

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

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

VALEK, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

PreOmics GmbH and Biognosys AG (“Petitioner”) filed a Petition (Paper 1, “Pet.”), seeking *inter partes* review of claims 1–4, 6, 7, 17, and 22–25 of U.S. Patent No. 11,435,360 B2 (Ex. 1001, “the ’360 patent”). Brigham and Women’s Hospital, Inc., (“Patent Owner”) filed a Preliminary Response. Paper 9 (“Prelim. Resp.”).

Considering the arguments and evidence currently of record, we determine the Petition demonstrates “a reasonable likelihood that [P]etitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Accordingly, we institute *inter partes* review of claims 1–4, 6, 7, 17, and 22–25 of the ’360 patent.

II. BACKGROUND

A. *Real Parties-in-Interest*

The parties identify themselves as the real parties-in-interest. Pet. 1; Paper 10, 1.

B. *Related Matters*

The parties do not identify any other matters involving the ’360 patent. Pet. 1; Paper 10, 1.

C. *The ’360 Patent*

The ’360 patent issued on September 6, 2022, and claims priority to a series of applications, the earliest of which was filed on December 16, 2016. Ex. 1001, codes (45), (60).

The ’360 patent discloses “sensor arrays for detecting biomolecules and methods of use.” Ex. 1001, code (57). This method involves contacting a biological sample with a plurality of particles with different particle types,

allowing biomolecules from the biological sample to bind and form “coronas” around them, where the coronas differ based on particle type and may comprise overlapping and distinct proteins. *See id.* at 86:52–87:3. A “biomolecule corona” forms when a particle is covered with a layer of different biomolecules, including proteins. *Id.* at 15:7–22. According to the ’360 patent, its “sensor array is able to detect changes in the compositions of the biomolecule corona,” which “allows for determining a unique biomolecule fingerprint” that can “stratify different health and disease states of subjects.” *Id.* at 14:49–58.

Figure 65 of the ’360 patent is reproduced below.

FIG. 65

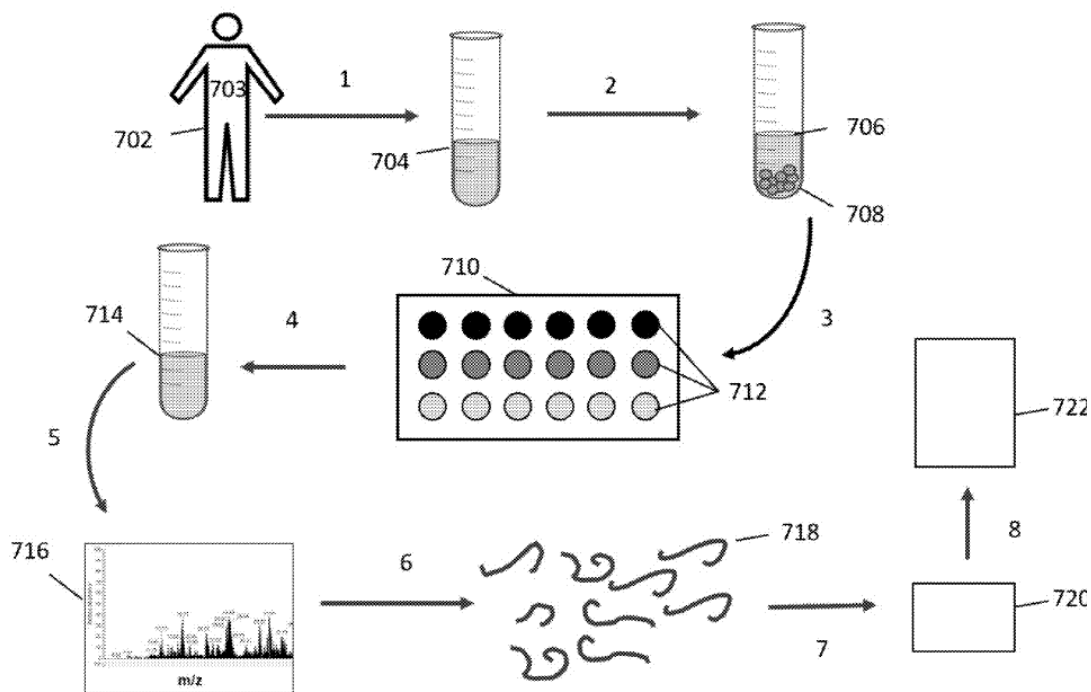


Figure 65 above is a “[s]chematic diagram of a method of distinguishing states of a complex biological sample.” Ex. 1001, 14:25–26. In the first step of the diagramed method, biological sample 704 is collected from a subject

702 expressing a biological state 703 (e.g., a disease state). The plasma 706 is then separated from the blood cells 708 of subjects expressing a biological state 703 in step 2. *Id.* at 21:14–29. In step 3, plasma 706 is incubated with sensor array 710 that includes a plurality of particles 712 with different properties to allow biomolecules (e.g., proteins) in the plasma to bind to the particles. *Id.* at 21:30–36. Next in step 4, biomolecules bound to the particles are isolated in a protein solution 714 to be analyzed “to determine the compositions of the proteins bound to each type of particle 712.” *Id.* at 21:36–42. In Figure 65, for example, the protein solution is characterized by “liquid chromatography-tandem mass spectrometry (LC-MS/MS) 716” (step 5) and the proteins identified by that analysis are used to determine a biomolecule fingerprint 718 (step 6). *Id.* at 21:43–50.

