

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the *Inter Partes* Review of U.S. Patent No. 7,883,848

Trial No.: Not Yet Assigned

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Assignee: Olink Proteomics AB

Title: REGULATION ANALYSIS BY CIS REACTIVITY, RACR

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Patent Trial and Appeal Board

United States Patent & Trademark Office

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PETITION FOR *INTER PARTES* REVIEW
UNDER 37 C.F.R. § 42.100

On behalf of Alamar Biosciences, Inc. (“Alamar” or “Petitioner”) and in accordance with 35 U.S.C. § 311 and 37 C.F.R. § 42.100, *inter partes* review (“IPR”) is respectfully requested for claims 1-20 of U.S. Patent No. 7,883,848 (“the ’848 patent”) (Ex. 1001). This Petition and supporting exhibits demonstrate a reasonable likelihood that claims 1-20 of the ’848 patent are unpatentable because each claim would have been obvious to a person of ordinary skill in the art (“POSA”).

The undersigned representative of Petitioner authorizes the Office to charge the \$41,500 Petition and Post-Institution Fees for all fees, to Deposit Account 50-3013, ref: 791009-600015.

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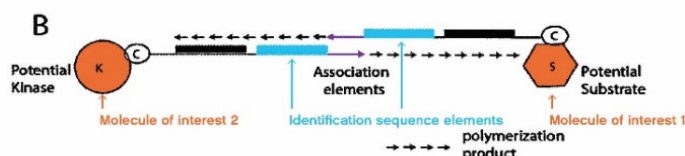
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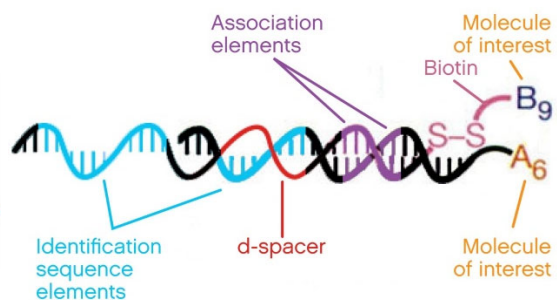
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I. Introduction

The claims of United States Patent No. 7,883,848 (the “848 patent”) are directed to a method for detecting functional-based interactions between molecules of interest (“MOIs”) coupled to oligonucleotides having MOI-specific identification sequence elements and complementary association elements that anneal to form associated oligonucleotides bringing the MOIs into proximity to allow a functional interaction to occur between the MOIs, and yielding a detectable trace that allows for selection and detection of the MOIs. Ex. 1001, Abstract; *id.*, 1:11-20, 5:23-40; *id.*, Cl 1. The Examiner allowed the claims without a prior art rejection. But these claims are an obvious combination of the DNA-templated synthesis (“DTS”) method of detecting functional interactions of Kanan (Ex. 1010) with the “self-assembly sequences” of Neri (Ex. 1011)—a reference and combination not considered during prosecution—which bring molecules into proximity to detect functional interactions.



Ex. 1001, Fig. 4(B)
(annotated)



Ex. 1005, ¶115
(annotated Kanan with Neri)

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Moreover, the Examiner did not know that Patent Owner (“PO”) contends that the claims cover the steps of proximity ligation assays (“PLA”)—a known method used to detect a predefined target through known affinities. Applying PO’s positions, references teaching PLA also render the claims obvious.

II. Requirements For IPR Under 37 C.F.R. § 42.104

A. Grounds For Standing Under 37 C.F.R. § 42.104(a)

Petitioner certifies the ’848 patent is available for IPR and Petitioner is not barred or estopped from requesting IPR challenging the patent claims on the grounds identified herein.

B. Identification Of Challenge Under 37 C.F.R. § 42.104(b) And Relief Requested

In view of the prior art and evidence presented herein, IPR of the claims 1-20 of the ’848 patent should be instituted, and they should be found unpatentable and cancelled based on the following grounds:

Grounds of Unpatentability	Exhibits
<u>Ground 1:</u> Claims 1-15 and 17-20 would have been obvious under 35 U.S.C. § 103 over Matthew W. Kanan et al., “Reaction discovery enabled by DNA-templated synthesis and <i>in vitro</i> selection” (“Kanan”) in combination with U.S. Patent Publication No. US 2004/0014090 (“Neri”).	1010, 1011
<u>Ground 2:</u> Claim 16 would have been obvious under 35 U.S.C. § 103 over Kanan in combination with Neri and in further view of Michael Famulok, “Bringing picomolar protein detection into proximity” (“Famulok”).	1010, 1011, 1012

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Grounds of Unpatentability	Exhibits
<u>Ground 3:</u> Claims 1-8 and 11-12 would have been obvious under 35 U.S.C. § 103 over U.S. Patent No. 6,511,809 (“Baez”) in combination with PCT Publication No. WO/0161037 (“Landegren”).	1003, 1004
<u>Ground 4:</u> Claims 14 and 15 would have been obvious under 35 U.S.C. § 103 over Baez in combination with Landegren and in further view of PCT Publication No. WO 2005/003778 (“Freskgard”).	1003, 1004, 1009

III. Background Information

A. '848 Patent Overview

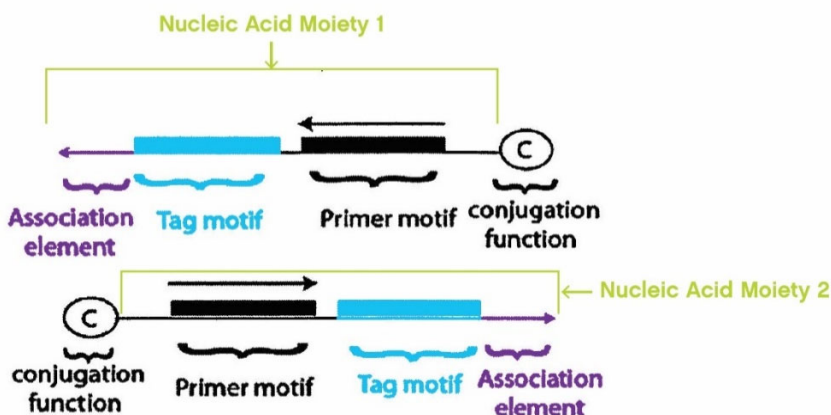
1. The Alleged Invention

The '848 patent claims are directed to a method for detecting functional interactions between MOIs. Ex. 1001, 1:11-20. The application purportedly identified “a need for methods which permit high throughput screening and identification of all partners of an interaction.” *Id.*, 1:29-30. The alleged invention would “allow[] investigation of all possible interactions within or between libraries of molecules, such as proteins, and also permits relative quantification of the detected interactions.” *Id.*, 5:25-28. The goal was to provide for new methods of investigating interactions between molecules, where the interactions (if any) between the molecules were previously unknown. And although the application discussed evaluating both functional and affinity interactions, the issued claims are limited to “functional interactions.” Ex. 1002, 499-503, 518-525.

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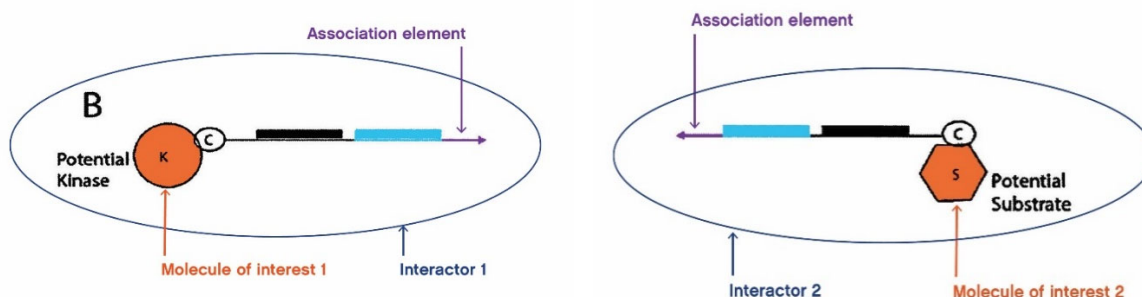
The application's "method of detecting functional interactions between at least two [MOIs]" begins with creating interactors. Ex. 1001, 6:4-6, 5:57-60, 9:33-34. The interactors "comprise at least two distinct parts which are coupled, one part is the molecule of interest (MOI) and one part is the nucleic acid moiety (NAM)." *Id.*, 10:45-48. The MOI "refers to a molecule about which interactive information is desired." *Id.*, 8:53-55. Further, each NAM comprises an "identification sequence element and an association element." *Id.*, Cl. 1. The "identification sequence element" (also "tag motif") is a unique nucleic acid sequence that enables downstream detection of that sequence, which infers involvement of the coupled MOI. *Id.*, 8:41-45.

Importantly, each NAM includes an "association element" that enables the NAM to anneal to other NAMs, referred to as an "associated oligonucleotide." *Id.*, 6:58-66. The MOIs are coupled to the NAM at the "conjugation function," creating an "interactor." *Id.*



Ex. 1001, Fig. 4(A) (color added and additional elements labeled).

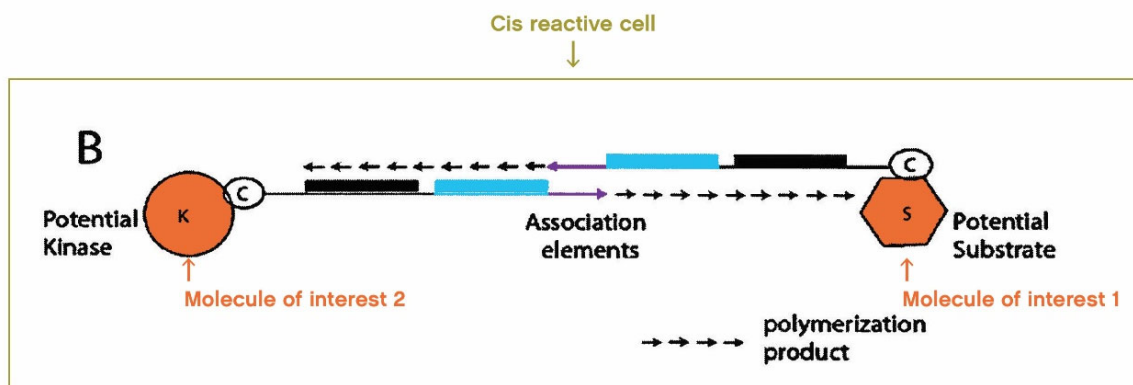
A library of these “interactors” is then developed. Ex. 1001, 5:57-58.



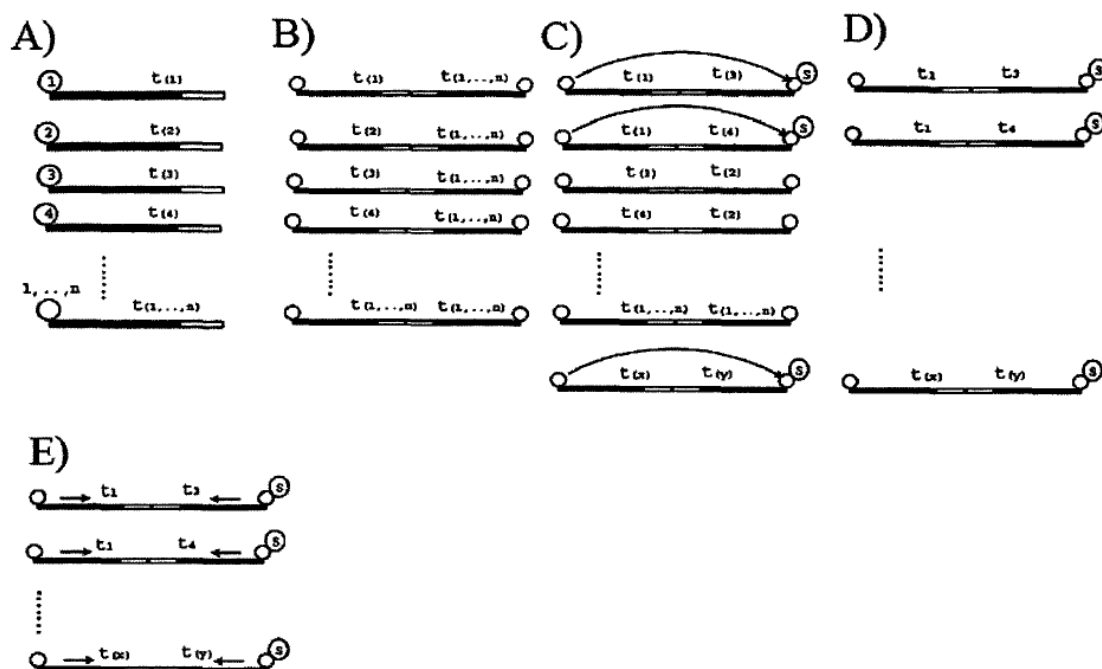
Ex. 1001, Fig. 4(B) (color added and modified to show two interactors separately).

The “association elements” in the two NAMs bind due to the complementary sequences of the association element portion of their respective NAMs, forming an “associated oligonucleotide” or an “association of NAMs.” *Id.*, 9:44-47, 16:63-17:6. This “[a]ssociation of interactors is a key feature of the current invention The binding of the interactors by their respective NAM association elements forms novel molecules . . . comprised of the nucleic acid tags Analysis of the associated oligonucleotide molecule formed from the combination of these tags permits identification of the interactor MOI components.” *Id.*, 16:63-17:6.

The bound set of interactors is called a cis-reactive cell (“CRC”). Ex. 1001, 6:28-33, Cl. 1.



Ex. 1001, Fig. 4(B) (color added and annotated). After the CRC library is constructed, the CRCs are then stimulated to create a detectable functional interaction between the two MOIs. *Id.*, 6:33-49, 9:54-59, 16:14-17. The '848 patent describes a functional interaction as an interaction “where two or more members affect each other in some detectable way[.]” Ex. 1001, 14:23-26.



Ex. 1001, Fig. 2 (showing a functional interaction in step C).

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Next, all CRCs that “contain MOIs that have been altered by the activation” are selected, and then associated NAMs are detected and/or quantified (e.g., by DNA sequencing). Ex. 1001, 6:41-49.

2. The Application Distinguished Its Alleged Invention From DTS and PLA

(a) DTS

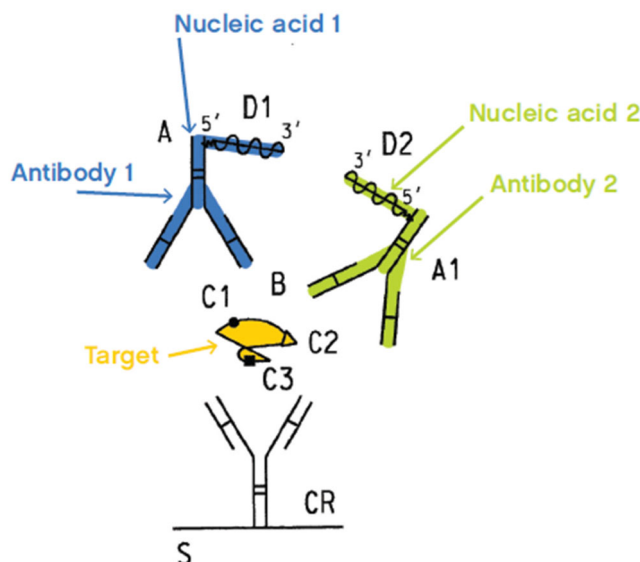
The application distinguished DTS because DTS relies on a template model where “one of the molecules forced together is attached to a ‘template’ nucleic acid which specifically directs the second compound by direct hybridization of the nucleic acid attached to the second molecule[,]” and this “‘template’ nucleic acid contains both tags used to identify the compounds which are forced together.” Ex. 1001, 3:48-55. The application criticizes Kanan, which teaches a method to promote and detect functional interactions between molecules that bond in a library using DTS, because synthesizing the number of “template” oligonucleotides requires that “one specific oligonucleotide has to be synthesized for each individual interaction on the library.” *Id.*, 3:58-60. The application further criticizes Kanan stating, “the link between nucleic acid identification tag and the molecule in the interaction depend[s] on correct hybridization of one tag molecule to the template nucleic acid,” so, if there is cross hybridization, “then the link between the tag and the identity of the interaction is unreliable.” *Id.*, 4:5-10.

