

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALAMAR BIOSCIENCES, INC.,
Petitioner

v.

OLINK PROTEOMICS AB,
Patent Owner

Case No. IPR2024-01353

U.S. Patent No. 7,883,848

PATENT OWNER'S PRELIMINARY RESPONSE

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EXHIBIT LIST

<i>Exhibit #</i>	<i>Description</i>
2001	File History Excerpts of U.S. Patent App. 17/330,331
2002	Wei Feng et al., <i>NULISA: A Proteomic Liquid Biopsy Platform with Attomolar Sensitivity and High Multiplexing</i> , 14 NATURE COMMUNICATIONS 7238 (2023) (“Feng”)
2003	Adam Bonislawski, <i>Alamar Biosciences Prepping Proteomics Platform for 2024 Launch</i> , GENOMEWEB (Apr. 13, 2023) (“Alamar Press Release”)
2004	Darmanis et al., <i>ProteinSeq: High-Performance Proteomic Analyses by Proximity Ligation and Next Generation Sequencing</i> , 6 PLoS ONE 9 (2011) (“Darmanis”)
2005	Rachel Y. Nong et al., <i>Solid-phase Proximity Ligation Assays for Individual or Parallel Protein Analyses with Readout via Real-Time PCR or Sequencing</i> , 8 NATURE PROTOCOLS 1234 (2013) (“Nong”)
2006	Zhi Wan et al., <i>Photocleavage-Based Affinity Purification of Biomarkers from Serum: Application to Multiplex Allergy Testing</i> , 13 PLoS ONE (2018) (“Wan”)
2007	U.S. Patent App. Pub. No. 2018/0292394 (“Soldo”)

I. INTRODUCTION

The Board should deny the Petition for *Inter Partes* Review (“Petition” or “Pet.”) of claims 1-20 (“the Challenged Claims”) of Olink Proteomics AB’s (“Olink”) U.S. Patent No. 7,883,848 (“the ’848 patent”) because Petitioner has failed to establish a reasonable likelihood that at least one claim is invalid.

As an initial matter, the Petition is deficient on its face because it does not meet the requirements of 37 C.F.R. § 42.104(b)(3). Although Petitioner acknowledges that it applied different claim constructions for the different asserted grounds of invalidity, the Petition entirely fails to set forth how the Challenged Claims should be construed. Not only does the Petition not identify the claim terms that are subject to the allegedly competing constructions, it also does not set forth the conflicting constructions the Petition allegedly applies. Petitioner’s lack of clarity regarding its arguments leaves both Olink and the Board having to guess at the arguments that Petitioner is trying to make. As a result, the Petition fails to meet the requirements of 37 C.F.R. § 42.104(b)(3) and should be denied.

Turning to the merits, the Petition should also be denied because Petitioner has failed to demonstrate a reasonable likelihood of prevailing with respect to at least one of the Challenged Claims. Regarding Grounds 1 and 2, the Petition fails to identify how the cited references disclose the element of “forming a

plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety,” and presents a hindsight-driven obviousness combination that does not adequately articulate a motivation to combine the cited references to arrive at the invention of the Challenged Claims. Regarding Grounds 3 and 4, the Petition cannot establish that Baez discloses the element of “selecting all cis-reactive cells exhibiting the detectable trace,” and like Grounds 1 and 2, provides only conclusory support for its alleged motivation to combine.

For these reasons, discussed in more detail below, Olink respectfully requests that the Board deny institution of *Inter Partes* Review.

II. THE '848 PATENT

A. The Subject Matter of the '848 Patent

Interactions between biological molecules are a fundamental phenomena underpinning most biological processes. For example, protein-protein or DNA-protein interactions can function to transmit biological signals (*e.g.*, activating a cellular growth process in response to sensing localized cellular nutrients) required for cellular function. These processes are frequently organized as a “molecular network” constituting a series of molecule-molecule interactions that produce a signaling cascade. Identifying molecules within these molecular networks, and their prospective interactors, provides invaluable information about cellular function—including the identification of unknown proteins,

detection of differences between normal and diseased states or identification of certain disease biomarkers, and identification of potential drug targets that inhibit or promote certain molecular interactions and signaling processes.

To characterize these complex molecular networks, information concerning the interacting molecules must be gathered, requiring information about the various molecules involved in the interaction. Ex. 1001 ('848 patent) at 1:24-26. Identifying the participants in a molecular network can be exceedingly challenging, particularly in humans, as the human genome contains approximately 30,000 genes that correspond to approximately 30,000 proteins. Assuming that these proteins only interact in pairs, which underestimates the realities of biological protein interactions, there would be 4.5×10^8 possible protein pairs. *Id.* at 1:32-35. In general, if there are n molecules of interest in a library, then there exists $(n^2+n)/2$ possible interaction pairs in the network. *Id.* at 1:35-37.

In order to investigate potential interactions within molecular networks, scientists developed molecular interaction-based methods wherein high-throughput information can be generated for both partners in an interaction. *Id.* at 1:37-41. At the time of the '848 patent, however, the available high-throughput techniques were only able to identify one of the interaction partners, were limited in scale, resulted in high background noise, and/or were very time

consuming and labor intensive. *Id.* at 1:24-31, 57-59, 1:60-2:11, 2:19-22, 3:26-60, 4:26-47. In contrast, the invention of the '848 patent is directed to novel, high-throughput methods for discovering, detecting, and selecting molecular interactors, which in turn provides information useful for the characterization of various molecular networks of interest. Ex. 1001 at 5:22-25, cl. 1.

