

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ALAMAR BIOSCIENCES, INC.,  
Petitioner

v.

OLINK PROTEOMICS AB,  
Patent Owner

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Case IPR2024-01353  
U.S. Patent No. 7,883,848

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**PATENT OWNER'S SUR-REPLY  
TO PETITIONER'S REPLY**

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**PATENT OWNER'S UPDATED EXHIBIT LIST**

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                            |
|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2001               | File History Excerpts of U.S. Patent App. 17/330,331                                                                                                                                          |
| 2002               | Wei Feng et al., NULISA: A Proteomic Liquid Biopsy Platform with Attomolar Sensitivity and High Multiplexing, 14 NATURE COMMUNICATIONS 7238 (2023) (“Feng”)                                   |
| 2003               | Adam Bonislowski, Alamar Biosciences Prepping Proteomics Platform for 2024 Launch, GENOMEWEB (Apr. 13, 2023) (“Alamar Press Release”)                                                         |
| 2004               | Darmanis et al., ProteinSeq: High-Performance Proteomic Analyses by Proximity Ligation and Next Generation Sequencing, 6 PLOS ONE 9 (2011) (“Darmanis”)                                       |
| 2005               | Rachel Y. Nong et al., Solid-phase Proximity Ligation Assays for Individual or Parallel Protein Analyses with Readout via RealTime PCR or Sequencing, 8 NATURE PROTOCOLS 1234 (2013) (“Nong”) |
| 2006               | Zhi Wan et al., Photocleavage-Based Affinity Purification of Biomarkers from Serum: Application to Multiplex Allergy Testing, 13 PLOS ONE (2018) (“Wan”)                                      |
| 2007               | U.S. Patent App. Pub. No. 2018/0292394 (“Soldo”)                                                                                                                                              |
| 2008               | Expert Declaration of Bradley L. Pentelute Ph.D.                                                                                                                                              |
| 2009               | Deposition Transcript of Norman C. Nelson (June 3, 2025)                                                                                                                                      |
| 2010               | <i>Curriculum Vitae</i> of Bradley L. Pentelute Ph.D.                                                                                                                                         |
| 2011               | Mullis et al., “Specific enzymatic amplification of DNA in vitro: the polymerase chain reaction,” Cold Spring Harb Symp Quant Biol, 51:263-73 (1986)                                          |
| 2012               | Sambrook et al., <i>Molecular Cloning, A Laboratory Manual</i> (3 <sup>rd</sup> edition), Cold Spring Harbor Laboratory Press (2001)                                                          |

| Exhibit No. | Description                                                         |
|-------------|---------------------------------------------------------------------|
| 2013        | Second Deposition Transcript of Norman C. Nelson (October 29, 2025) |

**TABLE OF AUTHORITIES**

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| <i>Nobel Biocare Serv’s. AG v. Instradent USA, Inc.</i> ,<br>903 F.3d 1365 (Fed. Cir. 2018).....                             | 11             |
| <i>Oatey Co. v. IPS Corp.</i> ,<br>514 F.3d 1271 (Fed. Cir. 2008).....                                                       | 11, 12         |
| <i>Osseo Imaging, LLC v. Planmeca USA Inc.</i> ,<br>116 F.4th 1335 (Fed. Cir. 2024) .....                                    | 11             |
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| <i>United States v. Dunkel</i> ,<br>927 F.2d 955 (7th Cir. 1991).....                                         | 6            |
| <i>Wasica Finance GmbH v. Continental Automotive Systems, Inc.</i> ,<br>853 F.3d 1272 (Fed. Cir. 2017).....   | 2, 6, 24, 25 |

## **Regulations**

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## I. INTRODUCTION

Petitioner fails to meet its burden for several reasons. First, Petitioner’s art combinations fail to teach or suggest all the elements of the challenged claims. POR, 20-36, 57-63; EX2008, ¶¶98-133, 175-191. This defect permeates the entire Petition and is fatal to Grounds 1-4. *Id.* Second, the Petition fails to account for significant technical roadblocks its obviousness theory creates—issues that would have been readily apparent to a POSA and would have dissuaded the artisan from modifying the art with a reasonable expectation of success. POR, 36-57, 63-67; EX2008, ¶¶134-173, 192-208. Thus, the Petition fails to show by a preponderance of the evidence that any challenged claim is unpatentable.

IPR petitioners have an obligation “to make their case *in their petition*....” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369-1370 (Fed. Cir. 2016); *see also SAS Institute, Inc. v. Iancu*, 584 U.S. 357, 366 (2018) (“the *petitioner’s petition* ... is supposed to *guide the life* of the litigation.”).<sup>1</sup> Unable to make its case in the Petition, Petitioner’s Reply introduces a new theory for Grounds 1-2. Petitioner now relies on different disclosures in Kanan to meet a claim element (even going so far as to import an additional reference, EX1013, into its basis for Grounds 1-2), and a newfound claim construction to encompass

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<sup>1</sup> Emphasis is added throughout unless otherwise indicated.

the new art disclosures. Petitioner follows the same playbook for Grounds 3-4.

Here, Petitioner belatedly attempts to correct inconsistencies in the Petition's claim mapping through backfilled explanations, mischaracterizations of the art, and reliance on new disclosures in its lead reference, Baez. "Rather than explaining how its original petition was correct, [Petitioner]'s subsequent arguments amount to an entirely new theory of prima facie obviousness absent from the petition.

