

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PREOMICS GMBH AND BIOGNOSYS, AG.,
Petitioner,

v.

THE BRIGHAM AND WOMEN'S HOSPITAL, INC.,
Patent Owner.

IPR2024-01473
Patent 11,435,360 B2

Record of Oral Hearing
Held: January 15, 2026

Before: JEFFREY N. FREDMAN, MICHAEL A. VALEK, and
JAMIE T. WISZ, *Administrative Patent Judges*.

APPEARANCES:

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P R O C E E D I N G S

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JUDGE WISZ: Good morning. Today we will hear arguments -- or good afternoon. We will hear arguments in IPR2024-01473 concerning U.S. Patent Number 11,435,360. I'm Judge Wisz, and I'm joined today by Judge Fredman and remotely by Judge Valek.

Let's start with appearances, beginning with Petitioner.

MR. COLSHER: Good afternoon, Your Honor. Patrick Colsher, Reichman Jorgensen Lehman & Feldberg LLP, along with my co-counsel, Christine Lehman and Stephen Bosco.

JUDGE WISZ: Thank you.

And, Patent Owner?

MR. ROSATO: Good afternoon, Your Honors. Mike Rosato appearing on behalf of Patent Owner. I have Jad Mills with me today at counsel table.

JUDGE WISZ: Thank you.

We each have a copy of the demonstrative exhibits that you provided, but for the benefit of those attending by video, please identify clearly and specifically each demonstrative referenced by slide or screen number so that everyone can follow along, and to ensure clarity and accuracy of the court reporter's transcript.

So as set forth in our hearing order, each party has 45 minutes to present their arguments. Petitioner will proceed first and may reserve time for rebuttal.

So, Petitioner's Counsel, would you like to reserve any time for

1 rebuttal?

2 MR. BOSCO: Yes, Your Honor. Stephen Bosco. I'd like to
3 reserve 15 minutes.

4 JUDGE WISZ: Fifteen minutes.

5 So I'll put 30 minutes on the clock, and you can start whenever
6 you're ready.

7 MR. BOSCO: And hopefully, we'll get this working, Your
8 Honors.

9 So good afternoon, Your Honors, Stephen Bosco for Petitioners. I
10 -- in view of our limited time, I'm going to jump right ahead to Slide 3. And
11 so Your Honors, on Slide 3, we have Independent Claim 1 depicted. That's
12 the only independent claim at issue, which of course limits the issues that are
13 being disputed this afternoon. And then the issues are further limited in that
14 the dependent claims that are challenged, there really aren't any independent
15 arguments for the dependent claim.

16 So in Petitioner's view, every -- everything stands or falls with
17 Independent Claim 1. And then the issues are even further limited in that
18 there's really -- even with respect to Independent Claim 1, there's not a lot
19 that's genuinely in dispute. And so what we put here on this slide, on Slide 3
20 in red, we've highlighted the claim language that -- where we think most of
21 the remaining disputes lie. And then even within these highlighted claim
22 language, the disputes are narrower still, and that the first two are really just
23 pure claim construction.

24 And those are based off of very narrow constructions that the
25 Patent Owner proffered in their Patent Owner Response and similar to

1 constructions that the board addressed in the institution decision, where the
2 board recognized that the Patent Owner was just trying to read limitations
3 into the claim. Now, there's going to be a lot of discussion, of course, about
4 Limitation 1C and the dynamic range comprising at least six orders of
5 magnitude. And we see from Patent Owner's demonstratives and from their
6 surreply, that seems to be their new focus.

7 But in Petitioner's view, that really shouldn't be something that
8 gives the board a lot of pause and really shouldn't be in dispute, and that's
9 because of the language of the patent itself. So I'm on Slide 5. And what we
10 have on Slide 5 here is an excerpt from the '360 Patent specification, column
11 20, lines 20 to 32.

12 And it starts off with the Patentee, the inventors saying that "The
13 present sensor array has a sensitivity and dynamic range of 10 orders of
14 magnitude."

15 So we understand right off the bat that the Patentee, the inventors,
16 they understood their invention to have a sensitivity of 10 orders of
17 magnitude. And then they go on to contrast their invention, what they
18 regarded as the invention, with prior art techniques. So we see that we've
19 got in the red underlining, they say, "This assay or approach has a much
20 greater dynamic range than current assays." And then they go on to describe
21 some of those current assays, some of those prior art assays that they
22 contrast with what they regarded as the invention.

23 And so it says, "For example, mass spectrometry only has a
24 dynamic range of 4 to 6 orders of magnitude." So right there, the inventors
25 are recognizing that prior art techniques, like mass spectrometry, had the

1 capability to achieve 6 orders of magnitude. So I think that right there
2 should give everyone a little pause and that that's exactly what's claimed. So
3 the Patentees, the inventors have acknowledged in their specification that the
4 very thing that was claimed was in the prior art.

5 And I would note that, you know, in -- at the Patent Owner -- in
6 the Patent Owner preliminary response, there was a lot of discussion about
7 the qualifications of the inventors and their advanced degrees and how much
8 experience they had. We haven't heard so much about that since then.
9 That's not really addressed in the Patent Owner Response. But those
10 inventors, those ones with the advanced degrees and all of that experience in
11 the field, they recognized that 6 orders of magnitude was already in the prior
12 art.

13 And so then moving ahead to Slide 6, we see more of the same.
14 Again, the Patentee is telling the public through their patent that existing
15 prior art spectrometry techniques were capable of achieving 6 orders of
16 magnitude.

17 JUDGE FREDMAN: So jumping ahead, Counsel, if we ask about
18 two of the grounds, Grounds 1 and 4, not the Cai -- or the Cai grounds. Are
19 you still defending those grounds, is that showing six orders of magnitude?

20 MR. BOSCO: I'm sorry, Your Honor. Can you repeat which
21 grounds you were asking about it?

22 JUDGE FREDMAN: The Grounds 1 and 4.

23 MR. BOSCO: We are still -- we do still contend --

24 JUDGE FREDMAN: Even though that there seems to be some
25 indication, for example, that in one of the grounds, your -- the expert, at least

1 the right -- your disclosure confused which of the forms of, I think, it was
2 the LDT protein, SDP protein?

3 MR. BOSCO: Right, Your Honor, so --

4 JUDGE FREDMAN: There's various of forms in your --

5 MR. BOSCO: So on that, well, look, our expert declaration speaks
6 for itself. You know, our expert had a different view of that as reflected in
7 our declaration. And those grounds both still rely on these very same
8 techniques that a person of ordinary skill would know achieve 6 orders of
9 magnitude.

10 JUDGE FREDMAN: But I guess so there's two questions. So
11 you're saying they still would achieve it even though the -- your examples
12 you give may not actually show that?

13 MR. BOSCO: I mean even -- Your Honor, yes, so even if the
14 board determines that those examples don't show it, we would still contend
15 that those grounds are viable as obviousness grounds, which is what they
16 were brought us.

17 JUDGE FREDMAN: And -- obviousness grounds, okay.

18 MR. BOSCO: Yes, Your Honor. Yes, Your Honor. So another
19 thing --

20 JUDGE VALEK: Counsel, before you get going again --

21 MR. BOSCO: Yes, Your Honor.

22 JUDGE VALEK: -- this is Judge Valek. I have a question
23 regarding Petitioner's interpretation of the dynamic range in Step C of Claim
24 1. And that question is: In Petitioner's view, does the dynamic range recited
25 there refer to the concentration of proteins in the biological sample or in the

1 subset of proteins of Step B?

2 MR. BOSCO: Thank you, Your Honor. That was a question that I
3 wanted to address and I'm glad to address it right at the beginning. So I'm
4 going to go to the claim language, so I'm back on Slide 3. And we're kind of
5 surprised this came up because I think it's plain from the language of Step C
6 --

7 JUDGE VALEK: Counsel, let me just interrupt you for a second.
8 Before you start explaining, please answer my question. Does the dynamic
9 range refer to the concentration of proteins in the biological sample or in the
10 subset of proteins of Step B?

11 MR. BOSCO: What -- as reflected in Step 1C, it's referring to
12 concentrations in the subset, which is how the claim goes on to say, that's
13 how you assay the biological sample. So yeah, and just to kind of expand on
14 that, that's something that's come up in the briefing, and we think that there's
15 just a misinterpretation of the claim language going on.

16 Because Step 1C says "assaying the subset". So it has to be the
17 subset, with an instrument to detect in the subset, proteins in the biological
18 sample at concentrations across the dynamic range. So all of that's
19 happening with respect to the subset, but by doing that, that's how you assay
20 --

21 JUDGE FREDMAN: No, no. The subset might be representative
22 of the sample, but it isn't the sample.

23 MR. BOSCO: Say again, Your Honor?

24 JUDGE FREDMAN: The subset might be representative of the
25 sample, but it is not the sample itself. It's the subset.

1 MR. BOSCO: Exactly. Exactly.

2 JUDGE VALEK: Let me ask a follow-up question to Judge
3 Fredman's question. Does the subset have to be representative of the protein
4 concentrations in the sample or not?

5 MR. BOSCO: I don't think the claim requires that, Your Honor. I
6 mean, I think reading what the claim says, it says assaying the subset. So as
7 long as you have a subset that meets the requirements of Step 1B and you
8 assay it consistent with the claim language, then that's all the claim requires.

9 JUDGE VALEK: Let me ask one more question because I'm
10 thinking this may be where Patent Owner is going to go with some of their
11 slides. Is there some place in the Petition where you make clear your
12 position that the recited dynamic range refers to the concentration in the
13 subset of proteins of Step B?

14 MR. BOSCO: So Your Honor, I -- I'll -- I -- I'll try and come up
15 with a better answer as soon as possible. I don't have one right at the tip of
16 my fingers. But what I will say is I know that each time in the petition, we
17 -- I mean, we refer to the claim language. We said it meets the requirements
18 of Step 1C. And that I think was so plain that it didn't need to be stated.

19 That -- I mean, that's what it says in Step 1C is that you're assaying
20 a subset of proteins from Step 1B. So I think it was one of those things
21 where we thought the claim language was so clear, it didn't necessarily need
22 to be stated. But I do think there -- there's a better answer in the petition and
23 I'll try and find it for you. So just to go back to -- were there any further
24 questions, Your Honor, on that issue?