Significantly, the invention of the '848 patent allows for investigation of all possible interactions within or between libraries of molecules, such as proteins, and also provides for selection and quantification of the interactors. *Id.* at 5:25-28, cl. 1. To accomplish this goal, the inventor of the '848 patent discovered a method for detecting interactions between at least two molecules of interest ("MOI") (*e.g.*, whole protein, protein domain, peptide or enzyme) by tagging each MOI with at least one nucleic acid moiety ("NAM") (*e.g.*, DNA or RNA). Each NAM is designed to comprise (i) a unique identification sequence for downstream detection and (ii) an association element that allows for association with other NAMs. *Id.* at 8:43-47, 8:53-63. A library of potential "interactors" is thus formed by the coupling of each MOI with a NAM, which provides information about the various interactors within a molecular network of interest. *Id.* at 6:4-32.

Further, the tagged MOIs are permitted to interact with one another, for example, by stimulating the library via shifting reaction conditions or adding

substrates of interest. *Id.* at 16:14-17. As explained in the '848 patent, the interactions will depend on the nature of at least one of the partners and the conditions permitting the interaction, and these interactions may include affinity interactions. *Id.* at 15:36-37. By stimulating a desired interaction, a secondary library of "cis-reactive cells" ("CRCs") is generated, each CRC comprising at least two interactors bound in proximity to one another by the NAMs' association elements. *Id.* at 6:25-34, cl. 1. This process co-localizes the interactors in a combinatorial fashion to create all possible CRC variants between the "n" interactors ($(n-n^2)/2$ unique combinations). *Id.* at 7:6-9, Fig. 2.

To select and further study the resulting interactions, the CRCs subjected to conditions that stimulate a desired interaction are designed to produce a detectable trace as a result of that interaction. *Id.* at 9:54-62, 19:40-43. Selection is accomplished, by way of non-limiting examples, through affinity purification or separation of the CRCs, but can be modified according to the nature of the interaction being investigated. *Id.* at 19:40-55, 20:25-30. The CRCs are subjected to an analysis that permits detection and selection of the at least two NAMs (via the identification sequence element). *Id.* at 20:48-58. Detection or readout of the library interactions is achieved by analysis of the NAM combinations, both quantitatively and qualitatively, by nucleic acid analysis (e.g., microarray analysis or sequencing approaches). *Id.* at 20:60-21:3, 21:35-

43. This information can be used to identify and characterize the interactors themselves, providing valuable information about the entire molecular network in which the interactors play a role.

B. The Specification Explains How the Claimed Invention Differs from the Prior Art

As Petitioner acknowledges, the specification of the '848 patent explains how the claimed invention differs from two prior-art methods: DNA-templated synthesis (“DTS”) methods and proximity ligation assays (“PLA”). Pet. at 7-9; Ex. 1001 at 3:26-4:25, 4:26-5:18.

1. The '848 Patent Does Not Claim Prior-Art DTS Methods

The '848 patent specification explains the ways that the invention differs from DTS methods. Notably, the specification explicitly distinguishes the disclosed invention from the DTS method taught by Kanan—one of the prior-art references Petitioner alleges renders the claims obvious. *See* Pet. at § V.A (Grounds 1 and 2).

DTS relies on a template model where, in each interaction, only *one* of the molecules forced together is attached to a template nucleic acid that contains identification tags. Ex. 1001 at 3:48-55. Put another way, and as admitted by Petitioner, only a portion of molecules being tested would be considered “interactors” of the '848 patent because only a portion of the molecules would have both an association element and a separate identification sequence as required by the claims. *Id.*; *see also* Pet. at 28. Each molecule in a DTS method, like that described

in Kanan, is thus not “coupled to a nucleic acid moiety comprising an identification sequence element and an association element,” as required by the claims. As a result, the combination of molecules in DTS cannot be combinatorial—as not all interactions between library members can be selected for further analysis. Ex. 1001 at 3:66-4:1. Further, in the DTS approach, all template nucleic acids can be amplified even though they have no interaction partner—resulting in false positives. *Id.* at 4:23-25. In addition, DTS methods only allow for synthesis of libraries of molecules other than proteins, which significantly limits their applicability to determining all interactors in a molecular network. *Id.* at 14:6-12.

In contrast, the invention of the '848 patent provides a method whereby each potential interactor has both an identification sequence and an association element, allowing selection of interactions between any of the molecules tested. *Id.* at 4:11-25. The specification of the '848 patent describes the advantages of using this combinatorial association of different nucleic acid tags, including amplification (detection) of only nucleic acids which have been joined to create a pair of molecules—reducing the detection of false positives. *Id.* at 4:15-23. The claimed method can also be used to create libraries of proteins, which are key molecules involved in molecular networks. *Id.* at 3:23-25, 5:25-28.

2. The '848 Patent Does Not Claim Prior-Art PLA Methods

The '848 patent specification also distinguishes the invention from PLA,

which is the method described in prior-art references Landegren and Baez, on which Petitioner relies. Ex. 1001 at 4:26-5:10 (distinguishing Landegren); *see also id.* at References Cited (Baez listed on face of patent); *infra* § IV.C. Similar to the DTS method described above, proximity ligation does not allow for analysis of interactions in a combinatorial fashion. Ex. 1001 at 4:45-47. In a PLA method, binders, *e.g.*, antibodies, with known affinity to the target, are coupled with nucleic acid fragments. The binders are allowed to interact with samples containing their target molecules and each other. The nucleic acid fragments attached to the binders are designed in a way that will bring the binders into proximity of each other enabling ligation of the nucleic acids located on the binder pairs. *Id.* at 4:26-34. Additionally, the Landegren and Baez PLA methods do not include the step of selecting CRCs to allow for further analysis.

