UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PREOMICS GMBH AND BIOGNOSYS AG.,

Petitioners,

v.

THE BRIGHAM AND WOMEN'S HOSPITAL, INC.,

Patent Owner.

Case No. IPR2024-01473

Patent No. 11,435,360

PETITIONER'S REPLY

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PETITIONER'S UPDATED EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 11,435,360
1002	File History of U.S. Patent No. 11,435,360 (*excerpts*)
1003	Declaration of Dr. Jessica Vargas
1004	*Curriculum Vitae* of Dr. Jessica Vargas
1005	Cai *et al.*, "Characterization of Carbon Nanotube Protein Corona by Using Quantitative Proteomics," *Nanomedicine: Nanotechnology, Biology and Medicine* 9 (2013) 583-593, with its supplementary data (Table S2) ("*Cai*")
1006	Walkey *et al*., "Protein Corona Fingerprinting Predicts the Cellular Interaction of Gold and Silver Nanoparticles," *ACS Nano* 8 (2014) 2439-2455 ("*Walkey*")
1007	Zaccaria *et al*., "Accessing to the Minor Proteome of Red Blood Cells Through the Influence of the Nanoparticle Surface Properties on the Corona Composition," *International Journal of Nanomedicine* 10 (2015) 1869-1883, with its Supplemental Materials ("*Zaccaria*")
1008	Hu *et al*., "Nanoparticle Size Matters in the Formation of Plasma Protein Coronas on Fe_3O_4 Nanoparticles," *Colloids and Surfaces B: Biointerfaces* 121 (2014) 354-361, including Appendix A (Table S1) ("*Hu*")
1009	Bryk *et al*., "Quantitative Analysis of Human Red Blood Cell Proteome," *Journal of Proteome Research* 16 (2017) 2752-2761, including supporting information ("*Bryk*")
1010	Hajipour *et al*., "Personalized Protein Coronas: a "Key" Factor at the Nanobiointerface," *Biomaterials Science* 2 (2014) 1210-1221 ("*Hajipour*")
1011	U.S. Patent No. 10,866,242 ("*Farokhzad*")
1012	Declaration of Nancy Adams
1013	*Curriculum Vitae* of Nancy Adams
1014	Nanjappa *et al*., "Plasma Proteome Database as a Resource for Proteomics Research: 2014 Update," *Nucleic Acids Research* 42 (2014) D959-D965 ("*Nanjappa*")
1015	Ahmed, "Sample Preparation and Fractionation for Proteome Analysis and Cancer Biomarker Discovery by Mass Spectrometry," *Journal of Separation Science* 32 (2009) 771-798 ("*Ahmed*")

Exhibit No.	Description
1016	Cao *et al*., "Latent Transforming Growth Factor-Beta Binding Protein-1 in Circulating Plasma as a Novel Biomarker for Early Detection of Hepatocellular Carcinoma," *International Journal of Clinical and Experimental Pathology* 8(12) (2015) 16046-16054 ("*Cao*")
1017	U.S. Provisional Patent Application No. 62/435,409 ("the '409 Provisional")
1018	Ishihama *et al*., "Exponentially Modified Protein Abundance Index (emPAI) for Estimation of Absolute Protein Amount in Proteomics by the Number of Sequenced Peptides per Protein," *Molecular & Cellular Proteomics* 4.9 (2005) 1265-1272 ("*Ishihama*")
1019	U.S. Patent No. 8,796,184 ("*Chilkoti*")
1020	Archival website for http:/www.plasmaproteomedatabase.org/faq.html as of Feb. 19, 2015, *available at* https://web.archive.org/web/20150219211334/http:/www.plasmaproteomedatabase.org/faq.html
1021	Dean, L. "Blood Groups and Red Cell Antigens," Chapter 1: Blood and the cells it contains, Bethesda (MD): National Center for Biotechnology Information (US) (2005), *available at* https://www.ncbi.nlm.nih.gov/books/NBK2263/.
1022	Norouzi, N. *et al*., "Sorting cells by their density," PLoS ONE, 12(7):e0180520 (2017) ("*Norouzi*")
1023	Archival website for https://www.ncbi.nlm.nih.gov/books/NBK2261/ as of Mar. 20, 2014, *available at* https://web.archive.org/web/20140320071602/https://www.ncbi.nlm.nih.gov/books/NBK2261/

Exhibit No.	Description
1024	Graves *et al*., "Molecular Biologist's Guide to Proteomics," *Microbiology and Molecular Biology Reviews 66*(1), (2002) 39-63 ("*Graves*")
1025	Berg *et al*., *Biochemistry, Sixth Edition*. W.H. Freeman and Company (2007) (*excerpts*) ("*Berg*")
1026	McDonald *et al*., "Shotgun Proteomics and Biomarker Discovery," *Disease Markers* 18(2), (2002) 99-105 ("*McDonald*")
1027	Aebersold *et al*., "Mass Spectrometry-Based Proteomics," *Nature* 422(6928), (2003) 198-207 ("*Aebersold*")
1028	Yates *et al*., "Proteomics by Mass Spectrometry: Approaches, Advances, and Applications," *Annual Review of Biomedical Engineering* 11(1) (2009) 49-79 ("*Yates*")
1029	Feist *et al*., "Proteomic Challenges: Sample Preparation Techniques for Microgram-Quantity Protein Analysis from Biological Samples," *International Journal of Molecular Sciences* 16(2) (2015) 3537-3563 ("*Feist*")
1030	Szabo *et al*., "Challenges and Developments in Protein Identification Using Mass Spectrometry," *Trends in Analytical Chemistry* 69 (2015) 76-87 ("*Szabo*")
1031	Bantscheff *et al*., "Quantitative Mass Spectrometry in Proteomics: A Critical Review," *Analytical and Bioanalytical Chemistry*, 389 (2007) 1017-1031 ("*Bantscheff*")
1032	Harris, D. *Quantitative Chemical Analysis, Seventh Edition*. W.H. Freeman and Company (2007) (*excerpts*)
1033	[*served not filed*] Second Declaration of Nancy Adams
1034	[*served not filed*] Declaration of Mina Ching
1035	Declaration of Stephen P. Bosco
[*New*] 1036	Deposition Transcript of Michael J. Cima, Ph.D.
[*New*] 1037	Dr. Ma Hongbao, "Hela Cells and Immortality," Cancer Biology 2017;7(3)
[*New*] 1038	Anna MacDonald, "HeLa Cells: Key Discoveries & the Science of Their Immortality," Technology Networks
[*New*] 1039	M. Islam et al., "A Review on Macroscale and Microscale Cell Lysis Methods," Micromachines 2017, 8, 83
[*New*]	Merriam-Webster's Collegiate Dictionary, 11th Edition (2005),