Shifting arguments in this fashion is foreclosed by statute, [legal] precedent, and Board guidelines." *Wasica Finance GmbH v. Continental Automotive Systems, Inc.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017). Petitioner should not be permitted to first present inconsistent and undeveloped arguments, and only after being challenged by Patent Owner, provide revised arguments with new theories and backfilled explanations in an attempt to salvage its failed Petition. *Id.*

Notwithstanding these improprieties, Petitioner still cannot meet its burden. The Reply fails to demonstrate that Kanan and Neri teach all the elements of claim 1(d) and 1(e), and still fails to grapple with the technical issues created by combining the art as Petitioner proposes. The Reply also fails to demonstrate that Baez and Landegren teach all the elements of claim 1(a), 1(d), and 1(e), and fails to resolve Baez's disclosures purporting to have already solved the alleged goals of a POSA stated in the Petition. The Board should reject the Petition and find all challenged claims not unpatentable.

## II. PETITIONER FAILS TO MEET ITS BURDEN ON GROUND 1.

### A. Kanan and Neri do not teach or suggest claim 1(d)'s selecting step

#### 1. Petitioner's new theory should be rejected

Petitioner cannot deny that its Petition and expert declaration rely exclusively on Kanan's disclosure of biotin-streptavidin affinity selection as allegedly teaching claim 1(d)'s "selecting all cis-reactive cells exhibiting the detectable trace." The Petition's claim mapping is explicit, arguing that "Kanan in view of Neri discloses this step" because "Kanan discloses that after bond formation '*[s]treptavidin affinity selection* of the resulting solution separates biotinylated from non-biotinylated sequences.'" Pet., 34-35. The Petition goes on to argue that "the *biotin-streptavidin capture would allow selection* of only the bond-forming combinations ... *which a POSA would have understood as 'selecting all cis-reactive cells* exhibiting the detectable trace.'" *Id.*, 35. The Petition's arguments for dependent claims 2 and 3 confirm this. Pet., 36 ("Kanan discloses that the bond forming pairs can be selectively detected *using streptavidin affinity selection...*"), 37 ("*streptavidin affinity selection* [is] a form of affinity purification."); *see also*, EX1005, ¶¶122, 124, 134-138 (parroting the same claim mapping approach); EX2009, 62:19-64:14.

As explained in the POR, Kanan's disulfide cleavage method would have cleaved and removed one of the nucleic acid moieties from the interactors prior to Kanan's biotin-streptavidin selection. POR, 20-28; EX2008, ¶¶114-134. Thus, the

bond-forming pairs “selected” in Petitioner’s proposed workflow would not have been “cis-reactive cells exhibiting the detectable trace” because the selected pairs meet neither the claims’ nor the specification’s defined criteria for CRCs. EX1001, 9:35-38, 41:43-49; POR, 20-28; EX2008, ¶¶98-119.

Petitioner’s Reply does not dispute the Petition’s claim mapping failures. Reply, 5-10. Rather, Petitioner belatedly introduces a new construction of the claim term, “selecting,” and pivots to *new* disclosures in Kanan as allegedly teaching claim 1(d). Petitioner now argues for the first time that “‘selecting’ can be a process,” and therefore under this new construction, *the combination* of Kanan’s *disulfide cleavage and* biotin-streptavidin selection teaches claim 1(d). *Id.*, 5; EX1051, ¶24. For example, compare Dr. Nelson’s testimony mapping Kanan’s disclosure of “selection” in his first and second declarations:

**Original position**

“A POSA would have understood that the use of the *biotin-streptavidin capture* would allow *selection of only the CRCs* with bond-forming combinations ... as shown above in Fig. 1.b. *Therefore*, in my opinion, *Kanan discloses selecting all cis-reactive cells* exhibiting the detectable trace.” EX1005, ¶124 (relying on EX1010, 545).

**Revised position**

“This confirms that *Kanan’s selection* is a process that *begins prior to the cleavage of the disulfide bond* of the pool B oligonucleotides.” EX1051, ¶24 (relying on EX1013, 7-8).

To bolster its new theory, Petitioner not only ignores the express language of the claims while mischaracterizing disclosures in the ’848 patent (*see infra*, Sections II.A.2-3), but also introduces new evidence not presented as part of the Petition’s Grounds. *See, e.g.*, Reply, 7; EX1051, ¶24 (now relying on Kanan’s *Supplemental Information* (EX1013, 7-8), for teaching a claim element). During cross-examination, Dr. Nelson admitted his Reply Declaration now relies on the combination of Kanan (EX1010), Neri (EX1011), and Kanan’s *Supplemental Information* (EX1013) as his basis for obviousness. EX2013, 231:8-12. Exhibit 1013 was not included in the Petition’s Grounds 1-2 or cited in the Petition’s mapping of claim 1(d). Pet., 2-3, 34-35. *See Intelligent Bio-Sys.*, 821 F.3d at 1369-

1370 (affirming the Board’s refusal to consider petitioner’s reply theory relying on references “which were not relied upon to support unpatentability in the Petition.”).

Petitioner and its expert also introduce substantively revised versions of figures originally presented in the Petition. Reply, 4, 9, 16; EX1051, ¶¶10, 27, 30, 57, 59. Unable to show its revised figures in the Petition, Petitioner requires the Board and Patent Owner to search through the record in hopes of finding “each component” of the new figures, which according to Petitioner requires an archaeological dig through 14 different pages of the Petition (taken from different sections of the brief, addressing multiple different claims), at least nine different paragraphs from its expert declaration (taken from different sections of the declaration addressing multiple different claims), and at least 4 different pages of testimony from a deposition transcript. Reply 5; *see also id.*, 9, 16. The Board, however, “should not be forced to ‘play arch[a]eologist with the record.’” *Parus Holdings, Inc. v. Google LLC*, 70 F.4th 1365, 1372 (Fed. Cir. 2023) (citation omitted); *see also United States v. Dunkel*, 927 F.2d 955, 956 (7th Cir. 1991) (“Judges are not like pigs, hunting for truffles buried in briefs.”).