According to the ’360 patent, “[t]he present sensor array has a sensitivity and dynamic range of ten (10) orders of magnitude in terms of protein detection using mass-spectroscopy approaches,” which is a “greater dynamic range than current assays” using mass spectrometry that “only ha[ve] a dynamic range 4-6 order[s] of magnitude.” Ex. 1001, 20:20–29.

D. Challenged Claims

Independent claim 1 is reproduced below, reformatted with the designations Petitioner uses to identify limitations shown in brackets.

1. [pre] A method for assaying a biological sample, comprising:
 - (a)[1] contacting the biological sample with a plurality of particles comprising different particle types
 - [2] to permit biomolecules of the biological sample to bind to the plurality of particles and form coronas around the plurality of particles,

[3] wherein the coronas corresponding to the different particle types (i) differ based on particle type, and (ii) comprise overlapping and distinct proteins;

(b) separating at least a subset of the plurality of particles comprising the coronas from the biological sample by removing the subset of the plurality of particles thereby producing a subset of proteins from the biological sample

(c) 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.

Ex. 1001, 86:77–87:3. Claims 2–4, 6, 7, 17, and 22–25 depend from and thus incorporate the limitations of claim 1.

E. Asserted Grounds of Unpatentability

The Petition raises four grounds of unpatentability. Pet. 3.

Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
1–4, 6, 7, 17, 22–25	103	Hu ²
1, 4, 6, 17, 22, 25	102	Cai ³
1, 4, 6, 17, 22, 25	103	Cai

¹ The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), included revisions to 35 U.S.C. §§ 102 and 103 that became effective prior to the filing of the application that led to the ’360 patent. Therefore, we apply the AIA versions of 35 U.S.C. §§ 102 and 103.

² Hu *et al.*, “Nanoparticle Size Matters in the Formation of Plasma Protein Coronas on Fe₃O₄ Nanoparticles,” *Colloids and Surfaces B: Biointerfaces* 121 (2014) 354–361, including supporting information (Ex. 1008) (“Hu”).

³ Cai *et al.*, “Characterization of Carbon Nanotube Protein Corona by Using Quantitative Proteomics,” *Nanomedicine: Nanotechnology, Biology and Medicine* 9 (2013) 583–593, including supplementary data (Ex. 1005) (“Cai”).

Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
1, 2, 4, 6, 7, 17, 22, 23, 25	103	Zaccaria ⁴

In addition to other record evidence, Petitioner offers the declaration of Dr. Jessica Vargas (Ex. 1003) in support of these grounds.

Petitioner’s grounds challenge largely the same set of claims and present similar issues, but on three different references. Having reviewed each reference, we begin our analysis below with the two grounds based on Cai.

III. ANALYSIS OF PETITIONER’S GROUNDS

A. Legal Standard

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). While the elements must be arranged or combined in the same way as in the claim, “the reference need not satisfy an *ipsissimis verbis* test,” i.e., identity of terminology is not required. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009); *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990). Thus, the dispositive question “is whether one skilled in the art would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference.” *Eli Lilly and Company v. Los*

⁴ 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, including supplementary data (Ex. 1007) (“Zaccaria”).

Angeles Biomedical Research Inst. at Harbor–UCLA Med. Ctr., 849 F.3d 1073, 1074–75 (Fed. Cir. 2017). Still further, “it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom.” *In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a); *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) when in evidence, objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

B. Level of Ordinary Skill in the Art

Factors pertinent to determining the level of ordinary skill in the art include the type of problems encountered in the art, prior art solutions to those problems, as well as the education level of the inventors and active workers in the field. *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). The disclosure in the prior art may also reflect an appropriate skill level. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Petitioner contends that a person of ordinary skill in the art (“POSA”) “would have had at least a bachelor’s degree in chemistry, biochemistry,

bioengineering, or a related field, and three years' experience in the field of proteomics, protein analysis, or mass spectroscopy." Pet. 11 (citing Ex. 1003 ¶¶ 24–27). Petitioner further contends, "[t]his description is approximate – a higher education or skill level might make up for less experience, and vice versa. Pet. 11 (citing Ex. 1003 ¶ 26). According to Petitioner, its declarant Dr. Vargas, "was at least a POSA as of the '360 Patent's earliest possible priority date, December 16, 2016." Pet. 11 (citing Ex. 1003 ¶¶ 5–10, 27; Ex. 1004, 1–3).

Patent Owner argues that Petitioner's definition of a POSA is insufficient because it suggests experience with mass spectroscopy alone is enough. *See* Prelim. Resp. 26–27. According to Patent Owner, this "definition is deficient because it excuses Petitioner's expert from having *any* expertise in proteomics assays, protein coronas, or applying mass spec to a biological sample (e.g., blood plasma)." *Id.* at 27. Citing the educational background of its named inventors, Patent Owner urges that "a POSA would have had at least three years of experience working with protein coronas and proteomics assays." *Id.* at 28 (citing Exs. 2004–2006). Based on this additional requirement, Patent Owner argues that Dr. Vargas is not a POSA because her "expertise is directed toward analytical chemistry and synthesis of polymeric materials" and she "does not purport to have performed mass spectrometry techniques specifically for protein analysis." *Id.* at 28–29.

