
**ALAMAR BIOSCIENCES, INC.,
Petitioner**

v.

**OLINK PROTEOMICS AB,
Patent Owner**

IPR2024-01353
Patent No. 7,883,848

Patent Owner's Oral Hearing Demonstratives
December 9, 2025



The '848 Patent

The '848 Patent's methods for detecting functional interactions

'848 Patent

(12) United States Patent Ericsson	(10) Patent No.: US 7,883,848 B2 (45) Date of Patent: Feb. 8, 2011
(54) REGULATION ANALYSIS BY CIS REACTIVITY, RACR	Gullberg M, Gustafsdottir SM, Schallmeiner E, Jarvius J, Bjarnegard M, Betsholtz C, Landegren U, Fredriksson S. Cytokine detection by antibody-based proximity ligation. Proc Natl Acad Sci U S A. Jun 1, 2004;101(2):8420-4. Epub May 21, 2004.
(75) Inventor: Olof Ericsson , Uppsala (SE)	Gunderson KL, Steemers FJ, Lee G, Mendoza LG, Chee MS. A genome-wide scalable SNP genotyping assay using microarray technology. Nat Genet. May 2005;375:549-54. Epub Apr. 17, 2005.
(73) Assignee: Olink AB , Uppsala (SE)	Gunderson KL, Kruglyak S, Graige MS, Garcia F, Kermani BG, Zhao C, Che D, Dickinson T, Wickham E, Bierle J, Doucet D, Milewski M, Yang R, Siegmund C, Haas J, Zhou L, Oliphant A, Fan JB, Barnard S, Chee MS. Decoding randomly ordered DNA arrays. Genome Res. May 2004;14(5):870-7. Epub Apr. 12, 2004.
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1029 days.	Hanes J, Pluckthun A. In vitro selection and evolution of functional proteins by using ribosome display. Proc Natl Acad Sci U S A. May 13, 1997;94(10):4937-42.
(21) Appl. No.: 11/483,825	Hardenbol P, Baner J, Jain M, Nilsson M, Namsaraev EA, Karlén-Neumann GA, Fakhrai-Rad H, Ronaghi M, Willis TD, Landegren U, Davis RW. Multiplexed genotyping with sequence-tagged molecular inversion probes. Nat Biotechnol. Jun. 2003;21(6):673-8. Epub May 5, 2003.
(22) Filed: Jul. 10, 2006	Hatch A, Sano T, Misasi J, Smith CL. Rolling circle amplification of DNA immobilized on solid surfaces and its application to multiplex mutation detection. Genet Anal. Apr. 1999;15(2):35-40.
(65) Prior Publication Data US 2007/0020669 A1 Jan. 25, 2007	Kanan MW, Rozenman MM, Sakurai K, Snyder TM, Liu DR. Reaction frequency enabled by DNA template synthesis and in vitro
Related U.S. Application Data	
(60) Provisional application No. 60/697,415, filed on Jul. 8, 2005.	

EX1001, face

The invention relates to methods for detecting affinity-based interactions and functional-based interactions, and the relative strengths of those interactions between molecules of interest. Libraries of interactors are constructed wherein the interactors comprise at least one molecule of interest coupled to at least one unique nucleic acid moiety. The inventive methods allow detection, interactor identification, and determination of relative strengths of all interactions possible within a library of interactors. Kits enabling rapid and efficient application of the inventive methods are also provided.

EX1001, 1:11-20; Pet, 3

tions, e.g., enzymes-substrate pairs. Significantly, the invention allows investigation of all possible interactions within or between libraries of molecules, such as proteins, and also permits relative quantification of the detected interactions.

EX1001, 5:25-28; POR, 5



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The '848 patent discloses methods of detecting affinity interactions and methods of detecting functional interactions

'848 Patent

Interaction Analysis

15 The present invention provides methods which permit analysis of the interactor library with respect to interactions between the interactor members, and, therefore, by inference, between the MOIs. One embodiment provides analysis based primarily on affinity interactions between the MOIs. Another
20 embodiment provides analysis based primarily on functionally-based interaction between MOIs. Affinity interactions are interactions where two or more members of the library display a binding affinity towards each other. Functional interactions are interactions where two or more members
25 affect each other in some detectable way and may include affinity interactions, though a person of ordinary skill in the art will appreciate that there are functional interactions which display very low or transient affinity.