Nor can Petitioner shift arguments in Reply, as it has here. *Wasica*, 853 F.3d at 1286; 37 C.F.R. § 42.23(b); *see also Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367-1368 (Fed. Cir. 2015) (“We see no error in the Board’s rejection of [petitioner]’s reliance, in its Reply submissions, on previously

unidentified portions of a prior-art reference to make a meaningfully distinct contention.”). Accordingly, the Board should “hold[] [Petitioner] to its word and disregard[] its new theory first raised in reply.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1331 (Fed. Cir. 2019).

## **2. The intrinsic evidence refutes Petitioner’s new construction**

Even on the merits of Petitioner’s new arguments, Petitioner cannot meet its burden. The Reply argues as if *Patent Owner* has introduced a new, “narrow interpretation” of the term, “selecting.” Reply, 5; EX2013, 205:17-206:16, 208:3-210:9. This is flatly wrong. “It is a ‘bedrock principle’ of patent law that ‘*the claims of a patent define the invention*’ to which the patentee is entitled the right to exclude.” *Phillips v. AWH Corp.*, 415 F. 3d 1303, 1312 (Fed. Cir. 2005) (en banc) (citations omitted). Petitioner ignores this bedrock principle by providing a new construction of the term “selecting” that is divorced from the express language of the claims and not supported by the specification or the file history.

Petitioner and its expert construe the single term “selecting” in claim 1(d), ignoring *what* must be selected: “all *cis-reactive cells* exhibiting the detectable trace.” EX1001, claim 1; Reply, 5-10 (construing only “selecting”); EX1051, ¶¶20-22 (same); EX2013, 205:17-208:8. A POSA would have understood that claim 1(d) requires just what it expressly states, “selecting all *cis-reactive cells* exhibiting the detectable trace.” EX2008, ¶¶94, 98-119. Claim 1(b) expressly defines CRCs

with specific criteria “compris[ing] *at least two interactors* bound in proximity to one another by *an associated oligonucleotide formed from the association between at least two nucleic acid moieties....*,” and claim 1(c) requires stimulating a “functional interaction having a detectable trace.” EX1001, 41:37-49; EX2008, ¶¶91-93; *see also* EX1001, 9:35-38.

Thus, a POSA would have understood from the plain language of the claims that “selecting all *cis-reactive cells* exhibiting the detectable trace” simply means selecting all of the molecules meeting the defined criteria for CRCs and exhibiting the detectable trace. EX2008, ¶¶94, 98-119. The language of the dependent claims confirms this. Dependent claims referencing the selecting step expressly refer to “selecting *all cis-reactive cells* exhibiting the detectable trace” (e.g., claims 2 and 3) or labeling “the *cis-reactive cells*” (claim 19). EX2013, 198:2-7, 198:19-199:2, 202:22-203:13.

Further support is found in the specification. For example, when describing methods of detecting *functional interactions*, the ’848 patent discloses that “the CRCs which display functional interactions *must be selected* for detection and/or analysis,” and further that “a ‘filter’ or a ‘filtering process’” for detecting functional interactions “is the means employed to selectively *separate the desired CRCs*.” EX1001, 19:41-48; *see also, id.*, FIG. 2D (depicting selection of CRCs), 6:41-50, 15:25-26, 20:1-3. In each case, the patent describes selecting all the CRCs

(which meet defined criteria of a CRC) exhibiting the detectable trace.

Further evidence is found in the file history—e.g., the original claims. EX1002, 64-73, 284-292. Just like claim 1 of the '848 patent, original claim 20 recites a method of detecting “functional interactions” and requires “selecting *all cis-reactive cells* exhibiting the detectable trace.” *Id.*, 68, 288. Compare that with original claim 1, which recites a method of detecting “affinity interactions” and requires not selecting CRCs, but rather “selecting the plurality of unique associated oligonucleotides.” *Id.*, 64, 284. Dr. Nelson acknowledges differences in these embodiments (EX1005, ¶55), yet apparently failed to consider them in his Reply Declaration. EX2013, 296:19-297:10.

### **3. Petitioner mischaracterizes the '848 patent to fit its new construction**

Petitioner argues that embodiments in the specification would be “improperly” excluded from the scope of the challenged claims, unless applying Petitioner’s new construction. Reply, 2 (citing EX1001, 19:7-9, 20:31-39, 30:56-67), 8-9 (same). Petitioner is wrong on the facts and the law. First, the disclosure at 19:7-9 relates to selection methods in embodiments of detecting *affinity interactions*, not functional interactions. *Compare* EX1001, 19:3, *with id.*, 19:40.

Second, Petitioner mischaracterizes an oligonucleotide array embodiment disclosed in the specification. Reply, 6; EX1051, ¶21; EX1001, 20:31-39. Here, the specification describes “conditional detection,” in which “[t]he *CRCs can be*

*hybridized* to a DNA oligonucleotide tag array where all possible combinations of identification sequences in the library are present.” EX1001, 20:31-39. That is, the patent expressly discloses *hybridizing the CRCs* to the array. This disclosure is not inconsistent with the plain and ordinary meaning of “selecting all cis-reactive cells exhibiting the detectable trace,” because it discloses adding *CRCs* to an array and then, e.g., selectively detecting the *CRCs* with the detectable trace via staining. *Id.* Contrary to Petitioner’s expert’s speculation, (EX1051, ¶ 21), the relied-upon disclosure does not even mention denaturing oligonucleotide strands of a double-stranded *CRC*. EX1001, 20:31-39. Moreover, Petitioner’s expert admits that claim 13, which recites using a “microarray analysis,” relates to claim 1(e)’s *analysis step*, not 1(d)’s selection. EX1051, ¶44; EX1001, 21:45-22:41.