Exhibit No.	Description
1040	definition of "subset"
[*New*] 1041	Notice of Allowance from U.S. App. No. 18/644,619 (annotated)

Petitioner submits this Reply to Patent Owner's Response (Paper 18, "POR"). Unable to meaningfully challenge the Petition's mapping of the prior art to the claims on the merits based on the plain meaning of the claims, Patent Owner resorts to extreme, hyper-narrow claim constructions that lack any support in the claim language or specification. The Board already expressed its "concerns" that Patent Owner's attempts to distinguish the prior art relied on an "overly-narrow interpretation of claim 1." Paper 11 ("ID"), 26. Rather than heeding that warning, Patent Owner doubles down on the same failed arguments. Accordingly, the Board should issue a Final Written Decision holding all challenged claims unpatentable for the reasons set forth herein and in the Petition.

I. CLAIM CONSTRUCTION

a. "biological sample"

Patent Owner contends that "the petition fails to give effect to what both parties' experts agree is an express definition in the specification for the claim term 'a biological sample.'" POR, 13. Not so. The Petition is entirely consistent with the specification's expansive description of what qualifies as a "biological sample." The specification states that "[t]he term 'sample' refers to a biological sample or a complex biological sample obtained from a subject." EX1001, 20:33-34. The specification then explains what the term "biological sample"—the actual claim term in question—means in the context of the patent, stating that "[s]uitable biological

samples include, but are not limited to, biological fluids, including, but not limited to, systemic blood, plasma, systemic blood, plasma, serum, lung lavage, cell lysates, menstrual blood, urine, processed tissue samples, amniotic fluid, cerebrospinal fluid, tears, saliva, semen and the like." EX1001, 20:34-40; *see also* 21:14-29; cl. 22; Pet., 23. Notably, during his deposition, Patent Owner's expert Dr. Cima testified that it was this broad second sentence that "defines biological sample."[1] EX1036, 63:19-64:7 ("A. ***So the second sentence defines biological sample***; right.").[2] In so doing, Dr. Cima simply confirmed what would have been plain to a POSA—that anything identified in the '360 Patent's list of exemplary "biological samples" satisfies the claim requirement for a "biological sample." All of the prior art samples that

[1] Dr. Cima attempted to walk back this admission in redirect testimony that he admittedly discussed with his attorney (EX1036, 84:2-85:17) but these glaring contradictions in his testimony only underscore the unreliability of his opinions. *See Interactive Commc'ns Int'l, Inc. v. Blackhawk Network Inc.*, IPR2024-00465, Paper 40, 3 (Director Oct. 9, 2025) ("The Board abused its discretion by improperly crediting expert testimony that has multiple material contradictions and that the Board found lacked credibility at least in certain respects.").

[2] All emphasis supplied unless otherwise noted.

Petitioner identified in the Petition plainly qualify as "biological samples" under the patent's broad disclosure.

Recognizing this, Patent Owner attempts to distinguish the prior art by injecting two artificially narrow, negative limitations into the definition that would improperly exclude embodiments in the specification.[3] Specifically, Patent Owner claims that because the specification says "'sample' refers to a biological sample … obtained from ***a subject***," that excludes "a lysate taken from an immortalized cell line that is engineered and grown in a laboratory (e.g., Cai's HeLa cell populations) rather than obtained from a subject." POR, 14 (emphasis in original). Patent Owner next contends that the same "obtained from a subject" language somehow "excludes a mixture of materials from different donors," a negative limitation that according to Patent Owner would, conveniently, exclude "Hu and Zaccaria." POR, 14. Neither of

[3] Patent Owner repeatedly and misleadingly insinuates that Petitioner's expert Dr. Vargas endorsed Patent Owner's artificial negative limitations. *See, e.g.*, POR, 24, 38. In fact, Dr. Vargas merely acknowledged that lines 33 through 45 of column 20 of the '360 Patent appeared to provide a definition for "sample" followed by specific examples of biological samples that satisfied that definition. EX2022, 35:16-36:9. Dr. Vargas was never asked about and never endorsed the extreme, hyper-narrow claim interpretations that Patent Owner proffers in the POR.

these contrived, litigation-inspired negative limitations has any basis in the '360 Patent's text or the relevant technology.

First, Patent Owner's attempt to exclude Cai's "HeLa" cells cell lysates fails at the outset because the '360 Patent specifically identifies "cell lysates" as exemplary "biological sample[s]." EX1001, 20:34-40; 21:14-29; cl. 22. As the Petition and Dr. Vargus explained, Cai discloses, for example, that (i) its method uses "a ***cell lysate prepared from the human cell*** line HeLa," and (ii) the "[p]roteins from HeLa cells were chosen because they provide ***a representative source of the human proteome***." EX1005, 585; EX1003 ¶184; *see also* EX1005, 591 ("A complete protein lysate of HeLa cells was used as an archetypal human proteome…."). This is just like the '360 Patent's disclosure, which expressly ***includes*** "cell lysate"[4] as an example "biological sample." EX1001, 20:34-40; 21:14-29; cl. 22. That alone should end the debate.

