

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,
Petitioner,

v.

LEPU BIOPHARMA CO. LTD.,
Patent Owner.

IPR2025-00685
Patent 10,792,370

Record of Oral Hearing
Held: July 15, 2026

Before JEFFREY N. FREDMAN, TAWEN CHANG, and RYAN H. FLAX,
Administrative Patent Judges.

IPR2025-00685
Patent 10,792,370

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P R O C E E D I N G S

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JUDGE FLAX: Hello, everybody. I am Judge Ryan Flax. We all met at the conference call several days ago. So welcome to the hearing. I'm here with my panel, Judge Fredman and Judge Chang, you can see on the screen up there. She can see you all and she can hear you all.

And I think she can see the demonstratives as you show them on the screen here. But if anything should happen during the hearing technically, we all have the entire record in front of us, we all have your demonstratives on our screens here. So whereas we can see them, I don't know if they're going to be shown up there or not.

It doesn't look like it's on. If you just call the slide number, we can always go to the demonstrative that you want us to look at. Likewise, as you go through your arguments, as you discuss the papers, whichever paper it may be, arguments therein, please identify which paper you're talking about.

With papers, you can just identify the name of it. But with exhibits, I would prefer that you identify the exhibit number and pages of the exhibit number so we can have a nice clean transcript for the record. Okay. So we are here today for the oral argument hearing in IPR2025-00685 concerning U.S. Patent 10,792,370.

The parties have changed since we started. So now we have CSPC Megalith Biopharmaceutical Company Limited as the Petitioner v. Lepu Biopharma Company, Ltd. as Patent Owner. I hope I said that correctly. If I'm incorrect about any of the things that I just said, please raise your hand and tell me where I'm wrong.

Otherwise, we can proceed. What we'll do is we will begin to hear

1 oral argument from Petitioner who bears the burden in this case, followed by
2 Patent Owner which interestingly here we're going to be hearing from Patent
3 Owner remotely. Which won't make any difference to us, we'll be able to
4 see.

5 We can see Mr. Qiu on the screen here, and I'm sure we'll be able
6 to hear him just fine. If it turns out we cannot see or hear him just fine, we
7 will stop and figure that out when it happens. But I'm sure it'll all be fine.
8 Counsel Qiu, if during this process you experience any technical issues, I
9 don't know how we're going to know that immediately, but as soon as we
10 can figure it out, we'll try to solve that problem immediately.

11 I don't foresee that there will be any problems because we've got
12 tremendous experience conducting hearings this way. So we'll just cross our
13 fingers and expect that everything will be perfect. As you argue, everyone
14 has asked for 60 minutes. You will have those 60 minutes, but you may
15 reserve time for rebuttal.

16 So when you get up and it's your turn to talk on opening, just let
17 me know how much time you want to reserve and I'll change it on the
18 countdown timer behind me, and we'll go from there. If I can, I'll try to
19 remind you as we get close to your time expiring, but you'll be able to see it
20 and you can regulate yourselves.

21 If you decide you don't want to stop and you want to eat into your
22 rebuttal time, that's your time and you can do whatever you want. There's
23 also no penalty for not using every of the 60 minutes that you've got. So
24 however you want to use your time is your choice. Anyone have any
25 questions at this point?

26 MR. SUH: No, Your Honor.

1 JUDGE FLAX: Okay. So if the --

2 MR. QIU: No, Your Honor.

3 JUDGE FLAX: -- Counsels could just introduce themselves for
4 the record, that would be great. Starting with Petitioner's Counsel.

5 MR. SUH: Good afternoon, Board. My name is Howard Suh,
6 from the law firm of Fox Rothschild. We represent Petitioner CSPC
7 Megalith Biopharmaceutical Company. And with me is my colleague, Dr.
8 Joe Chen, and also Ms. Erxin Du, also with Fox Rothschild.

9 JUDGE FLAX: Thank you. And Patent Owner?

10 MR. QIU: Your Honor, my name is Fangzhou Qiu, I'm with the
11 law firm, Sheppard, representing Patent Owner, Lepu Biopharma Company
12 Limited. I believe with me in the hearing room are my colleagues Chris
13 Ponder and Alex Nie.

14 JUDGE FLAX: I see them. They are here. Thank you. Okay. So
15 we can begin. Mr. Suh, you have the floor first. And as I said, you've got
16 60 minutes. Just let me know if you want to reserve any of that for rebuttal.

17 MR. SUH: Yes, Your Honor. We'd like to reserve 15 minutes for
18 rebuttal. And Petitioner will be sharing the oral arguments between me and
19 also my colleague, Dr. Chen. So if we could begin. This is going to be the
20 summary of our presentation this afternoon.

21 There's going to be an overview of the '370 Patent, the challenged
22 patent and its claims. We're going to talk about Ground 1, which is
23 obviousness over two prior art references, Wei and Liu. Ground 2,
24 obviousness over Leanna, Liu, and Wei. And I'll be dealing with those first
25 three points.

26 And my colleague, Dr. Chen, will be dealing with points four and

1 five, responding to Patent Owner's specific defenses and secondary
2 considerations which we believe do not rebut the prima facie case of
3 obviousness. So here is an overview of what the challenged claims are
4 about.

5 JUDGE FLAX: So Counsel, I realize that you just started, but
6 you've moved on to a different slide.

7 MR. SUH: Oh, yes.

8 JUDGE FLAX: So if you could just keep us --

9 MR. SUH: Of course.

10 JUDGE FLAX: -- apprised of where you're at in your slides, that
11 would be --

12 MR. SUH: Of course. Thank you for that reminder. So the
13 summary was Slide 2. And if we could go to the next slide, which is Slide 3.
14 This presents the overview of the challenged claims of the '370 Patent. So
15 the claims actually, they cover a broad genus of something called an
16 antibody drug conjugate, ADC for short, right?

17 JUDGE FREDMAN: Mr. Suh, the question is, so obviously, the
18 linker and the cytotoxic agent can be anything. The anti-EGFR antibody has
19 this BA03 CDR sequences. Can you just describe whether those sequences
20 are found in Wei? Is that correct?

21 MR. SUH: Well, the CDR sequences of the BA03 --

22 JUDGE FREDMAN: CDR generally, obviously, is both. Right.

23 MR. SUH: They actually exist in the Liu prior art reference.
24 Because the Liu prior art reference actually discloses the exact BA03
25 antibody.

26 JUDGE FREDMAN: And so that's identical to the one that's being

1 claimed.

2 MR. SUH: I'm sorry?

3 JUDGE FREDMAN: That's identical to the sequence being
4 claimed?

5 MR. SUH: Exactly. Identical. There's no dispute that the BA03
6 antibody contains all the claimed CDR sequences of the challenged claims.

7 JUDGE FREDMAN: And Wei, is that drawn to a different
8 antibody then?

9 MR. SUH: Wei comes very close, right? Because Wei also
10 discloses a humanized variant of cetuximab, which is attached to a cleavable
11 linker and a cytotoxic agent.

12 JUDGE FREDMAN: Okay.

13 MR. SUH: Right. Because there is similar -- our expert, Dr.
14 Bournazos, put forth in his expert report that there is substantial homology
15 between the CDR regions between the Wei antibody and BA03. I believe --

16 JUDGE FREDMAN: But in any case, both of the references teach
17 anti-EGFR antibodies.

18 MR. SUH: Correct. They're both anti-EGFR antibodies.

19 JUDGE FREDMAN: One of which is identical, one of which is
20 slightly different?

21 MR. SUH: And just to point out the structural similarity, Dr.
22 Bournazos showed that 68 out of the 73 CDR residues between the Y104
23 Wei antibody and the BA03 prior art antibody are the same.

24 JUDGE FREDMAN: All right. Thank you.

25 MR. SUH: Now, so as I just mentioned --

26 JUDGE FLAX: So I have a question about that.

1 MR. SUH: Yes.

2 JUDGE FLAX: You said 63 of the 78 are identical? Is that what
3 you said? 68 of 73?

4 MR. SUH: 68 out of 73.

5 JUDGE FLAX: 68 of 73. Well, two questions there. Am I right
6 that both the Wei antibody and BA03 antibody are derived from the
7 cetuximab antibody?

8 MR. SUH: Absolutely, Your Honor. And there's no dispute of
9 that because both the Wei ADC antibody and the ADC is a humanized
10 cetuximab antibody. There is one variant with respect to one of the
11 examples. It's called the Y104D variant, right? And that means that there
12 was a single substitution at position 104 amino acid, right? From Y to D. A
13 single substitution, right?

14 JUDGE FLAX: In Wei?

15 MR. SUH: In Wei. Right.

16 JUDGE FLAX: Okay. So that's a good segue to my second
17 question. The claims require certain sequences of amino acids to be there,
18 amino acids to be there in the antibody. Where is that one mutation of Wei
19 in those sequences? Is it inside those claimed sequences or is it outside
20 those?

21 MR. SUH: It's outside of the CDR sequences.

22 JUDGE FLAX: Okay. Okay. The 104 residue you're saying is
23 outside the claimed sequences?

24 MR. SUH: Yes. Yes, Your Honor. They're outside of the claimed
25 CDR sequences.

26 JUDGE FLAX: Okay. And then do we have -- do we know that

1 from the record? Where is the evidence of that in the record? How do we
2 know it?

3 MR. SUH: I think we can probably -- my colleague, Dr. Chen,
4 would be able to find out where that is in the record.

5 JUDGE FLAX: Okay. That would be useful because one of my
6 questions is this. There's tremendous argument in this case that the Patent
7 Owner has framed your case in terms of starting with Wei, throwing out
8 Wei's antibody, and replacing with the BA03 antibody.

9 And the argument there is that would -- one of the arguments there
10 is that would defeat the pH sensitivity and cancer cell targeting of Wei's
11 antibody as Wei describes it. If that 104 residue is not in the claim
12 sequences, what would foreclose somebody from making that same change
13 to the BA03 antibody and just still having the same result that Wei wants?

14 MR. SUH: I don't think it would foreclose the POSA to actually
15 make that substitution within BA03. However, we believe that -- and I
16 believe the Board recognized this, is that although these 104 mutations does
17 not exist in the Liu BA03 prior art reference, there were qualities of BA03
18 such as its high binding affinity, its high ADCC, antibody-dependent cellular
19 cytotoxicity.

20 Its lower immunogenicity because it is a humanized antibody, and
21 its stronger EGFR phosphorylation inhibition. That's complicated, but
22 essentially what that means is that this particular antibody is better able to
23 suppress over-expression of EGFR, which is the cancer, right?

24 So all of those qualities within BA03, provided strong motivation
25 for this BA03 antibody to be a ADC candidate. That's something that our
26 expert, Dr. Boumazos, testified to, and it is also supported in the file history

1 through its inclusion of the Goldmacher reference. Where Goldmacher
2 states that those qualities that are within BA03, are the reasons why someone
3 would want to use that antibody to make an ADC.

4 JUDGE CHANG: So this is Judge Chang. I just want to make
5 sure I understand your answer to Judge Flax's question. So Claim 1 requires
6 that the CDR regions comprise -- has sequence numbers 5, 7, and 12?

7 MR. SUH: Yes.

8 JUDGE CHANG: And 12 through 14. Are you saying that
9 position 104 is not within one of those sequences?

10 DR. CHEN: Allow me to clarify. First of all, the Wei's antibody
11 and Liu's antibody, both are cetuximab variant. They are different antibody.
12 There are some differences in the CDR region. And I want to correct my
13 colleague that 104 is not -- the mutation is in the CDR. That's in CDR3,
14 heavy chain CDR3.

15 And which means Wei does not have exactly the -- what have in
16 the Claim 1, there'll be anticipation. That's why we bring in Liu's BA03,
17 because all the recited CDR sequences are contained in Liu's BA03. So
18 what we are using the teaching from Wei is the prior art ADC platform.

19 Because Wei's ADC contains the payload, linker payload, vc-
20 MMAE, that's known. That's well known in the prior art. So we are
21 basically combining a prior antibody called BA03 with established ADC
22 platform, vc-MMAE, and to arrive at claim invention.

23 JUDGE CHANG: Okay. So just to make sure I understand.

24 DR. CHEN: Right.

25 JUDGE CHANG: So position 104 is within sequence ID number
26 7, I guess, CDR3?

1 DR. CHEN: Correct. CDR3. Yes, heavy chain CDR3.

2 JUDGE CHANG: So therefore, a skilled artisan cannot make the
3 change that's present in Wei and still meet the limitations in Claim 1,
4 because that will no longer contain sequence ID-7 if you have a mutation?

5 DR. CHEN: Yes. I think that, Your Honor, the -- our -- obviously
6 this theory relies on the combination of Liu's teaching and Wei's teaching. It
7 does not restrict the POSA to start from Liu or start from Wei. So either
8 way, it's a valid approach.

9 You can start from Liu's BA03 looking at Liu as a superior
10 property for ADC design, and look to the prior art ADC platform to arrive at
11 the claimed invention, right? You can also start from Wei's ADC. But that
12 involving kind of substitution of Wei's antibody with Liu's antibody, BA03.

13 And the fundamental argument from Patent Owner is that they
14 speculate that BA03 does not have pH selectivity. But where's the support?
15 The only support they have is from the post-filing evidence. That post filing
16 evidence is Petitioner's own Patent application published six years out of the
17 priority date of the '370 Patent. And that evidence is not available --

18 JUDGE FLAX: I'm sorry. Hold on. Are you saying that -- are
19 you saying right now that they have not adequately argued that BA03 is not
20 pH selective like Wei? They haven't argued that?

