

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

**PATENT OWNER RESPONSE
UNDER 37 C.F.R. § 42.120**

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PATENT OWNER'S UPDATED EXHIBIT LIST

Exhibit No.	Description
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 rd edition), Cold Spring Harbor Laboratory Press (2001)

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Cases	
<i>Dynamic Drinkware, LLC v. National Graphics, Inc.</i> , 800 F.3d 1375 (Fed. Cir. 2015)	4, 6
<i>Henny Penny Corp. v. Frymaster LLC</i> , 938 F.3d 1324 (Fed. Cir. 2019)	55, 59
<i>Inergy Tech., Inc. v. Force Mos Tech. Co., Ltd.</i> , IPR2024-00093, Paper 38, 17-22 (P.T.A.B., May 16, 2025)	58, 59
<i>Intelligent Bio-Sys. v. Illumina Cambridge</i> , 821 F.3d 1359 (Fed. Cir. 2016)	55, 59
<i>KSR Int’l v. Teleflex Inc.</i> , 550 U.S. 398 (2007)	3
<i>Personal Web Techs., LLC v. Apple, Inc.</i> , 848 F.3d 987 (Fed. Cir. 2017)	33, 47, 52
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005) (en banc)	7
<i>In re Van Os</i> , 844 F.3d 1359 (Fed. Cir. 2017)	33, 52
<i>Visa Inc. v. Universal Secure Registry, LLC</i> , IPR2018-01350, Paper 35, 14 (P.T.A.B., Jan. 30, 2020)	59
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I. INTRODUCTION

The '848 patent's inventive methods provide improvements over prior art methods for detecting functional interactions between molecules. Prior art detection methods such as yeast two-hybrid systems, phage display, DNA-templated synthesis, and proximity ligation assays had known limitations related to throughput, high rates of intrinsic false-positive results, the inability to assess molecular interactions in a combinatorial fashion, and/or strict requirements for detecting known targets with probes having known affinities. The '848 patent overcame these shortcomings in the prior art, providing a novel, inventive method for detecting functional interactions between at least two molecules of interest.

The '848 patent issued on February 8, 2011. Nearly 12 years later, in April 2023, Petitioner Alamar Biosciences announced the unveiling of its NULISA products for “early-access release later this year and a broad commercial launch in 2024.” EX2003, 1. Only now, after being sued for infringement, does Petitioner bring this IPR challenging the patentability of the '848 patent's methods. EX1007.

The Petition challenges claims 1-20 of the '848 patent based solely on obviousness grounds, all of which are fundamentally defective both in law and fact. *First*, the Petition fails to demonstrate that the combination of Kanan (EX1010) and Neri (EX1011) in Grounds 1 and 2 teaches or suggests all the elements of the challenged claims. In particular, Petitioner and its expert overlook

a critical feature in the Kanan reference that requires *cleaving* an oligonucleotide *before any selection occurs*. This requirement in Kanan's methods results in severing one of the two alleged interactors, and thus destroying the cis-reactive cells, all before any selection occurs. Petitioner's art combination therefore fails to teach or suggest the claimed selection step (step (d)), which requires *selecting cis-reactive cells*. This deficiency alone is fatal to both Grounds 1 and 2, as both grounds rely on the combination of Kanan and Neri. This same deficiency also extends to the Petition's argument for the claimed detection step (step (e)), which further underscores the Petition's deficiencies. And as Patent Owner's expert, Dr. Bradley Pentelute, explains, Petitioner's proposed modifications to Kanan in view of Neri and Famulok (EX1012) are plagued with technical problems that would have deterred a person of ordinary skill in the art from combining the references with any reasonable expectation of success.

The Petition's Grounds 3 and 4 fare no better. Here, the Petition's combination of Baez (EX1003) and Landegren (EX1004) fails to teach or suggest the claim elements of forming interactors (claim 1(a)) and selecting cis-reactive cells (claim 1(d)). The Board in its Decision on Institution already rejected Grounds 3 and 4 based on the Petition's inconsistencies in addressing step (a). DI, 26. Regarding the selecting step (d), the Petition relies solely on Baez for this claim element, but Baez at most teaches methods of detection, not selecting CRCs

with a detectable trace. And even if Baez's method were considered selecting, Baez teaches only selecting amplified ligation products, not selecting cis-reactive cells, as required by the claims. As with Grounds 1 and 2, the absence of key claim elements is fatal to both Grounds 3 and 4. Moreover, both Petitioner and its expert ignore express teachings in Landegren that caution *against* combining it with solid-phase assays such as those taught in Baez and Freskgard (EX1009).

Petitioner and its expert rely on half-baked technical theories, incomplete assessments of the prior art, and an incomplete legal standard for obviousness that omits considering objective indicia. Indeed, Petitioner's expert repeatedly testified that he only reviewed parts of his proposed art combinations, and did not review or analyze the full disclosures. *See e.g.*, EX2009, 113:13-22 (testifying regarding Famulok, "I did not read every word of this document, no I did not."), 45:2-7 (testifying regarding Landegren, "I don't think I read it word for word, cover to cover."), 103:16-104:6 (testifying regarding Neri's biopanning disclosures, "I did not analyze the references that they make to biopanning."). These deficiencies collectively underscore the hindsight nature of the Petition's arguments. "A factfinder should be aware, of course, of the *distortion caused by hindsight bias* and must be cautious of arguments reliant upon *ex post* reasoning." *KSR Int'l v.*

Teleflex Inc., 550 U.S. 398, 421 (2007)¹.

In IPRs, “the burden of persuasion is on the petitioner to prove ‘unpatentability by a preponderance of the evidence,’ 35 U.S.C. § 316(e), and that burden never shifts to the patentee.” *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1378-1379 (Fed. Cir. 2015). Petitioner has failed to meet its burden of showing that any of the challenged claims is unpatentable over its asserted art combinations. The Board should accordingly reject the Petitioner’s arguments and decide in Patent Owner’s favor.

II. STATE OF THE ART AND THE ’848 PATENT

Before July 8, 2005, methods for determining interactions between molecules of interest (MOIs) were limited in key areas such as accuracy, throughput, and utility. EX2008, ¶¶21-29. For example, prior art methods such as antibody arrays could only resolve one partner of an interaction in high throughput fashion, and could only assay in solid-phase. EX1001, 2:8-29; EX2008, ¶24. Other methods such as yeast two-hybrid systems also had known limitations in their ability to perform high-throughput analysis of both interacting partners, as well as a high intrinsic level of false-positive results. EX1001, 2:58-3:3; EX2008, ¶25. DNA-templated synthesis (DTS) methods allowed for detection of interactions

¹ Emphasis has been added throughout, unless stated otherwise.

between small molecules, but were limited in that they required individual synthesis of oligonucleotides for each individual reaction in the library. EX1001, 3:55-60; EX2008, ¶26. Prior art methods of proximity ligation assays (PLA) were limited in that they exclusively required detecting a pre-defined target, using molecules with pre-defined affinities. EX1001, 4:39-47; EX2008, ¶29.

The invention of the '848 patent overcame the limitations of prior art methods by providing novel methods for detecting molecular interactions. EX1001, 3:46-4:25; EX2008, ¶¶30-35. For example, the '848 patent explains that, unlike prior art PLA methods, the invention of the '848 patent is not limited to exclusively detecting pre-defined targets or using molecule with pre-defined affinities, expanding the abilities for detecting molecular interactions. EX1001, 4:48-53; EX2008, ¶34. As the '848 patent explains, “the invention allows investigation of *all possible interactions* within or between libraries of molecules, such as proteins, and also permits relative quantification of the detected interactions.” EX1001, 5:25-28.

The claims of the '848 patent are directed to methods of identifying functional interactions between at least two molecules of interest (MOIs). EX1001, 41:36-44:19. In the claimed methods, each MOI is coupled to at least one nucleic acid moiety (NAM), the NAM comprising an identification sequence element and an association element. EX1001, 41:39-42; EX2008, ¶¶32-33. The coupling of at

least one NAM to an MOI forms an “interactor.” *Id.* Interactors are then bound in proximity to each other via the association elements in the NAM. EX1001, 39-42; EX2008, ¶¶32-33. The binding of at least two interactors in proximity to one another by their association elements forms a “cis-reactive cell” (CRC). EX1001, 41:43-49; EX2008, ¶33. The CRCs are then subjected to conditions which stimulate a desired functional interaction that has a detectable trace. EX1001, 41:50-52; EX2008, ¶34. After stimulating the desired functional interaction, the CRCs with a detectable trace are selected and subjected to an analysis that permits detection of the at least two identification sequence elements. EX1001, 41:53-58; EX2008, ¶35.

The '848 patent issued with 20 claims, of which claim 1 is the sole independent claim. Claim 1 recites:

A method of detecting functional interactions between at least two molecules of interest, the method comprising:

- a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;
- b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises 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, wherein

the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;

- c. subjecting the plurality of cis-reactive cells to conditions which stimulate a desired functional interaction having a detectable trace;
- d. selecting all cis-reactive cells exhibiting the detectable trace; and
- e. subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis that permits detection of the at least two identification sequence elements.

EX1001, 41:36-38.

Dependent claims 2-20 recite additional features of the claimed method, such as specifying that the MOI comprises at least one protein (claim 8) or requiring that the association between interactors is via ligation (claim 16).

EX1001, 42:55-58, 43:20-22.

III. CLAIM CONSTRUCTION

Claim terms must be given their “ordinary and customary meaning ... as understood by one of ordinary skill in the art” in view of the specification and prosecution history. 37 C.F.R. § 42.100(b); *see also, Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). The Petition states that “the claims are assumed to be given their plain and ordinary meaning based on the understanding

of a POSA,” yet provides no “plain and ordinary meaning” of any claim terms.

Pet., 12-13.

The ’848 patent provides specific descriptions and definitions of several claim terms. The ordinary and customary meanings of certain claim terms are provided below. EX2008, ¶¶88-95.

Molecules of interest (MOI). Claim 1 recites the term “molecules of interest” in the preamble and in step (a). The ’848 patent states that “the term ‘molecule of interest’ (MOI) refers to a molecule about which interactive information is desired....” EX1001, 8:53-62; EX2008, ¶90. Petitioner’s expert, Dr. Nelson, agrees that this is the ordinary and customary meaning of MOI. EX2009, 34:22-35:20; EX1005, ¶45.

Nucleic acid moiety (NAM). Claim 1(a) recites the term “nucleic acid moiety,” reciting that each MOI is coupled to at least one NAM, and that the NAM comprises “an identification sequence element and an association element.” EX1001, 41:39-42. The ’848 patent specification further states that “[a] NAM comprises at least one unique identification nucleic acid sequence so that detection of that sequence infers involvement of the coupled MOI,” and that “[a] NAM also comprises at least one element which enables association with other NAMs.” EX1001, 8:41-52; EX2008, ¶91. Petitioner’s expert does not dispute this definition. EX2009, 36:4-37:6; EX1005, ¶46.

Interactors. Claim 1(a) recites “forming a plurality of interactors by coupling each [MOI] with at least one [NAM....” EX1001, 41:39-42. The ’848 patent specification states that “the term ‘interactor’ refers to at least one MOI coupled with at least one NAM.” EX1001, 9:33-34; EX2008, ¶92. Petitioner’s expert agrees that an interactor requires an MOI coupled to at least one NAM. EX2009, 37:12-38:8; EX1005, ¶44.

Cis-reactive cell (CRC). Claim 1(b) recites “forming a plurality of cis-reactive cells,” and further recites that a CRC “comprises 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.” EX1001, 41:43-47. The ’848 patent specification states that “the term ‘Cis Reactive Cell’ (CRC) refers to an association of at least two interactor moieties, joined by an associated oligonucleotide.” EX1001, 9:35-37; EX2008, ¶93. Petitioner’s expert agreed that a CRC of the ’848 patent requires at least two interactors bound in proximity to one another. EX2009, 38:18-39:20; EX1005, ¶49.

Selecting all cis-reactive cells. Claim 1(d) recites “selecting all cis-reactive cells exhibiting the detectable trace.” EX1001, 41:53-54. The antecedent basis for “cis-reactive cells” in step (d) is found in claim 1 steps (b) (forming cis-reactive cells) and step (c) (subjecting the cis-reactive cells to conditions). *Id.*, 41:39-52. The ’848 patent specification states that, “[t]o detect functional interactions in a

pool of CRCs *the CRCs* which display functional interactions *must be selected* for detection and/or analysis.” EX1001, 19:41-43; EX2008, ¶94. Petitioner’s expert agreed that the selecting step (d) requires *selecting cis-reactive cells*. EX2009, 43:15-24.

Claim terms not addressed above should also be given their ordinary and customary meaning.

IV. LEVEL OF ORDINARY SKILL IN THE ART

Before July 8, 2005, a person of ordinary skill in the art (POSA) would have had an advance degree, such as a Ph.D. in chemistry, organic chemistry, biochemistry, biotechnology, molecular biology, or a related discipline, with about 2 years of experience in laboratory research involving small molecule, proteins, nucleic acid chemistry, and hybridization techniques. EX2008, ¶¶79-80. A POSA would have had familiarity with high throughput assays, such as screening and sequencing techniques. *Id.*, ¶79. A POSA may also have had less formal education and more years of technical or professional experience. *Id.*

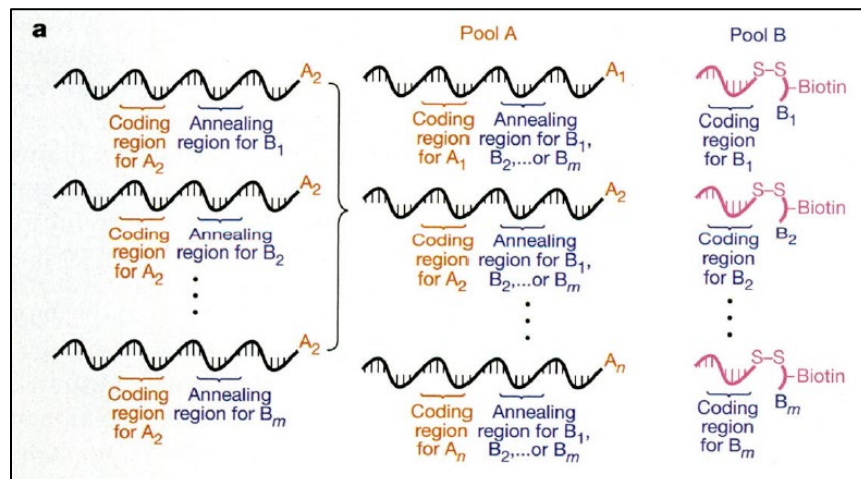
V. OVERVIEW OF PETITIONER’S ASSERTED ART

Petitioner relies on the combination of Kanan and Neri for all of its arguments in Ground 1, and further relies on the teachings of Famulok to challenge claim 16 in Ground to 2. Pet., 2. Petitioner relies on the combination of Baez and Landegren for all of its arguments in Ground 3, and further relies on the teachings

of Freskgard to challenge claims 14 and 15 in Ground 3. Pet., 3.