Second, even if the language "obtained from a subject" limits the definition of "biological sample," Patent Owner's argument fails because HeLa cells ***are*** "obtained from a subject" and squarely fit within the claimed "biological sample"

[4] A "cell lysate" is the preparation obtained after lysing a cell population using one of many known lysis methods, including mechanical means, chemical reagents and enzymes, and osmotic shock. *See* EX1038, 4-10.

consistent with the '360 Patent's disclosure. Notably, despite its attempt to carefully exclude HeLa cells from the scope of "biological sample," ***Patent Owner provides virtually no information in the POR about what HeLa cells actually are***. It is easy to see why. Basic information about HeLa cells establishes that they are "obtained from a subject" under any reasonable understanding of that term.

The term "HeLa" is shorthand for the name of the individual subject from whom ***all*** "HeLa" cells derive—Ms. Henrietta Lacks. Every so-called "HeLa cell" is a direct, genetically identical copy of the original cells that were taken directly from Ms. Lacks. EX1037, 3. HeLa cells are thus not engineered or human-created cells—***HeLa cells are Ms. Lacks' cells*** that have simply been kept alive and self-sustaining ever since they were first obtained from her in 1951. EX1037, 3 ("HeLa cells, like other cell lines, are termed immortal in that they can divide an unlimited number of times in a laboratory cell culture plate as long as fundamental cell survival conditions are met. There are many strains of HeLa cells as they continue to mutate in cell cultures, but ***all HeLa cells are descended from the same tumor cells removed from Lacks***."); EX1038, 2 ("[S]amples of cancerous tissue were taken from [Ms. Lacks'] cervix. These cells went on to become the immortal cell line known as HeLa.").

That the HeLa cell line has been preserved and processed through laboratory means does not change the analysis. Notably, the specification language that Patent

Owner relies upon does not say that a biological sample must be ***directly*** obtained from a subject. Further, Patent Owner's expert Dr. Cima testified that "in the context of this patent" a "biological sample" is "a sample ***derived from*** a patient." EX1036, 40:13-41:9; 39:10-14 ("…the biological sample in the claim is meant to be ***a sample derived from*** a subject or patient"); 41:15-17 ("The patent contemplates samples ***derived from*** a subject or a patient."). And Dr. Cima also expressly agreed that "Henrietta Lack[s] is the original donor from whom all HeLa cells ***derive***." EX1036, 57:9-11; 81:20-22. Thus under Dr. Cima's own characterization of the scope of "biological sample," HeLa cells indisputably qualify.

Further, Patent Owner's contention that a "biological sample" is "limited by definition to ***what is obtained from an individual subject*** or patient" (POR, 14 (emphasis modified)) is contrary to established scientific practice. Raw, unprocessed samples taken directly from patients are almost never used in the type of assays disclosed and contemplated in the '360 Patent—as Dr. Cima's own testimony demonstrates. EX1036, 43:8-44:7 (extensive processing occurs before samples can be used in techniques like mass spectrometry). It is thus unsurprising that the '360 Patent specification expressly contemplates extensive "process[ing]" of biological samples, including "centrifug[ing]," "minc[ing]," and "treat[ing] with enzymes." EX1001, 20:33-60; *see also, e.g.*, *id.* & cl. 22 ("biological sample" may be "*processed* tissue samples").

Patent Owner's hyper-narrow reading of the phrase "obtained from a subject," under which a "biological sample" must be the precise material "obtained from" a particular subject, would improperly read out embodiments the specification expressly encompasses. *See, e.g.*, *Epos Techs. Ltd. v. Pegasus Techs. Ltd.*, 766 F.3d 1338, 1347 (Fed. Cir. 2014) ("A claim construction that excludes a preferred embodiment is rarely, if ever[,] correct…"(citation modified)). Plainly, the HeLa cells used in Cai are "biological samples"—they are from a still-living cell line obtained from Ms. Lacks. Patent Owner's proposed negative limitation excluding Cai's HeLa cells from the term "biological sample" is meritless.

Equally unavailing is Patent Owner's attempt to exclude "a mixture of materials [obtained] from different donors" from "biological sample." Patent Owner attempts to read this negative limitation into the claims based on the unremarkable statement that a "'sample' refers to a biological sample or a complex biological sample obtained from ***a subject***," and asserts that it excludes the "pooled blood plasma or RBCs in Hu and Zaccaria, respectively." POR, 14. This argument fails for multiple reasons.

First, the biological samples that the Petition relied upon in Hu and Zaccaria are expressly included in the specification's list of "[s]uitable biological samples." EX1001, 20:34-39; Pet., 23 (explaining how the "human blood plasma proteins" in Hu are within the '360 Patent's exemplary "biological samples"); Pet., 64 ("Zaccaria

discloses a method of assaying blood samples (more particularly, RBC lysates or hemolysates)"). As noted above, a POSA would understand that any biological sample identified in the '360 Patent's enumerated list of "[s]uitable biological samples" is a "biological sample" within the scope of the claims—as both experts agree. EX1036, 63:19-64:7; EX1003 ¶¶49, 127, 133, 197. Patent Owner's attempt to manufacture a requirement that the claimed method have "the ability to assay a biological sample ***from any given subject***" (POR, 14) is a classic attempt to read an embodiment from the specification into the claims—the proverbial "cardinal sin" of patent law. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1320 (Fed. Cir. 2005) (*en banc*). Nothing in the claims or specification requires the output of the claimed method to be traceable to a particular individual, and there is no basis for reading into the '360 Patent's broad disclosure any prohibition against pooling of samples.