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In contrast to DTS, the alleged invention “provides a method whereby the nucleic acid encoding the tags to identify both members of the interaction are formed upon joining of the two molecules.” *Id.*, 3:61-64. Unlike DTS, the alleged invention allows investigation of “all interactions in a library of n members,” also known as “combinatorial association,” because of “the presence of all specific pairs [of] DNA templates which in turn direct the interactions.” *Id.*, 3:64-4:3. This method purportedly solves the cross hybridization problem because it relies on “NAM association” to identify the library members involved in the interaction, allowing the “link between the identification sequences . . . [to be] more effectively maintained.” *Id.*, 4:11-15.

(b) PLA

The application also disclaims its alleged “inventive method”—not just an embodiment—from the steps of PLA. First, it distinguishes its “inventive method” from “[a] method referred to as ‘proximity ligation’ [that] has been recently described ([Landegren (Ex. 1004)], U.S. Patent Application Ser. No. US2002051986 [application that issued as Baez (Ex. 1003)].” Ex. 1001, 4:26-29. The application acknowledges that PLA is directed to targeting a specific analyte, the binders are brought together through the analyte (i.e., target), and the “targets are detected by utilizing two or more binders, e.g. antibodies, with known affinity to the target.” Ex. 1001, 4:26-31, 4:33-34 (describing Landegren and Baez application, shown below).



Ex. 1003, Fig. 1 (Partial) (color added and annotated).

The “current invention” is the “association of the nucleic acid is combinatorial and the novel nucleic acid produced by this association is then identified to yield information concerning the molecular interactions in the library. This enables interrogation of all intra- or inter-library member interactions.” *Id.*, 4:54-58. In contrast, “[t]he proximity ligation methods always include at least one molecule which is not attached to a nucleic acid label and this ‘target’ is the molecule which is detected. Thus the co-localization/proximity of the binders and thereby the nucleic acid in the assay arises from the presence of a target molecule.” *Id.*, 4:58-63. Contrasting PLA, the application describes its alleged invention as detecting unknown interactions, and that “[t]he present inventive methods *do not utilize molecules with predefined affinities* but rather the *reverse*.” *Id.*, 50-51 (emphases added).

B. Prosecution History Overview

The '848 patent application, filed on July 10, 2006, claims priority to provisional Application No. 60/697,415 filed on July 8, 2005. Ex. 1034. The non-provisional application included 43 claims—related to detecting affinity interactions (claims 1-19), functional interactions (claims 20-37), compositions for the library of interactors (claims 38-40), and kits for assaying interactions (claims 41-43). Ex. 1002, 64-73.

The “affinity interaction” claims differ from the “functional interaction” claims because, *inter alia*, an “affinity interaction” relies on “associat[ion] based on any affinity(s) between [the MOIs],” and the claims require “promoting an association between at least two nucleic acid moieties from different interactors to form a plurality of unique associated oligonucleotides” (Ex. 1002, 284, Cl. 1). Whereas, a “functional interaction” relies on association from “affinity between their respective NAMs[,]” and the claims require “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” (*id.*, 288, Cl. 20) (emphases added). Thus, a key difference is that the functional interaction claims require the CRC to be formed ***from*** the binding of two interactors to each other by an associated oligonucleotide. *See id.*, 360-363; Ex. 1005, ¶55. The affinity interaction claims do not include this requirement.

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The pending claims received an Office Action on December 30, 2009. The Examiner rejected the “affinity interaction” claims (1-12, 15-17, and 19) under 35 U.S.C. §§ 102 and 103. Claims 3 and 21 were rejected under 35 U.S.C. § 112 for the term “enhancement” being indefinite. The Examiner allowed the “functional interaction” claims (20 and 22-37) but stated that “US 2009/0011957 [“Goulaev” (Ex. 1036)] or US 2006/0246450 [“Franch” (Ex. 1037)]” were “[t]he closest prior art” because they “teach the aspects of steps a-c of claim 20 [issued claim 1] except for the limitation that the desired interaction produces a detectable trace.” Ex. 1002, 316.

On June 29, 2010, the rejected claims were canceled and Claim 21 was amended to replace “enhancement” with “selective separation or selective detection of the cis-reactive cells,” described as “techniques well known in the art,” to traverse the indefiniteness rejection and added two dependent claims. *Id.*, 499-505.

On September 17, 2010, the Examiner issued a Notice of Allowance, which identified Liu (Ex. 1038) as close prior art, but which “did not teach or suggest the formation of an ‘associated oligonucleotide’ comprising the nucleic acid moieties attached to two interacting molecules . . . or analyzing such an ‘associated oligonucleotide.’” Ex. 1002, 522-525.

C. Level Of Skill In The Art

A POSA as of July 2005, the earliest possible priority date for the ’848 patent, would have:

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- (a) an advanced degree, such as a Ph.D., in organic chemistry, molecular biology, biochemistry, or a related field; and at least two years of experience in industry and/or laboratory experience relating to small molecules and proteins and would have been familiar with nucleic acid chemistry and conventional hybridization techniques; and
- (b) access to one or more team members having an advanced degree, such as a Ph.D., in organic chemistry, molecular biology, biochemistry, or a related field; and at least two years of experience in industry and/or laboratory experience relating to high throughput screening techniques such as nucleic acid sequencing.

Ex. 1005, ¶25. A person could also have qualified as a POSA with less formal education and more technical or professional experience. *Id.*

IV. Claim Construction

The Board gives claims their ordinary and customary meaning, or “the meaning that the term would have to a [POSA] at the time of the invention.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (*en banc*); 37 C.F.R. § 42.100(b). For Grounds 1 and 2, the claims are assumed to be given their plain and ordinary meaning based on the understanding of a POSA. For Grounds 3 and 4, the claim

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terms are given meaning based on PO's application of the claims in related litigation with Petitioner. *See* Exs. 1007, 1008, 1015. There are no prior claim construction rulings on the '848 patent; however, PO filed a Complaint (Ex. 1007) and later provided an infringement chart (Ex. 1008)¹ reflecting PO's application of the claim terms. Petitioner does not waive, and expressly reserves, claim scope arguments, constructions, and evidence it may raise in other proceedings and its right to respond to any claim construction arguments PO makes in response to this Petition.

V. Claims 1-20 Of The '848 Patent Are Unpatentable

A. Grounds 1 And 2: Claims 1-20 Are Unpatentable

1. Prior Art

(a) Kanan

Kanan, titled "Reaction discovery enabled by DNA-templated synthesis and *in vitro* selection," published on September 30, 2004, in Volume 431 in *Nature*, a leading journal. Ex. 1010; Ex. 1040, ¶¶4-6; Ex. 1005, ¶67. Kanan is prior art under at least pre-AIA 35 U.S.C. § 102(a).

Kanan teaches "a reaction discovery approach that uses DNA-templated organic synthesis and *in vitro* selection to simultaneously evaluate many combinations

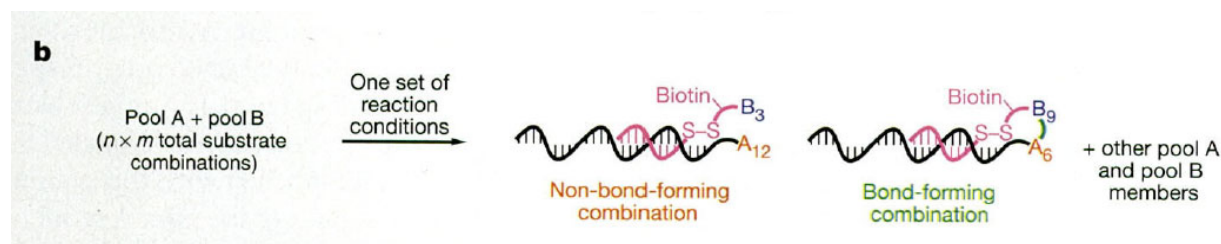
¹ Although PO labeled the chart "Confidential Communication" and "Subject to FRE 408," no duty of confidentiality existed. Ex. 1041, ¶5.

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of different substrates for bond-forming reactions in a single solution.” Ex. 1010, 545. The substrates in Kanan are linked to DNA with “ n substrates in pool A and m substrates in pool B. Each substrate in pool A is covalently linked to the 5’ end of a set of DNA oligonucleotides containing one ‘coding region’ (uniquely identifying that substrate) and one of m different ‘annealing regions’ (Fig. 1a). Each of the m substrates in pool B is attached to the 3’ end of an oligonucleotide containing a coding region that uniquely identifies the substrate and complements one of the m annealing regions in pool A.” *Id.* The six-step process to create pool A substrates and the two-step process to create pool B substrates are detailed in Kanan’s Supplementary Information.² Ex. 1013, 2-7.

“When pools A and B are combined in a single aqueous solution at nanomolar concentrations, Watson-Crick base pairing organizes the mixture into $n \times m$ discrete pairs of substrates attached to complementary sequences.” Ex. 1010, 545. “Only substrates linked to complementary oligonucleotides experience effective molarities in the millimolar range,” and “[t]his effective molarity-based design enabled reactions that might otherwise be suppressed by the preferential dimerization of one or both substrates.” *Id.*

² Kanan’s Supplementary Information was not disclosed or considered during prosecution. Ex. 1002, 109-25 (IDS and non-patent literature).



Id., 546, Fig. 1.b.

Kanan also discloses that members of pool B are linked to biotin that aids in the selection of the bond-forming pairs. *Id.*, 545. “After incubation 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.” *Id.* After selection, the “[r]eactive substrate pairs are identified by amplification of the selected sequences by polymerase chain reaction (PCR) followed by DNA microarray analysis[.]” *Id.*

Kanan (but not the Supplementary Information) was discussed in the application. The Examiner did not apply Kanan against any pending claims.

(b) Neri

Neri, titled “Encoded Self-Assembling Chemical Libraries (ESACHEL),” published on January 22, 2004. Ex. 1011. Neri is prior art under at least pre-AIA 35 U.S.C. § 102(b).

Neri discloses a self-assembly sequence that allows for the association of oligonucleotides containing identification sequence elements for both interactors

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involved in an interaction. Neri teaches “self-assembling libraries of organic molecules . . . , in which the organic molecules are linked to an oligonucleotide which mediates the self-assembly of the library and/or provides a code associated to each binding moiety.” Ex. 1011, [0005]. The “self-assembly sequence (b1)” is “capable of performing a combination reaction with at least one self-assembly sequence (b1’) of a complementary oligonucleotide . . . bound to another chemical compound comprising a chemical moiety. . . .” *Id.*, [0016].

Neri also discloses that “[a]fter the capture of the desired binding specificities on the target of interest, the ‘binding code’ can be ‘decoded’ by a number of experimental techniques[.]” *Id.*, [0005].

During prosecution, Neri was not disclosed, and the Examiner did not consider or apply Neri against the pending claims.

(c) Famulok

Famulok, titled “Bringing picomolar protein detection into proximity: Combining target recognition by two aptamers, enzymatic ligation, and PCR, the proximity ligation method enables the detection of minute amounts of proteins,” published on May 1, 2002. Ex. 1012; Ex. 1040, ¶¶17-19. Famulok is prior art under at least pre-AIA 35 U.S.C. § 102(b).

Famulok teaches detecting an antigen “by nucleic acid-based receptor molecules, so-called aptamers.” Ex. 1012, 448. “Each aptamer has a different DNA-

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sequence extension that does not interfere with its folding and is not required for target recognition.” *Id.* The “[b]inding of the aptamer pair brings the ends of the oligonucleotide extensions into close spatial proximity . . . so that a ‘splint’ oligonucleotide can hybridize to both ends, which are subsequently ligated together by T4 DNA ligase.” *Id.* “The ligated species can then act as a PCR template and the amplified PCR product can be monitored and quantified under real-time PCR conditions[.]” *Id.*

During prosecution, Famulok was not disclosed, and the Examiner did not consider or apply Famulok against the pending claims.

2. Motivation To Combine

Kanan and Neri are both in the same area of art that relates to encoding individual members of a library of chemicals with unique nucleotide sequences that can later be detected and analyzed to determine the identification of the members involved in the interaction. Ex. 1005, ¶¶67-76; Ex. 1010, 545; Ex. 1011, [0117]-[0119]. A POSA would have been motivated to look for a way to reduce the time required to synthesize the library members (substrates) of Kanan. Ex. 1005, ¶¶82, 97-99. Kanan discusses a desire to search “large number[s] of substrate combinations for unexpected reactions.” Ex. 1010, 548. Although Kanan describes that “a single researcher can evaluate thousands of combinations of substrates and reaction conditions in a two-day experiment,” it requires that “DNA-linked substrate pools are

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prepared,” which is time intensive. Ex. 1005, ¶98; Ex. 1010, 549; Ex. 1013 (detailing multi-step process to create substrate pools). Thus, a POSA would have understood that synthesizing the library members is the rate limiting factor in evaluating interactions between substrates. Ex. 1005, ¶98. As described in Kanan’s Supplementary Information, pool A members are created through a six-step process to create both the coding region for each A substrate and the annealing region for each B substrate. Ex. 1013, Fig. S1. This process 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}). *Id.*; Ex. 1005, ¶¶98-99. In Kanan, this tedious process is the only way to evaluate all possible interactions ($n \times m$). Ex. 1005, ¶99; Ex. 1010, 546, Fig. 1.

To 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. Ex. 1005, ¶99. Neri provides exactly that through its use of common “self-assembly sequences.” *Id.* Neri reduces the time to synthesize a library where all members can interact. *Id.*, ¶100. As Dr. Nelson explains, a POSA would have been motivated to add the self-assembly sequences of Neri in place of the annealing region of Kanan because Neri’s self-assembly sequence requires the synthesis of pool A members only be repeated for the number of A substrates (A_{1-n}). *Id.*, ¶¶97-101.

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Unlike Kanan alone, with Neri, the process to create pool A library members does not need to be repeated for each B substrate as the self-assembly sequence promotes binding of all pool A and pool B members. *Id.*, ¶101. And the self-assembly sequence is combinatorial, so it would yield the same desired information sought in Kanan without synthesizing annealing regions specific for each potential combination. *Id.*, ¶100. For example, in Kanan, to analyze the interaction between 100 A substrates and 100 B substrates, 10,000 (100^2) pool A members and 100 pool B members would have to be synthesized. *Id.*, ¶101. But with Neri's self-assembly sequence, a POSA would only have to synthesize 100 pool A members and 100 pool B members because all pool A members could interact with the 100 pool B members. *Id.* By combining Kanan with Neri, "improved efficiency is realized in a concrete way" through significant time savings to create the library. *Huawei Techs. Co. v. Iancu*, 813 Fed. App'x 505, 509-510 (Fed. Cir. 2020); Ex. 1005, ¶101.

