

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.,
Petitioner,

v.

HANGZHOU DAC BIOTECH CO., LTD.,
Patent Owner

IPR2022-01531
Patent 10,131,682 B2

Record of Oral Hearing
Held: June 12, 2025

BEFORE: ZHENYU YANG, DEVON ZASTROW NEWMAN, and
CYNTHIA M. HARDMAN, Administrative Patent Judges.

IPR2022-01531
Patent 10,131,682 B2

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The above-entitled matter came on for hearing on Monday,
June 12, 2025, commencing at 1:00 p.m., at the U.S. Patent and Trademark
Office, 600 Dulany Street, Alexandria, Virginia, and via videoconference.

P R O C E E D I N G S

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JUDGE NEWMAN: Good afternoon, Counsel. We are on the record. This is Judge Newman, and with me today are Judge Yang in the courtroom, and with me today Judge Hardman on video.

This is the final oral hearing in IPR2022-01531 in which Petitioner has challenged Claims 1 through 17, 20 through 21, 24 through 26, and 29 through 34 of U.S. Patent Number 10,131,682.

The parties are SynAffix B.V. versus Hangzhou DAC Biotech Company, Limited.

This is a hybrid hearing. We have two judges on video and one in the courtroom in Alexandria, Virginia. We have a court reporter present in the courtroom.

The Board will issue a transcript of this case and will make that transcript part of the record in due course.

Let us start by taking appearances. Counsel for Petitioner, would you please identify yourself, your team, and let us know who will be speaking today?

MR. HOUSTON: Good afternoon, Your Honors. My name is Michael Houston, counsel for Petitioner. And with me at the table is my colleague, Ms. Jolene Fernandes, who will also be speaking for part of the time.

JUDGE NEWMAN: Thank you, Counsel.

And, Patent Owner, would you please identify yourself and your team and let us know who will be speaking?

1 MR. CALVOSA: Good afternoon, Your Honors. Frank Calvosa
2 of Quinn Emanuel Urquhart & Sullivan on behalf of Patent Owner. With
3 me is Catherine Mattes and Jihong Lou, also of Quinn Emanuel. We
4 brought along a summer associate as well, Yucen Zhong. And I will be
5 speaking today.

6 JUDGE NEWMAN: All right. Under the order setting the oral
7 argument in this case, each side was granted 60 minutes to present its case
8 today. In addition, Petitioner's request for a LEAP practitioner to participate
9 was approved. And so, Petitioner has 75 total minutes to present.

10 The panel will do our best to keep track of time. We do have a
11 clock there in the courtroom. We suggest that you also just keep an eye on it
12 on your own end, so that you're aware of how much time you have left.

13 And Petitioner will present its arguments first. Petitioner, you may
14 reserve up to 20 minutes for rebuttal. Mr. Houston, would you like to
15 reserve any time?

16 MR. HOUSTON: Yes, Your Honor. We'd like to reserve 20
17 minutes for rebuttal.

18 JUDGE NEWMAN: And, Patent Owner, do you wish to reserve
19 any time?

20 MR. CALVOSA: Yes, Your Honor, we wish you to reserve 15
21 minutes.

22 JUDGE NEWMAN: Thank you. Those times have been noted.
23 Again, there's a hearing clock in that room with you, but I will also give you
24 a one- to two-minute warning just to let you know it's time to wrap up your
25 argument.

26 Please be mindful that because some of us are on video, there can

1 be a slight lag. So, please pause briefly before speaking. That prevents us
2 from speaking over each other and we get a clear record.

3 We have received demonstrative exhibits from both parties, and we
4 have access to the full record. However, the judges on video cannot see
5 what's being shown on the screen in the hearing room. And so, we need to
6 follow along on what's presented. And in order to do that, please identify for
7 us what demonstrative or document you are looking at and the citation. And
8 that also helps us keep the record clear as well.

9 Our expectation is that, unless absolutely necessary, counsel for
10 opposing party will not interrupt the other side's presentation.

11 And, with that, are there any questions? Are we ready to begin?

12 MR. HOUSTON: No questions, Your Honor. We're ready to
13 begin.

14 MR. CALVOSA: No questions from Patent Owner.

15 JUDGE NEWMAN: Okay. Great. So, by my count, Petitioner
16 has 55 minutes.

17 Give me just one moment here. I think we have an issue on our
18 side. We'll go off the record for just a moment, please.

19 (Whereupon, the above-entitled matter went off the record at
20 1:04 p.m. and went back on the record at 1:04 p.m.)

21 JUDGE NEWMAN: And, Petitioner, you have 55 minutes. You
22 may begin when ready.

23 MR. HOUSTON: Thank you, Your Honors. May it please the
24 Court. I know you're all very familiar with the details of this case already,
25 so I will skip the flowery introduction and get straight to the issues.

26 Our Demonstrative Slide 2 shows the grounds at issue in this

1 proceeding. And to give Your Honors a preview, I plan to cover the issues
2 that are raised in Grounds I and II, and then I will turn it over to my
3 colleague, Ms. Jolene Fernandes, who is much more the organic chemistry
4 expert than myself, and she will handle the issues that are specific to
5 Grounds III through IV.

6 Slide 3 shows the topics that we plan to cover today. As Your
7 Honors are aware, one issue that permeates, basically, all of the grounds in
8 one way or another is the interpretation of the Q Y T Z terms found in
9 certain of the challenged claims.

10 And in particular, there's a dispute about how those terms should
11 be interpreted with respect to the vinyl sulfone group that is relied on and
12 found in certain prior art references, and that's the first issue that I'd like to
13 dive into.

14 Slide 6 shows the claim limitations for the Y and Z terms from
15 Claim 1 of the '682 Patent. As the Board knows, there has already been a
16 decision by the Delegated Review Panel that specifically addressed this
17 claim interpretation issue, the main holdings from which are shown on our
18 Demonstrative Slide 7.

19 Specifically, the DRP found that vinyl sulfone can be mapped to
20 either the Q Y or the T Z terms, and that vinyl sulfone satisfies both the
21 enables reaction requirement for the Y term and the enables linkage
22 requirement for the Z term.

23 Now, to our understanding, when the DRP remands with a decision
24 like this for further proceedings consistent with that decision, that suggests
25 to us that the panel is supposed to continue to follow that decision for the
26 remainder of the IPR proceeding and not just for purposes of institution.

1 That said, we have not been able to find any clear precedent on that topic
2 one way or the other. It does seem to be an issue of first impression, to the
3 best that we can tell.

4 So, while it's our belief that the DRP decision should be treated as
5 though it's binding, even at this stage of the proceedings, nonetheless, we,
6 obviously, want to explain why we think the same outcome should be
7 reached on that claim interpretation issue in the final written decision, even
8 if the DRP decision isn't binding.

9 Your Honors are very well aware that intrinsic evidence is of
10 paramount importance in claim interpretation. And here, we think that all of
11 the intrinsic evidence the claims, the specification, and the prosecution
12 history show that the Q Y and T Z terms should continue to be interpreted
13 just as was determined by the DRP. I'd like to step through each one of
14 those sources in intrinsic evidence to make our argument.

15 First, if we look at the relevant claim language, as shown on Slide
16 10, it's important to understand exactly what it is that Patent Owner is
17 attempting to do with its limiting construction.

18 As between these limitations for Y and Z, Patent Owner now
19 admits that the vinyl sulfone satisfies the Z term, specifically, the Z and the
20 T term, where the vinyl sulfone provides the sulfone needed for T and the
21 vinyl serves as the Z to enable a linkage to a drug by forming one of the
22 listed types of bonds that you see there in the Z term.

23 Yet, Patent Owner is now trying to say that vinyl sulfone should
24 not apply in the same way to the Q and Y terms. What they're advocating
25 for is inserting a new limitation into that Y definition to require that it,
26 quote, "independently enables a reaction while not imposing that same

1 requirement on the Z term."

2 So, in essence, the way we see it is they want to take nearly
3 identical claim language -- identical language from these two claim terms,
4 but interpret them differently as between them. And as Your Honors know,
5 that's seldom a proper claim construction approach to adopt of treating the
6 same claim language differently, especially within the same claim,
7 especially if there's no express evidence indicating that it's proper to do that,
8 which is not present here.

9 They try to justify treating these claim terms differently by
10 pointing to the fact that Y enables a reaction while Z enables a linkage. But,
11 as you can see from our Slide 11 here, their own expert admitted that, in
12 order to enable a linkage, as required for Z, this necessarily requires
13 enabling a reaction, which is exactly what the Y term requires. The only
14 difference is that the Z limitation is more specific in that the reaction that it
15 has to enable is one that forms one of the listed bond types in the Z term
16 definition. So, in contrast, Y is unlimited. It just has to enable a reaction. Z
17 has to enable a specific reaction that forms one of those listed types of
18 linkages.

19 I will point out that Claim 20 is slightly different in terms of its
20 definition of Y, and I'm going to get there in a moment, because I believe it
21 provides its own independent insight as to how to interpret these claim
22 terms. So, I will address Claim 20 in just a moment.

23 But in regard to Claim 1 in the language for each of Y and Z, it's
24 our position that Z is more narrow than Y, and if Z can encompass the vinyl
25 from vinyl sulfone, which Patent Owner admits, then, certainly, Y must,
26 likewise, be able to encompass the vinyl from vinyl sulfone. There's simply

1 no reason to read the scope of these terms differently, and certainly no
2 reason to read Y as being more narrow than Z.

3 I'll move on to the specification. The specification doesn't
4 expressly speak to this issue, but it does provide what we think is some
5 helpful context for interpreting the claim language here. As we illustrate on
6 Slide 14, the specification teaches sort of what we'll call beginning linkers as
7 Formula I. That's the linker that still has the Y and Z groups prior to it being
8 reacted with anything.

9 Then, each of those Y and Z groups can be reactive with a cell-
10 binding agent and a drug, respectively, to form an intermediate linker that is
11 shown in Formulas III and IV, depending on which one you do first. And
12 then, whichever one you do first, you do the other one next, and that, then,
13 leads to the final form of the molecule that's shown there in Formula II,
14 which has a cell-binding agent, and a drug attached to each end of the linker.

15 The point I want to make here, and the reason I'm describing this,
16 is that, under Patent Owner's construction, vinyl sulfone could be used to
17 arrive at the linkers shown in Formulas II or III, and thereby, covered by the
18 claims, because no one disputes that vinyl from vinyl sulfone will, in fact,
19 react with and attach the linker to a cell-binding agent.

20 But Patent Owner's construction would take that same linker that
21 leads to those Formulas II and III, which are covered, and it would exclude
22 that linker from the claims covering Formula I. We think that that
23 construction is just inconsistent with the patent's overall intent to disclose
24 and claim all of these linkers, all of these formulas from I to IV, the starting
25 point being I; the ending point being II, Formula II; and the intermediates
26 being Formulas III and IV.

1 So, what Patent Owner's construction would do is it would capture
2 the resulting product of linkers having vinyl sulfone that would be the
3 claims covering Formulas II or III but it would exclude those same linkers
4 prior to them being attached to the cell-binding agent. And we just don't
5 think that makes sense in the broader context of the specification's
6 disclosure.

7 We certainly don't see anything in the specification that suggests
8 that when vinyl sulfone is used, only the resulting product was meant to be
9 captured in the claims, while the intermediate that's used to get there was
10 meant to be excluded. There's certainly nothing expressed like that in the
11 specification.