Further, nothing in the specification language "obtained from a subject" requires that the sample be derived from ***one and only one*** subject. Significantly, the ***claims*** include no mention of subjects or patients whatsoever, much less provide any indication that the quantity of individuals from whom the biological sample derives has any bearing. This is powerful evidence that the claims are not so limited. *See Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001) ("In construing claims, ***the analytical focus must begin and remain centered on the language of the claims themselves***..." (citation modified)). In short, there is

no basis in the claims or specification for reading Patent Owner's second proposed negative limitation into the readily understood term "biological sample," and no basis for concluding that biological specimens—like cell lysates and blood plasma—that the specification (and claims) expressly identify as "biological samples" are excluded from the scope of the claims.

b. "a subset of the plurality of particles comprising the coronas"

Patent Owner's contorted interpretation of this straightforward claim language fails as a matter of grammar. In the Institution Decision, the Board already expressly rejected Patent Owner's attempt to read limitations from limitation 1(a) into the straightforward claim language in limitation 1(b), (ID, 22) and the result should be no different in the FWD.

Patent Owner, again proffering a disfavored negative limitation, contends that the claimed "subset" excludes subsets that contain "only one particle type." POR, 15. This negative limitation fails as a matter of plain English and lacks specification support.

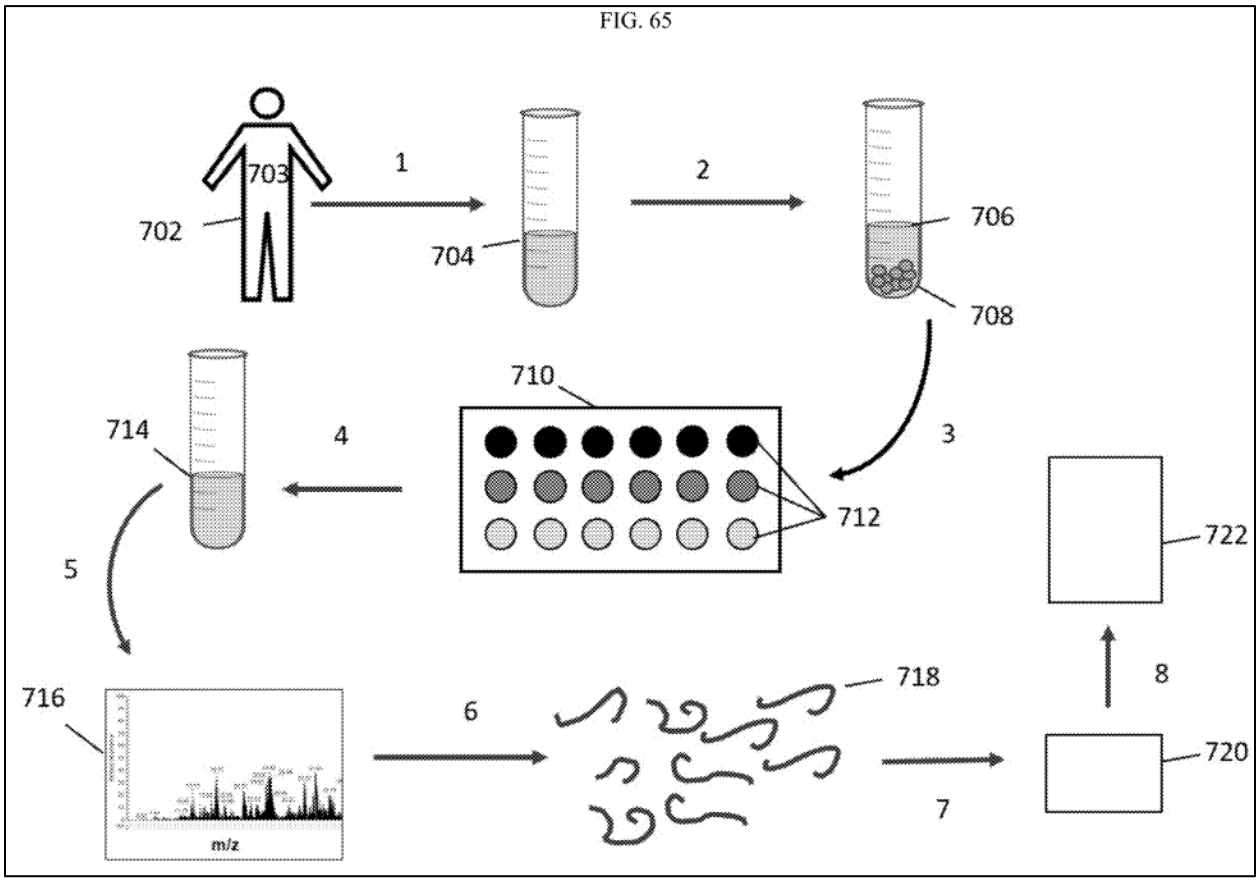
The claim language forecloses Patent Owner's narrow interpretation. It is undisputed that limitation 1(a) requires "a plurality of particles comprising different particle types" that "form coronas" that "differ based on particle type." Limitation 1(b) then requires "separating **at least a subset** of the plurality of particles comprising the coronas from the biological sample." Nothing in this language

requires or even suggests the claimed subset must comprise multiple particle types. In short, limitation 1(a) requires, *inter alia*, a group of particles of different types that facilitate formation of coronas of different types. Limitation 1(b) requires separation of at least one "subset" of that group of particles—there is no requirement whatsoever that the "subset" have all of the same characteristics as the set from which it is separated.

The lack of any such requirement is also definitional to the term "subset." *See* EX1040, 4 ("subset" is "a set each of whose elements is an element of an inclusive set"). Consider a claim that recites a plurality of particles called "Group Y" that consists of particle types A, B, and C, and then requires separating a subset of the particles in Group Y. Indisputably, absent some express language requiring a "representative subset" or a "subset containing multiple particle types," such a subset could contain particles of only type A, B, or C, as well as any combination. Dr. Cima agrees. EX1036, 70:3-14.

Patent Owner's proposed construction also lacks any specification support. Indeed, Patent Owner does not identify anything from the specification stating a subset must include multiple particle types. The one specification snippet it cites regarding "previous approaches limited to the surface of a single nanoparticle" (POR, 20 (citing EX1001, 19:65-20:2)) says nothing about whether the invention excludes subsets containing only one particle type. And Figure 65 of the '360 Patent

(below) shows an exemplary embodiment of a sensor array according to the invention that Dr. Cima admitted allowed for only a single particle type per "circle":



EX1001, FIG. 65, 21:30-33; EX1036, 73:12-18 ("But it could -- it could be two or it could be three. ***It could be one.***").