A. Kanan's methods require disulfide cleavage to uncouple an oligonucleotide from the substrate of interest.

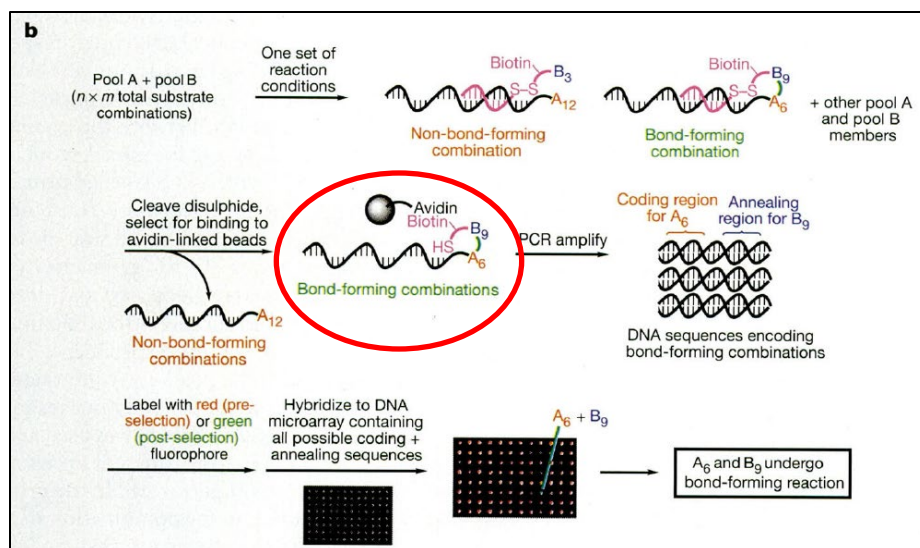
Kanan describes a method “that uses DNA-template organic synthesis and *in vitro* selection” for “bond-forming reaction[]” discovery. EX1010, Abstract; EX2008, ¶¶40-50. According to Kanan, its DTS methods leverage “DNA annealing [to] organize many substrates in a single solution into DNA sequence-programmed pairs.” EX1010, 545. Kanan teaches creating a library of two “pools” of DNA-linked substrates (pool A and pool B). EX1010, 545, Fig. 1; EX2008, ¶¶42-46. Kanan teaches coupling the pool B substrates to their corresponding oligonucleotides “by a linker containing a biotin group and a disulphide bond.” EX1010, 545, Fig. 1. Kanan provides a schematic overview depicting the pool A and pool B library members in Figure 1a, copied below:



EX1010, Fig. 1a; EX2008, ¶45. As evident in Kanan's figure and teachings throughout, pool B library members all comprise the linker containing a disulfide

bond. *Id.*

In Kanan's DTS methods, the library members of pool A and pool B are mixed together, allowing the oligonucleotides of pool A and pool B to hybridize together. EX1010, 545, Fig. 1; EX1013, 8; EX2008, ¶¶46-478. The mixture is then subjected to a set of reaction conditions to induce bond formation between the A and B substrates. *Id.* After the bond-forming reactions occur, Kanan teaches cleaving the disulfide bond in the linker of pool B library members to uncouple the oligonucleotide from the B substrates. EX1010, 545, Fig. 1; EX1013, 8; EX2008, ¶48. Kanan teaches that, after the disulfide cleavage and uncoupling of B oligonucleotides from B substrates, the bond-forming pairs of A and B substrates are selected using a "streptavidin affinity selection" to "separate[] biotinylated from non-biotinylated sequences." EX1010, 545; EX2008, ¶¶48-49. By isolating bioinylated sequences and anything bound to them, Kanan's selection method selects for the bond-forming pairs of A and B substrates. *Id.* Importantly, the complexes selected in Kanan's methods comprise only the A oligonucleotides, as the B oligonucleotides were cleaved off and removed in the disulfide cleavage step. EX1010, Fig. 1b; EX2008, ¶49. Kanan depicts this disulfide cleavage step, followed by its selection step, in its workflow overview in Figure 1b, copied below:



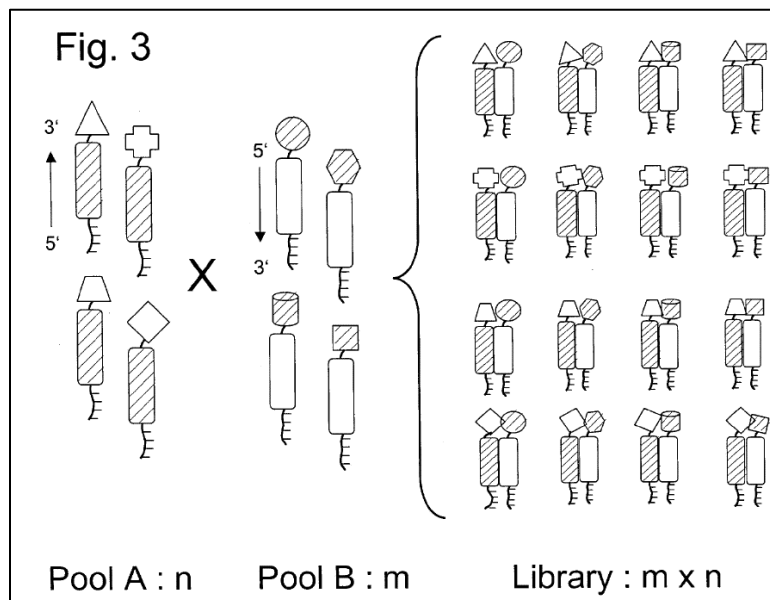
EX1010, Fig. 1b (annotated); EX2008, ¶49. As shown circled in the figure above, the molecules selected in Kanan's method only comprise the A oligonucleotide strand. *Id.*

Kanan teaches that bond-forming pairs of A and B substrates “are identified by amplification of the selected sequences by ... [PCR] followed by DNA microarray analysis.” EX1010, 545, Fig. 1b; EX2008, ¶50.

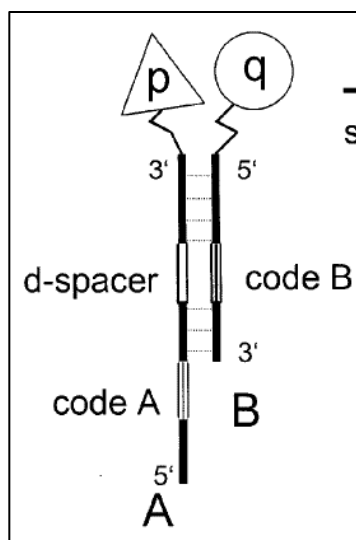
B. Neri's methods require assembly via hybridization and exclusively suggest polymerization only after biopanning.

Neri teaches a method for generating “self-assembling libraries of organic molecules.” EX1011, ¶[0005]; EX2008, ¶¶51-60. Neri teaches that its self-assembling libraries are useful for identifying binding properties between DNA-tagged chemical compounds and untagged target molecules. EX1011, ¶[0019], Fig. 1; EX2008, ¶52. Neri teaches first creating two libraries of DNA-tagged chemical compounds, referred to as “pool A” and “pool B.” EX1011, ¶[0027], Fig. 3;

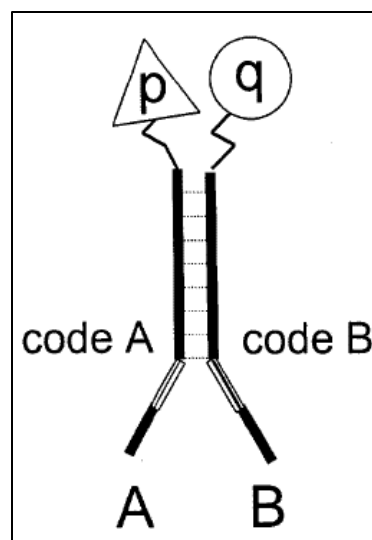
EX2008, ¶¶53-54. As Neri explains, the oligonucleotide strands conjugated to the chemical compounds comprise a “self-assembly sequence” (“oligomerization domain”) and can also include a unique “sequence tag” (or “code”). EX1011, ¶¶[0040]-[0045]; EX2008, ¶¶53-54. Neri teaches that the self-assembly sequence common to all the members of pool A and the self-assembly sequence common to all the members of pool B are complementary to each other and their hybridization allows for the heterodimerization of pool A and pool B chemical compounds. EX1010, ¶[0057]. Neri depicts the self-assembly of pool A and pool B library members in, e.g., Figures 3, 5, and 7, copied below:



EX1011, Fig. 3.



EX1011, Fig. 5.



EX1011, Fig. 7.

EX2008, ¶54. In each of Neri's embodiments, the library members of pool A and pool B self-assemble through DNA hybridization, depicted as horizontal lines in Neri's Figure 5 and 7. *Id.*

Neri teaches that its methods begin with a "biopanning" process, in which the self-assembled A and B library members are panned across an immobilized target molecule to identify binding properties between the library and the target molecule. EX1011, ¶¶[0031], [0059], [0072], [0083]-[0084], claim 19; EX2008, ¶56. Neri's methods do not investigate any interactions between the DNA-tagged chemical compounds in the library, but instead investigate interactions between the chemical compounds and an untagged target molecule. EX2008, ¶55. Neri teaches that its biopanning method can be performed by "exposing the library to the target protein on [a] bead, followed by the physical removal of the bead from the library

solution, followed by judicious washing of the bead, to reduce the amount of non-specific binders on the bead.” EX1011, ¶[0059] *see also, id.*, Abstract, ¶¶[0031], [0072], [0083]-[0084], [0144], claim 19; EX2008, ¶56. As Neri explains, the biopanning process is a selection process that achieves “physical separation of the complex between ESACHEL members and the target molecule, from the pool of non-bound ESACHEL members” by “immobilizing the target molecule of a solid support (e.g. a plastic tube, a resin, magnetic beads, etc.).” EX1011, ¶[0084]; EX2008, ¶56.

Neri teaches that, after the biopanning selection process, “it is desirable to learn about the code of the binding members displaying a desired binding specificity.” EX1011, ¶[0070]; *see also, id.*, ¶¶[0030], [0032], [0076], [0110], [0112], [0144]; EX2008, ¶¶59-60. In one embodiment, Neri teaches performing a DNA polymerase reaction after biopanning selection in which the code from the pool B oligonucleotide is copied onto to the pool A oligonucleotide, such as that “[t]he resulting DNA segment, carrying both code A and code B, can be amplified (typically by PCR)” and then sequenced to determine the code sequences. EX1011, ¶[0030]; *see also, id.*, ¶¶[0070], [0117], Fig. 5; EX2008, ¶¶59-60.

C. Famulok is a commentary on Fredriksson 2002.

Famulok is not an original research paper, but instead is a commentary note discussing another publication, Fredriksson 2002. EX1012, 448 (discussing

Fredriksson 2002, EX1020); EX2008, ¶¶61-65. Petitioner misleadingly suggests in the Petition that Famulok was not before the examiner. Pet., 17. While Famulok itself was not before the examiner, Famulok is simply a commentary note discussing Fredriksson 2002, which *was* plainly before the examiner. *See e.g.*, EX1002, 107, 174-177; EX1001, face. And, as Petitioner's own expert admits, he could not identify any meaningful differences between the Famulok and Fredriksson. EX2009, 113:13-22, 117:1-118:11. Famulok's disclosures are at best cumulative with those of Fredriksson. EX2008, ¶61.

D. Baez teaches a PLA method utilizing solid-phase assays.

Baez teaches “[a] process ... for the detection of an analyte utilizing a nucleic acid label as a reporter.” EX1003, Abstract; EX2008, ¶¶66-71. In particular, Baez teaches detection methods using reporter molecules referred to a “reporter conjugates,” each reporter conjugate comprising “a ‘nucleic acid-label’ coupled to one member of a binding-pair such as an antibody, lectin, receptor or binding protein or other moiety which can bind to an analyte.” EX1003, 7:48-57; EX2008, ¶¶68-69. In Baez's methods, pairs of reporter conjugates bind to the same target analyte, which brings the nucleic acid labels of each reporter conjugate into “spatial proximity,” after which the nucleic acid labels can be joined (e.g., via ligation) to form a single nucleic acid molecule. EX1003, 11:21-24; EX2008, ¶69. Baez teaches that, after ligation, the ligation products are directly amplified by e.g.,

PCR. EX1003, 16:19-60; EX2008, ¶69. After amplification, the amplicons are detected by, e.g., gel electrophoresis, intercalating dyes, isotopes or reporters, or hybridization of reporter probes. EX1003, 16:61-18:12; EX2008, ¶69.

In the embodiment relied upon by Petitioner, Baez's detection method utilizes a solid-phase support of "immobilized streptavidin or avidin." EX1003, 17:24-27; *see also, id.*, 17:52-54, claims 2, 12; EX2008, ¶¶70-71. Petitioner's expert agreed that a POSA would have reasonably understood Baez's disclosure of immobilized streptavidin or avidin as referring to a solid support. EX2009, 149:18-150:7.