The invention of the '848 patent differs from proximity ligation in that each NAM can interact with any other NAM and the novel nucleic acid produced by this association is then selected and analyzed to yield information concerning the molecular interactions in the library. *Id.* at 4:48-57. This means the information gained from the claimed method also differs from that gained from PLA. In the methods of the invention, combinations of interacting molecules are detected, selected, and quantified. *Id.* at 4:64-66.

C. The Challenged Claims

The Petition challenges all twenty claims of the '848 patent. Pet. at 2-3.

Claim 1 is the only independent claim and recites:

1. 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.

Ex. 1001 at cl. 1. As explained in detail below, Petitioner has not met its burden in showing that it is likely to succeed in challenging claim 1, and as such, has also not met its burden with respect to the dependent claims.

D. The District Court Litigation

Olink filed a complaint for patent infringement alleging that Petitioner infringes at least one claim of the '848 patent. *See* Ex. 1007 (Complaint). Petitioner filed a motion to dismiss the complaint, contending that (1) the accused products perform only prior-art PLA methods, and (2) Olink failed to adequately plead a claim for infringement because Olink allegedly disclaimed prior-art PLA from the scope of the claims. Ex. 1014 (Alamar Brief). As Olink explained to the District Court, both of these arguments are false. Ex. 1015 (Olink Opposition Brief). The first issue, however, is relevant to the positions that Petitioner has taken in this proceeding.

As discussed above, the claimed methods of the '848 patent are distinct from prior-art PLA methods—as are Petitioner's products that infringe the '848 patent. *See supra* § II.B.2. As discussed above, the '848 patent explicitly explains how the claimed methods are different from the prior-art PLA methods. While Petitioner attempts to portray its product as being based on PLA in an effort to escape infringement, Petitioner has repeatedly represented—including before the Patent Office—that its product, and the patent Petitioner obtained to cover its product, is

distinguishable from PLA. *See* Ex. 1015 at 10-11; Ex. 2001 (File History Excerpts of U.S. Patent App. 17/330,331); Ex. 2002 (Feng 2023); Ex. 2003 (Alamar Press Release).

For example, during prosecution of Petitioner's patent covering subject matter similar to the Challenged Claims, the examiner rejected the claims as unpatentable under 35 U.S.C. § 103 as obvious over Darmanis (Ex. 2004), Nong (Ex. 2005), Wan (Ex. 2006) and Soldo (Ex. 2007), which the examiner described as demonstrating various types of PLA (including solid-phase, traditional, and circular PLA). Ex. 2001 at 7-13 (Nov. 9, 2021 Non-Final Office Action). Petitioner argued, among other things, that the distinguishing features of their claims included those directed to the dual capture and release mechanism. Ex. 2001 at 23-38 (Jan. 26, 2023 Office Action Response). Olink agrees that these features are not in the prior-art PLA methods, but are indeed part of the Challenged Claims, and Olink took those issues into account when alleging infringement of the '848 patent. Ex. 1015; *infra* § IV.C.

III. THE BOARD SHOULD DENY THE PETITION BECAUSE IT FAILS TO SATISFY 37 C.F.R. § 42.104(b)(3)

The Petition is deficient on its face and should be denied on that basis alone. Petitioner admits that it is applying different claim constructions in its two sets of grounds—one for Grounds 1 and 2, and another for Grounds 3 and 4. *See* Pet. at 12-13, 23, 55. Petitioner, however, does not identify which claim terms it is construing and does not explain what constructions it is applying in each argument. As a result,

the Petition fails to satisfy 37 C.F.R. § 42.104(b)(3) and should be denied.

It is incumbent on Petitioner to set out its patentability contentions in a readily discernable way that does not require Olink or the Board to speculate as to the arguments being presented, including speculation about how the Challenged Claims are to be construed. *Lyft, Inc. v. Quartz Auto Techs., Inc.*, IPR2020-01450, Paper 7, at 13-14 (PTAB Mar. 4, 2021) (“We decline to speculate as to how Petitioner contends the challenged claims should be construed.”); *Eiko Global, LLC v. Blackbird Tech LLC*, IPR2017-00980, Paper 16, at 35-36 (PTAB Sep. 1, 2017) (“Here, the Petition makes the proper construction and application of the claim term “housing” a moving target, and, therefore, runs afoul of the requirements of [37 C.F.R. § 42.104(b)(3)-(b)(4)].”); *see also* 37 C.F.R. § 42.104(b)(3)-(b)(4). The rules require that Petitioner “must identify” in its petition “[h]ow the challenged claim is to be construed.” *See Volkswagen Grp. of Am., Inc. v. Mich. Motor Techs., LLC*, IPR2020-00229, Paper 13 at 9 (PTAB July 6, 2020) (finding that the Petition failed to satisfy the requirements of 37 C.F.R. § 42.104(b)(3) where Petitioner did not propose any express claim construction and provided “no more than a generic assertion that all claim terms should receive their plain and ordinary meaning.”). The Petition, however, provides no guidance whatsoever regarding the constructions that Petitioner is asking the Board to apply.

For Grounds 1 and 2, Petitioner provides no more than a generic assertion that

“the claims are assumed to be given their plain and ordinary meaning based on the understanding of a [person of ordinary skill in the art].” Pet. at 12; *see also Volkswagen*, IPR2020-00229, Paper 13 at 9. Petitioner later states Grounds 1 and 2 “do not apply [Olink’s] positions taken in the district court litigation with Petitioner.” *Id.* at 23. For Grounds 3 and 4, Petitioner shifts what the alleged meaning of the claims are, arguing the claims should now be “given meaning based on [Olink’s] application of the claims in related litigation with Petitioner.” Pet. at 12-13; *see also Eiko Global*, IPR2017-00980, Paper 16 at 35-36. These sparse statements are the entirety of Petitioner’s presentation regarding the constructions of the Challenged Claims.

