

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Alamar Biosciences, Inc.,
Petitioner

v.

Olink Proteomics AB,
Patent Owner

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

PETITIONER'S REPLY

MAIL STOP PATENT BOARD

Patent Trial and Appeal Board
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I. Introduction

Patent Owner's Response ("POR") takes a narrow view of the claim language, ignoring the realities of the various assays disclosed and claimed. Patent Owner ("PO") also exaggerates potential issues with the Kanan/Neri design by not considering a POSA's skills at the relevant time.

For Grounds 1/2, PO's claim that the cleavage of the disulfide bond in Kanan prevents it from teaching claim 1 step (d) ignores the specification's embodiments disclosing the process of "selecting" the CRCs in step (d). Additionally, as the Petition demonstrated, the Kanan/Neri design can include polymerization of pool A and pool B oligonucleotides, enabling detection of the two identification sequence elements. Further, PO's claim of "technical issues" with mishybridization and increased unreliability is simply expert say-so that disregards a POSA's skillset.

For Grounds 3/4, PO overlooks evidence demonstrating that Baez teaches both MOIs and interactors under PO's view of these terms. Regarding Baez, PO focuses on its use of the word "detection" without considering Baez's full teachings. Moreover, PO is wrong that Landegren teaches away from Baez, especially when a POSA only uses Landegren for its nucleic acid tags with Baez's nucleic acid sequence.

Additionally, PO attacks Petitioner's expert Dr. Nelson by arguing he did not review "every word" of the materials. POR, 3. But PO's expert admitted he did not read every word of Ex. 1012, "would go fast" while reading material, and only spent

“10 to 15 hours” reviewing all exhibits and preparing his declaration. Ex.1048, 31:19-32:7, 198:6-11, 203:14-19.

Claims 1-20 are obvious over the prior art.

II. PO’s Improper Claim Construction Excludes Embodiments

While PO appears to agree all terms in Grounds 1/2 should be given their plain and ordinary meaning as understood by a POSA in view of the specification and prosecution history, PO narrowly construes them to try to avoid prior art. POR, 7-10. In doing so, PO ignores dependent claims and excludes embodiments that are encompassed within the plain and ordinary meaning of the claim terms. For example, the specification describes various ways of “selecting,” such as selective amplification with PCR and oligonucleotide tag array paired with labelled affinity reagents (*e.g.*, Ex.1001, 19:7-9, 20:31-39, 30:56-67), which PO’s construction improperly excludes. *Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276-77 (Fed. Cir. 2008) (claim terms should not be interpreted “in a way that excludes embodiments disclosed in the specification” “absent probative evidence to the contrary”). Indeed, “there is a strong presumption against a claim construction that excludes a disclosed embodiment.” *Nobel Biocare Servs. AG v. Intradent USA, Inc.*, 903 F.3d 1365, 1381 (Fed. Cir. 2018). PO has neither provided support to overcome this presumption nor properly articulated its claim construction positions.

Additionally, PO does not address claim construction for Grounds 3/4, POR 7-10, where a POSA would have understood the claim terms in view of PO's district court positions. Pet., 12-13.

III. Level Of Skill In The Art

PO defined a POSA differently from Petitioner by including a person with a Ph.D in organic chemistry, POR, 10, likely to include PO's expert, Dr. Pentelute. But Dr. Pentelute did not qualify as POSA at the relevant time because his Ph.D. is from 2008, and he lacks pre-2006 publications. Ex.1048, 35:15-19, 185:6-9; Ex.2010.

Regardless, a POSA would reach the same conclusions under either definition. Ex.1051, ¶¶4-6.

IV. Patent Owner Fails To Demonstrate Why The Board Should Not Find All Claims Unpatentable

A. Grounds 1/2 Demonstrate Unpatentability Based On Kanan/Neri/Famulok

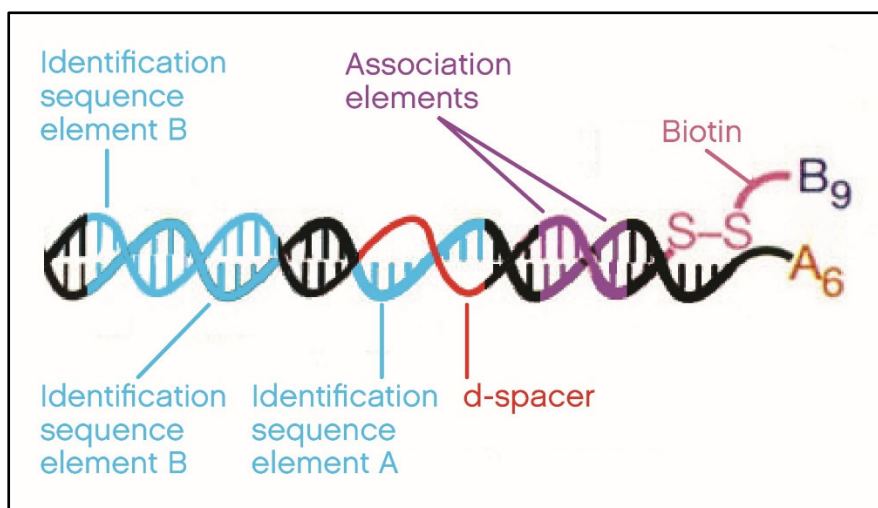
1. Kanan/Neri Discloses Claim 1

(a) Polymerization During CRC Formation Enables Detection of Both Identification Sequence Elements (Step (b))

Many of PO's positions rely on arguing that polymerization would either not occur in Kanan/Neri or, if it did, it would occur after selection (claim 1 step (d))—preventing detection of the two identification sequence elements. POR, 32-36. But the Petition establishes the “associated oligonucleotide formed from the *association*

between at least two nucleic acid moieties” can be “via *polymerization*,” which occurs during step (b), permitting selection of the CRCs with a detectable trace and detection of the two identification sequence elements. Pet., 20-23, 31-36, 43-44; Ex.1005, ¶¶122, 124, 129-130, 180-184. PO recognizes it would be nonsensical to polymerize after step (b), as a POSA’s entire motivation for combining Neri/Kanan would be lost. POR, 35-37.

Specifically, Neri teaches “associating the oligonucleotides of the library via polymerization.” Ex.1005, ¶¶180-184 (discussing the “polymerization” in dependent claim 17, which Dr. Pentelute agrees is “the association as described in claim 1 (b)[,]” Ex.1048, 103:4-104:20). Neri discloses “oligonucleotides of sub-library B ... can work as primers for a DNA polymerase reaction on the template A.” Ex.1005, ¶181. “With polymerization [in Kanan/Neri] ... [the pool A] interactor[] will not only contain its coding region but will also contain the anticodon of the ... [pool B] interactor.” *Id.*, ¶182. Kanan/Neri’s polymerization would be visualized as:



Ex.1051, ¶¶7-11 (each figure component is described and/or illustrated in Pet., 19-23, 27-33, 43-44 and Ex.1005, ¶¶105-106, 114-115, 180-184; Ex.2009, 163:3-22; 165:12-20; 167:1-168:24; 169:8-12 (after PO raised alleged discrepancy, Dr. Nelson explained that in the figures on pages 63 and 67 of Ex. 1005 black “vertical lines would represent bases, and it would -- and for this particular figure, it would represent hybridization.”)). Dr. Pentelute agrees polymerization “encodes the second identification sequence onto the other nucleic acid which is being polymerized.” Ex.1048, 108:14-20. Thus, the pool A oligonucleotides contain both identification sequence elements, which are then selected during step (d). Ex.1005, ¶182.