Third, Petitioner mischaracterizes Example 5 as “an assay falling within the scope of claim 1.” EX1051, ¶32; Reply, 2, 8 (citing EX1001, 30:11-41, 30:56-67); EX2013, 214:16-216:14. Example 5, however, describes an assay *different* from the claimed method. Example 5 discloses an assay detecting thiol dimerization, which according to the ’848 patent, “can be viewed as formation of an affinity interaction with infinite affinity.” EX1001, 30:7-8. Example 5’s assay comprises *first* creating an interaction (thiol dimerization), *then* associating and ligating the nucleic acid moieties, and *then* amplifying the ligated products for analysis on a microarray. EX1001, 30:10-41; EX2013, 219:19-220:1. Example 5 does not

mention selecting CRCs, or even use the term, CRC. EX1001, 29:64-32:38.

Fourth, Petitioner mischaracterizes Dr. Pentelute's deposition testimony. Reply, 7; EX1051, ¶¶22, 97. Petitioner's expert quotes Dr. Pentelute<sup>2</sup> as if he were testifying about "selecting" in the 848 patent, when the full context of Dr. Pentelute's deposition transcript shows Dr. Pentelute was discussing a "selection" step from *his own patent*, a document Dr. Nelson admittedly did not review for his Reply Declaration, nor did Petitioner even file it in the record. EX2013, 295:12-21; EX1049, 67:15-68:17, 73:11-14, 139:12-20, 140:1-12; *see also* EX1049, 5; Paper 30, 5.

Relying on *Oatey Co. v. IPS Corp.*, 514 F.3d 1271 (Fed. Cir. 2008), *Nobel Biocare Serv's. AG v. Intradent USA, Inc.*, 903 F.3d 1365 (Fed. Cir. 2018), and *Google LLC v. EcoFactor, Inc.*, 92 F.4th 1049 (Fed. Cir. 2024), Petitioner argues that construing "selecting" to mean *selecting CRCs* (as expressly claimed) would exclude embodiments disclosed in the specification. Reply, 2, 7. Petitioner's cases are inapposite. As discussed above, the plain and ordinary meaning of "selecting

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<sup>2</sup> Petitioner's allegation that Dr. Pentelute "did not qualify as POSA at the relevant time" (Reply, 3) is legally and factually wrong. *Osseo Imaging, LLC v. Planmeca USA Inc.*, 116 F.4th 1335, 1340-1341 (Fed. Cir. 2024); EX2010; EX2008, ¶¶4-16.

all cis-reactive cells exhibiting a detectable trace” does *not* improperly exclude embodiments of detecting functional interactions.

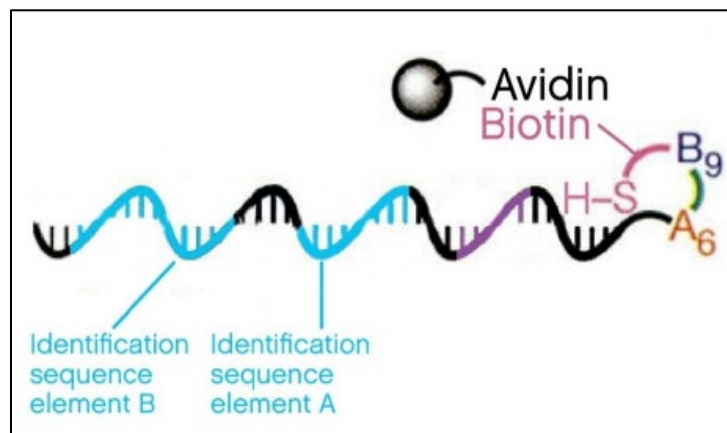
Petitioner follows the same erroneous rationale recently admonished by the Federal Circuit. *SIMO Holdings Inc. v. Hong Kong uCloudlink Network Tech. Ltd.*, 983 F.3d 1367, 1378-1379 (Fed. Cir. 2021). In *SIMO*, the Federal Circuit rejected the district court’s application of *Oatey*, cautioning that an embodiment in the specification must not “outweigh *the language of the claim*, especially when the court’s construction is *supported by the intrinsic evidence*.” *Id.* at 1379 (internal citation omitted). As *SIMO* explained, “*Oatey* ... recognizes that we should not infer that any particular embodiment is included in a claim when there is *probative evidence that sufficiently indicates the contrary*.” *Id.* at 1378; *see also PSN Illinois, LLC v. Ivoclar Vivadent, Inc.*, 525 F.3d 1159, 1166 (Fed. Cir. 2008); *TIP Systems, LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1373 (Fed. Cir. 2008). Here, probative intrinsic evidence—i.e., the language of the claims, the specification, and the file history—all support construing “selecting” in claim 1(d) to mean selecting *all CRCs*—as defined in the claims and the specification—exhibiting the detectable trace.

**4. Even under Petitioner’s new theory, Kanan and Neri do not teach or suggest claim 1(d)’s selection step**

There is no dispute that in Petitioner’s proposal, a POSA would have performed Kanan’s disulfide cleavage to remove one of the nucleic acid moieties

from the so-called CRCs, before performing biotin-streptavidin selection of the bond-forming pairs. POR, 20-28; EX2008, ¶¶98-119; EX2009, 62:19-63:7; Reply, 8 (“[t]his cleavage allows for any unbound oligonucleotides to be washed away ....”). Kanan’s disulfide cleavage applies to *all* the purported CRCs, regardless of whether there is a detectable trace—i.e., it is not selective. EX1010, 545; EX2008, ¶¶105-108.