Petitioner attempts to rely on the “positions” that Olink asserted in the litigation, but even this allegation is lacking. Not only is this an improper incorporation by reference requiring Olink and the Board to sift through exhibits to determine the arguments that Petitioner is advancing, but also Petitioner does not—and indeed cannot—point to any explanation in the district court papers regarding specific claims needing construction and how those claims should be construed. Neither party in the litigation has identified terms for construction or presented claim construction arguments.

Petitioner also fails to explain how the claim construction positions differ between Grounds 1 and 2 on the one hand, and Grounds 3 and 4 on the other. Absent

Petitioner providing a clear explanation of the claim constructions being asserted, Olink and the Board are left having to guess at the distinctions Petitioner is attempting to make. *Sinjimoru v. Geneze Innovation, Inc.*, IPR2021-00493, Paper 8 (PTAB July 28, 2021) (“We decline to abandon our role as adjudicator, or step into the role of advocate, to scour the record to discover whether the Petition, in fact, advances evidence sufficient to support institution of review . . .”).

Ultimately, the burden is on Petitioner to show the claims are unpatentable. *See Cisco Sys., Inc. v. C-Cation Tech, LLC*, IPR2014-00454, Paper 12 at 11 (PTAB Aug. 29, 2014). Petitioner has not met its burden and has instead created a scenario where the Board and Olink must guess and infer which terms Petitioner may construe differently and how these different claim constructions may influence the asserted grounds as the basis for why the claims are unpatentable. *Id.* Petitioner has not met its burden to set forth its claim construction position in support of its asserted invalidity arguments, and therefore the Board should deny institution.

IV. PETITIONER HAS NOT DEMONSTRATED A REASONABLE LIKELIHOOD THAT IT WILL PREVAIL ON ANY CHALLENGED CLAIM

Turning to the substance of Petitioner’s arguments, the Board should also deny the Petition because it fails to establish a “reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Petitioner argues that the Challenged Claims

would have been obvious in view of Kanan and Neri (Grounds 1 and 2) and Baez and Landegren (Grounds 3 and 4). Petitioner fails to establish a reasonable likelihood of prevailing on at least one Challenged Claim because (i) Petitioner fails to establish that its asserted references disclose all elements of the claimed method; and (ii) Petitioner also fails to adequately explain why a person of ordinary skill in the art (“POSA”) would have been motivated to combine the asserted references, providing nothing more than hindsight-driven, conclusory statements as to why a POSA would have made the numerous changes required to arrive at the claimed invention. As a result, the Board should deny the Petition.

A. Level of Ordinary Skill in the Art

Solely for the purposes of this Preliminary Response, Olink does not contest Petitioner’s definition of a POSA. *See* Pet. at 11-12.

B. Grounds 1 & 2: Petitioner Fails To Establish That the Challenged Claims Would Have Been Obvious in Light of Kanan and Neri

1. Kanan in Combination with Neri Does Not Disclose All Elements of the Challenged Claims

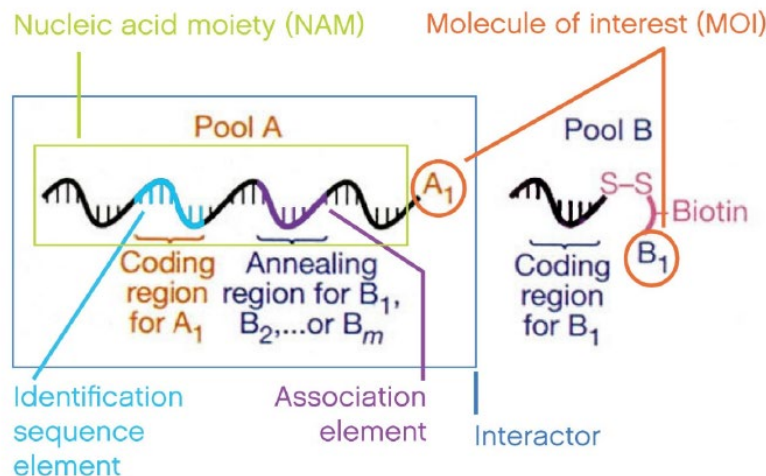
Petitioner’s asserted combination of prior art in Grounds 1 and 2 fails to disclose essential elements of the Challenged Claims. Specifically, neither Kanan nor Neri disclose forming a plurality of interactors by coupling each molecule of interest with at least one NAM. While Olink focuses on this specific

issue for the purposes of its Preliminary Response, Olink does not agree with Petitioner that all other elements in the independent or dependent claims are met. Further, the arguments presented here apply equally to Ground 2, which is directed to dependent claim 16.

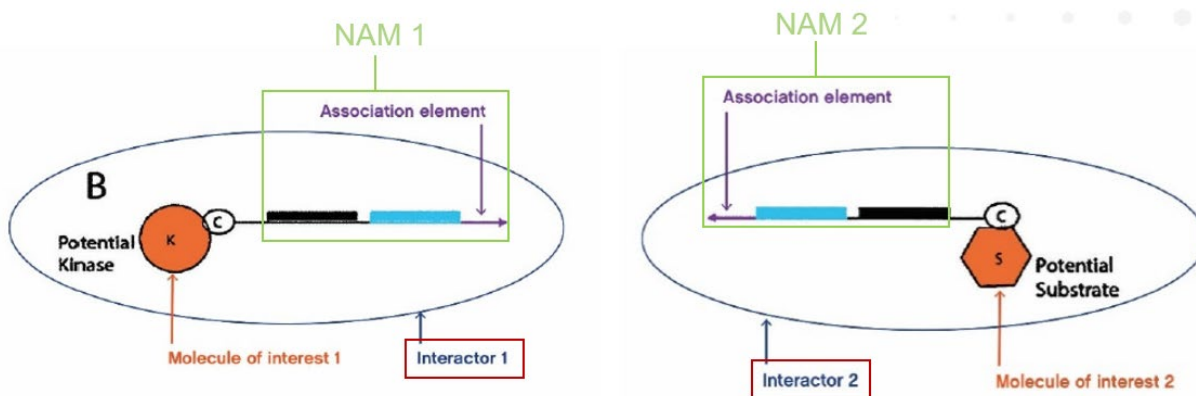
a. Kanan Does Not Disclose Forming a Plurality of Interactors by Coupling Each Molecule of Interest with at Least One NAM