At this stage, we find Petitioner's description of the level of ordinary skill in the art to be sufficient. According to the '360 patent, "[t]he field of the invention is related to sensor arrays for the detection and diagnosis of disease states." Ex. 1001, 1:28–29. The Specification describes accomplishing such by analysis of protein coronas using techniques such as

LC-MS/MS. *See id.* at 4:43–5:2 (describing Figure 1). The prior art cited by Petitioner also describes the analysis of protein coronas using similar analytical techniques. *See, e.g.*, Ex. 1005, 584; Ex. 1007, 1870; Ex. 1008, 355–356. Accordingly, the present record supports that a POSA would have an understanding of both proteins and the analytical techniques, e.g., mass spectrometry, that can be used to characterize them.

We understand Petitioner’s definition of a POSA to encompass these elements. It requires a formal degree in chemistry,⁵ which itself entails some knowledge of proteins and related analytical techniques, along with several years’ additional experience in proteomics, protein analysis, or mass spectrometry. Moreover, Petitioner’s definition is flexible in that it allows higher education or skill with, e.g., mass spectrometry, to make up for a lack of specific experience with proteomics assay and protein coronas. This explanation is reasonable and supported on the current record.

Patent Owner’s argument that Dr. Vargas lacks specific experience applying mass spectrometry for protein analysis, which “incurably taint[s] the Petition” such that institution should be “denied on this basis alone,” is unpersuasive for several reasons. *See* Prelim. Resp. 28–30. First, there is no dispute that Dr. Vargas is a POSA under Petitioner’s definition. Second, even if we accepted Patent Owner’s argument and narrowed that definition to require specific experience with proteomics assay and protein coronas, Dr. Vargas has additional formal education (e.g., a Ph.D. in chemistry from

⁵ Petitioner’s definition only requires a “bachelor’s degree.” Pet. 11. However, the educational background of the ’360 patent inventors and the authors of Cai, Zaccaria, and Hu suggests that a graduate degree is more typical for a POSA. While this issue does not affect our decision to institute, it would benefit from further development at trial.

Stanford University) and experience in related areas such as “biochemistry, and drug and gene delivery” that, at least on the current record, would make up for her alleged lack of specific experience in these areas. Ex. 1004, 1 (Vargas CV).⁶

Third, and perhaps most importantly, there is “no requirement for perfect match between an expert’s experience and the relevant field.” *See Consolidated Trial Practice Guide* (Nov. 2019) 34, *available at* <https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf> (“CTPG”). (citing *SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010)). A person need not be a person of ordinary skill in the art to testify as an expert under Federal Rule of Evidence 702, but rather must be “qualified in the pertinent art.” *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008). Here, there is no dispute that Dr. Vargas is qualified in the art of mass spectrometry and, on the current record, we discern no reason why she is not qualified to offer the testimony in her declaration. At most, Patent Owner’s argument that Dr. Vargas lacks experience “perform[ing] mass spectrometry techniques specifically for protein analysis,” goes to the weight we should afford her testimony at trial. *See Prelim. Resp.* 28–29. It is not a sufficient reason to deny institution, particularly given that Dr. Vargas’s testimony is only part of the showing offered in support of the Petition.

⁶ Patent Owner’s narrow characterization of Dr. Vargas’s experience (*see Prelim. Resp.* 28–29) is arguably inconsistent with the description in her CV (Ex. 1004). In any event, Patent Owner will have an opportunity to examine Dr. Vargas regarding her qualifications.

C. Claim Construction

In an *inter partes* review, claim terms “shall be construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b).

Petitioner “submits that no express construction of terms is necessary.” Pet. 15. Patent Owner agrees no construction is needed at this stage. *See* Prelim. Resp. 26.

We agree that no formal claim construction is necessary for this decision. *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) (“The Board is required to construe ‘only those terms that . . . are in controversy, and only to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). To the extent we have concerns regarding the parties’ apparent interpretation of the claim language, or in some instances Patent Owner’s attempt to read-in unrecited limitations, we address those arguments below.