25 JUDGE FREDMAN: Not right now.

1 MR. BOSCO: So just going back to the disclosure in the spec, and
2 I won't belabor this, but I think another notable thing about what's here in the
3 specification and the admission regarding the capabilities of prior art
4 spectrometry techniques is that Patent Owner never talks about this. So you
5 won't find this in their Patent Owner Response. You won't find it in their
6 expert declaration, in Dr. Cima's declaration. So I mean, we have a pretty
7 important statement by the inventors about what a person of ordinary skill in
8 the art knew about, and they just pretend it's not there.

9 So I think that's a pretty significant omission and sort of calls into
10 question the fidelity of their expert's analysis. And then the last point I'll
11 make on this for now is just that I think there's a flavor in the -- in their
12 demonstratives and in some of their briefing of, well, this is gap filling or
13 something like that, using an expert to fill gaps and that's not what we're
14 doing. I mean, there -- we made it clear in our petition what we're doing is
15 using this as highly probative evidence of what a person of ordinary skill
16 would know.

17 This is what they would know about these techniques, these
18 techniques that are recited in the prior art. They would know that it would
19 have these capabilities. So Your Honors, I think I will move on to claim
20 construction and I don't think we need to spend a lot of time on this. I'm
21 now on Slide 11. And actually, I'll just -- I'll go right to Slide 13. So first
22 term that the Patent Owner offered an express construction for is biological
23 sample. And again, we're just addressing this because it was featured
24 prominently in Patent Owner's Response.

25 We think this is pretty clear. It doesn't -- really isn't something the

1 board should need to construe. The patent comes right out and says what a
2 biological sample is. It's got a sentence that begins "suitable biological
3 samples" and then it provides a big long laundry list of specific examples of
4 what constitutes -- what can constitute a biological sample. And everything
5 we pointed to in the prior art is right on this list.

6 It's not even -- you know, we're not arguing by analogy. It's
7 expressly in the list. And so the Claim 22, and I'm on Slide 14, just
8 reiterates that. So Claim 22 modifies Claim 1 by specifying that the
9 biological sample can include all of these specific examples such as blood,
10 plasma, processed tissue samples, or any lysates or combinations thereof.
11 And of course --

12 JUDGE FREDMAN: So I think something Patent Owner is going
13 to argue probably is that the sample that HeLa cells, Henrietta Lacks, the
14 cells, aren't a sample because while they are -- I don't think they would argue
15 they're not cell lysates, although maybe they will.

16 But they're so heavily processed. They're so removed from Ms.
17 Lacks over the time that, you know, over 70 years it's been, that they are not
18 really a biological sample in that context. So do you want to address that?
19 This is for, obviously, Cai.

20 MR. BOSCO: Yes, Your Honor, of course. And yeah, no, I'm
21 happy to address it. And I think some of -- partially it can be addressed right
22 through this slide. So we see right here processed tissue samples. The
23 patent contemplates that a biological sample's going to be processed.

24 It says "chopped tissue, homogenized tissue". This is not
25 something that comes right out of a person. This is something that's been

1 processed in a laboratory, so that's one answer right there. The other --

2 JUDGE FREDMAN: I mean, but, you know, the question is: Does
3 that encompass passage for 70 years, whatever?

4 MR. BOSCO: Well, sure, Your Honor, and I think another answer
5 is also in the slides and I'm now on Slide 20. This is the testimony of Dr.
6 Cima about Ms. Henrietta Lacks. And so first -- well, first he has testimony
7 about what qualifies as a biological sample.

8 And he says, in the context of the patent, it's a sample derived from
9 a patient.

10 And then he was asked, So Henrietta Lacks is the original donor
11 from whom all HeLa cells derived, correct?

12 And he said, yes, that's right. So by his own understanding of
13 derivation --

14 JUDGE FREDMAN: Yeah, I mean, I -- that, I will safely dispute
15 that, but yes, I did read the book.

16 MR. BOSCO: Yes, Your Honor. No, I mean I think there's just
17 kind of stepping back to, there's nothing in the specification that would
18 exclude something like a HeLa cell. It's what Cai has is a cell lysate of cells
19 that derive from a particular human person and that's clearly within the
20 broad scope of what the specification contemplates.

21 JUDGE VALEK: Counsel, can you go back to your Slide 13, the
22 one that actually has the claim language from column 20 in it?

23 MR. BOSCO: Yes, Your Honor.

24 JUDGE VALEK: As I understand the Patent Owner's position,
25 they're reading that first sentence, the one that you don't have any highlights

1 in there, as a definition. And they're reading the last three words, from a
2 subject, to be definitional and apply to both of the options that are proposed
3 in that sentence, both the biological sample or the complex biological
4 sample.

5 They say with respect to both of those, it must be obtained from a
6 subject. Do you agree or disagree with that reading?

7 MR. BOSCO: So I mean, we disagree with it in that we think that
8 the second sentence is what controls. The second sentence is a clear
9 statement by -- to the extent they're inconsistent, and I'm not even sure that
10 they are. But to the extent there's inconsistency, the second sentence
11 specifically enumerates what the Patentee understood to be biological
12 samples.

13 And I know that the first sentence is defining the term samples, not
14 defining biological sample. So the second sentence is saying these are
15 suitable biological samples as used in this patent. So again, so we think to
16 the extent there's tension, it's that second sentence. And then again, this is
17 -- their expert said the same thing, and I'm on Slide 19. So right there in his
18 testimony, so the second sentence defines biological samples.

19 JUDGE FREDMAN: Well, I think there is an implicit argument
20 that I think Patent Owner is making that when he said it came from the
21 subject. I mean, essentially directly, right? That all the samples that are
22 recited are samples that come from relatively directly a subject, right?

23 I mean some of these maybe a little less so. But essentially these
24 are samples that the person is giving and they're being used within, you
25 know -- I mean, from a subject directly.

1 MR. BOSCO: Yeah, I mean, I don't read -- I think that they're
2 reading the directly in. I don't see that in the specification. I think that the
3 specification evidence is an intent to define biological sample very broadly.
4 And then the other thing is as we said --

5 JUDGE FREDMAN: Are there any examples in the specification
6 of such situations? Because there are situations in research -- samples that
7 are, like HeLa cells or other cell types or stored cells or tumor cells that have
8 been collected from patients, that sort of thing.

9 Is there any example other than the HeLa cells? HeLa cells even
10 used in the -- cell?

11 MR. BOSCO: I don't think -- yeah, I don't recall seeing HeLa cells
12 themselves.

13 JUDGE FREDMAN: Any cell line at all?

14 MR. BOSCO: I'll check on that, Your Honor. But again, I think
15 that this language here, I mean, cell lysates, what we rely on are cell lysates
16 and it says "and the like". And then I would go to Claim 22 as well again,
17 Your Honor. So here this is even arguably broader. So Claim 22 is saying
18 that it can be any lysate or combination thereof of anything in that preceding
19 list. So I think this is pretty strong intrinsic evidence and really all Patent
20 Owner has is that one sentence.

21 And then I will just add, Your Honor, since we've been talking
22 about this, is, you know, we did put in our Patent Owner Response or -- in
23 our reply to the Patent Owner Response that even if somehow their view
24 were adopted, this would still be obvious. This would -- this is a -- this is
25 hair-splitting, and it's not the type of obviousness inquiry that needed a new

1 expert declaration or anything like that. It's something that a panel of
2 technically trained judges can see for themselves that this would plainly be
3 obvious.

4 And that argument, by the way, is completely appropriate under
5 the Axonics case. You know, this was a claim construction that was not
6 anticipated. And so I think that's the other thing, is this is really much to do
7 about nothing. It's plainly obvious. There's no technical

8 -- and they don't contend that there's any technical barrier or
9 anything novel about having it being obtained from one person versus
10 pooled samples.

11 So with that, Your Honor, I will move on to the next claim
12 construction dispute subset. And this is another one that we think is pretty
13 clear, so this really is just about what the definition of subset is. And
14 arguably, at least, that's not really in dispute and that I think we all agree that
15 it's the plain meaning of subset which is something less than the entirety of
16 the set. And so just stepping back in Limitation 1A. Everyone agrees there's
17 a requirement that a plurality of particles comprising different particle types
18 are contacted with a biological sample.

19 And then in Step 1B, they're separating a subset of that plurality of
20 particles comprising the coronas. And now, they put a lot into the
21 comprising the coronas, but they're just reading a lot into it that the language
22 can't bear. The subset is of the set, which is defined by the plurality of
23 particles comprising the coronas. That's what was talked about in Step 1A.
24 And if you think of a Venn diagram, so Step 1A, you have a big circle which
25 has a plurality of particle types that have bonded and formed coronas, and

1 then you take a subset of that. You draw a smaller circle.

2 Somewhere in that big circle, that smaller circle might have
3 multiple particle types, it might just have one. This is just plain English.
4 And that's moving on to the next slide, on Slide 22, that's what the board
5 already concluded at the institution phase. And they challenged the Patent
6 Owner if there was going to -- if they were going to continue with this
7 construction to come forward with evidence, and they haven't. There's no
8 intrinsic evidence cited for this construction, none at all, which is just clearly
9 contrary to the plain meaning of the term subset.

10 And it -- you know, something that the board also noted at the
11 institution phase, this is sort of part and parcel of something Patent Owner's
12 been trying to do throughout, which is just read out an embodiment where
13 you have multiple isolation steps in parallel, or you have contact occurring
14 sequentially. They're just trying to read that out of the -- out of the claims
15 and there's no basis for that. And so Your Honors, I know I don't have too
16 much time left. Just briefly to return to sampling claim construction on
17 Claim 22.

18 You know, I did mention, and I'll go back to the slide there. Slide
19 14, so we've got this enumerated list. We have all the specific examples,
20 and it references combinations that includes both amniotic fluid and sperm.
21 So there's a clear implication there that there could be different donors,
22 different individuals implicated if you're going to have combinations of
23 those two types of samples.

24 Okay, so I am going to move onto some of the more ground-
25 specific arguments, although we've already alluded to some of them already.

1 And so as consistent with the institution decision and the way the parties
2 have briefed it, I'll start with Ground 2, anticipation by Cai. And I'm going
3 to go to -- so right here on Slide 32, we have the arguments that were in the
4 POR.