21 DR. CHEN: Correct. They have no support for that.

22 JUDGE FREDMAN: Evidentiary --

23 JUDGE FLAX: By that, I mean -- okay. I don't know if they'd
24 have a real burden to prove that. Liu doesn't say that it is, right?

25 DR. CHEN: Right.

26 JUDGE FLAX: Are you saying that someone of ordinary skill in

1 the art would just know that it was somehow?

2 DR. CHEN: No. Our argument is that if you -- even if you start
3 from Wei's teaching or ADC platform, right? You'll not necessarily go
4 through a pathway that I have to find another pH selective antibody to swap
5 out Wei's antibody. Because there's abundance of motivation provided by
6 Liu's BA03 independently because Liu provided express teaching of several
7 superior advantages.

8 JUDGE FLAX: Yes, I understand that.

9 DR. CHEN: Right. So --

10 JUDGE FLAX: And your colleague went through them, and I
11 remember that from your arguments.

12 DR. CHEN: Right.

13 JUDGE FLAX: I get it. And I've seen those same things in the
14 reference, it makes sense. I was just trying to understand your argument
15 right now. It seemed to be imposing some sort of burden on the Patent
16 Owner to prove that Liu's BA03 did not have the pH targeting selectivity
17 functionality, right? And I don't think that's their burden to prove it.

18 DR. CHEN: Your Honor, I think that we were addressing the
19 teaching of Wei because they were arguing Wei, teach away a POSA from
20 using BA03 because they believe BA03 does not have pH selectivity. We
21 say, no, no, no. First of all, you don't have evidence for that. Liu doesn't say
22 BA03 has or has no pH selectivity, right? You don't know.

23 JUDGE FLAX: We don't know.

24 DR. CHEN: We don't know, right?

25 JUDGE FLAX: From Liu itself.

26 DR. CHEN: Exactly. Exactly. So that's why there's no teach

1 away. You can't say Liu does not have pH selectivity, therefore a POSA
2 will be taught away from using BA03. That's something we try to address
3 the teaching away argument from Patent Owner.

4 JUDGE FREDMAN: So can I clarify something for myself? It's a
5 little more specific. So looking at SEQ ID 1 of, I think, the patent right here
6 that's at issue. So SEQ ID 7 in the '370 Patent, when you look at it on the
7 sequence of SEQ ID 1, begins at I think amino acid 98 and goes to amino
8 acid 108. Is that correct?

9 DR. CHEN: SEQ ID number 1, right?

10 JUDGE FREDMAN: SEQ ID number 1.

11 DR. CHEN: That's in the claim. Is it?

12 JUDGE FREDMAN: So SEQ ID number 1 is not in the claim, but
13 it encompasses all three. It's the variable regions of the heavy chain.

14 DR. CHEN: Okay.

15 JUDGE FREDMAN: It encompasses all three of these sequences,
16 5, 6, and 7. Okay. SEQ ID 7 I think is 98 to 108, where 104 is the tyrosine
17 at issue, the Y at issue. Is that correct?

18 DR. CHEN: Right. Right.

19 JUDGE FREDMAN: Right. Okay. Is that tyrosine present in
20 BA03?

21 DR. CHEN: That tyrosine, I think that that's a mutated form. I
22 believe it is in BA03.

23 JUDGE FREDMAN: Okay.

24 DR. CHEN: Yes.

25 JUDGE FREDMAN: We have a sequence for BA03 somewhere?

26 DR. CHEN: Yes. In our declaration our Petitioner's expert's

1 declaration, that's the Exhibit 1002.

2 JUDGE FREDMAN: Uh-huh.

3 DR. CHEN: So our expert did a sequence alignment that compares
4 BA03 sequences with all the sequences reciting the claim. They are 100
5 percent identical.

6 JUDGE FREDMAN: Okay.

7 DR. CHEN: 100 percent. And also, in the '370 Patent itself, they
8 admit that the antibody they use is BA03 from Liu. But our expert go extra
9 miles to demonstrate that sequence that really have 100 percent identical.
10 Yes. Yes. Also, I want to mention, Your Honor, is that Patent Owner's
11 expert provided theory regarding pH selectivity.

12 In his declaration, he mentioned that if you have a charged residue
13 such as aspartate, which is D, or histidine which is H, or glutamate, which is
14 E, if you have a charged residue in the CDR region, you're going to confer
15 pH selectivity. So interestingly, according to his theory, the BA03 should
16 have pH selectivity because you know why?

17 Because BA03 in the heavy chain CDR3 and the light chain CDR3
18 also has an aspartic acid, which is D. So according to Patent Owner's own
19 expert's theory, a POSA should realize the BA03, in fact, should have pH
20 selectivity. I want to point out that.

21 JUDGE FLAX: And that is, that's theoretical though? No one has
22 done any testing to evidence that BA03 has the same --

23 DR. CHEN: That's right.

24 JUDGE FLAX: -- pH selectivity?

25 DR. CHEN: But at least that is Patent Owner's own position.

26 JUDGE FLAX: Okay.

1 DR. CHEN: Yes. So my colleague will continue.

2 MR. SUH: And Your Honor, just to follow up on this point
3 regarding selectivity. There is evidence in the record, particularly in Wei,
4 which suggests that humanization of the antibody within the ADC increases
5 selectivity. And we know that BA03 is a humanized antibody. So if we go
6 to Wei -- all right, Your Honor. And if we go to example 22. So I know it's
7 kind of hard to see.

8 JUDGE FLAX: Gosh, does it have that many?

9 MR. SUH: But --

10 JUDGE FLAX: Okay, I'm there.

11 MR. SUH: -- in example 22 --

12 JUDGE FLAX: So that's page 138 of Exhibit 1005, just to be
13 clear?

14 MR. SUH: Yes.

15 JUDGE FLAX: Beginning at paragraph 1133?

16 MR. SUH: That's right. It's actually paragraph 1139. And what
17 they did here, what Wei did here is that it compared, says here, these results
18 show that ADC conjugates of the humanized forms of the Y104D and
19 Y104E anti-EGFR variants exhibit greater pH-dependent activity than the
20 chimeric Y104D MMAE conjugate.

21 For example, while each are as effective as the chimeric Y104D
22 MMAE for inhibiting tumor cell growth at pH 6.8, each humanized exhibit
23 reduced growth inhibition on non-tumor keratinocytes skin at pH 7.4
24 compared to the chimeric Y104D MMAE. Close quote.

25 So what this suggests, that the only difference between these two,
26 between the comparison here is that you had humanized Y104D versus non-

1 humanized Y104D. And the humanized version showed better selectivity.
2 And if the only difference is the fact that it was humanized, that suggests
3 that humanization does have a factor in increasing selectivity.

4 Which we believe would further motivate the POSA to use BA03
5 as a candidate for an ADC because BA03 is a humanized cetuximab
6 antibody. So we just wanted to finish up with that point. So I know we
7 went off on a little tangent, but if we could go to Slide 4.

8 JUDGE FLAX: These are the most important tangents.

9 MR. SUH: Yes. Yes. But if we could go to the next slide, which
10 is Slide 4, we have to remember, so what did Patent Owner actually do to
11 arrive at the challenged claims, right? So Example 1 of the '370 Patent, to
12 the reduced antibody, and this was BA03 in the prior art, added 1.1 times the
13 mole number of free thiol groups of vc-MMAE purchased from Haoyuan
14 Chemical Technology Company.

15 So what Patent Owner actually did to get these challenged claims,
16 is that they took the Liu prior art BA03 antibody, and they linked it up with a
17 vc-MMAE linker payload system that they bought off the shelf. And by
18 doing that, that's how they got their patent.

19 And there's no dispute about that. In fact, the institution decision
20 recognized that Paper Number 10, right? Example 1 of the '370 Patent
21 discloses the preparation of a specific ADC in which the previously known
22 BA03 anti-EGFR antibody is connected to a commercially obtained vc-
23 MMAE linker cytotoxic agent molecule.

24 That's Paper 1 of 10, institution decision three -- at four. Then if
25 we could go on to the next slide, which is Slide 5. Again, this is just Claim
26 1. It's very representative.

1 JUDGE FLAX: Counsel, can we skip these arguments on Claim 1
2 and move on to Claim 16 and the ones that followed that? So when we get
3 down to those claims, starting with 16, now we're talking about a method of
4 using this ADC.

5 MR. SUH: Yes.

6 JUDGE FLAX: Right?

7 MR. SUH: Yes, Your Honor.

8 JUDGE FLAX: And you need a therapeutically effective amount
9 of this new drug, new pharmaceutical to do its job. And what I'll say is that
10 what I see in your petition is that it looks like you're relying on Wei to talk
11 about this method, right? And we are no longer using Wei's antibody, we're
12 using Liu's antibody once the combination is made. So can you explain
13 that? Why are we looking to Wei for the rationale for using BA03 ADC in a
14 therapy?

15 MR. SUH: Because the antibodies between -- the antibodies -- the
16 BA03 antibody and the antibody within Wei are very similar. As we just
17 recognized, as we discussed this morning, they're derived from the same
18 cetuximab. They are both cetuximab based antibodies. And BA03 is a
19 humanized cetuximab antibody.

20 And Wei also discloses a humanized Y104 variant antibody within
21 an ADC. So that structural similarity that we talked about this morning, that
22 would provide the motivation to actually use BA03 in an ADC, similar to
23 Wei. And as we saw in Wei, Wei actually showed in both in vivo and in
24 vitro tests that that particular ADC was effective in inhibiting cancer cells.

25 JUDGE FLAX: And do we need to rely on the points that you all
26 just made about the ultimate similarity of BA03 and Wei's antibody

1 regarding, like selectivity for example, to accept that the advantages that
2 you've argued starting at page 60 of the petition, like selectivity, reduced
3 toxicity, maximal efficacy, minimal toxicity, and reduced side effects, these
4 things that you've argued are reasons why you would use it in a
5 therapeutically effective amount?

6 Your opposing Counsel has argued that the therapeutic window
7 here is going to be narrow, and so that's a reason why you wouldn't do this
8 combination. I mean, what are we relying on to understand that the person
9 of ordinary skill would know beyond, hey, I want to make this ADC.

10 Because we're looking for new ways to fight cancer, that makes
11 sense, to take the next step to say, okay, now we're using this therapy in a
12 cancer treatment as it's claimed in this claim and the subsequent claims.

13 MR. SUH: Yes. And also, but I also want to point out, Your
14 Honor, that these particular method claims, Claims 16 to 23, they don't say
15 that this method is for treating a human, right? I don't think it says
16 therapeutic effective amount, right? So therefore in vivo tests and certainly
17 mouse studies could confirm that --

18 JUDGE FREDMAN: I'm not sure that really matters. I mean, you
19 have enough in Wei. Wei is your motivation reference here, right?

20 MR. SUH: That's right.

21 JUDGE FREDMAN: I don't know that that's worth the time
22 actually.

23 MR. SUH: I mean, and remember in Wei, Wei actually shows that
24 the treatment of the humanized cetuximab ADC was effective in mice.

25 JUDGE FREDMAN: Right.

26 MR. SUH: Right?

1 JUDGE FREDMAN: And Wei is focused on preventing
2 worsening of symptoms or progression of cancer. So I think Wei addresses
3 -- I would actually, if it's okay with Judge Flax, like to move to Claim 13.
4 I'm in second --

5 MR. SUH: In 13?

6 JUDGE FREDMAN: Really secondary consideration, so maybe
7 your colleague would pick it up here.

8 MR. SUH: Right.

9 JUDGE FREDMAN: Because the other claims potentially have
10 commensurate in scope and nexus issues. Claim 13 is a picture claim.

11 MR. SUH: Yes. Well, Your Honor, respectively, Judge Fredman,
12 Claim 13 is a partial picture, right? So the picture that's actually shown
13 under Claim 13 is only the specific vc-MMAE linker payload system, right?
14 The actual antibody part still depends on Claim 1. And those CDR regions,
15 those very selective CDR regions within the variable regions, are just a small
16 portion of potential --

17 JUDGE FREDMAN: We understand that. Right. But the point is
18 that if those are the active relevant regions, it's still a claim -- 13 is different
19 than say 11, which is open to a number of other drugs. And so that wasn't
20 the actual drug that they presumably got approved by the Chinese equivalent
21 of the FDA if that's what that was.

22 MR. SUH: Right.

23 JUDGE FREDMAN: Right? And so the question is for a -- I hear
24 that you're saying there's still a nexus argument a little bit on this, and that's
25 fine. I'm still kind of interested in hearing really more about what does it
26 mean that the Chinese government, I guess, approved the drug? How is that

1 addressing the long felt need issue and those sorts of things?

2 MR. SUH: So my colleague, Dr. Chen, is going to be addressing
3 the secondary considerations arguments. But I just want to make sure this is
4 clear on the record, Judge Fredman. So Claim 13 is dependent upon Claim
5 9. Right? And Claim 9 is dependent upon Claim 1. So therefore, and this
6 was admitted by their expert, right?

7 The scope of Claim 13 and Claim 1 covers millions and millions of
8 different ADCs. And therefore, that broad coverage does not allow for the
9 nexus of their commercial success. So even Claim 13, we believe fails to
10 provide that nexus because it's too broad. It claims millions of different
11 antibodies, Your Honor.

12 JUDGE FREDMAN: Well, I understand.

13 MR. SUH: And my colleague, Dr. Chen, will address your --

14 JUDGE CHANG: Well, actually before you go, let me just ask a
15 question. So you're saying that there's a lot of different antibodies, and
16 therefore there's -- it's not commensurate in scope.

