

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.

Case IPR2024-01473
Patent No. 11,435,360

PATENT OWNER'S SUR-REPLY

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I. INTRODUCTION

Petitioners Reply offers no serious rebuttal to the argument and evidence raised in the Patent Owner Response (POR). Petitioners offer no reply declaration. Their cross-examination of Dr. Cima was largely a waste of time as a vast majority of his direct testimony was neither contested nor explored. In fact, Petitioners offer no material response to many of the deficiencies the POR identified, leaving most salient facts undisputed in favor of affirming the patent.

In particular, it is now beyond dispute that none of Petitioners' grounds satisfy the claimed assaying step (element 1[c]), which requires detecting "*proteins in the biological sample at concentrations across a dynamic range comprising at least 6 orders of magnitude.*"¹ Petitioners no longer argue that either their expert or Cai (Ground 2, 3) has any clue as to the concentrations of detected proteins in the Cai HeLa lysate (the identified "sample")—nor could they. Cai itself expressly states the cited emPAI values at best reflect abundance in an extracted mixture, not the alleged biological sample. Both experts agreed and the Reply does not assert otherwise.

Grounds 1 (Hu) and 4 (Zaccaria) are barely addressed in the Reply and fare even worse. The Reply offers no rebuttal to detailed expert testimony and evidence

¹ All bold-italic emphases added unless indicated otherwise.

that the relied-upon entries appear indistinguishable from background noise, as is commonly found in raw data from shotgun proteomics. Even assuming *arguendo* the “low abundance” proteins were detected, the secondary references (Ahmed, Cao, Bryk) have nothing to do with Hu or Zaccaria and cannot confirm the inherency allegation for a variety of reasons. The Reply offers no dispute to this.

Furthermore, all grounds fail to prove the materials mapped by the petition satisfy what Petitioners’ own expert identifies as a definition of “biological sample.” The Reply fails to show otherwise. Petitioners wasted most of their time during cross-examination trying to extract a sound bite based on objectionable deposition tactics, while ignoring their own expert’s testimony. EX1036, 79:11-14. Making matters worse, the Reply wildly states that Cai’s HeLa cells are “genetically identical” to an original donor, whereas evidence (including Petitioners’ own exhibit) clearly describes HeLa cells as a laboratory engineered, immortalized cell line that are genetically distinct from whatever was derived from the original donor many decades ago. Petitioners’ mapping to claim element 1(b) is similarly deficient.

Upon thorough review and a developed record, Petitioners failed to satisfy their burden of proof for these reasons and others. Accordingly, the Board should enter judgment affirming the challenged claims.

II. ALL GROUNDS FAIL UNDER UNDISPUTED FACTS

Each ground fails based on at least one of multiple independently-sufficient bases, premised entirely on undisputed facts, as discussed in detail below.

A. Ground 2 Fails Under Undisputed Facts

Petitioners' sole anticipation challenge fails based on at least three, independently-sufficient and undisputed facts. First, there is no factual dispute that Cai fails to disclose "concentration *in the biological sample* across six orders of magnitude" as required in element 1(c). Second, there is no dispute that the Cai Fig. 3 experiment, which the petition relies upon exclusively for the assaying step 1(c), fails to contact the same biological sample with multiple particle types as required by step 1(a). Third, Petitioners failed to resuscitate their theory that MWCNTs employed in the Cai Fig. 3 experiment satisfy the multiple particle type limitations. Each of Petitioners' undisputed failures of proof is sufficient to resolve Ground 2 in PO's favor.

1. Ground 2 Fails at the Claimed Assaying Step (1[c])

a. No Dispute Cai Fails at Concentration in the Sample Across Six Orders of Magnitude.

All challenged claims require "assaying the subset of proteins of (b) with an instrument to detect, in the subset, *proteins in the biological sample at concentrations across a dynamic range comprising at least 6 orders of magnitude*, thereby assaying the biological sample." EX1001, claim 1, element (c).