E. Landegren teaches a PLA method focused on solution phase assays and disparages solid-phase assays.

Landegren teaches a "rapid and convenient assay for the detection and/or quantification of one or several analytes in solution using so called proximity probes." EX1004, 1; *see also, id.*, Abstract; EX2008, ¶¶72-74. Landegren explains that a "proximity probe" comprises a binding moiety (e.g., an antibody or a nucleic acid, such as an aptamer) and a nucleic acid. EX1004, 3; EX2008, ¶73. Landegren teaches that "[a]ssays that use a solid phase require considerable time and effort for the analysis." EX1004, 1. Landegren further states that in solid-phase assays, "[t]he binding of reagents and analytes to the surface is a time consuming process and the washing steps must be precisely and reproducibly controlled between samples to give exact results." *Id.* Further, "[s]olid phase assays are also more difficult to

automate than homogenous assays.” *Id.*; EX2008, ¶¶73-74.

In contrast, Landegren teaches that its solution-phase methods provide the “ability to detect and quantify one or several analytes in solution in a homogenous one tube assay with high sensitivity and specificity.” EX1004, 2; EX2008, ¶¶73-74. As Landegren explains, its methods are “performed in solution without the need of a solid phase.” EX1004 Abstract; EX2008, ¶¶73-74. Petitioner’s expert admitted on cross-examination that he only “generally” reviewed Landegren to prepare his declaration, but he did not review it “cover to cover.” EX2009, 45:2-7.

F. Freskgard teaches a drug discovery method utilizing solid-phase assays.

Freskgard teaches “a method for identifying from a library a synthetic molecule having affinity towards a target.” EX1009, 1:10-13; EX2008, ¶¶75-78. Freskgard teaches using its methods in drug discovery to select “lead compounds,” which are usually “small organic molecule[s] that demonstrate[] a desired biological activity on a target.” *Id.*, 1:19-34; EX2008, ¶76. Freskgard’s methods utilize a solid-phase assay approach. EX1004, 43:6-44:15; EX2008, ¶77. In particular, Freskgard teaches creating a library of complexes, each complex comprising a drug candidate and a nucleic acid “identifier” linked to the drug candidate. EX1004, 35:31-33, 43:6-14; EX2008, ¶77. Freskgard teaches then panning the library over an immobilized target molecule to screen for drug candidates that bind the target molecule. EX1004, 43:6-44:15; EX2008, ¶¶77-78.

Freskard teaches that the target molecule is immobilized on a solid phase either before or after incubating it with the library. *Id.* After binding, Freskgard teaches washing away the non-bound library members, recovering the identifiers from the bound members, and then amplifying and decoding the identifiers to identify the drug candidates that bound the target molecule. *Id.*

VI. PETITIONER FAILS TO DEMONSTRATE THAT ANY OF THE CHALLENGED CLAIMS IS UNPATENTABLE OVER THE CITED ART.

A. Petitioner cannot prevail on Grounds 1 or 2.

As discussed below and supported by the declaration of Patent Owner's expert, Dr. Bradley Pentelute, the combination of Kanan and Neri fails to teach or suggest key claim elements of claim 1. EX2008, ¶¶96-133. Because dependent claims 2-20 depend directly or indirectly from claim 1 and require all the elements of claim 1, Petitioner fails to present a case of *prima facie* obviousness for the entirety of Grounds 1 and 2. EX2008, ¶¶96-133, 208. Additionally, Petitioner ignores fundamental technical defects in its art combination which would have belied any motivation to combine the references with a reasonable expectation of success. EX2008, ¶¶134-173.

1. Petitioner fails to demonstrate that Kanan and Neri teach or suggest all of the elements of the challenged claims.

a. Kanan and Neri fail to teach or suggest claim 1(d)'s selection step

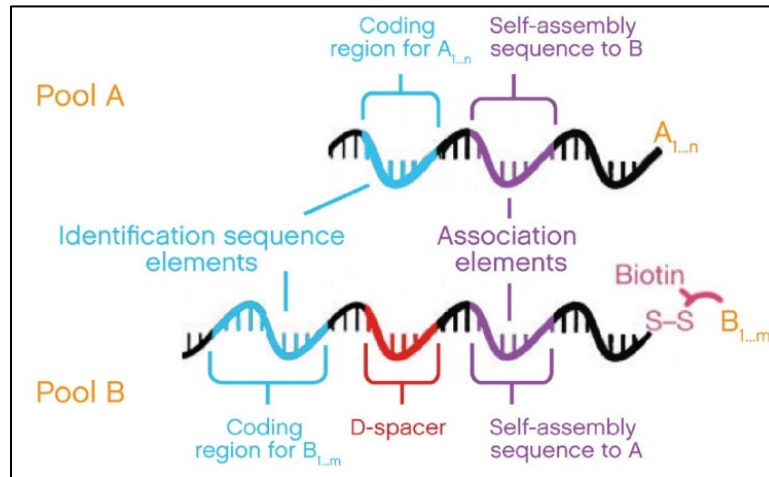
Claim 1(d) recites "selecting all *cis-reactive cells* exhibiting the detectable

trace.” EX1001, 41:53-54. Petitioner relies exclusively on Kanan’s “[s]treptavidin affinity selection” for this element. Pet., 34-35. But Kanan does not disclose or even suggest the claimed selection step because Kanan’s streptavidin affinity selection step occurs *after* the purported cis-reactive cells are destroyed; therefore, its method does not and cannot select cis-reactive cells as required by element 1(d). EX2008, ¶¶96-97. Because cis-reactive cells are not selected by Kanan, considered alone or in combination with Neri, EX2008, ¶¶98-119, Petitioner cannot prevail on Ground 1 or 2.

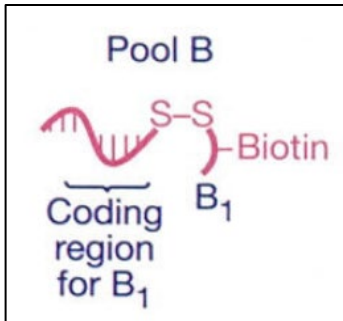
There is no dispute that a CRC of the ’848 patent requires at least two interactor molecules. Petitioner’s expert concedes that “a cis-reactive cell of the ’848 patent requires *at least two interactors* [bound] in proximity to one another....” EX2009, 38:18-39:20; *see also*, EX1001, claim 1(b) (“wherein a *cis-reactive cell comprises at least two interactors* bound in proximity to one another by an associated oligonucleotide...”); *id.*, 9:35-37; EX2008, ¶¶93, 98-99; Pet., 5; EX1005, ¶49. Nor is there any dispute that the claimed interactors require a molecule of interest (MOI) coupled with at least one nucleic acid moiety (NAM). Petitioner’s expert concedes that “interactors comprise at least two distinct parts which are coupled, one part is the molecule of interest and one part is the nucleic acid moiety.” EX2009, 37:12-22; *see also*, EX1001, claim 1(a) (“forming a plurality of interactors by *coupling each molecule of interest with at least one*

nucleic acid moiety..."); *id.*, 9:33-34; EX2008, ¶¶92, 98-99; Pet., 4; EX1005, ¶44.

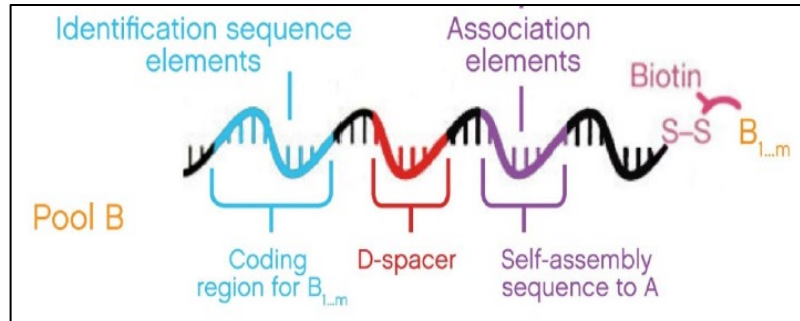
According to Petitioner, a POSA combining Kanan with Neri would have “create[d] two sublibraries of interactors” (pool A and pool B), depicted in Petitioner’s figure copied below:



Pet., 30-31; EX1005, ¶114. As evident in Petitioner’s own figure, Petitioner’s modified pool B members retain Kanan’s linker containing a biotin molecule and disulfide bond (“S-S”) between substrate molecule “B_{1...m}” and the corresponding oligonucleotide. EX2008, ¶¶101-102; EX1010, 545, Fig. 1; EX2009, 83:18-84:6. For comparison, consider Kanan’s pool B design (left) with Petitioner’s proposed modified pool B design (right), both of which include a linker containing biotin and a disulfide bond:

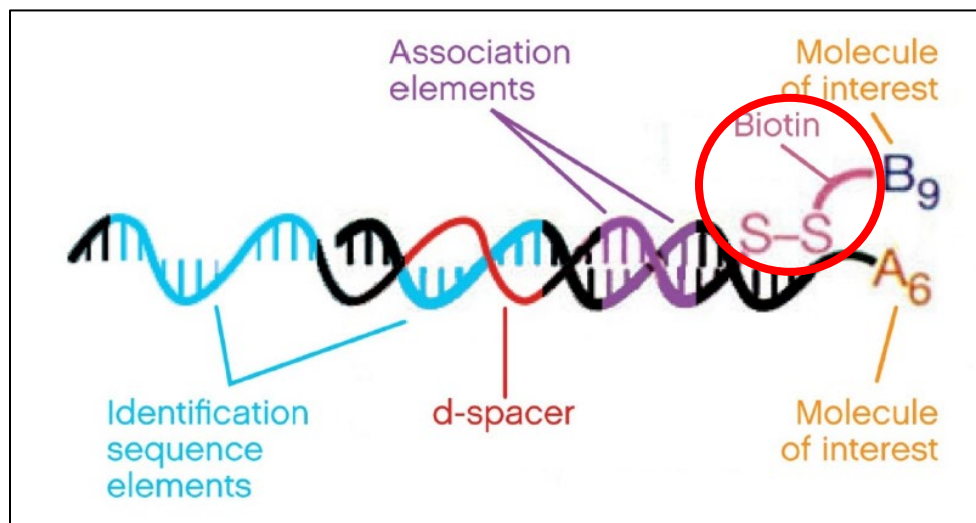


EX1010, Fig. 1.



Pet., 31.

According to Petitioner, combining the modified “pool A and pool B interactors” “forms a cis-reactive cell....” Pet., 32. Petitioner depicts its proposed CRC in the figure copied below:



Pet., 33 (annotated); EX1005, ¶115; EX2008, ¶103. As circled above, Petitioner’s hypothetical CRC again depicts a linker in the pool B “interactor” containing a biotin molecule and disulfide bond between substrate molecule “B₉” and the corresponding oligonucleotide. EX2008, ¶¶103-104; EX2009, 86:10-13, 92:1-4.

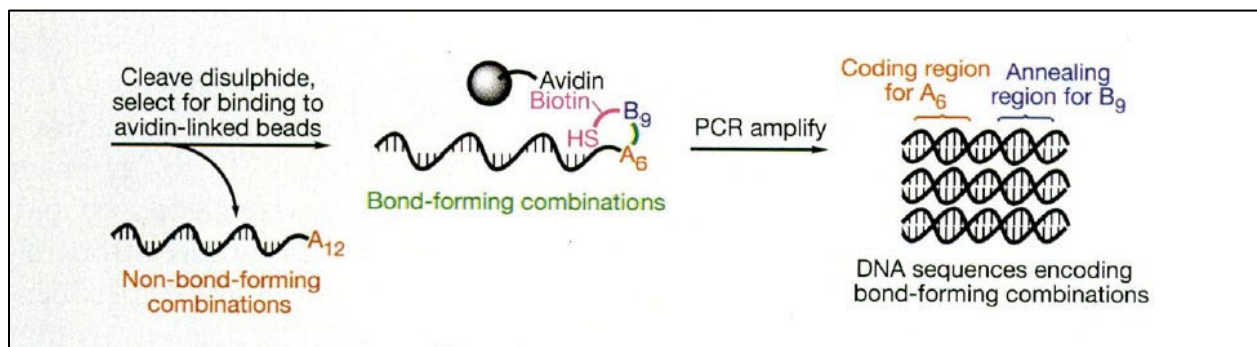
Petitioner then argues that the alleged “CRCs” would be subjected to “a set of chosen reaction conditions” taught in Kanan to stimulate bond formation

between substrates A and B. Pet., 33. According to Petitioner, “[a]ll of the cis-reactive cells would be subjected to the conditions in Kanan.” *Id.*; EX2008, ¶¶105-106.

After completing the bond-forming reactions, Kanan teaches *cleaving the disulfide bond* in the pool B oligonucleotides and then, only *after* disulfide bond cleavage, performing streptavidin affinity selection—i.e., performing selection *after* disulfide cleavage. EX1010, 545, Fig. 1; EX2008, ¶¶104-108. Kanan explains:

After incubations under a set of chosen reaction conditions, followed by cleavage of the disulphide bonds, only pool A sequences encoding bond formation between a pool A and pool B substrate remain covalently linked to biotin. Streptavidin affinity selection of the resulting solution separates biotinylated from non-biotinylated sequences.

EX1010, 545; EX2008, ¶106. This precise order of steps in Kanan’s method is also evident in Kanan’s Figure 1b, copied below:



EX1010, Fig. 1b; EX2008, ¶106. Shown above, Kanan expressly refers to “*cleave*

disulphide” and “*select* for binding to avidin-linked beads” as two separate and distinct processes, with disulfide cleavage occurring before streptavidin selection.

Id. Dr. Nelson conceded at deposition that Kanan teaches performing disulfide cleavage *before* selection:

Q Moving on in the figure, if we go down to the next row, after the bond formation, there's a step of cleaving the disulfide bond on Pool B oligonucleotides; is that right?

A Uh-huh.

Q And then after this disulfide cleavage, there's a selection of biotin molecules using streptavidin-linked beads; is that right?

A Avidin, but that is correct.

Q Okay. So, after disulfide cleavage, there's a selection of biotin molecules using avidin-linked beads; is that right?