EX1001, 14:13-27



The '848 Patent claims a method of detecting functional interactions

'848 Patent

1. A method of detecting functional interactions between at least two molecules of interest, the method comprising:
 - a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;
 - b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two nucleic acid moieties, wherein the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;
 - c. subjecting the plurality of cis-reactive cells to conditions which stimulate a desired functional interaction having a detectable trace;
 - d. selecting all cis-reactive cells exhibiting the detectable trace; and
 - e. subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis that permits detection of the at least two identification sequence elements.

EX1001, claim 1; POR, 6-7

POR, 5-6; EX2008, ¶¶30-35



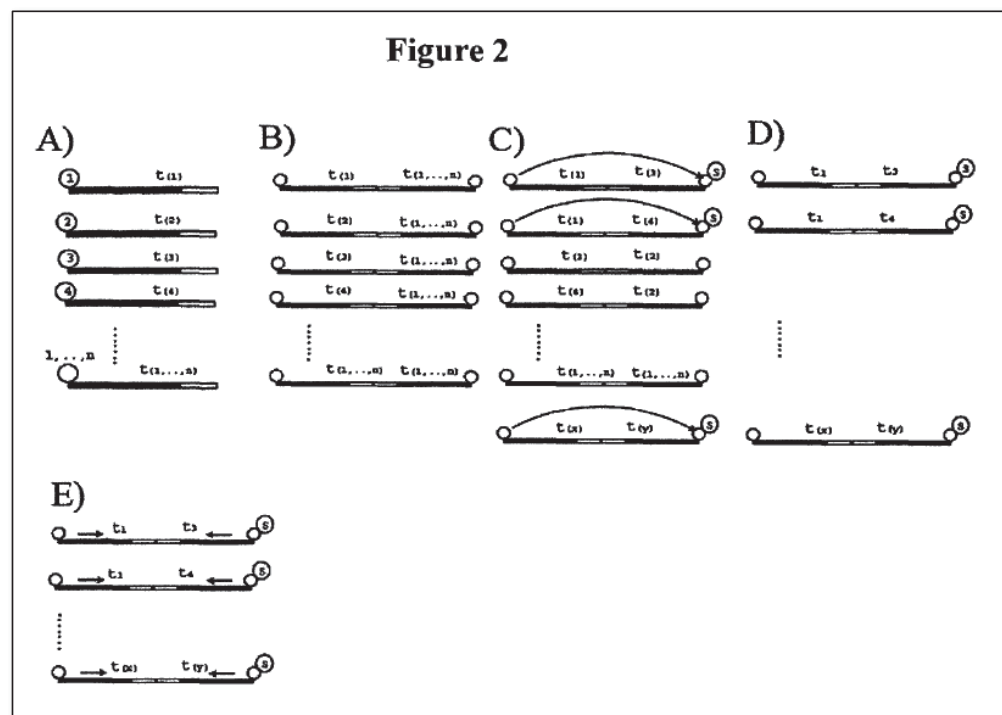
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The '848 Patent claims a method of detecting functional interactions

'848 Patent

1. A method of detecting functional interactions between at least two molecules of interest, the method comprising:
 - a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;
 - b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two nucleic acid moieties, wherein the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;
 - c. subjecting the plurality of cis-reactive cells to conditions which stimulate a desired functional interaction having a detectable trace;
 - d. selecting all cis-reactive cells exhibiting the detectable trace; and
 - e. subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis that permits detection of the at least two identification sequence elements.

