

1 RECORD OF ORAL HEARING
2 UNITED STATES PATENT AND TRADEMARK OFFICE
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4 BEFORE THE PATENT TRIAL AND APPEAL BOARD
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7 INTELLIGENT BIO-SYSTEMS, INC.
8 Petitioner
9 v.
10 ILLUMINA CAMBRIDGE LIMITED
11 Patent Owner
12 - - - - -
13 Oral Hearing Held: Friday, October 10, 2014
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15 Case IPR2013-00517
16 Patent 7,566,537
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19 BEFORE: LORA M. GREEN, FRANCISCO C. PRATS, and
20 SCOTT E. KAMHOLZ, Administrative Patent Judges.
21
22 The above-entitled matter came on for hearing on
23 Friday, October 10, 2014, at 10:01 a.m., Hearing Room A, at
24 the U.S. Patent and Trademark Office, 600 Dulany Street,
25 Alexandria, Virginia.

Columbia Exhibit 2032
Illumina, Inc. v. The Trustees of Columbia
University in the City of New York
IPR2018-00322

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IPR2013-00517
Patent 7,566,537

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P R O C E E D I N G S

(10:01 a.m.)

JUDGE GREEN: Good morning. Welcome, everyone.
This is the final oral hearing for IPR2013-00517, which
involves Patent No. 7,566,537.

The Board instituted this Inter Partes Review on
February 13, 2014.

At this time we would like counsel to introduce
yourselves and your colleagues, starting with Petitioner.

MR. SEGAL: Good morning, Your Honors. Mark Segal
on behalf of Petitioner, Intelligent Bio-Systems.

With me is lead counsel, Scott Marty, and backup
counsel, Robert Baron.

JUDGE GREEN: Thank you. Patent Owner?

MR. ZIMMERMAN: Good morning, Your Honor. Bill
Zimmerman of Knobbe Martens Olson & Bear on behalf of Patent
Owner, Illumina Cambridge.

With me is my partner, Kerry Taylor; Jeff Costakos
of Foley & Lardner; lead counsel, Bo Lawler, of Reinhart
Boerner Van Deuren; and Marcus Burch, counsel at Illumina.

JUDGE GREEN: Thank you. Welcome to the Board,
everyone.

Consistent with our previous order, each party has
45 minutes to present their argument. Petitioner will
proceed first and present its case as to the challenged

1 claims. Petitioner may reserve rebuttal time for its case.

2 Thereafter, Patent Owner will respond to
3 Petitioner's case.

4 Counsel for Petitioner, if you would like to
5 begin. If you have copies of your demonstratives for the
6 Panel and for the Court Reporter and for the other side. I
7 don't know what you have already exchanged.

8 MR. SEGAL: I have given it to the Court Reporter
9 and the other side.

10 Good morning, Your Honor.

11 JUDGE GREEN: Thank you so much. And then would
12 you like to reserve rebuttal time?

13 MR. SEGAL: I would. I would like to reserve 10
14 minutes for rebuttal.

15 JUDGE GREEN: 10 minutes. Okay. Thank you very
16 much. And you may begin whenever you are ready.

17 MR. SEGAL: May it please the Board. This is a
18 very straightforward case. Petitioner has challenged claims
19 1 through 6 and 8 of the '537 patent, and the Board has
20 instituted on the grounds that either Ju or Tsien, in
21 combination with Zavgorodny, render the claims obvious.

22 Put up slide 2, please. This is the only
23 independent claim at issue. And I know Your Honors are
24 familiar with this technology. I just want to mention a few
25 things.

1 First, the claim is directed to a method of
2 labeling, as it only requires here the incorporation of one
3 nucleotide or nucleoside molecule.

4 The rest of the recitation of the claim is related
5 to the attributes of the nucleotide or nucleoside molecule,
6 all of which is really, for the majority, is not disputed
7 here.

8 The label attached to the base, the fact that it
9 has a protecting group, all of that is in the prior art,
10 including in Ju and Tsien.

11 The one limitation that is at issue is the
12 protecting group comprises an azido group. The issue here is
13 whether that would be obvious to use the Ju and Tsien method.

14 Go to the next slide. Again, the dependent
15 claims, the majority of the limitation elements are not at
16 issue. Only ones in claim 6, where it is more specific now,
17 that the protecting group is an azidomethyl group.

18 So this azidomethyl group is in the art. If you
19 go to the Zavgorodny slide, slide 7. So before the priority
20 date, the azidomethyl group was shown in the art to protect
21 the same exact position that Ju and Tsien need for protection
22 and also that the '537 patent claims.

23 The azidomethyl group is on the 3 prime oxygen of
24 a nucleoside molecule, just as in the claim and just as
25 required by Ju and Tsien's methods.

1 Now, not only is it disclosed by Zavgorodny but
2 Zavgorodny actually calls it out, something of special
3 interest, because it could be removed under very specific and
4 mild conditions.

5 Now, Zavgorodny's teaching is very consistent with
6 Ju and Tsien. Ju gives us preferred examples, two groups,
7 allyl and MOM, and when they are attached to the 3 prime
8 oxygen they form an ether connection. The same thing with
9 the azidomethyl group, it is an ether linkage there.

10 Ju also directs one of skill in the art to small
11 protecting groups. I don't believe there is a dispute from
12 Illumina that azidomethyl is considered a small protecting
13 group.

14 Now, with regard to Tsien, Tsien says the same
15 thing, ether groups are preferred. And Tsien goes even
16 further and actually suggests using azido chemistry. So if
17 you can put that up.

18 Here is Tsien describing his invention, and he
19 lists in the middle of this paragraph the azido group. Now,
20 Illumina would like you to believe you have to ignore that,
21 ignore that sentence there. That wouldn't teach a person of
22 skill in the art anything.

23 And they rely mostly on that. They rely on
24 testimony from our expert, where he was asked a very specific
25 question: Well, what does that sentence mean to you? They

1 didn't ask him the more important question in that
2 deposition, that whether or not that would actually suggest,
3 in light of the entire reference, as you are not supposed to
4 atomize the prior art, you are supposed to look at it as a
5 whole, whether that would teach someone of ordinary skill in
6 the art, suggest to them, hey, look at azido chemistry for a
7 possible protecting group.

8 The last sentence there, which is all consistent
9 with that idea, is that Tsien is referring to this Kraevskii
10 reference for the fact that these groups can be incorporated
11 by polymerase.

12 So we think it is very clear that Tsien would
13 direct someone to a reference such as Zavgorodny,
14 particularly as it is on the exact same position that Tsien
15 is teaching, you need a reversible protecting group.

16 Go to slide 10. Tsien goes another step further.
17 Tsien actually says, okay, where can you find these
18 protecting groups? Go to the literature involved in chemical
19 DNA synthesis. Well, that's exactly what Zavgorodny is
20 directed to.

21 Illumina's expert, Dr. Romesburg, testified that
22 Zavgorodny is directed to synthons for manufacturing
23 oligonucleotides, and that's exactly chemical DNA synthesis.

24 What's more, we asked an Illumina employee who is
25 also an inventor about this. If you go to that slide, slide

1 8. We asked: Okay. If you are looking for a protecting
2 group for sequencing by synthesis back then, and you are
3 aware of the Zavgorodny reference, would this be something
4 you would try? He said: Yes, I agree with you, yes, it
5 would be something to try.

6 So faced with this combination, what does Illumina
7 argue here? They have got really essentially two arguments
8 against the combination of Ju, Tsien and Zavgorodny.

9 One is that Ju through Canard teaches a person of
10 skill in the art away from using the azido group. And their
11 second one is, well, Zavgorodny's conditions that he listed
12 as examples there of the cleavage conditions, would not work,
13 would not work with Ju and Tsien's methods.

14 I would like to address each of those in turn.
15 With regard to the so-called Ju teaching away point -- go to
16 slide 11 -- Ju is talking about an ester group here.

17 He says: An ester group was explored to cap the 3
18 prime OH group, but was shown to be cleaved by the
19 nucleophiles in the active site in the DNA polymerase. And
20 he cites the Canard reference.

21 Well, Ju actually got it wrong because Canard
22 actually said esters do work. If you go to that slide, slide
23 12, and here is two Canard papers. The one that Illumina
24 cites to is the top one, the '95 paper, but they both were
25 testing the same types of nucleotides.

1 The '94 paper says, very clearly, these results
2 clearly indicate that the 3'-anthranyloyl-deoxy nucleotides
3 can be used as reversible chain terminators in a stable and
4 reproducible manner. So Canard actually shows that they do
5 work.

6 And just to be clear, if you go to the reference,
7 what he is using there as the modified nucleotide is from
8 figure 1, compound 1.

9 Consistent with that, if you go to the '95 paper,
10 Canard shows that ester groups work with certain polymerases.
11 This is a figure from there, from the '95 paper, and it shows
12 to the right that it works.

13 It gets incorporated and it gets terminated after
14 the addition of one nucleotide. That's with the Taq
15 polymerase.

16 Now, what Canard found is that with certain
17 polymerases he was finding what he called this premature
18 catalytic cleavage. But the teaching is very limited. He
19 does say esters do work, so there really is no teaching away
20 here.

21 So how does Illumina then get to the azido group?
22 If you look at the Ju statement, Ju says nothing about azido
23 groups. Ju says nothing about ether groups. In fact, Ju
24 gives as examples two ethers that work.

25 So if you go to slide 14. They pull a sentence

1 from Canard and where do they find it? It is at the very end
2 of Canard's paper. It is in his discussion section. It is
3 not in his results section. It is in his discussion section
4 where he is looking at his data with respect to esters and he
5 is speculating on how, you know, what explains the results
6 that he is seeing, and then he is applying it to the azido
7 group.