12 Lastly, I want to talk about the prosecution history, which, of
13 course, is also intrinsic evidence, and in this case, we think it's likely the
14 most direct evidence we have regarding how to properly interpret these
15 claim terms.

16 Specifically, I want to draw the Board's attention to the
17 amendments that were made to Claim 20 during the re-examination that
18 occurred on this patent. The relevant parts of Claim 20 are shown here on
19 our Slide 15. And I appreciate the quality of the text is not so good. We
20 have a cleaner version on one of the later slides.

21 But I'll just mention that the part you see here that is in italics, that
22 is the amendment that was made in response to a rejection during the re-
23 examination. So, just keep in mind that italicized text is what was added in
24 response to the rejection.

25 Our Slide 17 shows in more detail what that rejection was that was
26 made by the examiner. It was based on a reference that disclosed a molecule

1 having a drug already attached at one end and it still had the vinyl sulfone
2 group at the other end. So, in Slide 17, you can see the examiner's mapping
3 to the claim on the lefthand side. You can see the drug there. You can see
4 the vinyl and the sulfone. And on the righthand side, it is taken from the
5 Applicant's remarks. And so, you can see their acknowledgment of that
6 mapping. And in both cases, the vinyl from the vinyl sulfone group is
7 mapped to that Y claim term, and the sulfone is mapped to Q.

8 What we think is very telling here is what the Applicant did do and
9 did not do in response to this rejection from the examiner. What they did
10 not do is tell the examiner that the Y and Q terms as they originally appeared
11 in this claim do not cover vinyl sulfone. They did not say that. What they
12 did do is to add a very specific carveout for the definition of Y in Claim 20.

13 And on Slide 18 is where we have a little bit cleaner version of that
14 carveout. It's the upper white box on Slide 18, the underlying text. That's
15 that same amendment that I showed back, I think, on Slide 15. That's the
16 same amendment just written out in a little bit cleaner form. That's the
17 amendment that they made relative to the Y term.

18 And in a nutshell, what that amendment says is that, when there is
19 only a single sulfone in the linker so, you can look at the introductory part
20 of that; it's when Q is sulfone, M is 1, and N is zero, or T is sulfone, N is 1,
21 and M is zero that's their way of saying, when there's a single sulfone in
22 the molecule, in that case and only in that case, Y has to be one of the types
23 of groups listed there in the amendment, which, as you can see, does exclude
24 vinyl. Vinyl is not listed there.

25 So, what they did via this amendment was to disavow claim scope
26 to exclude vinyl sulfone in the very limited circumstance when there is only

1 one sulfone present, and only in that case. So, in other words, when there
2 are two or more sulfones present, then the condition at the front of this
3 amendment is not met and vinyl sulfone can be applied again.

4 And looking at how this occurred and what happened in this
5 prosecution history during the re-exam, we think, very much parallels what
6 happened during the prosecution of the original application that the DRP
7 relied on in its decision. There it was the same as here. Instead of when
8 presented with a reference that taught vinyl sulfone, instead of disclaiming
9 the scope of the Q and Y terms to exclude vinyl sulfone altogether, they
10 merely gave a disclaimer that is commensurate with their claim amendment.
11 And that is just to avoid the very specific circumstance in which there is a
12 single vinyl sulfone present, and nothing more. And they did that to avoid
13 the specific compounds in each case that were cited against them in the
14 respective rejections.

15 So, to us, Your Honors, this prosecution history is really
16 dispositive of the intrinsic it's really dispositive intrinsic evidence, we
17 think, that the Applicant knew and intended that the basic definition of Y
18 and Q in the claims does, in fact, encompass vinyl sulfone, and the
19 Applicant chose to disclaim vinyl sulfone only when the specific conditions
20 of that amendment to Claim 20 are met.

21 Overall, in sum, we think that the claims, the specification, and the
22 prosecution history all support our interpretation of the Q Y and T Z terms.
23 That's the same interpretation reached by the DRP. We think it should,
24 again, be reached in the final written decision, even if that decision isn't
25 binding at this point in the proceedings.

26 If the Board maintains that construction, as we think it should,

1 then, of course, a great number of Patent Owner's arguments against the
2 various grounds of the petition simply go away. But there are a few issues
3 that I want to go through that should be entertained, regardless, or should be
4 entertained in the event that the Board does consider Patent Owner's
5 interpretation.

6 So, I'll move on to Ground I now. Ground I is anticipation by the
7 Morales-Sanfrutos reference. It's Exhibit 1005. And Slide 21 shows the
8 four compounds identified in the petition that anticipate Claim 1. All of
9 these compounds have two sulfones overall in the molecule, and they have a
10 vinyl sulfone on one end and a triple bond alkyne or sometimes it's
11 referred to as an alkynyl group on the other end. That's that bond that
12 looks like it has a triple bond.

13 And I apologize, Your Honors, I misspoke. The triple bond alkyne
14 appears in Compounds 2, 4, and 5. Compound 1 is a bis vinyl sulfone; it has
15 two vinyl sulfones. I apologize for that.

16 Because vinyl sulfones and alkynyl groups are known to react with
17 both the cell-binding agents and drugs when they are appropriately
18 functionalized, that is why these structures can be read on Claim 1 in either
19 direction; that is, you can map them to the Y or Z on either end.

20 And that's what we tried to show in Table B2 of the petition, and
21 we have some excerpts from that just limited to the Y and Z terms in Slide
22 22. So, we tried to just show the alternate mappings there.

23 One issue that arises from this Table B2 that I want to mention is
24 that the Board did raise a question in the institution decision regarding how
25 Morales-Sanfrutos' compounds map to the Claim 2 requirement for Z. And,
26 in particular, the one that we focused on was the Z. Z has a Markush group,

1 of course, of groups that need to be a part of Z. And the one we focused on
2 was where the Z comprises an amino group. That's just part of the Markush
3 group of Claim 2.

4 The mapping that we identified in the petition for Z is what's
5 known in the art as a propargyl amine group from Morales-Sanfrutos'
6 Compound Number 2 when the Y is mapped to the vinyl of vinyl sulfone.
7 That propargyl amine is what's shown here on Slide 22 as the Z group, for
8 example, for Compounds 2(a) and 2(b). So, you can see the structure of that
9 propargyl amine.

10 It actually does carry forward in Compounds 4(a) and 5(a), the
11 only difference being that instead of the NH that you see in 2(a) and (b),
12 Morales-Sanfrutos has attached either a rhodamine or a dansyl to that group
13 for some other purposes. So really, all of these compounds all of 2(a),
14 2(b), 4(a), and 5(a) show this propargyl amine group, and that would satisfy
15 Claim 2 of the patent.

16 JUDGE NEWMAN: Counsel, I'm going to ask a question there.
17 What is your direct evidence that the propargyl amine reacts with the
18 cytotoxic drug?

19 MR. HOUSTON: As explained in our opening expert declaration,
20 Your Honor, at paragraph 87, I believe, Dr. Chari discussed how alkynyl
21 groups again, that's that triple bond that's part of the propargyl amine are
22 known to react with what are called azide groups. And that's usually
23 depicted as an N3 group. And that's called click chemistry. It's a very
24 famous reaction that was discovered or brought forth in, like, 2001. I think
25 several Nobel Prizes were awarded for it. And so, it's click chemistry
26 involving an alkynyl and an azide, and it's known that you can just

1 functionalize whatever you want, whether it's drugs or proteins, with either
2 an alkynyl or an azide, and then, you have the opposite one on the other
3 molecule, and that's what, then, happens or then undergoes the click
4 chemistry reaction to attach the two.

5 Morales-Sanfrutos actually shows an example of doing exactly that
6 using biotin. So, it took biotin and functionalized it with an azide group, and
7 that, then, reacts with this triple bond alkynyl group to form the linkage.

8 So, what our expert said is, look, you can azide functionalize
9 anything you want, including cytotoxic drugs, and that was known. That
10 was known well before this patent. That's not something that these inventors
11 discovered.

12 So, I think that's how I would initially answer your question, Your
13 Honors but I'm happy to discuss that further, if you would like.

14 I can also, I think, illustrate it.

15 JUDGE NEWMAN: I understand.

16 MR. HOUSTON: Okay. I can also illustrate it on Slide 23. And
17 again, this was cited both in the opening expert declaration in paragraph 87,
18 and then, was discussed in more detail in the reply declaration. But this is
19 right out of this is Scheme 4, which the color figure you're looking at here
20 is Scheme 4 from Morales-Sanfrutos, and it's illustrating the alkynyl portion
21 on one of its molecules. That one happens to illustrate Compound 4.

22 Down at the bottom is the biotin that has been functionalized with
23 an azide group, and you get this click chemistry to attach the two. And that
24 always results in the heteroaromatic bond.

25 Your Honors, I suspect that what may have led to some confusion
26 about Claim 2 in the way it was addressed in the petition and the

1 accompanying declaration is that our expert also pointed out that the amine
2 portion if we could go back to Slide 22, please the amine portion of that
3 propargyl amine you see, for example, in Compound 2(a), 2(b) for the Z
4 group there's the alkynyl, there's that triple bond, but there's also the amine.

5 And what our expert did point out is that you can also attach a drug
6 to that reaction site. And, in fact, Morales-Sanfrutos illustrates that as well,
7 reacting that to a drug to form an amide bond and attach the drug that way.
8 And that's really just an alternate way of still meeting both Claims 1 and 2.
9 Claim 2 is the same because there's your amine group. For Claim 1, instead
10 of forming a heteroaromatic bond, that forms an amide bond. And again,
11 that was discussed in the opening declaration, and then, discussed again with
12 more explanation in the reply. So, Your Honors can see that, if you want to
13 see how we were applying those terms.

14 I will just finish by saying that second reading really isn't
15 necessary to our primary arguments. It was kind of put in there as a belt-
16 and-suspenders, just another way of doing it, sort of the same way we
17 mapped Morales-Sanfrutos in multiple ways in this table.

18 Another issue that I'll raise briefly is that, if Q and Y were
19 interpreted to exclude vinyl sulfone, our expert has pointed out, as
20 summarized on Slide 25, that there's another way to do this reaction. And
21 that is that the vinyl can be made to react with thiol groups on cell-binding
22 agents, just shown as here in this figure that you see on Slide 25. And that's
23 done by using a photo-induced reaction scheme, which, then, doesn't rely on
24 the sulfone at all. There is no sulfone in this reaction scheme. It shows that
25 vinyl alone can be made to react with thiols on cell-binding agents, and you
26 do that by including a photo initiator. And I'm not sure, I believe it's the

1 DPAP in that reaction scheme that you see there, acts as the photo initiator,
2 and that, instead, activates the vinyl, so that it connects to the thiol group.

3 And so, this would be another route for establishing that Morales-
4 Sanfrutos' Compound 2 has the functionality required by Claims 1 and 2,
5 just as we show in our table in B2, even if for some reason Your Honors
6 determine that you can't rely on the vinyl sulfone specifically or the
7 participation of the sulfone in that reaction.

8 I tend to think of it as the sulfone kind of provides an assist. When
9 vinyl sulfone reacts, sulfone does not actually react itself. It doesn't
10 participate in the reaction. It's sitting next to the vinyl and does provide an
11 assist to help the vinyl react, but it doesn't participate in the reaction itself.
12 And so, we think that's what's going on here, and there's just a different way
13 to make that vinyl react. You don't have to rely on the sulfone; you can just
14 use light and get the same reaction to occur.