The POR explained that Ground 2 fails because it relies exclusively on Cai's emPAI values to satisfy this limitation, but that Cai's emPAI is not abundance ***in the biological sample***, much less the required ***concentration in the biological sample***. POR 32-33. At best, as both parties' experts agree (and Cai states explicitly), emPAI reflects an estimate of abundance ***in the pulled-down corona***. EX2023, ¶65 (Dr. Cima); EX2022, 131:8-133:2, 134:21-136:18 (Dr. Vargas); Pet. 60 ("bound proteins"); EX1005, 587. Neither the corona, nor the mixture where it is found, is the biological sample identified in the petition. EX2022, 133:25-134:7, 148:7-22. Cai thus fails to anticipate assaying step (c).

Petitioners do not dispute any of these facts. Reply 18-21. Instead, Petitioners merely assert that abundance of proteins ***in the pulled-down corona*** could mathematically be converted to concentration of proteins ***in the pulled-down corona***. Reply 18-19.² Petitioners thus concede that Cai's emPAI range is, at best, a range "***in the subset***," not the range in the biological sample. Reply 19 (emphasis in original). Ground 2 thus fails based on undisputed facts.

b. Petitioner's "Concentration in the Subset" Argument Fails.

Anticipation requires disclosure of every element of the claim as arranged in

² Dr. Cima explained that Petitioners' calculations of molar percent is not the same as concentration. *See, e.g.*, POR 35. The Reply does not dispute this.

the claim. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). There is thus no legal justification for Petitioners' failure to demonstrate Cai discloses "assaying the subset of proteins of (b) with an instrument to detect, in the subset, **proteins in the biological sample at concentrations across a dynamic range comprising at least 6 orders of magnitude**, thereby assaying the biological sample." EX1001, claim 1, element (c). Petitioners provide no legal justification for ignoring the full requirements of the claims.

The Reply (at 19) attempts to sidestep the undisputed failure of Cai to reach the challenged claims by improperly ignoring language regarding concentrations of the detected proteins "in the biological sample," and instead focusing only on the clip-quoted language "in a subset." But Petitioners were well aware of the claim requirements at the filing date of their petition and never disputed them. Indeed, their own petition repeatedly identifies the claims as requiring detecting proteins that are present in a specified range of **concentrations in the biological sample**. Pet. 23 ("biological sample (*e.g.*, human blood plasma in Hu)"), 36 ("those proteins (such as serum albumin and LTBP-1) existed in certain concentrations **in the biological sample** being assayed"), 36 ("Hu detects the bound proteins **in the biological sample at concentrations** greater than 10 mg/mL (10⁻²) (*i.e.*, serum albumin) and less than 10 ng/mL (10⁻⁹) (*i.e.*, LTBP-1), comprising a dynamic range of at least six orders of magnitude."), 60 ("assaying **the biological sample**

using MS across a range large enough to detect both low abundant and high abundant proteins ***in the biological sample.***”), 65 (“***the biological sample*** (e.g., Zaccaria’s red blood cell (RBC) lysate, also referred to as hemolysate)”), 75 (“HBA1 is normally present in RBC lysate in a concentration of 1.47×10^4 pmol/mg and SBF1 in a concentration of 6.62×10^{-6} pmol/mg....Accordingly, the NPs in Zaccaria are detecting proteins ***in the biological sample at concentrations*** across a dynamic range comprising at least 6 orders of magnitude”). As such, Petitioners were fully aware that the claim language requires detecting ***proteins in the biological sample at concentrations across a dynamic range comprising at least 6 orders of magnitude***, but Petitioners simply failed to show Cai satisfies this limitation.

Petitioners’ anticipation theory was based on a misapprehension of Cai’s disclosure. The petition relied specifically on Cai’s emPAI values, uncritically seizing on the statement those emPAI values were “spread over 8 orders of magnitude.” Pet. 60. But Cai itself describes its emPAI values as “a semi-quantitative indication of the overall abundance of protein in the mixture,” not reflective of concentrations of any detected protein “in the biological sample” as recited in the challenged claims. POR 32; EX1005, 587. Both experts agree, rendering the relevant aspect of the challenged claims insufficiently addressed in the petition and missing from Cai. EX2023, ¶¶63-65; EX2022, 147:11-15. To the

extent Petitioners now attempt to direct argument only to concentration “in the subset,” such argument is improperly detached from both the challenged claims and previous argument in the petition.