A POSA would also have been motivated to combine other aspects disclosed in Neri with the method disclosed in Kanan. Ex. 1005, ¶102. A POSA would have been motivated to improve specificity of the binding between pool members in Kanan. *Id.* As Kanan's Supplementary Information describes, it considered ways "to minimize undesired reactivity arising from the mismatched hybridization of a pool B member with a non-complementary pool A member." Ex. 1013, 10; Ex. 1005, ¶102. The self-assembly sequence of Neri reduces the concern of mismatched hybridization

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because the pool A members are no longer designed to bind to only a specific pool B member. Ex. 1005, ¶102. A POSA also would have been motivated to maintain the identification of the pool B members involved in the interaction. *Id.*, ¶103. To do so, a POSA would be motivated to add the additional orthogonal tail disclosed in Neri to the members of pool B to create identification sequences in addition to the self-assembly region on all library members. *Id.* One of the goals of Kanan states, “the reactive substrate pairs must be identified efficiently.” Ex. 1010, 545. By creating a coding region of each library member as taught in Neri, the goal of Kanan is improved. Ex. 1005, ¶103. In addition, a POSA would have been motivated to efficiently identify the reactive pairs in Kanan. *Id.*, ¶131. By combining the sequencing of the identification sequences in Neri, a well-known method to detect and analyze nucleic acid sequences, with the method disclosed in Kanan, a POSA would have been able to identify the reactive pairs “efficiently.” *Id.*; Ex. 1010, 545.

Additionally, 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. Ex. 1005, ¶148; Ex. 1011, [0010]; Ex. 1023 (Pelletier 2001); Ex. 1032 (Winter 1994); Ex. 1025 (Guille 1997).

A POSA further would have been motivated to combine the polymerization of the substrate pair disclosed in Neri with the method disclosed in Kanan because the

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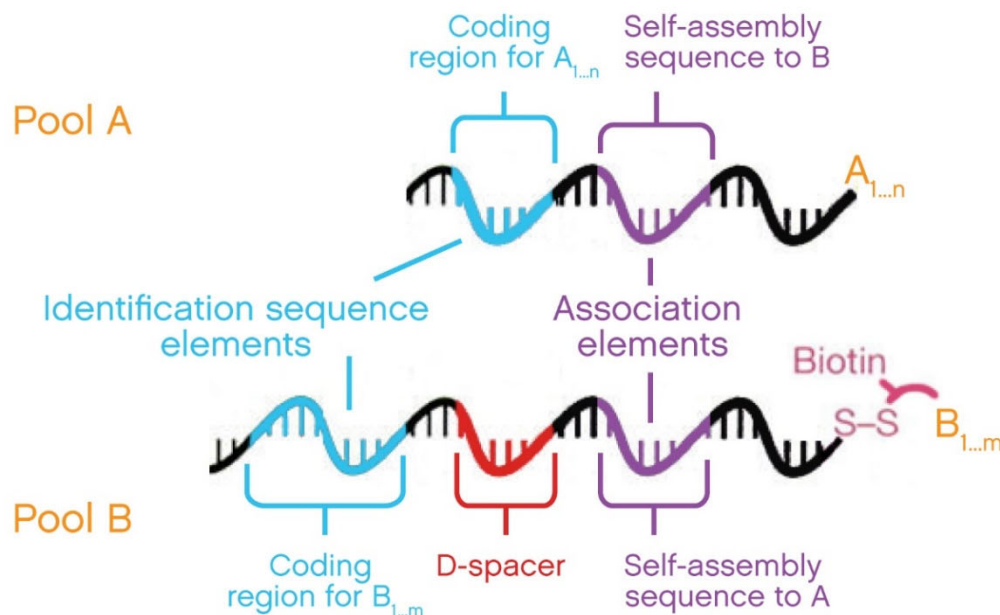
polymerization creates double-coding code on the extended nucleic acid sequence to increase the specificity of the assay. Ex. 1005, ¶182. Further, encoding the anticodon of the interactor would allow identification of a multistep interaction, if desired. *Id.*

Finally, a POSA would have been motivated to reduce errors in the polymerization step that would create false negatives. Ex. 1005, ¶177. A POSA would combine the splint oligonucleotide taught in Famulok with Kanan and Neri to do so. *Id.*

3. Reasonable Expectation Of Success

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. Ex. 1005, ¶104; *see Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (“[T]he expectation of success need only be reasonable, not absolute”). First, a POSA would have known that the difference between the interactors disclosed in Kanan and Neri are minimal, as both references teach libraries of oligonucleotides attached to a substrate that are designed to associate and interact with other members of the library. Ex. 1005, ¶104. Importantly, a POSA would review Neri and determine that it teaches a method of preparing organic molecules, peptides, and oligomeric proteins linked to an oligonucleotide that results in stable self-assembled associated oligonucleotides. *Id.*; Ex. 1011, [0082]. As such, the teachings of Neri directly include the “small

molecules” of Kanan. Ex. 1005, ¶104. The modification of the Kanan library members with the teachings of Neri would create the modified library member shown below, with a self-assembly sequence (association element) and an identification sequence element.



Id., ¶105.

Moreover, a POSA would have known that the method disclosed in Kanan could be altered based on the teachings of Neri to incorporate coupling a protein or nucleic acid to the nucleic acid labels because not only was it taught in Neri but it was also well-known at the time of the application to create peptide or protein libraries to understand the role and properties of proteins. *See, e.g.*, Ex. 1011, [0010], [0082]; Ex. 1023; Ex. 1005, ¶149. A POSA would have also known that the nucleic acid label disclosed in Kanan could be sequenced because sequencing nucleic acid was a

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standard practice when the application was filed. Ex. 1005, ¶171. A POSA would have known 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. Ex. 1005, ¶183.

Finally, a POSA would have a reasonable expectation of success in combining Kanan, Neri, and Famulok because Neri teaches how to design interactors that contain an overhang region (*see* Ex. 1011, Fig. 7) that can be ligated together using the method taught in Famulok, and the use of a splint and DNA ligase to connect oligonucleotides was well-known at the time of the application. *E.g.*, Ex. 1013, Fig. S1; Ex. 1005, ¶178. A POSA would have also known that all the references relate to encoding a molecule with a unique nucleotide sequence, allowing the encoded molecules to interact, and then detecting and analyzing the identification of the members involved in the interaction. *Id.*; Ex. 1010, 545; Ex. 1011, [0117]-[0119]; Ex. 1012.

4. Independent Claim 1

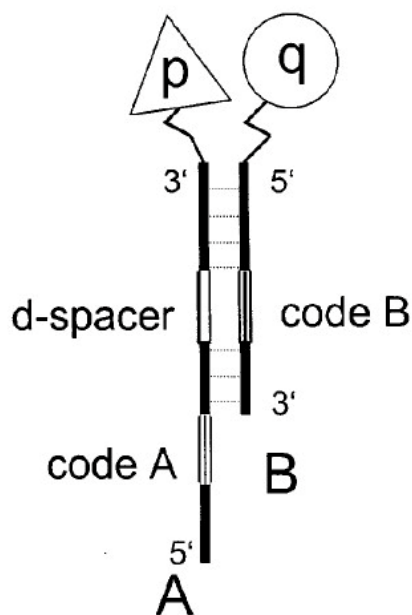
Grounds 1 and 2 are based on what a POSA would have understood regarding the scope of the claims of the '848 patent. Ex. 1005, ¶¶79-84. As such, Grounds 1 and 2 do not apply PO's positions taken in the district court litigation with Petitioner. *See* Section V.B.1 below.

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Grounds 1 and 2 rely on Kanan and Neri. Exs. 1010, 1011. While the '848 patent distinguishes Kanan (*see* III.A.2(a), *supra*), Kanan's Supplementary Information (Ex. 1013³) was never disclosed or considered. The '848 patent states that the alleged invention improves upon Kanan because the use of "combinatorial association" that allows "all library members to interact" and reduces "the number of oligonucleotides required [to be synthesized] is in the order of n" for a library of n members. Ex. 1001, 3:54-4:1.

While Kanan does not teach the use of self-assembly of all library members, it would have been obvious to a POSA to create interactors with a self-assembly sequence and separate identification sequence elements in view of Neri. Ex. 1005, ¶¶94-105. Neri discloses a method whereby the oligonucleotides associate through the self-assembly sequences and the nucleic acid encodes tags to identify both members of the interaction. Ex. 1005, ¶¶74-76.

³ Ex. 1013 was published and available in 2004. Ex. 1040, ¶¶7-16.



Ex. 1011, Fig. 5.

First, Neri discloses a self-assembly sequence; as shown above, the 3' ends of the oligonucleotides of sub-library A have a “DNA sequence [that] is designed to hybridize to the DNA sequences at the 5' extremity of oligonucleotides of sub-library B.” Ex. 1011, [0029]. Second, Neri discloses two discrete identification sequences; as shown above, the moiety p is attached to a nucleic acid sequence that has a unique sequence (Code A) that codes for “p,” and the moiety q is attached to a nucleic acid sequence that has a unique sequence (Code B) that codes for “q.” *Id.*, [0029]. Once self-assembled, “[t]he resulting DNA segment, carrying both code A and code B, can be amplified (typically by PCR), using primers which hybridize at the constant extremities of the DNA segment.” *Id.*, [0030]. Thus, the approach taught in Neri would allow interaction between all members of sub-library A and sub-library B and

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would result in DNA segments (i.e., NAMs) that code for both members of the interaction. Ex. 1005, ¶¶82-83.

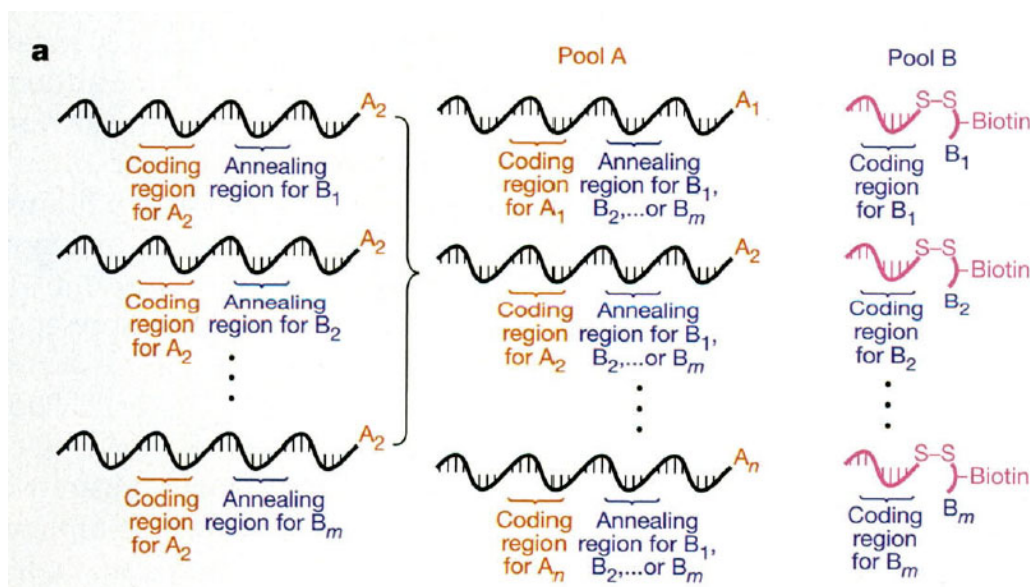
As shown below, the alleged invention in the '848 patent was not new but rather an obvious combination of known methods. Ex. 1005, ¶¶12, 79.

(a) Preamble: “A method of detecting functional interactions between at least two molecules of interests, the method comprising:”

To the extent the preamble is limiting, Kanan discloses this limitation. Ex. 1005, ¶¶85-87. Kanan discloses “a reaction discovery approach that uses DNA-templated organic synthesis and *in vitro* selection to simultaneously evaluate many combinations of different substrates for bond-forming reactions in a single solution.” Ex. 1010, 545. The MOIs described in Kanan include, among other things, small molecules. *Id.*, 547, 548, Fig. 3. These small molecules, which Kanan refers to as substrates, are “tethered to DNA strands” and use “Watson-Crick base pairing [to] control[] the effective molarities of substrates.” *Id.*, 545. Once in proximity, the substrates create “mild carbon-carbon bond-forming reaction[s],” which are the functional interactions. *Id.* The “bond-forming substrate combinations are then revealed using *in vitro* selection for bond formation” and analyzed using “PCR amplification and microarray analysis.” *Id.* In fact, the '848 patent concedes that the DTS-approach described in Kanan discloses “two molecules [that] are forced together by using nucleic acids to allow the molecules to interact[.]” Ex. 1001, 3:46-48.

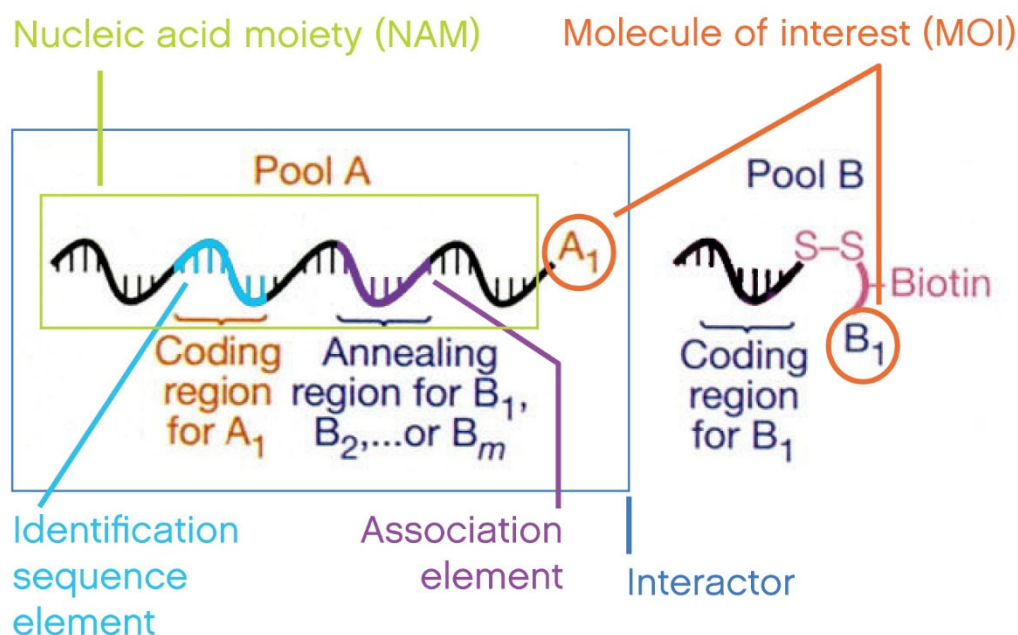
- (b) Step a: “forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;”

Kanan in view of Neri discloses this step. Ex. 1005, ¶¶88-106. Kanan discloses coupling “small molecules” to DNA with specific coding and annealing regions. Ex. 1010, 545-548, 546, Fig 1.a. As disclosed in Kanan, the “two pools of DNA-linked substrates” (MOI with a NAM) were prepared “with n substrates in pool A and m substrates in pool B. Each substrate in pool A is covalently linked to the 5’ end of a set of DNA oligonucleotides containing one ‘coding region’ (uniquely identifying that substrate) and one of m different ‘annealing regions’ (Fig. 1a). Each of the m substrates in pool B is attached to the 3’ end of an oligonucleotide containing a coding region that uniquely identifies the substrate and complements one of the m annealing regions in pool A.” Ex. 1010, 545.