15 Lastly on Ground I, the parties have had some back-and-forth
16 about Claim 3 regarding the construction of the cell-binding agent term and
17 as it relates to Morales-Sanfrutos' disclosure of HRP to satisfy that term.

18 I think our reply addressed those issues fairly well. We submitted
19 the declaration of Professor Baker, as well as her deposition transcript. I
20 think she definitively showed that HRP is known to be a cell-binding agent.
21 And I don't particularly feel the need to go into more detail and take up time
22 here, but, of course, I'm happy to address any questions or comments the
23 Board might have on that topic. Otherwise, I'll move on to Ground II.

24 Ground II

25 JUDGE NEWMAN: Just one

26 MR. HOUSTON: Yes, Your Honor.

1 JUDGE NEWMAN: which is, Patent Owner responds indicating
2 that the thrust of the patent is targeting cells and that Morales-Sanfrutos
3 would be a static cell, fixed, if I'm understanding that correctly, that
4 preserves the cells in their natural state. What is your comment on Patent
5 Owner's perspective?

6 MR. HOUSTON: Sure, Your Honors.

7 Dr. Baker went through the Straus reference and explained why it
8 demonstrates to a POSA that HRP binds to cells. Yes, it uses a technique
9 called cell fixation to conduct its experiments. And that's a technique where
10 you, basically, lock the cells into their existing state, just as they exist in
11 their living state or natural state, if you will. The idea is to lock them into
12 that configuration, not let them deteriorate, not let proteins leave or change.
13 And you use those cells to then conduct your cell-binding experiments. That
14 is a technique that has been well-known and used for decades. It is the
15 standard technique that is used to conduct cell-binding studies. Dr. Baker
16 herself estimated that she's done tens of thousands of these experiments.

17 And the idea is that you use this technique to determine what the
18 cell-binding properties are for a given protein. And Straus, in fact, does
19 determine that HRP binds to the surfaces of living cells of various types. It's
20 not all the same. You know, didn't see constant binding to every cell type.
21 It saw more binding in some cells, some cell types, and it saw less binding in
22 other cell types. And, in fact, Dr. Baker explained how that just bolsters
23 Straus' credibility in results and how a POSA would understand that, that it's
24 showing the binding to living cells.

25 Does that answer Your Honor's question?

26 JUDGE NEWMAN: Thank you. It does. Please continue.

1 MR. HOUSTON: Sure.

2 I'll move on briefly to Ground II. Ground II, the arguments there
3 from Patent Owner mostly address the same Q Y T Z claim construction
4 arguments. And really, those have been all the same as what we've already
5 discussed.

6 Their other argument for the Harris reference in Ground II appears
7 to just be that the disclosure in Harris is too broad to say that it anticipates
8 the claims.

9 The relevant disclosures from Harris are shown right here on our
10 Slide 30. And we think it quite clearly teaches linkers that have vinyl
11 sulfones on each end.

12 If you look at the formula that you see on the left that has an R and
13 a Y in it, not to be confused with the formula in the patent claims, this is
14 Harris' formula. And Harris goes on to teach in that little excerpt right
15 below the formula that Y can be one of two things. It can be vinyl sulfone
16 or it can be a haloethyl sulfone. So, it's one of two options for Y, and then, it
17 gives four options for R, one of which is, again, vinyl sulfone. So, vinyl
18 sulfone is one of only two expressly listed possibilities for Y and one of only
19 four expressly listed possibilities for R. And those express listings give a
20 total of eight combinations. We think that that allows a POSA to easily
21 envision the combination that involves vinyl sulfones on both ends of that
22 formula.

23 Not only that, we also point to a different part of Harris, and Your
24 Honors can find this at Harris, column 17. And I'll just point out that when I
25 say column 17, I do mean the column numbers at the top of the document,
26 not the page numbers at the bottom, which are a bit off. But column 17,

1 around line 5, slightly before, Harris also expressly discloses bis vinyl
2 sulfone. When you use the word bis there, that's a moniker for saying that
3 there's two. There's two vinyl sulfones in the molecule. So, it expressly
4 discloses the bis vinyl sulfone, and therefore, couldn't be any more clear in
5 terms of disclosing a linker with two vinyl sulfones.

6 And I'll mention, even though I don't think we specifically quoted
7 that bis vinyl sulfone language, we did cite this passage at multiple places in
8 the petition. At least pages 40 and 41 are probably the most relevant areas
9 where we cited that passage as well in the petition.

10 So, I'll just close by saying this is not a case where Harris is
11 disclosing a genus and the claims are covering a species. Harris discloses a
12 handful of distinct species, bis vinyl sulfone being one of them. And that
13 anticipates the challenged claims, as we've laid out in our papers.

14 The last thing I'll mention on that is we do need to make a
15 correction to the table that's on our Slide 31. In this table, it shows -- it
16 suggests that Harris' heterofunctional linkers those are linkers that have
17 vinyl sulfone on one end and something else on the other end. It suggests
18 that those heterofunctional linkers can be used to satisfy Claims 20 and 21
19 there.

20 But when this table was assembled, that limitation that was added
21 to the end of Claim 20 during re-examination was overlooked. And so, that
22 led to a mistake in the way this table was put together. So, we apologize for
23 that. The listing of heterofunctional linkers as satisfying Claims 20 and 21
24 in that table was an error and we apologize for any confusion that may have
25 caused.

26 If there are no questions on the topics I've covered so far, I would

1 like to turn it over to my colleague, Ms. Fernandes, to discuss the issues
2 specific to Grounds III through V.

3 Thank you.

4 MS. FERNANDES: May it please the Court. I'd like to start by
5 addressing Ground III of the petition, which challenges patentability in
6 Singh and Harris, starting from Slide 3 of our demonstratives.

7 Singh's figures show a variety of ADC linkers that include various
8 functional groups for the purpose of linking to a cytotoxic drug -- i.e.,
9 known as the Z group -- as well as other functional groups for the purpose of
10 linking two cell-binding agents, or CBAs, which is represented by the Y
11 group.

12 Exemplary Y groups that Singh shows in the figures do include
13 maleimides as well as haloacetamides. Although Singh doesn't show
14 sulfone groups in its exemplified linkers within its own figures, paragraph
15 134 of Singh does expressly suggest the use of vinyl sulfones as a thiol-
16 reactive functionality for attaching to cell-binding agents, and Singh does
17 teach the equivalence of vinyl sulfone to maleimides and haloacetamides for
18 the purpose of forming thioether linkages. Accordingly, Singh itself
19 suggests the interchangeability between maleimides, haloacetamides, and
20 vinyl sulfones for the purpose of linking to cell-binding agents, making the
21 use of vinyl sulfone as a simple substitution and rendering Claim 1 obvious
22 for at least that reason alone.

23 Additionally, turning over to Slide 34 of the demonstrative, Singh
24 does teach the benefits of having linkers that are more hydrophilic in nature,
25 one of which is to permit conjugation of high drug loads to an antibody,
26 while simultaneously preventing aggregation of precipitation, which

1 ultimately impairs clinical efficacy in vivo.

2 Accordingly, a POSA would have been motivated to further boost
3 or improve the water solubility of ADC linkers, so that they can be
4 conjugated to high loads of drugs, particularly hydrophobic drugs, which a
5 lot of chemotherapy agents are.

6 Moving on to Slide -- actually

7 JUDGE NEWMAN: Counsel, may I interrupt you there

8 MS. FERNANDES: Of course.

9 JUDGE NEWMAN: for a moment and ask you a question about
10 an allegation.

11 MS. FERNANDES: Yes, Your Honor.

12 JUDGE NEWMAN: So, Petitioner's allegations for Ground III
13 argued that the skilled artisan would have been motivated to substitute vinyl
14 sulfones. And then, there's a different allegation that said would have been
15 motivated to incorporate. Can you specify whether you mean substitute in
16 the sense that you are substituting at both ends entirely, or incorporate,
17 whether you are trying to add something to the molecule?

18 MS. FERNANDES: Well, the way we effectively treated it for our
19 purposes, Your Honor, we meant substitute. So, replace that particular thiol-
20 reactive functional group, so like the maleimide with the vinyl sulfone.

21 JUDGE NEWMAN: So, there are no maleimides in the molecule

22 MS. FERNANDES: Uh hum.

23 JUDGE NEWMAN: at the end of that?

24 MS. FERNANDES: Uh hum, uh hum. Which is consistent with
25 the mappings that we have provided throughout the petition, and then, also,
26 in the responsive reply, Your Honor.

1 JUDGE NEWMAN: Please.

2 MS. FERNANDES: So, as I was saying, in order to achieve --
3 improve hydrophilicity, a POSA would have been motivated to modify
4 Singh's plain language by replacing the maleimides or the NHS esters with
5 Harris' vinyl sulfones or other sulfones containing compounds disclosed in
6 Harris, such as the PEG bis vinyl sulfone which was already discussed, in
7 view of Harris' express teaching that sulfones containing PEG polymers are
8 infinitely water-soluble and enable otherwise insoluble molecules, such as
9 hydrophobic drugs, to be soluble in water. And the POSA would have a
10 reasonable expectation of success doing so because both Harris' sulfone-
11 containing PEG linkers and Singh's PEG linkers serve the same purpose;
12 that is, that they serve to attach two distinct biological molecules, such as
13 proteins and pharmaceuticals, via biolinkages. Harris also teaches that its
14 vinyl-sulfone-containing PEG linkers parent bio-based reactions which
15 result in hydrolytically stable bonds.

16 With that, turning to Slide 35 -- well, one particular concern that
17 we would like to address was a concern mentioned in the institution decision
18 at page 64, which was whether a POSA would be motivated to substitute an
19 NHS ester of Singh's PEG linker, which is shown to react with free amines
20 and proteins, with vinyl sulfone, as shown in Table C2 of the petition. And
21 this is illustrated on Slide 36.

22 So, per our petition, the excerpts put here are examples of Singh
23 linkers and the proposed substitutions. The full substitution on the left
24 assumes, like, an introduction of a single vinyl sulfone, where you have that
25 righthanded terminal NHS ester that's replaced with Q R T plus Y. And in
26 that case, the expectation is that's a single vinyl sulfone substitution.

1 On the right excerpt is pretty much our proposed mapping if two
2 vinyl sulfones were introduced, in which case the NHS ester would be
3 substituted with a single vinyl sulfone; thus, forming the Q and Y group, and
4 then, centrally located maleimide molecule, which is highlighted in blue,
5 which contains a blue highlight below, that gets replaced with another
6 sulfonyl ethyl group, which would then serve and satisfy the T R3 and R4
7 limitations.

8 So, moving on to Slide 37, with respect as to whether a POSA
9 would expect a vinyl sulfone group to be functionally interchangeable with
10 an NHS ester group, like NHS esters, Harris and Snow actually both
11 expressly disclose that vinyl sulfones can react with amines on proteins, like
12 if it's an antibody, and would, thus, form the same bonds. It does bond with
13 the same cell-binding agents or drugs as an NHS ester. The motivation for
14 doing so is as follows.

15 Getting back to Slide 36, as an example, looking at the lefthand
16 molecule, where we just performed a single vinyl sulfone substitution of the
17 NHS ester, it's like the benefit there is you can retain binding to your amine-
18 containing cell-binding agent or drug, but at the same time, by introducing
19 the vinyl sulfone right next to the PEG, it pretty much follows Harris'
20 teaching that PEG polymers along with vinyl sulfones have this elevated,
21 improved hydrophilic property. And given the importance of increasing
22 hydrophilicity in order to obtain this high drug-to-antibody ratio, there is
23 compelling reason as to why a POSA would be motivated to make that
24 modification.