(b) PO’s Narrow Interpretation Of “Selecting” Ignores The Plain and Ordinary Meaning And Excludes Disclosed Embodiments (Step (d))

Hyper-focusing on a single event within Kanan’s selection process, PO argues that Kanan/Neri fails to disclose step (d) because “Kanan’s *streptavidin affinity selection step* occurs after the purported cis-reactive cells are destroyed[.]” POR, 21 (emphasis added). But the claims do not require a “streptavidin affinity selection”—they require “selecting all [CRCs] exhibiting the detectable trace.” Ex.1001, Cl. 1. PO ignores that “selecting” can be a process, consistent with the dependent claims and the specification’s disclosure of “selecting” procedures. *Id.*, 19:1-20:46. PO’s view is unsupported by the claims, specification, or Kanan.

PO improperly construes “selecting” as a single capture event, excluding any procedure, POR, 20-25, which is inconsistent with the dependent claims and specification. **First**, “selecting” may occur in different procedures, such as those in dependent claims 2-3 and 19-20: “selective separation,” “selective detection,” “affinity separation,” or allowing for “modification [that] permits the selective detection.” Ex.1001, Cls. 2-3, 19, 20; *Littlefuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022) (“By definition, an independent claim is broader than a claim that depends from it, so if a dependent claim reads on a particular embodiment of the claimed invention, the corresponding independent claim must cover that embodiment as well.”) **Second**, it excludes embodiments disclosing “selecting” as a process. Ex.1001, 19:4-20:47 (describing “filtering process” as a method of selection). For example, the specification discloses one embodiment of “selecting” including multiple procedures—first, hybridizing to a DNA oligonucleotide tag array and, second, staining with a labelled affinity reagent. *Id.*, 20:31-39; Ex.1051, ¶¶20-24. Additionally, PO’s expert concedes the specification:

teaches that CRCs which display functional interactions must be selected for detection and/or analysis. Filtering ***processes***, including affinity purification, are employed during the ***process to selectively separate*** the desired CRCs. This selection step can be ***modified*** according to the nature of the functional interaction that is being investigated. Downstream of the filtering ***process*** of CRCs the compositions of associated NAMs are detected and/or quantified.

Ex.2008, ¶35 (cleaned up) (emphasis added). Moreover, the specification does not restrict “selecting” and or explicitly require a singular “selecting” event; thus, construing “selecting” as limited to a single event is incorrect. *Google LLC v. EcoFactor, Inc.*, 92 F.4th 1049, 1058-59 (Fed. Cir. 2024) (vacating PTAB decision construing claims to exclude disclosed embodiments). Even Dr. Pentelute agrees “selecting” can be a “process of selection,” and that the specification provides “many, many possibilities” for selection and the “list goes on.” Ex.1048, 73:11-14, 136:23-138:15, 145:7-146:3.

PO’s strained interpretation of Kanan/Neri’s selection process does not withstand scrutiny. Kanan describes “[a] general one-pot *selection and analysis method* for the detection of bond-forming reactions between DNA-linked substrates.” Ex.1010, 546 (emphasis added). And in Kanan/Neri, with polymerization, the CRCs’ pool A oligonucleotides contain both identification sequence elements. Ex.1005, ¶¶129-130, 181-182.

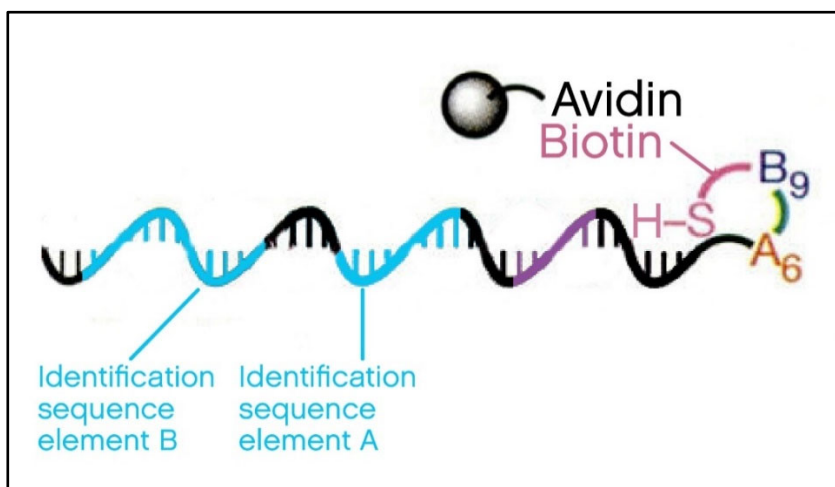
Kanan’s Supplementary Information includes a protocol for “Selections for Bond-Formation,” describing the procedure for selecting all CRCs exhibiting a detectable trace, including disulfide bond cleavage and streptavidin capture. Ex.1013, 7-8. For Kanan, Dr. Pentelute recognized that “the key part of the *selection* is the reaction discovery experiments and selection *procedure*.” Ex.1048, 164:3-16 (emphasis added). After stimulating CRCs to functionally interact, the solution

contains both “non-bond-forming combinations ...[and] bond-forming combinations[,]” e.g., CRCs that have and have not participated in a functional interaction. Ex.1048, 152:17-153:16. A reducing agent is then added, cleaving the disulfide bond between MOI B (bound to biotin) and the attached nucleic acid, allowing for selection of only CRCs with a detectable trace. Ex.1013, 8; Ex.1051, ¶¶26-30. Without cleavage, the streptavidin would bind all CRCs—regardless of whether they exhibited the detectable trace—because, according to Dr. Pentelute, “everything with biotin . . . will be captured[.]” Ex.1048, 154:13-155:5. This cleavage allows for any unbound oligonucleotides to be washed away after addition of streptavidin-linked magnetic particles, preserving the “associated oligonucleotides from the cis-reactive cells selected in step (d) [so as to be subjected] to an analysis that permits detection of the at least two identification sequence elements.” Ex.1001, Cl. 1; Ex.1010, 546, Fig. 1.b.; Ex.1005, ¶122; Ex.1051, ¶¶26-30.

Importantly, PO’s arguments that the CRCs cannot be modified in the process of selecting CRCs improperly construes “selecting” to exclude embodiments described in the specification. Ex.1001, 19:3-20:46. Step (d) can include separating or modifying interactors before analysis in step (e). *Id.*, 19:48-57, 30:11-41. For example, “selecting” includes “selective amplification of the different NAM combination” (i.e., PCR), Ex.1048, 88:17-22, which unbinds the interactors during the process. Ex.1051, ¶¶31-33. And because “this step [can] be modified according

to the nature of the functional interaction that is being investigated,” the specification also describes methods for selecting for CRCs where there has been “remov[al of] molecules or parts from one of the interaction partners” Ex.1001, 19:43-46, 20:10-16. Nothing in the claims or specification prevent the process of “selecting” CRCs from altering the CRCs in that process.