2. Ground 2 Fails at the Claimed Contacting Step (1[a])

In addition to failing to satisfy element 1(c), as discussed above, Ground 2 independently is deficient for failing to establish anticipation together with element 1(a). Before the assaying step (c), all challenged claims require “contacting the biological sample with a plurality of particles comprising different particle types to permit” coronas corresponding to the different particle types to form around the plurality of particles (step (a)). EX1001, claim 1. The POR explained that Ground 2 fails because neither one of Cai’s Fig. 1 or Fig. 3 experiments anticipate the claims. POR 21-22, 25-26. This also is factually undisputed and resolves Ground 2 in PO’s favor.

As stated plainly in Cai, the Fig. 3 experiment used “three populations of HeLa cells,” and never contacted a single biological sample with the asserted multiple particle types (CBs vs MWCNTs). POR 21-22 (“The SILAC experiment individually contacted *two different lysates* (each from a different population[] of HeLa cells) each with only *a single particle type*.”), 25 (Cai SILAC study “experiments with three different populations and no (singular) population is ever contacted by a plurality of particle types”); EX2024, ¶54 (Dr. Cima); EX1005, 586

(SILAC: three populations of HeLa cells); EX2022, 131:8-132:5 (Dr. Vargas confirming individual contacting and separation of individual corona types). There is certainly no dispute that the SILAC experiment exposed each particle type (CB vs. MWCNTs) to a different HeLa Cell population lysate. Reply 13-14. Indeed, the entire point of Cai's SILAC experiment was to expose each distinct HeLa cell population lysate to a single particle type. Accordingly, based on undisputed facts, Ground 2 again fails for all challenged claims .

Instead of disputing dispositive facts, Petitioners confirm that they rely exclusively on "the LC-MS/MS with SILAC encoding method...for limitation 1(c)." Reply 13-14. They profess not to be "mixing and matching embodiments," and then argue that the reference in the SILAC experiment (Fig. 3) to a pull-down invokes "the process depicted in Cai's Figure 1A...used to isolate the cell lysate proteins" bound by the particles, which pull-down mechanics a POSA would "at once envisage" as part of Fig. 3. Reply 13-14. As PO already explained, however, the pull-down mechanics employed in Fig. 3 are beside the point and do not remedy the petition's deficiencies. POR 26-28. Even assuming that the Fig. 3 process involves the same pull-down mechanics as the Fig. 1 experiment, this does not establish that "the LC-MS/MS with SILAC encoding method" contacted the same biological sample with multiple different particle types, as claimed. It clearly does not (e.g., as plainly illustrated in Fig. 3) and Petitioners offer no dispute on

this.³

Petitioners also do not dispute the fact that “at once envisage” was never argued in the petition. POR 26-27. The Reply identifies nowhere in the petition materials invoking the “at once envisage” theory because none exists. *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355-56 (2018). For this additional reason, Petitioners cannot remedy their deficient anticipation case.

For each of the independently sufficient reasons discussed above, Ground 2 fails under undisputed facts.

3. The Petition Fails to Establish MWCNTs in the Fig. 3 SILAC Experiment Included Multiple Particle Types.

As the Board already found in the institution decision (Paper 11, 16 n.8), the Petition argument (at 56) that the MWCNTs in the Fig. 3 SILAC experiment included multiple particle types is even weaker than its reliance on the full SILAC experiment. The record has not changed in any manner that benefits Petitioners, just the opposite. Indeed, the Reply doesn’t even address the Board’s reasoning and offers no rebuttal to Dr. Cima’s testimony reaching the same conclusion.

In contrast, the POR (at 25-26, 31-32) specifically addressed the petition’s

³ Not only do Petitioners fail to dispute the dispositive facts, but they fail to rebut the legal principle that an “at once envisage” theory cannot supply a missing claim limitation. POR 27 n.2 (citing *Nidec*). The Reply ignores *Nidec* entirely.

deficiencies, including with new evidence directly on point. Confirming that the Board's decision was correct, Dr. Cima testified that Cai's separate Fig. 3 experiment contacted "each different population" with "at most one single particle type," and specifically that Cai's MWCNTs in the Fig. 3 SILAC experiment do not provide different particle types as required. EX2023, ¶¶54-55, 61; EX1005, 586. But Petitioners have nothing to say in response (other than to ask the Board to ignore this deficiency). Reply 18. Petitioners submitted no reply testimony. They didn't even ask Dr. Cima a single question about this during cross-examination. Petitioners' mere attorney argument—asking for summary dismissal without countervailing evidence—provides no reason to reject Dr. Cima's testimony or to revisit the same failed argument on a record that is only worse for them.