17 MR. SUH: Yes.

18 JUDGE CHANG: And I think Patent Owner may have sort of the
19 opposite argument in your prima facie case or in your case that, well, if
20 there's so many different antibodies, then why would you necessarily pick
21 the one that's in Liu? Or are you saying that any of these antibodies will
22 potentially have -- there would have been motivation to use any humanized
23 antibody no matter how -- no matter if it's Liu or something else? Is it
24 obvious to combine basically any humanized antibody with this linker and
25 the drug?

26 JUDGE FREDMAN: Maybe humanized anti-EGFR, I think --

1 MR. SUH: And Judge Chang, one would use Liu, because Liu
2 discloses the exact same antibody that was the basis of the challenged
3 claims, because it discloses BA03.

4 JUDGE CHANG: Well, but we are not -- we're trying to not look
5 at the claims, right? When we're doing motivation to combine, we're saying,
6 why would the skilled artisan pick Liu without looking at the claims?

7 MR. SUH: Because one would look at -- because it's a humanized
8 cetuximab antibody. And I'm not sure whether impermissible hindsight
9 refrains the POSA from actually knowing at least what the claims are about.
10 And if the claims are covering a BA03 ADC, and if BA03 was disclosed in
11 the prior art, that should form the basis of the POSA's thinking.

12 And that was never disputed during Prosecution even. Remember,
13 in Prosecution, the examiner in its first rejection cited Liu, because of course
14 it's the same antibody used in the patent. The only way Patent Owners
15 overcame those rejections, is to say that there was no motivation to use a
16 cleavable linker because they made an argument that non-cleavable linkers
17 increased toxicity.

18 I don't think that's an argument that Patent Owner is now even
19 making today. Because the prior art is replete with examples of a cleavable
20 linker tied to an MMAE cytotoxic drug, right? That's disclosed in both Wei,
21 that's disclosed both in Leanna.

22 So I hope that answers your question, Your Honor. And my
23 colleague, Dr. Chen, will be talking about secondary considerations of non-
24 obviousness to answer Judge Fredman's questions.

25 DR. CHEN: Skip this slide. Your Honor, I will address some of
26 the Patent Owner's defenses raising the --

1 JUDGE FREDMAN: What slide are you on now?

2 DR. CHEN: Sorry about that. Slide 25. So before I start, I want
3 to mention that, Your Honor, in Patent Owner's surreply and also in their
4 original demonstrative for this hearing, they mentioned the number of issues
5 that are undisputed. You'll probably see that.

6 So I want to say that those are not true, those are
7 misrepresentation. Because every single issue they mentioned are heavily
8 disputed in the record. So last week when both parties exchanged
9 demonstratives, we raised that concern to Patent Owner.

10 Patent Owner removed some of the undisputed kind of
11 mischaracterization from their slide, but they are still in surreply. I just want
12 to bring that to both attention. Yes. I can go straight to Claim 13. So Claim
13 13, I can come back for other slide, but Claim 13 is the one we just asked
14 about, right?

15 And so why Claim 13 is still really broad. Judge Fredman, you say
16 that, right? Residues, what is defined in antibody? CDR region, right? But
17 antibody have framework region. Antibody have Fc region. There are many
18 residues. And probably CDR only account for a small portion of the
19 antibody.

20 JUDGE FREDMAN: And obviously they're not even claiming the
21 entire CDR, they're only claiming a portion of the CDRs. But is there a
22 reason to think that using a different humanized framework or a different Fc
23 region would matter?

24 DR. CHEN: It could. Because our expert Dr. Bournazos indicates
25 Fc region also play important function in the ADCC function sometime,
26 right?

1 JUDGE FREDMAN: Do you have evidence? Where is that in the
2 record?

3 DR. CHEN: That's in his declaration, I can point to that. Dr. --

4 JUDGE FREDMAN: Who? Which one? Dr. Bournazos?

5 DR. CHEN: That's Exhibit 1200. I can pull it up.

6 JUDGE FREDMAN: 1002 (sic) somewhere? Okay.

7 DR. CHEN: Yes. So I can go revisit that. Basically, Your Honor,
8 as the Patent Owner's expert admit that the ADC components, like antibody
9 component itself already cover millions of antibodies. And then the second
10 variable, Your Honor, is a drug to antibody ratio. Like Claim 13, we said
11 that ratio is between one to eight.

12 JUDGE FREDMAN: Right.

13 DR. CHEN: One to eight. And that's not even the integer number.
14 It's not a one, two, three, four, it's not an integer number. It can be 1.1, 1.11,
15 1.2, because it's average.

16 JUDGE FREDMAN: We understand.

17 DR. CHEN: Is there. Yes, right. So if you had two variables in
18 the claim, which means the scope of claim, even for Claim 13 is really
19 broad, can cover millions to billions of ADC. That's why that will -- we can
20 or even rebut the nexus argument from the Patent Owner.

21 JUDGE FREDMAN: Okay.

22 DR. CHEN: And we believe that a single species, even if you
23 have data for a single construct, does not support that broad scope of Claim
24 13 even. Yes. And Judge -- okay.

25 JUDGE FREDMAN: Let him finish because I have one more
26 point on this.

1 DR. CHEN: Sure.

2 JUDGE FREDMAN: Let's say that they -- they did not file an
3 amendment in this case. Let's say they had. And they've gone to literally
4 SEQ ID whatever, SEQ ID1, I guess, it probably would've been, and SEQ
5 ID, whatever the CDR sequence is. And they limited the framework as well.

6 DR. CHEN: Right.

7 JUDGE FREDMAN: So we have nexus.

8 DR. CHEN: Sure.

9 JUDGE FREDMAN: Take that issue off the table at this point.
10 Would there still be evidence with their argument about long felt needs still
11 be persuasive or not? That's kind of what I'm trying to get to.

12 DR. CHEN: I think that's still not sufficient because this is a very
13 strong prima facie case, right? You have prior antibody sitting there, BA03,
14 telling you there are superior properties all related to ADC design. And you
15 have a clinically well-established linker payload, vc-MMAE.

16 JUDGE FREDMAN: So your argument is essentially that, as the
17 Court has -- the Federal Circuit has said many times --

18 DR. CHEN: Yes.

19 JUDGE FREDMAN: -- just because you have secondary
20 consideration doesn't mean that renders a claim unobvious?

21 DR. CHEN: Right.

22 JUDGE FREDMAN: You're not saying that they're wrong on their
23 finding, you're simply saying that's not sufficient?

24 DR. CHEN: That's not sufficient. That's not sufficient because
25 everything -- every component is well known. And also the combination is
26 predictable, very predictable. As you can see from -- we cite Wei and Liu,

1 they demonstrate exactly same linker payload. Right? And BA03 is
2 standing out so clearly, they have so many advantages. So they're simply
3 put together, right?

4 JUDGE FREDMAN: Okay. Okay.

5 DR. CHEN: And that's why I have slides showing that, really,
6 even they try to argue unexpected result, I --

7 JUDGE FLAX: We are on Slide 40?

8 DR. CHEN: We are on Slide 40. Sorry about that, Your Honor.
9 So even they try to bring up unexpected results. So our position is really
10 there's no unexpected results, Your Honor. So first of all, the BA03 is a
11 prior antibody, has known superior properties. And then the linker payload
12 is clinically validated, it's in the drug approved in 2011, 15 years ago in the
13 Adcetris drug, right?

14 And then now you are basically use a conjugation chemistry to link
15 the linker payload to antibody. But that conjugation chemistry is well
16 established, well known, very conventional, right? And importantly, Your
17 Honor, when you goes to -- when you saw the results, they got to be head-to-
18 head comparison between BA03 ADC with prior ADC to show my ADC is
19 better than prior ADC.

20 But there's no such data. Only thing they have is to show BA03
21 ADC is more potent or more -- has a higher efficacy compared to its own
22 BA03. It doesn't compare any prior ADC. So any unexpected results they --

23 JUDGE FREDMAN: What you're saying is, I think, let me get it
24 right. They're saying that there's a comparison between the ADC and the
25 antibody alone?

26 DR. CHEN: Right.

1 JUDGE FREDMAN: Not the ADC, that the -- the linkage and
2 another BA03 that was actually linked to MMAE or some other kind of --

3 DR. CHEN: They do. In the Example 6 of '370 Patent, they
4 compare BA03 with cleavable linker, with MMAE. And also compare the
5 BA03 with a non-cleavable linker, NC linker, which is non-cleavable linker.
6 There they basically try to argue cleavable linker work better as a point.

7 That's why in the Prosecution history, everything is about linker.
8 The data doesn't show BA03 is better. Because now the only variable here
9 is a linker. They don't change the antibody, right? That comparison doesn't
10 tell you BA03 is better. Only tell you cleavable linker is better. And also, as
11 you can see in the record, Your Honor, the Patent Owner and their expert
12 focused really --

13 JUDGE FREDMAN: It does include all those elements, right? It
14 includes the antibody, the cleavable linker and the -- so the cleavable linker
15 is part of the claim.

16 DR. CHEN: No, that's right. But again, Your Honor, the scope of
17 claim is so broad. You only demonstrate a cleavable linker is better, but
18 there's no evidence showing that BA03 play any role. But in this IPR
19 proceeding, suddenly, Patent Owner switched their position saying, oh, it is
20 not obvious to use BA03.

21 But data doesn't support that. Data is really about linker itself.
22 And also, Your Honor, Patent Owner and their expert focused their analysis
23 entirely based on toxicity, right? Even their data in Example 6 talked about
24 nothing about toxicity, only about efficacy.

25 Nothing about therapeutic window, right? So their focus, toxicity.
26 You're going to hear from Patent Owner today, lots of toxicity, but their data

1 doesn't show that. Your Honor, if you have a further question, but I want to
2 go back to secondary consideration, Your Honor. So Slide 41, Your Honor.

3 So, Your Honor, Patent Owner presented secondary consideration
4 argument, but we believe that the Patent Owner still failed to establish the
5 nexus and long-felt need and copying, right? So for the first one, the nexus,
6 again, the rest of the claim will defeat that.

7 Because as we can see from Claim 1 and Claim 13, both claims,
8 even Claim 13, still very broad, right? Can still cover millions or billions of
9 different ADC. So you cannot support such breadth, such
10 (INDISCERNIBLE) claim using one species. And also failure of others.
11 What about that?

12 So Patent Owner cited four failed ADC programs. But that doesn't
13 help them. Here's why. These four ADC, in fact, they used not an antibody
14 similar BA03, they actually used antibody similar to antibody 1 in Leanna
15 because they are tumor selective. And this antibody only binds to EGFR
16 variant 3.

17 This EGFR variant 3 only expressed in tumor. That's why they are
18 tumor selective, right? And these four program in fact is exactly the strategy
19 before in Patent Owner's response. And Patent Owner really advocates that.
20 They basically say that POSA really should use tumor selective antibody
21 such as antibody 1 in Leanna. However --

22 JUDGE FLAX: Question.

23 DR. CHEN: Yes.

24 JUDGE FLAX: These failures, was Patent Owner really using
25 these as the failures of others quote unquote objective indicia? Or were they
26 identifying them as evidence that the market was trying to solve this

1 problem and no one had done it until their invention? Which one is it?

2 DR. CHEN: The long-felt need. Long-felt need, right?

3 JUDGE FLAX: Right. Right.

4 DR. CHEN: Yes.

5 JUDGE FLAX: It's not --

6 DR. CHEN: Yes.

7 JUDGE FLAX: I mean, it's a little bit mingled in the way they've
8 argued it.

9 DR. CHEN: Right.

10 JUDGE FLAX: But I took it, because their heading doesn't say
11 failure of others, it says long-felt and unresolved need. So I just took it as
12 evidence that the field was motivated to solve this problem.

13 DR. CHEN: Right.

14 JUDGE FLAX: What exactly the problem is --

15 DR. CHEN: Yes.

16 JUDGE FLAX: -- it's a new EGFR --

17 DR. CHEN: Yes.

18 JUDGE FLAX: -- cancer drug, I suppose.

19 DR. CHEN: Yes.

20 JUDGE FLAX: And these were evidence of the efforts.

21 DR. CHEN: Right.

22 JUDGE FLAX: We're trying to do it and it hadn't been done. Is
23 that right? So we don't really care why they failed or whatever. We just
24 know that they failed and it wasn't the invention. And until the invention, no
25 one had done it.

26 DR. CHEN: I think the problem, what people try to solve also

1 matters, right? Because when you have a number of programs failed, we
2 need to know exactly what's going on. And then asking whether the Patent
3 Owner provided a solution. So first of all, nobody know exactly, even a
4 Patent Owner don't know three out of four programs, why they terminated.

5 When a program, clinical study got terminated, there can be many
6 reasons, right? Can be efficacy, can be toxicity, can be dosing schedule, can
7 be variability of patient, even problem with manufacturability, all kinds of
8 reasons. There's nobody know what exactly, what's going on for the failure
9 of the program.

10 In a bankruptcy or on a patent fight, on a patent litigation, they
11 stop the program. So if you don't know exactly what problem associated
12 with the termination of program, you don't know what problem Patent
13 Owner exactly solved. So they claim they solved the problem because they
14 use a BA03 to make a ADC, right? That's their invention. Really just their
15 invention.

16 JUDGE FLAX: So potentially one of these failures, quote unquote
17 failures, could have succeeded, but we don't know why it ended?

18 DR. CHEN: We don't know.

19 JUDGE FLAX: Could have been a success?

20 DR. CHEN: Right. The clinical trial is very complex, right? We
21 don't know why the program got terminated. What problem is that. And
22 then if we don't know the problem, we don't know what solution Patent
23 Owner provides.