8 But all throughout the section, I urge you to read
9 this, it is very clear that it is purely speculation.

10 Illumina's expert agrees -- go to the next
11 slide -- there is no data. All the experts agree there is no
12 data, there was no data then, about the azido group reacting
13 with the polymerase, and there is no data now because people,
14 you know, didn't believe that.

15 And then actually Romesburg said he would actually
16 be suspicious of that, suspicious of that. Now, that is his
17 understanding today before Illumina jumped on that. That is
18 his understanding today.

19 So just to be certain we asked him about that in
20 2002. You figure he would come out definitively. I mean,
21 this is their whole case here. He couldn't. He couldn't
22 make a definitive statement. He made four qualifications in
23 one sentence: I think. I assume. I assume. Could.

24 Their own expert couldn't come out strongly on
25 that position because, again, the evidence shows, and if you

1 look at Dr. Metzker's declaration, it is clear that one of
2 skill in the art wouldn't believe it would react.

3 Now, if we can actually go to Canard's statement,
4 slide 16, I believe, here is what Illumina relies on in
5 conjunction with the Ju reference to argue a teaching away.

6 Now, they actually used the sentence beginning
7 "strikingly," but we added a more fuller citation here with
8 the first sentence, which also makes clear that this is
9 speculation. He says may also receive a nucleophilic attack.

10 What he also says, and Illumina doesn't really
11 point out, is that it is the position, it is the position of
12 the central nitrogen, which he say has a partial positive
13 charge, and it is in the same position as a carbonyl group.

14 His hypothesis is that the nucleophiles in the
15 enzyme attack the carbonyl group because it is at that
16 position from the 3 prime end of the DNA. And he says, well,
17 because you have a central nitrogen on the azido group, you
18 are going to get the same attack.

19 Well, it doesn't apply to azidomethyl group. If
20 you go to the next slide, I believe. 17 first. I mean,
21 Romesburg agrees, the top quotation we have in there, that it
22 is the position of the carbonyl groups. He says it can
23 attack these carbonyl groups -- he is talking about the
24 enzyme -- because they are in this position.

25 Go to the next slide. And we drew these

1 structures just so you can help visualize this issue. And
2 they are abstracted out, so we used our groups. We used our
3 group here. The first one, Canard tested an ester group.
4 There is the ester linked with the carbonyl. He says the
5 carbonyl receives a nucleophilic receives an attack.

6 Canard speculates with regard to azido. You can
7 see that the central nitrogen is in the same position as the
8 carbonyl.

9 However, with an azidomethyl group, it is going to
10 be two atoms further. That's because it is an ether
11 connection. It is not an ester connection. We have an ether
12 connection. When you attach azidomethyl to a 3 prime oxygen
13 you get an ether connection, just as Ju and Tsien say these
14 are the kind of groups you should use.

15 If you go back to slide 17, why is this important?
16 Because in an enzyme environment, short distances can be very
17 important. Dr. Romesburg testified three atoms, linear.
18 That's a lot of space moving that over. And here we have two
19 atoms but we submit that's still a lot of space.

20 Now, I would like to address their other argument,
21 that Zavgorodny's cleavage conditions would render it
22 inoperable and, thus, really teach away from the azidomethyl
23 group.

24 First, they misunderstand our argument. Our
25 petition is not a combination of Ju, Tsien, with Zavgorodny's

1 cleavage conditions. It is a combination with the
2 azidomethyl protecting group. We don't need the cleavage
3 conditions. The claims don't specify any cleavage
4 conditions.

5 One of skill in the art would be able through
6 routine experimentation develop cleavage conditions that
7 would be efficient enough and work with Ju and Tsien's
8 processes.

9 JUDGE GREEN: Do you have evidence of that in the
10 record, that that is the level of ordinary skill in the art?

11 MR. SEGAL: We do. We do have that in the record.

12 Actually Illumina itself says that. If we go to
13 the next slide, 21. This is from the '026 patent. This was
14 an issue in the '026 patent IPR, in the final decision, and
15 you see that quote there, that's from the '026 patent but it
16 is the same exact specification as we have here.

17 The last sentence: The process used to obtain the
18 3' OH group can be any suitable chemical or enzymic reaction.

19 And this was an issue in that decision, the '026
20 patent. And what the Board found, yes, we agree with
21 Illumina here. This is what they are saying, you know, in
22 order to obtain their patent and to argue that their patent
23 is enabled. It is conventional. It is conventional to one
24 of ordinary skill in the art to come up with cleavage
25 conditions.

1 JUDGE PRATS: If I could interject. You are
2 looking at their own specification. Aren't you piecing
3 together the invention from the specification in that
4 instance?

5 MR. SEGAL: No, we are not. We are just pointing
6 out how they have been inconsistent. Now when they are
7 arguing that patentability over a combination of reference,
8 you know, no one would be able to come up with these cleavage
9 conditions to get it right.

10 Well, they said something different to the Patent
11 Office. And our expert testified that it would be routine to
12 develop these cleavage conditions. And, I mean, it is really
13 standard stuff, you know, undergraduate organic chemistry
14 textbooks.

15 If you want to go to the next slide, here is the
16 textbook. It is really a simple proposition, we don't even
17 think you need one, but it is in textbooks that you vary
18 things, vary the reagents, vary the conditions to achieve,
19 you know, what you are looking for for your process to
20 improve efficiency, if needed.

21 JUDGE PRATS: Right, but ultimately your starting
22 point is Zavgorodny, correct?

23 MR. SEGAL: Ultimately our starting point is Ju in
24 combination with Zavgorodny, that's correct.

25 JUDGE PRATS: Correct. So then the only cleavage

1 conditions we know about are those specified by Zavgorodny,
2 correct?

3 MR. SEGAL: Illumina also specifies cleavage
4 conditions. Their expert has testified that there are other
5 cleavage conditions, and I can give you that cite.

6 We have also put in the record that there was
7 aqueous cleavage conditions known, in particular a reagent
8 called TCEP. That's in the record also.

9 So we think this is really dispositive here, that
10 we are not of their argument that you can't use Zavgorodny's
11 conditions, because one of skill in the art would be able to
12 design such conditions.

13 Now, they spend most of their Patent Owner
14 response arguing that Zavgorodny's specific conditions aren't
15 efficient enough to denature the DNA. So we felt compelled
16 to respond to that, and we have in our reply brief, and I
17 would like to say a few things about that today.

18 Zavgorodny's conditions, using a phosphine reagent
19 to cleave the azidomethyl group involved the Staudinger
20 reaction. That reaction has been around since 1919. It is a
21 very well-know reaction, known to be extremely efficient.

22 If you go to slide 23, there is stuff in the
23 record that it is quantitative, this type of reaction. That
24 first one is from Knouzi, which is the reference that
25 Illumina cites to for this reduction.

1 Also, in another exhibit, this is the Mag and
2 Engels exhibit, Exhibit 1041, which is following up on some
3 of the research in a reference that Illumina uses, the
4 Mungall exhibit, again, it identifies quantitative.

5 Now, this is the first step in the process. There
6 is a reduction of the azide group to an amine, which you then
7 end up with a methoxyamine, and then you hydrolyze that and
8 you remove the group to get the hydroxyl group.

9 Illumina has said this would happen extremely
10 rapidly. It is a very unstable group at that point. And our
11 expert has also testified to that effect.

12 JUDGE PRATS: I saw this slide. I'm wondering how
13 this slide squares with the 60 to 80 percent cleavage rate
14 that you get in Illumina?

15 MR. SEGAL: Well --

16 JUDGE PRATS: Do you see what I am saying? On the
17 one hand, is it saying quantitatively Illumina says, well,
18 ultimately cleavage is only 68 percent. I think one of the
19 experiments had 95. But I am just trying to square what you
20 are arguing with what Illumina says.

21 MR. SEGAL: That's a good question. The answer
22 is, is that Illumina is really relying on the wrong metric.
23 They rely on isolated product yields, which is going to
24 involve the purification of the product.

25 Their references are in solution. And the authors

1 in those references, they are organic synthesis references.
2 They are going to want to run the reaction using various
3 substrates and purify the final product.

4 So that involved a purification procedure, and you
5 are not going to necessarily get the super high yields, nor
6 are they necessarily motivated to get 100 percent yields
7 there.

8 You know, again, the organic chemistry textbook
9 which is well known, Vogel, points this out. The GLC yields,
10 which is a liquid chromatography, which will measure the
11 actual reaction efficiency, you don't need to purify using
12 that method, it is going to be greater than isolated yields
13 and often by a very significant amount.

14 So that's how you square that between what they
15 are looking at, isolated product yields, and what some of the
16 other references say, quantitative. Even that Mag and Engels
17 one, though, was able to get even the isolated product yields
18 very high. I believe that was their statement there.

19 And Illumina knows that that is really, if you are
20 going to measure for SBS, that's the system you are going to
21 use. Because an SBS, you don't have to worry about purifying
22 the final product.

23 Both Ju, Tsien and the '537 patent, they attach it
24 to a solid surface in an array pattern. That's how they do
25 the sequencing. You can just wash your cleavage agent in.

1 And you wash it and you flush it away. So you have it there.
2 You are not worried about a complex purification procedure.
3 That's why those isolated yields really aren't proper or
4 really aren't a proper metric here.

5 Illumina, like I said, Illumina itself knows this.
6 Just to note, in their unexpected results, the laboratory
7 notebooks, when they are measuring the efficiency of their
8 reactions, they use a method that measures the intrinsic
9 efficiency. They don't use a method where they actually have
10 to purify the final product.

11 So I think it is very telling that in certain
12 situations, when they want a high number, they use a method
13 that measures the intrinsic efficiency, but when they want to
14 show low numbers they use methods that rely on purifying the
15 product, like isolated yields.

16 The other issue with why it is different in
17 sequencing than the references that they rely on is that the
18 stoichiometry could be quite different.