Moreover, Petitioner continues to avoid the fact that the purportedly “selected” complexes would *still* not have been CRCs because they would not have comprised “*at least two interactors* bound in proximity to one another by an associated oligonucleotide.” EX1001, claim 1(b). Reply, 9; EX2008, ¶¶104-113. According to Petitioner, its new figure (copied below) is a visualization of the complexes selected in Kanan’s modified workflow:



Reply, 9; *see also*, EX1051, ¶30 (describing the above figure as occurring “*after* polymerization ... *and the selection process...*”); EX2013, 241:3-13. There is no dispute that a CRC comprises “at least two interactors,” and an interactor

comprises “a molecule of interest coupled with at least one nucleic acid moiety.”

EX1001, 41:36-49; EX2008, ¶¶92-93; EX2009, 37:12-38:8, 38:18-39:20. The “selected” complex depicted in Petitioner’s figure does not comprise two interactors and is not a CRC. *Id.*

Therefore, even under Petitioner’s new revisionist theory, Petitioner fails show that the art teaches or suggests claim 1(d)’s selection step.

**B. Kanan and Neri do not teach or suggest claim 1(e)’s analysis step**

**1. The Petition fails to explain how a POSA would have implemented Neri’s polymerization in Kanan’s workflow**

As explained in the POR, the Petition fails to provide any explanation of if, when, or how a POSA would have allegedly implemented a polymerization method from Neri into Kanan’s modified workflow. POR, 29-36; EX2008, ¶¶127-128. The Petition’s conspicuously absent argument addressing polymerization in claim 1 is underscored by the Reply’s repeated reliance on a vague, conclusory statement from a different section of the Petition discussing dependent claim 17. *Id.*; *see e.g.*, Reply, 4-5 (relying on Pet., 43-44 and EX1005, ¶¶180-184), 11-12 (similar). To satisfy its burden, Petitioner “cannot employ mere conclusory statements” and “must instead articulate *specific reasoning*, based on evidence of record, to support the legal conclusion of obviousness.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016); *see also Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 994 (Fed. Cir. 2017) (finding the Board’s

explanation “wanting,” because “the Board nowhere clearly explained, or cited evidence showing, how the combination of the two references was supposed to work.”). No such reasoning or explanation is found in the Petition. POR, 29-36; EX2008, ¶¶127-128. Nor does the Petition establish that a POSA would have been motivated to combine Kanan and Neri with a reasonable expectation of successfully modifying Kanan in view of Neri. POR, 36-49; EX2008, ¶¶134-158.

## **2. Petitioner’s Reply attempts to improperly backfill gaps in the Petition**

Petitioner’s Reply first cherry-picks from different sections of the Petition and its expert declaration, attempting to cobble together a trace argument that a POSA would have implemented a polymerization step from Neri into Kanan’s modified workflow. Reply, 11-12 (relying on Pet., 20-23, 31-33, and 43-44, and EX1005, ¶¶180-184). Again, even if accepting Petitioner’s revisionist history, there is no explanation *in the Petition* of when or how a POSA would have performed Neri’s polymerization in Kanan’s workflow. POR, 32-36; *Magnum Oil*, 829 F.3d at 1380; *Personal Web*, 848 F.3d at 994.

Petitioner now argues that “a POSA would not have relied on Neri for polymerization timing—and neither does the Petition.” Reply, 12. This was precisely Patent Owner’s point in the POR—the Petition provides *no explanation* of timing for Neri’s polymerization at all, other than stating “as taught in Neri.” POR, 34-35; Pet., 23. The Reply now attempts to backfill with a belated

explanation that Neri’s “polymerization would occur at the time of association ... prior to the functional interaction,” adding new figures depicting “how the polymerization process of the Kanan/Neri design ... would be visualized.” EX1051, ¶¶9-10. This belated explanation should be rejected.

Moreover, even with this do-over, Petitioner’s expert continues to provide inconsistent opinions, first testifying that “polymerization would occur at the time of association” and then later admitting that “polymerization [occurs] *after* the formation of the CRC”—i.e., *after association* and formation of the associated oligonucleotide. EX1051, ¶¶9, 42; *see also* EX2009, 86:17-88:19, 161:23-169:21 (inconsistent testimony regarding Nelson’s figures in his opening declaration); EX2013, 271:15-281:18, 297:23-299:9, 300:14-17, 301:25-305:19 (inconsistent testimony regarding Nelson’s understanding of the 848 patent’s Figure 5); EX2013, 299:11-300:7, 302:8-22 (inconsistent testimony regarding the relationship between ’848 patent Figures 4 and 5); POR, 39-41. The Board should not credit “expert testimony that has multiple material contradictions” and laden with “conflicting testimony.” *Interactive Commc’ns Int’l, Inc. v. Blackhawk Network Inc.*, IPR2024-00465, Paper 40 at 3 (P.T.A.B. Oct. 9, 2025); *see also, Homeland Housewares, LLC v. Whirlpool Corp.*, 865 F.3d 1372, 1378 (Fed. Cir. 2017) (explaining that expert testimony plainly inconsistent with the record or based on an incorrect understanding of the claims should be disregarded).

**3. Petitioner's new theory fails to remedy the Petition's failure regarding claim 1(e)**

As discussed above, Petitioner's new theory fails to demonstrate that Kanan and Neri teach or suggest selecting CRCs, as claimed in step (d). Therefore, Kanan and Neri likewise do not teach or suggest analyzing the "associated oligonucleotides *from the cis-reactive cells selected in step (d)*" as claimed in step (e) because Petitioner's art fails to teach selecting CRCs in the first place. POR, 28-32; EX2008, ¶¶120-126.