B. Ground 3 Fails to Remedy the Deficiencies of Ground 2.

Curiously, Petitioners assert the POR fails to dispute the obviousness of modifying Cai. Reply 21-22. They are wrong. The POR identified multiple deficiencies in the asserted obviousness case. POR 35-36. For example, the petition never identified prior art disclosure of the missing claim elements (e.g., assaying to detect, in the subset, proteins in the biological sample across a dynamic range comprising at least six orders of magnitude). Converting pull-down emPAI values into pull-down concentration values does not remedy these deficiencies. *See, e.g.*, Section II.A above.

Nor can Petitioners remedy missing claim limitations by vaguely invoking general knowledge. Pet. 63-64 (“motivated to search out protein concentrations... calculable from Cai’s data and a POSA’s knowledge”). Neither Petitioners nor its expert ever “searched out” or calculated a concentration for any detected protein “in the biological sample,” as recited in the claims. Regardless, both statute and regulation prohibit supplying missing claim limitation from notions of general knowledge without identifying actual prior art disclosure. 35 U.S.C. §311(b) (“patents or printed publications”); 37 C.F.R. §42.104(b)(4) (same); July 31, 2025 USPTO Memo, at 1 (“evidence that is not ‘prior art consisting of patents or printed publications’ (collectively, ‘general knowledge’) may not be used to supply a missing claim limitation.”). The Reply’s new argument (at 22) alleging it “would be trivially easy” to replace Cai’s HeLa cells with “other types of samples” is conclusory and not found in the petition. As such, the Board should find that Ground 3 fails.

C. Ground 1 Indisputably Fails at the Claimed Assaying Step (1[c])

Conceding no express disclosure of element 1(c) in Hu, the petition instead argued inherency based on two particular proteins (albumin and LTBP1)—pointing to unrelated Ahmed and Cao as somehow indicating inherently present concentrations of those proteins in Hu. POR 42, 46; EX1003, ¶161 (“this is inherently disclosed by Hu”). That inherency theory, however, collapses in view of

multiple facts unrebutted in the Reply or simply undisputed. POR 42-49.

1. The Reply Does Not Dispute Skepticism of LTBP1 Detection

As explained in the POR, the petition relied upon a particular entry for “LTBP-1” in the raw data table in Hu’s supplement but offered no analysis and ultimately failed to establish actual detection. POR 43-46. Dr. Cima critically reviewed the reference and provided a detailed, evidence-based explanation why a POSA would view the entry as more likely experimental error or artifact rather than a detection event. Petitioners did not ask Dr. Cima a single question about this during deposition and offer no rebuttal testimony here. The Reply (at 23) argues this “fails on its face” because an entry for LTBP-1 exists. Such conclusory and circular argument does not amount to meaningful rebuttal. As such, the evidence and argument in the POR is not in serious dispute—the petition uncritically cited an entry in Hu but failed to demonstrate actual detection of LTBP-1.

2. Ground 1 Indisputably Fails to Establish LTBP1 Concentration in Hu

First, PO explained that the petition’s “normally present” argument is both unsubstantiated and insufficient as a matter of law to establish inherency. POR 46-47. Even if considered (and even assuming *arguendo* actual LTBP1 detection in Hu), Petitioners failed to establish either “normally present” protein concentrations or concentrations in the Hu material. POR 47. Dr. Cima explained other references (e.g., Atlas database) report protein concentrations that, if reflective of “normally

present,” would destroy the petition’s “six orders of magnitude” argument. POR 48-49. The Reply doesn’t even address this point, let alone rebut it. As such, besides being legally misplaced, the petition’s “normally present” argument is unsubstantiated.

Second, there is no dispute that Ahmed and Cao fail to disclose protein concentrations for Hu. The references are unrelated and there are various reasons Hu is not even comparable to either Ahmed or Cao. POR 48-49. Petitioners dispute none of these points. Reply 24-25. PO also explained that Hu and Cao are not even addressing the same protein. POR 47-48. Petitioners do not dispute that either. Reply 24-25.