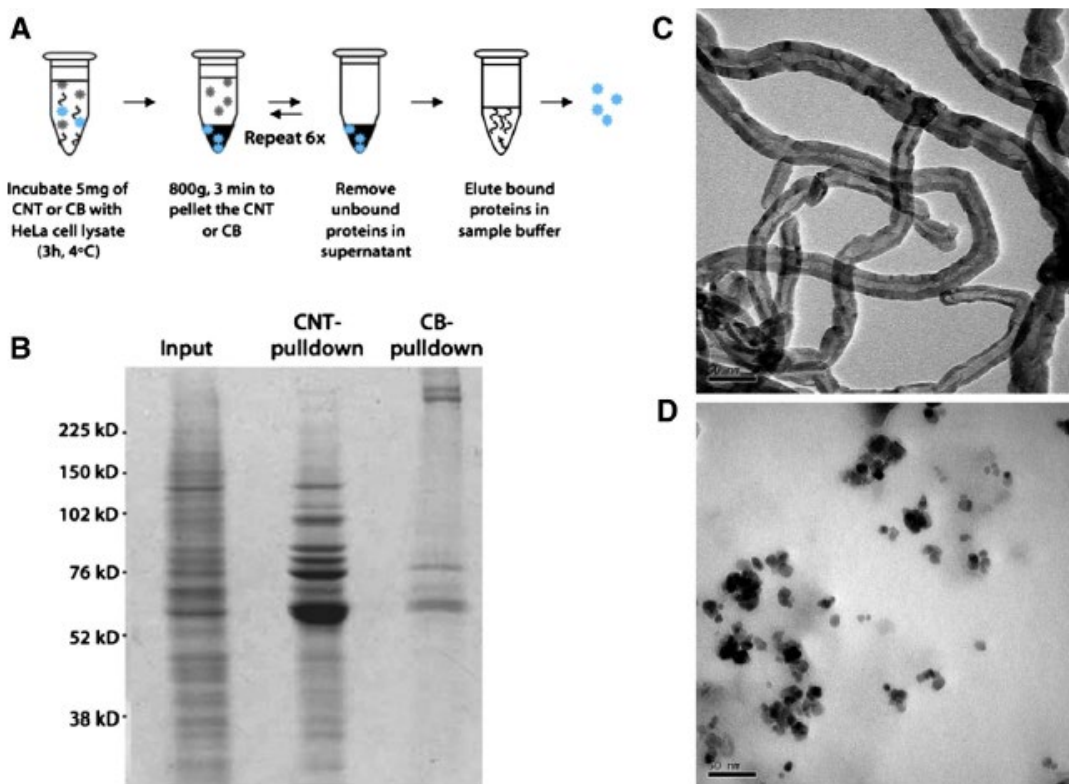
D. Asserted References

i. Cai

Cai is a journal article bearing a September 2012 publication date. Ex. 1005, 1. Patent Owner does not presently dispute that Cai is prior art to the challenged claims.

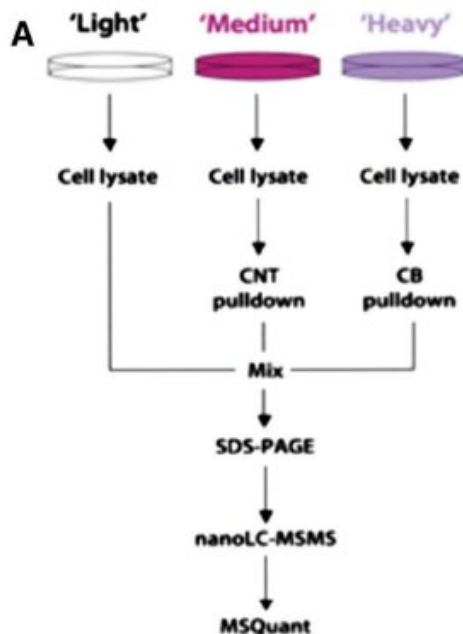
According to Cai, “[t]he protein corona of a nanomaterial is a complex layer of proteins spontaneously and stably formed when the material is exposed to body fluids or intracellular environments.” Ex. 1005, Abstr. Cai describes a study “utili[zing] stable isotope labeling by amino acids in cell culture (SILAC)-based quantitative proteomics to characterise the binding of human cellular proteins to two forms of carbon nanoparticles: namely multi-walled carbon nanotubes (MWCNTs) and carbon black (CB).” *Id.*

In Cai’s study, HeLa cell lysates were incubated with CB or carbon nanotubes (CNTs), and in some instances with “CNTs of different sizes.” Ex. 1005, 584. The proteins bound to those particles were then eluted for further analysis. *Id.* at Fig. 1 of Cai, reproduced below, illustrates this process.



Ex. 1005, 586. Figure 1A (top left above) schematically shows the incubation of a cell lysate with carbon nanotubes or carbon black, followed by elution of the proteins that bind to the particles. *Id.* at 585. Figure 1B (bottom left) shows separation of the bound proteins by SDS-PAGE⁷ in a “CNT-pulldown” and “CB-pulldown.” *Id.* at 586. The figure also shows TEM [transmission electron microscopy] images of the carbon nanotubes (C) and carbon black (D) on the right. *Id.*

Cai describes further testing “to compare the types of proteins that bound to . . . MWCNT with those that bound to CB.” Ex. 1005, 586. “Cell lysates were prepared from three populations of HeLa cells that had been metabolically encoded using three different SILAC media (‘light’, ‘medium’ and ‘heavy’, Figure 3, *A* and Methods).” *Id.* Figure 3A of Cai, reproduced below, illustrates this process.



⁷ According to Dr. Vargas, “Sodium Dodecyl Sulfate-Polacrylamide Gel-Electrophoresis (SDS-PAGE)” is a technique “widely used for protein separation.” Ex. 1003 ¶¶ 34, 179.

Id. Figure 3A above schematically shows a “CNT pull-down . . . performed on the ‘medium’ lysate, and a CB pull-down . . . performed on the ‘heavy’ lysate.” *Id.* “Equal volumes of the proteins eluted from these pull-down experiments were mixed” and “spiked with an equal amount of unfractionated ‘light’ lysate.” *Id.*; *see also id.* at 584 (referring to the light-labeled lysate as a “control”). “The mixtures were then separated by SDS-PAGE, and analyzed with the ‘gel-LC-MS/MS’ approach,” i.e., liquid chromatography and mass spectrometry. *Id.* at 586–587. The obtained spectra were then “quantified by the MSQuant programme” to identify unique peptides and “[t]he abundance distribution of each identified peptide among the ‘light’, ‘medium’ and ‘heavy’ categories.” *Id.* at 587.