Kanan/Neri does precisely what the claims require: selecting all CRCs exhibiting the detectable trace and then subjecting the associated oligonucleotide from those CRCs to an analysis to detect the identification sequence elements of the molecules involved in the functional interaction (step (e)). Ex.1001, Cl. 1. The associated oligonucleotides from the selected CRCs exhibiting a detectable trace, would be visualized as:



Ex.1051, ¶¶27-30 (each figure component is described and/or illustrated in Pet., 20-23, 33-35, 43-44 and Ex.1005, ¶¶ 114-116, 122, 182).

The remaining pool A oligonucleotides demonstrate (1) a functional interaction between a pool A substrate and pool B substrate (bond-forming combination) and (2) the identity of the pool A and pool B molecules involved in the interaction (through the pool A oligonucleotide containing both identification sequence elements after polymerization). Ex.1005, ¶¶125-133, 180-184; Ex.1051, ¶¶25-30, 37-38.

PO also argues Kanan/Neri does not teach step (d) because Kanan's rinsing would "effectively remove any remaining pool B oligonucleotides from the assay." POR, 27-28. While PO is correct that Kanan removes pool B oligonucleotides before microarray analysis, PO is incorrect that the two interactors be unmodified or bound in proximity throughout the entire selection process. Ex.1051, ¶¶31-38. Additionally, Kanan's wash steps are unremarkable because they are needed to remove oligonucleotides attached to CRCs not involved in a functional interaction. *Id.*, ¶¶28, 39-40; Ex.1013, 8.

Kanan/Neri teaches "selecting all cis-reactive cells exhibiting the detectable trace." Ex.1005, ¶124.

(c) Kanan/Neri Teach Detection of Both Identification Sequence Elements (Step (e))

PO argues the Petition fails to disclose step (e) because (1) it "requires analysis of the 'associated oligonucleotides *from the cis-reactive cells selected in step(d),*' not from 'bond-forming pairs,'" and (2) "Kanan's cleavage and removal of pool B

oligonucleotides results in removal of a purported identification sequence element.”

POR, 29. Neither is correct.

First, PO’s complaint that the Kanan/Neri design analyzes the “associated oligonucleotides” from the bond-forming pairs (not the CRCs) is a red herring. As the Petition explained, the CRCs with the detectible trace *are* those with bond-forming combinations. Kanan’s selects all CRCs with a detectible trace and subjects to analysis “the *resulting nucleic acid*, which includes the *two identification sequence elements* of Neri, that is *detected* and corresponds to each unique substrate.” Pet., 35 (emphasis added).

Second, PO incorrectly argues that Kanan/Neri detects and analyzes oligonucleotides containing only identification sequence element A. POR 29-32. A POSA would have understood the pool A oligonucleotides to be “associated oligonucleotides” that comprise “two identification elements derived from the at least two nucleic acid moieties.” Ex.1001, Cl. 1; Pet., 20-23, 34-36, 43-44; Ex.1005, ¶¶181-184; Ex.1051, ¶¶41-44. This is because the analyzed pool A oligonucleotides are the product of a pool A oligonucleotide hybridizing with a pool B oligonucleotide, and the pool B identification sequence element being transferred onto the pool A oligonucleotide using polymerization during CRC formation. Pet., 20-23, 31-34, 43-44; Ex.1005, ¶¶107-116, 180-184. PO may try to limit an “associated oligonucleotide” as double-stranded, but this would exclude embodiments such as “a

single stranded associated oligonucleotide.” Ex.1001, 8:17-25, Fig. 8; Ex.1051, ¶¶45-46; *Oatey*, 514 F.3d at 1277 (construction excluding an embodiment disclosed in a figure is incorrect). Indeed, PO’s expert agreed in an example that “they started with double stranded and then rejiggered it to get it into a format that would be compatible with the microarray,” which requires single-stranded DNA. Ex.1048, 62:22-24, 124:17-125:7.

Further, the Petition’s analysis of the pool A associated oligonucleotides permits detection of the “at least two identification sequence elements.” Pet., 35-36; Ex.1005, ¶¶125-133. PO argues that Kanan/Neri does not allow detection of the identification sequence elements because a POSA would rely on Neri to perform polymerization after biopanning. POR, 13-16, 32-36. Not so—a POSA would have understood that polymerization would occur during formation of the CRC (step (b)) to obtain both identification sequences. Pet., 20-23, 31-33, 43-44; Ex.1005, ¶¶180-184; Ex.1051, ¶¶7-8, 19.

PO also claims, based on Neri, a POSA “would have performed polymerization after Kanan’s streptavidin-affinity selection step.” POR, 34. But a POSA would not have relied on Neri for polymerization timing—and neither does the Petition. Pet., 20-23, 43-44; Ex.1005, ¶¶180-184. A POSA would have found it obvious to “use the polymerization of the oligonucleotides as taught in Neri with the creation of the paired substrates in Kanan[,]” (i.e., in forming CRCs, not after selection). Pet., 44. Indeed,

association occurs in claim 1 step (b) wherein the “associated oligonucleotide [is] *formed from the association between at least two nucleic acid moieties*[.]” Ex.1001, Fig. 5, Cl. 1 (emphasis added). And that association in step (b) can be “via polymerization,” prior to step (e)’s selection. Pet., 20-23, 43-44; Ex.1005, ¶¶180-184.

PO then argues that even if polymerization occurs during step (b), it “would run a risk of cleaving the disulfide bonds in the pool B oligonucleotides.” POR, 36. PO relies on its expert’s unsupported claim that “polymerase buffers can include a reducing agent” that would cleave the disulfide bond, Ex.2009, ¶132. A POSA would not choose polymerase buffers containing a reducing agent that would result in undesired disulfide bond cleavage. Ex.1051, ¶¶12-18. Instead, a POSA would “adjust the parameters so that the system is working as . . . desired,” and would either “make the polymerase” themselves, make their own buffer without a reducing agent, or choose a polymerase buffer containing either none or only a small amount of reducing agent. Ex.1048, 52:20-22, 56:15-23; 59:3-12; Ex.1051, ¶15. This is because a POSA “would set up a set of conditions that allow that enzyme to be functional” and balance “multiple variables . . . [for] the goal of the experiment.” Ex.1048, 54:12-25, 55:23-56:14. Thus, extension of the pool A oligonucleotides would have been feasible and routine for a POSA. Ex.1005, ¶183; Ex.1051, ¶¶13-14, 18.

As Dr. Pentelute testified, a POSA would have understood that polymerization would occur during “association as described in claim 1(b).” Ex.1048, 103:4-104:20.

Thus, even though Kanan removes the pool B oligonucleotides, it does not “remove” the second identification sequence element, because the pool A oligonucleotides contains both identification sequence elements (through polymerization) that can be detected (e.g., with microarray and sequencing). Pet., 20-23, 35-36, 43-44; Ex.1005, ¶¶122, 124, 180-184; Ex.1051, ¶¶19, 47-50.

Kanan/Neri teaches Claim 1 step (e).

