy experiment in Metzger

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1 is just not applicable to the allyl because they're not the same? One's a  
2 terminator and one is not?

3 MR. MURNANE: Correct.

4 JUDGE ANKENBRAND: And do you have -- did your expert  
5 opinion on that at all?

6 MR. MURNANE: Okay. Your Honor, that came up in the reply and  
7 that was before the expert, excuse me, after the expert --

8 JUDGE ANKENBRAND: But you had a --

9 MR. MURNANE: -- submitted his declaration.

10 JUDGE ANKENBRAND: -- surreply, right?

11 MR. MURNANE: We didn't submit a declaration from our expert.

12 JUDGE ANKENBRAND: Okay.

13 MR. MURNANE: In the surreply.

14 JUDGE ANKENBRAND: Okay. So you didn't respond to that  
15 argument in your surreply?

16 MR. MURNANE: We have just as our -- it's a lawyer point, Your  
17 Honor, and we are making lawyer argument in response.

18 JUDGE ANKENBRAND: Okay. I was just asking.

19 MR. MURNANE: Um-hum.

20 JUDGE WORTH: Can you also talk about Dr. Menchen's patents, is  
21 that relevant? Is that --

22 MR. MURNANE: We say no, Your Honor.

23 JUDGE WORTH: To better into the record?

24 MR. MURNANE: Those are Sanger sequencing cases. And that's,  
25 there are different requirements in Sanger sequencing. We have some slides

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1 if I may, Your Honor.

2 So here, Dr. Menchen, this is -- that's our slide, right? So Illumina  
3 slide 12, they are pointing to Dr. Menchen's 1998 patent. Where is ours?  
4 Okay. And we say that Illumina's dependence on Sanger results is  
5 misplaced because Sanger is fundamentally different from SBS --

6 JUDGE ANKENBRAND: What slide are you on?

7 MR. MURNANE: -- and we rely on -- I'm sorry?

8 JUDGE ANKENBRAND: What slide are you referencing?

9 MR. MURNANE: I'm sorry, forgive me, Your Honor. This is  
10 Columbia slide 56.

11 JUDGE ANKENBRAND: Thank you.

12 MR. MURNANE: And Dr. Romesberg's deposition and he says  
13 there, there is a question well, we are just talking about terminating DNA  
14 strands. We agree that for Sanger sequencing you can't terminate all of the  
15 strands because you wouldn't be able to generate a ladder, correct? Answer,  
16 they have different desires for the extent of termination.

17 And then the next question, okay, but for SBS, the goal would be to  
18 have very high termination, almost complete termination of the growing  
19 DNA strands to prevent out of phase sequencing, correct? Answer, sure.

20 JUDGE ANKENBRAND: So then you're saying they are irrelevant  
21 because one's a complete termination -- one wants complete termination and  
22 the other does not?

23 MR. MURNANE: Based on the testimony of Dr. Romesberg, Your  
24 Honor.

25 JUDGE ANKENBRAND: Okay.

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1 JUDGE WORTH: Can we go back to the cleavage conditions in  
2 Genet, and this seems like an important point so I want to make sure that we  
3 talk about that. And I guess the first question is, and petitioner will have the  
4 chance to reply if they want to, but is petitioner relying on Genet itself or  
5 just this article from the Ju lab that discusses Genet?

6 MR. MURNANE: I believe they're relying on Genet and the -- to be  
7 candid, I think the best shot they have to try to rely on it is the Columbia  
8 thesis from 2006, where in the historical background there is a reference to  
9 Genet, although they didn't go that way in the recommendation at the end.

10 What we have here though for sure, what we know for sure is that  
11 Illumina previously argued against allowing a newly proposed cleavage  
12 condition in reply briefing. We know that that's happened.

13 That at an oral hearing, its Exhibit 2032, when faced themselves with  
14 this situation they said, this is an argument that came out on reply for the  
15 first time, and so they, this is Illumina talking, the petitioner are limited to  
16 the conditions in the petition.

17 The petition didn't say one word about optimization, it didn't say one  
18 word about changing the conditions. It's a completely new argument in  
19 reply. And they were successful, the Federal Circuit ended up agreeing in  
20 the cite that we have there on slide 38.

21 JUDGE WORTH: Well the Federal Circuit discusses how the Board  
22 was reluctant to look at some of that testimony. So I think maybe that's sort  
23 of a separate issue about, you know, whether this is too late in the case. But  
24 --

25 JUDGE ANKENBRAND: I think also, I mean, isn't in that case was

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1 there a -- do we know whether there was a surreply? Here you have got a  
2 surreply, correct?

3 MR. MURNANE: Yes, we did.

4 JUDGE ANKENBRAND: I think this was before --

5 MR. MURNANE: We certainly did, Your Honor, yes.

6 JUDGE ANKENBRAND: -- some changes in our Trial Practice  
7 Guide that allowed for a patent owner surreply.

8 MR. MURNANE: I understand

9 JUDGE ANKENBRAND: So you were able to respond to arguments  
10 that were raised in the reply, correct?

11 MR. MURNANE: You're right, Your Honor.

12 JUDGE ANKENBRAND: Okay.

13 MR. MURNANE: That is a difference. I believe, I have to -- from  
14 the date there that I see on the screen, I believe that has to be right.

15 JUDGE RANGE: I wanted to circle back to the technical merits of  
16 Genet and I tried to ask this earlier but I don't know if I got quite what I was  
17 looking for. As of your priority date, would a person of skill have  
18 understood that Genet taught SBS compatible conditions?

19 MR. MURNANE: I'm not aware of that, Your Honor. I'm not -- I  
20 think that if there were such evidence I think that the petitioner would have  
21 provided it. And they haven't.