Claim 1 of the '848 patent recites “[a] method of detecting functional interactions between at least two molecules of interest” comprising “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.” Ex. 1001 at cl. 1[pre]-1(a). As explained above, the '848 patent explains that the claimed method requires tagging *each* MOI with at least one NAM. *Supra* § II.A. Each NAM comprises (i) a unique identification sequence for downstream detection and (ii) an association element that allows for association with any other NAM. *Id.* at 8:43-47.

As Petitioner admits, Kanan fails to disclose claim element 1(a) of the '848 patent because only pool A molecules have nucleic acid moieties that contain both an “identification sequence element” and an “association element”:



Pet. at 28 (Fig. 1a of Kanan as annotated by Petitioner). Pool B of Kanan does *not* comprise a NAM as required by claim 1(a) of the '848 patent as shown below:



Compare Ex. 1001 at FIG. 4(B) (annotated to show NAMs (green box) and interactors (red box)).

Notably, as explained above, the '848 patent explains how Kanan differs from the claimed methods. See Ex. 1001; *supra* § II.B.1. Kanan teaches a DTS method of assessing potential interactions between molecules using two separate “pools” of molecules. The molecules are first labeled with nucleic acid strands that

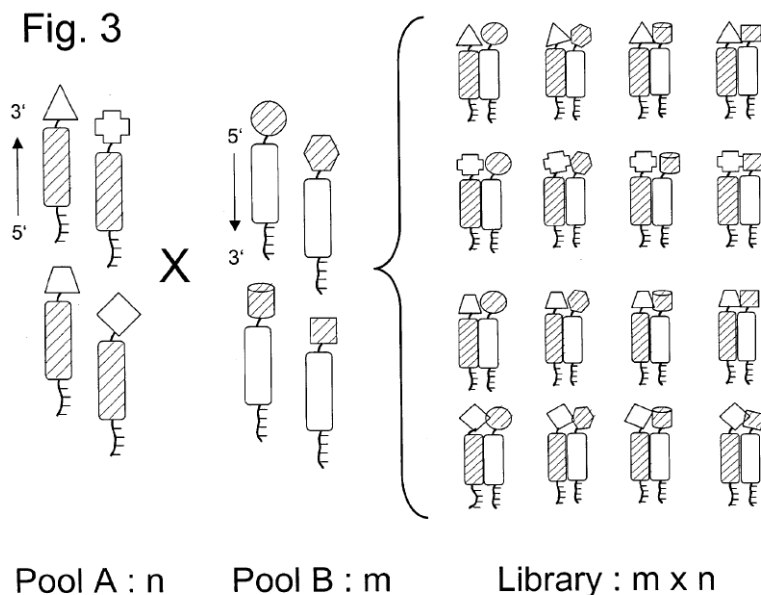
each contain a unique identification sequence for downstream detection only. Ex. 1010 at 545. Critically, not all nucleic acid strands in Kanan contain an association element that allows for association with any other nucleic acid strand. Rather, the nucleic acid strands in Kanan are designed such that one strand in a potential interacting pair (the “targeting strand”) specifically targets the nucleic acid strand of only *one* other molecule (the “receiving strand”). *Id.* at 545-46. As a result, there is no dispute that Kanan does not disclose claim 1(a) of the Challenged Claims.

b. Neri Does Not Cure the Deficiencies of Kanan

To overcome the deficiencies in Kanan, Petitioner alleges that a POSA would have looked to Neri’s disclosure of “self-assembling libraries of organic molecules.” Pet. at 17-21, 29-30. Petitioner’s arguments, however, misconstrue the disclosures in Neri.

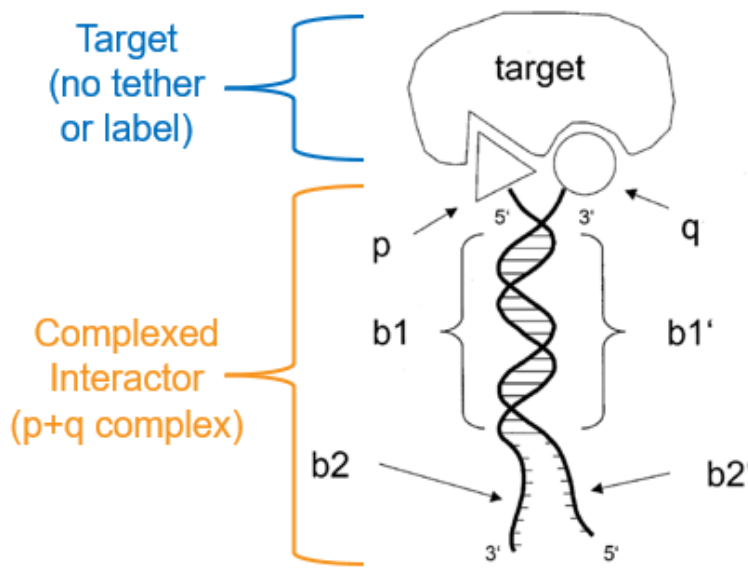
Petitioner describes Neri as “disclos[ing] a self-assembly sequence that allows for the association of oligonucleotides containing identification sequence elements for both interactors involved in an interaction.” Pet. at 15-16. Not so. Neri is concerned with developing methods to diversify a pool of chemical moieties for use in binding interactions. Ex. 1011 at Abstract. To do so, Neri discloses a method for tethering chemical moieties together by attaching each moiety to a nucleic acid containing (i) an identification sequence and (ii) a universal association element that

facilitates binding of the nucleic acids. *Id.* at [0025], Fig. 1. Using this approach, Neri discloses methods for generating libraries of various complexed chemical moieties as shown below:



Id. at Fig. 3.