Cai discloses that “[t]he relative abundance of the MWCNT-binding proteins” identified through this analysis “spread over 8 orders of magnitude.” Ex. 1005, 587. Cai further discloses that “while a small number of CB-binding proteins also bind to MWCNTs . . . most of the proteins with high CB-binding efficiencies bind to MWCNTs only marginally or not at all,” which indicates that these nanoparticles have “different protein binding specificities.” *Id.*

ii. Hu

Hu is a journal article bearing a June 2014 publication date. Ex. 1008, 354. Patent Owner does not presently dispute that Hu is prior art to the challenged claims.

Hu describes a study investigating “whether nanoparticle size affects the formation of protein coronas around Fe₃O₄ [nanoparticles].” Ex. 1008, Abstr. In Hu’s study, Fe₃O₄ nanoparticles (NPs) of varying sizes were mixed with human plasma to form nanoparticle-protein complexes that “were

collected by a magnet and washed at least 3 times to remove the loosely bound and unbound proteins.” *Id.* at 355. The complexes were then resuspended and divided into two parts, wherein one part was purified by SDS-PAGE “to illustrate the binding patterns of the plasma proteins on the Fe₃O₄ NPs.” *Id.* “The other portion was analyzed” with a “nanoparticle digestion shotgun proteomics method,” involving digestion with trypsin followed by analysis of “[t]he digested peptides from the human plasma protein corona” using LC-MS/MS. *Id.* A software program was then used to compare the MS/MS spectral data with a database to identify and quantify unique proteins. *Id.* at 356.

According to Hu, the results from these experiments show that “particle size does play an important role in the formation of plasma protein coronas on Fe₃O₄ NPs,” affecting both protein composition and abundance. Ex. 1008, Abstr.; *see also id.* at 359, Fig.4 (Venn diagram identifying overlap and non-overlap of proteins bound by different sizes of Fe₃O₄ NPs).

iii. Zaccaria

Zaccaria is a journal article bearing a March 2015 publication date. Ex. 1007, 1869. Patent Owner does not presently dispute that Zaccaria is prior art to the challenged claims.

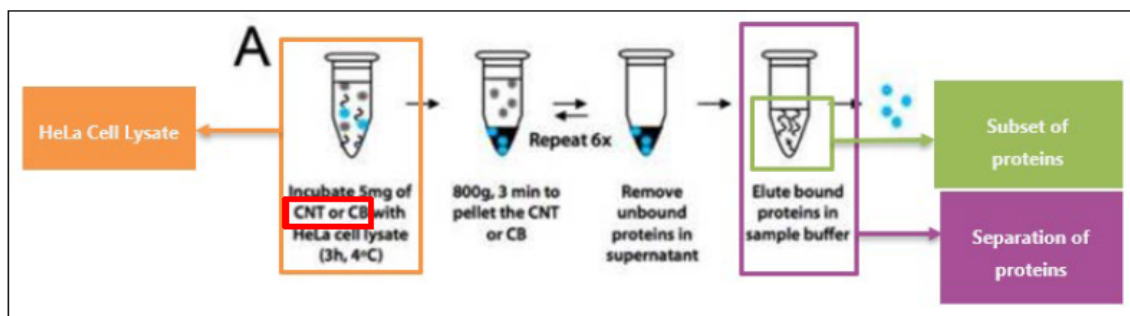
Zaccaria describes a study of protein coronas formed on “three [different] kinds of superparamagnetic NPs.” Ex. 1007, Abstr. In Zaccaria’s study, “each kind of NPs were individually incubated” with a hemolysate prepared from human blood samples. *Id.* at 1871. “Then, NPs were attracted to one side of the vial by an external magnet, and supernatant was removed.” *Id.* Bound proteins were then purified by SDS Page and analyzed using mass spectrometry (i.e., nano-LC-MS/MS) to identify and quantify the proteins in

the coronas of each of the three different kinds of NPs. *Id.* at 1871, 1873–1874. Zaccaria reports that the different types of NPs bound different proteins. *See, e.g., Id.* at 1873, Fig. 2A–C.

E. Alleged Anticipation by Cai

Petitioner contends claims 1, 4, 6, 17, 22, and 25 are anticipated by Cai. *See* Pet. 46–61. Beginning with claim 1, Petitioner asserts that “Cai’s method of analyzing the protein lysate from HeLa cells using various CNTs alone or with CB discloses the claimed method.” Pet. 48 (internal quotations omitted). In particular, Petitioner relies on Cai’s experiments involving MWCNT and CB, which it maps to limitation 1(a)’s recitation of contacting a “plurality of particles comprising different particle types” with the biological sample to form coronas comprising “overlapping and distinct proteins.” *See id.* at 50–57 (citing evidence).⁸ According to Petitioner, after the lysate is incubated with the MWCNT or CB, Cai discloses that the proteins bound in the coronas are eluted to produce a subset of proteins that are then further analyzed by SDS-PAGE. *Id.* at 57–58 (citing Ex. 1005, 585, Fig. 1A; Ex. 1003 ¶¶ 223–224). The Petition illustrates its position with an annotated version of Figure 1A of Cai, reproduced below.