22 JUDGE WORTH: Is that thesis that we are talking about usable to  
23 discuss what would have been the state of mind of a person of ordinary skill  
24 because it is using the word historical or talking about historical conditions?

25 MR. MURNANE: I would submit no, in these circumstances, Your

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1 Honor. This is different from frankly what we were, we are doing when we  
2 are looking at Metzger's 2007 and 2011 because that's Metzger himself  
3 talking about what Metzger was doing then. Okay.

4 We have the Columbia group, which as far as we have seen, Columbia  
5 group had all the big insights here. I was going to and maybe I will have a  
6 chance to talk about Welsh as well as others, some other prior art. But up  
7 until the Columbia inventors, nobody had the appreciation for the invention  
8 which ended up changing, we had a slide up there at the beginning.

9 1990 to 2000, nothing happening until what Columbia did. And now  
10 the fact that somebody who is working in Dr. Ju's lab with the insights that  
11 those people have, are able to look at some prior art references and maybe  
12 draw some conclusions themselves. That's different from what Metzger  
13 himself in 2007 and 2011 says about what Metzger was doing in, excuse me,  
14 in 1994. I think it is different.

15 JUDGE WORTH: In your surreply, you -- I believe you're saying  
16 that some of the evidence was inapposite because it is talking about a  
17 different functional group. Can you go into that again?

18 I think that you were saying well, that's -- in ether group or maybe it's  
19 the alloc group but --

20 MR. MURNANE: Oh, for sure.

21 JUDGE WORTH: But can you discuss whether it's the same type of  
22 chemical reaction that we are talking about in Genet?

23 MR. MURNANE: Your Honor, we have -- I'm not a Ph.D., but I did  
24 take chemistry and I knew that carbonyl groups are important groups in  
25 chemistry. There is no carbonyl group in the cap in the claims of the



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1 Columbia patents.

2       There is this carbonyl group that we see, the oxy carbonyl in Genet  
3 that they're relying on and again, all I can say, Your Honor, I believe that if  
4 there were prior art evidence that cleavage of these alloc groups were  
5 germane to the cleavage of the ether and that you could do it in an SBS  
6 compatible way, I think we would have seen it.

7       JUDGE WORTH: Did you take a second deposition of the expert,  
8 petitioner's expert after their second declaration?

9       MR. MURNANE: Yes.

10       JUDGE WORTH: And --

11       MR. MURNANE: Yes, Your Honor.

12       JUDGE WORTH: And did you go over this material?

13       MR. MURNANE: Yes, Your Honor.

14       JUDGE WORTH: So are we just relying on its -- are there any  
15 argument or is there -- was this drawn out in testimony?

16       MR. MURNANE: Your Honor, I'm -- as I stand here I'm unaware of  
17 evidence, of evidence that has been adduced which demonstrates that the  
18 Genet references were deemed prior or the critical date to be pertinent to  
19 SBS conditions.

20       JUDGE WORTH: So you're just saying that petitioner hasn't met  
21 their burden.

22       MR. MURNANE: Yes, Your Honor. But again, I'll be candid, I have  
23 been handed a note from somebody who was at that deposition, Your Honor.  
24 That I understand that at the deposition, Dr. Romesberg agreed Genet only  
25 related to alloc not to ethers.

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1 JUDGE ANKENBRAND: Did you by any chance get a cite for that?

2 And your colleague can look it up while you continue.

3 MR. MURNANE: Okay.

4 MR. MURNAN: He will, thank you. Your Honor.

5 JUDGE WORTH: Please proceed. Thank you.

6 MR. MURNANE: Thank you very much, Your Honors. Okay.

7 Would you like me to go into the cleavage conditions or can I talk a little bit

8 about Welsh? Was there anything in particular that you have an interest in

9 hearing, Your Honor?

10 JUDGE WORTH: Unless there is --

11 JUDGE ANKENBRAND: I have one question.

12 JUDGE WORTH: Yes.

13 JUDGE ANKENBRAND: About Tsien. And as I was looking at the

14 argument in the papers, it almost seemed to me as though you were making

15 an argument that Tsien is not enabled for perhaps what it teaches. But

16 maybe that's not the argument you were trying to make? I'm not sure.

17 MR. MURNANE: You're correct, it's not the argument

18 JUDGE ANKENBRAND: Okay. So can you just sort of step

19 through that argument about Tsien and why when it teaches an allyl ether as

20 something that can be used as a group that is cleavable no one would

21 actually I guess -- is the argument no one would actually believe what Tsien

22 is saying? Or people of skill in the art wouldn't have believed that?

23 MR. MURNANE: Thank you, Your Honor. Firstly, Tsien mentions a

24 lot of things. Tsien mentions some really big compounds. The example five

25 in Tsien which I believe was on page 38 of Tsien has a 2, 4-

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1 dinitrobenzenesulfenylate label on top of the cap okay. That's really big.

2 Okay.

3 So 2-nitrobenzyl is one of the preferred and I think it is on page 21 of  
4 Tsien. 2-nitrobenzyl is a preferred cap. Esters are preferred. The allyl ether  
5 comes on page 24 and it says allyl ethers. It doesn't say CH, it doesn't say  
6 CH<sub>2</sub>, CH double bond, CH<sub>2</sub>. It says allyl ethers, cites Gigg and Warren, and  
7 as Dr. Romesberg has testified and it's in our papers, that's a genus. Okay.  
8 So it has that. It has a lot of different things.

9 And let's look at what people they had a slide up earlier. I think it is  
10 their slide, Illumina's slide 10, where Metzger cites Tsien. And he did.  
11 Metzger cited Tsien. And Metzger in his paper, and Zach will give me the  
12 cite in a moment. Metzger in his paper says that with the exception of not  
13 the compound 3, with the exception of the -- it's the 3-O-methyl right? With  
14 the exception of the 3-O-methyl compound of the eight compounds he made,  
15 they're all novel except for the 3-O-methyl. Not compound 3.