5 The first two sets of arguments largely stand and follow with claim
6 construction in our view, and certainly the biological sample one does. And
7 then the remainder of it with -- putting Step 1C aside, largely hinges on
8 Patent Owner's contention that Cai discloses multiple distinct studies, and
9 that you can't look at one part of it and think that the teaching from one part
10 applies to another part. And that's just contrary to what the reference itself
11 says.

12 So Cai -- and I'm on Slide 38. Cai is saying this -- in this study,
13 this study is the first large scale characterization of protein corona on CNT.
14 There's no indication in Cai that these are different studies that were sort of
15 stitched together. It's all one integrated study.

16 And then moving to the next slide, on Slide 39, that's the same
17 thing the board already concluded at the institution decision. And again,
18 nothing changes. And to the contrary, the record has provided further
19 support for that.

20 So on Slide 40, we have an excerpt of Dr. Vargas' testimony
21 talking about Figure 3 in Cai, and she testifies that Figure 3 would rely on
22 the same general workflow that's depicted in scheme 1A, which is used for
23 the preceding step.

24 So she understood it, just as the board did, that Cai was an
25 integrated experiment, and that you can use the teachings from one part. It

1 -- it's meant to -- a person of ordinary skill looking at it would understand
2 that the teachings from one part apply elsewhere. So I think that's really
3 kind of an artificial distinction.

4 JUDGE VALEK: Counsel, I think you're going there, but in the
5 interest of time, let's move on to Step 1C.

6 MR. BOSCO: Yes, Your Honor. I was going right there. So Step
7 1C for Cai, obviously we're going to hear a lot about it. First of all, it's
8 expressly in Cai. So Cai says that eight orders of magnitude, it's right in the
9 reference, and their main argument against that is the mixing and matching
10 argument, but we've already addressed that.

11 JUDGE VALEK: Let me ask you about the statement that you
12 have up on your Slide 41. Do you agree that the statement refers to the
13 relative abundance of proteins that are in what's described as the mix in
14 Figure 3 of Cai?

15 MR. BOSCO: So that -- that's right, Your Honor, and that's
16 consistent with the understanding of Step 1C that I talked about earlier.

17 JUDGE VALEK: Okay. And so this statement -- Cai here when it
18 says that we can detect relative abundance of carbon nanotube binding
19 proteins that are spread over eight orders of magnitude, it's referring to the
20 subset of proteins, which you've identified as the subset of proteins of Step
21 B, as opposed to what you've identified as the biological sample, which I
22 understand to be the HeLa cell lysate.

23 MR. BOSCO: That's right, Your Honor. But again, by doing that,
24 consistent with the claim language, you are assaying the biological sample
25 as claimed. Yes, Your Honor. So with Cai, we have the express disclosure.

1 There's also an argument about, well, this is abundance and not
2 concentration. I think Dr. Vargas addressed that very well. There's -- Cai
3 expressly refers to another reference that tells you how to calculate it. It's a
4 trivial calculation. It's something that a person of ordinary skill would have
5 no trouble doing and would be motivated to do.

6 And then I'm on Slide 42, and look, that same logic that Dr. Vargas
7 applied is something that the patent office has already done. So in a later
8 application that claims priority -- to the same priority applications as the '360
9 Patent, the patent office found that Cai discloses six orders of -- a dynamic
10 range of at least six orders of magnitude, and the Patent Owner didn't try and
11 traverse it. And of course, Cai wasn't before the examiner during the '360
12 Patent Prosecution.

13 JUDGE VALEK: Counsel, let me push -- let me push back on that
14 a little bit.

15 MR. BOSCO: Yes.

16 JUDGE VALEK: It looks like the statement you're citing from
17 this other prosecution is in the reasons for allowance.

18 So why would the applicant have any reason to traverse it when the
19 examiner is allowing the claims?

20 MR. BOSCO: Well, if they wanted to be, you know, ensure that
21 that wasn't in the record or that they disagreed with it.

22 JUDGE VALEK: But doesn't that raise the Federal Circuit's case
23 law on acquiescence doctrine, which essentially says, if I understand it, that
24 you don't have to respond to every potentially inaccurate statement of the
25 examiner --

1 MR. BOSCO: For sure.

2 JUDGE VALEK: --to preserve the argument in the future?

3 MR. BOSCO: Absolutely, Your Honor. We're not saying they're
4 -- you know, that this is like an estoppel or something like that. We're just
5 -- the bottom line is the patent office found -- interpreted Cai this way and
6 had interpreted it the exact same way that Dr. Vargas did.

7 JUDGE VALEK: Fair enough.

8 MR. BOSCO: And again, that's no surprise. I'm not going to beat
9 this dead horse, but it's not a surprise that the patent office interpreted it that
10 way, because the patent says that this isn't a prior art again. So there
11 -- there's -- it's notable.

12 I mean, at this point in -- despite all the briefing, Patent Owner has
13 not come forward with any evidence that there was anything novel,
14 unexpected, unusual, anything patentable about that six orders of magnitude.
15 And we cited case law in the petition on pages 38 to 39 about that very issue.
16 You know, that when you're talking about a range, if you've got indications
17 that that range is in the prior art, the burden shifts to the Patent Owner to
18 explain what's new, what's unusual or unconventional about this range, and
19 they haven't met that burden.

20 So with my remaining time, which is not much, I'll quickly note.
21 So Ground 3 on Cai, even if the board has concerns about whether Cai can
22 be said to -- you know, disclose itself Step 1C, we have obviousness
23 arguments from Dr. Vargas on that. And I'm on now Slide 48.

24 And she goes into detail on why that range would be obvious
25 because there's nothing new about it, nothing unexpected. And that really

1 hasn't been rebutted. If you look at their Patent Owner Response, they
2 largely just incorporate, by reference, their anticipation arguments, but that's
3 not enough. This is obviousness.

4 JUDGE VALEK: Let me ask you one last question, Counsel,
5 before you sit down. Is mole percent a measure of concentration?

6 MR. BOSCO: It's directly convertible to it and through a trivial
7 calculation. So I think it's -- I would say yes, it's a measure of concentration,
8 Your Honor.

9 JUDGE VALEK: And what is the evidence -- and if you don't
10 have it now, you can give me a citation --

11 MR. BOSCO: Okay.

12 JUDGE VALEK: -- when you stand back up. But what is the
13 evidence supporting that argument?

14 MR. BOSCO: I think -- I mean, Dr. -- I'll get you something when
15 I stand back up, Your Honor.

16 JUDGE VALEK: Thank you.

17 MR. BOSCO: Yes, Your Honor. And I guess with that, I'll
18 reserve the remainder of my time for rebuttal.

19 JUDGE WISZ: And, Counsel, would you like to reserve time for
20 surrebuttal?

21 MR. ROSATO: Yes, Your Honor. Can I reserve 15 minutes,
22 please?

23 JUDGE WISZ: Okay.

24 MR. ROSATO: If I may get started.

25 JUDGE WISZ: Yes.

1 MR. ROSATO: Good -- sorry, I'm fighting a cold. Good
2 afternoon. And may it please the board. Before we get started, I do -- I'll
3 note a general objection, as the board will understand, to any new argument
4 that was advanced in the opening discussion there. There's a number of new
5 arguments that were raised. It was hard to keep up with them. I will try to
6 get to them as we move through. I'll identify a few of them I noted.

7 One was the argument that there is -- they disagree with the -- that
8 there was an expressed definition for biological sample. Arguments about
9 the concentration being in the subset versus the sample, that was never
10 argued, and we'll get to that. Arguing about combinations of samples, this
11 new argument about disputing that molar percent is different than
12 concentration. We addressed this in our briefing, that was never disputed.
13 There are a number of things. I don't know if I've caught everything, but I
14 will note the general objection.

15 With that being said as preliminary commentary, let's start -- we
16 can turn to Slide 2, and this just shows the grounds that we're all familiar
17 with. One thing I will say is a key common theme and defect in this petition
18 materials really stems from what is apparent is a lack of critical review and
19 analysis that went into examining the prior art references and presenting
20 them in the petition materials.

21 And as a result, the trial phase goes through this process, conducts
22 that type of critical review that's required. And through that process, what
23 we see is as a result, these are prior art references that simply lack disclosure
24 that hits multiple elements of the claim.

25 So that's the critical analysis we went through. We're going to

1 follow that process. There was specific argument advanced in the petition
2 materials. There's specific disclosure identified in the references, and that's
3 what the Patent Owner Response and the briefing focused on as it should, as
4 did the discovery process, and that's what we'll talk about here. So I think
5 we got away from that a little bit.

6 If we do that, if we follow that correct process, what we see -- and
7 this is something I agree with Counsel on. There's a comment that many
8 issues aren't in dispute anymore, and that is true, and that is particularly true
9 with regard to Step 1C of the claims, which we didn't hear a lot about that.

10 We heard very little when it came to Step -- Element 1C, what
11 prior art disclosure was cited, what was relied on in the grounds and argued,
12 what was addressed in the Patent Owner Response materials about why
13 those grounds were deficient with the prior art that they asserted, and the
14 fact that there was essentially no rebuttal to those arguments. So all grounds
15 fail, all grounds fail at least at Step 1C, and it's something that, you know,
16 we -- I think was sidestepped a little bit.

17 JUDGE FREDMAN: Can you be a little more specific than just
18 saying that?

19 MR. ROSATO: 100 percent, Your Honor. Let's -- I'll walk
20 through every single ground, and we can look at that.

21 JUDGE FREDMAN: For Step 1C in particular, what's the
22 problem with Cai?

23 MR. ROSATO: With Cai. Let's -- sure. Well, we'll start -- can I
24 walk through the slides to answer that question?

25 JUDGE FREDMAN: If you want to.

1 MR. ROSATO: Yeah. I'll answer at a high level, and then we'll
2 come back to it. The problem with Cai with regard to that limitation is they
3 are -- the disclosure they're citing to for these emPAI values and the
4 statement about eight orders of magnitude does not satisfy the limitations of
5 the claim.

6 Specifically, the claim requires assaying in a subset to detect
7 proteins that are characterized as proteins present in the sample at
8 concentrations across six orders of magnitude. The emPAI disclosure in Cai
9 does not disclose that for two reasons. One, the emPAI is --

10 JUDGE FREDMAN: So one thing you're implying is that it's the
11 sample that has that six orders of magnitude, not the subset.