Finally, Petitioners’ retreat to “general knowledge,” and argument “it was routine for a POSA to look up” protein concentrations in a database, do not salvage the failed inherency case. As discussed above, general knowledge is unavailable to supplement claim elements missing from the published art. *See* 37 C.F.R. §42.104(b)(3). Furthermore, unlike Petitioners, Dr. Cima did “look up” protein concentrations in the Atlas database, which contradict the theory advanced in the petition, and the Reply offers no rebuttal. The undisputed failure of the asserted prior art to disclose the claimed subject matter of element 1(c) provides sufficient reason that Ground 1 fails as to all challenged claims.

D. Ground 4 Indisputably Fails at the Claimed Assaying Step (1[c])

Similar to Ground 1, there is no serious dispute in Ground 4 that Zaccaria fails to disclose the “concentration in the sample” element, for which purpose the petition turns to Bryk. POR 55. Ground 4 is barely discussed in the Reply (at 25-26), leaving much of the POR argument and evidence unaddressed.

First, while the petition relies on specific proteins (e.g., “lower abundant” SBF1), it failed to establish actual detection of these particular proteins in Zaccaria. POR 55-60. For example, Zaccaria identifies multiple accession numbers for each identified entry, making SBF1 merely one of several “theoretical peptides possible.” POR 1, 58-59; EX1003, ¶39. Petitioners fail to dispute this. Reply 25-26. Dr. Cima’s detailed testimony discussing, *inter alia*, weak and non-reproduced signal (EX2023, ¶¶112-118) is simply ignored in the Reply.

Second, there is no dispute that Bryk fails to disclose the concentrations in the material of Zaccaria. PO explained that the petition’s “normally present” argument is insufficient as a matter of law to establish inherency. POR 60-63. Even if considered, Petitioners failed to prove that Bryk establishes protein concentrations in the Zaccaria material. POR 63. Indeed, different preparation and analysis methods materially alter concentration values, and Zaccaria uses materially distinct approaches as compared to Bryk. POR 63. Moreover, PO also explained that Zaccaria and Bryk are not necessarily even addressing the same

protein (allegedly SBF1) because Zaccaria identifies multiple accession numbers for that identified entry, making SBF1 nothing more than just one possibility among others. POR 58-59. Petitioners dispute none of this. Reply 25-26. Indeed, this issue was lost on both Petitioners and their expert, who didn't even consider that Zaccaria's disclosure of multiple different accession numbers indicated uncertainty as to which protein, if any, was actually detected. POR 60.

The un rebutted failure of the asserted prior art to disclose the claimed subject matter of element 1(c) provides sufficient reason that Ground 4 fails as to all challenged claims.

III. ALL GROUNDS FAIL AT THE CLAIMED SEPARATION STEP

None of the asserted references discloses separation from the biological sample of a single subset comprising the coronas (plural) corresponding to the different particle types. POR 28-32 (Cai Ground 2), 36 (Cai Ground 3), 38-42 (Hu Ground 1), 54-55 (Zaccaria Ground 4). As explained in the POR, all challenged claims obtain the subset of proteins that are assayed in step 1(c) by (in step 1(b)) separating from the biological sample *a* subset (singular) ***of the plurality of particles*** comprising ***the coronas*** (plural). POR 15-20. The petition does not propose or justify construing limitation 1(b) to be satisfied when only the corona from a single particle type is separated into the subset. Nonetheless, Petitioners argue "limitation 1(a)" is satisfied when "samples are incubated individually in

parallel.” Reply 9-12, 15-18, 23, 25. But Petitioners’ arguments about 1(a) are non-responsive to 1(b), and are premised on repeated mischaracterizations.

First, Petitioners argue that PO is proffering “[a] disfavored negative limitation” and that the word “subset” alone does not require a representative subset. Reply 9-10. But the word “subset” does not appear alone in the claim. The requirement to have a single subset comprising “the coronas” from the multiple particle types is an affirmative requirement of the claim language. Petitioners’ contrary reading renders the words “the coronas” in element 1(b) entirely superfluous. If Petitioners are correct, element 1(b) could have been written (and would have the meaning proffered by Petitioners) by striking out the words “comprising the coronas.” The Reply never squarely addresses “the coronas” language and provides no justification for rendering these claim words a nullity.