16 So they have a slide saying Metzger read Tsien and Metzger says my  
17 allyl is novel. Okay. He says that in a peer reviewed paper. After Tsien we  
18 have Welsh and Welsh cites Metzger -- excuse me. After Tsien we have  
19 Metzger, after Metzger we have Welsh.

20 Welsh cites both Tsien and Metzger. There is a statement in Welsh, I  
21 think it's on the second page when you turn Welsh, the second page. We  
22 have a lot of things going on here but when you're looking at Welsh, Your  
23 Honors, and you open it on the second page at the top, there is a paragraph  
24 and then there is the structure.

25 And it, the Roman numeral II structure is guess what, Metzger's

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1 compound 7, not the allyl. It's Metzger's compound 7.

2 And then we go to Stemple, and Stemple is referring to Welsh.

3 Excuse me. Stemple is also referring to Metzger. All over the place

4 Metzger. And throughout Welsh is relying on what? The 2-nitrobenzyl cap.

5 No mention of allyl. Not in Stemple, not in Welsh.

6 Metzger did it, and he never did it again. And nobody ever did it

7 again. So you have this statement in Tsien about allyl ethers not specifying

8 the 2-propenyl that we have been talking about.

9 You have Metzger and, correct, he cites Tsien. But he claims that his

10 allyl is novel to him. He claims that. Then we have people following

11 Metzger in Tsien, excuse me, in Welsh and Stemple and they're relying on

12 the 2-nitrobenzyl.

13 And then Welsh importantly, Welsh does a study. Nobody is

14 appreciating the need for this small capping group that Dr. Ju appreciated

15 and recognized.

16 Welsh here we are in 1999 and its Figure 3 when you are looking at

17 Welsh, Your Honors. Figure 3. He is looking at the, I think it is called the

18 T7 DNA polymerase. And he is thinking about getting things to fit.

19 He has got a capped 3' position just like we are talking about but he

20 has got a label on it and he has got all these different labels. And what does

21 he conclude at the end? I've got to find different polymerases.

22 And what he also concludes it the 2-nitrobenzyl is fine. He doesn't

23 conclude that I have a spatial problem and therefore, you know, I have to get

24 rid of the 2-nitrobenzyl. On, he says 2-nitrobenzyl is fine. Again, citing

25 Metzger.

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1       So it's a long-winded answer to your question, Your Honor, but if you  
2 start with Tsien and you see what happened thereafter, by those people who  
3 cited him, Metzger cited him. Welsh cited him. Nobody went with this allyl  
4 ether.

5       And after Metzger it was abandoned. Nobody did it.

6       JUDGE ANKENBRAND: Okay. You can continue.

7       MR. MURNANE: Okay.

8       JUDGE ANKENBRAND: You can continue.

9       MR. MURNANE: Would you like to talk about cleavage conditions  
10 or is anything there anything particular that Your Honors are interested in?

11       JUDGE WORTH: Yes. Please proceed with however you want to  
12 use your time.

13       MR. MURNANE: Okay.

14       JUDGE WORTH: Thank you.

15       MR. MURNANE: Thank you, Your Honor.

16       JUDGE RANGE: I had a question about the termination star in  
17 Metzger. It says the star means activity was incomplete. What activity is  
18 that referring to? Like what activity is incomplete? Is it the termination -- is  
19 it termination is incomplete or incorporation is incomplete?

20       MR. MURNANE: You see, denotes activity was incomplete. That's  
21 incomplete cooperation -- incorporation, Your Honor.

22       JUDGE RANGE: Incomplete incorporation. Okay.

23       MR. MURNANE: Right.

24       JUDGE RANGE: So --

25       JUDGE ANKENBRAND: And where --

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1 JUDGE RANGE: The question is --

2 JUDGE ANKENBRAND: Can I just interrupt for one second?

3 Where --

4 JUDGE RANGE: Yes, go ahead.

5 JUDGE ANKENBRAND: You said its incomplete incorporation.

6 Where do you get that from? I just wanted a cite.

7 MR. MURNANE: Incomplete termination is a better way of saying  
8 it. What Metzger himself later called it was efficient incorporation, Your  
9 Honor. I should have said that.

10 JUDGE ANKENBRAND: Okay. And is there a cite --

11 MR. MURNANE: Inefficient incorporation.

12 JUDGE ANKENBRAND: -- to Metzger or to your expert that is  
13 explaining what termination asterisk actually means?

14 MR. MURNANE: If we could put up the 2007 and 2011 Metzger  
15 papers? Have them up in a moment, Your Honor. Metzger himself --

16 JUDGE ANKENBRAND: You don't have to put the papers up.

17 MR. MURNANE: Okay.

18 JUDGE ANKENBRAND: I mean, we are familiar with it.

19 MR. MURNANE: Its Metzger himself, just said that it wasn't right,  
20 that it was poorly done. Here we have our slide, Columbia Slide 11. This is  
21 what termination asterisk means results from inefficient incorporation.

22 And in 2011, they noted we note that the 3-O-allyl-dATP is not  
23 efficiently incorporated by that polymerase and in 2007. This is unlike the  
24 situation for three prime modified nucleotides which typically act as poor  
25 substrates for DNA polymerases. Polymerases.

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1 For example, screening 3'-O-allyl-dAPT with eight different DNA  
2 polymerases revealed limited activity at high micromolar concentrations  
3 with only the Ventr(exo-) DNA polymerase.

4 JUDGE ANKENBRAND: Okay. I think I interrupted Judge Range.  
5 Sorry about that. I just wanted a cite for what you were telling us.