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Id., 546, Fig. 1.a. In Kanan, however, only pool A library members are considered interactors because pool A interactors are the only library members that have both an association element (annealing region) and a separate identification sequence element (coding region). Ex. 1005, ¶¶91, 93. Pool A's annealing region is specific for a specific pool B member, and will not interact with all pool B members. Ex. 1005, ¶93.

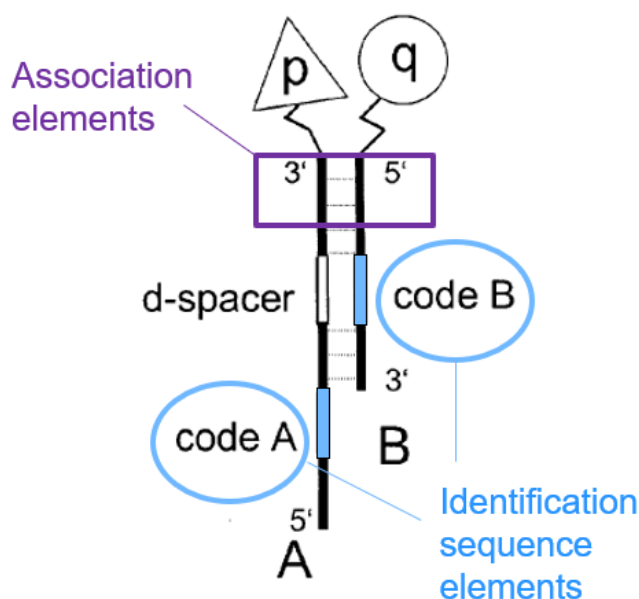


Ex. 1005, ¶91.

Neri, however, discloses “self-assembling libraries of organic molecules . . . in which the organic molecules are linked to an oligonucleotide which mediates the self-assembly of the library and/or provides a code associated to each binding moiety.” Ex. 1011, [0005]. Neri teaches creating conjugates (i.e., interactors) that contain a “reactive moiety” and a “DNA oligonucleotide.” *Id.*, [0048]. These conjugates are separated into pool A and pool B. “The oligonucleotides of pool A are designed to

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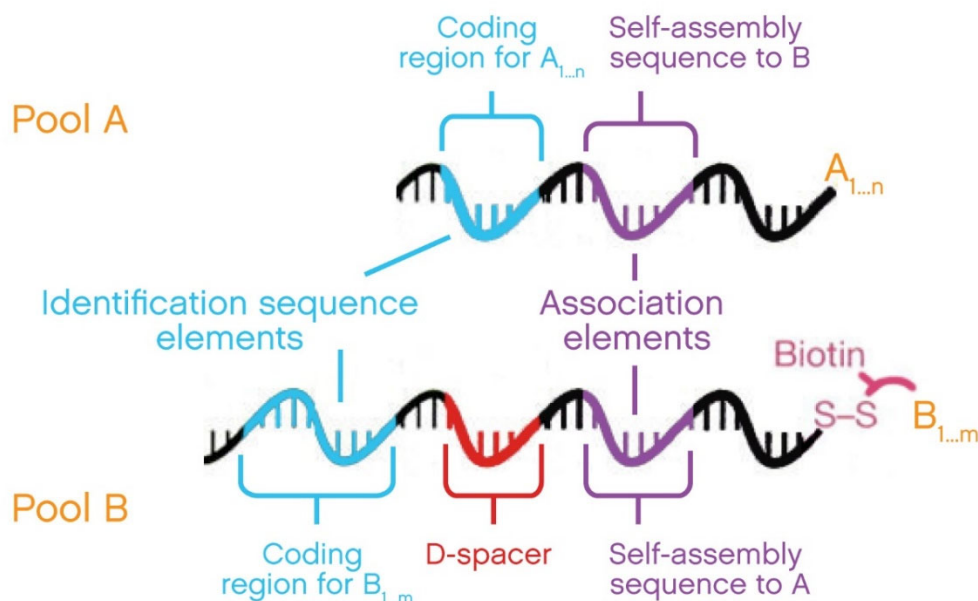
have: one portion of the DNA sequence which can hybridize to compounds of pool B[;] a distinctive DNA sequence for each of the n members of pool A[;] [and] additional portions of the DNA sequence judiciously designed for ‘decoding’ binding combinations[.]” *Id.*, [0048]-[0051]. Likewise, the “oligonucleotides of pool B are designed to have: one portion of the DNA sequence which can hybridize to compounds of pool A[;] a distinctive DNA sequence for each of the m members of pool B[;] [and] additional portions of the DNA sequence judiciously designed for ‘decoding’ binding combinations[.]” *Id.*, [0053]-[0056]. When pool A and pool B are mixed, “the resulting self-assembled $m \times n$ combinations will carry unique DNA codes, corresponding to the non-covalent but stable association (heterodimerization) of the DNA code of the member of Pool A with the DNA code of the member of Pool B.” *Id.*, [0057].



Id., Fig. 5 (excerpt; annotated).

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As taught in Neri, a POSA would have understood that Neri's "self-assembly" sequences constitute association elements because the sequences result in self-assembled $m \times n$ combinations of pool A and pool B library members. Ex. 1005, ¶96. In addition, Neri's "sequence tags," such as "code A" and "code B," provide a unique nucleic acid identification sequence for each conjugate that can be identified downstream. *Id.*, ¶97. To create two sub-libraries of interactors, a POSA would have modified pool A and pool B members in Kanan. *Id.*, ¶105. A POSA would have modified pool A by modifying the annealing regions to contain a self-assembly sequence. *Id.* That is, all pool A members would contain the same annealing sequence that is complimentary to all pool B members. *Id.* In addition, a POSA would have modified pool B members by replace the coding region that anneals with its pool A counterpart with a self-assembly sequence. *Id.* That is, all pool B members would contain the same annealing sequence that is complimentary to all pool A members. *Id.* Next, a POSA would modify pool B members to add the d-spacer taught in Neri, as this prevents the identification sequence element of pool B members from interacting with the identification sequence element of pool A members. *Id.* Finally, a POSA would modify pool B members to add the unique identification sequence of the pool B molecule, also taught in Neri. *Id.* As shown below, by combining Kanan with Neri, all of the resulting library members, including A_{1-n} and B_{1-m} , contain a self-assembly sequence (association elements) and an identification sequence element. *Id.*

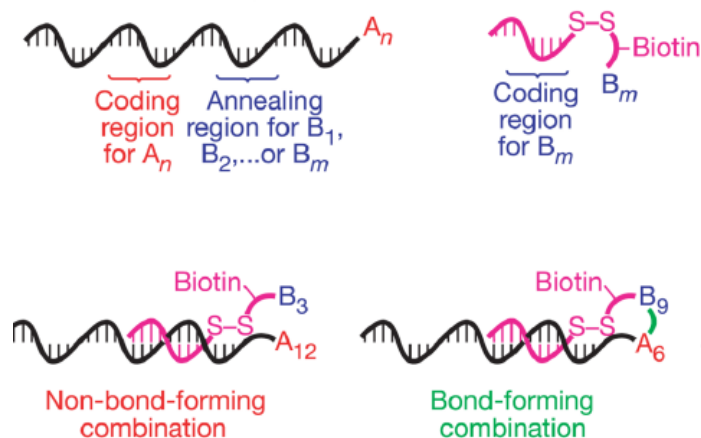


Ex. 1005, ¶105 (modified library members combining Neri with Kanan).

- (c) Step 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 oligonucleotides comprise at least two identification elements derived from the at least two nucleic acid moieties;”

Kanan in view of Neri discloses this step. Ex. 1005, ¶¶107-116. Kanan teaches that “[w]hen pools A and B are combined in a single aqueous solution at nanomolar concentrations, Watson-Crick base pairing organizes the mixture into $n \times m$ discrete pairs of substrates attached to complementary sequences.” Ex. 1010, 545. Further, as described above with regards to step a, Kanan in view of Neri discloses interactors, which are the DNA-linked substrates in pool A and pool B. Ex. 1005, ¶111.

In Kanan, pool A and pool B members are bound in proximity to one another through their respective coding-specific annealing regions. Ex. 1005, ¶112.

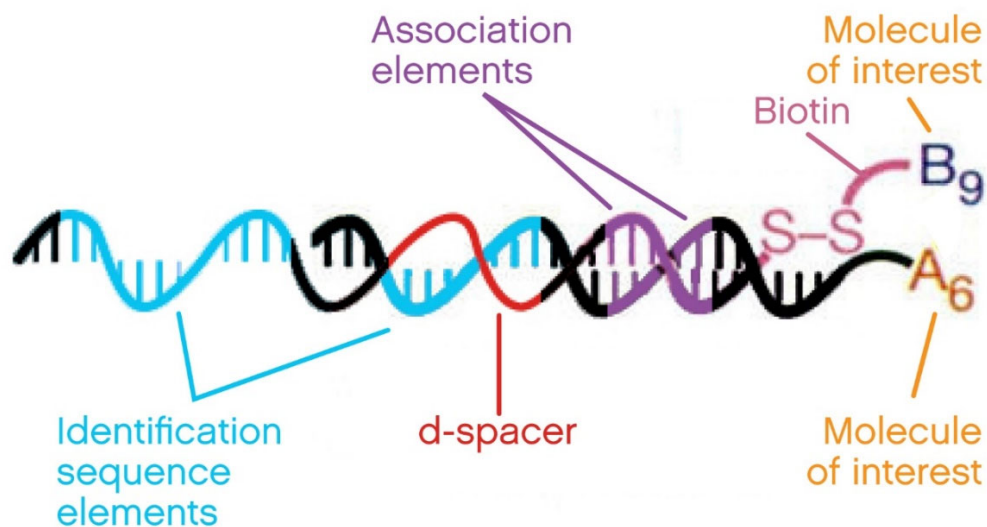


Ex. 1010, 546, Fig. 1.

Substrates A_{12} and B_3 are bound in proximity via the B_3 annealing region in A and the B_3 coding region in B. Ex. 1005, ¶112. Likewise, substrates A_6 and B_9 are bound in proximity via the B_9 annealing region in A and the B_9 coding region in B. *Id.* Based on the annealing regions (association elements), the DNA bind regardless of the interaction between substrates themselves. *Id.* Thus, the DNA in pool members A_{12} and B_3 bind despite no bond forming between A_{12} and B_3 . *Id.*

As Dr. Nelson explains, when Kanan is combined with Neri, pool A and pool B interactors comprise the common self-assembly sequences (association elements) and the two unique identification sequence elements, one on each interactor, found in Neri. Ex. 1005, ¶¶114-115. This forms a cis-reactive cell, as shown below. And because Kanan with Neri allows for all library members to interact from two sub-

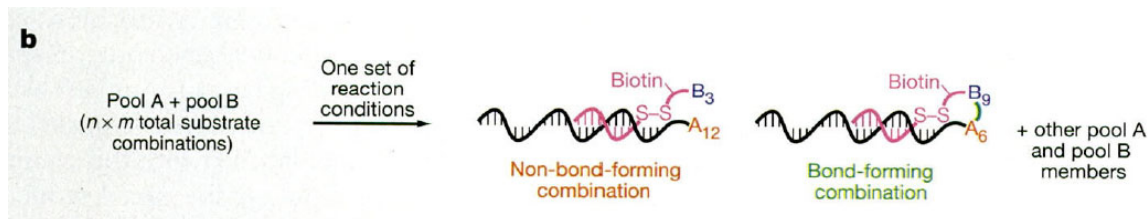
libraries, there would be two or more cis-reactive cells formed by interactors from the pool A and pool B library members, including any A_{1-n} and any B_{1-m} .



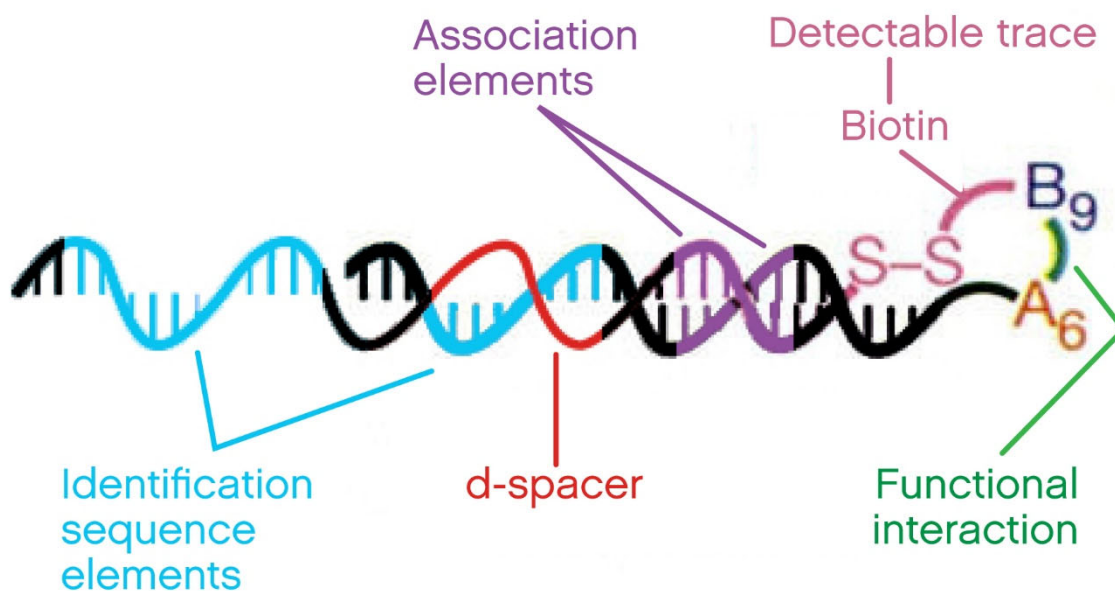
Ex. 1005, ¶115.

- (d) **Step c: “subjecting the plurality of cis-reactive cells to conditions which stimulate desired functional interaction having a detectable trace;”**

Kanan in view of Neri discloses this step. Ex. 1005, ¶¶117-120. Kanan teaches each pool B substrate is linked “to its corresponding oligonucleotide by a linker containing a biotin group and a disulphide bond.” Ex. 1010, 545. “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.” *Id.*, 545; Fig. 1.b (below). All of the cis-reactive cells would be subjected to the conditions in Kanan.



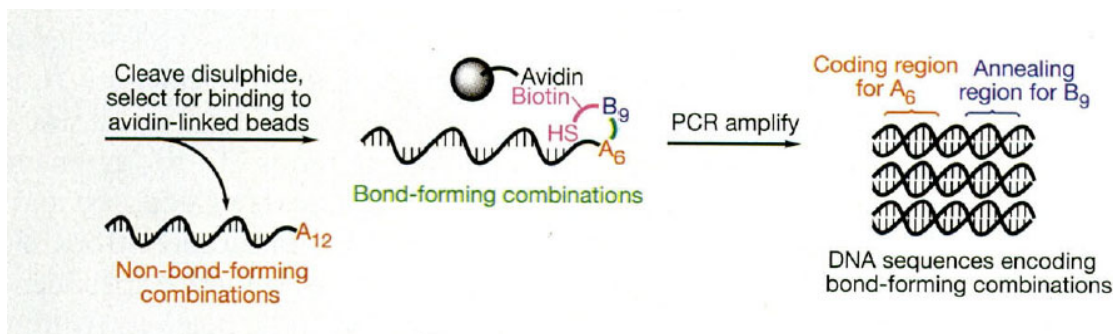
The bond formation between substrates A and B (i.e., the addition of substrate B₉ to A₆, below) would be considered the functional interaction between the substrates. Ex. 1005, ¶119. The biotin linked to the newly bound substrates is the detectable trace. *Id.*



(e) **Step d: “selecting all cis-reactive cells exhibiting the detectable trace; and”**

Kanan in view of Neri discloses this step. Ex. 1005, ¶¶121-124. Kanan discloses that after bond formation “[s]treptavidin affinity selection of the resulting

solution separates biotinylated from non-biotinylated sequences.” Ex. 1010, 545-546, Fig. 1.b. (below).