Second, Petitioners mischaracterize Dr. Cima as agreeing that the word “subset” in the claim means the subset is satisfied by separating only a single particle type. Reply 10 (citing EX1036, 70:3-14). Petitioners’ counsel specifically confined this line of questioning to contexts divorced from the claim. EX1036, 67:7-12 (asking about subset “outside the context of the ’360 patent”), 67:15-68:13 (answering about “mathematical definition of a subset”), 68:19-15 (counsel not interested in meaning “when I look at the claim”).

Yet, both Drs. Vargas and Cima testified that the words “the coronas” in

element 1(b) invoke ***the coronas*** corresponding to different particle types from element 1(a). POR 15-20; EX2023, ¶¶45-46 (Dr. Cima); EX2022, 26:6-27:2 (Dr. Vargas: “Q. You agree that those are both two requirements for what the claim calls ‘the coronas,’ correct? A. Yes.”); *see also* EX2022, 27:21-28:3 (Q. “[D]o you believe that the coronas in element 1B did not have to satisfy the requirements of the coronas in step 1A? A. I think they have to satisfy 1A....”), 28:22-29:7 (Q. “So you’re saying there, there needs to be at least two particle types; is that correct? A. The plurality of particles, operationally, how you do this is that it would be [at least two] types.”). Again, the Reply never squarely addresses the claim language, including “the coronas,” its own expert’s admission, or the corresponding argument in the POR. The petition challenge can be rejected for this independent reason alone.

Ultimately, Petitioners abandon discussion of the language of claim 1 and pivot to arguing about one figure in the challenged patent (Figure 65). Based solely on attorney argument, the Reply argues Figure 65 “shows the claimed subset can take the form of a plurality of different vials incubated in parallel—just as Cai discloses.” Reply 10-11, 16-17 (acknowledging at 11 Dr. Cima’s testimony “allowing for only a single particle type per ‘***circle***”). To the extent this misplaced argument is entertained, Petitioners identify no evidence that Fig. 65 depicts the claimed subset in different “vials” incubated in parallel.

Petitioners' new and misplaced theory about Fig. 65 is not supported by Dr. Cima's testimony. On the very page Petitioners cite, Dr. Cima testified that Fig. 65 depicts "that sample [singular] can be incubated with the entire sensor array, which is composed of a plurality of particles with different physicochemical properties." EX1036, 73:1-4. This is precisely what the patent specification describes. EX1001, 21:30-33 ("at step 3 of Fig. 65, **a complex biological sample** [singular] (e.g., plasma 706) can be **incubated with a sensor array 710** comprising a plurality of particles 712 with **different physicochemical properties**"), 21:36-41 ("as shown in step 4 of Fig. 65, the biomolecules (e.g., proteins) bound to the particles 712 can be isolated in **a protein solution 714** for further analysis, for example, to determine the compositions of the proteins bound to **each type of particle 712** (e.g., anionic, neutral, and cationic particles 712)"). Contrary to Petitioners' unsupported contention, Fig. 65 does not disclose separately incubating individual particle types with the biological sample in individual vials.

Because Petitioners failed to prove for each ground that there is separation of a singular subset of proteins comprising the coronas corresponding to multiple particle types, each of Grounds 1-4 should be rejected.

IV. ALL GROUNDS FAIL REGARDING "BIOLOGICAL SAMPLE"

All grounds fail to prove the materials mapped by the petition satisfy the patent's definition of "biological sample." The patent defines "biological sample"

as being obtained from an individual subject. POR 13-14; EX1001, 20:33-34 (“The term ‘sample’ refers to a biological sample or a complex biological sample **obtained from a subject.**”), 50:26-36 (“The terms ‘**individual,**’ ‘subject,’ and ‘patient’ are used interchangeably herein”). For Cai (Grounds 2-3), there is no genuine factual dispute that HeLa cells are obtained from a highly-mutated, immortalized cell line rather than a biological sample obtained from an individual subject. POR 23-24. For each of Hu and Zaccaria (Grounds 1 and 4, respectively), there is no factual dispute that Petitioners mapped to a mixture rather than a biological sample obtained from an individual subject. POR 38, 53.