6 JUDGE RANGE: Thank you. So my question was if the  
7 incorporation, the incorporation was incomplete, you just cited the paper  
8 where it says the activity was limited, does that mean that this would be  
9 unable to sequence any part of a DNA, or does it just mean that it couldn't  
10 efficiently do sequencing to where it couldn't sequence a whole DNA strand  
11 for example?

12 MR. MURNANE: Thank you, Your Honor. Could I have slides 72 to  
13 73 please? We are going to ask one more time, Your Honors, to look at  
14 Columbia slides 72 and 73.

15 JUDGE RANGE: Yes, I thought those related.

16 MR. MURNANE: Okay. So people had been trying for at least 10  
17 years to do this SBS work. And there were problems. As Stemple points  
18 out on the bottom of page 2 to the top of page 3, if you don't do it right, you  
19 have inefficient incorporation.

20 Our slide 72 shows what happens when it is efficient. This is what  
21 people want. You want to be able to read. The reader has to show the red  
22 light there we all have thymine that's been added. That was supposed to be.  
23 We know that.

24 If we go to slide 73, out of phase, if you have inefficient  
25 incorporation, this is what you end up with. A mess. And now you might as

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1 well not be doing it. The idea is to correctly do, you know, people have  
2 been trying to do it. There have been problems and if you get it efficiently  
3 done and it hadn't been done efficiently before, you get slide 72, as opposed  
4 to slide 73.

5 JUDGE RANGE: Okay. So I guess you're saying if its inefficiently  
6 incorporated you won't get any useful information at all essentially.

7 MR. MURNANE: Right. And that's what Stemple called a plague  
8 that had -- and he wrote that. They're filing date is 1999 and it was  
9 published just prior to our critical date. So Stemple was writing this after a  
10 lot of work had been done and he called it a plague.

11 JUDGE RANGE: Thank you.

12 MR. MURNANE: Thank you, Your Honors. Could we talk a little  
13 bit about cleavage because cleavage conditions? So I will be happy to  
14 answer any other questions Your Honors have it you would like?

15 JUDGE ANKENBRAND: You have a little over, a little under two  
16 and a half minutes left so you can use it as --

17 MR. MURNANE: Okay.

18 JUDGE ANKENBRAND: -- you see fit. Or you can reserve the rest  
19 for rebuttal if you want.

20 MR. MURNANE: I'll do that. I'll reserve for rebuttal.

21 JUDGE ANKENBRAND: Okay.

22 MR. MURNANE: Thank you, Your Honor.

23 MR. ZIMMERMAN: If you would bear with me for just a moment,  
24 Your Honor, while we switch over.

25 JUDGE ANKENBRAND: That's fine.



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1 JUDGE RANGE: While you're setting up I'll let you know, one point  
2 of interest I have is a follow up on the question I just asked the patent owner  
3 regarding whether there would be any utilities even if it -- incorporation  
4 wasn't efficient.

5 JUDGE ANKENBRAND: Are you ready to go?

6 MR. ZIMMERMAN: I am, Your Honor.

7 JUDGE ANKENBRAND: All right. So you have 11 minutes left.

8 MR. ZIMMERMAN: Okay. I would like to cover a few brief points  
9 but I'll start directly with Judge Range's question. So efficiency will lead to  
10 how long your read length is. 10 bases, 20 bases, 10,000 bases. The more  
11 efficient your incorporation the longer your read length.

12 So it also depends on how bad the incorporation is. But you can have  
13 incorporation that's not perfect and still get usable data for a certain number  
14 of iterations. And so it really is a question of how much are you looking to  
15 synthesize?

16 In a modern day instrument, you need on the order of 99 to 100  
17 percent because you are doing full genomes. At the time we are talking  
18 about, nobody had done more -- Metzger showed one round of incorporation  
19 but it wasn't labeled.

20 So in a period where there was no data on anything, including Dr. Ju's  
21 own patents, one or two iterations would have been pretty good at that at that  
22 time.

23 JUDGE ANKENBRAND: And is that what you are saying right  
24 now? Is that in the record at all somewhere?

25 MR. ZIMMERMAN: Dr. Menchen admits at Exhibit 2116, paragraph

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1 25 that there was no other data at the time. So --

2 JUDGE ANKENBRAND: Okay. I guess the thing about  
3 incorporation and incomplete incorporation and efficiency, the -- what you  
4 started out the argument with. Or is that just you responding now --

5 MR. ZIMMERMAN: That's me responding.

6 JUDGE ANKENBRAND: Okay.

7 MR. ZIMMERMAN: I don't think there was a direct -- somebody  
8 addressing inefficiency of incorporation. There was I believe a deposition  
9 transcript from a prior one that talked about how the error compounds  
10 iteratively and how many cycles you would be out of phase before there was  
11 no usable information.

12 JUDGE ANKENBRAND: Okay.

13 MR. ZIMMERMAN: I don't have that transcript cite at my fingertips  
14 though.

15 JUDGE ANKENBRAND: Okay. Maybe one of your colleagues can  
16 look it up while you're continuing.

17 MR. ZIMMERMAN: Thank you. I would like to point out there was  
18 a question about combining Tsien and Metzger and what a person of skill in  
19 the art had been motivated to do that based on Metzger's data.

20 In Exhibit 1012, paragraph 63 and 66 is Dr. Romesberg explaining  
21 why a person would have combined Tsien with Metzger in view of  
22 Metzger's data.

23 Now I would like to turn to cleavage conditions and we know that the  
24 Ju patents cite Kamal and only Kamal. There is no other chemistry in the  
25 patents for cleavage conditions.

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1        So there are only two options at that point. The first one is Kamal  
2 works. And this is perfectly good. I don't genuinely delude that's right. All  
3 the experts have testified that Kamal itself is not DNA compatible.