The use of the biotin-streptavidin capture would allow selection of only the bond-forming combinations, i.e., demonstrate the detectable trace, which a POSA would have understood as “selecting all cis-reactive cells exhibiting the detectable trace.” Ex. 1005, ¶124.

(f) Step 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.”

Kanan in view of Neri discloses this step. Ex. 1005, ¶¶125-132. Kanan teaches that the bond-forming pairs are amplified by PCR and analyzed with microarray analysis through the incorporation of fluorophores to identify the sequences encoding the bond-forming substrates. *Id.*, ¶127; Ex. 1010, 545-546. A POSA would have understood Kanan in view of Neri that the 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

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elements of Neri, that is detected and corresponds to each unique substrate. Ex. 1005, ¶127.

Neri also teaches sequencing of the identification sequences, which is a well-known method to identify the sequences encoding the bond-forming substrates (i.e., the identification sequence elements). Ex. 1005, ¶129.

As shown above, and explained by Dr. Nelson, claim 1 of the '848 patent is obvious over Kanan in view of Neri. Ex. 1005, ¶133.

5. Dependent Claim 2

Claim 2 depends from claim 1 and adds; “wherein selecting all cis-reactive cells exhibiting the detectable trace is accomplished via selective separation or selective detection of the cis-reactive cells.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶¶134-137. During prosecution, PO stated that “[b]oth selective separation and selective detection are techniques well known in the art[,]” (Ex. 1002, 505), and, thus, “admit[ed] that such things would be known to a POSA.” *McCoy v. Heal Sys., LLC*, 850 Fed. App’x 785, 789 (Fed. Cir. 2021); *see Qualcomm Inc. v. Apple Inc.*, 24 F.4th 1367, 1376 (Fed. Cir. 2022). In addition to a POSA knowing these techniques, Kanan discloses selective detection. Ex. 1005, ¶135. Kanan discloses that the bond forming pairs can be selectively detected using streptavidin affinity selection, which allows for selective detection of only the bond-forming combinations because only

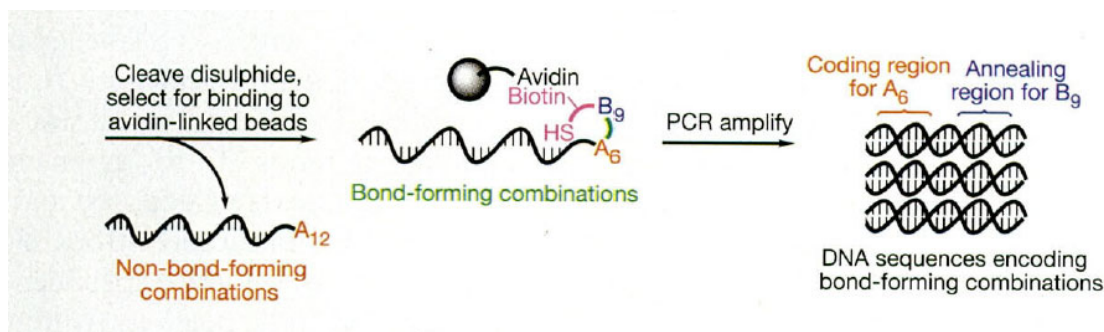
those combinations would have the affinity for the streptavidin. Ex. 1010, 545; Ex. 1005, ¶136.

6. Dependent Claim 3

Claim 3 depends from claim 2 and adds: “wherein selecting all cis-reactive cells exhibiting the detectable trace is accomplished by affinity purification.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶138. As in claim 2, Kanan discloses that the bond forming pairs can be selectively detected using streptavidin affinity selection. Ex. 1010, 545. A POSA would have understood streptavidin affinity selection as a form of affinity purification. Ex. 1005, ¶138.

7. Dependent Claim 4

Claim 4 depends from claim 1 and adds: “further comprising enhancing the selected associated oligonucleotides by PCR amplification.” Kanan in view of Neri discloses this claim limitation. Ex. 1005, ¶¶139-140. Kanan discloses the bond-forming pairs are amplified using PCR. Ex. 1010, 545-546; Fig. 1.b (below).



8. Dependent Claims 5 and 6

Claim 5 depends from claim 1 and adds: “wherein coupling is covalent or noncovalent.” Claim 6 depends from claim 1 and adds: “wherein coupling is covalent.” Kanan in view of Neri discloses these limitations. Ex. 1005, ¶¶141-143. Kanan discloses that “[e]ach substrate in pool A is covalently linked to the 5’ end of a set of DNA oligonucleotides containing one ‘coding region’ (uniquely identifying that substrate) and one of m different ‘annealing regions’ (Fig. 1a). Each of the m substrates in pool B is attached to the 3’ end of an oligonucleotide containing a coding region that uniquely identifies the substrate and complements one of the m annealing regions in pool A.” Ex. 1010, 545.

9. Dependent Claim 7

Claim 7 depends from claim 1 and adds: “wherein at least one molecule of interest comprises a protein, a protein domain, a peptide, a peptoid, a non-proteinaceous cellular product, a virus particle, a cell metabolite, a lipid, a carbohydrate, a nucleic acid, an inorganic compound, a reactive compound, or any combination thereof, however, wherein not all molecules of interest are nucleic acids.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶¶144-145. Kanan discloses that the substrates involved in the interactions are “small molecules.” Ex. 1010, 547-548. A small molecule would meet this claim limitation because it only

requires the disclosed MOI to be one of the items recited in the claimed list. Ex. 1005, ¶144.

10. Dependent Claim 8

Claim 8 depends from claim 7 and adds: “wherein at least one molecule of interest comprises at least one protein.” Kanan in view of Neri discloses this limitation, specifically Neri teaches the MOI as being a protein. Ex. 1005, ¶¶146-150. Neri discloses that “[t]he methodologies described in this Patent work not only for small organic molecules, but also for peptides and oligomeric proteins [e.g. antibody Fv fragments, consisting of a VH and VL domain; see Example 1].” Ex. 1011, [0082]. Neri also states that “one strength of ESACHEL technology is its compatibility with a variety of different chemical moieties, including peptides and globular proteins (e.g., antibody domains).” *Id.*, [0094]. It would have been obvious to use a protein as one of the substrates in Kanan. Ex. 1005, ¶148.

11. Dependent Claim 9

Claim 9 depends from claim 8 and adds: “wherein the protein is an expression product of a nucleic acid molecule, and further wherein at least some of the plurality of interactors are formed by coupling the protein with a nucleic acid moiety comprising an identification sequence element derived from the nucleic acid molecule.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶¶151-157. A POSA would have understood the limitations of claim 9 as describing phage display

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or mRNA display. Ex. 1005, ¶152; Ex 1001, 13:5-14, 13:43:14:5. A POSA would have known that in both phage display and mRNA display, the protein is coupled to a nucleic acid sequence that encodes for that specific protein. Ex. 1005, ¶152; Ex. 1032 (Winter 1994); Ex. 1033 (Wilson 2001).

As in claim 8, Neri is not limited to organic small molecules. Ex. 1011, [0082]. Neri also states that “one strength of ESACHEL technology is its compatibility with a variety of different chemical moieties, including peptides and globular proteins (e.g., antibody domains).” *Id.*, [0094].

It would have been obvious to use a phage display protein as one of the substrates taught in Kanan. Ex. 1005, ¶¶153-156.

12. Dependent Claim 10

Claim 10 depends from claim 7 and adds: “wherein at least one molecule of interest comprises at least one protein and at least one nucleic acid.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶¶158-162. Neri discloses that it “is therefore an object of the present invention to provide a chemical compound comprising a chemical moiety of any kind capable of performing a binding interaction with a target molecule (e.g. a biological target)[.]” Ex. 1011, [0015]. As with claim 8, Neri is not limited to organic small molecules. *Id.*, [0082]. Neri also discloses that the prior art taught “generation of libraries of genes.” *Id.*, [0010]. It would have been

obvious to use a protein as a substrate and nucleic acid as a substrate in the substrate pairs taught in Kanan. Ex. 1005, ¶¶160-161.

13. Dependent Claim 11

Claim 11 depends from claim 1 and adds: “wherein detecting further comprises quantifying the functional interactions.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶¶163-164. Kanan teaches that after the DNA-linked substrates are allowed to bond, the “[s]equences encoding bond-forming substrates pairs were captured with streptavidin-linked magnetic particles and amplified by PCR with a DNA primer labelled with the cyanine fluorophore Cy3.” Ex. 1010, 545-546. A POSA would have understood the use of fluorophores and the detection allowing calculations and ranks to determine positive bond formations as quantifying the bond forming interactions. Ex. 1005, ¶164.

14. Dependent Claims 12 and 13

Claim 12 depends from claim 1 and adds: “wherein the analysis comprises high throughput screening.” Claim 13 depends from claim 1 and adds: “wherein the high throughput screening comprises micro array analysis.” Kanan in view of Neri discloses these limitations. Ex. 1005, ¶¶165-167. Kanan discloses the “bond-forming substrate combinations” are detected using “DNA microarray analysis.” Ex. 1010, 545. A POSA would have understood that the “DNA microarray” method of detection allows for high throughput screening. Ex. 1005, ¶165.

15. Dependent Claims 14 and 15

Claim 14 depends from claim 1 and adds: “wherein the analysis comprises nucleic acid sequencing.” Claim 15 depends from claim 1 and adds: “wherein the analysis comprises sequencing by synthesis.” Kanan in view of Neri discloses these limitations. Ex. 1005, ¶¶168-174. Neri discloses that the pool A and pool B DNA-linked chemical entities are allowed to bond and then after bonding are analyzed by PCR followed by sequencing. Ex. 1011, [0111]-[0119]. A POSA would have understood Neri as disclosing Sanger sequencing, which is a form of sequencing by synthesis, because Sanger sequencing was a well-known form of sequencing at the time of the application. Ex. 1005, ¶173; Ex. 1028 (Wilton 2002). A POSA would have understood that Neri’s “sequencing” of the coding region allows identification of the chemical entity in which the “code” identifies. Ex. 1005, ¶169. Further, it would have been obvious to include the “sequencing” of Neri to the detection and analysis of the bond-forming substrates taught in Kanan. *Id.*, ¶¶170-171.

16. Dependent Claim 16

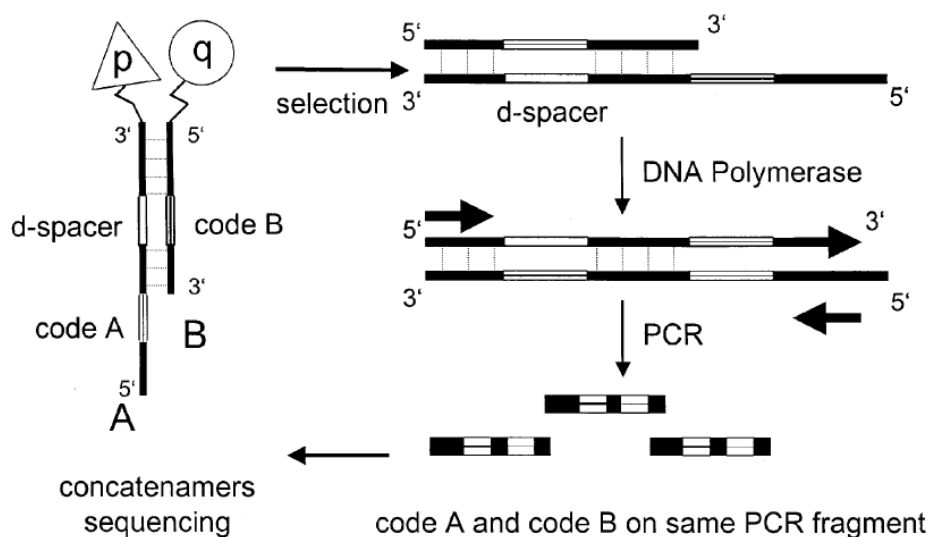
Claim 16 depends from claim 1 and adds: “wherein association is via ligation.” The combination of Kanan, Neri, and Famulok discloses this limitation. Ex. 1005, ¶¶175-179. Famulok teaches associating the oligonucleotides of the aptamers by connecting the two oligonucleotides to a third “splint” oligonucleotide that is incorporated into double-stranded DNA by DNA ligase. Ex. 1012. A POSA would

have understood 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. Ex. 1005, ¶¶177-178.

17. Dependent Claim 17

Claim 17 depends from claim 1 and adds: “wherein association is via polymerization.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶¶180-184. Neri discloses in Example 3 that the “[o]ligonucleotides 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. The resulting DNA segment, carrying both code A and code B, can be amplified (typically by PCR), using primers which hybridize at the constant extremities of the DNA segment (Fig 5).” Ex. 1011, [0117]; Fig. 5 (below).

Fig. 5



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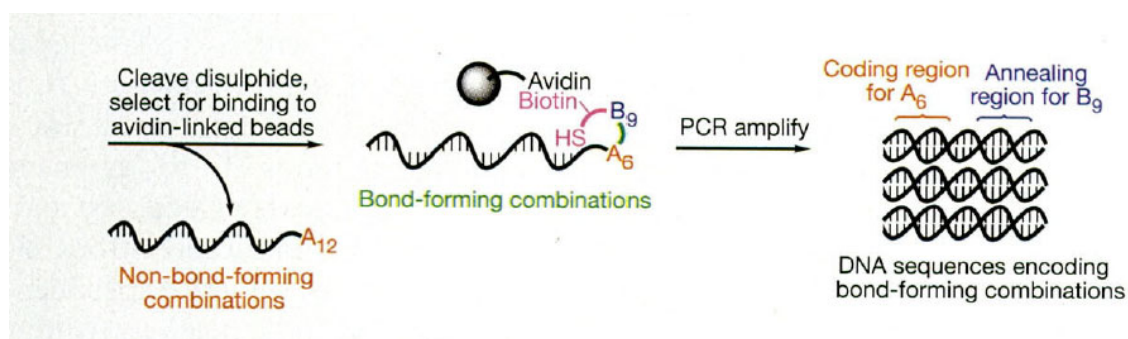
A POSA would have understood that it would have been obvious to use the polymerization of the oligonucleotides as taught in Neri with the creation of the paired substrates in Kanan. Ex. 1005, ¶¶182-183.

18. Dependent Claim 18

Claim 18 depends from claim 1 and adds: “wherein the conditions for stimulating the functional interaction between the at least two molecules of interest comprise manipulating conditions to maximize cis reactivity and to minimize trans reactivity between the at least two molecules of interest.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶¶185-186. Kanan discloses that “the system must organize complex substrate mixtures into discrete pairs that can react (or not react) without affecting the reactivity of other substrate pairs.” Ex. 1010, 545. To achieve this, Kanan discloses the “Watson-Crick base pairing organizes the mixture into $n \times m$ discrete pairs of substrates attached to complementary sequences. Only substrates linked to complementary oligonucleotides experience effective molarities in the millimolar range[.]” *Id.* A POSA would have understood that the disclosed organizational method of the substrate pairs would promote formation between pool A and pool B (maximizing cis reactivity) and thus would minimize formation of bonds between pairs that do not share complementary sequences (minimizing trans reactivity). Ex. 1005, ¶185.