19 In the references that Illumina is relying on, the
20 references are generally about molar equivalent, you can look
21 at the experimental section, or they use a slight excess,
22 because they have got to purify their final product from the
23 reagents. You are not going to want to use a thousand fold
24 over that.

25 But sequencing by synthesis, again, you can throw

1 as much reagent in there as you want. You are going to get a
2 more efficient reaction and you are going to get a quicker
3 reaction.

4 And, again, if you look at what Illumina is
5 relying on in their unexpected results, you look at what they
6 are using -- it is confidential so I won't mention it -- but
7 they are not relying on one-to-one equivalence. They are
8 much higher, much, much higher.

9 I want to say a few things about the denaturation
10 issue that they raised. Again, we don't think one of skill
11 in the art would be limited to just Zavgorodny's conditions.
12 There are other conditions that were known out there,
13 including an aqueous reagent, phosphine reagent, which
14 according to them, if you avoid that organic solvent, then
15 you would avoid that issue.

16 But we also don't believe that it actually would
17 denature, Zavgorodny's conditions would denature. They rely
18 on two references: A Li reference and a Kit reference. The
19 Li reference is not even directed to denaturation itself. A
20 supercoiling reference.

21 We pointed that out in our reply. Dr. Metzker
22 pointed that out. And they never even bothered
23 cross-examining on him. I don't know. I believe they
24 probably concede that point now.

25 With regard to Kit, they rely on a single sentence

1 in Kit. If you go up to the Kit reference, slide 19, I
2 think, and that's all there is. There really is no analysis
3 by their expert, if you look at their declaration, Dr.
4 Romesburg's declaration. He says, well, Kit says these
5 reagents are especially effective at denaturing. So that's
6 it. Everyone would know that. We are done.

7 With respect to Kit, for this statement, Kit cites
8 to this Gordon abstract. Dr. Romesburg said, he testified
9 that he did look at the Gordon abstract.

10 But what he didn't do, he didn't look to see if
11 there was a follow-up paper that actually explained the
12 testing here, Levine's testing. And what Levine did, his
13 results were all at high very high temperature conditions.

14 You can go to the next slide. So you can't
15 necessarily take from Levine that pyridine would denature at
16 room temperature. His assay involved heating the solution to
17 73 degrees, which is greater than 50 degrees more than
18 Zavgorodny's conditions.

19 So what he is testing there is how much of these
20 various agents are going to denature at the 50 percent at 73
21 degrees. So we don't think it really says anything about
22 room temperature.

23 Dr. Metzker actually did a more thorough analysis.
24 He looked at things like temperature and he looked at things
25 like pH and he discusses this. So you can compare Dr.

1 Metzker's analysis with Illumina's Dr. Romesburg's analysis
2 and you can come to the conclusion that it wouldn't denature.
3 One of skill in the art wouldn't think about denaturing.

4 People use phenol, for instance, in methods to
5 extract DNA all the time. It is a relatively high
6 concentration. And it is shaking in particular so that the
7 phenol comes in contact with the DNA. People don't use that
8 method if it would denature DNA. So, again, that indicates
9 that at room temperature you are not looking at necessarily
10 denaturation.

11 Another important point is that, if there was a
12 denaturation problem, Ju addresses it. Ju addresses the
13 issue by in one of his embodiments he suggests using a
14 hairpin primer. So it loops around from the template and is
15 directly attached by covalent bonds to the template.

16 Why does Ju use it? He says it solves a problem
17 of washing off the primer. Again, so there was a
18 denaturation issue. It would come -- it would reanneal
19 before the next step, before you wash in your polymerase.

20 It is also interesting to note that, if you look
21 at Ju's conditions that he suggests, and the Kamal and
22 Ireland reference for cleaving the allyl and MOM group, those
23 conditions use azidonitride, which, again, is an organic
24 solvent.

25 Ju is suggesting them so obviously Ju doesn't

1 believe that organic solvents denature. That's what he has
2 in his paper. Again, either because he doesn't believe they
3 are going to denature or he has a solution for that issue.

4 In the few minutes left I would like to discuss a
5 little bit about Illumina's secondary consideration. They
6 fail for a number of reasons.

7 One, Illumina has failed to show the required
8 nexus. They have to show that their secondary
9 considerations, their evidence of that, is tied to the
10 selection of the azido protecting group. They haven't done
11 that.

12 And I think as a good example of that is their
13 reliance on the Bentley Nature paper, exhibit -- or slide 29.
14 They rely on this on both praise and unexpected results.

15 And what is clear from this paper, there is a lot
16 of factors that go into sequencing, a lot. We just listed
17 some of them here: The selection of a polymerase, an
18 engineered polymerase here. A cleavage agent, particular
19 cleavage agent. Using clusters. Using algorithms to define
20 the base. And sophisticated imagers.

21 I mean, none of these things are in their claims.
22 They can't tie it specifically to the selection of the azido
23 protecting group.

24 The same thing with some of their copying
25 arguments. They argue that Ju and IBS copied a link or

1 copied a cleavage agent. That's completely irrelevant here.

2 That's not in their claims.

3 The next point is Illumina has failed to show that
4 the evidence is commensurate in scope with the claims. This
5 could probably be easily seen in their unexpected results
6 argument.

7 They give one cleavage condition and show the
8 results from one experiment, which is obviously done in one
9 particular concentration of reagent, one particular type of
10 reagent. Just the azidomethyl. They don't try any other
11 kind of azido containing groups. One pH. One temperature.
12 Obviously the claims are much broader than that.

13 So it is not commensurate in scope, and they
14 haven't given any reason why one of skill in the art would
15 believe it would cover all of the variations within that
16 claim.

17 JUDGE GREEN: Now, would you expect the chemistry
18 to differ that much if you go from a 2 prime to a 3 prime
19 oxygen, because their claims encompass the protecting group
20 is attached via the 2 prime or 3 prime oxygen atom.

21 It seems like everything we are talking about is
22 the 3 prime. I'm just kind of curious, what would the 2
23 prime -- what do you think the 2 prime would do if you
24 starting attaching your protecting group to the 2 prime
25 group?

1 MR. SEGAL: I'm actually very curious about that,
2 too. They haven't -- I'm not aware of anything in the record
3 that discussed attaching the protecting group in the 2 prime
4 position. Certainly Illumina actually hasn't shown any
5 examples in its patent specification.

6 I would expect that the cleavage efficiency would
7 be the same at that position, but there is really nothing to
8 know. I don't know if they believe they have shown that, you
9 know, that embodiment is really enabled by their claims.

10 With respect to their long felt need, they define
11 the long felt need, if you look in their papers, and both
12 their experts say this, the long felt need is for a fast and
13 efficient sequencing system. They say this repeatedly
14 throughout that section.

15 Well, again, the claims aren't directed to a
16 sequencing system. They are directed to a method of labeling
17 requiring at most one incorporation. So, again, they are
18 very narrowly defining their long felt need so they can argue
19 that, you know, azidomethyl would solve this.

20 JUDGE GREEN: But to a certain extent the art
21 that's being relied upon is all sequencing by synthesis,
22 i.e., so to a certain extent that's kind of the environment
23 that we are working in because that's what the challenges are
24 based on.

25 MR. SEGAL: Well, with respect to secondary

1 considerations, certainly you have to look at the scope of
2 the claim. And their claim, it's not limited to sequencing.

3 They had an opportunity to limit it to sequencing,
4 though I think there was a restriction requirement in this
5 case, they went with a method of labeling requirement.

6 They could write a claim to sequencing but they
7 haven't. See, they are trying to use evidence that goes to a
8 very narrow embodiment to get the broader embodiment, and it
9 is just, it is improper.

10 Third, with respect to their secondary
11 considerations, they rely on expert testimony of Dr. Burgess,
12 which is improper. I know we have raised this issue once
13 before with the Board on a phone call.

14 He doesn't have any particular expertise to read
15 e-mails. That's essentially all he does. Illumina's
16 attorneys give him selected e-mails from Columbia University
17 or from IBS, and he reads them into his declaration and then
18 he draws conclusions from them.

19 I mean, I'm sure you could judge for yourself that
20 it doesn't require any kind of expertise or organometallic
21 chemistry or whatever his Ph.D. is in. It is just really
22 attorney argument.

23 And why do they put it in Dr. Burgess'
24 declaration? Well, it gives them an end to run around the
25 page limitations. So it forced us to have to respond not

1 only to their 60 pages in the Patent Owner response, but
2 another 30 pages in Dr. Burgess' declaration. That is really
3 improper.

4 And another reason they do that is they also -- to
5 get in inadmissible hearsay. A vast majority of the
6 documents that Dr. Burgess relies on are from Dr. Ju's lab.
7 And Dr. Ju is not speaking on behalf of my client. So they
8 are inadmissible hearsay.

9 JUDGE GREEN: You have about four minutes left of
10 your 35.

11 MR. SEGAL: I just want to say one thing about
12 their copying argument. Their copying argument, again,
13 largely relies on these inadmissible hearsay statements.

14 But what they also found out, they say, well, Dr.
15 Ju switched over to azidomethyl when they learned of, you
16 know, when they learned of Illumina's methods.

17 Well, if you look at all those things on their
18 slide, that they have on their last slide, all of the theses
19 and the papers of Dr. Ju, they all acknowledge that
20 Zavgorodny was the one who developed the azidomethyl
21 protective group.

22 What you also have to look at is what Dr. Ju was
23 doing with that azidomethyl protective group. In almost all
24 of the papers there he is using it differently than Illumina
25 is using it.

1 Illumina is using it obviously with -- as a
2 protecting group along with a label, cleavable label attached
3 to the base.