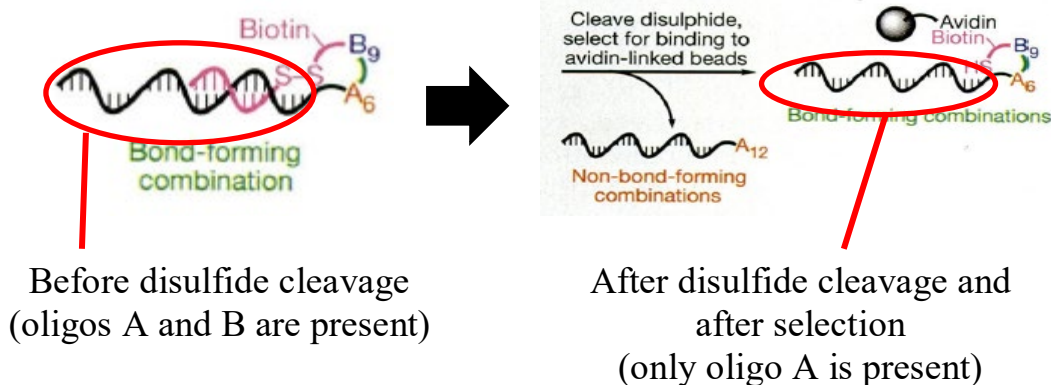
A From this figure, that appears to be what they're depicting, yes.

EX2009, 62:19-63:7; EX2008, ¶¶107-109.

Kanan’s Supplemental Information document confirms a POSA’s understanding that the disulfide cleavage occurs *before* the streptavidin affinity selection. EX1013, 8; EX2008, ¶110. Specifically, Kanan teaches that after the bonding reactions, a “0.1 M aqueous solution of tris(2-carboxyethyl)phosphine hydrochloride in 1.0 M sodium phosphate” was added “to effect disulfide

cleavage,” *and then* “[a]fter 1 h at 25 °C [i.e., *after disulfide cleavage*], this solution was added to a[n] ... aliquot of streptavidin-linked magnetic particles.” *Id.* As Dr. Pentelute explains, tris(2-carboxyethyl)phosphine hydrochloride (TCEP) is a common reducing agent known to those of skill in the art. EX2008, ¶132; EX1036, ¶[0369]. Dr. Nelson testified that he was unsure if TCEP was a reducing agent and would need to “research that further.” EX2009, 157:3-158:8. Regardless, Dr. Nelson conceded at deposition that Kanan’s disulfide cleavage occurs before streptavidin affinity selection. EX2009, 72:10-73:16.

By cleaving the disulfide bond in the linker of pool B library members before streptavidin affinity selection, Kanan’s method *uncouples* the pool B oligonucleotides from the pool B substrates and thus destroys the pool B “interactors.” EX2008, ¶¶111-113. An interactor of the ’848 patent must comprise an MOI coupled to at least one NAM. EX1001, claim 1(a); EX2008, ¶¶92, 98-99; EX2009, 37:12-38:8. After cleavage, the MOIs in Kanan’s pool B members are no longer coupled to the NAMs, and thus are no longer interactors. *Id.* Kanan’s loss of an “interactor” is evident in Kanan’s Figure 1b, which shows the B₉-A₆ bond pair comprising only oligonucleotide A after disulfide cleavage:



EX1010, Fig. 1b; EX2008, ¶¶117-118; *see also*, Pet., 35 (depicting Kanan Fig. 1b); EX2009, 64:4-65:12. According to Petitioner's expert, a POSA would have followed the same disulfide cleavage process when using the alleged CRCs made from the modified Kanan and Neri combination. EX2009, 92:5-93:11, 96:4-20.

For these same reasons, Kanan's disulfide cleavage step would also destroy the alleged CRCs, because a CRC of the '848 patent must comprise "at least two interactors." EX1001, claim 1(b); EX2008, ¶¶113, 117-118; EX2009, 38:18-39:20. A POSA would have recognized that, by destroying the pool B "interactors" via disulfide cleavage, Kanan also destroys the purported CRCs. EX2008, ¶¶113, 117-118. Petitioner and its expert ignore Kanan's disulfide cleavage step in their discussion of claim 1(d). Pet., 34-35; EX1005, ¶¶121-124. On cross-examination, however, Dr. Nelson testified that the alleged CRCs made from the Kanan and Neri combination would indeed be processed via Kanan's disulfide cleavage followed by streptavidin affinity selection. EX2009, 92:5-93:11, 96:4-20.

While the information above provides more than enough evidence that

Kanan in view of Neri does not teach or suggest the claimed selection step, Kanan additionally teaches twice rinsing the streptavidin beads with water, which a POSA would have understood to effectively remove any remaining pool B oligonucleotides from the assay. EX1013, 8 (“[t]he particles were rinsed once with 200 μ L H₂O...”), *id.* (“the supernatant was removed and the particles were rinsed with H₂O and washing buffer as above.”); EX2008, ¶¶114-116. As Dr. Pentelute explains, a POSA would have understood that Kanan’s water rinse steps would have separated any double-stranded DNA into single-stranded DNA due the low (zero) ionic strength of water, which would have further removed any residual cleaved pool B oligonucleotides from the assay. EX2008, ¶116; EX2009, 31:13-19.

In sum, because Kanan teaches performing the disulfide cleavage step *before* its streptavidin affinity selection (and thus destroys the interactors and CRCs before affinity selection), Kanan does not and cannot teach selecting “all *cis-reactive cells* exhibiting the detectable trace,” as required by claim 1(d). EX2008, ¶¶113, 117-118. Indeed, a POSA following Kanan’s method—even if modified in view of Neri—would not have selected *any CRCs at all* due to the disulfide cleavage step. EX2008, ¶118.

b. Kanan and Neri fail to teach or suggest claim 1(e)’s “subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis....”

Claim 1(e) requires “subjecting the associated oligonucleotides from *the cis-reactive cells selected in step (d)* to an analysis...” EX1001, claim 1(e). Petitioner argues that Kanan in view of Neri teaches step (e) because “Kanan teaches that *the bond-forming pairs* are amplified by PCR and analyzed with microarray analysis...” Pet., 35. Claim 1(e), however, requires analysis of “the associated oligonucleotides *from the cis-reactive cells selected in step (d)*,” not from “bond-forming pairs” as stated in the Petition. EX1001, claim 1(e); EX2008, ¶120. And as discussed above, Kanan fails to teach or suggest selecting *any CRCs* due to its disulfide cleavage step. *See* Section VI.A.1.a. Thus, Kanan and Neri do not teach or suggest claim 1(e) because in Kanan’s methods, there would have been no “cis-reactive cells selected in step (d)” and thus no associated oligonucleotides from any selected CRCs to analyze. EX2008, ¶120.

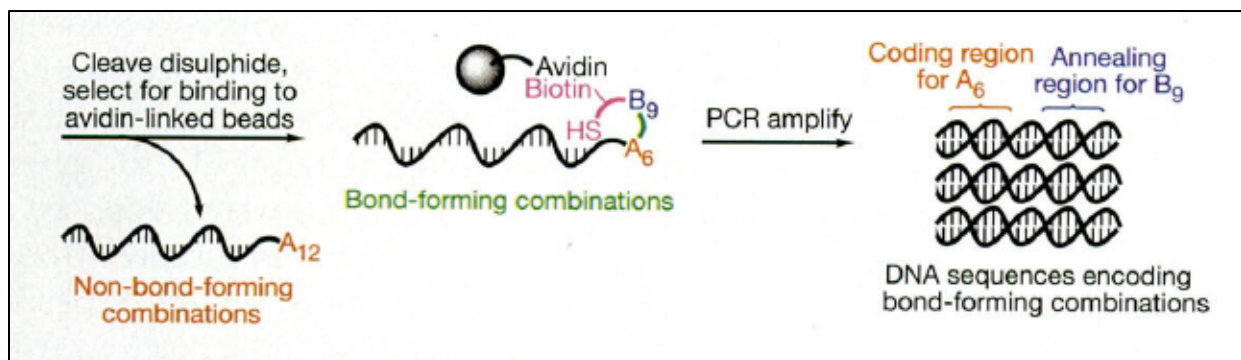
c. The Petition fails to show that Kanan and Neri teach claim 1(e)’s “detection of the at least two identification sequence elements.”

i. Kanan teaches removing the pool B oligonucleotides, resulting in only one identification sequence element for analysis.

Kanan further fails to teach or suggest claim 1(e) because Kanan’s cleavage and removal of pool B oligonucleotides results in removal of a purported identification sequence element. EX2008, ¶¶121-126. Claim 1(e) requires

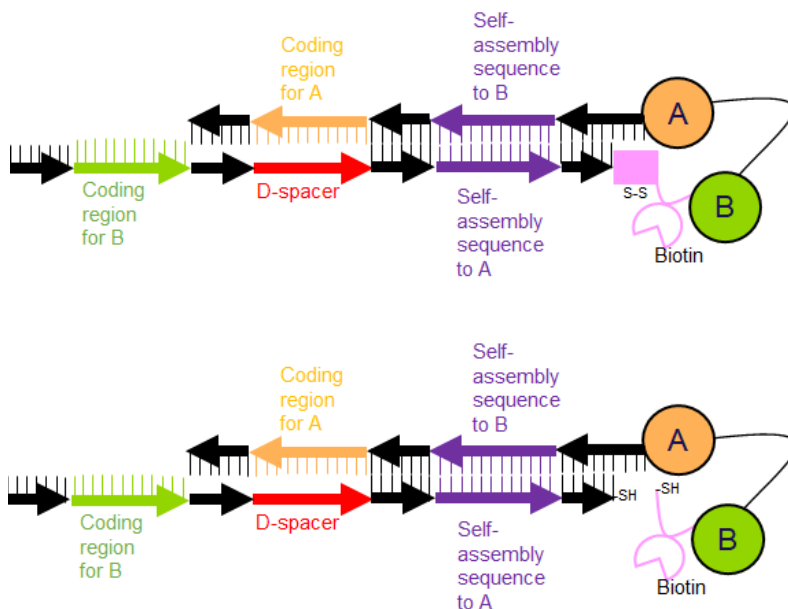
subjecting the associated oligonucleotides from the CRCs selected in step (d) “to an analysis that permits detection of the *at least two identification sequence elements*.” EX1001, claim 1(e). Petitioner argues that the combination of Kanan and Neri teaches claim 1(e) because “detection of the bond-forming substrates product permits the detection of the at least two identification sequence elements because it is the resulting nucleic acid, which includes the two identification sequence elements of Neri.” Pet., 23, 35-36. Petitioner’s expert provides the same conclusory explanation nearly verbatim. EX1005, ¶127. Petitioner and its expert are wrong because, as discussed above, Kanan’s workflow requires *cleaving and removing* the pool B oligonucleotides, which would have comprised one of the two identification sequence elements, according to Petitioner’s hypothetical combination. EX2008, ¶¶98-119; EX1010, 545-546, Fig. 1.

This is shown in Kanan’s Figure 1, where the resulting B₉-A₆ bond-forming pair that is analyzed comprises only the A oligonucleotide:



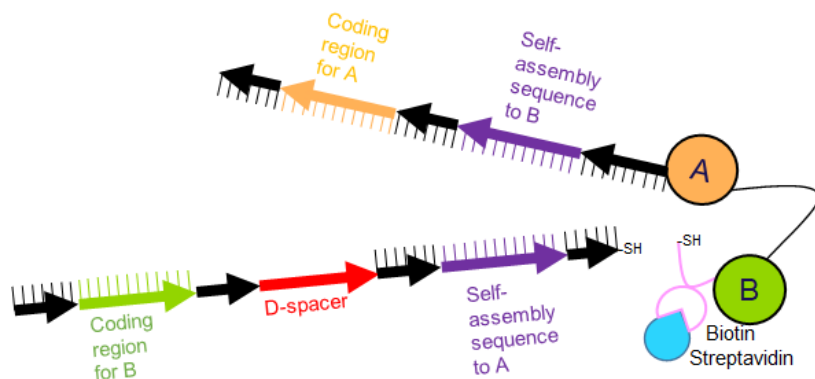
EX1010, Fig. 1b; EX2008, ¶124; EX2009, 64:4-65:12.

In Petitioner's proposed modification of Kanan, one identification sequence element is purportedly present in the pool A oligonucleotide ("Coding region for A"), and a second identification sequence element is purportedly present in the pool B oligonucleotide ("Coding region for B"). *See e.g.*, Pet., 31 (Figure), 34 (Figure); EX2008, ¶125. A POSA would have understood that Kanan's disulfide cleavage and subsequent selection steps would remove the pool B oligonucleotides from the assay and thus remove the "Coding region for B" identification sequence element, *before* the identification step (e). This is shown in Dr. Pentelute's figures below:

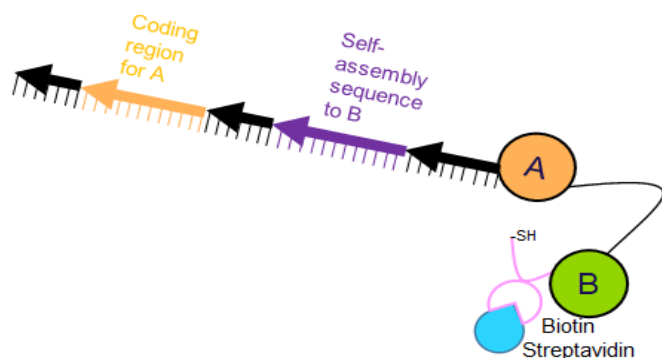


Before disulfide
cleavage and
streptavidin affinity
selection

Disulfide cleavage
uncouples purported
interactor B and CRC



DNA dehybridization
under streptavidin
affinity selection
conditions



Removal of pool B
oligonucleotides
under streptavidin
affinity selection
conditions

EX2008, ¶¶125-126.

Accordingly, Petitioner fails to show how its proposed modification of Kanan in view of Neri teaches or suggests an analysis that permits detection of “the *at least two* sequence identification elements,” because a POSA would have understood that Kanan’s methods would have removed one of the two proposed sequence identification elements (code B) from the system. *Id.*

ii. The Petition’s cursory reference to polymerization does not salvage its case.