2. PO’s Alleged Problems with Kanan/Neri Are Unsupported And Do Not Negate a POSA’s Motivation to Combine Kanan/Neri to Improve Assay Specificity and Efficiency

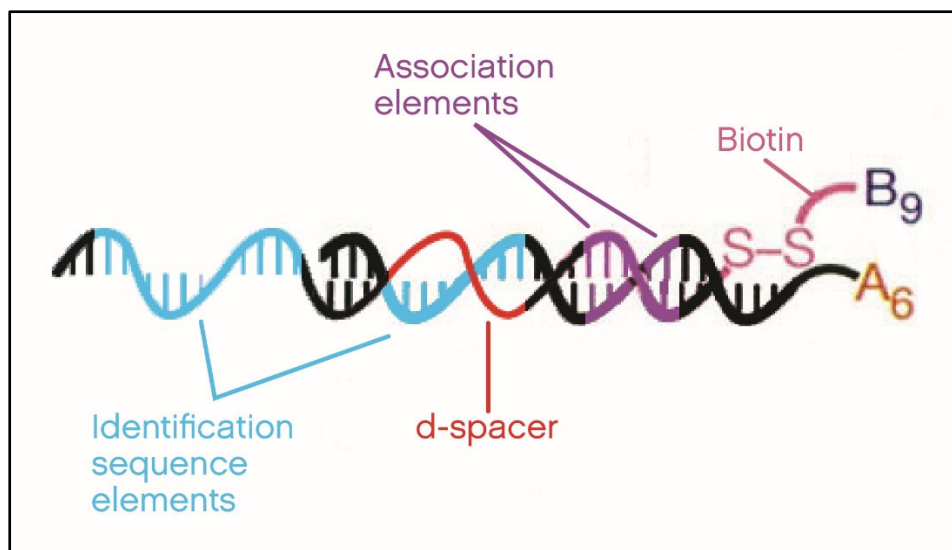
PO contends a POSA would not have been motivated to combine Kanan/Neri because it “would not yield useful information” or “improve specificity of the assay.” POR, 37. PO also argues Kanan/Neri “*increase[s]* ‘the concern of mismatched hybridization,’ and *reduce[s]* the ability to ‘efficiently identify the reactive pairs in Kanan.’” POR, 45. Both arguments are unsupported.

First, when the pool A oligonucleotides are analyzed using Kanan/Neri, both identification sequence elements can be detected. Pet., 20-23, 35-36, 43-44, Ex.1005, ¶¶125-133, 180-184. Thus, a POSA would have understood that using the self-assembly sequence and polymerization as the Petition describes would improve the assay’s specificity over Kanan alone, because it would reduce time required to synthesize the library, improve the specificity of the assay, and provide a more-

efficient way to identify bond-forming combinations. Pet. 20-23; Ex.1005, ¶¶82, 97-103, 182.

Second, PO argues the “polymerization step is incompatible with Petitioner’s proposed modifications” because “there is no double-stranded region for any priming and polymerase extension to occur” after the d-spacer in the Kanan/Neri design. POR, 38-41. PO’s argument seeks to create confusion, but only by ignoring figures in the Petition and Dr. Nelson’s explanation of the Kanan/Neri design. Pet. 21-26, 28-31, 33-34; Ex.1005, ¶¶105-106, 114-115, 180-184. As Dr. Nelson explained and depicted, Kanan/Neri includes hybridization after the d-spacer. Ex.1005, ¶¶96-97, 105, 111, 114; Ex.2009, 163:3-22; 165:12-20; 167:1-168:24; 169:8-12 (discussing figures at Ex.1005, pp. 63 and 67). Moreover, in depicting Kanan/Neri, Dr. Nelson relied on Neri’s Figure 5. Ex.1005, ¶96; Ex.1011, Fig. 5; . And there is no dispute that a POSA would understand that Neri’s Figure 5 shows “hybridiz[ation] except for the region in the d-spacer.” Ex.1048, 170:15-171:5. Dr. Nelson’s other figures show hatch-marks on the pool A and pool B interactors consistent with Neri’s Figure 5. Ex.1005, ¶105.

Contrary to PO, the Petition and supporting declaration reflect hybridization both before and after the d-spacer. Pet., 22, 25, 28-29, 31, 33-34; Ex.1005, ¶¶ 83, 92, 96, 105, 111, 114-115, 119; Ex.2009, 161:23-164:4. The hybridized interactors allow for priming and polymerase extension:



Ex.1051, ¶¶51-59. (each component of above figure is described and/or illustrated in Pet., 20-23, 27-33, 43-44 and Ex.1005, ¶¶105-106, 114-115, 180-184; Ex.2009, 163:3-22; 165:12-20; 167:1-168:24; 169:8-12 (discussing figures at Ex.1005, pp. 63 and 67). Thus, hybridization after the d-spacer is not “new”; regardless, PO understood there would be hybridization after the d-spacer because PO provided pages of rebuttal against it. POR, 41-45.

Finally, recognizing hybridization occurs after the d-spacer, PO argues that there still is a “fundamental flaw” in the design because “any member of pool A can hybridize to any member of pool B at that region,” “ultimately producing false-positive results.” POR, 42. PO’s expert generates various “what if” scenarios unsupported by anything more than expert say-so, using his own terminology divorced from Kanan/Neri’s scientific results. Ex.2008, ¶¶150-154. He ignores that reducing unintended hybridization is a common issue with all nucleic acid chemistry,

well within a POSA's skill to control and minimize. Pet., 11-12; Ex.1005, ¶¶ 25-26 Ex.1051, ¶¶60-63. Indeed, Dr. Pentelute fails to cite a single supporting reference (e.g., Ex.2008, ¶¶148-154, 158, 165-170) and "is entitled to no weight." *Google Inc. v. Art+COM Innovationpool GmbH*, IPR2015-00789, Paper 8, 13 (P.T.A.B. Sept. 2, 2015).

With Kanan/Neri, a POSA would control undesired hybridization by controlling assay conditions, including designing affinity of the two hybridizing regions to promote hybridization between the common self-assembly sequences. E.g., Ex.1011, [0118]; Ex.1051, ¶¶53, 61-62, 68. Additionally, Kanan/Neri's basic structure is based on Neri's Figure 5 (Pet., 29), which created a library of pool A and pool B interactors to interact for analysis and do not report any issues of unintended hybridization in the region after the d-spacer. Ex.1011, [0111]-[0119]; Ex.1051, ¶¶55, 62.

Accordingly, POSA would design the hybridization regions to promote hybridization between the self-assembly sequences and thus reduce hybridization between the universal region located after the d-spacer because local affinity between unbound interactors would remain low. Ex.1051, ¶¶53, 61-64. Therefore, a POSA would have understood that Kanan/Neri's pairs could be identified efficiently. Ex.1005, ¶82.

A POSA would have been motivated to combine Kanan/Neri. Pet., 17-21.

3. A POSA Would Reasonably Expect Success in Combining Kanan/Neri to Detect Both Identification Sequence Elements Without Increasing False Positives

PO argues a POSA would not reasonably expect success in combining Kanan/Neri because it “would not allow detection of the at least two identification sequence elements.” POR, 46. PO also argues “the pool A oligonucleotides would be expected to hybridize to multiple, different pool B oligonucleotides” POR, 47. These arguments fail.