Critically, the method taught in Neri is for screening these libraries of complexed chemical moieties for interaction with a separate binding partner lacking any nucleic acid tether or label. *See, e.g., id.* at Figs. 1, 2. These complexes are not designed to interact with each other. The identification sequences included in the complexed interactor are designed to allow the user to identify the subunits of the interactor. The binding target, however, does not have an associated identification sequence. *Id.* at [0040], [0066-0067]:



Id. at Fig 1 (annotated) (moieties “p” and “q” interact with target molecule only); *see also id.* at Figs. 2, 3, 10. As such, Neri does not disclose methods for making *a plurality of interactors*. At best, Neri discloses methods of making complexes that serve as one-half of the target interaction.

Therefore, as with Kanan, Neri does not teach use of these moieties for forming a “plurality of interactors” “by the coupling of each MOI with a NAM” as required by claim 1(a). Ex. 1001 at 6:4-32, cl. 1.

2. Petitioner Fails To Establish a Motivation To Combine Kanan and Neri with a Reasonable Expectation of Success

Petitioner further fails to show that a POSA would have been motivated to combine Kanan and Neri to arrive at the Challenged Claims. The burden to demonstrate patentability never shifts to Patent Owner, and Petitioner has failed to meet its burden here because it relies on hindsight and conclusory statements to

support its allegations that a POSA would have been motivated to combine Kanan and Neri. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F. 3d 1375, 1378 (Fed. Cir. 2015).

“To satisfy its burden of proving obviousness, a petitioner cannot employ merely conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380-81 (Fed. Cir. 2016). The factual inquiry into the reasons for “combin[ing] references must be thorough and searching, and the need for specificity pervades.” *In re NuVasive, Inc.*, 842 F.3d 1376, 1381-82 (Fed. Cir. 2016) (internal quotations and citations omitted).

Petitioner’s picking-and-choosing approach is a classic example of hindsight reasoning that the Board should reject. *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991) (“It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant’s structure as a template and selecting elements from references to fill the gaps.”); *see also InTouch Techs., Inc. v. VGO Commc’ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014) (reversing finding of obviousness and criticizing expert for relying on “the [challenged] patent itself as her roadmap for putting what she referred to as pieces of a ‘jigsaw puzzle’ together.”). Petitioner must demonstrate that a POSA would have arrived at the

claimed invention as evidenced by the prior art disclosures, not by using the patent itself to identify holes to be filled in with Petitioner's selected art. *Id.*; *see also Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017); *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (affirming JMOL of non-obviousness where defendant's expert offered only conclusory testimony).

Petitioner argues that “[a] POSA would have been motivated to look for a way to reduce the time required to synthesize the library members (substrates) of Kanan” and that “[t]o increase efficiency (ability to screen larger libraries faster), *inter alia*, a POSA would have been motivated to look to combine Kanan with a reference that teaches how to promote and detect interactions ***between*** members of a library but uses a common hybridization sequence to reduce the time required ***to synthesize the library members***” and asserts that reference to be Neri. Pet. at 18. As noted above, however, Neri does not teach a method of promoting or detecting interactions between library members. Rather, Neri teaches developing methods to diversify a pool of chemical moieties for use in binding interactions with a separate library of targets. Petitioner fails to provide a clear and factual rationale as to why a POSA would have understood that Neri would address the inefficiencies in the Kanan method.

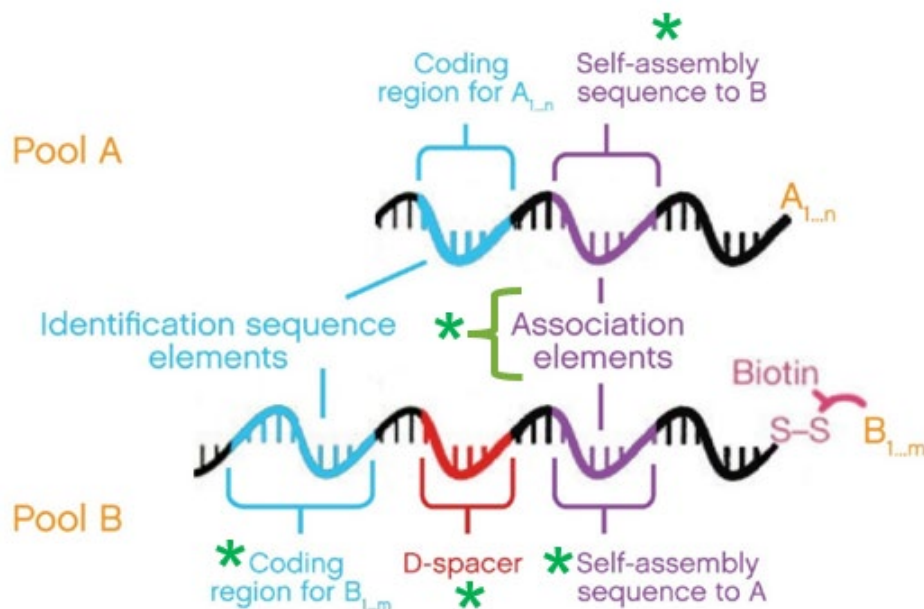
In support of its assertions, Petitioner relies on the declaration of Dr. Norm