The Petition’s discussion of claim 1 makes a cursory reference to a polymerization step in Neri when discussing a motivation to combine, but cites no actual disclosure from Neri. Pet., 20-21, 23. Rather, the Petition cites three

paragraphs from the Nelson declaration (EX1005, ¶¶182-183 and 177), all of which relate to Dr. Nelson’s discussion of claims 16 and 17. The Petition provides *no explanation* of when or how a POSA would have implemented Neri’s polymerization method in Kanan’s workflow. *Id.*; EX2008, ¶¶127-133. “Absent *some articulated rationale*, a finding that a combination of prior art would have been ‘common sense’ or ‘intuitive’ is no different than merely stating the combination ‘would have been obvious.’ Such a *conclusory assertion with no explanation is inadequate* to support a finding that there would have been a motivation to combine.” *In re Van Os*, 844 F.3d 1359, 1361 (Fed. Cir. 2017); *see also, Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 994 (Fed. Cir. 2017) (finding the Board’s explanation of a motivation to combine “wanting,” because “the Board nowhere clearly explained, or cited evidence showing, *how* the combination of the two references was supposed to work.” (emphasis in original)).

Moreover, Petitioner’s argument that a POSA would have been motivated to apply Neri’s polymerization step to Kanan’s workflow is fundamentally flawed because Neri teaches performing polymerization *after biopanning*. EX1011, ¶[0030] (“*After biopanning*, oligonucleotides of sub-library B remain stably annealed to oligonucleotides of sub-library A, and can work as primers for a DNA polymerase reaction on the template A.”), [0070] (“*After biopanning*, it is desirable to learn about the code of the binding members displaying a desired binding

specificity.”); *see also, id.*, ¶¶[0031]-[0032], [0071]-[0072], [0076], [0112], [0144], claim 19; EX2008, ¶¶128-130; EX2009, 110:17-23.

As Dr. Pentelute explains, a POSA would have understood that Neri’s biopanning method is a *selection method*, in which library members bound to the target analyte are selected and non-binding members are removed from the system. EX2008, ¶¶129-130; EX1011, ¶¶[0059], [0083]-[0084]. Thus, a POSA performing polymerization “as taught in Neri” would have performed polymerization after Kanan’s streptavidin-affinity selection step—too late to generate any useful data. EX2008, ¶¶129-130.

Petitioner’s expert, however, admitted that he did not consider this aspect of Neri’s method at all—in fact, he did not even do any analysis to understand what Neri’s biopanning method entailed, nor did he even understand what the term “biopanning” means in Neri:

Q Do you understand or do you have an understanding of what ESACHEL biopanning experiments are?

A I did not perform that analysis in regards to preparation for the case at hand here, so I would have to do that analysis to really understand that terminology.

Q You reviewed Neri to prepare your opinions in your declaration, did you not?

A I reviewed it. But as I mentioned, I didn't review every single detail of every single word.

EX2009, 99:15-25.

Q Do you agree that this process that's outlined here in paragraph 84 is the process of biopanning in Neri?

A I have not performed the analysis to understand exactly what they mean in this paragraph. I would have to perform an independent analysis. It's not part of my analysis for my declaration.

Q So you're not sure? You're not able to tell me one way or the other what the process -- what Neri's biopanning process is?

A As I stated for the biopanning, I would have to do a -- I didn't do that analysis.

Q Is it fair to say you didn't analyze Neri's methods of biopanning disclosed in this reference?

A I would say I did not analyze the references that they make to biopanning.

EX2009, 103:16-104:6; *see also, id.*, 98:1-19, 100:1-25. These admissions are notwithstanding the fact that Dr. Nelson cited and relied on disclosures in Neri that refer to biopanning. *See e.g.*, EX1005, ¶83 (citing EX1011, ¶[0030]).

Unlike Petitioner's expert, a POSA would have understood that performing polymerization "after biopanning" in Neri is analogous to performing

polymerization after streptavidin affinity selection in Kanan—i.e., *after disulfide cleavage and removal* of the pool B oligonucleotides. EX2008, ¶131. Thus, even if implementing polymerization “as taught in Neri” (Pet., 23), the pool B oligonucleotides would have already been removed by Kanan’s disulfide cleavage, precluding the ability to detect “*the at least two* identification sequence elements,” as required in claim 1 step (e). EX2008, ¶131.

Additionally, as Dr. Pentelute explains, reducing agents such as those present in polymerase reaction mixes were known in the art for their ability to break disulfide bonds. EX2008, ¶¶132-133; EX1036, ¶¶[0347], [0369]; EX2009, 158:9-16. Thus, a POSA would have understood that including a polymerase extension reaction in Petitioner’s modified Kanan approach would run a risk of cleaving the disulfide bonds in the pool B oligonucleotides. *Id.* This unintentional breaking of disulfide bonds would result in destruction of the alleged interactors and CRCs because the B substrate would no longer be coupled to pool B oligonucleotide, just as with the intentional disulfide cleavage discussed above. EX2008, ¶¶132-133.

- 2. A POSA would not have been motivated to modify Kanan in view of Neri.**
 - a. Petitioner’s proposed modifications of Kanan prevent the ability to identify both substrates**

The Petition alleges that a POSA “would have been motivated to improve

specificity of the binding between pool members in Kanan.” Pet., 19. Even if that were true, a POSA would not have pursued Petitioner’s proposed modifications of Kanan because the artisan would have known that Petitioner’s design would not improve assay specificity, but would instead do the opposite and make it worse. EX2008, ¶¶134-154. As discussed above, Petitioner’s proposed modification of Kanan requires cleaving the disulfide bond and removing the pool B oligonucleotide, which comprises the code B sequence identification element. *See* Section VI.A.1.a-b. Accordingly, a POSA would have understood that while practicing Petitioner’s proposed modification of Kanan might result in selecting bond-forming pairs of substrates, there would be *no ability to determine the identity of the two substrates* because only one of the two identification sequence elements needed is available for decoding. EX2008, ¶134. Without both identification sequence elements encoding for the two bonded substrates, a POSA would have understood that Petitioner’s proposed method would not yield useful information and thus would not “improve specificity” of the assay. Pet., 19. A POSA simply would not have had any motivation to modify Kanan in view of Neri as Petitioner alleges. EX2008, ¶134.

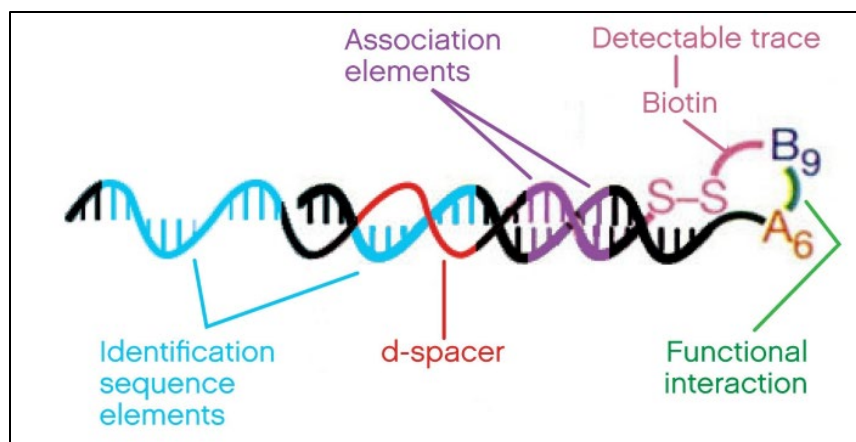
b. A POSA would not have been motivated to add a polymerization step in Petitioner’s modified version of Kanan in view of Neri.

As discussed above, the Petition fails to explain *how* a POSA would have

allegedly modified Kanan with Neri's polymerization step. And even if a POSA were to perform polymerization "as taught in Neri" (as the Petition alleges), Neri teaches performing polymerization after biopanning (after Neri's selection), which in Kanan would be akin to performing polymerization after disulfide cleavage and streptavidin affinity selection. *See* Section VI.A.1.c; EX2008, ¶135; Pet., 23. In other words, performing polymerization "as taught in Neri" is too late in Kanan's workflow because the pool B oligonucleotide would have already been removed. EX2008, ¶135. Moreover, fundamental technical issues associated with polymerization in Petitioner's proposed design would have further deterred a POSA from adding Neri's polymerization step to Kanan's modified workflow. EX2008, ¶¶136-154.

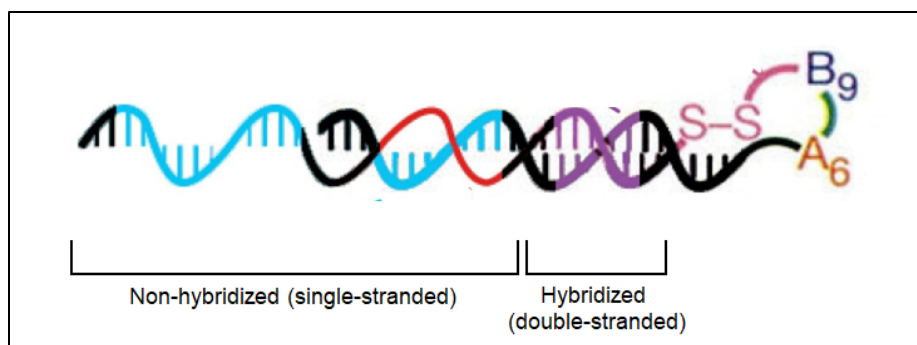
First, a POSA would have understood that a polymerization step is incompatible with Petitioner's proposed modification of Kanan in view of Neri. EX2008, ¶¶136-145. Petitioner alleges that a POSA would have been motivated to combine "the polymerization of the substrate pair disclosed in Neri" with the method of Kanan because polymerization would "increase the specificity of the assay." Pet., 20-21. But according to Petitioner's presented design, such modifications would *not* increase assay specificity; rather, Petitioner's modifications would render it useless. EX2008, ¶¶143-145.

Petitioner presents the following design in its modified version of Kanan:



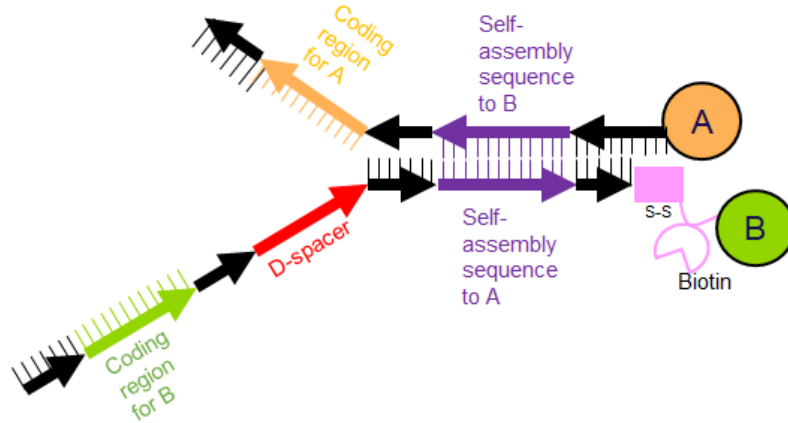
Pet., 34; EX1005, ¶119.

Petitioner alleges that “polymerization of oligonucleotides as taught in Neri could have been readily applied to oligonucleotides taught in Kanan because the use of primers and polymerase enzymes to extend oligonucleotides was a standard practice when the application was filed.” Pet., 23. According to Petitioner’s own diagram, the “association elements” (colored in purple) are complementary and hybridize to each other, represented by the matching vertical lines from each oligonucleotide strand. *Id.*; EX2008. ¶¶138-141. Dr. Nelson confirmed at deposition that the matching vertical lines in his figure represents DNA hybridization. EX2009, 86:17-87:11. However, according to Petitioner’s diagram, the remainder of the two oligonucleotide strands to the left of the purple association elements are *not hybridized* to each other, because neither strand to the left of the association elements has matching vertical lines to depict DNA hybridization. EX2008, ¶¶140-142; EX1005, ¶119; EX2009, 87:13-88:19. This is labeled in Dr. Pentelute’s figure below:



EX2008, ¶140. On cross-examination, Dr. Nelson discussed his depiction of hybridization in his figures and raised no issues of errors in the figures. EX2009, 86:17-88:19. And as Dr. Pentelute explains, depicting DNA hybridization using matching vertical lines was common in the art. EX2008, ¶142; EX1010, Fig. 1; EX1024, Fig. 14; EX1027, Figs. 4-5.

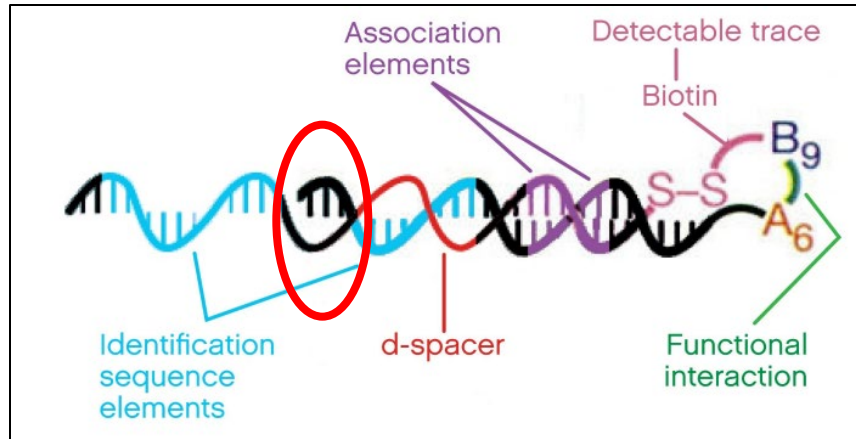
A POSA would have understood that the ends of the two strands in Petitioner's design are therefore *not hybridized* to each other and, contrary to Petitioner's portrayal, would be flexible and split out in a Y-shaped structure. EX2008, ¶142. Dr. Pentelute illustrates the Y-shaped structure in his figure copied below:



EX2008, ¶142.

Given this Y-shaped structure, a POSA would have understood that the design presented in the Petition and Nelson declaration would have prevented even the possibility of a polymerase extension step because there is no double-stranded region for any priming and polymerase extension to occur. EX2008, ¶¶142-143; EX2011, 263, 265-269; EX2012, 8.1-8.24. Accordingly, the POSA would not have had any motivation to add a polymerization step to Petitioner’s modified version of Kanan in view of Neri, because polymerization is incompatible with Petitioner’s presented design. *Id.* Petitioner’s proposed design would *not* “increase the specificity of the assay.” Pet., 20-21; EX2008, ¶¶143-145.