25 If Your Honors have no further questions regarding Ground III,
26 you can proceed to Ground IV. So, Ground IV, that's starting from Slide 39.

1 So, Ground IV challenges the obviousness of Claims 9 and 13 in
2 view of Singh, Harris, and Bhakta. Both claims depend from Claim 3,
3 which is the conjugate claim, wherein you have a drug that's attached to the
4 hydrophilic linker via a variety of bond types, which include disulfide bonds
5 or peptide bonds.

6 Claim 9 calls out val-citrulline as a possible linking component;
7 whereas, Claim 13 specifies that the conjugate is cleavable via protease.

8 So, at the bottom of Claim 39, you see two excerpts. On the left
9 side is an example of Singh's linker that comprises the disulfide linkage, and
10 the val-Cit-PAB linker of Bhakta is displayed on the righthand side.

11 Moving on to Slide 40, both disulfide linkages and the Val Cit
12 PAB peptide linkages are taught in the art as being functionally equivalent,
13 in that they are cleavable by proteases in vivo. While disulfides and Val Cit
14 PAB linkers serve the same purpose, that is, to facilitate in vivo drug release,
15 one key important difference here is that the disulfide linkages are cleavable
16 by proteases such as protein disulfide isomerases, as well as thioredoxins,
17 which are proteases that are fairly ubiquitously expressed throughout the
18 body.

19 In contrast, the Val Cit PAB linkers are cleaved by a specific type
20 of lysosomal proteases known as cathepsins, like cathepsin B and an amine
21 component of B. And cathepsins are typically found in high concentrations
22 at tumor-specific sites. For that reason, a POSA would have been motivated
23 to replace Singh's disulfide linkages with the Val Cit PAB linkage of Bhakta
24 to obtain more selective and effective drug release at the target disease site
25 or the cancer, where more of the drug is warranted.

26 This substitution is depicted more clearly on Slide 41. And while

1 appreciating, Your Honors, what's shown on Slide 41 does look complicated
2 with all these chemical formulas, the reality is that the chemistry of the Val
3 Cit PAB linker, actually, was well-known and established and proven in
4 human clinical trials well before the priority date of DAC's patent. So, the
5 POSA would have had a reasonable expectation of making the substitution,
6 given how well the chemistry of the Val Cit PAB linker was at the time.
7 That's really

8 JUDGE NEWMAN: Counsel?

9 MS. FERNANDES: Yes? Yes, ma'am?

10 JUDGE NEWMAN: Let me start with a question here for you.
11 Okay.

12 The substitution of the vinyl sulfone for the N group of the cell-
13 binding agents

14 MS. FERNANDES: Uh hum.

15 JUDGE NEWMAN: the compound on the left

16 MS. FERNANDES: Yeah.

17 JUDGE NEWMAN: is the vinyl sulfone being substituted for
18 NHS ester?

19 MS. FERNANDES: That's correct. Because the NHS ester was
20 the precursor that led to the reaction with the free amine on the antibody.

21 JUDGE NEWMAN: And why is that being made? What's the
22 rationale for that substitution?

23 MS. FERNANDES: Much like we talked about in the earlier
24 slides, so going to Slide 36 hold on. Yeah, if we can bump up to Slide 36?

25 So, as pointed out earlier, Your Honor, the linker on the left would
26 be able to serve as, like, your precursor that led to that final conjugate that

1 we were talking about that was depicted under Ground IV.

2 It's like by replacing the NHS ester with the vinyl sulfone, you still
3 retain the ability to react with the free amine within a protein and form the
4 bond via the nitrogen group. The benefit there being the increased solubility
5 that's conferred by having that sulfone group adjusted to the PEG as taught
6 by Harris --

7 JUDGE NEWMAN: And so, what kind of bond are you saying
8 that the NHS ester would be replaced with?

9 MS. FERNANDES: So, we proposed swapping out the NHS ester
10 with vinyl sulfone. That particular amide bond, when switched with the
11 sulfone vinyl ethyl group, would form an amine boost. So, it would be
12 S(O)₂, CH₂, CH₂, and NH, and the antibody.

13 JUDGE NEWMAN: But why does it not form a thioether bond
14 there?

15 MS. FERNANDES: Because in this particular it can and that's
16 definitely one possibility. Because vinyl sulfones, on top of being able to
17 react with thiol groups and form thioether bonds, they can also under certain
18 conditions react with the free amines on proteins and link to form an amine
19 bond.

20 JUDGE NEWMAN: Okay. So, walk me through one more time

21 MS. FERNANDES: Uh hum.

22 JUDGE NEWMAN: why the POSA would look at this
23 compound and decide to substitute a vinyl sulfone for the purpose of
24 forming an amine bond from the motivation standpoint.

25 MS. FERNANDES: So, because, unlike you mean why would
26 the POSA be motivated to substitute the amide bond in the conjugate with

1 the vinyl sulfone? I believe that is what Your Honor is asking.

2 JUDGE NEWMAN: Yes. Yes. The substitution that's happening
3 on the right, next to the cell-binding agent.

4 MS. FERNANDES: Right. So, the motivation would be the same
5 advantages, properties would apply. By including that sulfone group instead
6 of the amide group, you do boost up the hydrophilic properties off the
7 conjugate as well.

8 JUDGE NEWMAN: And where in the record did you cite this in
9 the petition? Where in the petition is it cited as a motivation?

10 MS. FERNANDES: I'm happy to look up the I'm happy to go
11 back to the petition and look for more details, but I think we just referred
12 back to the same properties as discussed in Grounds II and III and replicated
13 the same rationale there. We might have it's like -- if I can reserve some
14 time to just go and look back at that, I can address that.

15 JUDGE NEWMAN: That's fine. Thank you.

16 Okay. Please continue.

17 MS. FERNANDES: All right. Moving on to Ground V, Ground
18 V asserts that Claims 2, 25, and 32 through 34 are obvious in view Singh,
19 Harris, and Snow.

20 Like Harris, Snow discloses various PEG-vinyl sulfone conjugates.
21 The key difference here in Snow being that the bis vinyl portion is directly
22 coupled to the PEG, represented by the PAO group, via an E group between
23 the PAO and the sulfone. And that's shown at the bottom left of Slide 43.

24 While on the right side is a general formula that was disclosed in
25 Harris, where you have PEG between R and Y, where R and Y can either be
26 vinyl sulfones or sulfonyl ethyl chloride.

1 Now, both Harris' and Snow's PEG vinyl sulfone conjugates do
2 serve the same purpose, in that they do show preferential reactivity with the
3 thiol sulfhydryl groups on proteins. So, they're being used for the same
4 purpose.

5 The following slide

6 JUDGE NEWMAN: Well, I have a question about that.

7 MS. FERNANDES: Yes?

8 JUDGE NEWMAN: There's two things that happened here.

9 MS. FERNANDES: Yeah.

10 JUDGE NEWMAN: Why would the skilled artisan have selected
11 "a" smaller-case "a", lowercase "a" to be one? And then, what is the
12 reason for the selection for uppercase E?

13 MS. FERNANDES: All right. So, "a" can vary between 1 through
14 8 carbon alkylenes. So, that would be like a single bond alkyl. So, "a"
15 could be anything ranging from a methyl to an octyl on the large end. "E,"
16 according to the description in Snow, can range between an ethyl to an octyl.
17 For the purpose of the simplicity of mapping, we just chose the lower end,
18 but even if we were to apply the higher end of the alkynyl groups, specified
19 under "E" and "a," we would still meet the definition. But for the purposes
20 of -- for the simplicity of mapping, we just chose the lower ends. But,
21 regardless of those limitations

22 JUDGE NEWMAN: Right. And for the motivation for that
23 choice?

24 MS. FERNANDES: Sorry. Repeat that again, Your Honor?

25 JUDGE NEWMAN: Oh, what was the POSA's motivation for
26 selecting what's used for uppercase E?

1 MS. FERNANDES: For uppercase A?

2 JUDGE NEWMAN: The E group.

3 MS. FERNANDES: The uppercase E?

4 JUDGE NEWMAN: E.

5 MS. FERNANDES: E.

6 JUDGE NEWMAN: I'm sorry. For E. There's no lowercase "e".

7 MS. FERNANDES: Certainly. Certainly.

8 So, E for the purpose of, once again, for the purpose of the
9 mapping, we chose the lower end, but it can still be at the higher end, which
10 would be so, what we're proposing is just taking that particular generic
11 formula with "E" that can either range from either 2 to 8 or "a" that can
12 either be 1 through 8. And they would still be and the motivation for using
13 that particular PEG-bis-vinyl sulfone agent would be the same. And I'm
14 happy to walk through in the following slides for that.

15 JUDGE NEWMAN: Yes, I think understand. Thank you.

16 MS. FERNANDES: So, if we could move on to Slide 44?

17 JUDGE NEWMAN: Just as a note, you have about two minutes in
18 the principal argument. You're welcome to go into your rebuttal time, if you
19 would like.

20 MS. FERNANDES: And thank you, Your Honor.

21 So, once again, both Harris and Snow have discussed PEG spacers
22 with sulfone groups. Harris discloses that PEG spacers that include these
23 sulfone moieties that are highly water-soluble. So, the rationale for making
24 the substitutions here would be a POSA would be, once again, motivated to
25 improve the solubility of Singh's PEG linkers conjugated to exceptionally
26 hydrophobic drugs to achieve high drug loads that are prone to aggregation

1 and precipitation.

2 What we wanted to walk through specifically, Your Honor, is on
3 Slide 45. And this is in response to a question raised in the institution at
4 page 72, where it is our position that a POSA would have been motivated to
5 replace the entire maleimide-containing arm, which includes these
6 intervening amide linkages outside of the PEG group, which Snow defines
7 in the sulfone group for the purpose of enhancing hydrophilicity of the
8 linkers. This particular substitution, Your Honor, is simply a matter of
9 practical chemistry.

10 So, looking at Slide 45, in order to accomplish or in order to
11 attach the maleimide to a PEG, what Singh's linkers show is like an NHS
12 ester reaction to a PEG. Right? So, the resulting intervening amide linkages
13 that you see are pretty much remnants of that NHS ester reaction. So, the
14 intervening amide linkages, you know, merely just facilitate attachment of
15 the PEG moiety to the terminal maleimide group.

16 Unlike the above bis-maleimide PEG linkers of Singh, the thiol-
17 reactive vinyl groups that are discussed in Snow and Harris are directly
18 coupled to PEG without the need of any intervening amide linkages. And
19 that is shown more in detail in Slide 46, which is an exemplary scheme.

20 So, given that you can facilitate the straightforward attachment off
21 the PEG vinyl sulfone reagents of Snow or the PEG bis vinyl sulfone region
22 of Harris directly to the PEG, there is no need for these intervening amide
23 linkages. So, not only would these intervening amide linkages be
24 unnecessary, they wouldn't be present when you are taking these starting
25 reagents of the vinyl sulfone reagents of both Snow and Harris and coupling
26 them straight to the PEG.