24 JUDGE FLAX: I understand.

25 DR. CHEN: Yes. Okay. And then I want to emphasize that even
26 one of them actually failed because of efficacy, not because of the toxicity

1 that the Patent Owner keeps talking about, right? So there's also no copying.
2 And Your Honor, as we mentioned in our reply, we cited a case called *Iron*
3 *Grip*.

4 And *Iron Grip* say just because a competitor's product fall in the
5 scope of the claim, is not copying. And you need to have a replication of the
6 product. And here's not a replication. The only overlap is BA03. And that
7 BA03 is a prior art antibody. And the linker is different. And the payload is
8 different.

9 There's no replication. There's no copying. And as you can see in
10 the record, actually, this is from Patent Owner's paper, Your Honor. So the
11 record shows that Patent Owner licensed BA03 from a company called JMT.
12 And JMT was later acquired by Petitioner, right?

13 So first of all, this may not be really relevant, Your Honor, because
14 BA03 is a prior art antibody. It's in the public domain. You don't copy, it's
15 in the public domain. You don't really take proprietary information from
16 somebody. It's public information.

17 And Your Honor, one more thing that I want to really point out is
18 that there are some really critical omissions, and omissions made by Patent
19 Owner's expert, right? As I point to you, the Patent Owner's expert focused
20 analysis largely on toxicity.

21 JUDGE FLAX: On Slide 47?

22 DR. CHEN: Slide 47. I apologize, I didn't mention that. It's Slide
23 47. And he focused his analysis mostly on toxicity, but he failed to present
24 two important information passages from the reference. He himself cites,
25 Patent Owner cite is Exhibit 2011, right? And these two passages really go
26 to the core of their analysis.

1 Number one is that, "The risk associated with a severe skin
2 reaction is currently considered acceptable when managed properly." Right?
3 The second statement is, "Efforts to improve upon EGFR antibodies are
4 aimed at generating antibodies having even greater affinity for target
5 antigen."

6 So you're going to hear a lot from Patent Owner today, higher
7 binding affinity of anti-EGFR antibodies are no good because it will
8 necessarily generate a narrower therapeutic window. Number two is he
9 going to narrow down the issue to toxicity.

10 Our position is that, when a POSA design ADC, a POSA will
11 consider multiple factors, right? Including binding affinity, including
12 ADCC, including phosphorylation, including even a manufacturability and
13 anti-tumor efficacy, everything.

14 So importantly, Your Honor, BA03 actually is a very -- the
15 property is really relevant. The first three, right? Antibody binding affinity.
16 Stronger binding affinity means the target recognition is stronger, target
17 engagement is stronger. And --

18 JUDGE FLAX: I'll note that you're --

19 DR. CHEN: Yes.

20 JUDGE FLAX: -- exceeding your time. It's your time.

21 DR. CHEN: Okay. My time.

22 JUDGE FLAX: That's fine. But I do have a question about this. I
23 see that on the slide that you're on right now, Slide 47 --

24 DR. CHEN: Okay.

25 JUDGE FLAX: -- it's discussing that this very issue was discussed
26 with Patent Owner's expert at his deposition.

1 DR. CHEN: Correct.

2 JUDGE FLAX: And it says that he conceded that this wasn't
3 something that he presented to the Board in his deposition -- or in his
4 declaration testimony.

5 DR. CHEN: Right.

6 JUDGE FLAX: What did he say about this when you asked him
7 about it? What did he say about this as a fact, as it relates to his position that
8 when you -- you don't want to increase binding affinity because there's
9 potential for increased toxicity. And this says here that that's not as big a
10 concern as they want it to be.

11 DR. CHEN: Right.

12 JUDGE FLAX: What was his reaction to that?

13 DR. CHEN: First of all, we don't want to put a -- lend this
14 statement into his mouth. We don't say this is his opinion. We are saying
15 that since you cite a reference to Tikhomirov-346, you cite that, but you
16 failed to mention two very critical relevant parties to the Board. You didn't
17 present a full story to the Board from -- the full story of the reference.

18 JUDGE FLAX: Right. You asked him if these two passages
19 changed his opinion.

20 DR. CHEN: I did not ask specifically about that, but I just asked
21 him whether or not you present that passage to the Board, right? Because
22 that is relevant to his analysis because he keeps saying that antibody have
23 higher binding affinities necessarily is bad, and toxicity is the only thing you
24 need to worry about, right?

25 Which we heavily contest, right? And one more thing, Your
26 Honor, I want to quickly address that BA03, why BA03 is good, right?

1 BA03 has a higher binding affinity. So Patent Owner says it's no good,
2 right? So first of all, BA03 stronger binding means better target recognition
3 and stronger target engagement, number one.

4 And also in the record, our expert argued that for ADC, you
5 usually use a lower dose, right? For a lower dose, the target recognition and
6 target engagement actually quite important because at a lower dose, you
7 need to use a higher binding affinity to maintain the target engagement,
8 right?

9 Second, second is very important is that Patent Owner's expert
10 argued there should be parallel change. Basically, therapeutic window
11 basically involved two components, efficacy and toxicity, right? He
12 basically argued, okay, if you have stronger binding, you're going to increase
13 the efficacy and toxicity at same degree.

14 And which he has not provided any scientific support for that
15 because EGFR expression is much higher in the tumor cell than EGFR
16 expression on the normal cell. So if you have the stronger binding, you're
17 going to achieve higher efficacy compared to the increase of toxicity, which
18 means you will have wider therapeutic window.

19 In fact, during deposition, we asked him about that. He actually
20 retracted from his position. He basically said, no, no, no. I didn't say it's the
21 same degree. He basically said, the binding of the antibody happened in
22 both human cell and normal cell. Which everybody agreed.

23 But he said, I didn't mean the same degree. So he actually
24 retracted from his position. And also, he actually specifically said, it's
25 impossible to measure the effect on the human cell on the normal cell. He
26 basically kind of said that his declaration, what he said is wrong, it's

1 incorrect. I think I'm running out of time. Sorry. Yes.

2 JUDGE FLAX: Okay. All right. So we'll call that six minutes.
3 So nine minutes on rebuttal. Okay. All right. So Mr. Qiu, we have you on a
4 screen to my left. I believe that the camera that's showing us, it won't appear
5 as if we're looking right at you, but we are looking right at you. If that
6 makes sense.

7 MR. QIU: Okay. Thank you, Your Honor.

8 JUDGE FLAX: So we are paying attention to you, even if it looks
9 like we're looking away.

10 JUDGE FREDMAN: Yes, I think we'd have to look at the podium
11 to be looking right at you, which is probably not looking at you actually.

12 MR. QIU: Okay, got it. Thank you so much. Can you hear me
13 okay?

14 JUDGE FREDMAN: Yes.

15 MR. QIU: Okay. I think my colleague --

16 JUDGE FLAX: Before we get to the arguing, let me ask if you all
17 would like to reserve time for rebuttal.

18 MR. QIU: Yes, we would like to reserve 10 minutes for rebuttal.

19 JUDGE FLAX: Okay. When you're ready.

20 MR. QIU: Okay. So Your Honor, I want to start with -- start by
21 addressing several points that Petitioner made. First, I want to note that
22 BA03 is different from cetuximab. It is covered by the Liu Patent and the
23 Petitioner actually owns the Liu Patent.

24 So it is surprising to us that they suggested that the BA03 is in the
25 public domain and that BA03 is interchangeable with cetuximab. We want
26 to call your attention to Petitioner Slide 45. That's a slide where they

1 suggested that -- they suggested -- that slide creates the impression that
2 there's something wrong with Patent Owner patenting ADC based on
3 Petitioner's antibody.

4 Petitioner is in the wrong because they failed to mention that
5 Patent Owner obtained an exclusive license of developing ADCs using the
6 BA03 antibody. And this is shown on Patent Owner's Slide 43. If we can
7 show that on the screen.

8 So the BA03 antibody was developed by Shanghai JMT-Bio, Inc.,
9 and it was patented. The patent was owned by JMT. In 2015, JMT
10 exclusively licensed the Liu Patent to Patent Owner to develop ADCs. And
11 then Patent Owner's efforts in developing the ADC resulted in the
12 challenged patent.

13 Despite his knowledge about Patent Owner's exclusive license,
14 Petitioner decided to copy Patent Owner's idea of using BA03 to develop
15 ADC. This is shown in Petitioner's own '382 application which was filed in
16 2022. It discusses Patent Owner's ongoing clinical trial developing ADC
17 using the BA03 and compared BA03 with other candidates for ADC.
18 Petitioner later started clinical trials for its CPO301 ADC.

19 JUDGE FREDMAN: Excuse me, Counsel, can we distinguish
20 here?

21 MR. QIU: Yeah.

22 JUDGE FREDMAN: So you're arguing that they're using BA03,
23 but that is in the -- BA03 is in the prior art, right?

24 MR. QIU: Yes. BA03 is in the prior art.

25 JUDGE FREDMAN: Right. So from an invalidity standpoint, we
26 don't really care. I mean, there might be some infringement issues that

1 you're raising. Sure, they may be infringing you, or you might be infringing
2 them. I guess I'm not -- well, you have an exclusive license. So they might
3 be infringing you, I suppose. But that's not really the Board's concern.
4 We're concerned with validity.

5 MR. QIU: Okay. But --

6 MR. PONDER: Well, if I could make one point. I mean, the
7 argument that was made earlier is that cetuximab and BA03 are basically
8 interchangeable.

9 JUDGE FREDMAN: One of them is the humanized version of the
10 other, right?

11 MR. PONDER: Yes. And Wei is also humanized. There are all
12 these humanized antibodies and our point was, that we're saying here is, if
13 BA03 -- we're just surprised they're saying BA03, you would just use that in
14 place of cetuximab because it's basically kind of suggesting it's obvious over
15 cetuximab. But they're the ones that obtained a patent on BA03.

16 JUDGE FREDMAN: That doesn't mean it's not obvious.

17 JUDGE FLAX: Okay. Well, here's a question. Let's pursue this
18 idea that you all are bringing up, which I don't know if we've thought about
19 before, but would it be obvious to move to BA03 from cetuximab? Just that.
20 Is that obvious?

21 MR. QIU: Your Honor, that was the obvious in combination that
22 was considered during examination. The examiner cited to a reference that
23 teaches cetuximab-based ADC. And --

24 JUDGE FLAX: Let's not consider it as a conjugated antibody
25 without a drug conjugate, correct?

26 MR. QIU: Mm-hm.

1 JUDGE FLAX: And BA03 is the humanized version of cetuximab
2 antibody. Is that correct?

3 MR. QIU: So BA03 is not -- BA03 changed also several positions
4 in the CDR, in addition to humanization. So it's not a direct humanized
5 version of cetuximab. And then --

6 JUDGE FLAX: (INDISCERNIBLE)?

7 MR. QIU: I believe so, Your Honor.

8 JUDGE FLAX: Okay. So just considering these two antibodies, is
9 there a motivation? Is it obvious to use BA03 instead of cetuximab because
10 of its modifications?

11 MR. PONDER: Well, I think Mr. Qiu will go into this. The
12 problem is cetuximab ADCs were known and were known to fail, and were
13 too toxic. So if you thought BA03 is just a humanized version of cetuximab
14 and you know that cetuximab already is toxic, why would you have a
15 motivation to say, let's make a humanized version of a very toxic ADC?

16 That's why we're saying there would be just no motivation to
17 combine to go from cetuximab to BA03. The POSA knowing that the
18 cetuximab ADCs failed, would be thinking, okay, if I use another one that's
19 the same, adopting their logic that BA03 is just a humanized version, you
20 would think you're just making another toxic drug.

21 If you are POSA, you would be thinking, okay, what should we be
22 doing something different than using cetuximab?

23 JUDGE FREDMAN: Is cetuximab using the same toxic agent?

24 MR. PONDER: Mr. Qiu?

25 MR. QIU: Sorry. Your Honor --

26 MR. PONDER: He's asking about the --

1 JUDGE FREDMAN: Your colleague is making the assertion that
2 you wouldn't just switch cetuximab for BA03 because of the toxicity
3 concerns with cetuximab. My question is, cetuximab ADC, what was the
4 active agent in cetuximab ADC? Was it MMAE also, or was it something
5 else?

6 MR. QIU: Yes. So Your Honor, if you go to -- let's go to a slide
7 to talk about this. Let's go to Slide 30. On that slide, it shows that the prior
8 art, Tikhomirov, teaches about the specific cetuximab ADC, which is
9 cetuximab with a VC linker and then MMAE payload or active agent.

10 That is exactly the same linker and payload or agent as what
11 Petitioner has proposed for the obviousness combination. So the only
12 difference between their proposed ADC and the cetuximab ADC is the
13 antibody. So the prior art Tikhomirov teaches that the cetuximab-based
14 ADC was known to have an unviable therapeutic window.

15 As you can see in the code, because it potentially is that it's
16 toxicity against both normal cells and cancer cells. And Tikhomirov
17 concluded that a safe cetuximab-based ADC must use a non-cleavable
18 linker. Here, notably, we see is a cleavable linker.

19 JUDGE FLAX: Counsel, you're saying that we're looking at
20 Tikhomirov prior art right here. That's Exhibit 1009?

21 MR. QIU: That's Exhibit 1009. Yes.

22 JUDGE FLAX: So this is one of the foundations of your defense,
23 correct?

24 MR. QIU: This is one of them.

25 JUDGE FLAX: This reference says that if you don't use the non-
26 cleavable linker, you've got toxicity problems. Is that correct?