Second, on redirect examination, Dr. Nelson for the first time testified that his figures in his declaration are erroneous and should have depicted a second hybridized region to the left of the d-spacer (circled below):



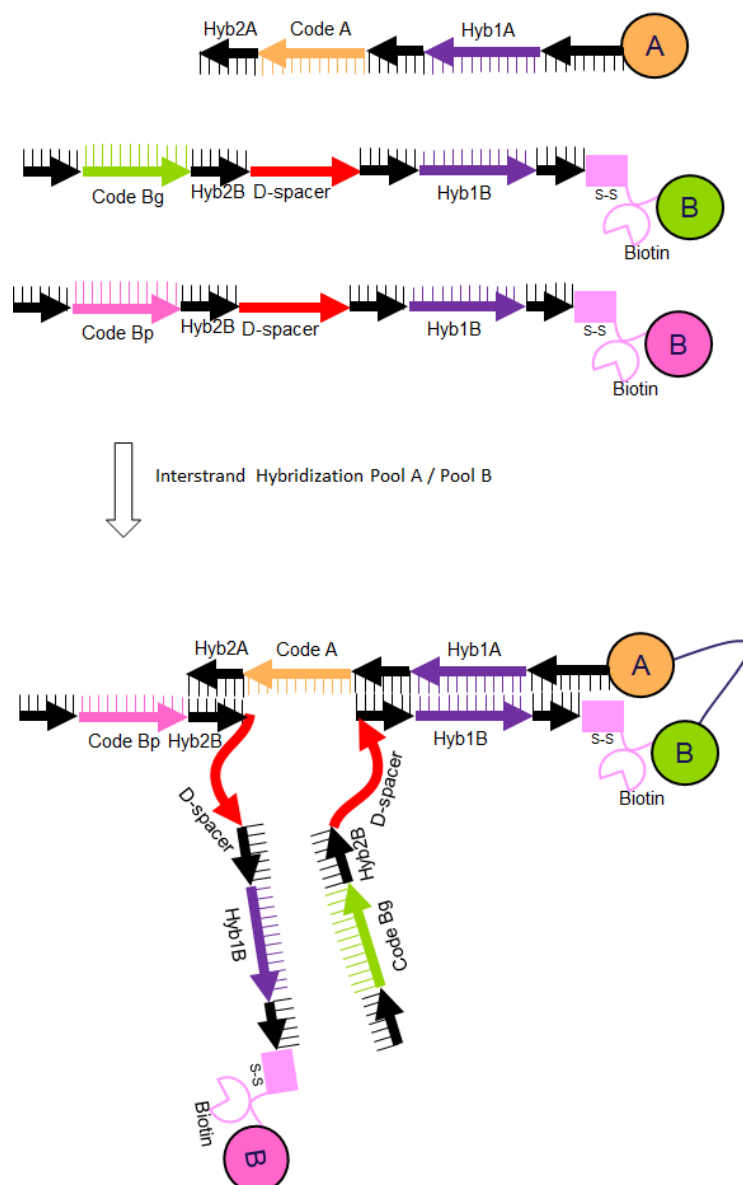
EX1005, ¶119 (annotated); EX2009, 163:5-10, 163:24-164:4.

The Board should reject Dr. Nelson’s new theory as it was not raised in the Petition or in the Nelson declaration. Dr. Nelson had already testified that he reviewed his declaration “cover to cover” before signing it and that he stood by everything in his declaration. EX2009, 18:2-12, 86:17-88:19. He had every opportunity to mention these alleged errors during cross-examination when discussing his depiction of hybridization in these same figures. *Id.* Only after presumably conferring with counsel between cross-examination and redirect examination did he pivot and introduce his new theory of a second hybridized region. EX2009, 163:5-10, 163:24-164:4.

Even if the Board were to accept Dr. Nelson’s new theory (which is not presented in the Petition or Nelson declaration), a POSA would have immediately recognized problems with such a design because, according to Dr. Nelson, the second hybridized region would have been a universal complementary region such that any member of pool A can hybridize to any member of pool B at that region.

EX2009, 167:22-168:6, 169:8-12; EX2008, ¶¶146-154. Dr. Nelson testified that the black region to the left of the d-spacer represents “primer binding sites,” which “are constant” and “would be the same for all pool members.” *Id.*

A POSA would have recognized that the fundamental flaw in this design is that a single pool A oligonucleotide could anneal to *two different pool B oligonucleotides* concurrently, ultimately producing false-positive results. EX2008, ¶¶149-150. This is shown in Dr. Pentelute’s figure below:

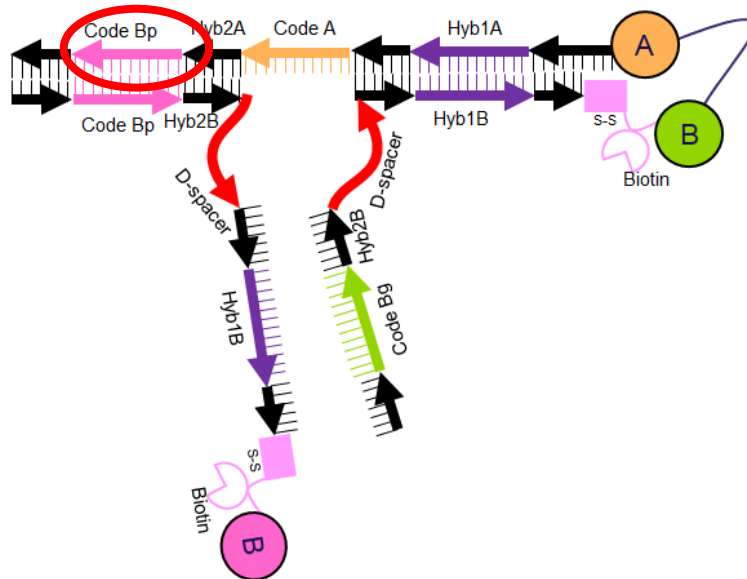


EX2008, ¶150.

A POSA would have expected that the self-assembly sequence of the pool A oligonucleotide (“Hyb1A”) would hybridize to the complementary self-assembly sequence of the green pool B oligonucleotide (“Hyb1B”), while second hybridization region of the pool A oligonucleotide (“Hyb2A”) hybridizes to the complementary “Hyb2B” sequence in the *pink pool B* oligonucleotide. EX2008,

¶151. The flexibility of the d-spacer in the B oligonucleotides further contributes to this configuration. *Id.*

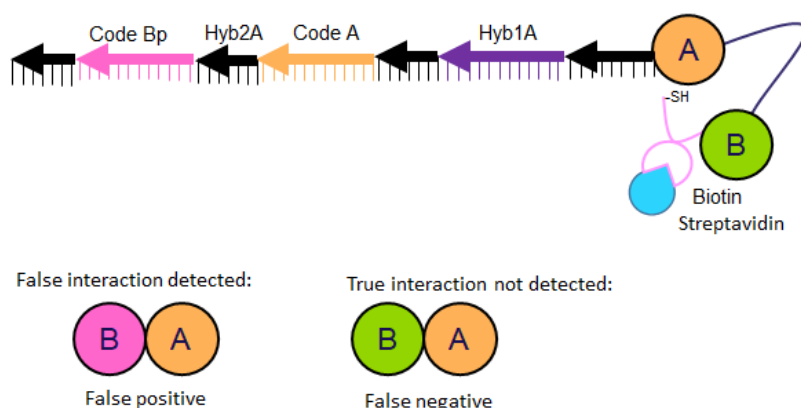
The POSA would have further understood that, if the above structure were subjected to a polymerization step, the polymerase would copy the *pink code B* onto oligonucleotide A (circled below), instead of the green code B:



EX2008, ¶152.

And as Dr. Pentelute explains, after following Kanan's disulfide cleavage, streptavidin affinity selection, PCR amplification, and microarray analysis, the result would suggest that the *pink B substrate* interacted with the orange A substrate, rather than the correct green B substrate and orange A substrate. *Id.*,

¶¶153-154. A POSA would have expected the false-positive final result below:



EX2008, ¶153. This configuration would also be expected to generate false-negative results, as the readout would indicate that green B did *not* interact with orange A. *Id.*

Petitioner alleges that a POSA would have been motivated to modify Kanan in view of Neri to “improve specificity of the binding between pool members in Kanan,” and that the “self-assembly sequence of Neri reduces the concern of mismatched hybridization....” Pet., 19. As explained above, a POSA would have expected just the opposite because Petitioner’s proposed modifications would *increase* “the concern of mismatched hybridization,” and *reduce* the ability to “efficiently identify the reactive pairs in Kanan.” Pet., 19-20; EX2008, ¶154.

Recognizing this fundamental design flaw in Petitioner’s setup, and the unreliable nature of any results generated from it, a POSA would have deemed it untenable and would not have had any motivation to pursue Petitioner’s proposed modifications of Kanan in view of Neri. *Id.*

3. A POSA would not have had a reasonable expectation of successfully modifying Kanan in view of Neri as Petitioner contends.

Petitioner argues that “[a] POSA would have a reasonable expectation of success in combining Kanan and Neri because the various elements disclosed in Neri *could be combined* with Kanan in a predictable way, even if there is some uncertainty.” Pet., 21. But the test for obviousness asks not what *could be* done, rather what a POSA would be motivated to do. *Personal Web*, 848 F.3d at 993-994. Given the fundamental technical flaws in Petitioner’s proposed design discussed above, a POSA would not have had any motivation to modify Kanan in view of Neri as Petitioner alleges, nor would the POSA have had any reasonable expectation of success. EX2008, ¶¶155-158.

As discussed above, a POSA would have known that Petitioner’s proposed modification of Kanan in view of Neri results in cleavage and removal of the pool B oligonucleotides, resulting in loss of one of the identification sequence elements. *See* Section VI.A.1.c; EX2008, ¶¶121-134, 155-157. A POSA thus would not have had a reasonable expectation of success in identifying a functional interaction between two molecules of interest, because following Kanan’s method as Petitioner contends would not allow detection of the at least two identification sequence elements. EX2008, ¶¶156-157.

Also discussed above, adding a polymerization step “as taught in Neri”

(according to Petitioner) would not have resolved this technical defect because Neri teaches to perform polymerization after Neri's selection step (after biopanning), which in Kanan would occur after disulfide cleavage and after streptavidin affinity selection. EX2008, ¶¶129-131. The polymerization thus would not provide any useful information because one of the identification sequence elements (code B) would have already been removed. *Id.* Additionally, a POSA would have known that modified design presented in the Petition is structurally incapable of viable polymerase extension due to the lack of a hybridized priming region to initiate polymerase extension. EX2008, ¶¶136-145, 157; *see* Section VI.A.2.b.

Moreover, even if accepting Dr. Nelson's newfound theory of a second hybridization region in Petitioner's design, a POSA would not have had a reasonable expectation of successfully implementing it because the pool A oligonucleotides would be expected to hybridize to multiple, different pool B oligonucleotides due to the universal complementary regions in each oligonucleotide. EX2008, ¶¶146-154, 158; EX2009, 167:22-168:6, 169:8-12. A POSA accordingly would have expected Petitioner's proposed design to generate unreliable false-positive results. EX2008, ¶¶146-154, 158. A POSA simply would not have reasonably expected Petitioner's proposed art combination to reliably detect functional interactions. EX2008, ¶¶155-158.

None of Petitioner's stated rationales for alleged reasonable expectation of success account for the fundamental defects in Petitioner's design. Pet., 21-23. Petitioner first downplays the "difference between the interactors disclosed in Kanan and Neri" as being "minimal," ignoring the significant and detrimental impact Neri's d-spacer and alleged multiple hybridization regions would have on Kanan's library that was designed for disulfide cleavage and removal of pool B oligonucleotides. Pet., 21; EX2008, ¶154. Petitioner then argues that the "nucleic acid label disclosed in Kanan *could be* sequenced." Pet., 22. The mere fact that nucleic acid labels "*could be* sequenced" ignores the fundamental incompatibility issues between Kanan's and Neri's libraries and methods. While nucleic acid labels *could be* sequenced, a POSA would not have reasonably expected to obtain any useful or reliable sequencing data from Petitioner's proposed modified version of Kanan. EX2008, ¶¶155-158; *see* Section VI.A.2.

4. Petitioner cannot prevail on its challenge to claim 16.

The Petition's Ground 2 challenges only claim 16, which depends from claim 1 and recites that the "association is via ligation." Pet., 2, 42-43; EX1001, claim 16. Petitioner relies on Famulok solely to meet the element of claim 16. Pet., 2, 42-43. Thus, the addition of Famulok in Ground 2 fails to reconcile the fatal deficiencies of Petitioner's Kanan and Neri combination discussed above for Ground 1, and therefore fails to establish unpatentability of claim 16 for at least the

same reasons discussed above. *See* Section VI.A.1-3. Indeed, Petitioner's challenge to claim 16 ignores Kanan's requirements for disulfide cleavage and uncoupling of the pool B oligonucleotide, which effectively destroys the purported B interactors and CRCs, and thus cannot meet the elements of claim 1. *See* Section VI.A.1.a. This is true regardless of whether the pool B oligonucleotide is uncoupled and washed away (as taught in Kanan) or somehow ligated to the pool A oligonucleotide before disulfide cleavage and uncoupling. EX2008, ¶164. In either case, the B oligonucleotides are uncoupled from the B substrate, thus destroying the purported interactor and CRC *before* Kanan's streptavidin affinity selection. *Id.* Thus, for the same reasons discussed above in Ground 1, the combination of Famulok with Kanan and Neri fails to teach or suggest all the elements of claim 16, which require the elements of claim 1.

The Petition's challenge to claim 16 also fails on its own merits. EX2008, ¶¶159-173. First, Dr. Nelson admitted at deposition that he only reviewed "parts" of Famulok, despite Famulok only being a two-page commentary:

Q Okay. And you reviewed this document in preparing the opinions in your declaration, correct?

A I reviewed parts of it as it was relevant to the -- my argument here.