4        So the second option is a person of skill in the art would have known  
5 of other cleavage conditions that would have worked. And we pointed to  
6 Genet and you heard esteemed counsel. He didn't say Genet doesn't work.  
7 He said the Genet papers are with alloc.

8        So would a person of skill in the art have expected Genet's method to  
9 work for allyl ether, the same way it worked for alloc?

10       JUDGE WORTH: Reasonably expected.

11       MR. ZIMMERMAN: Reasonably. And I can give you a direct  
12 answer. If we bring up Illumina slide 40 and I will tell you that the  
13 chemistry is beyond me so I will point you to the evidence.

14       Dr. Romesberg explains in detail in Exhibit 1119 paragraph 40  
15 through 43 and in his deposition testimony as cited here, that the --  
16 regardless of the particular allyl derivative, whether it be alloc or allyl ether,  
17 the palladium chemistry of Genet works the same. The mechanism is the  
18 same. And you'll see it on the screen, he explains it mechanistically.

19       So one of skill in the art would have expected it to work for allyl ether  
20 the same way as alloc.

21       JUDGE WORTH: I want to ask you something I asked earlier  
22 because patent owner's counsel is saying that allyl is genus and so when I  
23 asked whether petitioner is only relying on allyl are you relying specifically  
24 on this species that's in Metzger? That's the species of the allyl group that  
25 you are relying on.

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1 MR. ZIMMERMAN: We believe Tsien refers to allyl ethers as  
2 meaning the allyl, the 3 carbon allyl as the capping group and the reason he  
3 refers to ethers plural, if we could bring up slide -- the Greene and Wuts  
4 slide? Yes, slide 8.

5 Greene and Wuts, which is the treatise on protecting groups, talks  
6 about the allyl ether protecting group and it refers to allyl ethers. It doesn't  
7 change what the capping group is. It's what else hooks up to it.

8 So when Tsien says allyl ethers, it means the blocking group is the 3  
9 carbon allyl but you can give different nucleotides that it attaches to which  
10 give you a genus. It's not a genus of blocking groups, it's a genus of  
11 nucleotides with allyl caps.

12 So we are referring to the three carbon allyl is what the petition is  
13 based on.

14 JUDGE ANKENBRAND: And you're saying that Tsien's disclosure  
15 of allyl ethers is necessarily a disclosure of the 3'-O-allyl?

16 MR. ZIMMERMAN: It is. And if we look at slide, the Greene and  
17 Wuts, the -- yes. slide 9. Tsien refers to allyl ether and then cites to Gigg  
18 and Warren. The title of Gigg and Warren is the allyl ether meaning one.

19 And when you read Gigg and Warren, the allyl ether is compound LI  
20 as shown on slide 9. That is the 3 carbon allyl. Throughout Gigg and  
21 Warren when they refer to other allyl ethers, they do it by their long  
22 chemical name.

23 So it's fairly consistent that Tsien says allyl ethers meaning the 3  
24 carbon allyl capping different things and its reference to Gigg and Warren is  
25 the allyl ether which is the three carbon. So --

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1 JUDGE RANGE: For the other ground, the Dower ground, are you  
2 also relying on the 3 carbon allyl for that ground as well?

3 MR. ZIMMERMAN: Yes. And that comes out of Metzger. And  
4 Metzger everybody agrees is the 3 carbon allyl that is what he used as the  
5 capping group.

6 JUDGE RANGE: That makes sense.

7 MR. ZIMMERMAN: So --

8 JUDGE RANGE: So the, so that's the only capping group we really  
9 have to worry about in terms of --

10 MR. ZIMMERMAN: It is, Your Honor.

11 JUDGE RANGE: -- your challenges. Okay, thank you.

12 MR. ZIMMERMAN: And it is admitted to be small and there is no  
13 dispute that it actually works. There expert testified that it is cleavable  
14 under SBS conditions. It is incorporated. We know in the real world it does  
15 work.

16 JUDGE ANKENBRAND: But did people know that back in 1999?

17 MR. ZIMMERMAN: Well, it was --

18 JUDGE ANKENBRAND: Or did they expect, reasonably expect it?

19 MR. ZIMMERMAN: You would have expected it because Tsien says  
20 use it in my method and Metzger gave you data. And if we could go to  
21 Columbia's slide 16 and talk about that data for a minute.

22 So what did the world tell us about Metzger's data prior to this IPR?  
23 So Metzger himself says the protecting groups containing ether linkages at  
24 the three position compounds 1, 3, 4, 7, 8 were incorporated by some  
25 polymerase. Not kind of incorporated, not efficiently. They were

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1 incorporated. That was his conclusion. Prior to this dispute.

2 What did the patent owner tell the world prior to this dispute? It's the  
3 second box. 3-O-allyl-dATP was also shown to be incorporated. Not kind  
4 of incorporated, not semi incorporated, not inefficiently incorporated.

5 They're running from the cleavage conditions in their patent. Kamal  
6 is the only one cited. They're running from their statement of Metzger even  
7 though this is the only evidence of actual incorporation. So they want to rely  
8 on the prior art for purposes of getting the patent and then run from those  
9 statements in order to try to save it.

10 JUDGE ANKENBRAND: What about the rest of the later section of  
11 column 3 in their patent that they, that Mr. Murnane referred us to which  
12 says, I think it started in like around line 44 about the approach disclosed is  
13 to incorporate nucleotide analogues which are labeled what cleavable unique  
14 labels such as fluorescent dyes or mass tags and where the 3'-OH is capped  
15 with a cleavable, chemical moiety such as either a MOM group or an allyl  
16 group into the growing DNA strand as terminators.

17 And I think I asked Mr. Murnane at the time whether the claims  
18 require that incorporation as terminators and I thought his answer was yes.  
19 I'm going to ask you the same question. What does this -- what does this  
20 disclosure say to you and specifically in reference to what the claims require.