12 MR. ROSATO: Yeah. And I -- if I'm implying it, I don't mean to.
13 I'm -- I mean that expressly. That is what the --

14 JUDGE FREDMAN: The claim says assaying the subset and
15 measuring the concentrations across the dynamic range of six orders of
16 magnitude. It doesn't say that they have to be in the sample, the six orders of
17 magnitude. That's expressly not said in the claim.

18 MR. ROSATO: I would respectfully disagree with that, Your
19 Honor. The claim --

20 JUDGE FREDMAN: Where does it expressly say it?

21 MR. ROSATO: Assaying in the subset protein --

22 JUDGE FREDMAN: In the subset.

23 MR. ROSATO: Yes. The action occurs in the subset. It detects
24 proteins.

25 JUDGE FREDMAN: Yeah.

1 MR. ROSATO: The claim further characterizes those proteins as
2 ones that are present in concentrations in the sample across the dynamic
3 range, right? So it -- the action occurs in the subset.

4 JUDGE FREDMAN: It says it in the subset, twice. It's very clear
5 that it's referring to the proteins in the subset. I think to argue that they are
6 from the sample is simply inconsistent with the claim language.

7 MR. ROSATO: That has not been -- I would disagree with that,
8 and that has not been the position in the petition materials, certainly, and not
9 throughout the entire --

10 JUDGE FREDMAN: I think that's entirely what the Petitioner
11 understood the claim to mean.

12 MR. ROSATO: Pardon me, Your Honor?

13 JUDGE FREDMAN: I think that's what the Petitioner understood
14 the claim is.

15 MR. ROSATO: Well, let's -- I mean, I -- we have a slide that has
16 -- we addressed this in briefing.

17 JUDGE FREDMAN: You can interpret it however you like, but I
18 don't think it's consistent with either the claim or the petition.

19 MR. ROSATO: Okay. Well, let's -- I'll state my position, and
20 we're free to disagree with that. I respect that, Your Honor. But how
21 everyone has interpreted this claim, everyone, I would posture, is that the
22 detection action occurs in the subset, and the claim characterizes what is
23 being detected.

24 And that's the whole point of the invention, right, is to pull proteins
25 out and expand the dynamic range of what was being detected. That's the

1 entire point of the invention that's consistent with the background of the
2 technology and shotgun proteomics that was being discussed, and nobody
3 has ever disputed.

4 Let me -- I'll -- I'm going to jump to a slide here. I would refer
5 back to the surreply briefing because this is addressed in detail, but we
6 pointed out in the petition how time, and time, and time, and time again, the
7 petition is talking about this limitation and referring to proteins and their
8 concentrations in the sample. And that's true even in Ground 2, I would say
9 even in Ground 2 of the petition when it's talking about that. Yes, sir.

10 JUDGE VALEK: Sorry, I didn't mean to speak over you.
11 Counsel, I understand it's your position that the petition doesn't make this
12 argument, but I guess what I'm wondering is, is there anything in the
13 intrinsic record of your patent that supports the interpretation you're
14 advancing that even though claim element C may say what it says, the
15 specification supports our reading that the dynamic range is referring to the
16 concentration in the biological sample as opposed to the subset of proteins of
17 Step B?

18 MR. ROSATO: Yeah, I would say absolutely. Again, I'm going
19 to answer this in an informal manner because I do not believe this was ever
20 disputed. I think we can find incidence after incidence in the petition where
21 it's referring to concentrations in the sample. In fact, a lot of their argument
22 is talking about how would you do that, and they make this argument that
23 the specification says you can go look up sample concentrations in a
24 database, right? And that's what they're doing in multiple grounds. That's
25 their argument, right?

1 It's not -- of course you wouldn't look up at -- you couldn't possibly
2 look up a concentration in the subset that you just obtained in some
3 database, so that has never been their position in the petition materials. They
4 specifically argue for concentrations. Go -- you know, you can go look
5 these up in a database that tells you what the concentration is in a given
6 sample. So this is throughout their argument.

7 So to -- but to answer your question, I would say that's one
8 instance where the specification by their own argument supports that -- what
9 the claim is referring to as concentration in the sample itself, this idea that
10 what they care about is what the concentration -- you know, assay
11 -- detecting proteins across this, you know, that are present in a wide
12 dynamic range.

13 This is also discussed both in the patent and in the background art
14 in the context of shotgun proteomics where one of the big problems that are
15 identified in these approaches is the fact that you have high-concentration
16 proteins in the sample like albumin and so forth, that swamp out the signal
17 of these very low-concentration proteins that are present in the sample. And
18 that's a problem, and that's exactly the problem the entire invention is trying
19 to solve here, and it's discussed throughout.

20 So I would say there are lots of discussions and lots of content of
21 the specification that support this, and it was -- you know, it was -- I -- I'm
22 going to stick with that point. It was never in dispute. I think the record
23 bears that out.

24 JUDGE VALEK: Well, let me push back on that a little because
25 I'm just going off your own slide. If you turn to your Slide 9, you have a

1 quote from their reply here, and you clearly recognize that they made this
2 argument. I know your argument is that they didn't make it in the petition,
3 but certainly by the time of the reply, you knew this was there.

4 And so I'm a little bit concerned that you haven't identified what
5 you're saying is in the intrinsic record that shows that this interpretation is
6 incorrect, at least if we were to agree with Petitioner if they haven't waived
7 this argument.

8 MR. ROSATO: Yeah. I would actually -- I push back on that a
9 little bit, Your Honor. I don't think they actually are arguing that in the reply
10 brief. I think what they're trying to do in the reply brief is sidestep the issue,
11 right? They argue, hey, the detection -- detecting action happens in the
12 subset. That's true. We agree with that, that the subset is obtained and it's
13 being assayed.

14 That is true, but it sidesteps the issue of what is being detected, and
15 that I do not believe they address in the reply brief. So they tried to
16 misdirect, but I don't think they're arguing a new interpretation in that reply
17 brief. I don't think they've ever advanced this argument.

18 JUDGE FREDMAN: So on the merits of the question, in column
19 20 of this -- your patent, it talks about how the sensor array allows for the
20 sampling of a complex sample using multi nanoparticles with different
21 physical and chemical properties to significantly increase the number and
22 range of both low and high abundance proteins without protein depletion.

23 The implication I think of that sentence, and really this fact in
24 general, I think, is that one of the ways you're increasing dynamic range is
25 by the materials you use to pull the proteins out, because these materials

1 themselves function to broaden the dynamic range, which also suggests that
2 they're not really measuring the exact concentration, because if you're
3 selectively pulling out rare proteins, you've now changed their amounts in
4 the concentrations. You have to sort of back calculate using something like
5 the emPAI calculation.

6 MR. ROSATO: Well, I would agree with some of that, right?
7 Some of that is the idea that the proteins -- or excuse me, the particles that
8 are being used -- they're capturing a -- you know, some portion of proteins.

9 JUDGE FREDMAN: A subset.

10 MR. ROSATO: We'll call it a, yeah, subset. And they're -- what
11 they're capturing, what you end up on the particles, does not represent the
12 proportion that would be in the sample. And that's the whole point, right?

13 JUDGE FREDMAN: Right.

14 MR. ROSATO: Some of these particles are used to enrich for
15 -- that was the -- a lot of what the background art is doing is
16 looking for particles that went and captured the particular proteins they're
17 looking for.

18 JUDGE FREDMAN: So when you're challenging the
19 concentration, it's clear that it can't be directly linearly linked, right? I mean,
20 if you're enriching, you're already saying it's not the same.

21 MR. ROSATO: Well, it's not the --

22 JUDGE FREDMAN: Those can't be the same, right? We can't
23 have both ways. Either when you're enriching, and therefore you're not
24 exactly giving the concentration of the biological sample or even the
25 concentration in the subset, or you're not enriching, in which case you could

1 -- if you would then enrich, you could look at the original sample.

2 MR. ROSATO: Again, I --

3 JUDGE FREDMAN: You see the inconsistency I'm raising?

4 MR. ROSATO: I understand --

5 JUDGE FREDMAN: You may disagree with that, I have no
6 problem with that, but do you see it?

7 MR. ROSATO: I don't see -- I understand some of what you're
8 saying. I --

9 JUDGE FREDMAN: If you enrich, you can't get the -- that
10 concentration of the enriched material can't be the same as the original
11 concentration.

12 MR. ROSATO: Well, let's assume that's true, right?

13 JUDGE FREDMAN: Okay.

14 MR. ROSATO: Like, let's assume that's true. Let's assume the
15 very point of using particles is to pull out proteins at a different proportion to
16 what's in the sample.

17 JUDGE FREDMAN: Right.

18 MR. ROSATO: Right? That all could be true, and it could still be
19 true that what the -- what is an aspect of this invention is that they're now
20 -- by doing this process in the way they're doing, they're able to capture and
21 examine a larger proportion of proteins than they otherwise did in prior
22 approaches, and that all bears out with what's described in the background
23 literature.

24 JUDGE FREDMAN: The argument would be whether that's
25 different than Cai, who also does the same thing. He's also enriching, but

1 yes. I hear what you're saying.

2 MR. ROSATO: We're not saying enrichment is a point of novelty
3 here.

4 JUDGE FREDMAN: Okay.

5 MR. ROSATO: Right? But some of this is discussed, like, in the
6 background argument.

7 JUDGE FREDMAN: Then what are you saying is the point of
8 novelty?

9 MR. ROSATO: The point of novelty -- and I'll draw this in -- I'll
10 step away from the claims a little bit, because I don't want to be criticized for
11 trying to read things in.

12 But to answer your questions, what illustrates some of the point,
13 and I'll use -- I'll answer that in comparison to the background art that is
14 discussed, so this is not a, you know, an unaddressed issue discussed -- I
15 think it -- excuse me.

16 JUDGE FREDMAN: I trust you. Just --

17 MR. ROSATO: Yeah. Pages -- I think it's 3 through 8 of the
18 patent response and then other places, if I recall the page numbers correctly.
19 One of the problems with shotgun proteomics is this idea of swamping
20 -- swapping out -- swamping out the, you know, certain low concentration
21 proteins with high abundance. And the art describes that the result of this is
22 it lowered the detection range for mass spec when it came to shotgun
23 proteomics to, you know, one, two, three orders of magnitude. That was one
24 of the problems. That and --

25 JUDGE FREDMAN: So I think the argument -- let me see if I'm

1 summarizing it correctly on your side, is you're saying that your way of
2 enriching allows you to maintain the dynamic range that was present in the
3 original sample, and your argument is that the prior art was losing that
4 dynamic range in the sample.