19. Dependent Claim 19

Claim 19 depends from claim 12 and adds: “wherein the selective detection comprises labeling the cis-reactive cells with an affinity reagent.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶¶187-188. Kanan discloses that members of pool B are labeled with biotin and “[a]fter incubation under a set of chosen reaction conditions, followed by cleavage of the disulphide bonds, only pool A sequences encoding bonding formation between a pool A and pool B substrate remain covalently linked to biotin.” Ex. 1010, 545-546, Fig. 1.b (below).



A POSA would have understood biotin as an affinity reagent because the biotin allows for streptavidin affinity selection for the bond-formation combinations. Ex. 1005, ¶188; Ex. 1010, 545.

20. Dependent Claim 20

Claim 20 depends from claim 2 and adds: “wherein the selective detection comprises introducing a modified molecule wherein the modification permits the selective detection.” Kanan in view of Neri discloses this limitation. Ex. 1005, ¶¶189-190. Kanan discloses using biotin and streptavidin affinity selection to select the

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bond-forming pairs. Ex. 1010, 545. The biotin is introduced to the bond-forming pair because the substrate in pool B is linked to biotin. *Id.*, 546, Fig. 1.a. A POSA would have understood the substrate linked to biotin as a modified molecule because the substrate would not contain biotin without modification. Ex. 1005, ¶189.

B. Grounds 3 And 4: Claims 1-8, 11-12, And 14-15 Are Unpatentable

1. Pending Related Litigation

On November 15, 2023, PO filed a patent infringement claim against Petitioner asserting that Petitioner's NULISA platform to detect a known analyte infringes the '848 patent. Ex. 1007. The complaint alleges that Petitioner's NULISA platform "is based on the proximity litigation [sic] assay originally commercialized by Olink Bioscience[.]" Ex. 1007, ¶¶18-20, 35-39 (quotation omitted).

PO asserted the '848 patent against Petitioner's PLA-based NULISA despite the patent's disclaimer that its alleged invention is not PLA. Ex. 1005, ¶¶203-210. PO applies each claim element to the fundamental steps of PLA. Ex. 1007, ¶¶21-27. Further, PO provided an infringement chart (Ex. 1008) further applying each limitation of claims 1-8, 11-12, and 14-15 to the foundational steps of PLA. Ex. 1005, ¶¶207-208.

On April 1, 2024, Petitioner moved to dismiss PO's complaint because (1) it fails to state a claim for infringement and (2) the claim scope cannot cover NULISA's use of PLA based on the patent's disclaimer and disavowal of PLA. Ex. 1014, 3-6.

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In its opposition, PO claimed it did not disavow PLA, and that detecting a known analyte using known affinities is properly within the scope of the claims of the '848 patent. Ex. 1015, 15-17. Petitioner's motion remains pending.

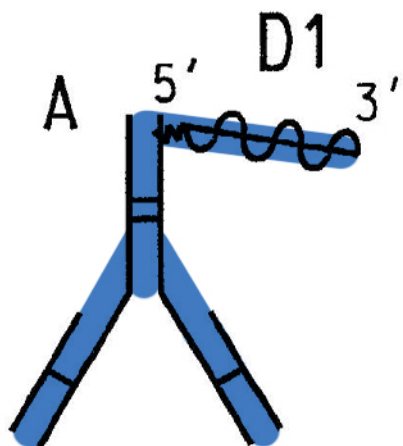
2. Prior Art

(a) Baez

Baez, titled "Method For The Detection Of An Analyte By Means Of A Nucleic Acid Reporter," published on January 28, 2003. Ex. 1003. Baez is prior art under at least pre-AIA 35 U.S.C. § 102(b).

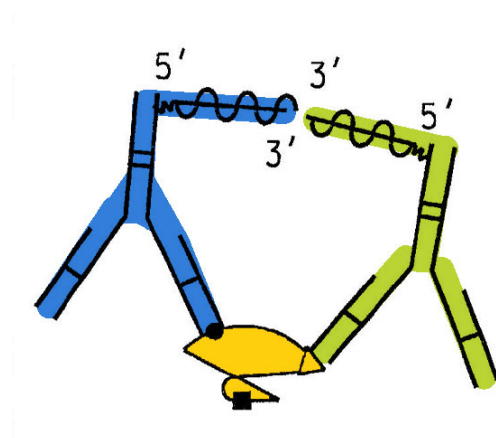
Baez is the patent from U.S. Patent Application Publication No. US2002051986 discussed in the application. Ex. 1001, 4:26-29. Baez was not used as a basis for rejection of any claims. Ex. 1002. Baez discloses "[a] process . . . for the detection of an analyte [or target] utilizing a nucleic acid label as a reporter." Ex. 1003, Abstract. "The nucleic acid can subsequently be quantified and the amount of nucleic acid corresponds to the amount of target." Ex. 1001, 4:36-38.

Baez teaches a "reporter conjugate," which can be "an antibody, lectin, receptor, or binding protein" that is coupled to a short "nucleic acid-label." Ex. 1003, 7:48-57, Fig. 1. The conjugate is designed to bind to a predefined analyte. *Id.*, 7:53-57.



Id., Fig. 2 (color added to show single conjugate in blue).

The analyte has binding sites that allow at least two conjugates to bind to a single analyte, forming an “analyte-dependent reporter-complex” (ADCR). *Id.*, 7:4-10, 7:58-62, 11:18-20; *id.*, 9:21-26, 12:59-61.

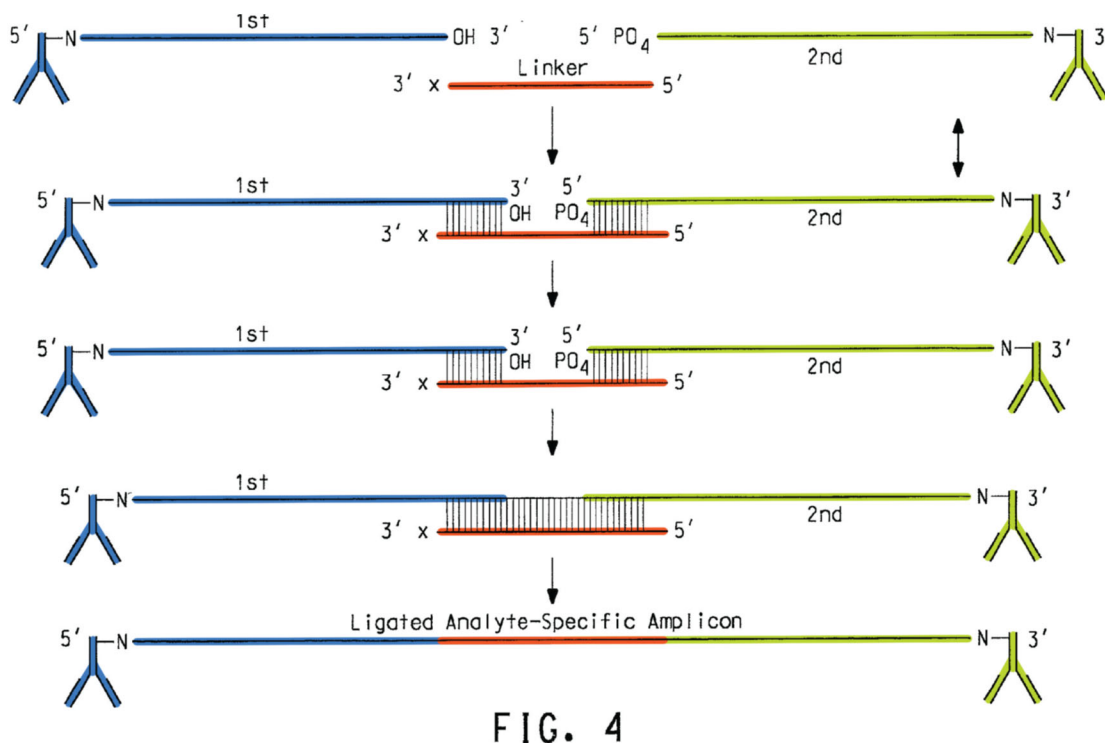


Id., Fig. 2 (color added to show conjugates in blue and green; analyte shown in yellow).

The binding of the conjugates to the binding sites brings the two nucleic-acid labels of each individual conjugate “in molecular proximity” to each other within the

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ADRC, as shown above, enabling “the labels to be joined” by ligation using a linker oligonucleotide. *Id.*, 9:61-65, 10:17-19, 11:18-24.



Ex. 1001, Fig. 1 (color added and annotated).

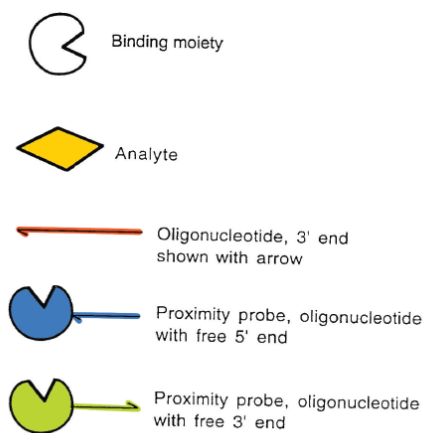
The binding of the nucleic-acid labels “results in the formation of assay analyte-specific amplicon (ASA).” Ex. 1003, 10:60-63. The ASA “is comprised of sequence elements from both nucleic acid-labels.” *Id.*, 11:30-32. The ASA can then be detected and analyzed through amplification. Ex. 1001, 11:43-45, 16:62-64. The amplified product is “characteristic of the analyte and proportional to the amount of analyte present [in a sample].” Ex. 1003, 12:49-53.

(b) Landegren

Landegren, titled “Methods And Kits For Proximity Probing,” published on August 23, 2001. Ex. 1004. Landegren is prior art under at least pre-AIA 35 U.S.C. § 102(b).

Landegren discloses “sensitive, rapid and convenient assays for detection and/or quantification of one or several analyte(s) in solution” using proximity probes (called “binders” in the ’848 patent). Ex. 1004, Abstract; Ex. 1001, 4:29-31. Landegren is disclosed in the application and was not used as a basis for rejection of any claims. Ex. 1001, 4:26-29; Ex. 1002.

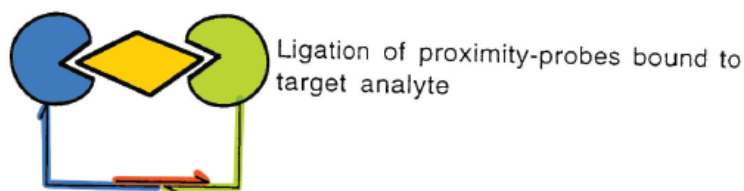
The proximity probes in Landegren “comprise a binding moiety and a nucleic acid.” Ex. 1001, 4:26-29. Landegren teaches that the proximity probes contain binding moieties that “may be proteins such as monoclonal and polyclonal antibodies” Ex. 1004, 3. Landegren also teaches the proximity probes comprise a “nucleic acid coupled to the binding moiety.” *Id.*, 3.



Landegren, Fig. 1 (color added).

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The binding moiety is designed “with affinity for the analyte.” Ex. 1004, 2. The analyte “may be proteins, nucleic acids or any other molecule of interest capable of specifically binding two or more proximity probes.” *Id.*, 2. The binding of two proximity probes to an analyte “acts in a way analogous to a catalyst by bringing the reactive probes close to one another and increasing their ability to interact through an increased local concentration.” *Id.*, 2. Once in proximity, two probes can hybridize to a linker oligonucleotide and be coupled through ligation. *Id.*, 7.



Id., Fig. 1 (partial and color added).

“The interaction between the coupled [probes] results in a detectable signal.” *Id.*, 2. And “[t]he resulting ligation between these nucleic acids is readily amplifiable by several reactions, such as polymerase chain reaction (PCR) These amplification reactions are thus designed only to give a product when the two nucleic acids have been crosslinked by ligation.” *Id.*, 4. “The resulting product can also be quantified by electrophoresis in gels.” *Id.*

(c) Freskgard

Freskgard, titled “A Method For Identifying A Synthetic Molecule Having Affinity Towards A Target,” published on January 13, 2005. Ex. 1009. Freskgard is prior art under at least pre-AIA 35 U.S.C. § 102(a).

Freskgard teaches “a novel method for enrichment of libraries of bifunctional complexes.” Ex. 1009, 4:5-6. Freskgard “relates to a method for identifying from a library a synthetic molecule having affinity towards a target. The synthetic molecule has initially been a part of a complex also comprising an identifier that codes for said synthetic molecule.” *Id.*, 1. The identifiers are used to identifying the molecule uniquely and “it is preferred that the identifier is a sequence of nucleotides.” *Id.*, 5-6.

In one embodiment of Freskgard, “[e]ach bifunctional complex in the library comprises a potential lead compound coupled to an identifier sequence. The identifier sequence is suitably a nucleic acid which uniquely identifies the potential lead compound. When a library of bifunctional complexes is screened against a target, one or more of the potential leads may bind to the target. After removal of the remainder of the library, the binding bifunctional complexes can be eluted and the lead compound identified by sequencing the identifier.” *Id.*, 2.

3. Motivation To Combine

Baez and Landegren are both in the same area of art that relate to the same foundational assay for detection and analysis of analytes. Ex. 1005, ¶¶211-226; Ex.

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1003; Ex. 1004. A POSA would have been motivated to combine Baez with Landegren, as Landegren teaches methods to reduce background signal in the assay. Ex. 1005, ¶238. As Baez explains, “[m]ethods for the reduction of background noise are continually being sought.” Ex. 1003, 1:32-33. The strategies employed in Landegren, such as use of unique identifier sequences, allows for the selection of only true positives. Ex. 1005, ¶238; Ex. 1004, 15. Further, the teachings of Landegren allows for the assay to be used as a multiplex protein detection assay. Ex. 1005, ¶238; Ex. 1004, 15. A POSA would have been motivated to create a multiplex assay to detect and analyze multiple analytes in a single assay. Ex. 1005, ¶238. Thus, a POSA would have been motivated to combine the two references because a POSA would be motivated to create an assay with reduced background signal and the ability to screen multiple analytes in a timely manner. *Id.*

In addition, a POSA would have been motivated to combine Baez and Landegren with Freskgard because a POSA would have been motivated to sequence the ligation product (i.e., ASA) as another method to detect and analyze the ASA. Ex. 1005, ¶293. Sequencing is a well-known method that would allow a POSA to determine the nucleic acid labels joined in the creation of the ASA. Ex. 1005, ¶¶293-294. A POSA would have also been motivated to combine Freskgard with Baez because Baez teaches that its nucleic acid products are detected “by sequence.” Ex. 1003, 3:63-64; Ex. 1005, ¶293. The sequencing of the nucleic acid taught in Freskgard

allows for the detection of the amplified nucleic acid products by sequence. Ex. 1005, ¶293.

4. Reasonable Expectation Of Success

A POSA would have a reasonable expectation of success in combining Baez and Landegren to achieve the claimed methods. Ex. 1005, ¶239. Both references relate to using “an antibody, lectin, receptor or binding protein or other moiety which can bind to an analyte” coupled to nucleic acid to detect an analyte. Ex. 1003, Abstract, 7:56-57; Ex. 1004, 1, 3; Ex. 1005, ¶239. Moreover, both Baez and Landegren disclose that the identification of the analyte is detected by the interaction of the nucleic acid sequences coupled to the binding moiety. Ex. 1001, Abstract; Ex. 1004, 1; Ex. 1005, ¶239.