1 JUDGE NEWMAN: All right. You have reached your time.

2 MS. FERNANDES: Yeah.

3 JUDGE NEWMAN: Would you like to go further into your
4 remaining time or do you --

5 MS. FERNANDES: Just one last comment, Your Honor, and
6 that's with the following slides, which would be 47, 48, and 49, pretty much
7 show the substitutions schemes, as discussed earlier by replacing the
8 maleimide-containing arms of Singh's linkers with the reagents of Snow or
9 the reagents of Harris. And that's clearly depicted out there to show that we
10 satisfy all the claim limitations of Claims 2, 25, 32 through 34.

11 If there are no further questions, Your Honor, we'd like to reserve
12 the remaining time for rebuttal.

13 JUDGE NEWMAN: I do have one question about that.

14 MS. FERNANDES: Yeah?

15 JUDGE NEWMAN: Earlier when I asked you about replacing the
16 maleimides

17 MS. FERNANDES: Yeah.

18 JUDGE NEWMAN: you indicated that it was substituted at both
19 ends of the molecule, but that figure does not show substitution at both
20 ends --

21 MS. FERNANDES: So, that was for Claim --

22 JUDGE NEWMAN: -- which was --

23 MS. FERNANDES: So, for demonstrative so, for Slide 47, Your
24 Honor, that's the substitution scheme for Claim 2, where the limitation is like
25 where you can comprise maleimide. So, that just assumes, like, one single
26 substitution scheme.

1 But to get to your point, Your Honor

2 JUDGE NEWMAN: And where was that slide in the petition?

3 MS. FERNANDES: This well, let me pull up that initial cite in
4 the petition, Your Honor, and I can address that during rebuttal as well.

5 JUDGE NEWMAN: All right. Thank you.

6 MS. FERNANDES: Thank you, Your Honor.

7 JUDGE NEWMAN: Okay. We'll move to Patent Owner. I show
8 Petitioner as having 18 minutes left for rebuttal. Mark that.

9 And we are going to start, and then Patent Owner wishes to reserve
10 15 minutes. So we have 45 minutes for initial arguments.

11 And, Patent Owner, please let me know when you're ready. Take
12 your time.

13 MR. CALVOSA: Ready, Your Honor.

14 JUDGE NEWMAN: You may begin.

15 MR. CALVOSA: May it please the Board, Frank Calvosa from
16 Quinn Emanuel Urquhart & Sullivan on behalf of Patent Owner.

17 As you heard in Petitioner's presentation, this IPR largely turns on
18 claim construction, and we're going to get there, and we're going to go
19 through, and we're going to see why they're incorrect on the Y term and why
20 they're incorrect on the cell-binding agent term as well.

21 But before we get there, I want to talk a little bit about what this
22 invention is. And I know we have 108 slides. I promise I'm not going to go
23 through them all, and I'm going to jump around a bit, and I will remember to
24 direct to the correct slide number the best I can.

25 So, if we go to Slide 15, what we have here is a general structure
26 of a linker. And on the sides are conjugation moieties, and those are

1 represented in the claims at issue here as the Y claim element and the Z
2 claim element.

3 In the middle, we have spacer elements. Those are the R groups
4 and importantly here the Q and the T groups. The Q and the T groups here,
5 if we go to Slide 16, are defined in the claims as either phosphinate, sulfone,
6 or sulfoxide. Along with the other claim elements, that's really the invented
7 feature of these claims. The inventors found that using these Q and T
8 components for the spacer elements led to hydrophilic linkers that reduce
9 aggregation of conjugates, result in a higher potency for the conjugates, and
10 allow the drug to be retained inside the target cell after the drug linker is
11 released from the conjugate. Because what this patent is all about, as Your
12 Honor recognized before, is the targeted delivery of drugs to a cell, for
13 example, a cancer cell in the body.

14 Going to Slide 17, I want to point something out. Petitioner is
15 trying to conflate the Y and Z claim terms. And I heard opposing counsel
16 say those claim terms use identical language. That is wrong.

17 As you see in the claim, both Y and Z must be functional groups,
18 and that's important, and we'll get to what a functional group is, as their
19 expert explained to us. But Y is a functional group that enables reaction,
20 while Z is a functional group that enables linkage. And there's a difference
21 in that.

22 And again, you don't have to take my word for it because
23 Petitioner's expert told us that. And through Petitioner's expert testimony, he
24 also told us that vinyl cannot be Y because vinyl does not enable reaction.
25 He repeatedly testified to that, and we'll get to that testimony as well.

26 As Federal Circuit case law holds, when claim language is

1 different and claim terms are different --

2 JUDGE NEWMAN: Counsel, I'm sorry to --

3 MR. CALVOSA: Yeah?

4 JUDGE NEWMAN: I'm sorry to stop you for just a moment.

5 We're having an audio connection issue. We're going to pause the time.

6 MR. CALVOSA: Okay.

7 JUDGE NEWMAN: And we're going to do a quick reconnection,
8 so that we can hear every word you're saying.

9 MR. CALVOSA: Understood.

10 JUDGE NEWMAN: We're off the record.

11 (Whereupon, the above-entitled matter went off the record at
12 2:06 p.m. and resumed at 2:08 p.m.)

13 JUDGE NEWMAN: We are back on the record. Yes?

14 MR. CALVOSA: Did you hear everything up until we stopped? I
15 just don't know where I cut out.

16 JUDGE NEWMAN: I did, yes.

17 MR. CALVOSA: Okay. So, as Federal Circuit case law holds,
18 when you have different claim terms with different language, they are
19 presumed to have different meanings minus some strong evidence showing
20 otherwise, which Petitioner has not pointed to for the Q sorry for the Z
21 and Y terms.

22 And I want to address, too, that the DRP decision is not
23 controlling. While Petitioner's counsel is correct there's no case law that has
24 addressed this new procedure yet, the Federal Circuit spoke in the
25 TriVascular case. It's at 812 F.3d 1068 pincite. And they said and I'll sum
26 it up for you. This is on Slide 19, the full quote. "But the Board is free to

1 change its view after institution, and should do so, as the record proceeds."

2 And as we saw in the DRP decision, in the conclusion, it based its
3 decision on, quote-unquote, "the present record," which did not have the
4 benefit of Dr. Chari's testimony at deposition and was solely based on a
5 prosecution history disclaimer argument. That is not what is at issue now in
6 the IPR after we have Dr. Chari's testimony.

7 So I'd like to move now to Slide 45. And I mentioned the term
8 that's shared between Y and Z, and that's a functional group. And Dr. Chari
9 agreed that a functional group means a specific identifiable group of atoms
10 within a molecule that directly contributes to its characteristic chemical
11 properties and reactivity. So, Y has to be a functional group, a particular
12 group of atoms that enables the reaction.

13 As we go to Slide 52, we asked Dr. Chari at deposition, is a vinyl
14 sulfone functional group different than a vinyl functional group?

15 And he said yes, it is. The vinyl sulfone group is much more
16 reactive. And he agreed, a POSA would have known in 2012, the priority
17 date for the patent, that vinyl and vinyl sulfone are different functional
18 groups.

19 If we go back to Slide 51, we asked Dr. Chari, because he had
20 mentioned that vinyl wouldn't react by itself, why wouldn't vinyl react by
21 itself?

22 He says it's not reactive. You need to have something next to it to
23 make it react, to enable the reaction.

24 And that's exactly what Petitioner's counsel said during the initial
25 presentation. When talking about the vinyl sulfone, he said the sulfone
26 assists the vinyl. When talking about the DPAP in Dondoni, he said the

1 DPAP the vinyl could be made to react with it. Can be made to react
2 means to enable, but the vinyl is not enabling. The DPAP is in Dondoni.
3 The sulfone is in the Morales reference and the other references that they
4 rely upon. And again, we'll get to Dr. Chari's testimony telling us just that.

5 So we asked Dr. Chari again, why would a POSA understand that
6 vinyl is unreactive by itself?

7 And he said a POSA would know what makes a reaction happen.
8 The carbon does not charge enough for it to the way reactions work is you
9 need to have an attack on the carbon. The carbon is not positively charged
10 enough for the reaction to occur. It needs something to activate the carbon,
11 something to enable the reaction.

12 The vinyl functional group does not enable the reaction. The same
13 is true of alkaline. These are carbon double bonds or triple bonds held
14 together. They're happy where they are because they have their electrons
15 there; they are not charged.

16 If we go to Slide 53, we specifically asked Dr. Chari, in the vinyl
17 sulfone, what is the atom that's enabling the reaction?

18 Remember, it has to be a functional group that's enabling the
19 reaction. For their argument to work, it has to be the vinyl that enables the
20 reaction. But what did Dr. Chari say?

21 He said you need some group that will activate. You need the one
22 that helps draw electrons from the vinyl to make it react. Sulfone would be
23 the reason why it would react.

24 On the right-hand side, so sulfone would be what would be
25 enabling the reaction?

26 Dr. Chari's unequivocal testimony, exactly.

1 If you remember nothing else from this presentation, that is what
2 you should take away because vinyl does not enable the reaction. Vinyl does
3 not meet the claim term.

4 Now, linkage is different than reaction. And if we go to Slide 27
5 remember, I told you we would see it from Dr. Chari? We asked him, what
6 would a POSA understand linkage to mean in the context? He said just to
7 connect the link together. It means to connect. You could say it's a covalent
8 bond.

9 Continuing on Slide 28, we then asked him what a POSA would
10 understand the reaction to be? And he said the reaction is how you get that
11 linkage together. So the carbon double bond or the alkaline triple bond
12 could enable linkage because once something enables the reaction, that bond
13 unfolds; it opens up. It enables the linkage, the connection.

14 Think of Legos. You have those round I don't know what you
15 call them the round things that stick out of the top of Lego blocks and the
16 round holes on the bottom of them. The round things on the top enable
17 linkage, but sitting there, that Lego block is not enabling the reaction. It
18 needs a hand. It needs a person. It needs that assist that opposing counsel
19 was talking about to enable the reaction, to enable the linkage. They're
20 different terms.

21 And we don't dispute that you need a reaction to enable the
22 linkage, but the claim term solely requires enabling linkage for Z, but Y, Y
23 itself, must enable the reaction. That's what the claim language says.

24 I want to now talk about the prosecution history and the examples
25 from the specification that the DRP decision relied upon. And if we go to
26 Slide 46 for that, we could see there that in each of the examples that the

1 DRP decision relied on, the vinyl is Z. Vinyl is never Y, and Petitioner
2 cannot point to any example in the specification where vinyl is Y. It just
3 doesn't exist there. And the specification is the single best evidence, aside
4 from the claims themselves, of what the claim term means.

5 But even assuming they flip these around, which they're not
6 flipped the other way in the specification, and I'd invite the Board to look
7 right there, and we haven't heard otherwise from Petitioner. But even if we
8 were to flip these around, we asked Dr. Chari in these structures what would
9 be Y.

10 And if we could go to Slide 54, compound 75 is showing the vinyl
11 as a Y. We asked him. We invited him to agree with his own --with
12 Petitioner's position. He said vinyl sulfone, I would say. Vinyl sulfone is Y.

13 The vinyl sulfone, in your opinion, together is Y? Again,
14 unequivocally, exactly. And he did that for all of the compounds depicted,
15 and then one more which we found on our own in the specification as well.

16 If you turn to Slide 65, Dr. Chari's answer was no different in the
17 context of Morales. They rely on compound 11.

18 And we asked him, what part of that molecule would correspond to
19 Y that enables reaction with the horseradish peroxidase, which we'll get to,
20 is not a cell-binding agent, but accepting it for this question.

21 Dr. Chari again said the vinyl sulfone in compound 11. And we
22 said, why do you say that? Because it's the only reactive group left.