4 Dr. Ju is using it as a hybrid method, if you want
5 to go to that slide, and here is one of his papers. It is
6 Exhibit 2058. And it is a hybrid method between the Sanger
7 method and a sequencing by synthesis method where he is using
8 the azidomethyl on unlabeled nucleotides. And he is using
9 dideoxynucleotides with the label.

10 So there is no copying here. It is not tied in.
11 There is no nexus to the claims.

12 So if there are no further questions --

13 JUDGE PRATS: Yeah, I have a question. Does
14 Petitioner dispute that the azidomethyl is better than the
15 allyl?

16 MR. SEGAL: We do dispute that. The allyl was
17 able to get 30 base pairs sequencing. Dr. Ju showed that.

18 JUDGE PRATS: You just mentioned Patent Owner's
19 last slide. It does seem to show that once this got out, for
20 lack of a better way of saying it, that everybody started
21 using the azidomethyl.

22 MR. SEGAL: Well, I don't think -- I mean, what we
23 have in the record is just Columbia and IBS. I don't think
24 everyone actually is using azidomethyl. IBS has tested other
25 protecting groups. And in certain situations azidomethyl may

1 be better than the allyl group.

2 But, again, as defined by these claims, it only
3 requires a single incorporation. I mean, the allyl certainly
4 met that standard.

5 Any further questions?

6 JUDGE GREEN: No. Thank you.

7 JUDGE PRATS: Thank you.

8 JUDGE GREEN: Counsel for Patent Owner, when you
9 are ready. Did you have copies of your demonstratives?

10 MR. ZIMMERMAN: I do, Your Honor.

11 JUDGE GREEN: And you have 45 minutes, whenever
12 you are ready to begin.

13 MR. ZIMMERMAN: Good morning, Your Honor. I'm
14 going to save my last five minutes for Mr. Costakos from
15 Foley & Lardner.

16 There are some documents that are subject to a
17 District Court protective order. We're not going to go into
18 the confidential nature of them, but he is going to discuss
19 them, and I have not seen those documents, so he is going to
20 do the last five minutes on this.

21 JUDGE GREEN: But you do understand that whatever
22 has been put in the record under seal, if we use it in the
23 final decision there is a possibility that it will become
24 public?

25 MR. ZIMMERMAN: Yes, Your Honor.

1 JUDGE GREEN: Okay. I just want to make sure that
2 you are comfortable with that?

3 MR. ZIMMERMAN: Yes.

4 JUDGE GREEN: Because if we decide this on
5 unexpected results, we may end up discussing some of that
6 data.

7 MR. ZIMMERMAN: Yes.

8 JUDGE GREEN: Okay.

9 MR. ZIMMERMAN: IBS bears the burden of proving
10 that claims 1 through 6 and 8 would have been obvious. And
11 Illumina submits that they haven't met that burden.

12 The evidence shows that one of skill in the art
13 would not have been motivated or have expected to succeed in
14 combining Zavgorodny's azidomethyl ether with Ju and Tsien's
15 SBS methods.

16 And I want to make sure that we are all on the
17 same page. Throughout their briefing the combination that
18 they presented was Ju or Tsien in combination with Zavgorodny
19 for no purpose other than SBS. They repeatedly referred to
20 Ju and Tsien as SBS references.

21 And if you will look at slide 3, the only
22 motivation that they presented in their petition was to
23 improve the efficiency, reliability and robustness of Tsien
24 and Ju's SBS methods.

25 So for purposes of looking at would one of skill

1 in the art have put these combinations together, this IPR
2 focuses solely on sequencing by synthesis.

3 Now, turning to the basis on which the Board
4 instituted trial, I would like to deal first with an issue
5 regarding the Tsien reference. In granting trial the Board
6 said that Tsien discloses an azido containing protecting
7 group. And this was based on the quote in slide 4.

8 JUDGE GREEN: Just a question. Was there a
9 problem that you can't get your slides up?

10 MR. ZIMMERMAN: No, I have got them in the book.
11 They are numbered.

12 JUDGE GREEN: No, no, I mean, we have a lot of
13 people who are here. I'm just wondering if they could also
14 follow along.

15 MR. ZIMMERMAN: I actually didn't bring copies on
16 computer. I normally just do them with the books.

17 JUDGE GREEN: Okay. Thank you. Just for the
18 future, because we are open to the public, I would prefer
19 that we could also share it with everybody else in the
20 hearing room only because that way they can follow along with
21 the argument a little bit better.

22 MR. ZIMMERMAN: Not a problem. Thank you, Your
23 Honor.

24 So looking at slide 4 is the quotation from Tsien
25 on which IBS bases the argument that Tsien discloses an

1 azide. But the evidence shows that that azide group can't be
2 removed or modified to expose a 3 prime OH.

3 If you look at slide 5, Dr. Branchaud admitted
4 that Tsien's N3 group is directly bound to the 3 prime carbon
5 and would not generate a 3 prime hydroxyl group. This is
6 Exhibit 1081 at page 101.

7 But his testimony in that deposition went further.
8 He testified that there are a number of blocking groups in
9 Tsien that can't be removed to generate a 3 prime hydroxyl
10 group.

11 He identified the fluoride, the amide, the amine
12 and the NHCOCH₃ group as all being groups that don't
13 regenerate a 3 prime hydroxy, and he admitted that this was
14 commonplace, that it was known in the art that there were
15 groups that incorporated but could not be removed to generate
16 a 3 prime hydroxyl group.

17 And that's completely consistent with Tsien's
18 citation to Kraevskii. Kraevskii specifically names these
19 compounds, shows that the 3 prime group is bound directly to
20 the carbon, and they are not removable to generate a 3 prime
21 hydroxyl group. And Dr. Romesburg explains this in
22 paragraphs 37 through 39 of his declaration.

23 And tellingly, when asked, go ahead and identify
24 the 3 prime azide protecting groups at the time of Tsien that
25 were known, that could be removed to generate a 3 prime OH,

1 Dr. Branchaud said he wasn't aware of any. And it is Exhibit
2 2055 at page 32, lines 15 through 18.

3 So the evidence clearly shows that Tsien does not
4 teach a removable prime protecting group that is an azide.
5 It teaches an azide that can only be used as an irreversible
6 terminator. It can't be used for sequencing by synthesis.

7 Even more tellingly, if you look at where it is in
8 the Tsien reference, on page 20 and 21 of the Tsien reference
9 there is a section labeled Blocking Groups and Methods For
10 Incorporation. He cites to the amine group and the other
11 groups to show that they could be incorporated. He doesn't
12 cite to them in that section to say they can be deblocked.

13 Indeed, pages 23 and 24 of Tsien deal with groups
14 that can be deblocked, and you will notice the azide group is
15 omitted from that section.

16 Now, moving on to Ju and Tsien, each of them teach
17 very particular requirements for their SBS methods. Slide 6
18 shows the requirements of Tsien's method and slide 7 shows
19 what Ju refers to as fundamental requirements.

20 IBS has not disputed that Ju and Tsien state these
21 requirements and that they are relevant. In their reply they
22 didn't fight that these are the relevant requirements of
23 these references. And one of skill in the art would not have
24 been motivated to combine Zavgorodny's azidomethyl group with
25 either of Ju or Tsien's method because it wouldn't have been

1 expected to meet the stated criteria.

2 If you look at the first criteria of Tsien, it is
3 the ability to accurately and efficiently incorporate the
4 dNTPs. One of skill in the art wouldn't have expected that
5 because the electrophilic characteristics of an azido group
6 would react with strong nucleophiles in the polymerase active
7 site, and because other groups, other 3 prime groups have
8 been shown to interfere with incorporation.

9 This is the warning we get from Ju and it is shown
10 on slide 8 where Ju indicates that chemical groups with
11 electrophiles such as ketone groups are not suitable for
12 protecting the 3 prime OH of the nucleotide in enzymatic
13 reactions due to the existence of strong nucleophiles in the
14 polymerase. And this is based on Canard.

15 Now, IBS has gone through a long recitation of
16 Canard. They go through his '94 paper. They go through his
17 '95 paper. They mine it for data. They say a person of
18 skill in the art would have understood Canard a particular
19 way and that Ju was limited to esters and ketones. They do
20 everything they can to cabin in those warnings.

21 I would urge the Panel to look at what Ju said in
22 his specification at a time when there was no IPR hearing and
23 no litigation. Ju was a person of skill in the art. He was
24 a person who founded IBS.

25 And when you look at what he said, he looked at

1 Canard and said don't use electrophiles. He didn't say don't
2 use groups that have electrophiles at particular places. He
3 didn't say don't use esters but other electrophilic groups
4 are okay.

5 Ju read this information, processed it based on
6 the knowledge of one of skill in the art, and said don't use
7 electrophiles. The teaching is clear.

8 And the evidence in this case overwhelmingly shows
9 that one of skill in the art would have understood an azido
10 group to have the electrophilic characteristics that are
11 expressly prohibited in Ju's SBS method.

12 And I will point you to Exhibit 2011. It is
13 paragraph 31 of the Romesburg declaration, and Exhibit 2141,
14 pages 5 and 10, which show the positive charge on the central
15 atom of an azide group, as well as Exhibits 1032 and 2140.

16 Now, in its original petition, IBS didn't express
17 Ju's explicit warning at all. It was only on reply. And as
18 I said, what they tried to do is dismiss it as it is limited
19 to a ketone. And that's not what Ju says.

20 And then they say the Canard papers, if you read
21 them, actually show incorporation of electrophilic groups.
22 That's not what the Canard paper showed.

23 In 1994 Canard looked at this and said these might
24 be groups that give you incorporation. And then in '95 in
25 his second paper he shows that electrophiles can lead to

1 premature de-protection, and it is dependent on the template
2 and the conditions. Some do. Some don't.

3 But he doesn't provide you any guidance as to
4 which ones will and which ones won't, and how you prevent
5 this premature de-protection problem.