**C. A POSA would not have been motivated to combine Kanan and Neri with a reasonable expectation of success**

Dr. Pentelute explains in detail that a POSA following Petitioner's proposed workflow would have expected insurmountable technical problems due to Neri's d-spacer and the multiple, common hybridizing regions within Petitioner's hypothetical library members. EX2008, ¶¶134-158; POR, 36-49. A POSA would have expected Petitioner's design to create extensive false-positive and false-negative results, defeating the Petition's stated rationale for making the modifications in the first place. EX2008, ¶¶148-154; POR, 42-45.

Petitioner's Reply argument boils down to an unsupported assertion that a POSA would have been able to figure it out, offering no substantive explanation dealing with the unintended hybridization issues created by Petitioner's Kanan/Neri combination. Reply, 18-19 (arguing a POSA "would have had the

skills to design the assay conditions to promote hybridization between the intended hybridizing regions.”); *id.*, 16-17. Petitioner also argues that Neri does not disclose any issues with unintended hybridization. *Id.*, 17.

Contrary to Petitioner’s unsupported argument, unintended hybridizations were reflected in the art. For example, Kanan’s Supplemental Information discloses needing “computer algorithms to minimize *undesired reactivity* arising from the *mismatched hybridization*.” EX1013, 10. Fredriksson similarly discloses issues with “*target-independent ligation events*” (i.e., false-positives). EX1020, 474. While Kanan and Fredriksson proposed solutions to mitigate their issues, each of their methods involved using probes designed to specifically hybridize or bind with a specific partner. Neither Kanan nor Fredriksson involved combinatorial or multiplexed methods using library members comprising d-spacers and multiple, universal hybridization regions like Petitioner’s proposed Kanan/Neri combination. EX2008, ¶¶40-50, 61-65.

Further, Neri’s silence on unintended hybridization is immaterial. Reply, 17 (citing EX1011, ¶¶[0111]-[0119]). First, Petitioner’s expert mistakenly characterizes Neri’s Example 3 as working example, when it in fact is prophetic with no experimental results. EX1051, ¶62; EX2013, 259:9-263:22. It is thus no surprise that Neri reports no unintended hybridization. Second, Neri discloses that the library members in Example 3 only include *two oligonucleotides* intended to

hybridize with each other—there would have been no other oligonucleotides in the assay to create unintended hybridization events. EX1011, ¶¶[0111]-[0119]; EX2013, 266:17-269:6.

The Petition fails to establish that a POSA would have been motivated to combine Kanan and Neri with a reasonable expectation of success, and Petitioner’s Reply does nothing to show otherwise.

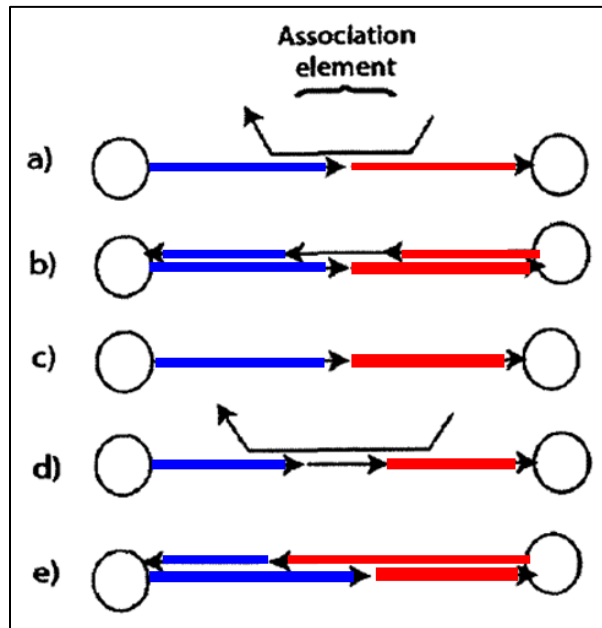
### III. PETITIONER FAILS TO MEET ITS BURDEN ON GROUND 2

#### A. Kanan, Neri, and Famulok do not teach or suggest the elements of claim 16

Claim 16 requires that the “association is via ligation.” EX1001, 43:20-22. There can be no dispute that in Neri’s Figure 7 (relied upon by Petitioner in Ground 2), the purported interactors are *already associated* via hybridization and have *already formed an associated oligonucleotide*, all before allegedly implementing Famulok’s ligation with the splint oligonucleotide. POR, 50-51; EX2009, 128:23-129:2, 130:23-131:19, 134:14-135:16.

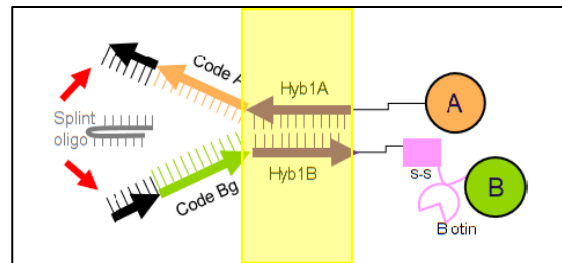
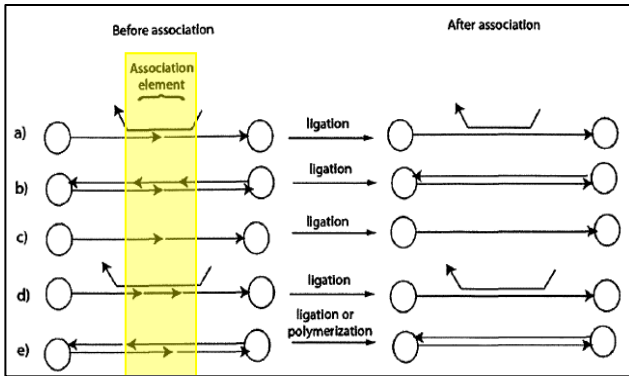
Petitioner argues in Reply that embodiments in the ’848 patent’s Figure 5 contemplate “association between NAMs before ligation.” Reply, 19; EX1051, ¶72. Petitioner again mischaracterizes the ’848 patent. First, Petitioner’s expert wrongly testifies that Figure 5 “a, b, d, and e” show “*hybridization[] between the interactors* before the ligation.” EX1051, ¶72. As shown below, the nucleic acid moieties of the interactors in 5a, 5b, 5c, and 5d (colored blue and red) are not

hybridized *with each other*:



EX1001, Fig. 5 (color added). During cross-examination, Dr. Nelson conceded he was uncertain about what is depicted in Figure 5a (“can’t tell exactly”), 5b (“difficult to tell,” “not sure”), 5c (“difficult to say”), 5d (“I’m not clear on what figure D represents”), and 5e (“difficult to say”). EX2013, 275:15-281:18.