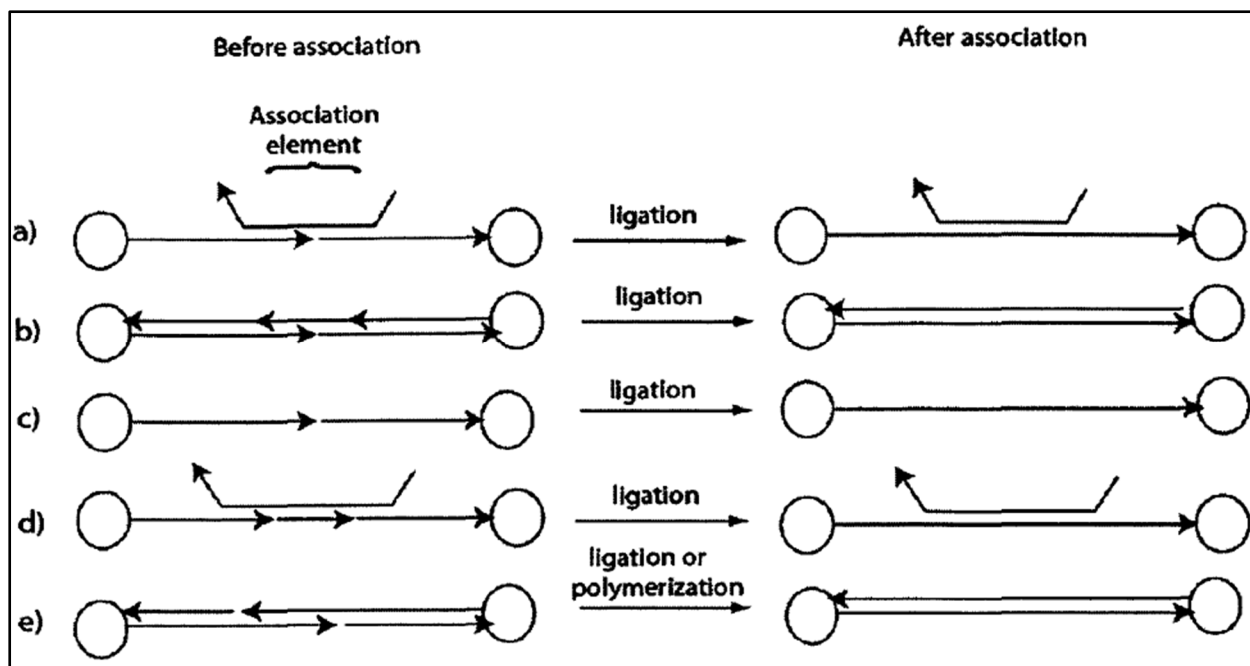
A POSA would reasonably expect success in combining Kanan/Neri because they detect both identification sequence elements and do not increase false positives. Pet., 21-23; Ex.1005, ¶131; Ex.1051, ¶¶65-69. And the Kanan/Neri design, including polymerization, is well within a POSA’s skillset. Pet. 11-12. Specifically, a POSA would reasonably expect success in modifying Kanan’s nucleic acid sequence to incorporate Neri’s self-assembly sequence elements, Ex.1005, ¶¶ 104-105, and would also reasonably expect success with polymerization during step (b) because (1) Kanan/Neri allows for polymerization and (2) polymerization was well-known and routine at the relevant time. *Id.*, ¶¶180-184; Ex.1001, 17:32-40 (identifying prior art teaching polymerization). Lastly, PO’s arguments regarding unintended hybridization would not change a POSA’s reasonable expectation of success because they would have had the skills to design the assay conditions to promote hybridization

between the intended hybridizing regions. Pet., 11-12, 21-23; Ex.1005, ¶¶25, Ex.1051, ¶¶68-69.

A POSA would reasonably expect success in combining Kanan and Neri. Pet., 21-23.

4. Kanan/Neri/Famulok Teach Claim 16 Through Association via Ligation

PO argues Petitioner fails on claim 16 because Kanan/Neri's CRCs "are made from interactors *associated by hybridization*[,] "*not by ligation*["] POR, 50-51. This is inconsistent with the plain and ordinary meaning of "association via ligation" because it excludes embodiments from the specification. For example, Figure 5 provides examples of association via ligation and discloses embodiments with association between NAMs before ligation. Ex.1001, Fig. 5; Ex.2008, ¶33; Ex.1051, ¶¶70-72. Thus, PO is incorrect that Kanan/Neri/Famulok fail to teach claim 16.



Ex.1001, Fig. 5(a)-(e).

PO next argues the Petition lacks “any rationale” for implementing “Famulok’s ligation technique” into Kanan/Neri. POR, 51. But the Petition demonstrates a POSA would be motivated to make this combination to reduce polymerization errors and would reasonably expect success because ligation was a well-known technique, and all three references relate to using nucleotides to detect inter-molecular interactions. Pet., 21-23.

PO then argues Petitioner’s Famulok combination has “technical design flaws” relating to cross-hybridization and mis-ligation. POR, 51-53. But, even with a common splint using Neri’s Figure 7 design, (POR, 53), concern for mis-ligation is minimal. Ex.1051, ¶¶75-79. As with undesired hybridization, undesired ligation can be controlled by designing the appropriate assay conditions—well within a POSA’s

skill. *Id.*, ¶¶77-78. A POSA would have understood that this design would allow the splint to stably bind only when the two tails are held in proximity, as Neri's Figure 7 shows. *Id.*, ¶77. Put differently, the interactors must be in spatial proximity for the splint to hybridize to the interactors. *Id.* Without initial interactor hybridization to bring the strands in spatial proximity, there is minimal risk of the splint ligating to another, separate interactor. *Id.*, ¶¶77-78. Indeed, Famulok does not describe any issues of ligating different aptamers together. *Id.*, ¶78; Ex.1012. Thus, a POSA would have not understood Kanan/Neri/Famulok to increase false positives or negatives. Ex.1051, ¶¶74, 79.

Lastly, PO argues that a POSA would not have implemented "the embodiment in Neri's Figure 5" in Kanan/Neri/Famulok, based on Dr. Nelson's testimony that a POSA may also rely on Neri's Figure 5 for claim 16. POR, 54-55. But Dr. Nelson's comments regarding Neri's Figure 5 embodiment did not mean that Neri's Figure 5 must be used, but that Neri's Figure 7 is not the only way to achieve a structure compatible with association via litigation. Ex.1051, ¶80.

B. Grounds 3/4 Demonstrate Unpatentability Based On Baez/Landegren/Freskgard

1. Baez/Landegren Discloses Claim 1

(a) The Petition Identifies Baez’s Antibodies as Molecules of Interest Consistent with PO’s Accusations (Step (a))

PO feigns ignorance of Baez’s MOIs and interactors. The Petition reflects that Grounds 3/4 rely on PO’s claim mapping against Petitioner’s NULISA Platform, Pet., 55—a fact PO understood (POR, 62 (arguing Petitioner misunderstood PO’s infringement chart)). This chart identified antibodies as the molecules of interest. Ex.1008. Thus, Petitioner mapped Baez/Landegren as disclosing claim 1(a)’s “forming a plurality of *interactors* [reporter conjugates] by coupling each *molecule of interest* [antibody] with at least one *nucleic acid moiety* [DNA label].” Pet., 56. A complete reading of the Petition and declaration shows the “molecules of interest” are Baez’s *antibodies*, consistent with PO’s position.