The Board squarely addressed this issue in the Institution Decision and nothing in the POR provides any basis for reaching a different conclusion:

> Indeed, limitation 1(b) does not require that all of the protein coronas formed in limitation 1(a) be separated, but instead recites "separating *at least a subset* of the plurality of particles comprising the coronas." Ex. 1001, 86:61-62 (emphasis added). ***Given its ordinary meaning, this***

language suggests limitation 1(b) could be met by separating particles from only one of the different particle types in limitation 1(a).

ID, 22; *see also* ID, 25-26 (explaining how claims 13 and 14 show that, under the doctrine of claim differentiation, non-simultaneous contacting of different particle types separately must be within the scope of claim 1). Patent Owner's renewed attempt to read a negative limitation into the claims should be rejected.

II. GROUND 2 – ANTICIPATION BY CAI

Patent Owner's principal arguments for distinguishing Cai hinge on its misguided, hyper-narrow claim constructions and fail as a matter of law.

a. Patent Owner's assertion that Ground 2 fails because "Cai's HeLa cell lysate is not 'a biological sample' as claimed" (POR, 23) is meritless.

First, as discussed above, the specification's broad definition of biological sample expressly includes "cell lysates" (as do the claims). EX1001, 20:34-40; *see also* 21:14-29; cl. 22; Pet., 23. Accordingly, consistent with the testimony of both parties' experts, Cai's cell lysates satisfy the claimed "biological sample." EX1036, 63:19-64:7; EX1003 ¶¶49, 127, 133, 197. ***Second***, even if Patent Owner's narrow view of "biological sample" is adopted, Cai's HeLa cell lysates still qualify. All HeLa cells are direct copies of cells obtained from Ms. Henrietta Lacks. *Supra* §I.a. Patent Owner's own expert agrees that (1) cells derived from humans meet the definition of "biological sample" and (2) all HeLa cells are derived from Ms. Lacks.

EX1036 40:13-41:9; 39:10-14; 41:15-17; 57:9-11; 81:20-22. Thus, there is no credible debate that cell lysates of HeLa cells, as in Cai, are "biological sample[s]" as that term is used in the '360 Patent.

Patent Owner also (confusingly) reprises its POPR argument regarding alleged "piecemeal" mapping of Cai as part of its "biological sample" argument. *See, e.g.*, POR, 25. The Board rejected this argument in the Institution Decision: "Cai describes a ***single study*** 'to characterize the binding of human cellular proteins to two forms of carbon nanoparticles: namely multi-walled carbon nanotubes (MWCNTs) and carbon black (CB)' involving the use of several analytical techniques." ID, 18-19 (quoting EX1005, Abstract). Consequently, "a POSA would have understood that the process depicted in Cai's Figure 1A was used to isolate the cell lysate proteins bound to the MWCNT and CB particles for subsequent testing, including the LC-MS/MS with SILAC encoding method that produced the results Petitioner relies upon for limitation 1(c)." ID, 19. That understanding is consistent with Cai, Petitioner's mapping to Cai, and Dr. Vargas's testimony—as, again, the Board already correctly concluded. ID, 19 (citing Pet., 57; EX1005, 584-85, 588; EX1003, ¶223); *see also* EX2022, 125:17-20; 125:25-126:2; 129:14-20 ("***In figure 3, it includes both the SILAC encoding and the, what they refer to as CNT pull down, which relies on the general work flow that's depicted in…figure 1A***."). Patent Owner's attempt to artificially isolate Cai's teachings into discrete, unrelated

experiments has no basis in Cai's text or in how a POSA would naturally interpret the reference. The Petition does not rely on "mixing and matching embodiments" as Patent Owner contends (POR, 26)—Cai describes an integrated experiment comprising a number of steps, as a POSA would readily understand. *See, e.g.*, EX2022, 129:14-20; 127:10-19; 125:17-20; 125:25-126:2.

Even if Cai did comprise wholly distinct experiments as Patent Owner contends (it does not), the Board was correct that a POSA would "at once envisage" the patented method from Cai's disclosure. ID, 20 (case cites omitted). As Dr. Vargas testified, Figure 1A depicts and describes "a general work flow" and "schematic" for "protein corona formation," with the coronas later subject to follow-on analysis and experimentation using methods disclosed in Cai, such as mass spectrometry. EX2022, 129:14-20; 127:10-19; 125:17-20; 125:25-126:2. Further, Cai's Figure 1 discloses an elution method and Cai expressly specifies that elution is a preliminary step to be completed before the use of mass spectrometry ("MS"). EX1005, 585 (explaining that "[t]he peptides were eluted" prior to use of MS). The notion that a POSA would interpret Cai as disclosing completely distinct embodiments that were meant to be considered in isolation has no basis in fact or law.

b. Patent Owner's argument that Cai does not disclose limitation 1(b) is equally unavailing.