Thus, Landegren’s disclosure of PLA would have provided a POSA with reasonable expectation of success in combining Baez with Landegren to achieve the claimed method of detecting functional interactions. Ex. 1005, ¶239.

In addition, a POSA would have a reasonable expectation of success in combining Baez and Landegren with Freskgard because all three references relate to tagging a molecule with nucleic acid and analyzing the molecule’s affinity toward a target by way of the nucleic acid label. Ex. 1003, Abstract, 7:53-56; Ex. 1004, 1, 3; Ex. 1009, Abstract; Ex. 1005, ¶294. A POSA would have known that sequencing as taught in Freskgard was a known technique that could have been readily applied to

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the nucleic acid labels taught in Baez and Landgren, as there would be no challenge to sequence the nucleic acid sequences taught in Baez and Landegren. Ex. 1005, ¶294.

5. Independent Claim 1

Grounds 3 and 4 apply PO's positions taken in the district court litigation as if a POSA would have applied the claims in the same way at the time of the application. *See* Section V.B.1. Petitioner's application of PO's positions is not an admission that the claims cover Petitioner's NULISA platform.

(a) Preamble: "A method of detecting functional interactions between at least two molecules of interests, the method comprising:"

To the extent the preamble is limiting, Baez discloses the preamble. Ex. 1005, ¶¶231-233. Baez discloses detecting nucleic acid sequences generated by the bonding of two reporter conjugates once they are brought into proximity to each other through affinity to an analyte. Ex. 1003, 11:10-35, 11:55-69; Ex. 1005, ¶231.

PO contends that MOIs include "matched antibody pairs." Ex. 1008, 1. Thus, MOIs include Baez's antibody-nucleic acid conjugates. Ex. 1001, 10:51-56; Ex. 1008, 1; Ex. 1005, ¶232. Further, PO contends that the "step of introducing the ligation mix stimulates a desired function interaction (ligation)" of the antibody-nucleic acid conjugates. Ex. 1008, 4; Ex. 1001, 14:23-27. Thus, a functional interaction includes Baez's ligation of the conjugates. Ex. 1001, 9:27-31; Figs. 2, 4; Ex. 1005, ¶232.

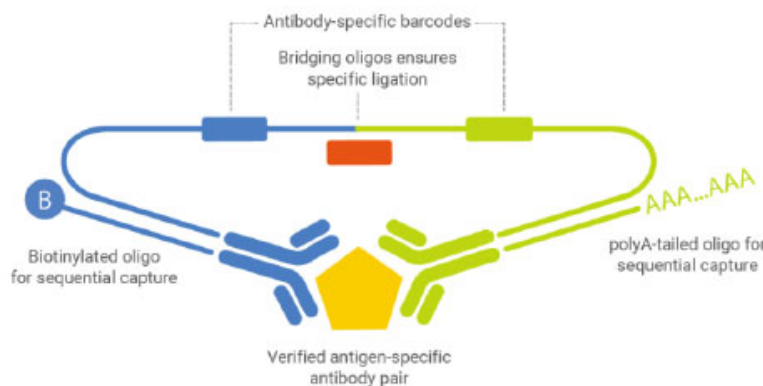
- (b) **Step a: “forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;”**

Baez in view of Landegren discloses this step. Ex. 1005, ¶¶234-240. Baez teaches that the plurality of conjugates, which can be “an antibody, lectin, receptor or binding protein,” are tagged with a nucleic acid moiety, creating “reporter conjugates.” Ex. 1003, 7:54-57, 7:48-53. PO contends that antibodies coupled to NAMs are the “interactors.” Ex. 1008, 1. Thus, the interactors include Baez’s “reporter conjugates.” Ex. 1003, 7:53-56, 10:51-56; Ex. 1005, ¶235.

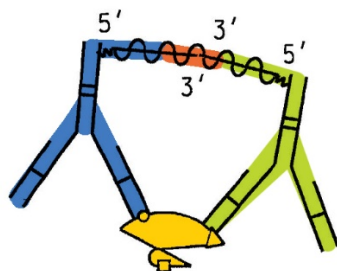
Baez further discloses that the two nucleic acid labels are connected to each other through a linker—the association element. Ex. 1003, Fig. 4; Ex. 1005, ¶236. Landegren also discloses that the nucleic acid coupled to the proximity probe (i.e., conjugate) has a sequence identification element or “tag.” Ex. 1004, 11; Ex. 1005, ¶237. These tags generate a positive signal “when the two matching sequence identification tags (ID:A and ID:B) are united.” Ex. 1004, 11. As Dr. Nelson explains, it would have been obvious to add the “sequence identification tags” of Landegren to the nucleic acid labels of Baez because the identification element would allow analysis of a multiplex assay and help reduce background noise in the assay. Ex. 1004, 15; Ex. 1005, ¶¶238-239.

- (c) **Step 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 oligonucleotides comprise at least two identification elements derived from the at least two nucleic acid moieties;”**

Baez in view of Landegren discloses this step. Ex. 1005, ¶¶241-245. PO contends that an “immunocomplex with ligator” is a CRC that comprises the interactors. Ex. 1008, 2. Specifically, PO contends a CRC is “(two matched antibodies conjugated with at least one nucleic acid moiety, shown in blue and green in the figure [below]) bound in proximity to one another by an associated oligonucleotide formed from the association between the at least two nucleic acid moieties and the ligator sequence[.]” *Id.*



Id. Thus, CRCs include Baez’s and Landegren’s reporter strands of antibody conjugates hybridized to a linker after the conjugates are bound to an analyte or target (i.e., the ASA). Ex. 1005, ¶242.

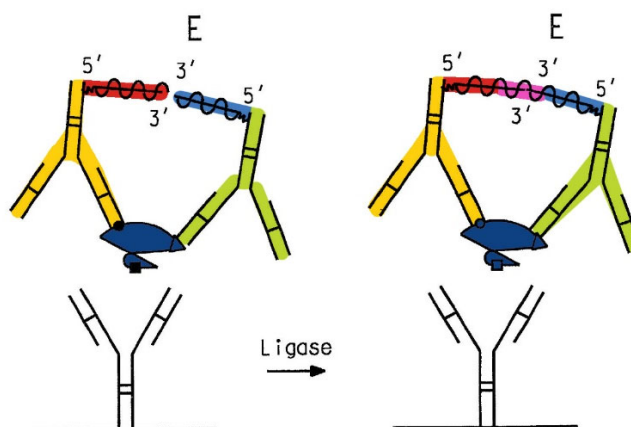


Ex. 1003, Fig 2 (partial and color added). Ex. 1004, Fig 1 (partial and color added).

Baez teaches the formation of an “analyte-specific amplicon” (ASA) that refers to the joining of the nucleic acid labels from the two reporter conjugates in the presence of a ligation linker once the labels are brought into proximity to each other. Ex. 1003, 9:26-30, 10:17-19; Ex. 1005, ¶243. As shown regarding step (b), the nucleic acid labels from the reporter conjugates each include an identification element. Ex. 1005, ¶244; *see* Section V.B.5(b).

(d) Step c: “subjecting the plurality of cis-reactive cells to conditions which stimulate desired functional interaction having a detectable trace;”

Baez in view of Landegren discloses this step. Ex. 1005, ¶¶246-249. PO contends that “ligation” of the reporter conjugates “produces a ligated nucleic acid [that i]s a detectable trace.” Ex. 1008, 4. Thus, the detectable trace includes Baez’s nucleic acid sequence generated after the ligation of nucleic acid labels coupled to the antibodies. Ex. 1005, ¶247.



Ex. 1003, Fig 2 (partial and color added).

Ex. 1008, 4.

In Baez, in the ligation format, once the ligation linker is bonded to the nucleic acid labels, the labels and linker are ligated together using DNA ligase (the desired functional interaction). Ex. 1005, ¶¶247-248; Ex. 1003, 10:19-26, 14:41-46.

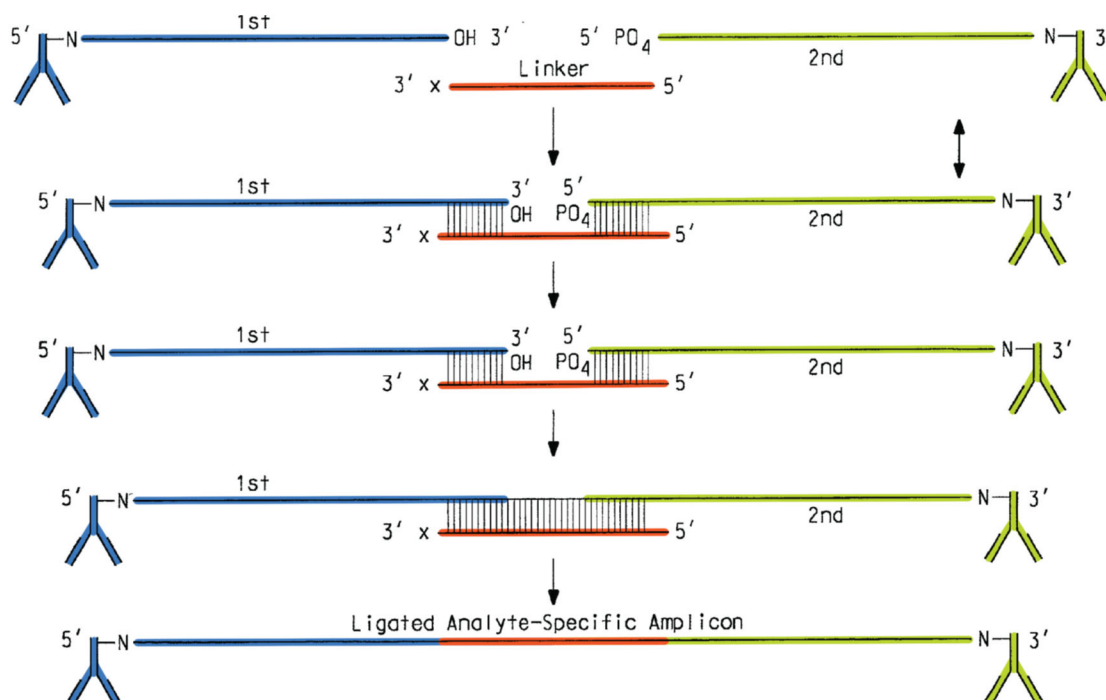


FIG. 4

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Ex. 1003, Fig. 4 (annotated and color added); Ex. 1005, ¶248. The newly created sequence within the ligated ASA can be detected through either the double-stranded DNA or through the linker oligonucleotide itself—the detectable trace. Ex. 1003, 17:49-58; Ex. 1005, ¶¶247-248.

(e) Step d: “selecting all cis-reactive cells exhibiting the detectable trace; and”

Baez in view of Landegren discloses this step. Ex. 1005, ¶¶250-253. PO contends that “selecting” the CRCs with a detectable trace includes a biotin-streptavidin additional wash (after ligation) and elution of paired antibodies. Ex. 1008, 5. Thus, selecting the CRCs includes Baez’s isolating CRCs (ASAs in Baez) comprising a biotin label using immobilized streptavidin. Ex. 1005, ¶251.

Baez discloses that the ASAs can be selected using affinity purification. This involves detecting the ASA “through the linker oligonucleotide itself.” Ex. 1003, 17:52-53. In one example, the linker oligonucleotide is “engineered to contain a label such as biotin[.]” *Id.*, 17:53-54. Once the linker is bound in the ASA, the incorporation of biotinylated bases provides means of isolating the ASA from the solution onto an immobilized streptavidin. *E.g.*, Ex. 1003, 17:25-28.

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—the detectable trace—because only those ASAs would have the affinity for the immobilized streptavidin. Ex. 1005, ¶252.

- (f) Step 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.”**

Baez in view of Landegren discloses this step. Ex. 1005, ¶¶254-258. PO contends that detecting the identification sequence elements includes “quantification by qPCR” of the final eluate. Ex. 1008, 5. Thus, detecting the identification sequence elements includes amplifying the ASA with PCR and subsequent detection as taught in Baez. Ex. 1005, ¶255.

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[.]” Ex. 1003, 5:26-29, 5:38-42, Fig. 5. 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. Ex. 1005, ¶256. Further, it would have been obvious to perform the PCR amplification after the selection of the ASA using the biotin linker. Ex. 1005, ¶257.

Accordingly, under PO’s position as detailed above, Baez in view of Landegren discloses Claim 1. Ex. 1005, ¶259.

6. Dependent Claim 2

Claim 2 depends from claim 1 and adds: “wherein selecting all cis-reactive cells exhibiting the detectable trace is accomplished via selective separation or selective

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detection of the cis-reactive cells.” Baez in view of Landegren discloses this limitation. Ex. 1005, ¶¶260-264. During prosecution, PO stated that “[b]oth selective separation and selective detection are techniques well known in the art[,]” (Ex. 1002, 505), and, thus, “admit[ed] that such things would be known to a POSA.” *McCoy*, 850 Fed. App’x at 789; *see Qualcomm*, 24 F.4th at 1376. In addition to a POSA knowing these techniques, Baez discloses selective detection. Ex. 1005, ¶262. PO contends that the “selective detection” of the CRCs is the biotin-streptavidin wash and elution. Ex. 1008, 6. Thus, the selective detection includes using affinity interactions between the CRCs (ASAs) and a solid support structure as taught in Baez. Ex. 1005, ¶¶262-263.

Baez discloses that the ASAs can be selectively detected using a linker oligonucleotide “engineered to contain a label such as biotin[.]” *Id.*, 17:53-54. Once the linker is bound in the ASA, the incorporation of the biotin label provides means of isolating the ASA from the solution onto an immobilized streptavidin or avidin. *E.g.*, Ex. 1003, 17:25-28. A POSA would have understood that the use of the biotin-streptavidin wash would allow selective detection of only the ASAs that have been ligated together because only those ASAs would have the affinity for the immobilized streptavidin. Ex. 1005, ¶¶262-263.

7. Dependent Claim 3

Claim 3 depends from claim 2 and adds: “wherein selecting all cis-reactive cells exhibiting the detectable trace is accomplished by affinity purification.” Baez in view of Landegren discloses this limitation. Ex. 1005, ¶265. PO contends that “[the] wash and elution steps [of reporter molecules] are selection steps that constitute affinity purification.” Ex. 1008, 6. Thus, affinity purification includes Baez’s isolation of the ASA in the solution using an immobilized streptavidin or avidin. Ex. 1003, 17:25-28; Ex. 1005, ¶265.

8. Dependent Claim 4

Claim 4 depends from claim 1 and adds: “further comprising enhancing the selected associated oligonucleotides by PCR amplification.” Baez in view of Landegren discloses this limitation. Ex. 1005, ¶¶266-269. PO contends that “detection of the selected associated oligonucleotides (i.e., the reporter molecules) is enhanced by PCR amplification.” Ex. 1008, 7. Thus, detecting the functional interactions and enhancing the selected associated oligonucleotides by PCR amplification includes PCR amplification of the ASA product as taught in Baez. Ex. 1005, ¶267.

Baez teaches that the nucleic acid sequence of the ASA product can be amplified using PCR. Ex. 1003, 8:17-24, 22:41-42; Fig. 5. As shown in Figure 5 below, the two nucleic acid labels are ligated together and amplified using PCR,

enhancing the ligated nucleic acid sequence. Ex. 1003, Fig. 5 (below) (color added); Ex. 1005, ¶268.