5 So irrespective of whether they could measure the dynamic range
6 in that subset that they captured, that was still losing it from the sample; is
7 that correct?

8 MR. ROSATO: In prior art approaches, because of interference
9 and complexity of the sample, one of the problems was high concentration
10 proteins swamping out the ability to pick up low concentration. That limited
11 the detection range to a narrow dynamic range. The solution here -- and
12 again, I'm going to step away from the claims, please.

13 JUDGE FREDMAN: I understand.

14 MR. ROSATO: But the solution here was that the idea of using a
15 plurality of particles. Rather than searching for that magic particle that
16 caught, like, just the right protein, the approach was to go in a different
17 direction, use a plurality of different particles with the idea that with this
18 entire plurality, they're going to -- in the subset, you're going to get more
19 equalized levels of the various different proteins. Now you don't have that
20 issue where albumin is completely swamping out, you know, protein X.

21 JUDGE FREDMAN: Right.

22 MR. ROSATO: Right? Protein X with the number of particles
23 that used was raised up, and now it's more on par. So now when you take
24 that isolated subset and put it in your mass spec, you are now able to pick up
25 in the mass spec, without all these interference problems, a -- you know, a

1 wider dynamic range of particles from -- that are present at different
2 concentrations in the sample now that you've used all these particles to bring
3 them up and even out the amounts in the substrate, so it doesn't mess up the
4 mass spec machine.

5 JUDGE FREDMAN: Yeah. Thank you.

6 MR. ROSATO: That's the idea.

7 JUDGE FREDMAN: Yeah. I understand.

8 MR. ROSATO: So I appreciate those questions. I mean, it's
9 -- you understand how there's -- you know, from a Patent Owner's
10 perspective, we love to talk about, like, the -- you know, the -- what -- the
11 cool aspects of the technology, but do so without risking being, you know,
12 mistaken as trying to read things into the claim, which we're not trying to do,
13 Your Honor.

14 JUDGE FREDMAN: Okay.

15 MR. ROSATO: So that's on Cai, and we covered Cai in a very -- I
16 would say quick, very disjointed, and informal, but I want to make sure I'm
17 addressing that, because -- you know, I would say Cai comes down to -- let's
18 go back to Slide 8, please -- or excuse me. Slide 7.

19 All right. So this is -- I mean, as far as what Cai discloses, this is a
20 point where there's no dispute, right? It is -- for this emPAI, it's -- Cai states
21 explicitly what it's referring to, its abundance in the mixture, and the mixture
22 is not what the petition identifies as the claim sample. So that's a big issue,
23 and nobody has ever disputed that.

24 I'll stick with 1 -- well, let's stick with 1C and let's turn to Slide 10,
25 please. I'm going to talk briefly about Ground 3. This is the alternate

1 obviousness ground in view of Cai, right? So the argument here in the
2 petition materials was Petitioners seem to recognize that emPAI was not a
3 measure of concentration. Their argument is, well, it would have been easy
4 to convert that abundance value to a concentration value, and they provide a
5 specific calculation where they calculate the molar percent.

6 And Your Honor asked a question about this, which got a different
7 answer, but I would say there are two problems with this obviousness
8 ground. It fails for two reasons: one, molar percent is not concentration.
9 They don't -- they didn't appear to recognize this. Dr. Cima pointed it out.
10 It's discussed in the Patent Owner Response at page 35, Dr. Cima's
11 declaration at paragraph 69.

12 They never addressed this. Molar percent is not concentration, and
13 it was never addressed until today. This is the first time I ever heard them
14 address that. The other problem is this mixture versus sample issue. So
15 even if emPAI values were properly converted to a concentration value, it's
16 still reflective of this mixture, not what they identify as the sample.

17 Okay. So that's Ground 3. If I may, I'll turn to Ground 1. That's
18 on Slide 12. And I'm happy to address any of the issues. I'm just focusing
19 on things that are, from our understanding, not in dispute and should be
20 dispositive of the grounds. So on Slide 12 we'll talk about Ground 1. This is
21 obviousness in view of Hu, and we're still on Claim Step 1C here.

22 JUDGE FREDMAN: Can we go back to the previous thing? I
23 still have questions. I'm just -- I was thinking about it, and I'm sorry to make
24 you change gears.

25 MR. ROSATO: Your questions are great, Your Honor.

1 JUDGE FREDMAN: I'm reading the claim now, and it says,
2 "Assaying the subset of proteins to detect, in the subset, proteins in the
3 biological sample at concentrations across the dynamic range."

4 Do you have to actually measure the concentrations or is it just that
5 the concentrations have to inherently be at that dynamic range? You see the
6 distinction? That's really the distinction in this claim.

7 MR. ROSATO: Well, that's a good question. I would say,
8 sticking with the grounds that were advanced and what was cited in the --

9 JUDGE FREDMAN: Well, they point to proteins that are at that
10 dynamic range, so that -- and whether that's true or not and for some of these
11 other grounds, that may be a little more questionable, but yeah.

12 MR. ROSATO: Well, they don't point to proteins that are within
13 that.

14 JUDGE FREDMAN: I think they --

15 MR. ROSATO: They try to in Grounds 1 and 4, and we've got
16 some response on that.

17 JUDGE FREDMAN: Okay.

18 MR. ROSATO: Is that what you're getting at in Ground 1?

19 JUDGE FREDMAN: No. I wasn't really looking at 1 and 4. I
20 was looking more for 2, but go for 1 and 4. Go ahead.

21 MR. ROSATO: Okay. Well, let's -- let --

22 JUDGE FREDMAN: Deal with them first, anyway and get them
23 out of the way.

24 MR. ROSATO: Okay. Let me try to answer your question, then I
25 will turn to those.

1 JUDGE FREDMAN: Go ahead.

2 MR. ROSATO: But let's be clear about this. There are no
3 concentrations for any proteins in Cai. Cai doesn't report the concentrations
4 back in the sample. Petitioner doesn't know what they are. Nobody knows
5 what they are, so there are no concentrations. They never take an approach
6 for Ground 2 or Ground 3, the Cai grounds, where they say, we know the
7 concentrations. Here they are. They just point to the emPAI statement
8 about eight orders of magnitude --

9 JUDGE FREDMAN: Right.

10 MR. ROSATO: -- and, you know, they call it good. That's the
11 extent of the argument on that ground. Ground -- let's talk about Ground 1.

12 JUDGE VALEK: Counsel.

13 MR. ROSATO: Yes, sir.

14 JUDGE VALEK: Let me just interrupt. I'd appreciate if you could
15 answer Judge Fredman's question. His question was -- and I'm going to
16 paraphrase. Is the method in Claim 1 a qualitative method or is it
17 quantitative in that it actually requires one to measure and quantify the
18 concentrations of proteins in the biological sample? Start there, and --

19 MR. ROSATO: Yeah, yeah, yeah.

20 JUDGE VALEK: -- answer that question --

21 MR. ROSATO: Yeah, yeah.

22 JUDGE VALEK: -- before you go on to what's argued.

23 MR. ROSATO: Sure. I would say that the action in the claim
24 does not require that concentration detection to occur in the claim. Claim 1
25 doesn't require the action to occur. It does require that the proteins be

1 detected to meet that limitation, right? You see the difference there?

2 JUDGE VALEK: I don't think I do.

3 MR. ROSATO: Okay. So Step C is an action step. It's assaying,
4 and then it tells you what you were assaying or what you were detecting. So
5 the requirement is that you take the action to detect proteins in the subset,
6 and then it describes what those proteins are that you have to have detected,
7 and those are proteins that are present in the sample at concentrations across
8 six orders of magnitude. So the --

9 JUDGE VALEK: Let me ask a follow-up on that. What if your
10 biological sample doesn't have proteins at different concentrations that are at
11 six orders of magnitude or greater? What if the proteins in there are all
12 within a relatively narrow band of concentrations but you do all the steps of
13 the claim otherwise, is that still practicing the method?

14 MR. ROSATO: If I'm understanding your question, you have a
15 sample that has a narrow dynamic range, say one, right, of protein
16 concentration?

17 JUDGE VALEK: Sure. Yeah.

18 MR. ROSATO: Okay. And you --

19 JUDGE VALEK: Or five.

20 MR. ROSATO: Okay. Five. Great. And you ran this, I would
21 say no, it does not satisfy the claim.

22 JUDGE VALEK: So the claim is only practiced if not only you
23 perform these steps, but the particular sample that you're studying meets
24 these requirements?

25 MR. ROSATO: Yes. I would state it a little differently, but yes.

1 Yeah. I would probably state it as you -- it would be impossible to satisfy
2 the claim with a sample that can't possibly have proteins across six -- greater
3 than six orders of magnitude. It's a very interesting question. I don't know if
4 you were getting at this, but one of the --

5 JUDGE VALEK: Let me respond to that. You said "can't
6 possibly." I mean, any sample can have -- can possibly have it, but I -- what
7 I understand you to be saying is, if my particular sample, all the proteins in it
8 are five orders or less magnitude difference in relative concentration, you
9 can't practice this claim on that sample, correct?

10 MR. ROSATO: Correct.

11 JUDGE VALEK: Okay.

12 MR. ROSATO: Yeah. I don't know if you're -- and I think of you
13 guys as very smart, so if I'm giving you too much credit, excuse me. It's
14 actually an interesting question because there are, like, cell lines that are
15 specifically used because they have a very small dynamic range of different
16 proteins.

17 Turns out one of those are HeLa cells. It's one of the reasons why
18 they're examined and used in research. They have a very -- you know, very
19 defined and small, you know, set of proteins, but there are cell lines that are,
20 you know, simplified for that reason.

21 JUDGE FREDMAN: So sorry. I have to go back to Cai again. I
22 apologize to -- the other two aren't as interesting to me. In the petition, they
23 talk about their expert declaration. I believe they point to paragraph 229 of
24 the expert declaration, where the expert points to the supplemental data at
25 the very end and points to the emPAI values of detected proteins which span

1 from .02 to 2,254,683.