Q Which parts of it did you review?

A Those related to ligation.

Q And you didn't review other parts of the document?

A I did not read every word of this document, no, I did not.

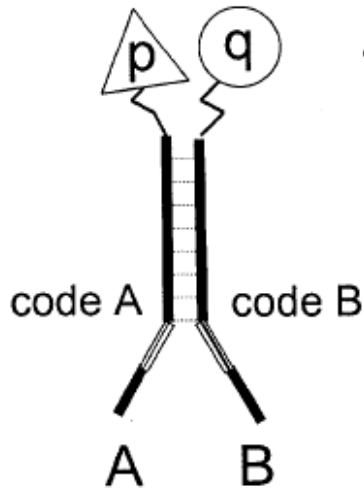
EX2009, 113:13-22. That Dr. Nelson did not bother to “read every word” of a two-page document contained in Petitioner’s obviousness grounds should inform the weight the Board affords his testimony. *See* 37 C.F.R. § 42.65(a).

Additionally, Dr. Nelson testified that for his challenge to claim 16, he relied upon the embodiment depicted in Neri’s Figure 7 to combine with Famulok and Kanan. EX2009, 126:17-127:17; EX1005, ¶¶175-179. In this embodiment, Neri teaches that the “A” and “B” conjugate molecules are first *associated by hybridization* of the A and B oligonucleotides. EX1011, ¶[0032] (“Sub-libraries A and B form a heteroduplex...”), [0076] (same); EX2008, ¶¶161-163. Dr. Nelson admitted at deposition that the alleged interactors in Neri’s Figure 7 are associated by hybridization. EX2009, 128:23-129:2, 130:23-131:19. Indeed, Dr. Nelson testified that a POSA combining Kanan, Neri, and Famulok would have *first* associated the interactors via self-assembly hybridization of the oligonucleotides (as taught in Neri), and *then* performed Famulok’s ligation method using a splint oligonucleotide. EX2009, 134:14-135:16. Thus, in Petitioner’s challenge to claim 16, the purported CRCs are made from interactors *associated by hybridization* of the self-assembly region in the oligonucleotides, *not by ligation*, as required by

claim 16. EX2008, ¶163; EX2009, 128:23-129:2, 130:23-131:19. For this additional reason, Petitioner fails to demonstrate that the combination of Kanan, Neri, and Famulok teaches or suggests all the elements of claim 16. EX2008, ¶163.

Further, the Petition fails to articulate any rationale as to how or why a POSA would have implemented Famulok's ligation technique into the combination of Kanan and Neri, providing only a single conclusory statement that "it would have been obvious to use the ligation of the oligonucleotides as taught in Famulok with the creation of the paired substrates in Kanan." Pet., 43. "Such a *conclusory assertion with no explanation is inadequate* to support a finding that there would have been a motivation to combine." *In re Van Os*, 844 F.3d at 1361; *Personal Web*, 848 F.3d at 994.

Petitioner's art combination with Famulok in Ground 2 is also fraught with its own technical design flaws, which are ignored in the Petition and Nelson declaration. EX2008, ¶¶165-173. Petitioner's challenge to claim 16 relies on the design depicted in Neri's Figure 7, copied below:



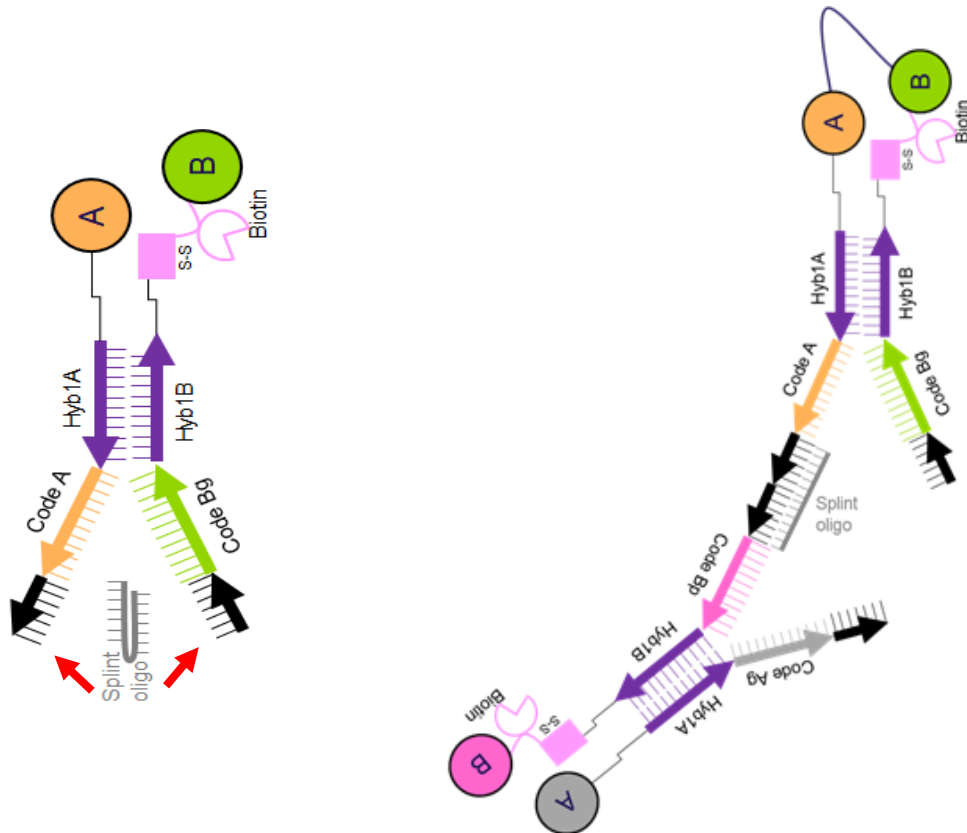
EX1011, Fig. 7; EX1005, ¶178. Dr. Nelson testified that the “overhang region” in Neri’s Figure 7 “can be ligated together using the method taught in Famulok.”

EX1005, ¶178. This is yet another argument Petitioner has not thought through.

As Dr. Pentelute explains, if the distal ends of the “overhang region” in Neri’s Figure 7 were to be ligated, the sequences on the ends must either be unique sequences for each pair of A and B, or common sequences for all pairs of A and B. EX2008, ¶¶165-168; EX1011, Fig. 7. If the end sequences are unique to each pair of A and B in Petitioner’s embodiment, the POSA would need to synthesize a splint oligonucleotide *for each combination of A and B*, undermining Petitioner’s stated rationale for modifying Kanan in the first place. Pet., 17-18 (referring to Kanan’s “tedious process” that “must be repeated for each different A substrate (A_{1-n}) and must be repeated so each A substrate can anneal to all B substrates (B_{1-m}).”); EX2008, ¶166. If the end sequences are common to all A and B library members in Petitioner’s embodiment, then the POSA would have expected cross-

hybridization of the splint oligonucleotide between *different library members*.

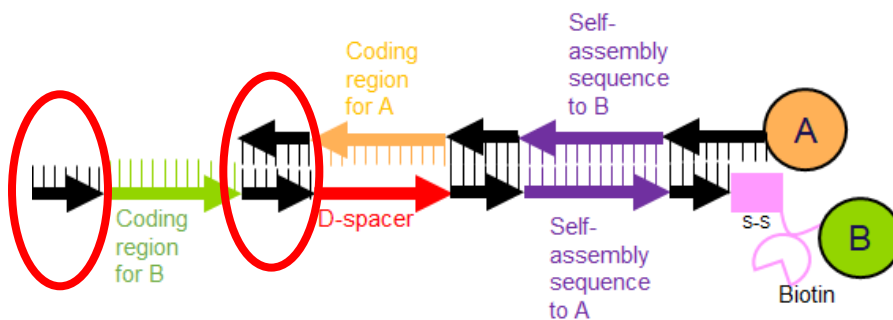
EX2008, ¶167. That is, the splint oligonucleotide would hybridize to the ends of separate pool members. *Id.* This is shown in Dr. Pentelute's figures below:



EX2008, ¶168. As shown above, a POSA would have expected the splint oligonucleotide (shown in grey) to not only connect the A and B ends of individual library members (e.g., orange A and green B, left panel), but also to connect the ends of *different* library members (e.g., orange A and pink B, right panel). *Id.* This would be expected to increase the number of false-positive and false-negative results, rendering Petitioner's proposed embodiment inefficient and unreliable.

EX2008, ¶¶168-170.

Dr. Nelson testified at deposition that a POSA might also rely on the embodiment in Neri's Figure 5 to practice the combination of Kanan, Neri, and Famulok for claim 16. EX2009, 137:3-8, 138:11-20. Nowhere is this discussed in the Nelson declaration or in the Petition's arguments for claim 16. EX1005, ¶¶175-179; Pet., 42-43. To the extent Petitioner pivots in its Reply and attempts to change its theory to rely on Neri's embodiment in Figure 5, the Board should reject it as new argument. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1329–1331 (Fed. Cir. 2019); *Intelligent Bio-Sys. v. Illumina Cambridge*, 821 F.3d 1359, 1369-1370 (Fed. Cir. 2016). Petitioner cannot belatedly change its rationale in its Reply. Moreover, such an embodiment would still be expected to provide unreliable data. EX2008, ¶¶171-173. For example, if using Dr. Nelson's new embodiment raised during his deposition in which the modified CRCs comprise two hybridization regions (see Section VI.A.2.b), a POSA would have understood there would be no "overhang region" on the A and B sublibrary members to ligate:



EX2008, ¶¶171-172. In the figure above, sublibrary B has an overhang region

(circled, left), while the distal end of sublibrary A is allegedly hybridized to its complementary region in sublibrary B (circled, right). EX2009, 163:5-10, 163:24-164:4. There is no “overhang region” in each of A and B in Petitioner’s embodiment that could be ligated using Famulok’s splint oligonucleotide methods. EX2008, ¶¶171-172. Indeed, Famulok teaches bringing the two “*free ends* ... “into close special proximity,” which allows the “connector oligonucleotide to *hybridize to both ends*, acting as a template for enzymatic ligation.” EX1012, 449, Fig. 1; EX1020, 473 (“When pairs of probes bind PDGF-BB, *the free ends* of their sequence extensions are brought sufficiently close to hybridize together to a subsequently added connector oligonucleotide, *allowing the ends to be joined* by enzymatic DNA ligation.”); EX2008, ¶172.

Further, even putting aside the lack of ligatable ends, a POSA would not have been motivated to implement the embodiment of Neri’s Figure 5 in the Kanan, Neri, and Famulok combination because the resulting ligation product would include Neri’s d-spacer region, which Neri teaches is “composed of phosphodiester backbone *without bases*” (i.e., abasic). EX1011, ¶[0029]; EX2008, ¶173; EX2009, 87:25-88:13. A POSA would have understood that the high flexibility and lack of bases in the d-spacer would render the molecule unable to effectively bind PCR or sequencing primers and thus not provide a useful readout. EX2008, ¶173. This is evident from Neri itself, which discloses amplifying and

sequencing only the pool A oligonucleotides that lack the abasic d-spacer.

EX1011, ¶¶[0117]-[0119].

B. Petitioner cannot prevail on Grounds 3 and 4.

The Petition’s Grounds 3 and 4 are also fatally deficient. Much like Grounds 1 and 2, Petitioner’s combination of Baez and Landegren—the basis for Grounds 3 and 4—also fails to teach or suggest key claim elements of claim 1. EX2008, ¶¶174-191. And because dependent claims 2-20 depend directly or indirectly from claim 1 and require all the elements of claim 1, Petitioner fails to present a case of *prima facie* obviousness for the entirety of Grounds 3 and 4. EX2008, ¶¶174-191, 208. Additionally, express disclosures in Baez and Landegren show that a POSA would not have been motivated to combine Baez, Landegren, and Freskgard as Petitioner alleges. *Id.*, ¶¶192-207.

- 1. Petitioner fails to demonstrate that Baez and Landegren teach or suggest all of the elements of the challenged claims.**
 - a. Petitioner fails to demonstrate that Baez and Landegren teach or suggest claim 1(a)’s forming a plurality of interactors.**

Petitioner cannot prevail on Grounds 3 and 4 due to the Petition’s inconsistent and disconnected claim mapping of claim 1, step (a). Petitioner identifies the “molecules of interest” in Ground 3 as “*Baez’s antibody-nucleic acid conjugates.*” Pet., 55; EX1005, ¶232 (“a POSA would have understood the *antibody conjugates* disclosed in Baez as a *molecule of interest.*”). The “antibody

conjugates” of Baez are comprised of an antibody probe conjugated to a nucleic acid label, which Baez refers to as “reporter conjugates.” EX1003, 5:51-54, Fig. 2; EX2008, ¶175. Thus, Petitioner and its expert both identify the antibody-nucleic acid conjugates of Baez as the molecules of interest in the ’848 patent.

However, when addressing the “interactors” of claim 1(a), Petitioner and its expert argue that “the *interactors* include Baez’s ‘reporter conjugates.’” Pet., 56; EX1005, ¶235 (“a POSA would have understood the ‘reporter conjugates’ disclosed in Baez are ‘interactors.’”). Thus, Petitioner and its expert rely on the *same antibody-nucleic acid conjugate* in Baez as meeting *both* the MOI and interactor limitations of claim 1. If Baez’s antibody-nucleic acid conjugates constitute the MOIs as the Petition contends, then the Petition fails to identify any nucleic acid moiety that is coupled to the MOI to form a plurality of interactors, as required by claim 1(a). EX2008, ¶¶175-176.