1 MR. PONDER: Well, I think --

2 MR. QIU: Yes, so --

3 MR. PONDER: -- what it's saying is --

4 MR. QIU: -- you wouldn't take --

5 MR. PONDER: Go ahead.

6 MR. QIU: So yes. So the Tikhomirov does teach that, but we are
7 relying on it for a much narrower teaching. So the example that Tikhomirov
8 gave with this specific cetuximab vc-MMAE ADC. And it teaches that it
9 does not meet the safety requirements. So that's the teaching we're relying
10 on. But you are correct that Tikhomirov also teaches that when you have a
11 fully antagonist antibody, you should not pair it with the cleavable linker.

12 JUDGE FLAX: So I understand. I mean, I've looked at this
13 reference because it's so important to your defenses. And one of the things I
14 noted is that in the paragraph that spans pages 5 and 6 of the reference, it
15 says that a non-cleavable linker is substantially resistant, et cetera, et cetera,
16 whereas cleavable linkers, which can be used optionally but less desirably,
17 are linkers that can be cleaved by one or more of these recited cleaving
18 agents. So what I take from that is that yes, non-cleavable linkers are
19 important to Tikhomirov and are the preferred embodiments of Tikhomirov,
20 but it is certainly saying that you may optionally use cleavable linkers. How
21 do you respond to that? No one seems to have brought this up. Which is
22 astounding.

23 MR. QIU: We are not -- sorry. Sorry for talking over you. Your
24 Honor, we are not relying on Tikhomirov for teaching the proposition that
25 cleavable linker are not okay. Our reliance on it is focused on the specific
26 teaching, that when you pair cetuximab and the cleavable linker, VC linker,

1 and the MMAE payload to form ADC, that is too toxic. So we are not
2 relying on Tikhomirov to argue that, hey, no cleavable linker can be used,
3 and they are all novice. That's not our position.

4 JUDGE CHANG: So I have a question for you on that. So I
5 understand your argument is that if cetuximab is toxic, then you wouldn't
6 -- it wouldn't make sense to use humanized version. But I think Petitioner's
7 argument is that Liu itself teaches that a humanized version has benefits over
8 cetuximab, which will give you the motivation.

9 And I think they also argue that even the humanized version of
10 Wei's variant, which does not also appear to have greater pH selectivity than
11 the chimeric version. So it seems like they're arguing that the humanized
12 version will give you the motivation to use, even assuming that there's some
13 evidence that cetuximab gives you high toxicity. So how do you respond to
14 that?

15 MR. QIU: Your Honor, your question provides a great starting
16 point for what I was planning to discuss next. So we actually show that
17 evidence would suggest the -- be it if you replace cetuximab with the BA03,
18 the ADC will become even more toxic. Let's go to Slide 31 of Patent
19 Owner's demonstratives.

20 So basically, Petitioner argues that the POSA would have been
21 motivated to use BA03 because of its higher binding affinity. That's one of
22 its key characteristics. But evidence shows that a POSA would have
23 expected higher binding affinity, making it even less from the selective
24 cetuximab, which is already bad.

25 So this slide shows the Crombet article, one of the figures in there.
26 So what the figure shows that when an antibody has a higher binding affinity

1 than cetuximab, its ability to selectively target tumor cells becomes even
2 weaker. In other words, there was a known negative correlation between
3 binding affinity and tumor selectivity.

4 And Dr. Atanackovic explains that in his paragraphs 23 to 29, 60
5 to 61. Please go to Slide 32. Petitioner has no independent evidence that
6 contradicts Crombet's teaching, but only presents testimony from its expert
7 to cast doubts on Crombet.

8 However, this is a peer-reviewed article in a top journal, and it is
9 also independently confirmed by the Garrido article. What this comes to is
10 that -- let's go to Slide 33. The negative correlation between binding affinity
11 and selectivity has been applied in ADC design, right?

12 So if you look at the Tikhomirov 346 reference, it describes how
13 an anti-EGFR antibody with a tenfold weaker binding affinity than
14 cetuximab is better. If you look at the middle quote, it notes that the
15 antibody substantially eliminates binding to cells presenting EGFR at a
16 normal EGFR density.

17 And in the lower quote it states that such an ADC provides a broad
18 therapeutic window. So what this comes to is that, based on the teachings of
19 those references, Dr. Atanackovic in his paragraphs 61, which is on Slide 34,
20 explains that a POSA would have expected the BA03-based ADC to have an
21 even worse therapeutic window than cetuximab based ADC.

22 This is because BA03 was expected to have poor ability to
23 selectively target tumor cells. So at the same level of killing of tumor cells,
24 it would be expected to have more killing of normal cells. So it is even less
25 safe. Please go to Slide 35.

26 JUDGE FREDMAN: So Mr. Qiu, if we can just jump in for a

1 second. I have two questions. First, on the point you just raised that there
2 would be a narrower therapeutic window, I think that there's pretty clear
3 case law that you don't have to be the best, right? You can have a situation
4 where it's slightly inferior for the use and can still be desirable.

5 And in cancer therapy in particular, toxicity is allowed to be at
6 levels that would not be allowed in any other indication, right? There are
7 toxicities that are much higher. And then just second, in the Tikhomirov
8 Exhibit 1009, the 062 one, it does talk about this discussion that there's
9 safety data -- this is at page 26, 1563 for us.

10 Of the record, page 26 of that reference says the safety data further
11 validates in vitro results that on target toxicities of the fully naked anti-
12 EGFR antibodies isn't potentiated as a result of conjugation to cytotoxic
13 payloads. So they're saying that it's not really that much worse.

14 So I'm a little bit not sure. I hear what you're saying. I hear what
15 you're saying, you're saying that you want a less efficient, a lower KD,
16 essentially, antibody, because that will bind -- you're less likely to bind to
17 normal EGFR and will bind to the cancer EGFR.

18 Or because there's more targets on the cancer cells, there'll be more
19 of them that will get hit. And so that sort of undercuts their motivation is I
20 think what you're trying to make the argument that it does. But nonetheless,
21 you don't have to have the best antibody, you just have to have one that's
22 known in the art and that would be expected to be effective. Right? That's
23 *In re Mouttet* or whatever case you like for that.

24 MR. QIU: Yes. Your Honor, let me answer your first question.
25 So here, in case we're talking about the obviousness to try theory, let's go to
26 Slide 50. So I want to first comment that the obviousness to try theory does

1 not work here. Because as you can see on this slide, Petitioner's expert
2 admitted that there were hundreds of anti-EGFR antibodies available, and
3 there were millions of ways to modify cetuximab. You just cannot try all of
4 them. So what Petitioner needs to show --

5 JUDGE FREDMAN: But when you're trying, wouldn't you first
6 look at known patents that have known antibodies that work? I mean,
7 honestly, this is essentially -- when you think about *O'Farrell*, right? The
8 picking and choosing type cases, the reasonable expectation of success issue,
9 where there's two categories it talks about.

10 One where there's lists that you pick from, like in *Wrigley* or
11 *Perricone*, and one where there are just -- usually those are chemical cases
12 with genres of 47 R groups, and you have to pick from all those different R
13 groups, and that's considered the bad case.

14 This isn't that case. This is closer to the first case. We have a list
15 of fairly narrow sets of things. We have antibodies that were known and
16 used. We have payloads that were known and used. We have linkers that
17 were known and used.

18 I mean, you're not arguing that those are not known, right? Are
19 you arguing that there is not -- that the antibodies, that EGFR antibodies -- I
20 mean, so you're arguing that, yes, there's a lot of choices -- I mean, there are
21 choices, but you're picking from known choices, from lists, not from
22 genres.

23 MR. QIU: Right. So the question is whether a POSA would have
24 picked Liu's BA03 antibody based on what the POSA knows at the time of
25 the event, right? So we showed multiple reasons why a POSA would not
26 have chosen BA03.

1 First, we showed on Slide 34 that the BA03 was expected to have a
2 narrower therapeutic window than cetuximab based ADC. Chris, can you
3 please go to Slide 34? And it is not just that BA03 is not as good as
4 cetuximab in forming ADC, but also that cetuximab was known to not work
5 as ADC.

6 Tikhomirov uses -- that specific ADC does not work. So if you
7 have a ADC that's worse than that, it certainly wouldn't -- like a POSA
8 certainly wouldn't pick it. And then if we go to Slide 23 of Patent Owner's
9 demonstratives, we can see that in terms of the product that Petitioner
10 actually uses, we have shown that the therapeutic window of the BA03
11 would have been expected to be worse than them as well. And more
12 importantly --

13 JUDGE FREDMAN: As I said, the problem with that argument is
14 that just being slightly worse is not a teaching away, right? That's simply an
15 alternative choice. People make choices that are worse and that's allowed in
16 obviousness cases. So I hear you, but I don't think that that's the definitive
17 argument that you have. We'll get to some of the secondary considerations
18 arguments later, I guess, but --

19 MR. QIU: Your Honor, so for the comparison between Wei and
20 Leanna, those are focused on the lack of motivation to modify them. For the
21 comparison with cetuximab that is a definitive argument that a POSA would
22 not have chosen BA03. This is because cetuximab-based ADC was already
23 known to not work. And if you have a worse ADC than that, it certainly
24 wouldn't work. So I just want to clarify our position there.

25 JUDGE CHANG: Let me just clarify one thing. So your
26 argument, the Patent Owner's argument that cetuximab's ADC will not work

1 is based on Tikhomirov, right? And is there any other evidence other than
2 your expert's, I guess, declaration? So but your primary evidence is based
3 on that reference. Is that correct? I just wanted to make sure that you have
4 cited all the evidence that you are relying on.

5 MR. QIU: That's correct, Your Honor.

6 JUDGE CHANG: Okay. Thank you.

7 MR. PONDER: And just one thing to note. They didn't start with
8 a reference that used cetuximab and then argue replacing cetuximab with
9 BA03 and provide a motivation to combine for that. They chose Wei and
10 they chose Leanna, different antibodies, not cetuximab. And they gave
11 specific limited motivations to combine.

12 And I don't think there's motivation -- on the motivation to
13 combine arguments, page 40 and 41, for example, in Wei, I don't see where
14 they articulated, well, you could actually start with an antibody first and then
15 turn it into an ADC. They certainly didn't do that with Wei. And they don't
16 explain the obvious to try. And you mentioned the limited number. We just
17 saw that their own expert said there's hundreds of antibodies.

18 JUDGE FREDMAN: Well, there's hundreds of antibodies, but
19 essentially, right, Liu gives us a particular set of antibodies, right? If we're
20 looking at the art that's here, even the art in general, there are antibodies, but
21 it's not quite the same as your claim, which does include all of these changes
22 in the framework in the FC, which is Liu is a particular antibody, right? It's
23 a particular set of antibodies?

24 MR. PONDER: Yes. But we don't have convincing evidence
25 from the Patent Owner that would show -- I'm sorry, from the Petitioner,
26 how they get from this universe of known in the literature hundreds, by their

1 own expert's admission, of antibodies to picking this antibody or some
2 limited subset of those. So that's not an argument that they put in the record.

3 JUDGE FLAX: Well Counsel, if you look at page 40 of the
4 petition, doesn't that sort of indicate that they're -- when they're talking about
5 combining Wei and Liu, they say first, Liu discloses BA03. And then
6 second, they go over what Liu -- Wei and Liu teach together, and that it can
7 be an ADC and so on and so on.

8 So why doesn't that sort of suggest to you that they went in the
9 opposite direction that you were arguing, which is start with Wei, throw out
10 the antibody, toss in Liu's antibody. Why doesn't that suggest, hey, here's
11 BA03 that Liu says had a lot of advantages over cetuximab. Here's a second
12 reference that also wants to improve over cetuximab, and that makes it into
13 an ADC. Why does that not suggest let's add a conjugated drug to BA03?

14 MR. PONDER: Because when you look at the analysis on 40 to
15 41, there's no discussion about why an ADC would be better than just a
16 naked antibody treatment. Naked antibody treatments were known. They
17 don't go into why an ADC would be better. Their analysis assumes that you
18 want an ADC, and they say we have this ADC platform, Wei --

19 JUDGE FLAX: Right. But doesn't Wei suggest that you want an
20 ADC?

21 MR. PONDER: Sorry?

22 JUDGE FLAX: Doesn't Wei suggest that you would want an
23 ADC?

24 MR. PONDER: I mean, we're talking about what was their
25 reasoning they expressed. Their petition didn't lay that out. Their petition
26 starts with, we're a POSA, we have an ADC, we're looking at something like

1 Wei, and then we see there's this other antibody, and we think we can
2 improve it --

3 JUDGE FREDMAN: But at page 4 they do really say we have
4 Liu, Liu has the antibody, and then we want to do it. I mean, I think they go
5 both ways. And we think about obviousness, right? I agree with them, and I
6 think it's pretty old Federal Circuit case law and actually CCPA case law
7 that A in view of B and B in view of A don't matter.

8 And this argument you're making is you're trying to -- you're kind
9 of trying to confine them in a rigid box here. And I don't think that that's
10 what *KSR* says. I don't think that's what -- I don't remember the name of the
11 really old case. They're like a person's name that said A in view of B and B
12 in view of A doesn't matter, but --

13 MR. PONDER: Yes. But the problem here too is Wei and Leanne
14 also indicates that cetuximab wouldn't work. And so they were also -- and
15 that's kind of Mr. Qiu can go through --

16 JUDGE FREDMAN: Right. But Liu tells us, humanized BA03
17 has better anti-tumor activity than other things like Erbitux, right? So it tells
18 us expressly there are reasons to pick it. Liu gives reasons, it's not totally
19 silent.

20 MR. QIU: Your Honor, I want you to go to --

21 MR. PONDER: Mr. Nie is going to address this.

22 MR. NIE: Yes. I think we can discuss the scientific issues a little
23 bit. Let's talk about BA03 from Liu, right? BA03 allegedly mentions a few
24 advantages of BA03. Number one, is high affinity. Number two,
25 humanized.