As Dr. Nelson’s initial declaration explained: applying PO’s positions, “Baez discloses *antibodies* as *molecules of interest*.” Ex.1005, ¶279; Ex.1051, ¶¶85-90. Moreover, “the *antibodies* taught in Baez are *molecules of interest* being a protein.” *Id.*, ¶276. The Petition explained “PO contends that MOIs include ‘matched antibody pairs’” and “antibodies coupled to NAMs are the ‘interactors.’” Pet., 55-56. Accordingly, the Petition identified “Baez’s ‘reporter conjugates’” as the interactors (MOI coupled to nucleic acid). Pet., 56 (citing Ex.1003, 7:53-56, 10:51-56; Ex.1005,

¶235). And that reporter conjugate of Baez “can be ‘an *antibody*, lectin, receptor, or binding protein’ that is *coupled to* a short ‘*nucleic acid-label*.’” Pet., 47 (citing Ex.1003, 7:48-57, Fig. 1.).

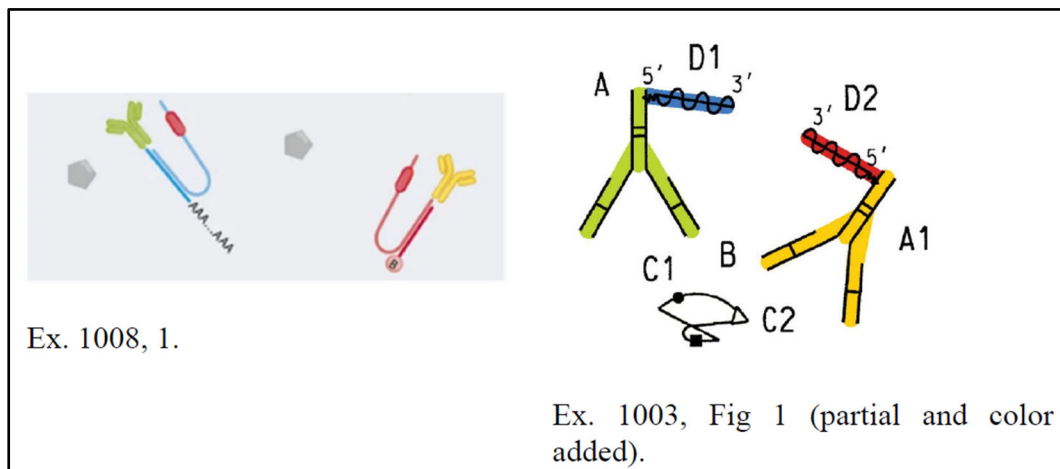
The Petition’s discussion of “coupling [each molecule of interest with at least one nucleic acid moiety] is covalent” in dependent claims 5-6 confirms the MOI is Baez’s antibody:

Baez discloses that the “*DNA labels*” “were covalently attached to their respective *antibodies* through 5’ terminal amine groups,” and thus, this limitation includes a *covalent bond between the antibody and oligonucleotide* as taught in Baez.

Pet., 64; Ex.1051, ¶91. Discussing dependent claims 7-8, the Petition explains the “at least two *MOIs include the antibodies* taught in Baez and Landegren.” Pet., 65 (citing Ex.1003, 7:54-57; Ex.1004, 14; Ex.1005, ¶¶277-279); Ex.1051, ¶92. Indeed, regarding Ground 4, the Petition explains that Baez/Landegren/Freskgard all “relate to tagging *a molecule* with *nucleic acid* and analyzing the *molecule’s affinity toward a target*[.]” Pet., 54.

Moreover, Dr. Nelson’s Declaration provided side-by-side graphics comparing Baez’s interactors (right) with PO’s identified interactors (left). Ex.1005, ¶235. PO contends “the matched *antibody pairs* . . . (shown in *green* and *yellow* in the figure below) are *molecules of interest* . . . , and the matched antibody pairs are conjugated

with at least once *nucleic acid moiety* (*oligonucleotides*, shown in *blue* and *red* in the figure below)[.]’” *Id.* (emphasis and color added).



Id. Dr. Nelson colored Baez’s *antibodies* in *green* and *yellow* as the same *molecules of interest* identified by PO—and colored the *DNA labels*, shown in *blue* and *red*, as the same *nucleic acid moieties*. *Id.*

PO’s cited law is distinguishable. POR, 57-58. In *Inergy Tech., Inc. v. Force Mos Tech. Co., Ltd.*, IPR2024-00093, Paper 38, 19 (P.T.A.B., May 16, 2025), the “Petition fail[ed] to identify . . . the ‘base layer’ limitation” and did not “explicitly identify or discuss the specified ‘base layer’ in “the entirety of the Petition’s analysis . . . [or] the entirety of Dr. Lui’s declaration.” Likewise, in *Visa Inc. v. Universal Secure Registry, LLC*, IPR2018-01350, Paper 35, 14 (P.T.A.B., Jan. 30, 2020) the petition lacked “any discussion explaining an assertion that relies on such a configuration” in the new claim mapping in petitioner’s reply. Here, the facts are

more analogous to *Ericsson Inc. v. Intellectual Ventures LLC*, 901 F.3d 1374, 1380-81 (Fed. Cir. 2018), where the Federal Circuit held it was error to disregard arguments “the Petition expressly contemplated” and that “expressly follow from the[] contentions raised in the Petition” Here, Petitioner’s identification of Baez’s antibody as the molecule of interest is rooted in the Petition and supporting materials and are not new rationales or theories. POR, 57-58.

Baez in view of Landegren teaches claim 1(a).