⁸ Petitioner presents this as an “alternative” argument to its separate reliance on Cai’s experiments involving different types of CNTs “alone constituting the claimed ‘*plurality of particles comprising different particle types*’” in limitation 1(a). Pet. 50. However, since most of Petitioner’s showing for the other claim limitations is focused on Cai’s disclosure as it relates to MWCNT and CB (*see* Pet. 51–60), we view it as the stronger of Petitioner’s arguments and focus on it here.



Petitioner’s annotated version of Figure 1A includes an orange box around the incubation step on the far left, identifying the HeLa cell lysate (biological sample) that is incubated with the “CNT or CB” (plurality of particles) identified with a red box to form coronas of bound proteins. Petitioner annotates the “elute bound proteins” step on the far right with a purple box and a smaller green box around the proteins themselves, which it contends constitute a “subset of proteins” as recited in limitation 1(b).

For limitation 1(c), Petitioner argues that Cai “discloses multiple methods of assaying the isolated protein coronas taken from the bound carbon nanoparticles, including gel electrophoresis, LC-MS/MS with SILAC encoding and Western Blotting.” Pet. 59. In particular, Petitioner relies on the results from the LC-MS/MS with SILAC encoding testing that Cai states show “[t]he relative abundance of the MWCNT-binding proteins spread *over 8 orders of magnitude.*” *Id.* at 60 (quoting Ex. 1005, 587). According to Petitioner, this result demonstrates “that Cai’s MS analysis detected protein concentrations in the subset across a dynamic range comprising the claimed ‘*at least 6 orders of magnitude.*’” *Id.* (citing Ex. 1003 ¶¶ 97, 229) (emphasis in original).

Petitioner’s showing above is sufficient to establish a reasonable likelihood that it will prevail in demonstrating that claim 1 is anticipated by Cai. At this stage, Patent Owner raises two arguments against the merits of

Petitioner's showing. *See* Prelim. Resp. 39–45. Neither of these arguments is persuasive to overcome Petitioner's showing on the current record.

First, Patent Owner attacks Petitioner's mapping of Cai to the limitations of claim 1. *See* Prelim. Resp. 39–43. Patent Owner asserts “there is a disconnect between what the Petition maps as the ‘subset of proteins of (b)’ and what the Petition maps as being assayed for step (c).” *Id.* at 41. According to Patent Owner, “[t]he Petition mapped the claimed ‘subset of (b)’ to the individual subset of proteins eluted in sample buffer in Cai’s first experiment” (referencing Petitioner’s annotated version of Cai Figure 1A), but relied on a “different experiment,” i.e., Cai’s LC-MS/MS with SILAC encoding testing, for limitation 1(c). *Id.* According to Patent Owner, this experiment did not involve the same subset of proteins identified for limitation 1(b), but rather a different mixture “manufactured by spiking ‘[e]qual volumes of proteins eluted from these pull-down experiments’ with ‘an equal amount of unfractionated ‘light’ lysate.’” *Id.* at 42 (quoting Ex. 1005, 586). Thus, Patent Owner contends, “Cai does not attribute the ‘8 orders of magnitude’” observed from its mass spectrometry data “to the concentrations in either ‘the subset of (b)’ or the ‘biological sample’ mapped by the Petition.” *Id.*

At this stage, Patent Owner's first argument is unavailing for several reasons. First, we do not agree with Patent Owner's characterization of Cai as disclosing “two separate studies” that Petitioner has improperly pieced together. *See* Prelim. Resp. 22, 42. Rather, 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.

Ex. 1005, Abstr. The current record supports that 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).

This interpretation is consistent with our present understanding of Cai's disclosure. As Petitioner points out, Cai discloses that after the proteins bound in the coronas were eluted (as depicted in Figure 1A) they were analyzed by SDS-Page. Pet. 57 (citing Ex. 1005, 585; Ex. 1003 ¶ 223). Cai refers to this as a "pull-down," presumably referring to the separation of bands of proteins as they move down the gel. Ex. 1005, 585. For the mass spectrometry testing, a "CNT pull-down" was prepared using a medium-encoded lysate to form coronas on the MWCNT and a "CB pull-down" was prepared using a heavy-encoded lysate to form coronas on the CB. *Id.* at 586. Equal parts of the proteins from these two pull-downs were mixed with a "control cell lysate (light)" and analyzed using LC-MS/MS to characterize and quantify the proteins bound in the MWCNT and CB coronas.⁹ *See id.* at 584–585 (Methods – Protein corona isolation), 588 (Fig. 3A). Cai states that these "mixed protein samples were electrophoresed, gel-sliced and digested as described previously." *Id.* at 585. Thus, on the current record, we

⁹ Our understanding is that because the proteins from these different pull-downs and the control are separately-labelled, i.e., heavy, medium, light, the subsequent mass spectrometry analysis can distinguish data corresponding to proteins that were bound to the MWCNT from data corresponding to proteins bound to the CB and proteins in the control cell lysate. To the extent that understanding is inaccurate, the parties are encouraged to clarify this point with evidence at trial.

understand Cai to teach that the pull-downs for the LC-MS/MS testing are the same subset of proteins Petitioner maps to limitation 1(b), i.e., the bound proteins eluted according to the process depicted in Figure 1A and further analyzed with SDS-PAGE. *See* Pet. 57–58.