6 Ju was aware of that. He was one of skill in the
7 art. He read the papers. And his take-away as a skilled
8 artisan is don't use 3 prime protecting groups that are
9 electrophiles. This clearly teaches against the combination
10 of either Ju or Tsien with Zavgorodny.

11 Now, IBS also argues that incorporation is
12 polymerase dependent, and that would have been within one of
13 skill in the art, and that the warning of Ju doesn't apply to
14 all polymerases.

15 Again, that's not what the Ju reference taught.
16 If you look at Exhibit 2154, pages 59 through 61, it is their
17 expert, Dr. Metzker, admitting that Ju's warning is not
18 limited to a particular polymerase.

19 Ju is not saying use electrophiles with certain
20 polymerases. Ju is saying don't use electrophiles, and it is
21 not polymerase dependent.

22 Now, turning to the second criteria of Tsien, it
23 is the ability of mild conditions for rapid and quantitative
24 de-blocking. The parties agree that whether conditions are
25 mild depends on context.

1 And if you look at slide 13, it shows Dr.
2 Branchaud's admission that what might be mild for one context
3 isn't mild for another. And here the only context we are
4 looking at is the SBS methods of Ju and Tsien, and whether
5 the conditions specified in Zavgorodny are mild in those
6 conditions. And they weren't.

7 Canard's '94 paper, Exhibit 2043, expressly
8 states: We reasoned that ether bonds would be hard to cleave
9 under mild conditions compatible with DNA chemical stability.

10 So even in '94 there was a hint that the
11 conditions needed to cleave an ether weren't going to work in
12 DNA synthesis.

13 So what does IBS give you in this -- as evidence
14 in this? They didn't address it in their petition at all.
15 They didn't tell you, here is why the conditions would be
16 rapid, here is why Zavgorodny's conditions would be
17 quantitative. And they wouldn't be.

18 First of all, the conditions would denature DNA.
19 If you look at slide 11, Zavgorodny's removal conditions are
20 triphenylphosphine in aqueous pyridine. And they are very
21 particular conditions. And those conditions would have been
22 known to denature DNA.

23 If you look at slide 15, which is the Kit
24 reference, Exhibit 2018, it expressly teaches that pyridine
25 is an especially effective DNA denaturant.

1 Now, there was some discussion that you would pick
2 a different organic solvent. The Li reference, Exhibit 2021,
3 expressly teaches that other organic co-solvents denature
4 DNA.

5 And while it refers to unwinding of the DNA
6 duplex, Kit teaches -- and as shown in slide 14 -- that this
7 unwinding -- and it is in parentheses, and I believe it is
8 the second line down -- is denaturation. So Li, while it
9 talks about unwinding, teaches the same denaturation taught
10 in Kit.

11 So we have this problem that the organic solvents
12 are going to denature DNA. When questioned about this in his
13 deposition, Dr. Branchaud testified that he didn't know
14 whether pyridine and other organic solvents denatured DNA.
15 It is Exhibit 2039 at page 113.

16 So IBS had to bring in another expert to address
17 the denaturation issue, and that's Dr. Metzker. And Dr.
18 Metzker's own patent application, which is Exhibit 2143 at
19 paragraph 75, states: Hydrophobic solvents will disrupt
20 interactions between the hydrophobic bases, thus denaturing
21 DNA.

22 So even their own expert in his pre IPR
23 applications, admitted that it was known that these type of
24 solvents cause a problem.

25 Moreover, Exhibit 1035, which is one that they

1 rely on for efficiency, teaches that when you react an azide
2 with a phosphine, it produces an amine that cleaves the
3 phosphate ester backbones of DNA. And so the specific
4 conditions of Zavgorodny wouldn't work with Ju or Tsien's
5 methods.

6 Now, their retort is that Levine, Exhibit 1048,
7 shows that denaturation only occurs at high temperature.

8 IBS misunderstands what Levine did. Levine was
9 trying to determine a ranking of denaturants. And the
10 experiment was designed with a particular DNA and particular
11 conditions, including temperature, so that small changes in
12 concentration of solvent would lead to large changes in
13 denaturation, and you would get the curves that he saw.

14 But the experiment is designed to rank things and
15 give you these curves. It wasn't designed to test whether
16 other temperatures denatured DNA. And that's Exhibit 1048 at
17 page 169, left-hand column, bottom paragraph.

18 Now, the question remains: Would you get
19 denaturation at 25 degrees? Well, the Kit references
20 expressly teaches that many organic solvents denature DNA at
21 25 degrees C.

22 But there is more. The very reference IBS relies
23 on, the Levine reference, did the ranking and said here is
24 the ranking of denaturants. And it ranked pyridine as a
25 better denaturant, meaning a stronger denaturant, than

1 formamide, methanol, ethylene glycol, and dimethyl formamide.

2 Hanlon, Exhibit 2142, then tested formamide,
3 methanol, ethylene glycol, and dimethyl formamide at 25
4 degrees C and they all showed denaturation. And their very
5 own references, pyridine is an even better denaturant. So
6 +it, too, would denature DNA at 25 degrees C.

7 Now we get to the question of would Zavgorodny's
8 cleavage conditions have been rapid or quantitated? IBS
9 didn't provide any empirical data in its petition and they
10 haven't even offered testimony on what removal efficiency you
11 need.

12 But the evidence shows that, first of all, the
13 reaction with the azidomethyl wouldn't proceed rapidly. It
14 would take between three and 72 hours. This is paragraph 50
15 and 53 of Romesburg's declaration. And that's just not a
16 sufficient time frame for the methods of Ju and Tsien.

17 And then we get to what would the yields be? And
18 the prior art shows that you would get yields that were
19 highly variable and unpredictable and as low as 50 percent.

20 If you look at the Loubinoux reference, which is
21 shown in slide 12, it is the most relevant evidence on the
22 point, and it reports 60 to 80 percent removal efficiency of
23 an azidomethyl group from phenyl derivatives using
24 triphenylphosphine at 25 degrees C.

25 And it states that, regardless of the reduction

1 method used, the products are obtained as pure products at
2 yields between 60 and 80 percent.

3 Now, if you look at the methods that were used,
4 the triphenylphosphine is at the lower end of that range, and
5 the other methods that got higher results are not compatible
6 with DNA synthesis.

7 Now, one of skill in the art would have expected
8 Zavgorodny's aliphatic azidomethyl group to be removed with
9 an even lower efficiency than what you see in Loubinoux
10 because phenolic ethers are generally more easily cleaved.
11 And that's Romesburg, paragraph 48. And Dr. Branchaud
12 admitted this in his deposition at Exhibit 2039, pages 166
13 through 68, and page 140.

14 Now, IBS first asserts that, well, these are pure
15 product yields so we can't look at them. And they rely on a
16 general chemistry textbook from Vogel. And Vogel says that
17 70 percent may be good enough. 80 percent may be good
18 enough. Not in the context of Ju and Tsien.

19 What they are ignoring here are these are
20 sequencing by synthesis methods, and 60, 70, 80 percent isn't
21 going to get you there. The testimony is that you need to be
22 closer to 98, 98 and a half.

23 When you look at what Ju teaches, he is talking
24 about sequencing 100 base pairs. He denigrates prior art
25 that did 30 base pairs. In order to get to that level of

1 sequencing by synthesis, you are not going to be able to do
2 it with 70 percent.

3 So the statements from Vogel just don't apply.
4 They are general chemistry statements that have no bearing in
5 the SBS context. And Dr. Branchaud expressly refused to say
6 whether Vogel's efficiencies were good enough in the context
7 of Ju or Tsien. And it is Exhibit 2155, pages 224 through
8 27.

9 Now, IBS now relies on Exhibit 1038, which is
10 Knouzi, as showing quantitative yield. That reliance is
11 misplaced. And, Judge Prats, you had asked a question about
12 this particular exhibit in contrast to Loubinoux.

13 IBS didn't cite this Exhibit, 1038, anywhere in
14 their petition or anywhere in their reply. It is buried in a
15 string cite once in Branchaud's second declaration. It is
16 not an exhibit that the Board should consider.

17 But even if it wasn't improperly incorporated,
18 Knouzi only obtained yields of 79 to 95 percent, and Dr.
19 Branchaud testified that Knouzi didn't provide any
20 explanation for his statement that that was quantitative.
21 Moreover, Knouzi didn't test nucleotides or nucleosides, so
22 it is of little relevance.

23 We also know that azides on nucleotides are
24 reduced less efficiently than azides on nucleosides, and when
25 you do the Staudinger reaction, which is the reaction we are

1 talking about in this case, you get side products. And that
2 is shown by, for example, Exhibit 2151, at page 6270 through
3 71.

4 When you do this reaction with nucleotides you get
5 more side products and a lower yield. And that's Exhibit
6 2151 and 2152.

7 Now, IBS then comes back with Exhibit 1041, which
8 is the Mag and Engels reference. And this is a retort to
9 Mungall, which showed low efficiencies when using nucleotides
10 and azides. Then you get the Mag reference, which is Exhibit
11 2141, and this reference used a two-step process.

12 The first step used 100 percent pyridine, followed
13 by a second step involving water. So it is clearly a
14 reactant that we are not talking about in the SBS context. I
15 don't think anybody is going to get up here and tell you that
16 that level of pyridine wouldn't denature DNA.

17 Moreover, the Mag reference didn't show
18 quantitative yield for a nucleotide, which is what we are
19 dealing with. And Dr. Branchaud admitted that Exhibit 1041,
20 Mag, doesn't use the Staudinger reaction, which is the
21 reaction we have all been talking about.

22 And he admits in his deposition it uses a reaction
23 that is an Arbusov rearrangement and it is not the kind of
24 reaction we are looking at in this IPR.