23 Not the vinyl alone? No. I think vinyl alone will not react.

24 Again, when asked what Y is, for their theory to work, it has to be
25 vinyl, not what their own expert said at deposition. Vinyl sulfone is what he
26 said.

1 Walking through now the prosecution history, which we already
2 have the claims that support Patent Owner's construction, the specification
3 that's, of course, Patent Owner's construction. The prosecution history
4 doesn't lead to a different result.

5 So if we go, first, to Slide 35, what the DRP decision relied upon
6 was a response to a rejection overcoming the Lees reference, and very
7 clearly there, vinyl is not what the Patent Owner said Y is. They said it for
8 Z. Again, Z is different. It just has to enable linkage; it doesn't have to
9 enable reaction, like Y does. Z is vinyl; Y is not.

10 Moving on to the next portion that we saw counsel rely upon, if we
11 go to page 42 of the slides, we heard opposing counsel said aha, Patent
12 Owner admitted that Y could be vinyl during the prosecution history for
13 Claim 20. All Patent Owner said in repeating the examiner's argument, the
14 portion allegedly corresponding to Y.

15 For Applicant's statement in the prosecution history to be in
16 agreement with the examiner, Federal Circuit case law, the 3M Innovative
17 case holds, 350 F.3d, at pincite 1373 through 74, that it has to be clear and
18 unmistakable acquiescence to the examiner's characterization. Putting
19 "allegedly discloses" before what the examiner said is not clear and
20 unmistakable acquiescence. If that was the case, every brief written would
21 rise to the level of clear and unmistakable acquiescence.

22 I want to now move on more specifically to Ground I, although we
23 already saw Dr. Chari testifying that the Y in Morales is not vinyl; it's the
24 vinyl sulfone. But I did want to address the Dondoni reference that's
25 brought in. I touched on it briefly.

26 But we also have Dr. Chari's testimony there on Slide 72. And if

1 you look at the right-hand side, what Dondoni is describing is a UV light-
2 induced reaction using that DPAP radical initiator that counsel said would
3 provide the assist; it's going to make it react, enables the reaction of the
4 vinyl itself.

5 And we asked Dr. Chari, second question down, so without the UV
6 light the vinyl group in compound 1(a) will not react with BSA; right?

7 He goes, that's what I think. You need some radical catalyst. You
8 need something to enable the reaction. The vinyl is not enabling the
9 reaction.

10 Similarly, if we go to Slide 73, for the alkaline groups that they
11 rely on, the triple bonds, Dr. Chari agreed there's not a single example in
12 Morales's reference of an alkyne reacting with a cell-binding agent. It
13 doesn't show that it enables reaction. There's no evidence there. There's no
14 evidence anywhere. And that's at pages 30 to 32 of Exhibit 2037, his first
15 deposition.

16 And at his second deposition, at page 61, lines 8 through 10, he
17 confirmed that a terminal alkyne would need a copper catalyst, similar to
18 Dondoni for the vinyl. That multi-bond carbon is not enabling reaction.
19 You need something else.

20 I'd now like to move on to the cell-binding agents, if there's no
21 questions on Y. And for the cell-binding agent, if you go to Slide 57, you
22 will see that Patent Owner's construction is what makes sense in the context
23 of this patent. A cell-binding agent is a molecule that binds to, complexes
24 with or reacts with a moiety of a cell population sought to be therapeutically
25 or otherwise biologically modified.

26 That's what this patent is all about, delivering drugs to a specific

1 cell through the use of a cell-binding agent. The cell-binding agent, with the
2 help of the linker, finds the cell that it's targeting.

3 And if we look at the specification, we have, if not clear
4 lexicography, strong evidence from the specification on Slide 58 which says
5 that a cell-binding molecule that comprises the conjugates and the modified
6 cell-binding agents of the present invention may be of any kind presently
7 known, or that become known, molecule that binds to, complexes with, or
8 reacts with a moiety of a cell population sought to be therapeutically or
9 otherwise biologically modified. That's Patent Owner's construction right
10 from the specification.

11 Now, Petitioner tried to make a big deal on Slide 27 of their set,
12 their demonstratives, that Patent Owner's expert Dr. Tumey said well, a cell-
13 binding molecule is different than a cell-binding agent, and therefore this
14 definition doesn't apply. They cite four lines of testimony. It doesn't show
15 the -- it doesn't show the question; it doesn't show the complete answer.

16 It doesn't show the follow-up questions that continue onto page 61
17 of his deposition, where he explains that the patent uses the terms
18 synonymously because this cell-binding molecule, what allows for the
19 binding of the complex and the reacting is the cell-binding agent portion.
20 That is what does it in the molecule, and that's what Dr. Tumey explained,
21 and that's what Petitioner did not show you today.

22 In Morales now, I'd like to move on to Slide 77. Morales does not
23 disclose that horseradish peroxidase, and I'll say HRP, is a cell-binding
24 agent. It's used as a reporter for biological assays in that reference, and
25 Petitioner knows that.

26 So what did Petitioner do? Well, similar to bringing in Dondoni

1 and -- for the alkyne references, they brought in about 10 of those, they add
2 Straus from 1986 and other Straus references from before that. I think if I
3 counted correctly, Petitioner is up to about 15 references for their
4 anticipation ground.

5 That's not how anticipation works. It needs to be a single
6 reference, everything within the four corners in the way it's arranged in the
7 claim. You can rely on secondary references if it sheds light on what is in
8 the primary reference.

9 That's not what they're doing here. They rely on Straus, and in
10 Straus, as Dr. Chari testified, those are highly artificial conditions. It's a
11 reference from 1986, where it's all the support they found for HRP allegedly
12 acting as a cell-binding agent.

13 And Dr. Chari couldn't even testify to that. They bring in Dr.
14 Baker. Now, what Petitioner left out, it's very clear from Dr. Baker's
15 declaration, Dr. Baker is not a POSA. She doesn't qualify under Petitioner's
16 own definition which Patent Owner has adopted.

17 To opine on invalidity, under Federal Circuit law, once again, you
18 have to be a POSA. Dr. Straus is not a POSA, and horseradish peroxidase is
19 not a cell-binding agent. Those highly artificial conditions

20 JUDGE NEWMAN: Counsel, did you raise the issue of Dr. Baker
21 not being a POSA anywhere during the trial?

22 MR. CALVOSA: We did not, Your Honor. It is their burden to
23 establish that she is a POSA, and that comes directly from her declaration
24 that she is not. She does not have the education that would qualify her.

25 JUDGE NEWMAN: And you did not move to strike or exclude
26 the testimony on that basis, correct?

1 MR. CALVOSA: Not on that basis, Your Honor, that's correct.

2 JUDGE NEWMAN: Thank you. Proceed.

3 MR. CALVOSA: Okay. So for those reasons, Petitioner cannot
4 satisfy their burden on Ground I, both the Y term, the cell-binding term. If
5 no questions, I'll move on to Ground II.

6 Ground II is where we have Harris and anticipation and
7 obviousness. And if you remember from Slide 30 of Petitioner's
8 presentation well, let me start with something else.

9 If we win on our constructions, we win on Harris. But even if we
10 lose on our constructions, Petitioner said in Ground in Slide 30 of their
11 presentation, Harris only has a couple examples. There's eight of them if
12 you put them all together. Well, that's because Petitioner only showed a
13 very small portion of Harris.

14 If we look at Slide 87, when you look at the prior art reference as a
15 whole, as Federal Circuit case law requires we do, the options become much
16 broader. You have a much broader genus.

17 And as the Federal Circuit taught us in Atofina v. Great Lakes
18 Chemical case, and this is at I'll get you a pincite for that. That is 441 F.3d
19 at 991, and it's been followed by various courts since for both anticipation
20 and obviousness. When you have a broad genus in the prior art, you can't
21 just pick and choose to come up with a compound to allegedly anticipate or
22 render another reference obvious. And that's what Petitioner does. I'll go
23 into the motivation a little bit more, but that's, first and foremost, the issue
24 that's here.

25 And we asked Dr. Chari on Slide 88, because it's Petitioner's
26 burden, did you do any calculations to see how many different total numbers

1 of linkers and spacers and conjugation moieties could be used, and he said
2 no. Did you know the possible number of total combinations? Again, no.

3 There's no evidence that a POSA looking at Harris would at once
4 envisaged as the compound that they rely upon to try to make their case.
5 Their argument fails for anticipation, based on Atofina, and it also fails for
6 obviousness; it is hindsight.

7 Moving on to Ground III, we have the Singh reference in view of
8 Harris. And I'll point out that the Singh reference, if we look on Slide 91, is
9 very near in time to the priority date of the '682 Patent. The Singh reference
10 is May of 2010, and the '682 Patent is from 2012.

11 And notably, if you look at the inventors, or the named inventors,
12 on the Singh Patent publication correction there, it's not a patent; it's a
13 patent publication you see the last one right there is Dr. Chari. This is his
14 own reference.

15 And we asked Dr. Chari about Singh at deposition. And I think
16 what's important, and I wanted to note this, is that you had asked counsel
17 this difference between incorporation versus substitution of the vinyl sulfone
18 based on Singh. And we believe they started with incorporation. Now,
19 they're saying substitution. That was our understanding as well, is that they
20 were saying incorporation at first.

21 But when Dr. Chari was asked at deposition, this is on Slide 98,
22 because their only motivation theory is better hydrophilicity, better
23 solubility. It's for every ground where they offer obviousness. We asked
24 him, so with your publication in 2010, you thought it was sufficient to use
25 PEG alone to achieve hydrophilicity?

26 He said right. For what we needed, yes. Asked him, did you have

1 any regret about that? No.

2 And then, in your view, there was no reason to add anything else?

3 Not at that time, right.

4 And Petitioner and Dr. Chari cannot identify anything else between
5 2010 and 2012 to allegedly increase hydrophilicity with a vinyl sulfone,
6 either incorporated in or substituted in. Instead, they look back to 1995,
7 whether for the Singh combination or any of their other ones, or Harris
8 alone. They rely on the 1995 Harris reference and say somebody's going to
9 go backwards, and they're going to do it differently.

10 And again, if we win on construction, we win. No issue here. But
11 if we lose, this is at issue because it just shows the hindsight that they're
12 using. Somebody's going to go and work backwards instead of forwards.

13 And the Federal Circuit in

14 JUDGE NEWMAN: Counsel?

15 MR. CALVOSA: Yeah.

16 JUDGE NEWMAN: Counsel, a question for you. Do you have
17 any evidence that it would not have been within the skill of the artisan to
18 make the substitutions? Or do you concede that it was within the skill of the
19 artisan to do so?

20 MR. CALVOSA: The response to that is I don't believe that's the
21 correct question under Federal Circuit law. And I don't mean to speak

22 JUDGE NEWMAN: I understand.

23 MR. CALVOSA: Yes.

24 JUDGE NEWMAN: I understand that. I think it's a portion of the
25 KSR inquiry, and I'm just trying to understand that there's no dispute
26 regarding whether or not a POSA would have been capable of doing so.