And while the interactors of Figure 5e are depicted as hybridizing with each other, they hybridize *only as required for the ligation to occur*—i.e., the ligation takes place at the hybridization/association site. EX1001, FIG. 5e. As shown below (left, highlighted), in each embodiment of Figure 5a-e, the ligation takes place at the association site.



EX1001, FIG. 5 (highlighting added). EX2008, ¶167 (highlighting added).

Indeed, when discussing the '848 patent's Figure 5, Petitioner's expert admits that "the interactors must be in in close spatial proximity to each other for the ligation to occur." EX1051, ¶72. This is markedly different from Petitioner's proposed Famulok combination (above, right), in which the ligation with the splint oligonucleotide is distant from and unrelated to the interactor hybridization/association site (highlighted). EX2008, ¶¶162-162; EX2009, 128:23-129:2, 130:23-131:19.

Petitioner thus fails to demonstrate that Kanan, Neri, and Famulok teach or suggest claim 16's "association by ligation."

## B. Ground 2 remains riddled with unresolved technical issues

As Dr. Pentelute explains, a POSA would not have been motivated to combine Kanan, Neri, and Famulok with a reasonable expectation of success. EX2008, ¶¶159-173. If the ligatable "tails" of Petitioner's modified Neri interactors all have common hybridization regions to allow hybridization with a

common splint oligonucleotide, a POSA would have expected the splint to hybridize with multiple different interactors, creating a mess of false-positive and false-negative results. EX2008, ¶¶166-169. On the other hand, if the tails of the Neri interactors have unique hybridization regions such that they can only hybridize with a corresponding unique splint oligonucleotide, the POSA would be forced to synthesize unique interactors and unique splints for every pair of probes, defeating Petitioner's stated motivations for performing the ligation embodiment. *Id.* The Petition addresses none of these issues. POR, 51-56.

In its Reply, Petitioner argues with no support that "concern for mis-ligation is minimal" and a conclusory assertion that POSA would have been able to figure out the "appropriate assay conditions." Reply, 20-21. Petitioner cannot meet its burden relying on belated and conclusory arguments. *Magnum Oil*, 829 F.3d at 1380; *Personal Web*, 848 F.3d at 994. And as explained above in Section II.C, concern for unintended hybridization was far from "minimal" in Petitioner's proposed art combination comprising multiple common hybridization regions and potential d-spacers. EX1013, 10; EX1020, 474; EX2008, ¶¶148-154, 167-173. Petitioner argues that Famulok "does not describe any issues of ligating different aptamers together," but this is unsurprising because Famulok is merely a *commentary* on another paper, Fredriksson. Reply, 21; EX1012, 448; EX2008, ¶62.

#### **IV. PETITIONER FAILS TO MEET ITS BURDEN ON GROUNDS 3 AND 4**

##### **A. Baez and Landegren do not teach or suggest claim 1(a)'s forming interactors step**

As the Board already correctly determined, the Petition's inconsistent claim mapping fails to clearly explain how Baez and Landegren teach or suggest the elements of claim 1(a). DI, 36; POR, 56-58. Nothing in the developed record warrants a different conclusion.

Petitioner's Reply not only attempts to rewrite the Petition's inconsistent claim mapping, but its expert remarkably blames his own inconsistencies on language in Patent Owner's district court complaint. EX1051, ¶85. A review of the evidence shows otherwise. When discussing the NULISA system in its district court filings, Patent Owner refers to "probes consisting of an antibody and a nucleic acid" that form "interactors" (EX1007, ¶21), and "matched antibody pairs" as "molecules of interest" (EX1008, 1). Meanwhile, the Petition relies on the "reporter conjugates" disclosed in Baez as meeting *both* the MOI *and* interactor limitations of claim 1. Pet., 55-56; POR, 56-57; DI, 36. Petitioner cannot now revise these fatal inconsistencies in the Petition. In *Ericsson Inc. v. Intellectual Ventures LLC*, 901 F.3d 1374, 1380-81 (Fed. Cir. 2018), the petitioner "merely expand[ed] on a previously argued rationale." Here, Petitioner seeks to rewrite its original claim mapping strategy to correct the fatal defects in the Petition—a

strategy “foreclosed by statute, [legal] precedent, and Board guidelines.” *Wasica*, 853 F.3d at 1286.