26 JUDGE FREDMAN: Right.

1 MR. NIE: Number three, increased phosphorylation inhibition.
2 Number four, there's ADCC, right? Now, there's two categories of this
3 points. One category is humanization. Certainly, less toxicity to normal
4 cells because less -- it's not against human cells in there. Second category is
5 a bunch of --

6 JUDGE FREDMAN: Humanization. What it does is
7 humanization removes the ability of the immune system to pull it out.

8 MR. NIE: Yes.

9 JUDGE FREDMAN: It doesn't affect the toxicity of the cells.

10 MR. NIE: Yes. That's the first category. Second category is about
11 activity. Phosphorylation, ADCC, affinity, right? So let's talk about first
12 category, humanization. Yes, humanization, other than Petitioner's
13 argument is, yes, certainly has benefit. But humanization is a fairly easy
14 approach.

15 Every antibody can be humanized. So if you were taking any
16 antibody, yes, it can be humanized. So it is an advantage, but it's relatively
17 readily available, reasonably small advantage, I would say.

18 JUDGE FREDMAN: Right. But it is an advantage.

19 MR. NIE: It is an advantage, yes. Very easy to get. Now, second
20 category, which is about the ability to kill, right? ADCC and
21 phosphorylation, and affinity, those are all ability to kill cells. So now,
22 there's another thing of the ADC which is related to ability to kill cells, that
23 is the payload.

24 So there are many, many payloads to choose from. Some payloads
25 are very toxic, some are less toxic. So now, when you're designing ADC,
26 you can choose the very toxic payload or less toxic payload. Now, alongside

1 that, there's also this ADCC phosphorylation and affinity.

2 It can also be designed to be more active or less active. Now, look
3 at this list, two things together. They are about one single thing, that's to
4 make ADC more potent or less potent. ADCC makes the ADC more potent.
5 Phosphorylation, same thing.

6 Now, the potency is exactly within Mr. Qiu's discussion of the
7 therapeutical window. Because whether you can increase potency or
8 decrease potency, the key here is whether you can use the potency correctly
9 against tumor cells.

10 So now, if you don't have the right antibody to target the right
11 cells, whether you increase potency or decrease potency doesn't really
12 matter. So therefore, in the context of the whole thing, all those categories
13 -- huh? I'm sorry.

14 JUDGE FREDMAN: I hear you. I don't know if you've ever
15 heard of Derek Lowe, he has an article from 2023 where he cites a paper
16 -- and the paper talks about the fact that actually ADCs don't really operate
17 that way. And there's a lot of papers that say that. So I'm a little suspicious
18 of that statement.

19 But I think that -- I hear your point. What you're saying is that you
20 want to increase specificity, right? Essentially, right? And that your
21 argument is that BA03 wouldn't necessarily increase specificity because by
22 being more effective as a binder, it could then target cells you don't want to
23 target and it could have off-target effects, right?

24 MR. NIE: Yes, exactly. So all this advantage is the question in
25 Liu --

26 JUDGE FREDMAN: But, I think that that's -- the argument you're

1 trying to make that I think as a teaching away, it doesn't really -- you still
2 want to get targeting to the tumor cells, right? And people in cancer
3 therapies do accept toxicities that would not be accepted, as I said earlier, in
4 any other context, right?

5 Although the therapeutic window in cancer therapies is much
6 narrower, you would not accept that in an antibiotic, supposedly going to kill
7 the person. You certainly wouldn't accept it in an analgesic, right? So we're
8 talking about a situation where the fact that there's increased toxicity isn't all
9 bad, right? Because you want toxicity in cancer drugs. So I hear what
10 you're saying. I understand the argument. I'm not sure I buy it. That's all.

11 MR. NIE: Yes. To put it in context, cetuximab is one of the first
12 antibodies approved in the U.S., right? For any kind of (INDISCERNIBLE).
13 Now, 20 years after cetuximab was available, there's no ADC at all approved
14 in the U.S. So it's really challenging to develop ADC targeting EGFR. I
15 don't know why it's toxicity alone, but has not been done before. So here,
16 choosing a right antibody, actually is very critical, very difficult.

17 JUDGE FREDMAN: And so that's where I'm actually more
18 interested in your secondary considerations. We have some time. If you
19 want to move to that, I would like to hear those. I'd like to hear a little bit
20 about just Claim 13 in particular as well, but secondary considerations
21 generally in Claim 13.

22 MR. PONDER: Specifically, you want to just go to secondary
23 considerations?

24 JUDGE FREDMAN: We (INDISCERNIBLE). I don't want to tell
25 you what to do, but --

26 MR. QIU: Yes, let's go to secondary considerations. Please go to

1 Slide 41. So first we want to note a significant development after the
2 institution. In the institution decision the Board -- so before institution, we
3 showed that Patent Owner's ADC candidate received fast track and
4 breakthrough therapy designations.

5 And the Board found in the institution decision that these
6 designations indicate promise but not fulfillment of a long-felt and
7 unresolved need. But there was a significant development. After the
8 institution, Patent Owner's ADC that embodies the claim they mentioned
9 became the first regulatory approved anti-EGFR ADC worldwide. Please go
10 to Slide 42.

11 JUDGE FREDMAN: But when you say worldwide, first, it was
12 approved in China, it wasn't approved by the FDA, was it?

13 MR. QIU: What we mean by that is the world's first approved
14 anti-EGFR ADC. Yes, any country.

15 JUDGE FREDMAN: So the first that was approved by anybody
16 that would approve these drugs?

17 MR. QIU: Mm-hm. Yes. Yes. It was approved in China.

18 JUDGE FREDMAN: Right. Okay. And just for those of -- I'm
19 not as familiar, I apologize, with the Chinese, and the equivalent of the Food
20 and Drug Administration. But that's what this is. When it says the National
21 Medical Products Administration, that's essentially the FDA in China?

22 MR. NIE: Yes.

23 MR. QIU: Yes. That's correct.

24 JUDGE FREDMAN: Okay. Thank you.

25 MR. QIU: And then so starting in -- let's go to the next Slide 42.
26 Starting from 2012, multiple clinical trials on anti-EGFR ADCs were

1 conducted, but unsuccessful. Patent Owner's MRG003 ADC being the first
2 approved ADC that targets EGFR addresses the long-felt and unresolved
3 need for clinically viable anti-EGFR ADC.

4 We also want to note that Petitioner's candidate, the CP0301, is the
5 second most advanced anti-EGFR ADC currently in clinical trials. And this
6 ADC also embodies the claims of the '370 Patent. Petitioner
7 (INDISCERNIBLE) exact same antibody. This is shown on their Petitioner
8 Slide 44.

9 JUDGE CHANG: So I have a question for you. So on this page,
10 on Slide 42, it says the success of MRG003 was at least partially attributable
11 to BA03's high binding affinity. So it seems that it's the binding affinity that
12 contributes to the success. Is that the argument here? And is it really the
13 antibody that sort of provided the success?

14 MR. QIU: There are multiple properties of the antibody that
15 resulted in the success, and something that Patent Owner --

16 JUDGE FREDMAN: But this argument is kind of inconsistent
17 with the Tikhomirov argument that you made before, right? Where a high
18 binding affinity is bad. I'm just saying --

19 MR. QIU: Your Honor, this is totally consistent. So the features
20 of high binding affinity and the other features such as internalization were
21 discovered like by Patent Owner. And what we are arguing is that before the
22 priority date of the patent, the conventional wisdom of the field is that high
23 binding affinity is bad.

24 But based on our discovery, we discovered that an antibody with a
25 high binding affinity can actually work. And this is almost an unexpected
26 result. And this further shows that --

1 JUDGE FREDMAN: They knew that it had a better EC50. I don't
2 know. I mean, I'm not sure that the binding affinity was known by Liu,
3 wasn't it? Didn't Liu know that there was good binding affinity for BA03?

4 MR. QIU: Liu knows that the BA03 antibody has high binding
5 affinity, but based on --

6 JUDGE FREDMAN: What you're going to say, I think, is that it's
7 better because it works better with the conjugate part of it. That's essentially
8 what you're saying, that that was what was improved?

9 MR. QIU: That's right.

10 JUDGE FREDMAN: Not just the antibody itself. Okay.

11 MR. QIU: Yes. A POSA would have --

12 JUDGE FLAX: So Counsel, did you all ever explain this publicly
13 that -- because I think if you're right on the one hand, that the entire world of
14 ordinary skilled artisans would think that an ADC with this antibody which
15 had a high binding affinity would be a disaster. And now your client is
16 extolling the virtues of that same ADC --

17 JUDGE FREDMAN: Can we pause for one second because Judge
18 Chang is frozen.

19 MR. QIU: She's frozen?

20 JUDGE FREDMAN: I'm sorry. And pardon. Let's freeze the
21 clock too, if you can, at least we'll just pay attention to it.

22 MR. CHARLIE: Okay.

23 JUDGE FREDMAN: 16:27.

24 MR. CHARLIE: Where's the pause?

25 JUDGE FREDMAN: Mr. Easton, if you can -- or Mr. Charlie, if
26 you can hear me, we can reconnect Judge Chang.

1 MR. CHARLIE: Yes. Standby.

2 JUDGE FLAX: All right. You can think about that question.

3 JUDGE FREDMAN: Sorry, Mr. Qiu.

4 MR. CHARLIE: Hold on. She's back.

5 JUDGE FREDMAN: Okay, Judge Chang is back.

6 JUDGE FLAX: Okay. You're back?

7 JUDGE FREDMAN: She's muted, but she's back. Okay.

8 JUDGE FLAX: Your mic volume.

9 JUDGE FREDMAN: She's back, I think.

10 JUDGE FLAX: Okay. You can hear us okay?

11 JUDGE CHANG: Yes, now I can hear you.

12 JUDGE FLAX: Wonderful. Wonderful. All right. So back to the
13 question is this -- oh, did we lose Counsel? Is he there?

14 JUDGE FREDMAN: No, he's still there.

15 JUDGE FLAX: Okay. So Counsel, here's my question. Did your
16 client ever inform the public that contrary to everything that they probably
17 believed up to that point, that the high binding affinity of their product was
18 actually an advantage, and why as opposed to that conventional knowledge?
19 Or did they not think that was necessary?

20 MR. QIU: I don't believe there's evidence in the record where our
21 client announces that. So I'm not totally sure whether they have done that or
22 not. But we believe the main question is -- and as a pharmaceutical
23 company, I can understand that as long as their drug, they have a drug that
24 works and they can make it to use, I'm not sure whether they're interested in
25 engaging in the academic discussion in public documents.

26 JUDGE FLAX: Well, we think there would be questions, right,

1 from the audience about, hey, you say this is good, but we know it's bad.
2 Why are you saying it's good if your other foundational argument is right?

3 MR. QIU: I think --

4 JUDGE FREDMAN: Or the regulator.

5 MR. QIU: Yes. The data from the clinical trials does show that
6 our ADC candidate performs well against the expectation from back before
7 its development.

8 MR. NIE: Yes. I don't think the client has really developed very
9 good understanding why this worked. And then there have been multiple
10 hypotheses going on. One, it may be still the affinity may be beneficial, may
11 not be beneficial. And second is that there may be the antibodies another
12 property which is the ability to trigger internalization of the ADC into the
13 cell.

14 That may be relevant, may not be relevant. So in terms of what is
15 the mechanism while it has worked has not been very well studied yet.

16 JUDGE FREDMAN: Okay. Great. Going back to 13, because
17 you can tell that's my interest. Can you talk about what your view is on the
18 scope of that? I mean, for this unexpected result?

19 MR. NIE: We're not relying on unexpected result to support --

20 JUDGE FREDMAN: Oh, no, no. For this secondary
21 consideration, I'm sorry. I apologize. You had said unexpected result.

22 MR. NIE: Yes. One thing I can highlight is that not only has our
23 antibody been accepted, approved in China, the Petitioner's ADC, which is
24 falling under scope of Claim 1 is also the number two candidate, which can
25 be potentially approved in China as well. So that also shows there's nexus
26 between the antibody's ability to support ADC.

1 JUDGE FREDMAN: Right. But I mean, I guess I'm asking about
2 the scope of Claim 1, I guess, relative to the antibodies. You do have
3 limited to the particular CDRs, right? It's limited to CDRs, just having for
4 heavy chains, 12 to 14 for light. Does the rest of it matter?

5 Or can we say -- in other words -- so in other words, when we talk
6 about commensurate in scope or nexus or whatever you want to say, can we
7 ignore the Fc region and the framework? I mean, what is your view on that?
8 Because you don't limit it to that. I mean, you don't have a SEQ ID of the
9 antibody itself.

10 MR. NIE: To the extent I understand it scientifically, I don't think
11 the others matter. Here, certainly in the antibody's ability to bind to the
12 target and maybe to trigger internalization may be the key reason why this
13 can be successful. And the framework regions and payloads may not matter
14 as much.

15 JUDGE FREDMAN: Right. I don't know if Mr. Qiu wants to say
16 anything or not.

17 MR. QIU: No, I think (CROSSTALK) Mr. Nie is commenting.

18 JUDGE FREDMAN: Okay. Keep going. I'm sorry. I don't want
19 to totally hijack you.

20 MR. NIE: Yes. And then we want to go to Slide 43, where we
21 explained copying, which we did offer an overview at the beginning.
22 Basically, Petitioner specifically, they knew that we had the exclusive right
23 to develop ADCs under the Liu Patent. But they still decided to pursue the
24 same antibody in their ADC. So that shows strong copying evidence.