Nelson. Ex. 1005. However, Dr. Nelson's testimony is just as conclusory as the Petition, parroting several stated goals from Kanan and stating, without explanation, that a POSA would have arrived at the relevant disclosure in Neri. Pet. at 19-20, Ex. 1005 at ¶¶ 102-103, 131. Petitioner and Dr. Nelsons's over-broad conjecture that "a POSA would have been motivated to combine the study of protein interactions in Neri with the method disclosed in Kanan because it was well known at the time of the application to create peptide or protein libraries to understand the role and properties of proteins" likewise relies on Petitioner's erroneous understanding of Neri's teachings, as the disclosures relied upon in Neri do not pertain to developing the same type of libraries as disclosed in Kanan. Despite Kanan and Neri using similar biological molecules in their methods (i.e., nucleic acids for identification of elements of the reactions), the methods of Kanan and Neri serve different purposes and are not directed at studying the same types of chemical interactions. Petitioner and its expert gloss over these differences. Petitioner's argument does not provide the clear and thorough specificity required to establish a motivation to combine. *In re NuVasive, Inc.*, 842 F.3d 1376 at 1381-82.

Further highlighting the hindsight-driven nature of the arguments, Petitioner identifies at least five changes that a POSA would have needed to make to the method of Kanan to arrive at the claimed invention and asserts various, disparate motivations that would have allegedly led a POSA to make these changes. For

example, Petitioner argues that a POSA would have been motivated to: (1) “improve specificity of the binding between pool members in Kanan,” (2) “maintain the identification of the pool B members involved in the interaction,” and (3) “efficiently identify the reactive pairs in Kanan.” Pet. at 19-20. However, Petitioner fails to adequately articulate why a POSA would have looked to Neri, a reference entirely unconcerned with the functional screening method disclosed in Kanan to resolve these issues. Indeed, Petitioner is merely listing the many ways the method claimed in the ’848 patent improves upon DTS, and attempts to retroactively plug the holes in the Kanan disclosures with cherry-picked elements of Neri to argue that a POSA would have combined the two for “efficiency.” *InTouch Techs.*, 751 F.3d at 1351; *In re Gorman*, 933 F.2d at 987.

Petitioner’s blanket statements that a POSA would have been motivated to make numerous modifications to the moieties described in Kanan using Neri with a reasonable expectation of success are unsupported. The various changes required to ***both*** pool A and pool B described in Kanan, using Neri to fill in the holes to allegedly arrive at the claimed invention, are represented by the green asterisks in the figure depicted below:



Pet. at 31 (“modified library members combining Neri with Kanan”) (annotated).

First, a POSA would need to modify pool A to replace the annealing sequence with the “self-assembly sequence” of Neri, which Petitioner argues—without any support—would then function as an association element as described in the ’848 patent. Pet. at 30. Petitioner argues a POSA would have been motivated to add the self-assembly sequence of Neri in place of the annealing region of Kanan for efficiency. Pet. at 18; Ex. 1005 at ¶¶ 97-101. However, Petitioner does not explain *why* a POSA would have looked to Neri, a method that is not combinatorial, to modify Kanan, another method that is not combinatorial, to create a screening method whereby each member in the library would be coupled with a NAM and would provide for a combinatorial approach. Petitioner only states that by

combining Kanan and Neri, “‘improved efficiency is realized in a concrete way’ through significant time savings to create the library.” Pet. at 19. These conclusory statements are insufficient to support an argument that a POSA would have been motivated to combine Kanan and Neri in this way.

Additionally, according to Petitioner’s argument, a POSA would have needed to modify pool B by replacing the coding region that previously annealed with its pool A counterpart with a self-assembly sequence, which would now associate with the self-assembly sequence in pool A. *Id.* According to Petitioner, a POSA would then have needed to add the “D-spacer” taught in Neri “to prevent the identification sequences of pool B from interacting with the identification sequences of pool A.” *Id.* Finally, a POSA would have needed to further modify pool B to add the unique identification sequence. *Id.* Petitioner does not provide a clear rationale for why a POSA would have been motivated to make all of these modifications to Kanan to arrive at the Challenged Claims. Petitioner’s arguments amount to nothing more than using the ’848 patent’s disclosure to fill in the gaps of Kanan to arrive at the Challenged Claims

As a result, Petitioner has failed to establish that a POSA would have been motivated to combine Kanan with Neri. Petitioner’s arguments are based purely on conclusory expert testimony and improper hindsight reasoning, and should be rejected.

C. Grounds 3 & 4: Petitioner Fails To Establish That the Challenged Claims Are Obvious in Light of Baez in Combination with Landegren

Like Grounds 1 and 2, Petitioner similarly fails to demonstrate that the combination of Baez and Landegren discloses all elements of the Challenged Claims. Specifically, neither Baez nor Landegren discloses selecting all CRCs exhibiting a detectable trace. Further, the Petition fails to establish a motivation to combine these references to arrive at the Challenged Claims. While Olink focuses on this specific issue for the purposes of its Preliminary Response, Olink does not agree with Petitioner that all other elements in the independent or dependent claims are met. Further, the arguments presented here apply equally to Ground 4, which is directed to dependent claims 14 and 15.