2 Why is that not more than a six order of magnitude detection?

3 You're saying it's not a concentration but it's reflective of concentrations?

4 MR. ROSATO: Well, I don't know if I would agree it's reflective
5 of concentration. It's emPAI values, right?

6 JUDGE FREDMAN: Which reflect something, right?

7 MR. ROSATO: Yeah. They both --

8 JUDGE FREDMAN: What do they reflect?

9 MR. ROSATO: It tells us exactly what they reflect. They're a
10 semi-quantitative indication of abundance in the mixture.

11 JUDGE FREDMAN: So abundant -- and what is abundance? Is
12 abundance relative to concentration?

13 MR. ROSATO: I would think the --

14 JUDGE FREDMAN: Or you're saying that abundance is not
15 relative to concentration, that the --

16 MR. ROSATO: Well --

17 JUDGE FREDMAN: -- amount of something is not the
18 concentration of it?

19 MR. ROSATO: Amount is not the same as concentration. You're
20 giving a --

21 JUDGE FREDMAN: The amount in the HeLa cells, right? So we
22 have a certain amount of HeLa cells that they took and they have a certain
23 amount of this, so that's the amount in the HeLa cells. Is that not
24 concentration?

25 MR. ROSATO: Okay. So I want to make sure we're not getting

1 our statements crossed. Two answers to that question: Amount is not --

2 JUDGE FREDMAN: Not amount.

3 MR. ROSATO: -- the same as concentration --

4 JUDGE FREDMAN: Concentration is amount per volume?

5 MR. ROSATO: Correct.

6 JUDGE FREDMAN: Okay. They have a value here that comes
7 from a certain volume of material and is an amount?

8 MR. ROSATO: If it does, they never tell us that volume.

9 JUDGE FREDMAN: I think the table tells it. Okay. Fine. Go
10 ahead.

11 MR. ROSATO: I don't think they ever tell us the -- and again, this
12 is the mixture, right? So emPAI is referring to the mixture, right? There's
13 no concentration, and it sure isn't concentration back in that HeLa cell lysate,
14 right? So how -- I don't think anybody --

15 JUDGE FREDMAN: Well it started with a certain amount of it,
16 but okay. Go ahead.

17 MR. ROSATO: There was some amount at some point. What that
18 is --

19 JUDGE FREDMAN: Okay.

20 MR. ROSATO: -- what was the amount of lysate that was taken --

21 JUDGE FREDMAN: Do you need to know the concentration to
22 meet your claim? Is that a requirement of the claim? You have to know
23 -- does that number have to be revealed to the inventor or the experimenter
24 doing the math?

25 MR. ROSATO: I'm not sure what concentration the claim

1 requires.

2 JUDGE FREDMAN: Any concentration. Are there any
3 concentrations in the claim that the experimenter has to know, starting or
4 final?

5 MR. ROSATO: They would -- to satisfy the claim, you would
6 have to know that the proteins that were detected are present in the sample at
7 concentrations.

8 JUDGE FREDMAN: So if someone did something that was a six
9 -- we're saying an infringer here now. They did a six order of magnitude but
10 they didn't actually know it. They happen to be six orders of magnitude, but
11 they wouldn't be infringing because they didn't know it?

12 MR. ROSATO: I don't know how to answer that question in the
13 context of this prior art case.

14 JUDGE FREDMAN: Okay.

15 MR. ROSATO: I mean --

16 JUDGE FREDMAN: That's fair.

17 MR. ROSATO: You understand that, Your Honor?

18 JUDGE FREDMAN: I think I do.

19 MR. ROSATO: Yeah. Okay. Do we care about claims 1 and
20 -- I'm sorry, Grounds 1 and 4? Because I agree. I don't think they're really
21 defended in the --

22 JUDGE FREDMAN: I think they're weaker. I -- that's --

23 MR. ROSATO: Yeah. I'll just --

24 JUDGE FREDMAN: Write it off.

25 MR. ROSATO: Yeah. If I may, I'll touch on -- and I'll take an

1 extra five. I see I'm coming up on my time, and I really appreciate all the
2 questions. I'll comment very quickly. If I may, I'll address Grounds 1 and 4
3 together because they really follow the same format, right? They look at
4 -- they all reference Hu in Ground 1, Zaccaria in Ground 4, and they identify
5 two proteins for each one.

6 They say, you know, here are two proteins. They were detected in
7 the reference. The reference doesn't tell you the concentrations, but you
8 -- by the way, you could go look it up in a database and see what the
9 concentration is in a sample. And they then turn to secondary references and
10 say, well, these other secondary references provide concentrations in the
11 sample and they argue inherency on that basis.

12 So each of those grounds, I would say, you know, fail for very
13 similar reasons: one, flawed inherency case. Their argument is normally
14 present. It does not meet the exacting standard of inherency, which is
15 necessarily present, but they never even address what's normally present.
16 They just cherry-pick a couple references. We've given counter-examples
17 that show vastly different concentrations back in the samples that would
18 destroy the six orders of magnitude. So it's a flawed and unsubstantiated
19 inherency argument.

20 One of the other issues, and this is true for both cases, but, you
21 know, it really does illustrate what is pervasive in this petition. That's a lack
22 of critical review of the petition materials. Let's turn to Slide 19. Right. So
23 in both of these grounds, their theory was, you know, two particular proteins
24 were detected in the references, and they argue inherency based on the
25 concentration.

1 This is addressed and explained in detail in the Patent Owner
2 Response and by Dr. Cima. It looks like what they did is they just flipped
3 through a data table, picked an entry, and never critically analyzed the data
4 presented in those references. We see this in both instances, where they pick
5 an entry out of the data table, never give it critical review. Dr. Cima went
6 through this and explained -- you know, he looked at the data and gave
7 detailed explanation why these data entries wouldn't even be believable as
8 actual detection events. And again, this was never challenged.

9 This example we're showing here is particularly egregious, and this
10 is with the Zaccaria reference. They point to an entry in a data table that
11 actually lists multiple different accession numbers. So for a given entry, it
12 identifies multiple different possible proteins, and the reference itself
13 confirms this. It says, well, some of these, the computer identified multiple
14 different protein matches. We don't know which one it was, so we listed
15 them all. So these are the types of, you know, just lack of critical review of
16 the references that we see.

17 I'll turn briefly to this issue of, you know, the definition of
18 biological sample, and I want to make one thing perfectly clear. It was
19 incorrectly presented in the opening remarks as Patent Owner's proffered
20 construction. That is not true. The way this came up was during the
21 discovery process.

22 Dr. Vargas specifically cites repeatedly in her declaration to this
23 very provision in the specification when addressing biological sample, and
24 she was asked about this during cross-examination. "Is this what you
25 understand to be" -- or, "Why are you pointing to this? Is this what you

1 understand the -- to be a description of the term?" And her answer --

2 JUDGE FREDMAN: Which slide are you pointing to?

3 MR. ROSATO: Pardon me?

4 JUDGE FREDMAN: Which slide is that? What number?

5 MR. ROSATO: Sorry. This is --

6 JUDGE WISZ: Slide 37.

7 JUDGE FREDMAN: 37.

8 MR. ROSATO: Slide 37.

9 JUDGE FREDMAN: Thank you.

10 MR. ROSATO: I don't know why I'm looking over here. I have a
11 bigger version right here.

12 JUDGE FREDMAN: Okay.

13 MR. ROSATO: So yes, she was -- look, this is why we conduct
14 the discovery process. Why did you point to that? How does this fit into the
15 obligation of a Petitioner to tell us how the claims are construed, how that
16 construed claim is met by the art? This is the discovery process. And she's
17 the one that said, this is a definition, and yes, I followed this.

18 The rest of the argument after that is evaluating whether the cited
19 material meets what is identified as a definition or not. We say it isn't. They
20 say it is. And this is particularly true with the HeLa cell situation, right?
21 And there are -- you know, we -- I think the board understands our argument
22 why HeLa cells don't meet that definition and we disagree with the rebuttal
23 argument that these are genetically identical copies from what was obtained
24 from Henrietta Lacks back in 1951, highly mutagenic cells. There are
25 multiple references in the record that say these look nothing like Henrietta

1 Lacks' cells anymore.

2 So I just want to be clear on who's making the claim interpretations
3 and the process that we're all familiar with with how a petition case is
4 evaluated and responded to. Thank you, and I'll reserve the rest of my time.

5 MR. BOSCO: All right. Thank you, Your Honors. I'll just briefly
6 address that last point about the proffer of construction. I'm not sure it could
7 be any more clear that it was Patent Owner that proffered that construction.
8 I think the testimony of Dr. Vargas on that is being greatly exaggerated, to
9 say the least, and she made clear in her declaration over and over again
10 exactly what her understanding of biological sample was. And time and
11 time again in her declaration and as was cited in the petition, she explained,
12 you know, cell lysates are specifically on the list. That's why they qualify as
13 biological samples, and she did that for each one of the references.

14 I think I'll quickly move to questions about Ground 1, Your Honor,
15 Judge Fredman, about questions that you had about that. So look, there's
16 more here in Ground 1 as to Step 1C than just the identification of the
17 particular proteins. There's a broader obviousness argument that was made,
18 and that's reflected here on Slide 58, which has excerpts from Dr. Vargas's
19 declaration.

20 And she explained how a person of ordinary skill would have
21 understood the need and desirability of an analysis method that could
22 achieve dynamic ranges, including six orders and beyond. She explained
23 how that could be achieved using known techniques such as LC-MS, and
24 then she talked about the fact that the '360 Patent already said that those
25 methods could achieve those very same dynamic ranges. So there's a

1 broader obviousness argument there. I just don't want you to think that those
2 grounds stand and fall on the specific issue of whether you agree with her on
3 those proteins. So to -- hopefully, I'll cover all the very specific questions I
4 had to do some homework on.

5 On mole percentage, to your question, Judge Valek, so that is
6 concentration. The mole percentage is concentration. Paragraph 239 of Dr.
7 Vargas's declaration, among other places, she addresses that, and she
8 explains how Ishihama converts emPAI to mole percentage and how that's a
9 traditional concentration. And there are even tables in Figure 1 of Ishihama
10 that have emPAI on one axis and concentration on the other. So the
11 explanation of how you get to concentration is right there in her declaration,
12 it's right there in Ishihama, which, of course, is cited in Cai.