This inconsistency in claim mapping is fatal to the Petition’s argument, and any attempt by Petitioner to recast its argument in Reply should be rejected as new argument not raised in the Petition. *See e.g., Inergy Tech., Inc. v. Force Mos Tech. Co., Ltd.*, IPR2024-00093, Paper 38, 17-22 (P.T.A.B., May 16, 2025). In *Inergy Tech.*, the Petition inconsistently identified portions of a semiconductor figure in the prior art (“layers 13 and 14”) as meeting a “body region” claim element, and then also relied on the same layer 13 in the figure as meeting a different “base

layer” claim element. *Id.*, 17-18. In its Reply, the petitioner argued for the first time that “layers 13 and 14 together” met both the “body region” and “base layer” claim elements. *Id.* The Board held that due to these inconsistencies, “the Petition fails to identify structure in [the prior art reference] that corresponds to the ‘base layer’ limitation of claim 1[a]” and further rejected the petitioner’s attempt to revise its argument in Reply. *Id.*, 19-20 (noting that “Petitioner’s arguments are moving targets on this record.”); *see also, Visa Inc. v. Universal Secure Registry, LLC*, IPR2018-01350, Paper 35, 14 (P.T.A.B., Jan. 30, 2020) (“We conclude that the Petition does not raise the mapping on which Petitioner now relies.”); *Henny Penny*, 938 F.3d at 1329–1331; *Intelligent Bio-Sys.*, 821 F.3d at 1369-1370. The Petition’s inconsistencies here are likewise fatal.

Indeed, the Board in its Decision on Institution correctly identified the Petition’s inconsistent claim mapping, raising “doubts that Petitioner is reasonably likely to prevail on Grounds 3 and 4.” DI, 36. As the Board correctly concluded, “[t]o the extent the antibody-nucleic acid conjugates are asserted to be the molecules of interest, the Petition fails to clearly explain what nucleic acid moiety is then coupled to it to form the interactors.” *Id.*

For at least this reason, the Petition fails to meet its burden on Grounds 3 and 4. EX2008, ¶¶175-178.

**b. Baez and Landegren fail to teach claim 1(d)’s
“selecting all cis-reactive cells exhibiting the
detectable trace.”**

Petitioner relies exclusively on Baez for meeting claim 1(d)’s “selecting” step, alleging that “selecting the CRCs *includes Baez’s isolating CRCs* (ASAs in Baez) comprising a biotin label *using immobilized streptavidin.*” Pet., 60. In its claim mapping argument, Petitioner and its expert rely on Baez’s disclosures in column 17:25-28 and 17:52-54. Pet., 60; EX1005, ¶252.

As Dr. Pentelute explains, a POSA would have understood that these disclosures in Baez relate not to “selection” of CRCs, but expressly teach methods of *detection* of Baez’s ligation product. EX2008, ¶¶179-182; EX1003, 16:65-17:58. The entirety of the Petition’s relied-upon disclosures in Baez’s column 17 are found under Baez’s section header entitled, “*Detection of Nucleic Acid Products.*” EX1003, 16:65; EX2008, ¶¶181-182. Baez also expressly discloses that “[t]he ASA can be *detected* through the linker oligonucleotide itself,” and that a biotin label “could be *detected* through antibody conjugates, direct fluorescence, or fluorescent energy transfer (FET), for example.” EX1003, 17:52-57; EX2008, ¶182. Additionally, Dr. Nelson admits in his declaration that Baez’s biotin detection method “involves *detecting* the ASA...” EX1005, ¶252; *see also* Pet., 60 (similar); EX2008, ¶182. A POSA thus would have understood that Baez’s teaching regarding detecting biotinylated products on immobilized streptavidin is a

method of *detecting the ASAs* resulting from ligation, not selecting all CRCs having a detectable trace, as required by claim 1(d).

Moreover, even if Baez’s biotin/streptavidin-mediated detection method were considered a “selection” (it is not), it would not involve *selecting cis-reactive cells* as required by claim 1. EX1003, 17:25-28, 17:52-54; EX2008, ¶183. Baez’s biotin/streptavidin detection method isolates only the *biotinylated amplicons*, not CRCs. *Id.* Claim 1, however, requires *selection of CRCs*, which comprise at least two interactors bound in proximity to one another by an associated oligonucleotide. EX1001, claim 1(d); EX2008, ¶¶183-185; EX2009, 43:15-24. Thus, even if interpreted as a “selection,” Baez’s biotin/streptavidin method at most “selects” only amplicons and not CRCs. *Id.*

Accordingly, the Petition fails to demonstrate that Baez and Landegren teach or suggest claim 1(d)’s selection step. EX2008, ¶¶179-185.

c. Baez and Landegren fail to teach or suggest claim 1(e)’s “subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis....”

Petitioner argues that step (e) is met because “Baez teaches that the ASA product is amplified by PCR and the ‘PCR amplification product can be detected by various methods known in the art[.]’” Pet., 61. Claim 1(e), however, requires analysis of “the associated oligonucleotides *from the cis-reactive cells selected in step (d)*,” not from the allegedly selected “ASA product” as stated in the Petition.

EX1001, claim 1(e); EX2008, ¶¶186-187. As discussed above, Baez fails to teach or suggest *selecting CRCs* because Baez’s biotin/streptavidin method is a method of *detection*, and even then it only detects biotinylated amplicons, not CRCs. *See* Section VI.B.1.b. Thus, the combination of Baez and Landegren fails to teach or suggest claim 1(e) because there would have been no “cis-reactive cells selected in step (d).” EX1001, claim 1(e); EX2008, ¶¶186-187.

d. Baez and Landegren fail to teach or suggest claim 1(e)’s “analysis that permits detection of the at least two identification sequence elements.”

The Petition again resorts to inconsistent claim mapping in its arguments for step (e)’s “analysis that permits detection of the at least two identification sequence elements.” EX2008, ¶¶188-191. When discussing claim 1(a), the Petition expressly relies upon Landegren’s disclosures of “tags” as meeting the “identification sequence element” of claim 1(a). Pet., 56 (referring to Landegren’s “tag” and “the ‘sequence identification tags’ of Landegren.”); EX1005, ¶237; EX2009, 143:11-144:5. When discussing claim 1(e), the Petition argues that mere detection of PCR amplicons satisfies the “detection of the at least two identification sequence elements.” Pet., 61 (“A POSA would have understood that *detection of the amplified ASA product* permits the detection of the at least two identification sequence elements because it is the resulting nucleic acid, which includes the identification sequence elements, that is amplified with PCR.”); EX1005, ¶256.

Thus, Petitioner relies on Landegren's tags as meeting claim 1(a)'s "at least two identification sequence elements," and then relies on Baez's amplicon detection as satisfying claim 1(e)'s detection of the "at least two identification sequence elements." EX2008, ¶¶188-189.

Petitioner bases its position on an incorrect interpretation of Patent Owner's preliminary infringement chart submitted with its complaint in district court. Pet., 61; EX1008, 5. A POSA would have understood that detecting the "amplified ASA product" in Baez at most detects the presence of a *ligation product*, and would not determine whether Landegren's tags (which, according to Petitioner are the "identification sequence elements" in Grounds 3 and 4) are present in or absent from the detected ligation product. EX1003, Figs. 6-9; EX2008, ¶190. Petitioner provides no technical explanation otherwise of how a POSA would have detected Landegren's tags solely by detecting Baez's ligation product. Pet., 61. Accordingly, the Petition fails to demonstrate that Baez and Landegren teach or suggest claim 1(e)'s detection step. EX2008, ¶¶188-191.

- 2. A POSA would not have been motivated to modify Baez in view of Landegren.**
 - a. Petitioner's purported motivations were already satisfied in Baez.**

Petitioner argues that a POSA would have been motivated to combine Baez and Landegren "to create an assay with reduced background signal and the ability

to screen multiple analytes in a timely manner.” Pet., 53; EX1005, ¶238. These goals, however, were already provided in Baez. EX2008, ¶¶192-196. For example, Baez teaches that its methods provided “a means *to reduce assay background* and *to improve signal to noise ratio* of binding assays.” EX1003, 3:25-27; EX2008, ¶¶192-194. As Baez explains, its methods are “the first to apply assay principle that essentially distinguishes between analyte-specific binding reagent recognition and nonspecific reagent binding.” EX1003, 3:27-30; EX2008, ¶¶192-194. Baez also discloses a “multianalyte assay format,” in which “*multiple analytes* can be *detected simultaneously* in the same assay milieu.” EX1003, 13:18-20; EX2008, ¶¶195-196. Thus, Petitioner’s alleged motivations for modifying Baez were already satisfied by Baez itself. A POSA would not have seen any need for further improvements on what Baez characterizes as detection methods with reduced background noise and the ability to detect multiple analytes. EX2008, ¶¶192-196.

b. Landegren expressly cautions *against* Petitioner’s proposed art combination

Additionally, Petitioner ignores express tensions between the teachings in Landegren and Baez that would have deterred a POSA’s motivation to combine the references. EX2008, ¶¶197-201. There is no dispute that the Petition’s relied-upon disclosures in Baez utilize a solid-phase support. Pet., 60; EX1003, 17:25-28, 17:52-54; EX2008, ¶197. In particular, Baez teaches incorporating biotinylated bases into its nucleic acid labels, which can be detected using “immobilized

streptavidin.” EX1003, 17:25-28; EX2008, ¶197. Baez explains that the molecules “can be detected directly on the solid-phase support.” EX1003, 17:31-32; EX2008, ¶197. And as Dr. Pentelute explains, a POSA would have understood that Baez’s reference to “immobilized” streptavidin refers to streptavidin immobilized on a solid support. EX2008, ¶197; EX1016, 2; EX1017, 1; EX1038, ¶[0097]. Dr. Nelson also admitted at deposition that Baez’s methods utilize a solid-phase support. EX2009, 150:21-151:20, 155:15-156:4; *see also*, EX1005, ¶251 (referring to the “*streptavidin solid support structure as taught in Baez.*”).

In stark contrast with Baez, Landregren teaches *against* using solid-phase support and extols the benefits and advantages of its methods for detecting analytes *in solution*. EX1004, 1-2; EX2008, ¶198. Landegren explains that assays using “a solid phase require considerable time and effort for the analysis,” and are “a time consuming process.” EX1004, 1. Landegren also states that solid phase assays are “more difficult to automate than homogenous assays.” *Id.* In contrast, Landegren teaches that its methods provide the “ability to detect and quantify one or several analytes *in solution* in a homogenous one tube assay with high sensitivity and specificity.” EX1004, 2; EX2008, ¶¶198-199. Landegren repeatedly and consistently discloses and even claims that its methods are designed for use in solution-phase assays, not solid-phase assays. EX1004, Abstract, 2, 5, 6, 9, 21 (claim 1), 22 (claim 8); EX2008, ¶¶198-199. Landegren further teaches that its

“[p]roximity-probing provides an alternative means to screen large sets of ligand candidates *without the need for a solid phase*.” EX1004, 16; EX2008, ¶¶198-199.

Petitioner and its expert both fail to grapple with Landegren’s express teaching against using solid-phase support—teachings a POSA would not have ignored—in view of Baez’s express teachings to use solid-phase support. EX2008, ¶¶200-201. Indeed, Dr. Nelson admitted at deposition that he did not consider Landegren’s disparagement of solid-phase assays when preparing his declaration. EX2009, 48:23-49:8 (testifying that “I’ve just not done that analysis”); *see also*, *id.*, 50:10-16, 53:23-55:10.

Accordingly, for this additional reason, a POSA would not have been motivated to modify Baez’s solid-phase support methods in view of Landegren’s solution-phase methods because Landegren expressly teaches against using solid-phase assays. EX2008, ¶¶197-201.

3. A POSA would not have had a reasonable expectation of successfully modifying Baez in view of Landegren as the Petition contends.

Landegren expressly teaches against the use of solid-phase support, noting that such assays “require considerable time and effort for the analysis,” are “a time consuming process” that “must be precisely and reproducibly controlled between samples to give exact results,” and that solid-phase assays are “more difficult to automate than homogenous assays.” EX1004, 1; EX2008, ¶¶202-204. In view of

these teachings in Landegren, a POSA would not have had a reasonable expectation of successfully modifying Baez’s methods, which utilize solid-phase support. *Id.*; *see also*, EX1003, 17:24-32. As Dr. Pentelute explains, a POSA would have expected that Baez’s solid-phase support methods to be “time consuming” and require “considerable time and effort,” in addition to being “difficult to automate,” limiting the ability for high throughput assays. EX2008, ¶203; EX1004, 1.

Petitioner’s stated rationales for a POSA’s expectations of success all relate to alleged similarities between Baez, Landegren, and Freskgard. Pet., 54-55. Moreover, the only evidence Petitioner relies on is its expert’s discussion of *claim 14*, not claim 1. *See id.* (citing EX1005, ¶294). Indeed, Petitioner’s expert fails to address a POSA’s reasonable expectation of success (or rather, lack thereof) when discussing claim 1 in Grounds 3 and 4. EX1005, ¶¶231-259. Regardless, both Petitioner and its expert ignore Landegren’s teachings regarding the difficulties of solid-phase assays—just like the solid-phase assays Petitioner relies upon in Baez and Freskgard. EX2008, ¶¶202-204.

4. The addition of Freskgard in Ground 4 does not cure the fatal deficiencies in Ground 3.

The Petition’s Ground 4 only challenges claims 14-15, which depend directly or indirectly from claim 1 and recite that the analysis comprises nucleic acid sequencing and sequencing by synthesis, respectively. Pet., 3, 67-68; EX1001,

claims 14-15. Petitioner relies on Freskgard solely to meet the sequencing elements of claims 14-15. Pet., 3, 67-68. Thus, the addition of Freskgard in Ground 4 fails to reconcile the fatal deficiencies of the Baez and Landegren combination discussed above for Ground 3, and therefore fails to establish unpatentability of claims 14-15 for all the same reasons discussed above. *See* Section VI.B.1-3; EX2008, ¶¶205-207. Indeed, Petitioner's Freskgard combination relies on the Petition's inconsistent claim mapping for claim 1(a), and ignores Baez's teaching of using biotin/streptavidin for *detecting* ASA amplicons (not for selecting CRCs) as required in claim 1(d). EX2008, ¶¶175-191, 205; *see* Section VI.B.1.a-b.

Additionally, the methods of Freskgard are solid-phase assays. EX1009, 43:6-44:15, claim 20; EX2008, ¶206. The POSA thus would have had the same concerns over combining Freskgard with Landegren and Baez in view of Landegren's disparagement of solid-phase assays. EX2008, ¶207; EX1004, 1, Abstract.

VII. CONCLUSION

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

Respectfully submitted,

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

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I certify that the above-captioned **PATENT OWNER RESPONSE**
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