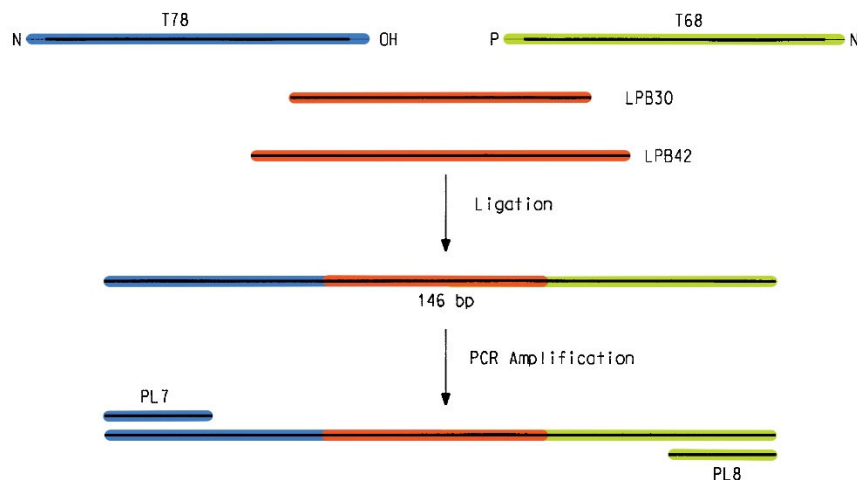


FIG. 5

9. Dependent Claims 5 and 6

Claim 5 depends from claim 1 and adds: “wherein coupling is covalent or noncovalent.” Claim 6 depends from claim 1 and adds: “wherein coupling is covalent.” Baez in view of Landegren discloses these limitations. Ex. 1005, ¶¶270-274. PO contends that the “coupling of the molecule of interest (antibody) with [a] nucleic acid moiety (oligonucleotide) is covalent.” Ex. 1008, 7. Baez discloses that the “DNA labels” “were covalently attached to their respective antibodies through 5’ terminal amine groups,” and thus, this limitation includes a covalent bond between the antibody and oligonucleotide as taught in Baez. Ex. 1003, 26:57-59; Ex. 1005, ¶¶271-272, 274.

10. Dependent Claims 7 and 8

Claim 7 depends from claim 1 and adds: “wherein at least one molecule of interest comprises a protein, a protein domain, a peptide, a peptoid, a non-proteinaceous cellular product, a virus particle, a cell metabolite, a lipid, a carbohydrate, a nucleic acid, an inorganic compound, a reactive compound, or any combination thereof, however, wherein not all molecules of interest are nucleic acids.”

Claim 8 depends from claim 7 and adds: “wherein at least one molecule of interest comprises at least one protein.” Baez in view of Landegren discloses these limitations.

Ex. 1005, ¶¶275-279. PO contends that these limitations are met when “at least one molecule of interest (e.g. capture antibody or detection antibody) is a protein.” Ex. 1008, 8. Baez and Landegren teach that the conjugates can be antibodies, and thus at least two MOIs include the antibodies taught in Baez and Landegren. Ex. 1003, 7:54-57; Ex. 1004, 14; Ex. 1005, ¶¶277-279.

11. Dependent Claim 11

Claim 11 depends from claim 1 and adds: “wherein detecting further comprises quantifying the functional interactions.” Baez in view of Landegren discloses this limitation. Ex. 1005, ¶¶280-283. PO contends that quantifying the functional interactions is satisfied by “Quantify by PCR” of the ligation product. Ex. 1008, 9. Thus, quantifying the functional interaction includes quantifying the ASA product as taught in Baez. Ex. 1005, ¶281.

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Baez discloses that its assay “provides means for both qualitative and quantitative analyte detection.” Ex. 1003, 12:2-3. Baez further discloses that “[d]uring the assay, both the type of analyte-specific amplicon formed and the amount of the nucleic acid amplification product produced are characteristic of the analyte and proportional to the amount of analyte present[,]” allowing the analytes to be “detected and quantified.” *Id.*, 12:49-53; *see also id.*, 7:41-43, 11:60-12:3, 13:13-17. It would have been within the knowledge and experience of a POSA to use the well-known method of quantitative PCR for quantification of the ASA product in Baez. Ex. 1005, ¶282; Ex. 1027.

12. Dependent Claim 12

Claim 12 depends from claim 1 and adds: “wherein the analysis comprises high throughput screening.” Baez in view of Landegren discloses this limitation. Ex. 1005, ¶¶284-288. PO contends that “fully automated, high-throughput” screening of the ligation product satisfies this limitation. Ex. 1008, 9. Thus, this limitation includes the high throughput screening of the ASA product as taught in Landegren. Ex. 1005, ¶285.

Landegren teaches that the ligation product (i.e., ASA) and its identification tags “may be detected by any of several methods, such as DNA microarrays, mass spectrometry, gel electrophoresis (different lengths of products), or other.” Ex. 1004, 15. A POSA would have understood that the “DNA microarray” method of detection

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allows for high throughput screening because it allows for analysis of a large number of samples in a short period. Ex. 1005, ¶286; Ex. 1001, 47-49. Further, it would have been obvious to combine the high throughput screening of the ligation product taught in Landegren with the analysis of the ASA product in Baez because high throughput screening allows for quicker assay results. Ex. 1005, ¶287.

13. Dependent Claims 14 and 15

Claim 14 depends from claim 1 and adds: “wherein the analysis comprises nucleic acid sequencing.” Claim 15 depends from claim 14 and adds: “wherein the analysis comprises sequencing by synthesis.” Baez in view of Landegren discloses these limitations. Ex. 1005, ¶¶289-296. PO contends that sequencing of the ligation product satisfies this limitation. Ex. 1008, 9. Thus, this limitation includes the sequencing of the identifiers as taught in Freskgard. Ex. 1005, ¶¶290-292.

Freskgard discloses that the identifier (i.e., the nucleic acid tag) is identified by sequencing. Ex. 1009, 2. Freskgard also discloses that the identifier (i.e., the nucleic acid tag) is identified by sequencing by synthesis. *Id.*, 69-70. In one example, “[a] sample of each PCR product was then treated with Exonuclease I (USB) and Shrimp Alkaline Phosphatase (USB) to remove degrade[d] single stranded DNA and dNTPs and sequenced using the DYEnamic ET cycle sequencing kit (Amersham Biosciences) according to the manufacturer’s instructions and the reactions were analyzed on a MegaBace 4000 capillary sequencer (Amersham Biosciences).” *Id.* A

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POSA would have understood Freskgard as disclosing Sanger sequencing, which is a form of sequencing by synthesis well known in the art to POSAs. Ex 1005, ¶¶292; Ex. 1029. Further, it would have been obvious to include the “sequencing” of Freskgard to the analysis of the ligation product (i.e., ASA) and its identification tags, as taught in Landegren and Baez because sequencing is a well-known method to determine the nucleic acid labels. Ex. 1005, ¶¶293-294; Ex. 1004, 15; Ex. 1003, 5:38-42, Figs. 5-7.

VI. There Are No Discretionary Factors That Counsel In Favor Of Denial

The Board should not exercise its discretion under either §§ 314(a) or 325(d) to deny this Petition.

A. The *Fintiv* Factors Favor Institution

The Board should institute as “there is a reasonable likelihood” that at least one claim is unpatentable. 35 U.S.C. § 314(a). PO’s litigation against Petitioner on the ’848 patent does not counsel otherwise, as there is no scheduling order and no set trial date. The latest Judicial Caseload Statistics report a median time of 38.0 months to trial in the District of Delaware⁴, which projects trial in January 2027. The district court case is in its early stages—fact discovery has not begun; infringement and invalidity contentions have not been served; and claim construction has not commenced. Petitioner moved to dismiss the complaint on April 1, 2024. As of the

⁴ Ex. 1039.

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filing of this Petition, Petitioner's motion to dismiss is pending. Even at the time of expected institution, the district court case will be in its infancy. Because of the strong unpatentability showing made herein, and because the district court litigation is still in its early stages and will reach trial long after any Final Written Decision here, the Board should institute IPR.

B. The *Becton* Factors Favor Institution

The Board should not exercise its discretion under § 325(d) to deny this Petition because the Patent Office never considered Neri, Kanan's Supplementary Information, or the specific prior art combinations or arguments set forth herein. Further, the Examiner did not have the benefit of PO's position detailing how the patent's claims cover the steps of PLA.

Grounds 1 and 2 rely on Neri—a reference the Examiner never considered during prosecution. And, Neri is not cumulative to Goulaev, Franch, or Liu—the references the Examiner substantively considered—because Neri teaches crucial steps each of these references is missing.

Goulaev and Franch. The Examiner's December 30, 2009 Office Action found that Goulaev and Franch “teach the aspects of steps a-c of claim 20 [now claim 1] except for the limitation that the desired interaction produces a detectable trace[.]” Ex. 1002, 316. Even if the Examiner was correct that Goulaev and Franch “teach steps a-c,” neither reference teaches a POSA how to select CRCs exhibiting a

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detectable trace or detect the identification sequences of both members involved in the interaction—steps d and e of claim 1. Ex. 1005, ¶¶191-197, 199-200, 202. Kanan with Neri, however, teaches steps a-c *and d-e*, as Kanan teaches the detectable trace and Neri teaches detection of the identification sequences coupled to the molecules involved in the interaction through separate, unique sequence codes. Ex. 1005, ¶¶74-76, 194. And Neri provides advantages to Kanan not found in either Goulaev or Franch, such as a way to (i) allow combinatorial interactions with Neri’s self-assembly sequence as opposed to synthesizing oligonucleotides for each specific interaction, significantly reducing the time required to synthesize interactors and preventing mis-hybridizations between Kanan’s substrates, and (ii) identify both members in an interaction as opposed to relying on correct hybridization of a pool A member to its designed pool B member, providing more accurate assay results. Ex. 1005, ¶¶198, 201.

Liu. In the Notice of Allowance, the Examiner found Liu does not teach a key claim limitation—“associated oligonucleotides.” Ex. 1002, 522-525. Neri cannot be cumulative to Liu because Neri specifically teaches associated oligonucleotides with its disclosure of its self-assembly sequence. Ex. 1005, ¶202.

And, while the application discusses Kanan, Kanan did not form the basis of any rejection nor was it mentioned in any Office Action and the Examiner was unaware of Kanan’s Supplementary Information. Kanan’s Supplementary

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Information details the tedious process to create the library of Kanan, which Neri's self-assembly sequences solve. Ex. 1005, ¶¶99-106.

Further, no overlap exists with the arguments made during prosecution and Grounds 1 and 2 because the Examiner made no argument that the prior art met all the steps of the pending functional interaction claims. In addition, the considered prior art lacked self-assembly sequences that form associated oligonucleotides to bring molecules into proximity to detect functional interactions and lacked unique sequence codes to detect the two identification sequence elements. Ex. 1005, ¶¶191-202.

The Examiner erred in a manner material to patentability because, unlike the Petition, the Examiner failed to locate and apply prior art that teaches all claimed limitations. The Examiner also erred in overlooking the disclosure of Kanan in allowing the claims as Kanan teaches a detectable trace—a limitation not found in the references the Examiner substantively considered. Ex. 1005, ¶194. Additionally, had the Examiner not erred, a review of Kanan and its Supplementary Information—which was not considered—would have demonstrated the shortcomings in Kanan that were resolved by Neri. Neri is undoubtedly material to patentability, given it solves the application's criticisms of Kanan and improves the efficiencies of making interactors—and the combination meets all the limitations of at least claim 1. Ex. 1005, ¶¶85-133. The Examiner's error supports that the Board should not deny this

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Petition under § 325(d). *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential).

For Grounds 3 and 4, a related prior publication (U.S. Application No. 02/051986 leading to Baez) was disclosed on the IDS and cited in the specification, but not Baez itself. Ex. 1002, 106. Landegren (Ex. 1004), also disclosed in the specification, was not identified on the IDS, and thus not considered by the Examiner. *See* MPEP § 609.04(a) (Aug. 2005); 37 C.F.R. 1.98(b). Neither Baez nor Landegren, nor any PLA art, were ever applied against the claims or discussed in any Office Action.

Grounds 3-4 do not overlap with arguments made during prosecution because, notwithstanding the application's disclaimers, PO never told the Examiner that it interpreted the claims to cover the fundamental steps of PLA. Applying the claims in a manner that directly contradicts disclaimers in the application is material to the patentability of the issued claims. *See* 37 C.F.R. § 1.56. Thus, the Examiner failed to apply Baez, Landegren, or any PLA art against the pending claims. *See* Section III.A.2(b). The Examiner's failure to apply Baez or Landegren was in error because had the Examiner understood PO's application of the claims to the steps of PLA (Exs. 1007, 1008, 1015), the Examiner would have rejected those claims as obvious based on Baez in view of Landegren as in Grounds 3 and 4.

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Grounds 1-4 do not present a scenario in which “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). Under these circumstances, the Board has consistently declined to invoke § 325(d). *See, e.g., Oticon Medical v. Cochlear*, IPR2019-00975, Paper 15 at 20 (P.T.A.B. Oct. 16, 2019) (precedential); *Intel v. VSLI*, IPR2019-01192, Paper 15 at 10 (P.T.A.B. Jan. 9, 2020) (citing cases).

VII. Mandatory Notices Pursuant To 37 C.F.R. § 42.8(a)(1)

Pursuant to 37 C.F.R. § 42.8(a)(1), the mandatory notices identified in 37 C.F.R. § 42.8(b) are provided below as part of this petition.

A. 37 C.F.R. § 42.8(b)(1): Real Parties-In-Interest

Alamar Biosciences, Inc. is the real party-in-interest for Petitioner.

B. 37 C.F.R. § 42.8(b)(2): Related Matters

The '848 patent is currently the subject of litigation in the pending case in the United States District Court for the District of Delaware captioned *Olink Proteomics AB and Olink Proteomics Inc. v. Alamar Biosciences, Inc.*, C.A. No. 1:23-cv-01303-MN, filed on November 15, 2023.

C. 37 C.F.R. § 42.8(b)(3), (4): Lead And Back-Up Counsel And Service Information

Petitioner provides the following designation of counsel:

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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney accompanies this petition. Please address all correspondence to lead and back-up counsel at the addresses above. Petitioner also consents to electronic service by email at the email addresses listed above.

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VIII. Conclusion

Petitioner therefore requests that the Patent Office order an IPR trial and then proceed to cancel claims 1-20.

Date: August 23, 2024

Respectfully submitted,

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,883,848

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing petition for *Inter Partes* Review of U.S. Patent No. 7,883,848, including all Exhibits, was served on August 23, 2024 via UPS Overnight delivery directed to the following correspondence address of record for the patent:

Porter Wright Morris & Arthur, LLP
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CERTIFICATE OF WORD COUNT UNDER 37 C.F.R. § 42.24(a)

I, the undersigned, do hereby certify that the attached petition contains 13,951 words, as measured by the Word Count function of Microsoft Word 2016. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24(a)(i).

Date: August 23, 2024

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APPENDIX OF EXHIBITS

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

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

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

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

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Exhibit No.	Description
1039	UNITED STATES COURTS, FEDERAL JUDICIAL CASELOAD STATISTICS 2018–2023 (2023)
1040	Declaration of Maria P. Garcia
1041	Declaration of S. Christian Platt