The Reply argument is remarkably disconnected from the record evidence—this includes both the testimony of its own expert (e.g., identifying an express definition) and Petitioners’ own cited exhibits. For Cai, Petitioners frivolously argue that various HeLa cell lysates satisfy the express definition because, allegedly, “[e]very so-called ‘HeLa cell’ is **a direct, genetically identical copy of the original cells** that were taken directly from Ms. Lacks.” Reply 5 (citing EX1037, 3); *see also* Reply 12 (“All HeLa cells are direct copies of cells obtained from Ms. Henrietta Lacks.”). This argument is so blatantly false it constitutes sanctionable conduct. 37 C.F.R. §§42.11, 11.18 (authorizing sanctions for advancing frivolous argument).

Indeed, the falsity of Petitioners’ assertions is confirmed by the very source

Petitioners cite on the same page of the Reply. Reply 5 (“There are *many strains of HeLa cells as they continue to mutate in cell cultures...*” (quoting EX1037, 3). This also was addressed by Dr. Cima, both in his direct testimony and during cross-examination, where he cited evidence demonstrating that HeLa cells are laboratory engineered and bear no resemblance to whatever was derived from the original donor many decades ago. EX2026 (“a HeLa genome is no longer a human genome.”); EX1035, 82:1-15 (discussing EX2026 stating “[t]he HeLa genome is no longer Henrietta Lacks personal genome”), 83:9-20 (Q: You mentioned Dr. Heng [EX2026] saying the HeLa cells have 70 to 90 chromosomes; correct? A: That’s right. Q: Are you aware of any human being that has 70 to 90 chromosomes? A: No.”). It is unclear why Petitioners would advance argument they know is demonstrably incorrect.

Beyond mischaracterizing facts and record evidence, Petitioners ask the Board to ignore what its own expert identified as an express definition. Reply 1-9, 12-13. Petitioners do not rebut the case law requiring application of an express definition. POR 13-14. Petitioners’ own expert agreed that the patent itself provides this definition. POR 14; EX2022, 33:3-36:9, in particular at 35:25-36:9 (Dr. Vargas: first lines of paragraph “set up the definition and after that there are specific examples”), 36:10-37:8 (Dr. Vargas confirming). Dr. Cima agrees. EX2023, ¶¶43-44 (Dr. Cima); EX1036, 78:10-79:14 (“I don’t see a difference, any

light between our interpretations.”). There can thus be no genuine question that the specification expressly defines the claimed “a biological sample” to be “a biological sample obtained from a subject.”

In the face of uncontradicted agreement between both parties’ experts, Petitioners attempt to manufacture a false dispute by using misleading deposition tactics and by mischaracterizing the testimony obtained thereby. In particular, Petitioners mischaracterize Dr. Cima as agreeing that any “cells derived from humans meet the patent’s definition of ‘biological sample,’” and that “HeLa cells thus satisfy the patent’s definition of biological sample because they are derived from Ms. Lacks.” Reply 5-6, 12-13 (EX1036, 40:13-41:9, 39:10-14, 41:15-17, 57:9-11, 81:20-22). That is demonstrably false.

Dr. Cima never testified that any mutated or mixed material qualified as a biological sample so long as it descended from a patient. He certainly never testified that HeLa cells qualify. In response to Petitioners’ own questioning, Dr. Cima repeatedly rejected Petitioners’ attorney argument that HeLa cells qualify as the biological sample. *See, e.g.*, EX1036, 61:4-21 (“the limit [the patent] puts is that the sample has to be **from a donor...**”), 49:7-20 (“The patent contemplates **taking a sample from a patient** and processing those cells.”), 49:22-51:18 (“I’ll give you **a case where it’s not [a biological sample]** as decided by the ’360 patent”; **HeLa cells** are “immortalized cancer cells...they’re famously, **literally**

famously, different than the sample taken from the patient... So they are not the same as the biological sample taken from a subject.”), 51:20-53:14 (“each time it divides, *it gets more and more different.*”), 55:18-20 (HeLa cell “*doesn’t really represent the cancer* that the original donor had”), 56:2-7 (“they have been passaged so many different times that they *bear no resemblance to the original...* cells obtained from the donor”), 60:1-12 (“those cells are *not from the donor.* They are *different from the cells taken from the donor.* That’s my point....”), 61:22-62:10 (“As well as the fact that *the cells are different from what was originally taken.*”); see also EX1036, 61:4-21, 45:17-49:20, 53:15-54:22.