Second, even if we agreed with Patent Owner that the Petition relies on two different experiments that are not explicitly combined in Cai, it does not necessarily follow that Cai would fail to anticipate. Patent Owner correctly observes that in order to anticipate, a reference must disclose all elements of the claim arranged as in the claim. Prelim. Resp. 43 (citing *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017)). However, it is also true that “a reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Microsoft*, 878 F.3d at 1068 (quoting *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (alteration in original)); *see also Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1342–43 (Fed. Cir. 2016) (affirming anticipation finding where the Board disagreed with the patent owner’s characterization of the anticipatory reference as “disclosing multiple, separately isolated methods” and instead found it “contemplate[d] combining the disclosed functionalities” even if did not provide an explicit example of such).

On the current record, the latter precedent would appear to apply here because the process in Cai’s Figure 1A is described as part of the general methodology for “[p]rotein corona isolation” used to prepare samples for all of Cai’s analyses, including the mass spectrometry analysis Petitioner relies

upon for limitation 1(c). *See* Ex. 1005, 584–585. Thus, a POSA would envisage combining the isolation steps in Figure 1A with the steps from the LC-MS/MS testing. That said, this case is still at a preliminary stage and these issues would benefit from further development at trial.

Patent Owner’s second argument is that Cai fails to disclose the separation of particles comprising “the coronas” of a plurality of particles of different particle types as recited in limitations 1(a) and 1(b). *See* Prelim. Resp. 43–45. Referring again to Petitioner’s annotated version of Cai’s Figure 1A, Patent Owner asserts:

The Petition highlights in red Cai’s individual incubation in experiment 1 of CNTs *or* CBs with HeLa cell lysate. The Petition then points to the proteins eluted from the individual particle type as “the Subset of proteins” (highlighted in green). . . . [T]he subset of proteins of an individual particle type mapped in Cai does not satisfy the claim requirement of step (b) because the Petition fails to demonstrate that the mapped “subset of proteins” is produced by separating a plurality of particle comprising “the coronas” from the two different particle types.

Id. at 44 (citation omitted).

This argument is also unavailing. Cai discloses contacting its biological sample (i.e., HeLa cell lysate) with two different particle types (i.e., CNT and CB) and subsequently isolating a subset of proteins from the coronas formed on both particle types. *See, e.g.*, Ex. 1005, 585 (stating that the binding of the protein corona formed by incubating HeLa cell lysate with CNTs was tested “in parallel” with the same testing for CB). While Figure 1A depicts the incubation of “CNT or CB” each in its own test tube, we discern nothing in the language of claim 1 that requires that the contacting of

the biological sample with “different particle types” recited in limitation 1(a) occur in the same reaction vessel or at precisely the same time.

To the extent Patent Owner argues otherwise, its argument is not well-presented in the Preliminary Response. As best we understand it, Patent Owner’s argument is premised on the recitation of “the coronas” in limitation 1(b), which refers back to the coronas formed on the plurality of particles in limitation 1(a). *See* Prelim. Resp. 43–44. But it is unclear how that distinguishes Cai’s process where protein coronas are formed on CNT particles in one test tube and CB particles in another test tube and the bound proteins subsequently isolated from each. 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). Accordingly, to the extent Patent Owner continues this argument at trial, it should explain how it construes claim 1 to support the distinction it attempts to draw with Cai and identify any intrinsic or extrinsic support for that construction.

For these reasons, and based on the current record, Petitioner has shown a reasonable likelihood it will prevail in demonstrating that claim 1 is anticipated by Cai.

Petitioner’s showing for dependent claims 4, 6, 17, 22, and 25 is also sufficient for institution. The Petition presents evidence and argument to support Petitioner’s assertion that Cai discloses the additional limitations recited in each of these claims. Pet. 60–61 (addressing additional limitations

in claims 4, 6, 17, 22, and 25). At this stage, Patent Owner does not make any arguments against Petitioner’s showing for these claims beyond its arguments for claim 1, which are unavailing for the reasons explained above.

F. Alleged Obviousness over Cai

Petitioner contends that “[t]o the extent that Cai is found not to disclose limitation 1[c] regarding the orders of magnitude . . . Cai would still render obvious claims 1, 4, 6, 17, 22, and 25.” Pet. 62. Petitioner explains that “Cai discloses protein concentrations in the form of empirical peptide abundance index data (emPAI).” *Id.* at 62–63 (citing Ex. 1005, 12–17 (Table S2, “Supplementary Table 2: Data reported in Figure 3”)).¹⁰ Petitioner then relies on testimony and calculations from Dr. Vargas to convert the largest and smallest emPAI values in Table S2 into “more traditional concentration numbers,” i.e., “mol %,” resulting in values that differ by 8 orders of magnitude. *Id.* at 63 (citing Ex. 1003 ¶¶ 239–240; Ex. 1018, 1267 (conversion formula)). Based on these calculations, Petitioner argues that “[a] POSA would have understood, or at least found it obvious . . . that proteins” in the subset analyzed in Cai’s mass spectrometry analysis “are detected with the instrument at concentrations across a dynamic range comprising six or more orders [of] magnitude” as recited in limitation 1(c). *Id.* at 62.