**B. Baez and Landegren do not teach or suggest claim 1(d)’s selecting step**

The Petition wrongly relies upon Baez’s disclosure of *detecting ASAs* to meet claim 1(d)’s “selecting all cis-reactive cells exhibiting the detectable trace.” Pet., 60; POR, 59-60; EX2008, ¶¶179-185. As Dr. Pentelute explains, Baez teaches *detecting* “analyte-specific amplicons” (ASAs), which (i) are *not CRCs* as claimed, and (ii) Baez teaches *detecting* the ASAs, not selecting them. EX2008, ¶¶179-185. Petitioner’s argument is founded on an erroneous conflation of *ASAs* in Baez with *CRCs* of the ’848 patent. Pet., 60 (equating “*CRCs*” with “*ASAs in Baez*”). Baez, however, expressly defines an ASA as “the *nucleic acid product* formed by [] joining the two assay nucleic acid-labels ... due to the formation of the analyte-dependent reporter-complex.” EX1003, 9:27-31. Dr. Nelson acknowledged this definition during cross-examination. EX2013, 282:11-18. Thus, Baez indisputably limits an “ASA” to a *nucleic acid product*, which does *not* include its antibody probes. *Id.*; EX2008, ¶¶183-184. Baez’s disclosure of *detecting ASAs* is therefore not a teaching or suggestion of selecting *CRCs*, as claimed. POR, 59-60.

Petitioner’s Reply doubles down on the same erroneous conflation, arguing that “the ASA ... is the complex with the two antibodies connected via ligation of their nucleic acid labels.” Reply, 26; *see also, id.*, 27 (equating “*CRCs*” with

“Baez’s ASAs”); EX1051, ¶100 (“To be clear, the ASA in Baez includes the complex containing two antibodies connected via the ligation of their respective nucleic acid labels.”). Again, Baez’s definition of ASA expressly contradicts Petitioner’s argument—ASAs are not equivalent to CRCs of the ’848 patent. EX1003, 9:29-31; EX2013, 282:11-18. And, even if accepting Petitioner’s interpretation of Baez’s *detection* methods as “selecting,” Petitioner fails to demonstrate how (alleged) selection of *analyte-specific amplicons*—which Baez expressly defines as a *nucleic acid product*—satisfies “selecting *all cis-reactive cells* exhibiting the detectable trace,” as claimed.

Petitioner also argues that “PO only analyzes Baez’s column 17.” Reply, 25. Petitioner and its expert, however, relied exclusively upon Baez’s column 17 when discussing claim 1(d). Pet., 60; EX1005, ¶252; POR, 59. Patent Owner simply responded to the arguments and evidence as presented in the Petition. *Id.* In Reply, Petitioner and its expert now expand their original arguments to rely upon new disclosures in Baez’s column 11. Reply, 25 (citing EX1003, 11:52-55); EX1051, ¶96. *Wasica*, 853 F.3d at 1286. Regardless, Baez’s disclosures in column 11 do not change its express definition of an ASA or teaching of *detecting* the ASAs. EX1003, 9:27-31, 16:65-18:12.

**C. Baez and Landegren do not teach or suggest claim 1(e)’s analysis step**

Because Baez and Landegren do not teach or suggest claim 1(d)’s selecting

step, they likewise cannot teach or suggest claim 1(e) because 1(e) requires “subjecting the associated oligonucleotides *from the cis-reactive cells selected in step (d)* to an analysis.” POR, 61-62. Additionally, the Petition indisputably relies on Baez’s disclosure of amplifying and detecting “the amplified ASA product” as allegedly meeting the elements of claim 1(e). Pet., 61. Absent from the Petition’s argument addressing claim 1(e) is any explanation of how a POSA would have detected the *identification sequence elements* solely by detecting a ligation product or amplicon thereof. POR, 62. Petitioner has not shown how detecting the presence of a ligation product (or its amplicon) satisfies detection of the at least two identification sequence elements, as claimed. EX2008, ¶¶188-191.

Petitioner’s Reply changes nothing. The Reply argues that the identification sequence elements are *included* in the “ligation product” (Reply, 27), again failing to explain how detection of a ligation product or its amplicon—which the Petition relies on as meeting step 1(e)—satisfies detecting the *identification sequence elements*. EX2008, ¶¶188-191.

**D. A POSA would not have been motivated to combine Baez, Landegren (and Freskgaard), with a reasonable expectation of success**

As Dr. Pentelute explains, Baez purports to have already satisfied the POSA’s alleged goal (according to Petitioner) of creating an “assay with reduced background signal and the ability to screen multiple analytes in a timely manner.”

EX2008, ¶¶192-196. In its Reply, Petitioner takes out of context a single statement from Baez’s background section that “[m]ethods for the reduction of background noise are continually being sought.” Reply, 28 (citing EX1003, 1:32-33). Petitioner fails to substantively rebut the fact that Baez *purports to provide those sought-after methods* through its disclosures. EX1003, 5:33-34 (disclosing that “background is minimized, or is potentially eliminated, improving sensitivity.”); *id.*, 3:25-30, 13:18-20; POR, 62-63. The Petition fails to reconcile these teachings in Baez, along with the tension between solid-phase and solution-phase assays created by Petitioner’s art combinations. POR, 63-67.

At best, Petitioner’s reasoning in Grounds 3-4 “say[s] no more than that a skilled artisan, once presented with the two references, would have understood that they *could* be combined. And *that is not enough*: it does not imply a motivation to pick out those two references and combine them to arrive at the claimed invention.” *Personal Web Techs.*, 848 F.3d at 993-994. Petitioner fails to meet its burden of showing a motivation to combine Baez and Landegren (Ground 3) and Freskgaard (Ground 4) with a reasonable expectation of success.

## **V. CONCLUSION**

Petitioner failed to meet its burden of persuasion. The Board should reject the Petition and find all challenged claims not unpatentable.

Respectfully submitted,

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**CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))**

1. This Patent Owner's Sur-Reply complies with the type-volume limitation of 5,600 words, comprising 5,594 words, excluding the parts exempted by 37 C.F.R. § 42.24(c).
2. This Patent Owner's Sur-Reply complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word in 14-point Times New Roman font.

Respectfully submitted,

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**CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))**

I certify that the above-captioned **PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY** and Exhibit 2013 were served in their entirety on November 6, 2025, upon the following party via electronic mail:

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