During Dr. Cima’s deposition, Petitioners’ counsel improperly attempted to elicit a “gotcha” by repeating the same ill-conceived questions while refusing access to underlying documents. EX1036, 36:22-37:21 (“*if I were allowed to look at it*, I would give you a more complete answer.”), 34:22-35:7, 38:12-21 (“But *that’s not the complete story.* So I’m very hesitant to create a record that is going to allow you to put words in my mouth.”), 35:8-22 (MR. BOSCO: I’m asking him to *answer the question without looking at the document.*”). Confirming Petitioners had little interest in discussing claim terms in light of the specification, as legally required, Petitioners’ counsel expressly instructed Dr. Cima to actually ignore their context in the patent. EX1036, 35:2-38:9, in particular at 38:2-9 (“So my question was just about the plain meaning, not what the patent said...”), 39:2-

41:9 (“I didn’t ask him for the context of the patent.”), 39:2-16 (“MR. BOSCO: I’m going to move to strike that as non-responsive.”). Petitioners’ mischaracterizations of answers to plainly objectionable questioning during deposition—that they moved to strike—do not support their argument.

Petitioners attack a strawman in arguing that the ’360 patent identifying “cell lysates” as “exemplary ‘biological sample[s]’” should “end the debate.” Reply 4 (citing EX1001, 20:34-39), 5-7. PO never argued that a cell lysate is *per se* excluded as a biological sample. Rather, HeLa cells are a laboratory engineered, immortalized cell line—not anything obtained from a subject. This is true whether referring to intact HeLa cells or their lysates. EX1036, 62:11-65:2, in particular at 64:17-65:2 (explaining the listed examples must be “obtained from *a* subject” or “from *a* patient”). Even Petitioners acknowledge that status of lysate refers to a “preparation” process applied to the obtained material. Reply 4 n.4. The fact that the specification lists materials that can be a biological sample when obtained from an individual subject does not negate what Petitioners’ own expert agrees is an express definition.

Finally, Petitioners argue it would be improper to read an embodiment into the claims because the claims do not mention “subjects or patients whatsoever.” Reply 8. This argument is misplaced as reading in an embodiment is not proposed and is different than giving effect to what Petitioners’ own expert agrees is the

definition in the '360 patent specification. Applying an express definition is not only legally permissible, it is required. The Reply fails to show otherwise.

V. PETITIONERS' REPLY ATTEMPTS TO DISTRACT FROM THEIR OWN EXPERT'S LIMITED QUALIFICATIONS

Cross-examination confirmed that much of the asserted prior art lacked critical analysis in the petition materials. For example, Dr. Vargas overlooked basic details, like that Zaccaria didn't actually report detection of SBF1 or PIK3R4, but instead listed those proteins as one possibility among several others. In fact, Dr. Vargas didn't know what an accession number was. EX2022, 58:21-24; EX2023, ¶¶112, 117. In other words, Zaccaria doesn't know what protein was detected, and neither do Petitioners. PO was right to call attention to her limited qualifications and question the weight to afford her testimony, and the record substantiated those concerns.

In Reply, Petitioners attempt to change the subject by criticizing Dr. Cima. But their criticism is misguided, premised on factual mischaracterizations, and doesn't even make sense. Reply 26 (curiously arguing Dr. Cima is not a molecular biologist when presenting a polymer chemist as their witness). Dr. Cima's relevant experience in proteomics is extensive and not in dispute. EX1036, 18:3-19:2 (counsel cutting off Dr. Cima discussing relevant experience), 20:7-21:19, 33:2-12 (prior testimony as analytical chemist relevant to molecular biology and mass spec), 23:4-29:7 (research appointment at Koch cancer research institute); *see also*

EX2024; EX2023, ¶¶1-9. Petitioners' criticisms are illogical and just an attempt to distract from the lack of merits in their case and the limited qualifications of their own expert.

VI. CONCLUSION

The challenged claims should be affirmed.

Respectfully submitted,

Date: December 10, 2025

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

CERTIFICATE OF COMPLIANCE

Pursuant to §42.24(d), the undersigned certifies that this paper contains no more than 5,600 words, not including the portions of the paper exempted by §42.24(b). According to the word-processing system used to prepare this paper, the paper contains 5,532 words.

Respectfully submitted,

Date: December 10, 2025

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CERTIFICATE OF SERVICE

I certify that the foregoing Patent Owner's Sur-Reply was served on
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