13 So next there were, I think, a couple questions about this issue of
14 Step 1C and whether we've been -- Petitioner has been consistent about
15 saying that it's the assaying of the subset, and we have. So I mean, this is
16 non-exhaustive, but in the petition on pages 35 to 36 in Ground 1 we
17 specifically reference the subset, page 60 with reference to Cai, page 74 with
18 reference to Zaccaria. There's nothing new there at all. The fact that it
19 wasn't said every single time we talked about Step 1C doesn't really make a
20 difference. That claim language was plain, as I said earlier.

21 And then just a kind of broader thematic point: There were no new
22 arguments, and this dovetails with exactly what I was talking about. I mean,
23 we've been accused of making some new arguments. We don't think
24 anything is new. We think this is all just what we put in the petition and in
25 our papers. But what is new is to hear Patent Owner talk about what's

1 actually in the specification. And we heard some attempts at that just now,
2 but throughout this process, you know, they've really avoided the content of
3 their own patent.

4 And as I said in the beginning, you know, they never once in their
5 Patent Owner Response, never once in Dr. Cima's declaration did they ever
6 engage with the fact that their own patent says that six orders of magnitude
7 was achievable through prior art methods. So with that, Your Honors,
8 unless there are further questions, I'm happy to give everyone back some
9 time.

10 JUDGE VALEK: Sure. I have a question --

11 MR. BOSCO: Yes.

12 JUDGE VALEK: -- for you about the arguments in the petition
13 relating to element 1C and the mapping to Cai. So I'm on page 60 of the
14 petition. And I see there a reference to the quote from Cai where it says that
15 the emPAI values spread over eight orders of magnitude.

16 And then you say that "shows that Cai's MS analysis detected
17 protein concentrations in the subset across a dynamic range comprising the
18 claimed 'at least six orders of magnitude,' which is further confirmed by the
19 concentrations detected in Cai."

20 See that sentence?

21 MR. BOSCO: Yes, Your Honor. Yes.

22 JUDGE VALEK: Okay. And then in the citation for that below,
23 you refer to the '360 patent's reliance on a known lookup table to determine
24 the concentrations across the dynamic range. What was the point you were
25 trying to make there with that citation to the lookup tables?

1 MR. BOSCO: With respect to Cai, it's really just that it was
2 known to go somewhere -- to go to another source to confirm your
3 concentration. So in Cai's case, you know, for the calculation, it goes to
4 Ishihama, and that's consistent with what the '360 patent said.

5 JUDGE VALEK: Okay. So to confirm your concentration in
6 what? The concentration in the subset of proteins that are isolated from the
7 coronas or in the underlying biological sample?

8 MR. BOSCO: In the subset. Yeah. And, Your Honor, I think
9 we've been consistent throughout that that's how we're reading the claim, is
10 that we're -- with Step 1C, the action steps that occur in Step 1C are with
11 respect to the subset. And then the patent, as claimed, indicates that by
12 doing that, that's how you -- through the process of that, that's how you
13 learn, that's how you assay the biological sample.

14 JUDGE VALEK: That may be the case for the grounds based on
15 Cai, but it seems like you've taken a different approach in the other two
16 grounds. In those, you look at the mass spec data that's in the reference and
17 the supplementary information and then you go to other references that
18 describe typical concentrations of the proteins that are in that spectral data,
19 and say those show that the concentrations are greater than six orders of
20 magnitude, correct?

21 MR. BOSCO: Yes. Yes.

22 JUDGE VALEK: So it -- do you understand that it's a little bit
23 inconsistent from what you're telling me now? At least with respect to Cai,
24 you seem to be saying, it's the concentrations, the dynamic ranges of the
25 concentrations that are detected by my mass spec experiment. But with the

1 other two grounds, it seems like you're saying what we're really talking
2 about are the concentrations of these proteins in the underlying blood
3 sample.

4 MR. BOSCO: Well, with the other grounds, what -- by going to
5 the other references, and I'm referring to Grounds 1 and 4, what we're doing
6 there is explaining why this would all be obvious to a person of ordinary
7 skill. That they, by -- if they go to that lookup, they recognize the normal
8 concentration of that particular protein, then they would understand that they
9 assayed a protein that has a dynamic range of six orders of magnitude.

10 JUDGE FREDMAN: You see the inconsistency that Judge Valek
11 is concerned with, right? Because in Cai, you say in paragraph 97, your
12 expert says there's empirical peptide abundance index, right? So that's kind
13 of a -- clearly that's talking about the subset, right?

14 MR. BOSCO: Right.

15 JUDGE FREDMAN: I think pretty clearly in Cai. But these other
16 references, you're kind of -- you are going to these other references to give
17 their actual starting values, which may or may not reflect what you detect in
18 your --

19 MR. BOSCO: Yes, Your Honor. So I mean, I think to the extent
20 there's inconsistency, what we were going for there is that they're using
21 those other references to teach what was found in the subset as evidence that
22 a person of ordinary skill would have used to recognize that they had found,
23 in the subset, the appropriate concentration.

24 Your Honor, you looked like you were going to ask another
25 question, so I wanted to --

1 JUDGE FREDMAN: No.

2 MR. BOSCO: -- just make sure.

3 JUDGE VALEK: Yeah. Is there -- so this is going to come out
4 inarticulate, because I'm trying to figure out a way to articulate it, and I'm
5 not sure I have. I believe it's pretty clear from the text of Cai that the emPAI
6 values that they detected in their experiment that they spread across at least
7 eight orders of magnitude -- but as everyone seems to agree, that reflects the
8 relative abundance in the mix from their experiment in Figure 3 as opposed
9 to the relative abundance of those proteins in the HeLa cell lysates, right?

10 MR. BOSCO: Well, I think it's certainly indicative of the relative
11 abundance in the HeLa cell lysate. But yes, I mean, specifically that's what's
12 being calculated there.

13 JUDGE VALEK: That's exactly my question. So is there
14 evidence that shows that it is indicative of that, other than just your attorney
15 argument?

16 MR. BOSCO: I mean, I guess my first answer is I don't think we
17 have to show that because that's not what the claim says. So the claim says
18 you do it to the subset and then there's basically an effect that comes from
19 that, according to the claim language which is then you've assayed the
20 biological sample. So I don't think we have to show that.

21 JUDGE VALEK: Sure.

22 MR. BOSCO: And I think just more broadly, if you look at the
23 entirety of Dr. Vargas' declaration, the references themselves, and I know
24 I'm being a little general here, but I mean, they tell you that, yeah, that that's
25 how, when you do this over and over again, then you learn what was in the

1 biological sample. I mean, there would be no point to it if you're not gaining
2 information about what was in the biological sample. And of course, the
3 subset comes from the biological sample.

4 But I think the short answer is we've shown exactly what the claim
5 requires. And I think definitionally, if you look at the language of limitation
6 1C, if you perform all the -- everything that goes up to the comma where it
7 says, "Thereby assaying the biological sample." If you perform everything
8 up to there, you've done it. You've satisfied the claim. And then the rest of
9 it is saying, yeah, if you've done that, you've assayed the biological sample.

10 JUDGE VALEK: Is that true even if the spread of protein
11 concentrations in your biological sample is all less than six orders of
12 magnitude?

13 MR. BOSCO: I was expecting a question like that, based on your
14 questions to Counsel before. So I mean, I'll -- just since you asked the
15 question, I don't think there has to be an actual detect. I don't think the claim
16 language requires that. That's not core to our grounds. But it says, "With an
17 instrument to detect in the subset." It doesn't specify that it was actually
18 detected. But again, I don't think that's core to, you know, the answer to that
19 question I don't think alters the result here. And I have nothing else, Your
20 Honors, if there are no further questions. And I appreciate the time.

21 JUDGE FREDMAN: Thank you.

22 JUDGE VALEK: Thank you.

23 MR. ROSATO: Okay. Sorry. Sorry for the technical difficulties.
24 I'm going to address two things here. One is back to this idea of what they
25 specifically argued. I think we're all in agreement that with regard to

1 Grounds 1 and 4, it's very clear that for concentrations, they're pointing to
2 the sample. I would say that's true of Ground 2 as well. And I want to point
3 to the petition at page 60, please.

4 There's a paragraph at the top of that page, and then there's the
5 comment at the end that Judge Valek pointed to. But let's start with the
6 paragraph at the top. And it actually, you know, starts on page 59. But let's
7 look at what they're actually arguing there. They start by arguing -- they're
8 talking about Cai and this element 1C. And they're arguing Cai is the -- you
9 know, the point of Cai is to go grab high concentration proteins and low
10 concentration proteins. And that last sentence in the paragraph there states,
11 "In other words, a POSA would have understood that these results were
12 from assaying the biological sample using MS across a range large enough
13 to detect both low abundant and high abundant proteins in the biological
14 sample." Right?

15 So they're referring specifically to the biological sample. Now,
16 then they point to this emPAI, eight orders of magnitude limit, excuse me,
17 disclosure in Cai, and conclude that it meets the limitation. But as Judge
18 Valek pointed out, and I mentioned earlier, they end that with saying, and by
19 the way, look at section, you know, above, where we told you you can find
20 concentrations by going and looking them up in a table. So I would say that
21 the reasonable interpretation of this is I think they just didn't understand the
22 reference when they cited this. They're talking about concentrations in the
23 sample. They misapprehended the reference, they saw the magic words
24 eight orders of magnitude. They put it in there, but they didn't understand
25 what it was referring to. And it wasn't until the trial process when this was

1 pointed out, they realized they have a problem, and I think they're changing
2 their story on that. The --

3 JUDGE VALEK: Counsel, what if I disagree with you, and I think
4 that what they've actually said here is Cai allows you to do both? That
5 because it shows that you can detect signals spread over eight orders of
6 magnitude in the mix, or at least the relative abundance of those, that that is
7 indicative of being able, at least capable, of detecting protein concentrations
8 in the recited dynamic range and the sample. And that's why they're citing
9 to the fact that the patent refers to using a table lookup process to look up
10 typical concentration ranges in whatever your biological sample may be.

11 And so isn't that what they're saying here? That they're actually
12 saying both? And I agree that's different than what they've done in Grounds
13 1 and 4. But here it seems like they're referring to both things.