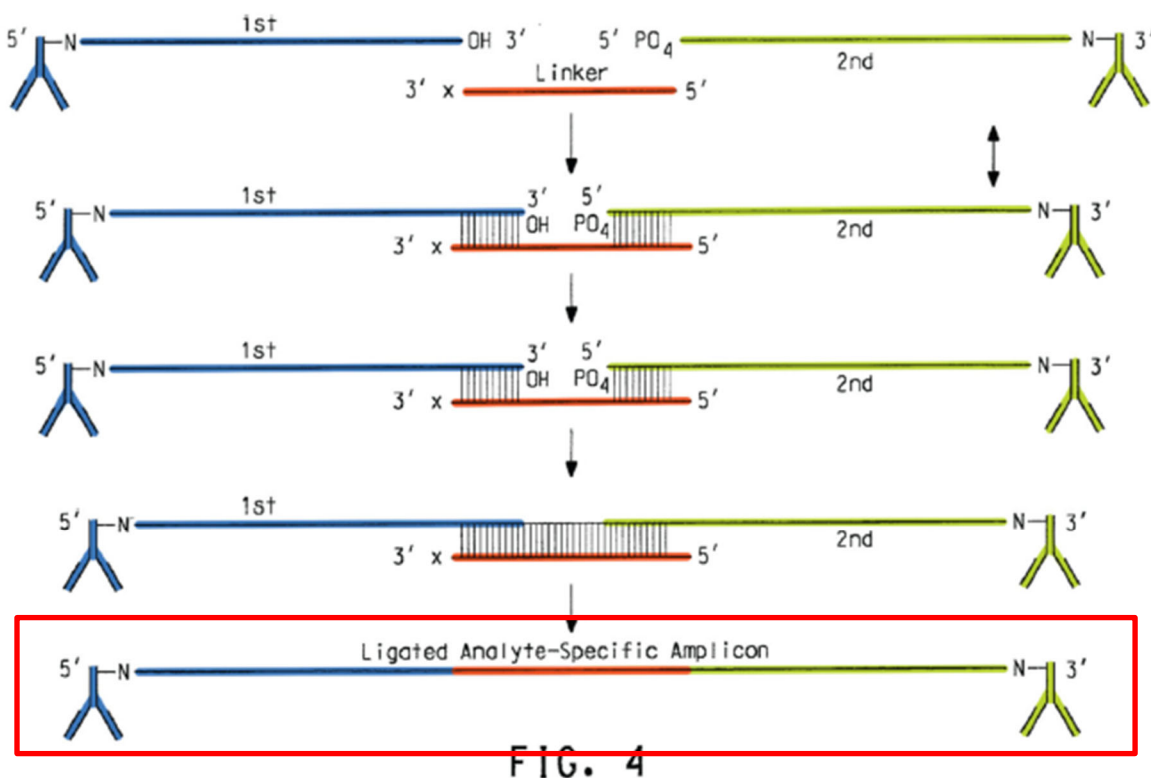
**(b) Baez’s Affinity Purification Method Satisfies the
“Selecting” Limitation (Step (d))**

PO contends Baez’s capture of “biotinylated products” on immobilized streptavidin teaches detection, not selection. POR, 59-60. This argument ignores Dr. Nelson’s analysis and Baez’s complete teaching. *E.g.*, Ex.1005, ¶282.

First, PO only analyzes Baez’s column 17 and appears to limit Baez’s teachings to solid phase assays. POR, 59. But Baez discloses: “Both the ligation and overlap methods may be conducted in either a heterogenous format where the analyte is immobilized, or if in a homogeneous format *where the analyte is free in solution.*” Ex.1003, 11:52-55 (emphasis added). Baez’s disclosure of biotin incorporated to the linker to isolate the ASAs from solution is a form of affinity purification. Ex.1005, ¶¶ 252, 282; Ex.1048, 140:1-12; Ex.1051, ¶¶93-97.

Second, Petitioner did not argue that Baez teaches selecting a “biotinylated amplicon,” POR, 60, but instead identified that Baez’s biotin-streptavidin capture

would select Baez's ASA, which is created "by joining the nucleic acid reporter labels of the analyte-dependent reporter complex [ADRC][.]" Ex.1003, 12:66-13:4; Ex.1005, ¶217; Pet. 60; Ex.1051, ¶¶98-101. Put differently, the ASA (circled) is the complex with the two antibodies connected via ligation of their nucleic acid labels, shown in Baez Figure 4:



Ex.1003, Fig. 4 (color added, showing ASA); Ex.1005, ¶217.

Baez in view of Landegren teaches claim 1(d).

(c) Baez/Landegren Teach Analysis of Nucleic Acid From The Selected CRCs (Step (e))

PO argues the Petition fails to teach step (e) because the associated oligonucleotides subjected to analysis are from "the allegedly selected ASA product,"

not CRCs. POR, 60-61. PO misconstrues Baez. Step (e) requires subjecting the associated oligonucleotides from the selected CRCs to an analysis. Ex.1001, Cl. 1. Baez discloses selecting CRCs (Baez's ASAs) through affinity purification (step (d)), and that after selecting the CRCs, the selected CRCs' nucleic acid (nucleic acid of the ASA, i.e., the "ASA product") is analyzed with PCR. Pet., 60-61. Thus, the ASA *product* is not selected in step (d). Ex.1051, ¶¶101-102, 104. Put differently, only after the CRC (ASA in Baez) is selected is the nucleic acid portion subjected to analysis. Ex.1005, ¶¶252, 256-257; Ex.1051, ¶¶101-102, 104. And as described above, Baez discloses selecting CRCs.

PO further contends that detection of Baez's "amplified ASA product" would not detect the identification sequence elements (Landegren's tags). POR, 61-62. This ignores how Baez/Landegren result in an ASA with ligated nucleic acid labels that include "tags," which are then selected and amplified for detection. Pet., 56-61. A POSA would have understood that Baez's ASA nucleic acid labels, when combined with Landegren, would each contain an identification sequence element. Pet., 56; Ex.1005, ¶¶237-240. After ligating the nucleic acid labels, each interactor's identification sequence element is maintained. *Id.*, ¶¶ 243-244. Thus, when the ligation product is detected and analyzed (step (e)), the nucleic acid includes the two identification sequence elements (Landegren's tags). Pet., 61-62; Ex.1005, ¶256; Ex.1051, ¶ 105-106.

Baez in view of Landegren teaches claim 1(e).

2. A POSA Would Have Been Motivated To Combine Baez/Landegren

PO argues “Petitioner’s alleged motivations for modifying Baez were already satisfied by Baez itself.” POR, 63. But a POSA would still be motivated to improve Baez. As Baez explains, “[m]ethods for the reduction of background noise are continually being sought,” Ex.1003, 1:32-33, motivating a POSA to add Landegren to better allow analysis of a multiplex assay and selection of only true positives. Ex.1005, ¶238; Ex.1051, ¶¶108-109.

PO argues a POSA would not be motivated to combine Baez/Landegren because “Landegren teaches *against* using solid-phase support.” POR, 63-65. But Landegren’s touting of its solution method would not be interpreted by a POSA as teaching away from Baez for several reasons. Ex.1051, ¶110. First, contrary to PO, Baez also discloses that its methods work without initial capture of the analyte on a solid phase. *Id.*, ¶111. Second, at the relevant time, Baez’s solid-phase capture was a well-known, popular technique. *Id.* Third, the Petition’s reliance on Landegren’s identification tags is not dependent on being performed in solution. *Id.*, ¶112. Thus, a POSA would still be motivated to combine Baez and Landegren. *Id.*

3. A POSA Would Have A Reasonable Expectation Of Success for Grounds 3/4

PO claims a POSA would not have reasonably expected success in combining Baez/Landegren because Baez's solid-phase support methods are "time consuming" and "difficult to automate." POR, 66. But the Petition relies on combining Landegren's identification tags with Baez's nucleic acid labels. Pet., 56. Baez's reporter conjugates are similar to the proximity-probes in Landegren—both are antibodies coupled to nucleic acid. Ex.1005, ¶ 239. Thus, modifying Baez's nucleic acid to include Landegren's identification sequence would be routine for a POSA. Pet. 11-12, 54-55; Ex.1051, ¶¶113-114. Thus, a POSA would reasonably expect success in combining Baez/Landegren. Ex.1005, ¶239.