25 So for them to rely on that reference as this is

1 my basis for quantitative, it just doesn't fit in this
2 context.

3 Turning to the third criterion of Tsien, you must
4 have the de-blocking -- I'm sorry, you must reinitiate DNA
5 synthesis subsequent to de-blocking. One of skill in the art
6 would have understood that Zavgorodny's conditions would have
7 allowed reinitiation of DNA synthesis prior to de-blocking.

8 And this is, again, from the Ju patent itself,
9 Exhibit 102, column 3, lines 12 through 20, where he talks
10 about the ester group prematurely causing reinitiation of
11 synthesis.

12 Now, we talked about Tsien's three fundamental
13 requirements. Ju has four. They largely overlap. IBS used
14 a subset of them. And what they said was that any 3 prime
15 protecting group that is stable during the polymerase
16 reaction does not interfere with recognition and is
17 cleavable, works.

18 And Ju sets forth those criteria but he also sets
19 forth his four requirements that I showed you on slide 7.
20 We submit that a person of skill in the art would have read
21 the entirety of Ju. They would have understood that you had
22 to meet both sets of requirements in order for the process to
23 move forward.

24 And IBS doesn't really dispute that on reply.
25 They haven't raised any issue with the four fundamental

1 criteria we raised. So I'm not going to spend a lot of time
2 on them. And Ju's second and third criteria largely overlap
3 with Tsien.

4 So unless there are questions, I'm going to move
5 straight to requirement 4 of Ju, which is that the DNA should
6 survive the washing, detection and cleavage process and
7 remained annealed to the DNA template.

8 Zavgorodny's removal conditions, which use
9 pyridine, would cause the DNA to not remain annealed. And
10 this comes out of Exhibit 2011, Romesburg paragraph 55.

11 Now, on reply IBS argues that Ju has a
12 self-priming embodiment that could be used to address the
13 denaturation issue. This is a new argument on reply. We
14 didn't get a chance to have our expert address it.

15 But if you look at what Ju actually teaches, the
16 Ju reference says that the self-prime embodiment is used in
17 order to maintain a continuous hybridized primer extension
18 product with the template DNA.

19 And so if you were using pyridine, you would have
20 this extension primer, but every time you ran it you would
21 unanneal it and reanneal it, unanneal it and reanneal it.
22 And Dr. Romesburg testified that serial melting and
23 reannealing would not be acceptable even with a self primer.

24 It is Exhibit 1025, page 146, lines 10 through 20.
25 It would cause sequencing errors if you did this

1 reannealing and -- I'm sorry, melting and reannealing. And
2 so this is clearly not what Tsien was using that method for.
3 And in Tsien's SBS method, doing that every sequence simply
4 wouldn't be practical.

5 Now, I would like to spend some time on the issue
6 of optimization, because you heard here today that one of
7 skill in the art could easily change Zavgorodny's removal
8 conditions and optimize.

9 This is an argument that came out on reply for the
10 first time. It is an improper new prima facie case. If you
11 read the petition, the sole reason to pick Zavgorodny, and
12 the azidomethyl group, out of the countless other groups that
13 are out there, is because of the special conditions that are
14 mild that are taught in Zavgorodny.

15 And now they say: But you can change those. That
16 wasn't in the petition anywhere. And the reason it wasn't
17 there is because, if you do that, there is no reason to pick
18 Zavgorodny's azidomethyl ether in the first place other than
19 hindsight.

20 And so they are limited to the conditions in the
21 petition. The petition didn't say one word about
22 optimization. It didn't say one word about changing the
23 conditions. This is a completely new argument on reply.

24 Now, as support for this idea that you would
25 optimize and optimization was known in the art, IBS cites two

1 things. The first one is Exhibit 2003. It is an Illumina
2 notebook. It is not prior art. It doesn't show what people
3 of ordinary skill in the art did at the time of the
4 invention. This is a non-prior art work by the inventor. It
5 doesn't show that optimization was common.

6 The second one is Exhibit 2043, the Canard paper.
7 And when asked if Canard succeeded in his optimization
8 efforts, Branchaud testified no. That's Exhibit 2155, page
9 68, lines 1 through 8. So they presented no evidence that
10 this optimization was commonplace or would have happened or
11 was within one of skill in the art.

12 Indeed, Dr. Branchaud testified, and it is in our
13 observations at page 6, that there were at least 10 different
14 factors that would have to be optimized, including reaction
15 time, temperature, effect of various solvents, molar ratio of
16 reactants, pH, pressure testing, different phosphine
17 reagents, additives, catalysts and screening polymerases.

18 Branchaud also testified that this is an empirical
19 process that is very unpredictable. Now, here is one of the
20 most important points about this whole optimization issue.
21 Dr. Branchaud admitted during his deposition that he has no
22 experience optimizing 3 prime protected nucleotides for SBS.
23 It is Exhibit 2155, page 49, line 24, through page 50, line
24 6.

25 Meanwhile, IBS' other expert, Dr. Metzker, who has

1 actually done this work in SBS, and tried to optimize these
2 things, stayed silent. He didn't say a word on the issue.
3 And the reason is he couldn't say that optimization was
4 something that was routine.

5 Given that the witness they gave you on this is
6 the person who has never done it, and the person who has sat
7 there silent, Branchaud's optimization testimony, if you even
8 get to the issue of optimization, should be given little, if
9 any, weight.

10 Moreover, IBS didn't give you any test data.
11 There is no test results that says, oh, here are the tests
12 that show you can very easily optimize Zavgorodny's removal
13 conditions. They didn't present them because they know how
14 difficult that is. This just isn't what happens in the real
15 world.

16 In 2002 there were at least 12 different groups
17 that were looking to find the ideal 3 prime protecting group.
18 They are listed on pages 5 and 6 of Illumina's response.
19 None of them were looking at azides. They were all looking
20 at different 3 prime groups and trying to optimize them.

21 And so the starting point of azido, getting to an
22 azidomethyl protecting group, IBS hasn't given you any reason
23 to do that other than the special conditions in the
24 reference, and those conditions don't work with Ju or Tsien's
25 method.

1 Now, to the extent you look at optimization is
2 easy, look at what Ju did. Ju spent years on the allyl group
3 trying to optimize the conditions. Paper after paper after
4 paper trying to make it better. And what did he do after he
5 saw the results with the azidomethyl group? He switched. It
6 wasn't something that optimizing these 3 prime to nucleotides
7 is easy. It is something that is very difficult.

8 Dr. Metzker in Exhibit 2024 said that there were
9 stringent requirements, and that forming such nucleotides was
10 a formidable obstacle.

11 And at Exhibit 28 Welch says that a major
12 challenge in the development of SBS, however, is that the 3
13 prime blocking group must be removed in aqueous medium using
14 reagents conditioned that do not denature or modify double
15 stranded DNA.

16 So the idea that optimization is easy is a
17 fiction. The record simply doesn't show that. They have
18 isolated unsupported statements Dr. Branchaud, but no
19 evidence showing that this was within the skill of the
20 ordinary artisan.

21 They cited to the decision of this Panel in the
22 026 IPR. That decision isn't even of record in this case.
23 And so it is simply not in evidence for that purpose.

24 Turning to --

25 JUDGE GREEN: Before you -- do you just talk about

1 the cleavage conditions that you need in the '537 patent?

2 MR. ZIMMERMAN: In the patent itself it doesn't
3 give you specific reaction conditions. It does have a
4 section that talks when reductive conditions. And it
5 specifically identifies the azide group in figure 3, but it
6 doesn't give you particular reduction conditions in the
7 reference itself.

8 JUDGE GREEN: But the ordinary skill in the art
9 would have understood what those conditions would have been?

10 MR. ZIMMERMAN: A person of ordinary skill, if
11 they were directed to use an azide protecting group in SBS,
12 and it will work, can you find conditions? Yes. But the
13 prior art didn't give you any of that. It didn't tell you to
14 use an azide as specifically as azidomethyl in the SBS
15 context.

16 Would it have taken some experimentation to figure
17 out those conditions? Yes.

18 Now, the only reagent that they give you as an
19 option to -- alternative to the pyridine and
20 triphenylphosphine of Zavgorodny is TCEP. And they cite to
21 two exhibits in their briefs. It is Exhibits 1035 and 1036.

22 With respect to Exhibit 1035, they don't provide
23 any explanation as to why this reference teaches you to use
24 TCEP to get a quantitative result. Branchaud couldn't
25 identify any experimental data in the reference that showed

1 reduction efficiency of an azide group by TCEP.

2 Moreover, this is another one of those references
3 that isn't cited in their petition or in their reply. It is
4 buried in the Branchaud declaration in one paragraph.
5 Another improper incorporation to expand the record.

6 And that reference, Exhibit 1035, expressly
7 teaches at pages 85 and 86 that when you react an azide with
8 TCEP you form an amine that spontaneously attacks the
9 phosphate ester linkages, resulting in cleavage of the DNA.

10 So Exhibit 1035 doesn't help them. It is not
11 compatible with Ju or Tsien's methods.

12 The next one is Exhibit 1036, and this reference
13 isn't prior art. Importantly, this article, though, is
14 teaching a new use of TCEP to reduce azides. So after
15 Illumina's invention, the use of TCEP to reduce azides was
16 new. If anything, it shows that TCEP wasn't available to the
17 common, ordinary artisan and wasn't developed until after our
18 invention.

19 Now, there was a statement about Dr. Liu's
20 testimony supporting an obviousness to try argument. And I
21 am going to tread gingerly here because Dr. Liu's testimony
22 is under seal.

23 Dr. Liu is not a native English speaker. And if
24 you read the transcript portions provided, you will
25 understand that. But if you will look at Exhibit 2044, pages

1 41, 45 and 46, 79 to 83, and 276, he talks about the options
2 that were tried and whether use of Zavgorodny's azidomethyl
3 would have been an obvious to try on that one statement.
4 When you read them in context I think it is pretty clear that
5 he was not saying this would have been an obvious selection
6 to a person of skill in the art.