25 JUDGE CHANG: So let me ask you something about that. So it
26 seems that the only -- there are case law that says just because the Petitioner

1 uses the same antibody as in your patent's ADC, that does not -- that's not
2 enough to show copying. Because otherwise infringement basically
3 collapses into -- copying basically collapses into infringement.

4 So I don't think that's sufficient. So then you have this argument
5 about Petitioner has an application that talks about several other candidates,
6 but they ended up choosing this one. But that also doesn't seem -- I mean,
7 they actually suggest, right? They look at different candidates and they
8 picked one. So why does it show that it's copying?

9 MR. NIE: Yes. So Your Honor, so we also cited -- yes, I agree
10 with like mere infringement is not enough. And we cited in our surreply on
11 page 28, a case by *Liqwd* where we -- where it says that there -- like what's
12 important is evidence that shows like affirmative act of copying.

13 So here, I want to note one aspect is that in the '382 application,
14 Petitioner compared the BA03 antibody with the three other derivatives. It
15 showed that BA03 was less safe than the other three derivatives. Because
16 those other derivatives had pH selectivity.

17 So if you just look at the '382 application, you'll see that there's no
18 reason to pick BA03. So based on that study that they did, the only reason
19 they could have picked BA03, was because we have achieved success using
20 BA03. And that's additional evidence. And this is certainly not a situation
21 where there's just infringement by accident, because they totally know that
22 we have the license to BA03, and they know the Liu Patent. So yes.

23 JUDGE CHANG: So the evidence you just cited is a lot less
24 strong than the evidence that's available in that case that you cited, right?
25 Because that's actually an affirmative. I think there was actually some
26 affirmative evidence showing that the Petitioner copied. And here, I think

1 you're saying, well, based on their application, it seems that they should
2 have chosen something else, but they didn't. That is basically the basis of
3 your copying?

4 MR. NIE: Your Honor, we're pointing to that -- yes. Your Honor,
5 we pointed to that application and we -- like Petitioner did not point to any
6 evidence where -- they did not explain why they ended up choosing the
7 BA03 after considering several better alternatives of that application. So I
8 would just end by noting that.

9 And then please go to Slide 44. There it shows that the success of
10 the two most advanced anti-EGFR ADCs is attributable to their
11 commonality. This is something Petitioner admits. So the two most
12 advanced drug candidates, they share the BA03 antibody, and their linkers
13 are both cleavable.

14 However, their specific linker and payload are different. So the
15 natural implication from that is that the success is attributable to the
16 common features, which are claimed in the '370 Patent. Yes. So that's our
17 presentation on the secondary consideration.

18 JUDGE FREDMAN: Okay. I mean, it is -- yes, I just switched to
19 *Liqwd* real quick. And it does look like that's one where there was non-
20 public information that was copied, not here it's -- if it was anything, it was
21 public information. So that's a difference. I don't know if it matters, what to
22 think about it.

23 MR. QIU: Yes. Your Honor, I want to -- since you mentioned
24 earlier that the -- oh, sorry. First, I want to make sure I didn't mishear you.
25 Was there a question that --

26 JUDGE FREDMAN: No, no, there wasn't. I was just --

1 MR. QIU: Oh, okay.

2 JUDGE FREDMAN: Sorry.

3 MR. QIU: Got it. Got it. Since there was an earlier discussion
4 about the purported benefits of BA03 in terms of properties like binding
5 affinity, phosphorylation inhibition, ADCC, and humanization, I want to
6 discuss a little more on those. Please go to Patent Owner's Slide 15.

7 So Petitioner also mentioned in their discussion that they relied on
8 the Goldmacher article to show that certain properties were believed to be
9 desirable. But as we can see from this slide, Slide 15, that the very next
10 sentence to what they quoted, Goldmacher states that it remains unknown
11 how much any of these properties contribute to or interfere with the anti-
12 tumor efficacy of ADCs.

13 So I want to note that their purported beneficial properties are
14 speculative at most. And another note I want to make is that, at the time of
15 the relevant invention, the main concern or primary challenge in the field
16 was to mitigate toxicity without undermining efficacy.

17 If you go to Slide 9 of Patent Owner, their Dr. Atanackovic knows
18 that the primary challenge in anti-EGFR for ADC design was to mitigate
19 toxicity. In other words, widening the therapeutic window. This is showing
20 the prior art. For example, Tikhomirov explains that development of anti-
21 EGFR immunoconjugates based on approved anti-EGFR antibodies has not
22 been pursued because of concerns over enhanced skin toxicity.

23 And people were specifically designing ADCs to address the safety
24 concerns. And this is on Slide 10 of Patent Owner. Let's move to Slide 11
25 of Patent Owner. There Tikhomirov teaches that if you use the approved
26 cetuximab to form ADC, it does not work. And then on Slide 12, Dr.

1 Atanackovic --

2 JUDGE FREDMAN: In Slide 11, it says, for example, a safe anti-
3 EGFR ADC should incorporate a strongly antagonistic anti-EGFR antibody.
4 Implication being it should be a -- have a high binding efficiency, the way
5 that's stated.

6 MR. QIU: Yes. Yes. By a non-cleavable linker.

7 JUDGE FREDMAN: When BA03s are known to be the higher
8 binding efficiency, so it almost is suggesting to use BA03 or something like
9 that.

10 MR. QIU: So Tikhomirov teaches that it only works with a non-
11 cleavable linker. If you pair it with the cleavable linker, it doesn't work.

12 JUDGE CHANG: Sorry. So I think one of our questions is sort of
13 the combination of the two, right? Because you are citing this to say that
14 -- you've cited something to say that you want to have a lower binding
15 affinity than you're citing Tikhomirov to say that it's better with a non-
16 cleavable linker.

17 But I think there's evidence, I think Judge Flax mentioned earlier
18 that Tikhomirov also said that a cleavable linker might be okay. And here it
19 says that you could have, it might be better to have a strong binding affinity.
20 So that seems that the combination of the totality of evidence may not
21 support the idea that you're arguing, which is it's not obvious to combine the
22 two.

23 MR. QIU: Your Honor, let me clarify that. So if you go to Slide
24 12 of Patent Owner, we show the -- like we show that Dr. Atanackovic
25 surveyed the existing design strategies for anti-EGFR ADCs. And none of
26 the strategies directed one to use a high binding affinity antibody with a

1 cleavable linker.

2 And while Petitioner has a chance to develop evidence on that,
3 they still do not point to a single example where anti-EGFR ADC was
4 developed with a high binding affinity antibody with a cleavable linker. So
5 --

6 JUDGE CHANG: Okay. Thank you.

7 MR. QIU: I also want to address Petitioner's argument that they
8 showed evidence that Liu has -- the BA03 antibody has pH selectivity.
9 Please go to Slide 22 of the Patent Owner. Oh, by the way, let's go back to
10 Slide 21 for Patent Owner. There we show that there was no basis to believe
11 that the BA03 antibody has ability to select the target tumor cells by pH
12 selectivity and other mechanisms.

13 So we submitted evidence in terms of Dr. Atanackovic's
14 declaration, and also deposition transcript. For example, in paragraphs 57
15 and 70 of his declaration, he explained that tumor selectivity is very hard to
16 achieve and usually requires creating a large number of mutated antibodies.

17 MR. NIE: Fang, can I chime in here? Talk about science for a
18 minute. It's very important to understand pH selectivity in here, because
19 Petitioner has emphasized we failed to provide evidence to traverse BA03
20 may not have pH selectivity. Let's give me one -- let's give you one piece of
21 evidence in Wei.

22 Wei was trying very hard to identify an antibody that is pH
23 selective. They screened over 700 mutations, 700, out of which at least 60
24 have the same kind of mutation to E or D. Charged amino acids. Out of
25 700, we tried 70 or almost 70 having these charged mutations.

26 However, out of screening 700-plus, whatever 60 charged

1 mutations, only one at most one worked as pH selective. Even that one,
2 104E or D, according to the expert, may not be pH selective. So they argued
3 because our BA03 has one or two charged mutations, you must have pH
4 selectivity. No, according to Wei, it's very, very rare to have pH selectivity
5 based on their own data out of 700.

6 JUDGE FREDMAN: I want to point out why does pH selectivity
7 matter? Why do we care?

8 MR. NIE: Because two --

9 JUDGE FREDMAN: The claim doesn't recite it.

10 MR. NIE: Exactly. Well, that's their point. I just try what's their
11 point. It's important because tumor has lower pH.

12 JUDGE FREDMAN: Tumor environments can sometimes have
13 different pH.

14 MR. NIE: Yes.

15 JUDGE FREDMAN: Yes, I know that.

16 MR. NIE: Yes.

17 JUDGE FLAX: So what about the Leanna reference? They don't
18 really care about pH selectivity, do they?

19 MR. NIE: So let me go to both Wei and Leanna. They are very
20 consistent. Both of them trying to address this single issue that is cetuximab
21 may not be a good candidate. So where do we go? Wei says, well,
22 cetuximab because it's not enough to distinguish tumor from normal, let's
23 add pH, right?

24 Leanna says, well, let's find an epitope, an EGFR protein, which
25 only is present in tumors. So let's say it is mutation of EGFR, which only
26 occurs in tumors. If you talk about that mutation, you only target tumor. So

1 both references target tumor selectively.

2 JUDGE FREDMAN: That's obviously a different thing when
3 you're like a PD-1 antibody that would be targeted just to the PD-1, which is
4 generally found only in tumors.

5 MR. NIE: Exactly. So both are addressing the problem of
6 cetuximab. So going back to cetuximab is against the teaching of Wei and
7 Leanna.

8 JUDGE FLAX: Was Liu's -- I'm sorry. Take that back. Was
9 Leanna's antibody another cetuximab derivative?

10 MR. NIE: It's not. It's specific to a different EGFR protein. It's a
11 mutation.

12 JUDGE FLAX: So it's not a derivative of the cetuximab --

13 JUDGE FREDMAN: Pause for a second. Mr. Qiu seems to have
14 fallen off now.

15 MR. NIE: It's called antibody 1.

16 JUDGE FLAX: Okay. We can wait a second. I think we lost
17 your colleague.

18 (Whereupon, the above-entitled matter went off the record at 2:50
19 p.m. and resumed at 2:50 p.m.)

20 JUDGE FLAX: So just so you know, your red light is on and you
21 are overtime, but it is your time.

22 MR. QIU: Okay. I disconnected at a point --

23 MR. NIE: I think we were finishing -- oh.

24 JUDGE FLAX: The question was whether that antibody 1 was
25 related to cetuximab in any way. And you had just said --

26 MR. QIU: Okay.

1 JUDGE FLAX: -- you didn't think it was, I think is what you said.

2 MR. QIU: Oh, that's right. So let's go to Slide 27 for Patent
3 Owner. Let me close on that. So antibody 1 is not a derivative from
4 cetuximab. And here I want to show what Petitioner is proposing. So Wei
5 Leanna both provides an improvement on top of the benchmark cetuximab
6 based ADC.

7 Wei improves it by adding pH selectivity so that it's -- the ADC
8 can selectively target tumor cells. Leanna improves it by adding -- by
9 targeting a tumor-exclusive epitope. So that also that mitigates toxicity to
10 normal cells. However, what Petitioner is proposing to do is to just revert
11 those benefits or improvements provided by Wei and Leanna.

12 And to be clear, this is not about implementing an alternative
13 design strategy that was known to work. Petitioner shows no design strategy
14 taught in the prior art that would suggest using antibody like BA03 with a
15 cleavable linker in ADC.

16 And there's a strong case law stating that if you -- if we go to Slide
17 28, there's strong case law stating that if your combination requires dropping
18 the very feature that gave the prior art its advantages property, or if you
19 propose a modification on first a prior art inventive concept, there's a teach
20 away.

21 At least there's a strong advice against motivation to combine.
22 And this is exactly the case here. Wei and Leanna both use tumor selectivity
23 to solve the problem of toxicity to healthy cells. And a POSA will not want
24 to make a modification that simply takes away those design features. To
25 that, we'll reserve the remaining time for rebuttal.

26 JUDGE FLAX: Okay. All right. So we'll just call that three

1 minutes. So we'll say seven minutes on rebuttal.

2 MR. QIU: Okay.

3 JUDGE FLAX: Okay. So turning back to Petitioner's Counsel,
4 whenever you're ready, sir.

5 MR. SUH: Yes. Thank you, Your Honor. So I'm going to be very
6 brief. I know we only have nine minutes. But I just want to address a
7 question that you actually asked also, Judge Fredman, to Patent Owner. And
8 the obviousness from cetuximab to BA03. Obviously, BA03 is a humanized
9 version of cetuximab. We pointed out in our petition there's obviously --

10 JUDGE FREDMAN: Can I ask which slide that is? Which slide
11 are you looking at?

12 MR. SUH: Slide 18, sir. There's obviously the potential for
13 immunogenicity, obviously goes low when you go from murine to chimeric
14 to humanized. And I think that's (INDISCERNIBLE) ADCs were a failure,
15 right? But that's not true because if you look at Wei, right? In Wei, they
16 compared cetuximab vc-MMAE, vc-MMAE elements of the challenged
17 claims.

18 And they compared that with the Y104D vc-MMAE, which is
19 supposed to be better selected because of this 104D mutation, right?
20 Inhibition on cancer cells, virtually identical, right? They were the same.
21 They were both highly effective, right? On cell activity, right? And this is
22 at example 1005 Wei, paragraphs 130 to 1131, right?

23 In addition to the skin cells at maximum doses, cetuximab was
24 about 80 percent CGI. This selective, better selective, Y104D, at maximum
25 doses, about 70 percent CGI. So even their selective antibody was still
26 killing 70 percent of the skin cells, and cetuximab wasn't even that different.