And while PO contends a POSA would not combine Freskgard with Landegren/Baez because "of Landegren's disparagement of solid-phase assay," POR, 67, for the same reasons regarding Baez/Landegren, a POSA would not have any issue also combining Freskgard. Ex.1051, ¶115.

V. Dependent Claims

Because the dependent claims depend directly from claim 1, claims 2-20 are obvious over the prior art. Ex.1051, ¶¶ 81,116.

VI. Conclusion

For the foregoing reasons, Petitioner requests the Board cancel claims 1-20.

Date: September 22, 2025

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing **Petitioner's Reply**, including all Exhibits, was served on September 22, 2025 upon the following parties via electronic mail::

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CERTIFICATE OF WORD COUNT UNDER 37 C.F.R. § 42.24(c)

I, the undersigned, do hereby certify that the attached petition contains 5,587 words, as measured by the Word Count function of Microsoft Word 2016. This is less than the limit of 5,600 words as specified by 37 C.F.R. § 42.24(c)(1).

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APPENDIX OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 7,883,848 (the “848 patent”)
1002	Prosecution History of U.S. Patent No. 7,883,848
1003	U.S. Patent No. 6,511,809 (“Baez”)
1004	PCT Publication No. WO01/61037 (“Landegren”)
1005	Declaration of Norman C. Nelson, Ph.D.
1006	<i>Curriculum Vitae</i> of Norman C. Nelson, Ph.D.
1007	Complaint in <i>Olink v. Alamar</i> , Case No. 1:23-cv-01303-MN, Dkt. 1 (D. Del. Nov. 11, 2015)
1008	Olink Infringement Chart
1009	PCT Publication WO2005/003778 (“Freskgard”)
1010	Kanan et al., <i>Reaction Discovery enabled by DNA-templated synthesis and in vitro selection</i> , 431 NATURE 545–49 (2004) (“Kanan”)
1011	U.S. Application No. 04/0014090 (“Neri”)

Exhibit No.	Description
1012	Famulok, <i>Bringing picomolar protein detection into proximity</i> , 20 NATURE BIOTECHNOLOGY 448–49 (2002) (“Famulok”)
1013	Kanan et al., <i>Reaction Discovery enabled by DNA-templated synthesis and in vitro selection</i> , <i>Supplementary Information</i> , NATURE (2004), https://www.nature.com/articles/nature02920 (“Kanan Supplementary Information”)
1014	Alamar’s Brief in Support of its Motion to Dismiss, Case No. 1:23-cv-01303-MN, Dkt. 9 (D. Del. Apr. 1, 2024)
1015	Olink’s Brief in Opposition Brief to Alamar’s Motion to Dismiss, Case No. 1:23-cv-01303-MN, Dkt. 15 (D. Del. Apr. 15, 2024)
1016	Hage, <i>Immunoassays</i> , 71 ANALYTICAL CHEMISTRY 294–304 (1999)
1017	Reen, <i>Enzyme-Linked Immunosorbent Assay (ELISA)</i> , 32 METHODS IN MOLECULAR BIOLOGY 461–66 (1994)
1018	<i>Sano et al.</i> , Immuno-PCR: Very Sensitive Antigen Detection by Means of Specific Antibody- DNA Conjugates, 258 SCIENCE 120–122 (1992)
1019	Gullberg et al., <i>Cytokine detection by antibody-based proximity ligation</i> , 101 PNAS 8420–24 (2004)
1020	Fredriksson et al., <i>Protein detection using proximity-dependent DNA ligation assays</i> , 20 NATURE BIOTECHNOLOGY 473–77 (2002)

Exhibit No.	Description
1021	Brenner & Lerner, <i>Encoded combinatorial chemistry</i> , 89 PNAS 5381–83 (1992)
1022	Needels et al., <i>Generation and screening of an oligonucleotide-encoded synthetic peptide library</i> , 90 PNAS 10700–04 (1993)
1023	Pelletier & Sidhu, <i>Mapping protein-protein interactions with combinatorial biology methods</i> , 12 CURRENT OPINION IN BIOTECHNOLOGY 340–47 (2001)
1024	Li & Liu, <i>DNA-Templated Organic Synthesis: Nature’s Strategy for Controlling Chemical Reactivity Applied to Synthetic Molecules</i> , 43 ANGEWANDTE CHEMIE INTERNATIONAL EDITION 4848–70 (2004)
1025	Guille & Kneale, <i>Methods for the Analysis of DNA-Protein Interactions</i> , 8 MOLECULAR BIOTECHNOLOGY 35–52 (1997)
1026	U.S. Patent No. 6,692,918 (“Kurn”)
1027	Reischl & Kochanowski, <i>Quantitative PCR</i> , 3 MOLECULAR BIOTECHNOLOGY 55–71 (1995)
1028	Wilton, <i>Dideoxy Sequencing of DNA</i> , ENCYCLOPEDIA OF LIFE SCIENCES 1–16 (2002)
1029	AMERSHAM BIOSCIENCES, MEGABACE 4000 INSTRUMENT ADMINISTRATOR’S GUIDE VERSION 3.2 (2002)

Exhibit No.	Description
1030	Heather & Chain, <i>The sequence of sequences: The history of sequencing DNA</i> , 107 GENOMICS 1–19 (2016)
1031	Evans, <i>Sanger sequencing: past successes and current applications</i> , CYTIVA, https://www.cytivalifesciences.com/en/us/news-center/sanger-sequencing-past-and-present-10001 (last accessed August 16, 2024)
1032	Winter et al., <i>Making Antibodies by Phage Display Technology</i> , 12 ANNUAL REVIEW OF IMMUNOLOGY 433–55 (1994)
1033	Wilson et al., <i>The use of mRNA displays to select high-affinity protein-binding peptides</i> , 98 PNAS 3750–55 (2001)
1034	U.S. Application No. 60/697415
1035	PCT Publication No. WO2005/026387 (“Thisted”)
1036	U.S. Patent Application Publication No. 2009/0011957 (“Goulaev”)
1037	U.S. Patent Application Publication No. 2006/0246450 (“Franch”)
1038	U.S. Patent Application Publication No. 2009/0203530 (“Liu”)
1039	UNITED STATES COURTS, FEDERAL JUDICIAL CASELOAD STATISTICS 2018–2023 (2023)

Exhibit No.	Description
1040	Declaration of Maria P. Garcia
1041	Declaration of S. Christian Platt
1042-1047	Intentionally Omitted
1048	Sealed Deposition Transcript of Bradley R. Pentelute (September 15, 2025)
1049	Public Redacted Deposition Transcript of Bradley R. Pentelute (September 15, 2025)
1050	[Proposed] Stipulated Protective Order
1051	Second Declaration of Norman C. Nelson, Ph.D.
1052	Rogers et al., <i>Immobilization of Oligonucleotides onto a Glass Support via Disulfide Bonds: A Method for Preparation of DNA Microarrays</i> , 266 ANALYTICAL BIOCHEMISTRY 23-30 (1999)
1053	Shimkus et al., <i>A chemically cleavable biotinylated nucleotide: Usefulness in the recovery of protein-DNA complexes from avidin affinity columns</i> , 82 PNAS 2593-97 (1985)
1054	Second Declaration of S. Christian Platt