21 MR. ZIMMERMAN: That disclosure simply says you have a 3'  
22 capping group that stops incorporation until you remove it. It, whether you  
23 call it a blocking group, a terminator, it just means it's a cap until you  
24 remove it chemically.

25 The claims, the nucleotide claims don't require that. The method

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1 claims require capping, but not uncapping to start the next round. Now he  
2 used the word terminator trying to differentiate the Metzger paper.

3 But Metzger '94 directly says termination and I know for allyl its  
4 termination star but Metzger is recognizing that these are terminators. And  
5 that's what they're used for. So --

6 JUDGE WORTH: I have a question about Kamal and I just want to  
7 be clear before I ask the question. So we are not going to be adjudicating  
8 112 in any way, shape or form. It's beyond the scope of this IPR. Best  
9 mode is off the table post issuance, and so that's not before us.

10 But I just want to figure out the extent to which you are relying on a  
11 presumption of validity when you are relying on Kamal? Or are you relying  
12 on Kamal in combination with Genet?

13 MR. ZIMMERMAN: I am not relying on a presumption of validity. I  
14 am saying that the representations that a patent owner makes in their patent  
15 have to be taken as true. And the representation of this patentee is Kamal  
16 gives you cleavage conditions.

17 JUDGE WORTH: Where is your legal license for that?

18 MR. ZIMMERMAN: That representations in the specification are  
19 binding?

20 JUDGE WORTH: Yes.

21 MR. ZIMMERMAN: Its cited in our petition, I don't have a page  
22 number but we will get you a page number.

23 JUDGE WORTH: And is that different than a presumption of  
24 validity? Because I think that what I was hearing you say is that, and you  
25 can correct me if this is not what you were saying, but what I was hearing

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1 you say is that it was enabled or fully enabled based on Kamal.

2 MR. ZIMMERMAN: So the cite, Your Honor, first of all is *Pharma*  
3 *Stem Therapeutics*, 491 F. 3d, 1352 at 1362. Federal Circuit 2007.

4 Admissions in the specification regarding the prior art are binding on  
5 the patentee for purposes of a later inquiry into obviousness.

6 JUDGE WORTH: Okay. And so --

7 MR. ZIMMERMAN: And we --

8 JUDGE WORTH: -- is it possible that that could be true that  
9 admissions are binding, but that also that there is something that is -- that is  
10 not in Kamal?

11 MR. ZIMMERMAN: No. Because there is no -- there are no  
12 cleavage conditions in the patent whatsoever other than Kamal's. Kamal's  
13 are in Figure 14. Figure 14 of the patent is Kamal's cleavage conditions and  
14 apart from the cite to Kamal, there are no other cleavage conditions.

15 But we didn't leave it to chance. We said the admission in the  
16 specification is binding, under which case Kamal is perfectly good. We win.  
17 But in case it's not, the chemistry a person of skill in the art actually would  
18 have used is the palladium chemistry of Genet.

19 And so it is kind of a belt and suspenders approach that if we take the  
20 patentee at their word, we win. If not, here is the actual real world what  
21 people of skill in the art would have done. And it was the palladium  
22 chemistry.

23 And you didn't hear any statement that Genet's palladium chemistry  
24 didn't actually work. And in fact that is what Dr. Ju's lab has used for years  
25 and I believe continues to use.



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1 JUDGE WORTH: So I think their argument, and you can respond to  
2 this, is that it was not recognized at the time of Genet, you know, it was not  
3 recognized at that time of Kamal that it could have been combined in that  
4 manner.

5 MR. ZIMMERMAN: Well, and that's where I think the parties differ.  
6 They look at each reference one at a time, almost as an automaton. And we  
7 have looked at the state of the art where you have Qian and Boss and  
8 developments in palladium history that ultimately get you to Genet, and  
9 there are further tweaks on Genet, namely Milton which counsel referred to.

10 The Milton work is an advancement in palladium chemistry that was  
11 done by Illumina. And so it's a continuum, but the skilled artisan would  
12 have known of the palladium chemistry in general and would have been able  
13 to apply Genet out of Exhibit 1094, 1114, and 1115 in an SBS context to  
14 make it work with a reasonable expectation of success.

15 And in fact, in Exhibit 21, I'm sorry, Exhibit 1116, Ju's student admits  
16 that the chemistry has been known for decades and applies to allyl ethers.  
17 So does that answer your question?

18 JUDGE WORTH: I don't have any questions right now.

19 MR. ZIMMERMAN: I did have one other point that I wanted to  
20 address --

21 JUDGE RANGE: And one thing on that --

22 JUDGE ANKENBRAND: We are already --

23 JUDGE RANGE: -- point. That bit you just explained, is that in your  
24 expert declaration?

25 MR. ZIMMERMAN: It is. The Genet description is in Dr.

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1 Romesberg's declaration Exhibit 1119, paragraphs 40 to 43.

2 JUDGE RANGE: Okay, thank you.

3 JUDGE ANKENBRAND: And we are five minutes over time so I'm  
4 going to cut you off there. I know you wanted to make one more statement,  
5 but I'm going to cut you off.

6 MR. ZIMMERMAN: I appreciate it, Your Honor, thank you.

7 JUDGE ANKENBRAND: All right, thank you. Mr. Murnane, I'm  
8 going to give you 13 minutes even though you had 8 because we went 5  
9 minutes over with Mr. Zimmerman.

10 MR. MURNANE: Thank you very much, Your Honor.

11 JUDGE ANKENBRAND: Just let me know when you are ready to  
12 proceed.

13 MR. MURNANE: Thank you, Your Honors.

14 JUDGE ANKENBRAND: Ready?

15 MR. MURNANE: We are ready.

16 JUDGE ANKENBRAND: All right, go ahead.

17 MR. MURNANE: I would like to add some information that I was  
18 requested to provide earlier. We have it and thank you for your patience,  
19 Your Honors.