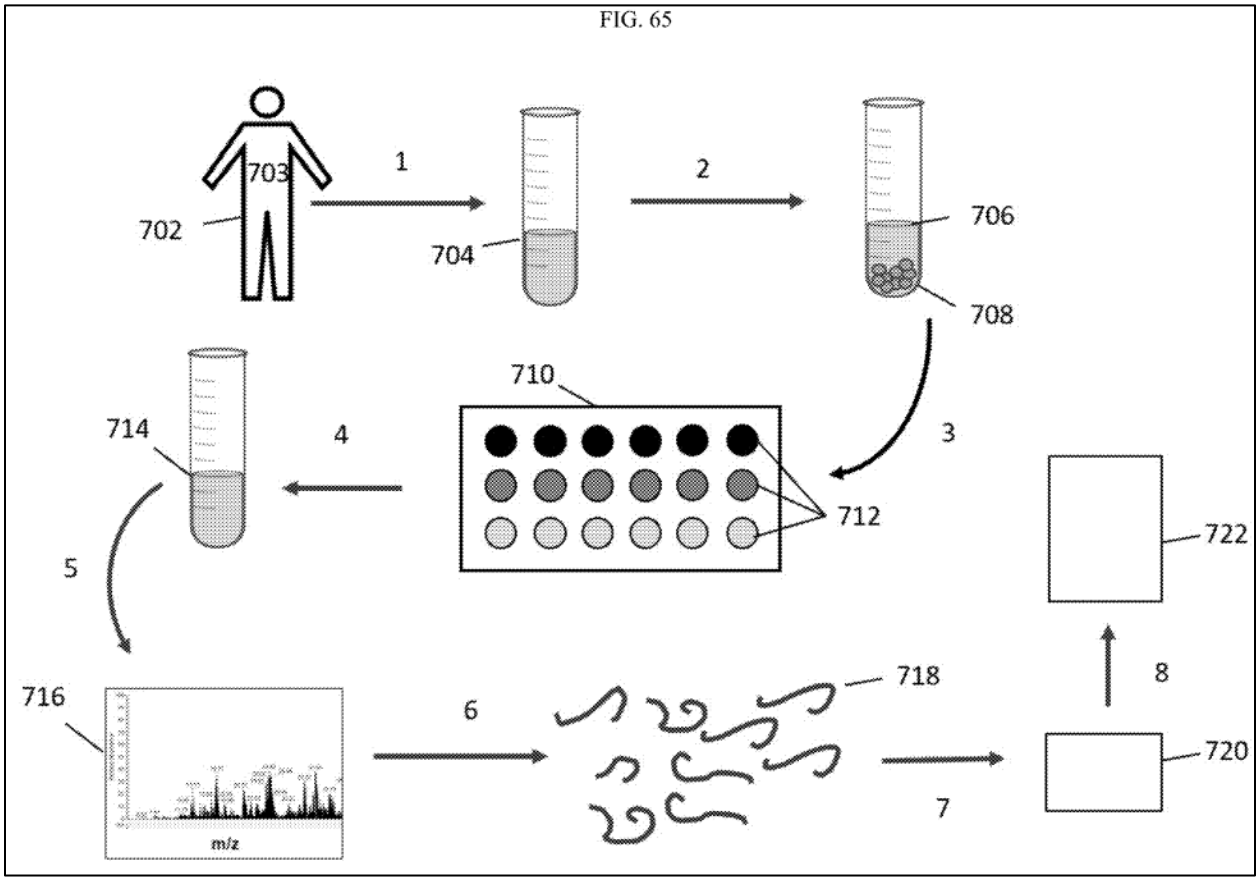
Patent Owner's argument that Cai does not disclose limitation 1(b) is ultimately just a reprise—dressed up as claim construction—of its already rejected argument in the POPR. It fails for the same fundamental reasons now.

First, Patent Owner's contention that the "claims [at limitation 1(b)] require the separated particles to have both (1) different particle types and (2) coronas corresponding to the different particle types comprising overlapping and distinct proteins" is wrong as matter of claim construction. POR, 28-29. Nothing in the language of the claims or the specification justifies this extreme interpretation. *Supra* §I.b. Patent Owner's arguments in this section all fail as a matter of law because they hinge on an incorrect claim construction.

Second, Patent Owner rehashes the argument that in Cai "there is never disclosed separating a subset of particles comprising coronas from more than one particle type" because instead "samples are incubated individually in parallel." POR, 29. As an initial matter, even if it were appropriate to look at each instance of incubation—instances that Patent Owner admits occur "in parallel"—in isolation, limitation 1(b) does not require that the "subset" include multiple particle types. *Supra* §I.b. Thus the individual incubations that Patent Owner admits occur in Cai satisfy limitation 1(b) even standing alone—as the Board already recognized. *See*

POR, 29 (citing EX1005, FIG. 1A and acknowledging incubation of "CNT ***or*** CB" (emphasis in original)); ID, 22 ("Given its ordinary meaning, this language suggests limitation 1(b) could be met by separating particles from only one of the different particle types in limitation 1(a).").

Further, even if Patent Owner's construction of limitation 1(b) were correct (it is not), Cai still discloses it because the multiple vials that Patent Owner admits are "incubated individually in parallel" (POR, 29) ***collectively constitute the claimed "subset."*** There is no reason the claimed "subset" must be contained in a single vial or otherwise defined by the contents of any particular vial. Indeed, an embodiment of the '360 Patent described as "an exemplary scheme of the presently disclosed array system" (EX1001, 21:14-15), depicted in Figure 65 (below), shows the claimed subset can take the form of a plurality of different vials incubated in parallel—just as Cai discloses.



EX1001, FIG. 65; *see also id.*, 21:30-33. And Dr. Cima confirmed that there could be only one particle type per circle in the depicted array. EX1036, 73:12-18 ("But it could -- it could be two or it could be three. ***It could be one.***").

Thus, by Patent Owner's expert's own admission, the configuration depicted in Figure 65 is no different from Cai's parallel incubation of separate by vials, with each vial having a single particle type. The '360 Patent contemplates the very parallel incubation configuration of Cai that Patent Owner erroneously argues is outside the claims. This also supports the Board's finding that such parallel incubation is within the scope of claim 1—a finding Patent Owner never

meaningfully rebuts. ID, 26 ("Thus, we do not presently discern a basis in claim 1 for distinguishing approaches where proteins from the coronas formed on multiple particle types contacted with the same biological sample are assayed in parallel, but with each particle type in a different reaction vessel or, as Patent Owner puts it, 'one-at-a-time.'").