1 So I don't see how Patent Owner can make this argument that the
2 prior art showed a failure of cetuximab vc-MMAE, right? And my
3 colleague, Dr. Chen, will continue.

4 DR. CHEN: Your Honor, we don't have much time left, but there
5 are too many issues to address. And first of all, Judge Flax, you mentioned,
6 asked Patent Owner, did they tell to public about -- anything about high
7 binding affinity? Here it is. This is a document. This is an exhibit actually
8 cited by Patent Owner, Exhibit 2032. And we are on page -- let me see. We
9 are on page 300, I believe. 310.

10 JUDGE FLAX: 2032?

11 DR. CHEN: Yes. 2032.

12 JUDGE FLAX: Page 310?

13 DR. CHEN: Page 310.

14 JUDGE FLAX: Thank you.

15 DR. CHEN: On page 310, Patent Owner tell investor, this is a
16 public offering prospectus. And Patent Owner tell investor that you have the
17 MRG003, have several competitive advantages. And one of them is the high
18 binding affinity, right? So basically, their expert says high binding affinity
19 is disqualifying, is no good.

20 But in the meantime they tell investor, high binding affinity is
21 competitive advantage. Okay? And now, Your Honor, I want to go back to
22 the Tikhomirov Patent Owner keeps talking about. So this is a relevant on
23 Tikhomirov Exhibit 1009, page 5. As you can see, Your Honor, the criteria
24 for selecting anti-EGFR antibody for ADC is that the antibody need to
25 compete with cetuximab.

26 So means the antibody in fact need to bind to AGFR stronger than

1 cetuximab. This really contradicts everything they say. They say need to
2 have weaker binding. That's not true. And Your Honor, also goes to Figure
3 13, right? Figure 13 in this -- let me find this Figure 13. This is actually
4 Patent Owner's Slide -- let me see. Slide 11. Patent Owner's Slide 11.

5 So look, this is a so called cataract comparison, Your Honor,
6 between the 2ADC, right? And 2ADC, the antibody is the same,
7 Tikhomirov, right? Payload is different. Payload is MNAE compared to
8 DM1. The linkers are also different. In this one, linker is a VC linker. And
9 in this one, the linker is a non-cleavable linker. So when you compare --

10 JUDGE FLAX: What exhibit is that?

11 DR. CHEN: This is the Exhibit 1009.

12 JUDGE FLAX: Okay.

13 DR. CHEN: Is that Tikhomirov. Yes. On their Slide 11. So
14 basically, when you compare 2ADC, you have two variables. The linkers
15 are different. Payload are different. And yet, Patent Owner wants to draw a
16 conclusion, saying, oh, linker must be good. The non-cleavable linker must
17 be good. You can't do that, right?

18 JUDGE FREDMAN: What you're saying is that it's not clear that
19 it's the linker and not the payload here?

20 DR. CHEN: Your Honor, we just cannot draw a solid scientific
21 conclusion because there's no head-to-head comparison. Because when you
22 compare two things, there are two variables there, two variables there. And
23 this is why nobody even get to the statement Judge Flax mentioned that
24 -- they are only saying this is probably the best, but they don't really say
25 teach away, say other style -- other lower binding is no good. They don't
26 even say that.

1 JUDGE FLAX: Well, I mean, in the history of this patent, this
2 prior art reference is important because it instigated the amendment to a
3 cleavable linker. Is that correct?

4 DR. CHEN: That's correct. That's correct. And I think that at that
5 time, examiner does not have the full breadth of the prior art like we cited
6 today. And Wei and Liu plus Leanna. And also, we believe examiner was
7 misled by the unexpected result based on Figure 13. And Figure 13 does not
8 support the conclusion that non-cleavable linker is good.

9 Because it's not a head-to-head comparison. Your Honor, I want to
10 jump to their Slide 37, Patent Owner Slide 37. Okay. So Your Honor, the
11 Slide 37 is the fundamental argument that Patent Owner make. Number one
12 is because of BA03 has a stronger binding, therefore it cannot distinguish
13 normal cell and tumor cell, therefore, there's no selectivity, right?

14 And also, there's a narrower therapeutic window. I actually
15 mentioned that Patent Owner is going to argue that. But that's entirely a
16 speculation, right? Also, Patent Owner say the conventional understanding
17 is you need to use a weaker binding. But then there's no such conventional
18 understanding.

19 If you look at the expert's declaration, the consistent pattern is that
20 he doesn't need to cite to any scientific reference. He doesn't make this
21 statement. Do that again and again. So for his conclusion about the BA03
22 must have a narrower therapeutic window, why he said that?

23 So he's based on entirely on this -- let me go to the slide. I do have
24 a slide there. It is based on the Crombet reference. Give me one second.
25 Yes. So Your Honor, the Crombet reference is pretty unreliable. This is --

26 JUDGE FREDMAN: What slide are we looking at, sir?

1 DR. CHEN: Yes. This is Slide 32.

2 JUDGE FLAX: 32, thank you.

3 DR. CHEN: Slide 32. Crombet reference compared two
4 antibodies, so antibody R3 and antibody cetuximab. Like antibody R3 is a
5 humanized antibody and cetuximab is a chimeric antibody. So the model
6 was developed for the NICD antibody. There's no ADC related parameter
7 being considered in this model.

8 It doesn't consider the drug antibody ratio and linker or payload.
9 And the data is from different clinical trial, different doses was used. And
10 importantly, Your Honor, Crombet only says higher affinity is not
11 necessarily the best. That's all it says. It never says the higher binding
12 affinity is disqualifying.

13 All it says it is not necessary the best. Also, Your Honor, the last
14 is that Crombet also provides three alternative reasons for its model, right?
15 So one is R3 is a humanized antibody. This actually provide a stronger
16 reason why you need to humanize -- use a humanized antibody.

17 Second, it says that R3 antibody has a better pH. Number three is,
18 it explained that R3 antibody actually is a (INDISCERNIBLE) in the human
19 percentile rather than the culture cell. So it actually does not support the
20 conclusion that Patent Owner expert draws from that reference.

21 JUDGE FLAX: Okay.

22 DR. CHEN: Thank you very much.

23 JUDGE FLAX: So you've summed up your last point. We'll call
24 your time up.

25 DR. CHEN: Thank you.

26 JUDGE FLAX: Thank you. Okay. So seven minutes. And I

1 won't shut you off in the same way. I didn't --

2 MR. QIU: Your Honor I want to address Petitioner's arguments,
3 first regarding Wei's teachings about whether cetuximab and the Wei's
4 Y104D antibodies are similar. Petitioner is trying to give you an impression
5 that Wei considers cetuximab and Y14D as two alternatives that are similar
6 to each other. That's not the case.

7 Wei set out to solve a problem with cetuximab where its
8 publication is limited by its equal targeting of tumor and normal cells. And
9 the solution is to give pH selectivity. And this data suggests that pH
10 selectivity provides significant performance improvement.

11 If you go to Slide 18 of Patent Owner's slides, Wei teaches that
12 cetuximab MMAE exhibit approximately 50 percent CGI at a concentration
13 of approximately 0.1 -- like a microgram per milliliter. Whereas to achieve
14 50 percent CGI, Y104D MMAE requires 10 times the dose.

15 So that's a tenfold difference in the therapeutic index as Dr.
16 Atanackovic provides. The data that Petitioner shows you is about the
17 maximum doses. And those are achievable in any clinical setting. And the
18 second argument I want to address is their attack on Crombet. And please
19 go to Slide 31 of Patent Owner's slides.

20 JUDGE FLAX: Can you hold on one second, Counsel? I think
21 we've lost our other Judge. Only for a sec. Okay. She's back.

22 MR. QIU: Okay. Thanks.

23 JUDGE FLAX: Sorry for the interruption.

24 MR. QIU: Yes.

25 JUDGE FLAX: Go ahead, sir.

26 MR. QIU: So the second I want to address their attack on

1 Crombet, which is on -- please go to Slide 31 of Patent Owner. First, I want
2 to note that whether Petitioner has thought about Crombet's scientific
3 methods is less relevant to this case because what we consider is what a
4 POSA would have known and have learned from Crombet's teachings.

5 As Dr. Atanackovic noted that Crombet was a peer reviewed
6 article published in a highly respected journal. So a POSA would have
7 learned from its results. And the results as shown in Figure 3A clearly
8 shows this negative correlation between binding affinity and ability to
9 selectively target tumor cells. Further, I will note on the next --

10 JUDGE FREDMAN: But Crombet is just the antibody, right?
11 He's not an ADC.

12 MR. QIU: Crombet is --

13 JUDGE FREDMAN: Crombet is not an ADC, antibody alone.

14 MR. QIU: That's correct.

15 JUDGE FREDMAN: So he's relying solely on the antibody's own
16 activity to drive immune cells in, essentially, right?

17 MR. QIU: That's correct. So Crombet is focused on the ability --

18 MR. NIE: Crombet focuses on the ability of the antibody to just --

19 JUDGE FLAX: Hold on. Hold on. Decide who's going to --

20 MR. NIE: Focuses on the ability of the antibody to distinguish
21 normal cells from tumor cells.

22 JUDGE FREDMAN: Right. But its activity is based on --

23 MR. NIE: Naked antibody.

24 JUDGE FREDMAN: Right. Naked antibody. It's not based on
25 the MMAE or some other --

26 MR. NIE: Yes.

1 JUDGE FLAX: So one of the things that I noticed in reading
2 Crombet is what your opposing Counsel brought up a second ago, is that it
3 doesn't really conclusively say what you're holding it out to be, which is that
4 you don't want higher affinity.

5 It says on page -- I think it says 1652, which is your page 7 as
6 you've renumbered it of Exhibit 2022, that higher affinity is not necessarily
7 the best. So something not being the best is not necessarily the same as, hey,
8 don't use that thing, right?

9 JUDGE FREDMAN: Especially in a different context where
10 you're adding more stuff.

11 JUDGE FLAX: I mean, the case law is pretty clear that things
12 don't need to be the best to be obvious. They just need to be desirable for
13 some reason, have to have some advantage.

14 MR. QIU: So, Your Honor, the reason that Crombet commented
15 that higher affinity is not the best, is because of this negative correlation
16 between affinity and the selectivity, right? So I think there might be some
17 conventional wisdom saying affinity is a good thing. And that Crombet is
18 trying to rebut that.

19 And I also want to know that Crombet is not our only evidence to
20 show this negative correlation. Crombet's result is independently verified by
21 Garrido, which Petitioner provides no rebuttal to. And then --

22 JUDGE FLAX: What page of that Garrido --

23 MR. QIU: -- your question whether Crombet's results are
24 applicable to the ADC design situation -- oh, sorry, Your Honor. I might
25 have talked over you. Sorry.

26 JUDGE FLAX: I just was wondering what page of Garrido, which

1 is Exhibit 2023, do you like the best?

2 MR. QIU: Page 8.

3 JUDGE FLAX: Page 8. Okay.

4 MR. QIU: And also, there's evidence that Crombet's results are
5 applicable in ADC design. That is shown on Slide 33 of Patent Owner.
6 Their Tikhomirov-346 actually applied it to ADC design. And it chooses
7 antibody with weaker binding affinity and they work well.

8 Since we mentioned Tikhomirov, I also want to rebut one of
9 Petitioner's argument about Tikhomirov-346, teaches that toxicity was not a
10 concern. Please go to Patent Owner's Slide 13. There they cite to two
11 statements in Tikhomirov-346 saying Wei associated with toxicity was
12 considered acceptable.

13 We just want to note that those statements concern naked
14 antibodies and do not show a lack of toxicity concern for anti-EGFR ADCs.
15 And Dr. Atanackovich did not mention those statements for a reason
16 because they're irrelevant. Both experts agree that just because antibodies
17 does not have toxicity --

18 JUDGE FLAX: You say that's irrelevant, but doesn't -- I mean,
19 you're citing Crombet in the same way, correct? I mean, Judge Fredman just
20 pointed that out, that that's a naked antibody, this is a naked antibody. So on
21 the one hand, you love it, on the other hand, you don't like it.

22 MR. QIU: No. I mean Your Honor, so I mentioned that it's
23 irrelevant in the sense that the lack of toxicity on antibody does not show the
24 lack of toxicity for ADC. So those statements does not support Petitioner's
25 position that toxicity was not a concern for ADC. I guess I didn't mean it is
26 generally irrelevant. But yes, because we have several references of ADCs

1 --

2 JUDGE FLAX: If a naked antibody's affinity for binding -- if a
3 naked antibody's affinity for binding is too high, that's a negative in the
4 common understanding of it before your client's achievements in the field.
5 Similarly, in the Tikhomirov-346, but you're saying the opposite. If it's
6 looking at a naked antibody and it's saying that some toxicity is okay, then
7 that's not -- we shouldn't consider that. It doesn't make sense to me.

8 MR. QIU: Your Honor, can you --

9 JUDGE FLAX: Oh, I think you're out of time, but I'll let you
10 finish up your last thought, please.

11 MR. QIU: Yes. So on that Slide 13, we just want to point out that
12 just because antibody was known to not have a toxicity concern does not
13 mean when building to ADC, it doesn't have a toxicity concern. Because the
14 toxicity of ADCs are amplified by the binding to a highly toxic payload.

15 JUDGE FLAX: Okay. Well, thank you, Counsel. So we'll stop
16 now. And we appreciate everyone's arguments today. We also appreciate
17 the flexibility in conducting the hearing in this way. And so we'll close the
18 record at this point. We'll consider the arguments you made today and we'll
19 return with the final decision in due course. So thank you all very much.

20 (Whereupon, the above-entitled matter went off the record at 3:12
21 p.m.)

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