20 With respect to the Romesberg deposition, Dr. Romesberg agreed that  
21 Genet related to alloc, a-l-l-o-c, not ethers, it's our surreply at page 18, 19,  
22 citing Romesberg deposition Exhibit 2140 at page 184 line 10 to 185 line 6.  
23 Page 186 line 13 to 187 line 7. And 188 line 16 to 189 line 10.

24 Also, had a moment over there to take a look at the thesis again in  
25 light of some of the questions. In the thesis, it doesn't say that Genet

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1   cleaved allyl ethers. What the thesis says is that Genet's conditions cleave  
2   esters, carbonates and carbamates.

3           I would also point out that even if Genet's conditions could cleave an  
4   ether and there is no prior art evidence showing this, Illumina has not shown  
5   that the results would be SBS compatible, that is quantitative, et cetera.

6           JUDGE WORTH: Can we go back to what I was just conversing with  
7   petitioner's counsel about, which is petitioner's argument that the  
8   specification of Ju, and we didn't differentiate which patent, cites Kamal and  
9   that it is therefore understood that Kamal -- it was in -- this is petitioner's  
10   argument. One form of it is that it's an admission that Kamal taught  
11   cleavage conditions.

12          MR. MURNANE: The information provided in Kamal and cited by  
13   Dr. Ju and his colleagues is for the synthesis of nucleotides. Not as  
14   reversible terminators.

15          So as we were talking about earlier this morning, Your Honors, when  
16   we were talking about the insights that Dr. Ju had based on his consideration  
17   of the prior art and he appreciated, he alone -- he and his colleagues  
18   appreciated and they alone appreciated you ought to have the small cap,  
19   which couldn't be a ketone ester or methoxy and he talks about the prior art  
20   there.

21          And then he says if you want to make a particular compound, look at  
22   this. And those references will teach you synthesis conditions. But  
23   synthesis conditions and if we take Kamal, that's not SBS compatibility  
24   because it is not SBS. But if you want to make the compound, which I'm  
25   telling you you could use as a cap, there is a reference and if you incorporate

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1 them by the reference at the beginning of the patent they say in all the

2 patents they say these references are incorporated in their entirety.

3 So Metzger is incorporated in its entirety and so forth. And when you  
4 see, when you read them in their entirety you see what respect to Kamal it's  
5 not SBS compatible and it's not teaching you SBS. It's teaching you how to  
6 synthesize something. That's what it's there for.

7 The question of -- may I turn to the question of efficiency that was  
8 asked? And it was asked by Judge Range of all of us. In fact, I think  
9 everyone has been talking about it.

10 So if we take a look at Zach, could we look at Metzger, Illumina  
11 Exhibit 1016, table 2. So here is the table we have been talking about. This  
12 is Columbia's slide 10, Your Honors.

13 And so the table 2 and this is the table that has been the focus of so  
14 much attention in these IPR's. The activity matrix of RPHPLC purified 3'  
15 blah, blah, blah. So it's the activity. And then when you see what they say  
16 the results are, they have the results on the table and then at the bottom, all  
17 compounds were assayed at a final concentration of 250 micromolar  
18 according to the conditions specified in table 1.

19 Dash means no activity was detected. Termination means the  
20 termination bands mimic ddNTP termination bands. Okay, so there's  
21 termination. And inhibition means the rate of DNA synthesis is reduced in a  
22 non-specific manner.

23 Asterisk means the activity so this is the activity that this table is all  
24 about which we know from the top was incomplete at a final concentration  
25 of 250 micromolars.

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1           So if we go back, if I can, Zach, to slides -- Columbia slides 72 and

2   73. If you have efficient incorporation you have complete termination.

3   Here we see on slide 72 complete termination.

4           If you have inefficient incorporation, can we go to slide 73 please?

5   You have the activity that's incomplete. You have the termination which is

6   incomplete. It's out of phase which is what Stemple talked about and

7   characterized as the plague.

8           JUDGE ANKENBRAND: Did your expert opine on the teachings of

9   Metzger in 1994 and what termination asterisk meant and what you're

10   discussing now about out of phase and in phase? And if you so, can you

11   provide us some citations to where your expert opined?

12           MR. MURNANE: We will look for those citations --

13           JUDGE ANKENBRAND: Sure.

14           MR. MURNANE: -- right now, Your Honor.

15           JUDGE ANKENBRAND: That's fine. You can continue --

16           MR. MURNANE: Okay. I'll continue.

17           JUDGE ANKENBRAND: And your colleague can look.

18           MR. MURNANE: And Mr. Garrett will find the citation.

19           JUDGE WORTH: And while you're looking, I just wanted to ask you

20   to turn to petitioner's slide 32 and that's the part of the specification we were

21   just discussing.

22           It's Exhibit 1001 at column 28, lines 15 to 22. And so Metzger is

23   cited for at the end of the sentence talking about synthesis and then Kamal is

24   cited at the end of the sentence talking about removed chemically. And then

25   the following sentence says the chemical cleavage of the MOM and allyl

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1 groups is fairly mild and specific so as not to degrade the DNA template  
2 moiety.

3 So I just wanted to circle back because this seemed to be a key point  
4 about whether Kamal teaches mild conditions.

5 MR. MURNANE: Thank you, Your Honor. And this is I'm just  
6 going to, if I may, look at my patent. That's column 26.

7 JUDGE ANKENBRAND: I think it's 28.

8 MR. MURNANE: Oh, sorry.

9 JUDGE ANKENBRAND: Lines 15 to 22.

10 MR. MURNANE: 28. Thank you, Your Honor. Sometimes the  
11 context is helpful. Okay. If we go up a little bit, if we could, Zach, could  
12 you put that full paragraph on? The synthesis of nucleotide analogues? It  
13 starts I believe at line 9. Okay.