7 This is an inventor talking in hindsight about
8 what he did 10 years later and he wasn't talking about what
9 the ordinary skilled artisan would have done in 2002. So I
10 urge you to look at that.

11 I would like to spend just a few moments on
12 secondary considerations.

13 JUDGE GREEN: You have until 11:20 before you have
14 five minutes left.

15 MR. ZIMMERMAN: Okay. So on secondary
16 consideration, Illumina bears the burden of production. And
17 they have come forward with evidence of long felt need,
18 unexpected results, copying and industry praise.

19 JUDGE GREEN: Doesn't Illumina also bear the
20 burden to demonstrate nexus?

21 MR. ZIMMERMAN: They do.

22 JUDGE GREEN: Okay.

23 MR. ZIMMERMAN: And with these secondary
24 considerations, they are a guard against hindsight. And the
25 burden to prove obviousness remains with IBS.

1 Looking at long felt need, we presented evidence
2 showing that there was a long felt need for these 3 prime
3 protecting groups in the SBS context, and that's the only
4 context that this invention has been used in.

5 JUDGE GREEN: But your claims cover 2 prime
6 protecting groups, correct?

7 MR. ZIMMERMAN: Yes, and 2 prime protecting
8 groups, 3 prime protecting groups, it is not in the record, I
9 concede that, but from a scientific perspective there isn't a
10 difference, and IBS didn't raise a challenge saying you
11 haven't shown for a 2 prime group.

12 JUDGE GREEN: No, but it is your burden to show
13 nexus. Is there even a statement in the record that you
14 would expect the 2 prime to work the same way as the 3 prime,
15 i.e., all your evidence is drawn to the 3 prime, and your
16 claims encompass any linking group, any of this, and also
17 encompass 2 prime protecting groups.

18 It would have been nice to at least have a
19 statement in the record that, oh, by the way, the ordinary
20 artisan would have expected the 2 prime to act the same way
21 as the 3 prime and, therefore, we do have nexus.

22 MR. ZIMMERMAN: Yeah, and I don't know if in one
23 of the paragraphs of Dr. Romesburg, in secondary
24 considerations, he addressed that point or not. I don't
25 believe he did. But if he did, it would be in the 75 to 81

1 paragraph range.

2 Now, IBS argues first that you could use a
3 terminal transferase with the invention, and, therefore,
4 there is scope beyond SBS. And they point to Exhibit 1045.
5 It is the one on their slides.

6 This is disingenuous at best. The testimony
7 explains that in this method you don't use labeled
8 nucleotides, which is what the claims of the '537 patent
9 require.

10 The testimony explains that this method leaves
11 scars when you cleave off the 3 prime group, and those scars
12 are not compatible with Ju and Tsien's method. But, most
13 importantly, the reference itself at column 2, lines 13 to
14 15, states that the blocked method, the very thing they put
15 on the slide and rely on, was abandoned.

16 This is not something that anybody does. It is
17 not a viable use of the claim. This is something that was
18 tried once, abandoned. And for them to say you have to show
19 unexpected results or long felt need for a use that nobody
20 uses because it was abandoned, simply doesn't make sense.

21 Now, the other argument they make is that Dr. Ju
22 didn't copy, that he credited Zavgorodny. The evidence shows
23 that Zavgorodny was out there for years. And Dr. Ju never
24 once used azidomethyl. Dr. Ju only used azidomethyl after
25 seeing Illumina's patent publication, after seeing Illumina's

1 commercial product, and he switched to the azidomethyl group.

2 And so he did it based on Illumina. He didn't do
3 it based on Zavgorodny. He saw what Illumina was doing and
4 he copied it.

5 The evidence of unexpected results is at
6 paragraphs 79 and 80 of Dr. Romesburg's declaration. Were
7 there any questions on that point? If not, I will leave it
8 to Jeff.

9 JUDGE GREEN: Thank you.

10 MR. ZIMMERMAN: Thank you.

11 MR. COSTAKOS: Thank you, Your Honors. As Mr.
12 Zimmerman indicated, objective evidence can be some of the
13 most important evidence in the record because it is a guard
14 against hindsight. The Federal Circuit has pointed out that
15 it is important to consider it when it is presented because
16 it will avert the trap of hindsight.

17 I think if we look at the secondary consideration
18 evidence here, it will show the flaw in IBS' hindsight
19 obviousness argument. And in particular, you will see from
20 the confidential secondary consideration evidence that there
21 is evidence of IBS' and Columbia's failure with the prior art
22 allyl block, and Columbia switched to the claimed azidomethyl
23 cap.

24 You will see praise in the record by Columbia and
25 others of the unexpected effectiveness of the azidomethyl

1 cap, and there is evidence in the record of Columbia's
2 copying of the azidomethyl cap from Illumina.

3 And much of the evidence, as Mr. Zimmerman
4 indicated, is marked as confidential. And given the public
5 nature of the hearing, I'm going to speak a little bit
6 elliptically about it.

7 But I will only be using sort of public
8 characterizations in the papers that are filed or
9 non-confidential characterizations of the contents of these
10 documents.

11 But I think, nonetheless, we can talk about the
12 exhibits with those limitations and they are instructive
13 here. If we look first at a set of exhibits beginning with
14 2097 through 2099, you will see there that in Exhibit 2097
15 there is a reference to problems with the prior art
16 chemistry.

17 And if you look at the second sentence of Exhibit
18 2097, there is a rather colorful statement about the problems
19 with the prior art work that was being done.

20 If you look at -- this is from June of 2007 and is
21 a document directly from IBS. If you look then at Exhibit
22 2098, which is a companion document to this, it was prepared
23 at the same time, also from June of '98, you will see a
24 specific reference in the exhibit -- and it is a one-page
25 exhibit, again, from IBS -- to a flaw in the prior art

1 chemistry itself.

2 So this is setting up the issue that IBS and
3 Columbia were facing with the very prior art that they are
4 relying on here today and that they said would have been
5 obvious.

6 If you look at Exhibit 2099, you will see here
7 that IBS is reaching out to others in the field to try to
8 help solve the problems with their prior art chemistry that
9 they were using.

10 So I think this shows that it wasn't quite as
11 obvious as IBS is saying here today. Remember, 2007, this is
12 seven years after the Ju patent application. So seven years
13 later they are still struggling with the allyl chemistry.
14 And these documents show the problems they were having and
15 the steps they were taking to attempt to solve it.

16 And there was discussion of cleavage conditions,
17 and I'm not going to go into the details here, but if you
18 look at these documents with cleavage conditions in mind, I
19 think you will see some of the problems that were with the
20 prior art chemistry and the solutions that were attempted in
21 order to try to solve that.

22 If you turn to page -- excuse me, Exhibit 2117,
23 which is another confidential exhibit, this is a document
24 that -- in IBS' paper, this is Paper 53, they refer to as Dr.
25 Ju "praising cleavage efficiency." So those are their words.

1 Those are already in the public.

2 If you look at the second -- and this document is
3 from June of 2008. So in slide 16 of Illumina's
4 demonstratives you see a time line of the publicly known
5 research by Dr. Ju and his group. And you will see in there
6 there is a switch from the work that was being done with the
7 allyl group to azidomethyl.

8 June of 2008 is after that switch. And you will
9 see in Exhibit 2117, on the second page, there in the fourth
10 paragraph at lines 6 through 10, there is a direct comparison
11 of the invention with the prior work. There is specific
12 praise of the claimed invention and the benefits as compared
13 to the prior work.

14 This is in the fourth paragraph at lines 15
15 through 17. And there is a nexus to the claimed invention
16 because there is a specific reference to the claimed
17 invention.

18 And you will see, I won't say exactly what he
19 says, but you will see that he even italicizes the results.
20 And this is in the last sentence on the second page of
21 Exhibit 2117. So this, again, is showing praise by Dr. Ju of
22 the switch which it took him and his group at least seven or
23 eight years to discover.

24 If you look at Exhibit 2101, there is a document
25 that IBS, again, characterizes in their papers as expressing

1 excitement over read length. This is a document from October
2 2007. It makes specific reference to azidomethyl.

3 It praises a specific -- and that's in lines 1 to
4 6 of the document. Again, it is a short document. It
5 praises a specific feature of the claimed invention compared
6 to the prior work. It uses the words very exciting, in
7 quotes, I'm quoting that, with an exclamation point. And it
8 recognizes the problems that they were having with the prior
9 art.

10 JUDGE GREEN: Counsel, you have about one more
11 minute.

12 MR. COSTAKOS: Okay. Finally, if you look at
13 Exhibits 2109 and 2110, I'm not going to say what is in these
14 documents. I will just ask the Board to compare the first
15 three bullet points in Exhibit 2109 with the first two bullet
16 points in Exhibit 2110. And I think you will see there the
17 failure of the prior art as compared to the claimed
18 invention.

19 And this real world evidence shows the
20 non-obviousness and the hindsight reconstruction that IBS is
21 attempting here. It wasn't as obvious as they are saying to
22 modify the SBS prior art, Tsien and Ju with azidomethyl.

23 It certainly wasn't obvious to them. It took them
24 a long time, a lot of experimentation, and ultimately took
25 their knowledge of Solexa's and Illumina's work to solve the

1 problem.

2 So I think copying, praise, unexpected results,
3 long felt need, are all shown by the confidential exhibits
4 which have been submitted by Illumina.

5 Thank you.

6 JUDGE GREEN: Thank you. So you have 10 minutes.
7 Whenever you are ready.

8 MR. SEGAL: Thank you. I would like first to
9 address the optimization point. Mr. Zimmerman makes the
10 point that, well, there is tons of factors you have to
11 consider, the pH, the temperature.