1. Baez Does Not Disclose Selecting CRCs Exhibiting a Detectable Trace

As explained above, the '848 patent describes that a library of “interactors” is formed by the coupling of each MOI with a NAM. Ex. 1001 at 6:4-32. The interactor library is permitted to interact, creating a secondary library of “cis-reactive cells” (“CRCs”), which comprise at least two interactors bound in proximity to one another by the associated NAMs. *Id.* at 6:25-34, cl. 1. The CRCs are subjected to conditions which stimulate a desired interaction having a detectable trace, and all CRCs are *selected* and further analyzed. *Id.* at 9:54-62, 16:14-17, 19:40-55, 20:25-30, 20:48-58. With respect to the selecting step,

claim 1 of the '848 patent requires “selecting all cis-reactive cells exhibiting the detectable trace.” *Id.* at cl. 1[pre], 1(d).

Petitioner relies exclusively on Baez for the “selecting” limitation, but there is no such teaching in Baez. Baez is directed to immunoassays and the use of nucleic acid amplification as a reporting means of the **detection** of an analyte. Ex. 1003 (Baez) at 1:13-15 (emphasis added); *see also id.* at Title, Abstract. Specifically, the analyte detection in Baez is achieved by forming an analyte dependent reporter complex (“ADRC”), joining the reporter labels, amplifying the joined product of the two labels, and detecting the amplification product. *Id.* at 1:15-19. Baez repeatedly describes the invention as a means of **detection**, and nowhere does Baez describe **selection** of CRCs and further analyzing the selected CRCs, as required in the claims. In fact, the term “selection” is completely absent in Baez. *See generally*, Ex. 1003.

Petitioner incorrectly argues that “selecting the CRCs includes Baez’s isolating CRCs (ASAs in Baez) comprising a biotin label using immobilized streptavidin.” Pet. at 60. This concept is not disclosed in Baez and Petitioner merely provides conclusory statements that the ASAs in Baez are equivalent to the claimed CRCs. *Id.* Each time Baez describes the possible uses of biotin, it is referring to detection, not selection. Ex. 1003 at 17:23-28 (“These approaches afford several **detection** strategies. For example, the incorporation of biotinylated or ligand

modified bases provides means of isolating the amplified nucleic acid products from solution onto a immobilized streptavidin or avidin. The addition of an avidin-signal-generating conjugate then facilitates *detection.*”), 18:8-12 (“For example, once the overlap has formed, the 3’ ends would be extended by DNA polymerase 1 in the presence of the four nucleotides, one which would be *labeled* (i.e., biotin or fluorescein, for example)); *see also id.* at Examples 2-4. These descriptions are consistent with the invention of Baez, which is focused on “methods for detection.” *Id.* at Title, Abstract.

Petitioner’s argument is essentially that this element is satisfied because an element of Baez could potentially be used for a selection step. Petitioner includes a single conclusory remark regarding “selecting”: “A POSA would have understood that the use of the biotin-streptavidin capture and wash would allow selection of only the ASAs that have been ligated together.” Pet. at 60. But Baez does not disclose that capture and wash step, and Petitioner fails to explain why a POSA would have used the detection method described in Baez for anything beyond what is disclosed in that reference. Petitioner also fails to provide any explanation of why a POSA would make this modification to Baez. It is not sufficient to infer a selection step from Baez’s use of “biotin” in its method to meet the limitation of the Challenged Claim, and Petitioner has not demonstrated how use of biotin for means of detection in Baez meets the claim requirement of “selecting all CRCs exhibiting the detectable

trace” and further analyzing the selected CRCs.

Petitioner does not rely on Landegren for this claim limitation, citing only to alleged disclosures in Baez. Pet. at 58. Petitioner’s vague statement that “Baez in view of Landegren discloses this step” is not sufficient to establish that Petitioner is relying on any disclosure within Landegren to fill in the gaps of Baez. *Id.* Thus, Petitioner has failed to establish that all elements of the Challenged Claims are disclosed or taught by the combination of Baez and Landegren, and the Board should deny the Petition.

2. Petitioner Fails To Establish a Motivation To Combine Baez and Landegren

The Board should independently deny institution because Petitioner fails to establish that a POSA would have been motivated to combine Baez and Landegren. Petitioner’s analysis for why a POSA would have been motivated to combine these two references is nothing more than conclusory statements. Pet. at 52-53, 56.

According to Petitioner, Baez states “[m]ethods for the reduction of background noise are continually being sought” and Landegren teaches “methods to reduce background signal.” *Id.* Petitioner immediately jumps to the conclusion that a POSA would have been motivated to combine them. *Id.* Petitioner, however, fails to provide *any* explanation for why. Dr. Nelson provides nothing further and simply parrots the conclusory arguments contained in the Petition. Ex. 1005 at ¶¶ 238-39. Petitioner has not explained why a POSA would have been motivated to combine

these references in a thorough, searching, and exacting manner, as required by the Federal Circuit. As a result, Petitioner has not met its burden here. *See In re NuVasive, Inc.*, 842 F.3d at 1381-82.

V. CONCLUSION

For the foregoing reasons, Olink respectfully requests that the Board deny institution of an *inter partes* review.

Dated: December 11, 2024

Respectfully submitted,

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IPR2024-01353

U.S. Patent No. 7,883,848

CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **Patent Owner's Preliminary Response** complies with the type-volume limitation of 37 C.F.R. §§ 42.24(a)(1)(i) and 42.24(b)(1). The Response contains 6,547 words, excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1), as measured by the word-processing system use to prepare the Response.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on December 11, 2024, a copy of the foregoing **Patent Owner's Preliminary Response** and all supporting documents were served on the counsel of record for Petitioner by filing the same through the P-TACTS System as well as delivering a copy via electronic mail to the following addresses:

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