Finally, Patent Owner's attempt to distinguish Cai's disclosure of MWCNTs comprising different particle types (POR, 31) fails for multiple reasons. First, it hinges on Patent Owner's incorrect construction of limitation 1(b). Second, the argument fails on its own terms since Cai's clear disclosure of differences in the amount of proteins bound based on diameter shows different particle types. EX1005, 586-87, FIG. 2; Pet., 55-56. Further, Patent Owner has no meaningful expert support, as the cited portion of Dr. Cima's declaration is a near-verbatim copy of the attorney argument itself and adds no independent analysis. *Compare* POR, 31 *with* EX2023 ¶61.

c. Patent Owner's Limitation 1(c) Arguments Do Not Change the Fact that Cai Discloses the Claimed Concentration Range.

The Petition described how Cai discloses that "relative abundance of the MWCNT-binding proteins spread over 8 orders of magnitude," (Pet., 60 (citing EX1005, 587 and EX1003 ¶¶229, 97) and further showed how Cai utilizes "empirical peptide abundance index data (emPAI)" that is convertible to "more

traditional concentration numbers using a formula provided" in cited reference Ishihama (EX1018). Pet., 62-63. Petitioner thus showed that Cai discloses abundance data and cites a reference for converting that data to concentration data, and further showed that when that reference's conversion formula is applied, Cai discloses the claimed "concentrations across a dynamic range comprising at least 6 orders of magnitude." Pet., 72. In other words, Cai's disclosed abundance data is directly convertible to concentration data using a known formula (from a reference cited in Cai) and, when converted, satisfies the claim requirement. That is anticipatory.

Nothing in the POR changes the analysis. Patent Owner again improperly strains the claim language by arguing that Cai does not disclose detecting proteins in the claimed concentration range "in the sample," purportedly because the detection occurs with respect to "a mixture of proteins from the ***pulled-down corona***." POR, 33 (emphasis in original). But the claim language expressly requires "***assaying the subset*** of proteins of (b) with an instrument to detect, ***in the subset***" proteins in the sample at the required concentration range. EX1001, cl. 1. Thus the actions claimed in limitation 1(c) occur with respect to the subset, not the biological sample. Patent Owner's attempt to distinguish Cai in this regard only confirms that Cai discloses limitation 1(c).

Patent Owner also argues that Ishihama's conversion methodology is somehow not validated for the ranges disclosed in Cai, but provides no evidence for any lack of validation. Ishihama places no limits on its validated range, states that "the emPAI approach seems to provide a reasonably accurate estimate for comprehensive absolute quantitation" (EX1018, 1268), and expressly proposes "routine use [of its methods] in the reporting of proteomic results." EX1018, 1271. There is no basis in either Cai or Ishihama for questioning the applicability of its conversion formula. And as the Petition pointed out, this reliance on a known conversion formula is consistent with "'360 Patent's reliance on a known lookup table to determine the concentrations across the dynamic range comprising as least 6 orders of magnitude." Pet., 60 (citing EX1003 ¶¶229, 97; Pet. §IV.A).[5]

Further, during prosecution of a continuation-in-part of the '360 Patent, the examiner expressly found—and Patent Owner did not challenge—that Cai teaches "measure[ment] [of] concentration across a dynamic range of at least 6 orders of magnitude." EX1041, 6. Thus the Office has already found that Cai discloses this

[5] Patent Owner does not include any meaningful independent arguments for challenged dependent claims in this or any other ground. Thus they are not addressed herein.

limitation—and Patent Owner acquiesced to that finding. It should not be heard to argue otherwise now.

III. GROUND 3 – OBVIOUSNESS IN VIEW OF CAI

Patent Owner's arguments for Ground 3 largely restate the arguments used with respect to limitation 1(c) in the Petition and fail for the same reasons. For all the reasons stated in the Petition, to the extent Cai does not disclose the claimed concentration range, it would be obvious to convert its express disclosure of "relative abundance of the MWCNT-binding proteins spread over 8 orders of magnitude" to traditional concentration numbers. Pet., 60-63. Ishihama, cited in Cai, provides a readily available means for doing so. Further, Patent Owner is incorrect that Ishihama does not disclose calculating concentrations—it expressly discusses "calculat[ing] the absolute concentrations," and explains how its emPAI approach provides similar results. EX1018, 1268. Fundamentally, the difference between abundance and concentration is a matter of data conversion; a POSA plainly would have been capable of and motivated to effectuate such a conversion. *See* Pet., 60-63.

Patent Owner's other arguments simply restate its claim construction arguments and other arguments addressed above. Even if Patent Owner's extraordinarily narrow claim construction for "biological sample" were adopted, however, and HeLa cells were somehow excluded, the disclosures relied upon in Cai

would still render the claims obvious, since it would be trivially easy to apply the same methodology to other types of samples.

Lastly, Patent Owner does not address (as to Cai) the Petition's explanation (supported by Dr. Vargas) of the obviousness of including the claimed dynamic range in Cai. Pet., 63-64 (citing, *e.g.*, Pet., §V.B.1 (regarding limitation 1[c] explaining same)). This stands unrebutted and further demonstrates the obviousness of the challenged claims (notwithstanding any argument in the POR).

IV. GROUND 1 – OBVIOUSNESS IN VIEW OF HU

a. Patent Owner's First Two Hu Arguments Fall Away as a Matter of Claim Construction.

Patent Owner's initial arguments against Hu rely on its faulty claim constructions and fail for that reason. First, Patent Owner argues that Hu's "combined blood plasma" from multiple different individuals is not a "biological sample"—an argument that fails as explained above in the claim construction section.[6]

Second, Patent Owner relies on its faulty, myopic claim construction argument that the claims exclude parallel incubation of different particle types individually.

[6] Even if the argument could be credited, plainly Hu's disclosure of pooled blood samples would render obvious a "biological sample" taken from a single individual.