1 MR. CALVOSA: Correct, and I there's no dispute on that.
2 There is a dispute under Federal Circuit law whether and I'll recite the
3 Federal Circuit law as the question is not whether a POSA could modify the
4 prior art. The question is whether a POSA would have been motivated to do
5 so. And we are not disputing --

6 JUDGE NEWMAN: Yes, and

7 MR. CALVOSA: -- that a POSA could it if it was within their
8 skill.

9 JUDGE NEWMAN: Continue. Thank you.

10 MR. CALVOSA: And on the motivation question, whether there's
11 evidence both for motivation and reasonable expectation of success, which I
12 didn't hear that phrase at all when Petitioner was up, you have to be
13 motivated to modify with a reasonable expectation of success you're going
14 to get your result. Petitioner's burden on both. There's no evidence that
15 using a vinyl sulfone group or the halo-ethyl sulfone group that they rely
16 upon from Harris, from Singh, from any other reference will increase the
17 hydrophilicity, will increase the solubility.

18 And we know that because we asked because we asked Dr. Chari
19 that at Slide 100. He has no calculations. He has no data. This is Exhibit
20 2046, page 114, line 9, through page 116, line 2. They have no evidence to
21 support their motivation theory, and we haven't even heard about reasonable
22 expectation of success, which is also required under Federal Circuit law.

23 Stepping back to Slide 92, I believe I heard Petitioner admit it, and
24 I know their expert admitted it at deposition. There is not one structure in
25 Singh that uses vinyl sulfone as the reactive functionality, not a single one of
26 them. And there, too, Petitioner relies upon hindsight to search through the

1 reference and find one paragraph where, out of many reactive functionalities
2 listed there, vinyl sulfone is listed.

3 But if you look at paragraph 14 on the left here, on Slide 92, from
4 Singh, it says the reactive functionality represents Z, and that has to form the
5 bond. It has to enable reaction. That's what it's saying. So again, under our
6 construction, this would not suffice, either.

7 The arguments for Grounds IV and V are largely the same that you
8 heard. If we win on claim construction, we win. And also, the hindsight
9 that is used and I'll draw your attention to Slide 108 to really illustrate the
10 hindsight for Ground V. They try to pick and choose through the
11 specification to try to come up with a compound that allegedly would render
12 ours obvious, a combination from many different areas, from many different
13 substituents to choose from.

14 Snow, again, discloses a broad genus. Notably, it disclosed
15 preferred, more preferred, and even more preferred embodiments. Their
16 compound doesn't fall within any of those.

17 You have to look back at the time before the invention, right
18 before it, without the benefit of hindsight, without the claims, looking at the
19 prior art, would a POSA come up with what's claimed. There's no evidence
20 of that.

21 And I know I have about 14 minutes remaining, but I'm through
22 my presentation. And obviously, if you have questions, I'm happy to answer
23 them, but, otherwise, I'll sit down and then use my reserve time as needed in
24 response to what Petitioner says.

25 JUDGE NEWMAN: Give us just a moment before you sit down.

26 MR. CALVOSA: Yes, Your Honor.

1 JUDGE NEWMAN: I think we are okay for now. We will reserve
2 those 14 minutes to add onto your 15 reserved.

3 And we can have Petitioner come back up.

4 MR. CALVOSA: Thank you, Your Honor.

5 JUDGE NEWMAN: And we have 18 minutes for Petitioner.

6 MR. HOUSTON: May it please the Court. I'd like to address
7 opposing counsel's comments regarding the claim construction issue and a
8 few comments on Grounds I and II before turning it back over to my
9 colleague.

10 Opposing counsel went through a lot of testimony from Dr. Chari
11 during his deposition. None of that testimony adds anything new. None of
12 it adds anything that we didn't already know prior to that testimony.

13 There is no dispute, we have never disputed that in a Michael
14 addition-type reaction, the one that's expressly shown in Morales-Sanfrutos,
15 the vinyl the sulfone adjacent to the vinyl does help that vinyl be more
16 reactive. There's nothing new about that. It was in their expert's opening
17 declaration in the preliminary response. All of that was before the DRP and
18 this panel, when each of you made your respective decisions.

19 The issue is that the claim terms are supposed to be interpreted in
20 accordance with the prosecution history. That is expressly stated in 37 CFR
21 100(b), this tribunal's rules.

22 And what the DRP did in the first instance was go look at that
23 prosecution history and see that the Applicant see how the Applicant was
24 treating the claim terms, whether it's calling for the Y or the Z enables
25 reaction, enables linkage, and Q and T.

26 And what came out of that investigation of the original prosecution

1 history is it was unmistakable that the Applicant was treating vinyl and
2 sulfone, even when they are vinyl sulfone group, as able to satisfy either the
3 Q and Y or the T and Z.

4 And so however you want to break it up, whether you want to say
5 the vinyl sulfone is the functional group and the sulfone is simply
6 participating as part of the Q or as part of the Y or Z, and also satisfying
7 the T or Q, that's fine. Or you can consider it in terms of what's actually
8 reacting. In both cases, it's the vinyl that's actually reacting.

9 You can look at it either way. The point is the prosecution history
10 makes clear that the Applicant is treating vinyl sulfone as meeting those two
11 limitations.

12 What you heard opposing counsel say very little about is the
13 prosecution history that happened during the re-exam. That's where Y was
14 expressly mapped to vinyl; Q was expressly mapped to sulfone.

15 And opposing counsel tried to use the language of clear and
16 unmistakable acquiescence. They've been trying throughout their papers to
17 suggest that it's us seeking a disclaimer or a disavowal of claim scope, and
18 nothing could be further from the truth. The reality is just the opposite.

19 They are the ones seeking to limit the meaning of Q and Y to
20 exclude vinyl sulfone. So they are the ones that are seeking to disclaim
21 claim scope through their arguments. They are the ones that need to show a
22 clear and unmistakable disavowal of that claim scope.

23 And they can't point to anything. And, in fact, that's because the
24 evidence actually shows just the opposite. And I think that was most clearly
25 shown with the rejection of Claim 20 and the Applicant's response to that
26 objection.

1 Yes, the Applicant used the words that Y was allegedly mapped to
2 vinyl. They showed it in their mapping. So they acknowledged that that's
3 what the examiner had done. They did not take issue with it.

4 And what they did affirmatively do is introduce a claim limitation
5 to overcome that, introduce a claim limitation that only in very specific
6 circumstances then excludes vinyl sulfone. That is an acquiescence. That is
7 an affirmative act that the Patent Owner took to indicate their agreement
8 with the mapping and to then adjust their claims to avoid it, again, only in
9 the limited circumstance where there is a single sulfone in the linker, not
10 multiple sulfones.

11 So we think that is a clear and unmistakable agreement with the
12 examiner. Certainly, they have not shown any clear or unmistakable
13 disavowal of claim scope, aside from the claim amendment that they
14 inserted during that prosecution.

15 That's the exact same analysis that the DRP went through. So
16 regardless of whether you think that DRP decision should continue to be
17 binding, we think it's very instructive, and this panel should undergo the
18 same analysis. Look at exactly what was laid out by the examiner and what
19 the Applicant did in response, and they parallel each other almost
20 identically.

21 Now, it is true that in the re-examination they didn't have the
22 further statement that these amendments are supported by blank. And I
23 suspect that's because they actually don't have support in the spec for those
24 amendments. That's not at issue here. We haven't gotten into that. I don't
25 know, but I just want to make it clear that that may be one reason why you
26 don't see that added statement from the Patent Owner during the re-

1 examination.

2 So again, I also want to make clear that the sulfone assisting the
3 vinyl is something that happens in the Michael addition-type reaction. All of
4 that testimony you heard from Dr. Chari, he clarifies he's talking about the
5 Michael addition-type reactions. You can look at his reply declaration,
6 Exhibit 1076, starting at paragraph 6, and he explains all of this.

7 Alternatively, there's another way to get vinyl to react. It does not
8 depend on the sulfone. That's with the photo-induced reaction.

9 For some reason, Patent Owner wants to read into the claims some
10 prohibition against that as well. That's nowhere in the claims. It's nowhere
11 in the specification.

12 You can find throughout their specification examples of where
13 they have things present in various reaction schemes, like acids, for
14 example, to assist the reactions. Acids are acting as catalysts just the same
15 as photo initiators are for light. So there's just no indication in the patent
16 whatsoever that you should be carving out things from the claims in the way
17 that Patent Owner is suggesting that you do here.

18 The claim language functional group that enables is the same for Y
19 and Z, and there's simply no reason to interpret that portion of each of those
20 claim terms differently as between them. But to make no mistake about it,
21 that's exactly what Patent Owner is asking you to do.

22 Counsel mentioned the TriVascular case and said for the
23 proposition that the Board is free to change its view after institution. I don't
24 dispute what the TriVascular case says, but it is talking about the Board's
25 institution decision versus final written decision. It does not speak to what
26 does the Board do when there's a DRP decision. We just don't know what to

1 do. So, in that situation, the TriVascular case certainly doesn't answer that
2 question.

3 Counsel said something to the effect that we're up to 15 references
4 for showing anticipation, and that's just absolutely false. The anticipation
5 we're relying on in Ground I is are the molecules right there expressly
6 disclosed in Morales-Sanfrutos.

7 Now, do we rely on Straus to show that it was known in the art that
8 HRP is not only a reporting molecule, but also a cell-binding agent? Sure,
9 we do, and that's perfectly allowed. We don't have to show that Morales-
10 Sanfrutos expressly recognized that functionality. That's not something we
11 have to show for that reference to be an anticipatory reference. We're
12 allowed to rely on Straus to show that.

13 Opposing counsel also now for the first time has attacked Dr.
14 Baker as not being a POSA. I think the critical distinction there, aside from
15 the fact that they hadn't raised it until today, is that Dr. Baker never opined
16 on invalidity. She is not an expert opining the validity of these claims.

17 She was brought into this proceeding to correct the
18 mischaracterizations that Patent Owner made in its Patent Owner response
19 about how a POSA would interpret Straus. She is an expert in cell-binding
20 experiments. She's as good of an expert as you could find in the world in
21 terms of how to conduct and interpret cell-binding experiments, and she was
22 brought in to lay to rest Patent Owner's characterization of those as
23 somehow not showing that HRP is a cell-binding agent.

24 Real quick, I want to talk about that cell-binding agent issue. Let's
25 see. We don't seem to have the slides up. Oh, there we go.

26 So I'll be brief, and then I'll turn it over to my colleague.

1 Let's just go to Slide 27. Are you able to go to Slide 27?

2 JUDGE NEWMAN: I'm there.

3 MR. HOUSTON: Okay. Thank you.

4 We just want to point out and actually, I'll preface this by saying
5 I'm not sure why this dispute matters in the broader context. Yes, we have a
6 dispute about whether HRP is a cell-binding agent. It's not clear to me how
7 construing that term in the way Patent Owner wants you to construe it
8 affects the dispute, is I guess what I want to point out, first and foremost.

9 Secondly, what's in the patent specifically refers to the cell-binding
10 molecule. And when it talks about sought to be therapeutically or otherwise
11 biologically modified, we just think that's what that's talking about is the
12 entire linker. The linker that has the drug as a part of it. So that's the intent
13 of the entire linker that's disclosed. That's not the intent of the cell-binding
14 agent itself. The cell-binding agent is just what it says: it's an agent that
15 binds to cells.

16 All this other stuff is talking about the full molecule as you create
17 it. So I just want to clarify that, even though I'm not quite sure why it
18 matters.

19 And then lastly on Harris, we heard opposing counsel say that
20 Harris discloses a lot of things. And I can't necessarily dispute that. But
21 what they can't dispute is that one of the things Harris expressly discloses is
22 bis vinyl sulfone. That's the exact molecule we rely on. It's expressly
23 disclosed in Harris. And so it really doesn't matter if Harris discloses other
24 things as well.