14 MR. ROSATO: Well, if that's the case, how does that possibly
15 satisfy anticipation? To say something is anticipated because it doesn't do it,
16 but it could do it if you do something else. That's not anticipation. That's
17 not a valid anticipation theory. That would be an obviousness theory.

18 JUDGE VALEK: But they have that in Ground 3, don't they?

19 MR. ROSATO: No --

20 JUDGE FREDMAN: How is that not anticipation if they say, we
21 -- by enriching the material in our sample, we have now created a situation
22 where we can have the capacity to detect six orders of magnitude? How is
23 that not anticipation?

24 MR. ROSATO: Of emPAI numbers, right?

25 JUDGE FREDMAN: Which is reflective of the concentration.

1 MR. ROSATO: It's not reflective of the concentration.

2 JUDGE FREDMAN: Right, if we're enriching low ones, which is
3 kind of what we've all said, and I think you've even said yourself were
4 happening, we're clearly increasing the dynamic range. So it's clear that
5 we're not decreasing it. And so if we can do six orders of magnitude or eight
6 orders of magnitude, the implication of this is that these low abundant
7 proteins could even be more separated. That with this capacity you could do
8 a nine orders of magnitude, because you get that very, very low abundant
9 protein.

10 MR. ROSATO: I understand the argument. I don't think it holds
11 water for multiple reasons. One, I don't think that's what was argued. Two,
12 like, again, we were talking about emPAI. Not concentration. This is
13 discussed in the Ishihama reference. This is a -- and identified in Cai as
14 what? "A semi-quantitative indication of abundance." It's not even
15 quantitative, it's semi-quantitative. So they're doing these conversions and
16 it's a rough, you know, shot at, you know, at some form of abundance, right?

17 And it's even worse than that because -- and we address this in the
18 Patent Owner Response, and I don't think there was meaningful rebuttal here
19 either. But digging into Ishihama, it actually talks about the, you know, the
20 -- there's a very -- pretty narrow range of reliability, even when it comes to
21 emPAI.

22 So I don't accept that this is a, you know, a proxy or reflection of
23 concentration. I don't that has anything -- you know, I don't think it -- I don't
24 think it does. And I don't think there's any record evidence to suggest that it
25 does.

1 JUDGE FREDMAN: I mean, I think back to paragraph 229 of the
2 expert declaration she says that. But you can disagree with --

3 MR. ROSATO: And she said that. And what does Cai say about
4 it?

5 JUDGE FREDMAN: All right. But an expert says it. You're
6 disagreeing with an expert. That's fine. You can do that, but --

7 MR. ROSATO: Well, I -- no.

8 JUDGE FREDMAN: We'll give that the weight it -- consistent
9 with that.

10 MR. ROSATO: I wouldn't characterize it -- I would say, I would
11 point out that the prior art is contradicting what -- even if she says that, the
12 prior art is saying something completely different. And this is, you know,
13 this is part of the IPR process.

14 She also said a lot of things, like references detected proteins
15 without even looking at what was going on. So clearly, there are problems
16 with what the expert says and there are credibility issues. And the issue of
17 whether something the expert said was ever substantiated in the first place.
18 And those problems are littered throughout her declaration, so.

19 JUDGE VALEK: Counsel, just so that I understand your position,
20 when you say that she's saying something completely different than the prior
21 art, are you referring to the fact that Cai refers to emPAI as a measure of
22 relative abundance or something else? Or something in addition to that?

23 I'm just trying to understand what you're relying on in the prior art
24 that you say is completely different.

25 MR. ROSATO: Well, I'm -- you know, I should look at the

1 paragraph. But Judge Fredman asked me a question of, you know, didn't
2 -- was it 239, was it?

3 JUDGE FREDMAN: 229, I think it was.

4 JUDGE VALEK: 229.

5 MR. ROSATO: Okay. As I understood the question was, doesn't
6 Dr. Vargas say emPAI is concentration? My response was, I don't really
7 care if she said it because the reference is telling us exactly what the emPAI
8 is. If she said that, then she was clearly mistaken, as illustrated by the
9 reference she's referring to which does not say that. It says something
10 different. So if she did say that -- and I'll --

11 JUDGE VALEK: It calls it relative abundance, right?

12 MR. ROSATO: A semi-quantitative indication of abundance is
13 what it calls --

14 JUDGE VALEK: We've already gone through this. Claim 1 isn't
15 a quantitative method. You just have to detect the proteins. You don't have
16 to quantify the concentration. And so is the fact that it's abundance as
17 opposed to concentration, is that your argument?

18 Again, I'm trying to drill down and understand what you say is
19 completely different that undermines Dr. Vargas's testimony in paragraph
20 229.

21 MR. ROSATO: Okay. Let me get -- because we're going back
22 and forth between claims and paragraph 229. So let me -- sorry. Let me go
23 back to that. Okay. So I think what Judge Fredman is referring to is a
24 sentence that says, "A POSA would" -- and I'm reading from paragraph 229
25 of Dr. Vargas's declaration where she says, "A POSA would have

1 understood that the relative abundance of bound proteins, quote, spread over
2 eight orders of magnitude, end quote, shows that Cai's MS analysis detected
3 protein concentrations in the subset across the dynamic range." Okay. So
4 she does say concentrations. She's citing to a specific sentence in -- or piece
5 of disclosure in Cai.

6 And let's put -- can you put up Slide 7, please?

7 Right. So I would dispute that what she's citing to supports her
8 assertion that what's being reported here are concentrations. It does not say
9 that. It describes what emPAI is, and it describes it as "a semi-quantitative
10 indication of the overall abundance of protein in the mixture."

11 It does not say concentration. Both -- or Dr. Cima has weighed in
12 and said, that is not concentration. It's not concentration in the mixture, it's
13 not concentration in the lysate. So Dr. Vargas is wrong when she used the
14 term concentration. And there's never been any dispute on that.

15 So I would encourage everybody to go look at the reply brief and
16 see if there's any dispute that emPAI is anything other than exactly what Cai
17 says it is. There is no dispute. So I hope that answers your question. I'm
18 trying to tie the 229 and Judge Fredman's question to that answer. But no.
19 And this is -- you know, this is what we do in IPR. They cited to something,
20 said it -- it says, you know, X, and satisfies the claim. They're wrong in
21 what they pointed to and how they characterized that. They misunderstood
22 the reference, so. I probably had one other thing. I'll cover it quickly. But I
23 think there was -- I think I heard an argument. And, Judge Valek, this was
24 in response to one of your questions.

25 But I think I heard a suggestion that whatever was detected in the

1 subset of -- or the mixture of Cai was, you know, indicative of
2 concentrations in the lysate. That is not true. That is exactly the opposite of
3 what Cai is trying to accomplish here.

4 They pulled -- they used these two different particles, and they
5 showed -- the point of them showing this spread is to show that the different
6 particles were capturing, you know, different groups of proteins. So one
7 particle -- and these are the figures that are shown in 3D and 3E here on
8 Slide 7. They're showing a completely different profile of proteins.

9 So of course it's -- and different emPAI values. So I want to push
10 back on this notion that whatever the particles capture, this is somehow, you
11 know, translatable to back calculate or reflect what's in the lysate. I don't
12 know if that's where you were going with it, but I heard the answer, and I
13 wanted to make that point for clarification.

14 JUDGE VALEK: Fair enough. So let me ask a follow-up on it.
15 So I agree with you that Cai is saying that the relative abundance of proteins
16 in the mix in Figure 3 is not the same as the concentration, the relative
17 concentration of those things in the lysate. It says that explicitly.

18 But what they're saying, as I understand, and particularly in their
19 Ground 3 they say, one of skill in the art would have been motivated, after
20 you see this data, you know, that you -- spreading over eight orders of
21 magnitude in the spectral data, that they say -- and I'm quoting here. It's on
22 page 63 of the petition.

23 They say, "One of skill in the art would have been motivated to
24 search out protein concentrations." In other words, once you detect that
25 these proteins are present, perhaps they've been amplified by the binding to

1 these particles, you could just go out and search out the protein
2 concentrations by looking in references or lookup tables or whatnot, if you
3 were so motivated to do.

4 So why isn't that exactly what your patent is talking about?

5 MR. ROSATO: Well, it -- okay. Putting aside what -- let me
6 address this in two -- what you just said illustrates precisely why they were
7 never arguing this concentration in the subset issue. What you just pointed
8 out is their backup obviousness ground was, okay, even if Cai doesn't tell
9 you the concentration in the sample, or wherever, you could go look it up.

10 Let me ask, how would you possibly look up in a data table what
11 Cai obtained in this mixture in this particular experiment? Of course that's
12 not what they're referring to, right? They're referring to looking up what's
13 -- presumably what you would find in a lysate. So I agree in their
14 obviousness ground. They do have this vague statement of, like, you would,
15 you know, go look it up.

16 JUDGE FREDMAN: Cai has a supplemental table --

17 JUDGE VALEK: Why isn't that obvious?

18 JUDGE FREDMAN: Cai --

19 Wait, wait.

20 Cai has supplementary table that gives me the list of all the protein
21 names. With those protein names, I could call a company, get the antibody,
22 very easily find the abundance myself in an experiment. How is that not
23 disclosed?

24 MR. ROSATO: Well, let's assume you did.

25 JUDGE FREDMAN: And I have the concentration.

1 MR. ROSATO: And you have the concentration. And the answer
2 is they only differ by three orders of magnitude in the sample.

3 JUDGE FREDMAN: Okay. I mean, if that's your argument. I
4 think that it's clear that these -- they don't. But okay.

5 MR. ROSATO: How is that clear that -- you just said you'd have
6 to go conduct this experimentation to go find out the concentrations.

7 We all agree we have no idea what the concentrations are in Cai's
8 HeLa sample. Nobody knows that. So if you went and conducted that
9 investigation, what would you find? I have no idea. I don't think anybody
10 in this room knows either. But one possibility is what you come back with
11 is a narrow dynamic range that doesn't meet the claim, right?

12 JUDGE FREDMAN: I hear what you're saying.

13 MR. ROSATO: Okay. Thank you very much. I don't have
14 anything further.

15 JUDGE WISZ: Thank you very much for your helpful
16 presentations today. This matter is now submitted to the panel for
17 determination and preparation of a final written decision.

18 We're adjourned.

19 (Whereupon, the above-entitled matter went off the record at 3:37
20 p.m.)

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