12 They did. They went through those with our expert
13 one-by-one. Can you adjust the pH? Can you adjust the
14 temperature? Of course, he said yes, those are all things
15 you can adjust.

16 The understanding, if you look at his testimony,
17 was that it is a very systematic and routine process. You
18 know, you work in a lab, you change a couple of the
19 parameters, you see what direction you are going, and you
20 quickly hone in on what is important.

21 And I think it was very telling that when Judge
22 Green asked him about the '537 patent, again, he said once
23 you have the particular group, the azidomethyl group, one of
24 skill in the art would be able to design cleavage conditions.

25 Well, that's what you are going to have here. You

1 have Ju and Tsien. They are going to direct you directly to
2 Zavgorodny.

3 Now, they say somehow in our petition we are only
4 relying on the cleavage conditions of Zavgorodny. I don't
5 think there is anywhere in our petition where we say these
6 cleavage conditions would work great with Ju and Tsien. No.

7 We say the azidomethyl group because, look, it is
8 out there. It is on the exact same 3 prime hydroxyl, what
9 you need to use in Ju and Tsien's process, one skilled in the
10 art would think to use that.

11 Tsien suggests using the N3 chemistry. And you
12 would be directed there because, in addition, Ju and Tsien
13 talk about ether linkages, and, again, it is an ether
14 linkage.

15 So there is really -- I mean, they have
16 essentially conceded that point that it would be routine to
17 develop conditions to work with Ju and Tsien's methods.

18 And what we also have, we actually have a real
19 life example that's in the record. Ju, like I mentioned
20 earlier, Ju identifies the allyl group. And Ju in his patent
21 application or his patent identifies the reference Kamal.
22 And Kamal again uses acetonitrile.

23 And in that cleavage condition they are using
24 sodium iodide in that paper. What does Ju say about those
25 cleavage conditions in his patent? He says almost the exact

1 same thing that Zavgorodny says. Well, this looks good
2 because it can cleave under mild and specific conditions.

3 But to Ju, we have what Ju ended up doing later in
4 the record because Illumina has put in all of Ju's published
5 papers. And you will see that Ju shifted from that
6 particular sodium iodine method. He shifted to a palladium
7 cleavage mechanism because I guess it worked better in this
8 process.

9 Again, it is routine experimenting. He didn't say
10 because Kamal identified these particular cleavage
11 conditions, well, if those don't work I'm backing away from
12 allyl. He didn't do that. He went ahead and he got
13 excellent results.

14 While I'm on that topic, I would like to talk
15 about the copying. They keep saying that Ju and IBS failed.
16 Well, Dr. Ju is working in an academic institution. And if
17 you follow his papers, right away his first public paper he
18 gets extremely high cleavage efficiency. I think within 30
19 seconds he gets complete cleavage. I think that is Exhibit
20 2047, if I'm right, published in 2005.

21 And later he uses the full -- the allyl, and he
22 uses a label on the base, and he does some tests and he gets
23 20 base pairings. So I don't see how that is not a success.
24 Certainly it is success as measured by the claims. Now,
25 maybe it is not as successful as Illumina's HiSeq machine,

1 but certainly as it relates to the claims it is a success.

2 After that success you can see that Ju, and you
3 can look at the exhibits they identified and look in his
4 papers, again, once he had this success, okay, that basic
5 method of sequencing I'm done with, the protecting group on
6 the 3 prime oxygen and the label on the base.

7 I'm now going to move to a hybrid approach. I'm
8 going to show that slide again. And, again, what he is using
9 the azidomethyl for is a different approach to sequencing.

10 He is not going to spend endless amount of time on
11 allyl. He is not a commercial lab. He is not an Illumina.
12 He has got himself and he has got some graduate students
13 working for him.

14 This is what he switches to. This is what he uses
15 the azido for. Now, whether or not he thought it was better,
16 it doesn't really matter. It is irrelevant with respect to
17 these claims.

18 I just want to mention also the point that the
19 claims are limited to sequencing by synthesis. Well, what do
20 they say about those nucleotides in their patent? Put up
21 that slide. It is one of the early numbers, I believe.

22 What they say is that they are not limited --
23 okay, here it is: The use of the modified nucleotides is not
24 limited to DNA sequencing. There are other techniques you
25 can use it. So, I mean, now they are up here when they are

1 trying to argue for the patentability of these claims. Of
2 course they want to limit to SBS because that's where their
3 evidence is, that's where, you know, their commercial
4 embodiment is. But, again, that is not what the claims are
5 limited to.

6 If you want to go to that slide 21 and 22, this
7 slide makes it clear that it can't be limited to SBS. So
8 claim 1 designates that this is incorporated, the nucleotide
9 and nucleoside molecule is incorporated into the template.

10 And claim 2 lists particular enzymes that are used
11 to incorporate it. One of them is terminal transferase.
12 Terminal transferase is template independent, so it can't be
13 used for sequencing by synthesis.

14 We put in an article by Illumina's own scientist
15 which says it is not -- terminal transferase cannot be used
16 for sequencing. So it is very clear that the claims are
17 broader than sequencing by synthesis, and it is very
18 important here with respect to secondary considerations.

19 Also, they bring up the motivation to combine in
20 the petition. We did argue that one skilled in the art would
21 believe and go to Zavgorodny to try to improve Ju and Tsien's
22 methods. Ju and Tsien at that time, it's 2002, there is no
23 sequencing data there. So any results that you get are going
24 to be an improvement of that.

25 But that's not the only motivation to go to

1 Zavgorodny. As we said before, the Ju and Tsien reference
2 actually say use any suitable protecting group that fits our
3 criteria.

4 So you are going -- to look at those criteria you
5 are going to look at what else Ju and Tsien say about it and
6 you are going to be directed to a reference that uses a
7 chemical DNA synthesis, which is the same kind of references
8 that all the art tells you to look at, to try to get a very
9 fast and efficient method.

10 The other thing with the -- in our petition with
11 regard to motivation, we also, if you look at our claim
12 charts, we make it clear that the first step of Ju and Tsien
13 really is the incorporation of a labeled nucleotide. So
14 right there that is a method of labeling.

15 So as KSR instructs us, you are not limited, a
16 person of ordinary skill in the art is not limited to the
17 purpose of the primary reference. You can look outside of
18 that.

19 As in KSR, where it was a mechanical linkage of
20 the pedal, the Supreme Court found, look, someone of skill in
21 the art would know, because you have a single pivot point
22 there, maybe you can use it for an electronic pedal.

23 The same thing here. You have an incorporation of
24 a labeled nucleotide. One of skill in the art would know
25 that you could use it for method of labeling. And if you

1 could use that method for method of labeling, you could also
2 look to other kinds of alternatives for protecting groups.

3 Also, he talks about, you know, what is the best
4 method. He wouldn't use this method because it is not great.
5 It was abandoned. I don't think that is clear at all from
6 the record. But, again, that is not the standard. The
7 standard is whether or not it would be a viable option.

8 And the Board here, with respect to the scope of
9 the claims, they actually rejected our claim construction and
10 found, you found earlier that the 3 prime hydroxyl protecting
11 group -- or here it has to be 2 prime or 3 prime -- doesn't
12 have to be removed.

13 Well, in the sequencing process you are going to
14 have to remove it to get the next nucleotide incorporation.
15 So I think it abundantly clear that the claims are much
16 broader than sequencing by synthesis.

17 They attack -- Mr. Zimmerman makes very particular
18 attacks on certain references. A lot of these depend on
19 references that were introduced during the cross-examination
20 of our witness. Anything above 2139, those exhibits were
21 introduced during that. So our experts haven't had an
22 opportunity to comment on those.

23 But the discussion of those references and our
24 particular rebuttal to many of his points are in our response
25 to the observations, cross-examination, so I urge you to look

1 at that.

2 I can bring up a couple things. They refer to an
3 exhibit that was actually in the record before
4 cross-examination, the Stanton paper, the Exhibit 1035. And
5 they say, well, the azido group was known to cleave the
6 phosphodiester bond.

7 Well, in that paper, if you look at it, the azido
8 group is not on the 3 prime position. It is on the 4 prime
9 position. And it is going to be next to the 5 prime position
10 where you have the phosphodiester bond there. So it is not
11 really relevant to the issues here.

12 Another point I wanted to address that Mr.
13 Zimmerman brings up is the time issue. He said, well, the
14 prior art all showed that this is going to take too long, the
15 three hours to cleave it or whatever.

16 And, again, that goes back to the fundamental
17 differences between the types of references that they are
18 looking at and the sequencing by synthesis process.

19 Again, in the reference they are looking at the
20 stoichiometry of the reactions are generally one-to-one or
21 maybe a slight excess.

22 In sequencing by synthesis you are going to be
23 able to use a large amount of reagents. That is going to
24 drive the reaction quicker. I don't think there is any
25 dispute on that point.

1 JUDGE GREEN: Counsel, you have about one minute.

2 MR. SEGAL: Just one other point. They said it is
3 not going to work with nucleotides. Everything that we have
4 in the record is about nucleosides. When you use it with
5 nucleotides it is going to cause all these side reactions.

6 Well, again, they cite two references that were
7 only introduced at the cross-examination of Dr. Branchaud,
8 and neither one of those are a Staudinger reaction. You can
9 look at those. One is a Staudinger type ligation, again, a
10 very complicated molecule, and the other one uses a different
11 reagent. You are not going to have those issues here.

12 So if there are no further questions?

13 JUDGE GREEN: No. Thank you very much.

14 MR. SEGAL: Thank you.

15 JUDGE GREEN: Thank you, both. We will have a
16 decision in due course. And this hearing is adjourned.
17 Thank you.

18 (Whereupon, at 11:37 a.m., the hearing was
19 adjourned.)
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