POR, 41. This argument fails for the reasons discussed in the claim construction section and in the discussion of the similar arguments for Cai. Patent Owner admits that in Hu "30-, 200-, and 400-nm samples [are] incubated individually" (POR, 41) but nonetheless argues that this is somehow outside the scope of the claims—despite the claim language in no way precluding this configuration and Dr. Cima admitting that the '360 Patent's Figure 65 contemplated such individual incubation (as discussed above). There is no basis in science or the claims for this "overly-narrow" view that limitation 1(b) turns on which specific vial particular particles are placed in, as the Board already concluded. ID, 26. The Board should reject it for good in the FWD.

b. Patent Owner's Argument That Hu Fails to Disclose the Claimed Dynamic Range is Refuted by the '360 Patent Itself

Patent Owner acknowledges that Hu's data table lists LTBP1 as among the detected proteins yet speculates that express disclosure of detection somehow does not count because it "was more likely experimental artifact rather than an actual detection event." POR, 44-45. This argument fails on its face. Hu indisputably discloses that LTBP1 was detected multiple times. Patent Owner's argument that these express disclosures of detection somehow do not count hinge in Patent Owner and Dr. Cima's criticism of MS and "[p]rior art shotgun proteomics approaches" that were purportedly "known to lack sensitivity and specificity." POR, 43.

But the ’360 Patent repeatedly states (and claims) that MS and shotgun methods can be used. *See, e.g.*, EX1001, cl. 4 (“The method of claim 1, wherein the assaying is performed using… mass spectrometry…”), 4:43-54, 21:43-50, 77:47-51, 85:33-67 (describing use of “shotgun proteomic analytical approach” and “tandem mass spectrometry”). Dr. Cima admitted as much as to both MS and shotgun methods more broadly. EX1036, 65:10-67:4. Thus, whatever shortcomings MS and shotgun methods may have, Patent Owner should not be heard to argue that they fail to provide sufficient sensitivity and specificity for use with the patented method ***because the patent says they do***. Patent Owner’s arguments that are based on alleged sensitivity shortcomings of MS and shotgun methods are groundless.

Patent Owner’s arguments in opposition to Petitioner’s inherency and obviousness arguments fail for much the same reason. As explained in the Petition, it was routine for POSA to look up “known protein concentrations in a known database” to determine concentrations, and the ’360 Patent uses that exact approach to show that the patented method detected proteins in the claimed dynamic range. Pet., 36-37 (citing EX1001, 66:63-69:67, 82:16-21, FIG. 12; EX1014, D959-D962; EX1003 ¶¶167-170, 56-59). Thus, Hu’s disclosure of, *e.g.*, detection of serum albumin and LTBP-1 necessarily discloses detection of those proteins in accordance with their known concentration ranges, and certainly renders such detection obvious, for all of the reasons set forth in the Petition and the evidence cited therein. Pet., 33-

39. The POR's arguments to the contrary largely hinge on assertions about the insufficiencies of MS and shotgun methods that are refuted by the '360 Patent and Patent Owner's own expert.

V. GROUND 4 – OBVIOUSNESS IN VIEW OF ZACCARIA

Patent Owner's Zaccaria arguments all fail for fundamentally the same reasons as its Hu arguments. Patent Owner makes the same deficient claim construction argument regarding pooled samples not being "biological samples" (POR, 53) and it fails for the same reasons. Patent Owner also reprises its defective argument that claim 1 excludes the use of separate containers in limitation 1(b) for different particle types (POR 54-55); that argument fails for the reasons already explained herein. Finally, Patent Owner's limitation 1(c) arguments are conceptually almost identical to its corresponding Hu arguments—it acknowledges that Zaccaria's data table on its face shows detection of the SBF1 protein (among others), but contends that this should not be interpreted as actual detection because of deficiencies in shotgun methods. POR, 54-60. That argument fails for the same reasons that similar Hu arguments failed—as do Patent Owner's arguments that regarding the inherency and obviousness arguments made in the Petition with respect to Zaccaria. POR, 61-64. As explained in the Petition, Zaccaria discloses detection of low abundant proteins such as SBF1, and a POSA would know that such detection necessarily shows, or at least renders obvious, detection of concentrations across the

claimed range. Pet., 72-77. Patent Owner's nitpicking does nothing to disturb this fundamental conclusion.

VI. DR. CIMA'S OPINIONS ARE UNRELIABLE AND ENTITLED TO LITTLE OR NO WEIGHT

Dr. Cima directly contradicted himself on a core claim construction issue (*supra* n.1) and was evasive and refused to directly answer questions during his deposition. *See, e.g.*, EX1036, 35:8-41:2 (extended refusal to provide testimony on the plain meaning of "biological sample"); 12:6-17:6; 21:20-23:3. Further, Dr. Cima has never taught a molecular biology course (EX1036, 24:9-13), has never been in a biology department (EX1036, 28), and could not identify any prior admissions as an expert in molecular biology cases or biological assays (EX1036, 28:10-29:18), or cases with claims relating to mass spectrometry (EX1036, 20:1-6). He is a material science professor with only scattered, sporadic experience in proteomics, and it is not clear that he satisfies Patent Owner's POPR statement of the level of skill of a POSA (which Patent Owner appears to have abandoned). His qualifications pale in comparison to Dr. Vargas's, and Patent Owner's attacks on her qualifications and the Petition's proposed level of skill are meritless.

Respectfully submitted,

REICHMAN, JORGENSEN, LEHMAN & FELDBERG LLP

Dated: October 16, 2025

/*Patrick Colsher*/
Patrick Colsher (Reg. No. 74,955)

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that Petitioners' Reply consists of 5,510 words, excluding the table of contents, certificate of service, this certificate of compliance, or table of exhibits. The Reply complies with the type-volume limitation of 5,600 words as mandated in 37 C.F.R. §42.24. In preparing this certificate, counsel has relied on the word count of the word-processing system used to prepare this paper (Microsoft Word).

Dated: October 16, 2025 */Patrick Colsher/*

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CERTIFICATE OF SERVICE

I hereby certify that the foregoing document and any exhibits not previously served were served by email on Patent Owner's counsel of record as follows on October 16, 2025:

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