14 So here, you see this, the synthesis of nucleotide analogues and then  
15 its referring to Figure 9 and this is a synthesis paragraph here I believe. If  
16 we look at Figure 9 in the patent, in any of the patents you will see Figure 9.  
17 This is a synthesis slide.

18 So it's not -- he is not saying Kamal is teaching you SBS conditions.  
19 These are the synthesis conditions.

20 JUDGE WORTH: So the-- what you are saying is the context of the  
21 paragraph?

22 MR. MURNANE: Yes, Your Honor.

23 JUDGE WORTH: Is of synthesis.

24 MR. MURNANE: If you look at the whole paragraph. Figure 9 is  
25 referenced there and I believe it is synthesis related.

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1 JUDGE WORTH: Okay. And I know we have covered some of this  
2 ground already but can you respond to petitioner's argument that because the  
3 specification is enabling, this is petitioners' argument, therefore it's obvious  
4 that or that a person of ordinary skill would have had a reasonable  
5 expectation of putting together Kamal with Tsien?

6 MR. MURNANE: All right, thank you, Your Honor. No, we submit  
7 in the contrary. When one looks at the entirety of the prior art, all the prior  
8 art that has been cited and one looks at the entirety of the specification  
9 what's there, we incorporate it by reference in their entirety, the references  
10 he cited.

11 One sees that you don't have obviousness at all. Because firstly,  
12 they're saying that the claimed inventions are obvious because if you look at  
13 Tsien you use an allyl ether. As we pointed out here, Tsien is not telling you  
14 to take the particular allyl that Dr. Ju and his colleagues mentioned in the  
15 patent.

16 He has got a genus there and he also has the problems of Gigg and  
17 Warren which we have talked about. So you're not getting it out of Tsien in  
18 and of itself, okay.

19 Then we move to the next thing that is in the line, Metzger. You see  
20 in Metzger, the only place where someone tried the allyl and by the way as  
21 we saw Metzger calls it his novel compound.

22 JUDGE ANKENBRAND: Can I interrupt you for just a moment?

23 MR. MURNANE: Yes.

24 JUDGE ANKENBRAND: Because I think Mr. Zimmerman referred  
25 to Gigg and Warren and specifically the reference to the allyl ether which

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1 was compound L1 which is I believe the allyl ether that we are all talking  
2 about in this case. And it's on slide 9 of, yes, you have it up. Of petitioner's  
3 demonstratives.

4 MR. MURNANE: Thank you, Your Honor. And I'm looking at it.  
5 Its 9. And what is not highlighted there if we look at the second paragraph  
6 in the box on the left, we have shown that gamma substituted allyl ethers are  
7 eliminated to give dienes by treatment with potassium tert butoxide and  
8 dimethyl sulfoxide and this has been confirmed by others.

9 What is not highlighted the gamma substitute allyl ether. That's what  
10 you see in Gigg and Warren. In Gigg and Warren yes, you can always find  
11 in a bag of a million marbles, you can always pick one marble out. Okay.  
12 But here they've got a lot of allyl ethers --

13 JUDGE ANKENBRAND: Right. But I think the point of their  
14 argument was when Tsien says or allyl ethers what it means is when it cites  
15 Gigg and Warren, it's speaking about the allyl ether compound LI.

16 And you're saying -- are you saying well, look. When you actually  
17 look at Gigg and Warren it talks about three or four or a bunch of different  
18 kinds of allyl ethers so that's really not an argument that's stands up?

19 MR. MURNANE: Correct.

20 JUDGE ANKENBRAND: Okay.

21 MR. MURNANE: And Dr. -- as we say in our papers, Dr. Romesberg  
22 admitted that in deposition. That a genus is disclosed there. That it's not  
23 just the 2 propenyl.

24 JUDGE ANKENBRAND: You have a little less than a minute and a  
25 half remaining.



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1 MR. MURNANE: Okay. Thank you, Your Honor. So again, if  
2 incorporation efficiency is low and we certainly see that in Metzger, there is  
3 no motivation to pick the allyl in Metzger, in Tsien or anywhere else  
4 because Tsien's SBS required -- Tsien's SBS conditions require efficient  
5 incorporation.

6 And so -- and Stemple, we have bookends here if we look at our  
7 slides. We have a chart that goes from Tsien on the left to our invention on  
8 the right but right before our invention is Stemple and both of them are  
9 emphasizing and we have those slides which 72 and 73 show beautifully the  
10 problems if you don't have efficient incorporation.

11 Oh, I have some cites that I was asked to provide. Cites for  
12 explanation of termination and in resulting in out of phase sequencing.  
13 Exhibit 2116 starting at paragraph 31 Menchen explains a termination  
14 asterisk. Exhibit 2126, page 76 line 24 to page 77 lines 10, line 10. Dr.  
15 Romesberg admits that inefficient incorporation results in out of phase  
16 sequencing.

17 JUDGE ANKENBRAND: Okay. I believe you are out of time so  
18 thank you.

19 MR. MURNANE: Thank you, Your Honors.

20 JUDGE ANKENBRAND: Okay. I'm just going to check really  
21 quickly to make sure my colleagues don't have any other questions. I think  
22 that's a no. So --

23 JUDGE RANGE: No.

24 JUDGE ANKENBRAND: -- I just wanted to thank everybody for  
25 their time today. The case has now been submitted and it has been very

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1 helpful to us.

2 MR. MURNANE: Thank you, Your Honors.

3 JUDGE ANKENBRAND: Thank you again. You can sit down, we

4 might be up here for a few minutes.

5 (Whereupon, at 11:22 a.m., the oral hearing was concluded.)

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