25 That disclosure, by the way, is at column number 17 at the top of
26 the page, line 1. And we cited that in our petition at pages 640 to 41 and 49.

1 I'll rest there, unless the panel has questions, and turn the rest of
2 my time over to my colleague.

3 JUDGE NEWMAN: That would be fine. Thank you.

4 MS. FERNANDES: Thank you, Your Honor.

5 JUDGE NEWMAN: Ms. Fernandes, you have about six minutes
6 and 15 seconds.

7 MS. FERNANDES: All right.

8 JUDGE NEWMAN: You may start when you're ready.

9 MS. FERNANDES: All right. Thank you so much.

10 Petitioner would like to respond to the comment about the
11 motivation to substitute the vinyl sulfones for the as a final reactive group
12 for the sorry, let me start again.

13 Petitioner would like to respond to Patent Owner's claim that PEG
14 alone was sufficient; there was no motivation to include vinyl sulfones or
15 other vinyl or other sulfone-related compounds into the PEG linkers
16 disclosed in Singh.

17 First and foremost, as Dr. Chari responded within the reply
18 declaration in Exhibit 1076, the point there was, for the purposes of the
19 drugs they were using which focused on the maytansinoid class of drugs, the
20 PEG linker alone was sufficient enough to provide that solubility.

21 That said, though, as discussed in Dr. Chari's reply declaration on
22 pages 18 to 19, there are examples of other chemotherapeutic drugs which
23 are known to be exceptionally hydrophobic and much more difficult to deal
24 with compared to the maytansinoids. The examples given in Dr. Chari's
25 reply declaration include paclitaxel and cryptophycin.

26 The other thing that we want to make clear is that just because

1 there are examples of conjugates where the vinyl sulfone substitutions are
2 not required, it doesn't preclude that there are other examples within that
3 genus of chemotherapeutic compounds, where the additional assistance
4 provided by the additional sulfones to boost solubility will help.

5 Similarly, within the Singh reference itself, there was a discussion
6 that, you know, that just modifications of the PEG link by itself may not
7 give you the desirable outcome. Petitioner referenced Figure 36 within the
8 reply to Patent Owner's response of Singh where which clearly
9 demonstrated that the shorter PEG linker was required in order for the ADCs
10 to have in order to have an optimal drug uptake. So, once again, messing
11 around with the PEG by itself may not be an entire solution, the perfect
12 solution to deal with this whole class of chemotherapy drugs and agents.
13 Other modifications and solutions would be required. The vinyl sulfone
14 provides a solution, a technical solution, to overcome the same.

15 JUDGE NEWMAN: Counsel, can you point to where in the
16 petition that argument was made, the advantages for Harris for using vinyl
17 sulfone?

18 MS. FERNANDES: So for those we cite to so within the
19 petition, we direct Your Honors' attentions to pages 50, 52, and 66.

20 On page 50, I direct your attention to the paragraph which
21 expressly states a POSA would have been motivated to incorporate
22 Singh/Harris's vinyl sulfones and related sulfonyl functionalities, which are
23 reactive functionalities that can form a thioether bond, into Singh's expressly
24 shown ADC linkers to obtain their aforementioned benefits. A POSA would
25 have appreciated that the resulting PEG linkers provide active sulfone
26 moieties that are hydrolytically stable, enable water-insoluble molecules,

1 example hydrophobic drugs, to be dissolved within water, promote the
2 selective attachment of cysteine units on the proteins, and preserve activity
3 for specific proteins.

4 Similarly, on page 52, the relevant paragraph there would be thus,
5 modifying the PEG-containing ADC linkers of Singh to include vinyl
6 sulfones or related sulfonyl derivatives as a reactive functionality that can
7 form a thioether bond with a cell-binding agent or drug would be expected to
8 have comparable, if not higher, hydrophilicity, and such conjugates would
9 be expected to exhibit the same advantageous properties, such as enhanced
10 potency, less precipitation, already recognized by Singh for its ADC linkers.

11 And on page 66, it's like the same concept is reiterated by saying
12 that a POSA would have expected that the ADCs that include hydrophilic
13 vinyl sulfones or related sulfone moieties of Harris would exhibit improved
14 solubility and thus enhanced therapeutic properties.

15 So like the basis for those particular -- the basis for the motivation
16 to substitute is clearly aligned with in the petition multiple times, at least at
17 pages 50, 52, and 66. And it goes beyond just the mention of replacement of
18 just vinyl sulfones. It's -- we expressly say the other sulfonyl related
19 sulfone functionalities as disclosed within Harris.

20 JUDGE NEWMAN: And those are all related to Ground II, is that
21 correct?

22 MS. FERNANDES: Yeah. So 50

23 JUDGE NEWMAN: All right. Never mind. We're at the end of
24 our time.

25 MS. FERNANDES: Yeah.

26 JUDGE NEWMAN: I don't want to waste time on that.

1 MS. FERNANDES: Yes.

2 JUDGE NEWMAN: Did you have any other final arguments?

3 MS. FERNANDES: That was pretty much what I wanted to wrap
4 up and get on the record, Your Honor.

5 JUDGE NEWMAN: Okay, great.

6 All right. Thank you, Ms. Fernandes.

7 Patent Owner, you have, I believe, 29 minutes for rebuttal, should
8 you choose to take it all.

9 MR. CALVOSA: I'll do my best to be quick, Your Honor.

10 JUDGE NEWMAN: That's fine. It is your time.

11 MR. CALVOSA: I want to start with something I mentioned after
12 the 57 minutes of their initial argument, and now we're through 75 minutes,
13 the whole argument. Not once did you hear anything on reasonable
14 expectation of success. The words were never uttered. I mentioned it last
15 time. They didn't rebut that.

16 There's no evidence on it. There's no evidence of increased
17 solubility or hydrophilicity. We asked Dr. Chari. He didn't have it. It's not
18 in the petition. It's not in his declaration, other than just say-so. And that
19 doesn't suffice.

20 Now we'll go to where you left off on the motivation with Singh.
21 That's for Ground III, not for Ground II, Your Honor. And what was
22 striking was you had asked counsel on the other side, during the first part of
23 their presentation, were they relying on the substitution sulfonyl theory or
24 the incorporation theory? And you asked for cites here.

25 Each cite she pointed you to, on page 50 of the petition, page 52,
26 and page 56, was about incorporating vinyl sulfone. But during her

1 presentation, she said, we're not relying on that. She said, we're relying on a
2 substitution. That's not there.

3 And the reason it's not there, and the reason they're walking away
4 from the incorporation, is because of Dr. Chari's testimony. He said there
5 was no reason to add the vinyl sulfone in. That is in 2010.

6 And again, going back to Harris in 1995, much earlier reference,
7 that's saying, let's use what existed decades earlier and put it in. The Federal
8 Circuit, in the Leo Pharm. v. Rea case, 726 F.3d, at pincite 1357, says that's
9 hindsight. That's not obviousness. There's no motivation. There's no
10 reasonable expectation of success.

11 We also heard counsel admit that, yeah, Harris does disclose a lot
12 of things. He says that doesn't matter because it discloses this, too.

13 I cited the Federal Circuit case law the first time, the Atofina case.
14 It does matter. If there's broad genuses in the prior art, you can't just pick
15 and choose what you want for anticipation and obviousness. That's not the
16 way it works.

17 Moving on to claim construction, opposing counsel said there was
18 nothing new after the DRP decision. Well, Dr. Chari changed his testimony
19 from what he said in his declaration to what he said at deposition. It could
20 not be more clear. Prime example, Morales, when in the declaration, he
21 says, well, Y in Morales is vinyl. When asked at deposition it was on
22 Slide 65 of our presentation when asked, what is Y, an open-ended
23 question, he candidly answered, it's the vinyl sulfone. Not the vinyl. It's a
24 big change.

25 Now, I started you, in the claim construction argument the first
26 time, with the claims. The Federal Circuit tells us to do that. We move to

1 the specification that supported us, as well. And then, despite what counsel
2 said, I walked through the prosecution history.

3 And he tries to make it seem like we're arguing disavowal. We're
4 not arguing disavowal. We're arguing you apply the claim terms under
5 Federal Circuit law. Claims, spec, prosecution history. Not one thing in the
6 prosecution history overcomes the plain language of "enables reaction."

7 You heard him say, well, functional group that enables, that's the
8 same between Z and Y. Yeah, I agree, 100 percent. That's not what matters.

9 What matters is the language past that. Z enables linkage, as Dr.
10 Chari told us, connected, those Lego blocks, and Y enables reaction. It
11 needs to make the reaction happen. And not one person, not even counsel,
12 said that vinyls can make the reaction happen. You need that assist.

13 So, what did we hear him say? He said, well, maybe the sulfone
14 can now be part of Q. It could be Q, it could be part of Y.

15 No, it can't serve both Q and Y. They're separate claim elements
16 under the Becton Federal Circuit case law, recently reapplied in the
17 Regeneron case from the Federal Circuit. When you have separate claim
18 terms, they have to be satisfied by separate elements from the prior art.
19 Nothing here overrides that.

20 He talks about -- we see sulfone, DPAP, acids, aging reactions.
21 Never for Y. You never see that once in the specification. All you see is,
22 again, never vinyl alone getting you to an enabled reaction, never vinyl
23 enabling reaction at all. Dr. Chari said it can't happen. The electrons are
24 happy. There's no reactivity whatsoever. It can't be Y.

25 On the cell-binding agent, opposing counsel said, well,
26 construction doesn't matter. If that was true, opposing counsel and

1 Petitioner would agree with Patent Owner's construction. Of course, the
2 construction matters. Under our construction, there is no disclosure,
3 teaching, suggestion in the prior art of any cell-binding agent in their
4 references.

5 We heard counsel say -- you know, they didn't dispute Dr. Baker is
6 not a POSA. He says, well, that doesn't matter because she's an expert; she's
7 as good as an expert as any; she's the most expert in the field. Well, then
8 she's super-skilled.

9 But he goes he admitted she was reading she was trying to tell
10 you how a POSA would understand stress, but she's not a POSA. So they
11 have no evidence on that. That's their burden. They have to establish she's a
12 POSA. I don't have to establish or even argue she's not. They have to
13 establish it. And they, quite frankly, admitted she's not, because they know
14 she said that in her declaration.

15 And she, therefore, can't tell anybody how a POSA would read
16 anything. She's not a POSA. If a POSA was going to do that, it should have
17 been Dr. Chari. But he didn't, because everybody agreed that the
18 horseradish peroxidase is not a cell-binding agent, whether under our
19 construction or otherwise.

20 And in terms of the additional references that they rely upon, there
21 were 15. We counted. I did not misrepresent anything with the alkaline
22 references, with the Straus references, with Dondoni.

23 And now, he's saying, well, it's not expressly there. To the extent
24 they're arguing inherency, it has to happen each and every time. It certainly
25 doesn't happen and it would be a new argument but it certainly doesn't
26 happen in Morales. They had to try to look elsewhere.

1 Unless any questions from the Board, I'm happy to rest otherwise
2 on the briefs, including for the Motion to Exclude.

3 JUDGE NEWMAN: Understood. Give me just a moment to
4 confer with the panel. All right. Counsel, we appreciate we do not have
5 any further questions. We appreciate everyone's work in preparing for this
6 today. We will go off the record.

7 (Whereupon, the above-entitled matter went off the record at 3:04
8 p.m.)

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