As explained above, Petitioner has demonstrated a reasonable likelihood that it will prevail in showing that claims 1, 4, 6, 17, 22, and 25 are anticipated by Cai. Petitioner’s additional showing for the “dynamic

¹⁰ Petitioner offers the declaration of Nancy Adams, a librarian, who testifies that Table S2 is part of Cai’s “[s]upplementary data,” which she obtained at the URL provided in Cai. Ex. 1012 ¶ 33 (quoting Ex. 1005, 592).

range” limitation in its obviousness ground is also sufficient on the current record. Petitioner’s additional showing for limitation 1(c) above is also sufficient on the current record. Accordingly, Petitioner has demonstrated a reasonable likelihood that it will prevail in showing that claims 1, 4, 6, 17, 22, and 25 are obvious over Cai.

At this stage, Patent Owner disputes Petitioner’s showing for the obviousness ground based on Cai by reiterating its arguments for the anticipation ground. *See* Prelim. Resp. 45–47 (urging that “Petitioner’s obviousness challenge fails to address or cure the deficiencies of its anticipation challenge”). On the current record, those arguments are unavailing for the same reasons explained above in the context of the anticipation ground.

G. Petitioner’s other grounds

Petitioner contends claims 1–4, 6, 7 17, and 22–25 are obvious over Hu and that claims 1, 2, 4, 6, 7, 17, 22, 23, and 25 are obvious over Zaccaria. *See* Pet. 21–46, 64–80. Patent Owner disputes these contentions. *See* Prelim. Resp. 30–39, 47–60.

Because the burden for institution has been met for the Cai-based grounds we need not determine whether Petitioner has also shown a reasonable likelihood of prevailing on its challenges based on Hu and Zaccaria. However, to provide guidance for developing these issues at trial, we note our initial skepticism regarding some of Patent Owner’s arguments in the Preliminary Response.

At this stage, many of the arguments Patent Owner advances to distinguish Hu and Zaccaria boil down to its assertion that these references teach “screening different nanoparticles individually,” i.e., where “a given

particle type was separated from the biological sample, one-at-a-time.” *See* Prelim. Resp. 30–31, 47–49. Patent Owner contrasts this with what it calls the “sensor array approach” in the ’360 patent. *Id.* at 10–12 (describing supposed distinctions from prior art approaches). However, claim 1 does not appear to be so limited.

We say this for several reasons. First, neither claim 1, nor any of the other challenged claims, recite a sensor array or otherwise state that the different particle types must be contacted with a biological sample at the same time. Second, the recitations in claims 13 and 14 (which are not challenged in the Petition) affirmatively suggest that claim 1 is not so limited.¹¹ *See InterDigital Commc’ns, LLC v. Int’l Trade Comm’n*, 690 F.3d 1318, 1324 (Fed. Cir. 2012) (“The doctrine of claim differentiation is at its strongest in this type of case, ‘where the limitation that is sought to be ‘read into’ an independent claim already appears in a dependent claim.’”) (quoting *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004)). Third, the repeated emphasis Patent Owner places on the recitation of “the coronas” in limitation 1(b), e.g., when it suggests the subset of proteins produced in that step must be derived from the coronas of all of the different particle types in limitation 1(a) (*see* Prelim. Resp. 12–13), is undermined by the fact that limitation 1(b) only requires separating “a subset of the plurality of particles comprising the coronas from the biological sample.” Ex. 1001,

¹¹ Claim 13 depends from claim 1 and further recites detecting a protein from the corona of a first particle and a protein from a second particle from among the plurality of particles “at the same time, wherein the first particle and the second particle are different particle types.” Ex. 1001, 87:40–45. Claim 14 depends from claim 13 and further recites that “the detecting is performed on an array.” *Id.* at 87:46–47.

86:61–62 (emphasis added). 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.” *See* Prelim. Resp. 31, 49.

We also note that claim 1 is a “comprising” claim and therefore does not exclude additional steps from the claimed method. This is significant because some of Patent Owner’s current arguments appear to assume otherwise. *See, e.g.*, Prelim. Resp. 50–52 (emphasis added) (arguing that “[w]hat the Petition points to [in Zaccaria] as the subset of step (b) was not put through LC-MS/MS” because “*following additional isolation and processing steps*, a different combination is subjected to LC-MS/MS)). Accordingly, to the extent Patent Owner continues these arguments at trial, it would be well-advised to try to address our concerns above regarding what we presently view as an overly-narrow interpretation of claim 1.

IV. CONCLUSION

Based on the current record, we determine Petitioner has shown a reasonable likelihood that it will prevail in establishing that at least one claim of the ’360 patent is unpatentable. Accordingly, we institute review of all claims challenged on all of the grounds in the Petition. *See* CTPG 64.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim. Our view with regard to any finding or conclusion reached in the foregoing analysis could change upon completion of the record.

V. ORDER

Accordingly, it is:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–4, 6, 7, 17, and 22–25 of the ’360 patent based on the unpatentability challenges presented in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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