EX1001, claim 1; POR, 6-7



EX1001, Fig. 2; Pet., 6; PO Sur-Reply, 8



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The Petition's Asserted Grounds

Ground	35 U.S.C.	Claims	References
1	§ 103	1-15, 17-20	Kanan and Neri
2	§ 103	16	Kanan, Neri, and Famulok
3	§ 103	1-8, 11-12	Baez and Landegren
4	§ 103	14, 15	Baez, Landegren, Freskgard

Pet, 2-3

Petitioner cannot prevail on Grounds 1-4

- **Ground 1 (Kanan and Neri)**
 - Petition fails to show Kanan and Neri teach claim 1(d)'s selecting step
 - Petition fails to show Kanan and Neri teach claim 1(e)'s analysis step
 - Petition fails to show motivation to combine with a reasonable expectation of success
- **Ground 2 (Kanan, Neri, and Famulok)**
 - Fails for same reasons in Ground 1
 - Petition fails to show that Kanan, Neri, and Famulok teach claim 16's association via ligation
 - Petition fails to show motivation to combine with a reasonable expectation of success
- **Ground 3 (Baez and Landegren)**
 - Petition fails to show Baez and Landegren teach claim 1(a)'s forming interactors step
 - Petition fails to show Baez and Landegren teach claim 1(d)'s selecting step
 - Petition fails to show Baez and Landegren teach claim 1(e)'s analysis step
 - Petition fails to show motivation to combine with a reasonable expectation of success
- **Ground 4 (Baez, Landegren, and Freskgard)**
 - Fails for same reasons in Ground 3



GROUND 1:
The Petition fails to demonstrate that Kanan and Neri teach or suggest selecting all cis-reactive cells exhibiting the detectable trace (claim 1(d))



Claim 1(d) requires selecting all cis-reactive cells exhibiting the detectable trace

'848 Patent

The invention claimed is:

1. A method of detecting functional interactions between at least two molecules of interest, the method comprising:
 - a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;
 - b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two nucleic acid moieties, wherein the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;
 - c. subjecting the plurality of cis-reactive cells to conditions which stimulate a desired functional interaction having a detectable trace;
 - d. selecting all cis-reactive cells exhibiting the detectable trace; and
 - e. subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis that permits detection of the at least two identification sequence elements.

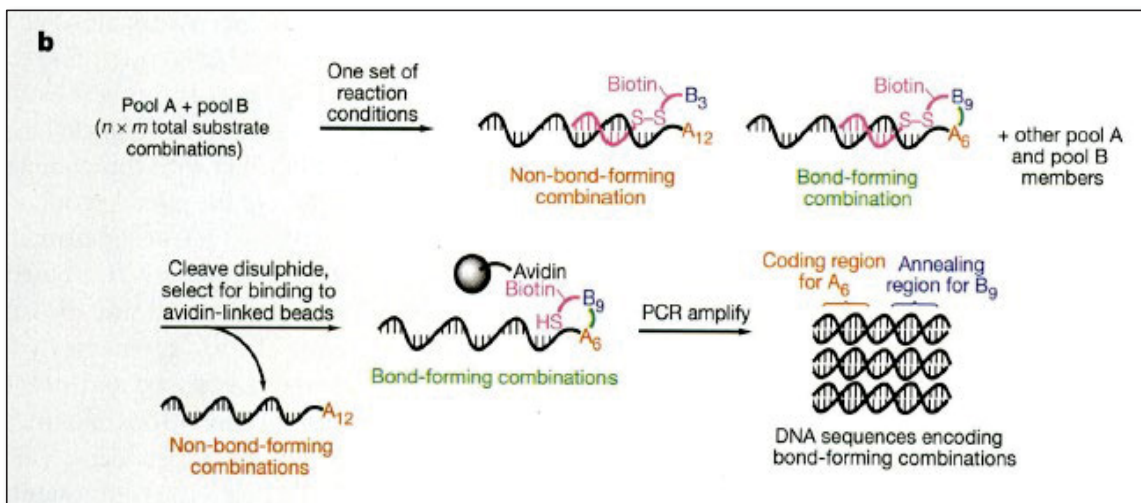
EX1001, claim 1



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Kanan's method utilizes biotin-streptavidin affinity selection

Kanan



Ex. 1010, Fig. 1b; POR, 13, 24, 27

The separation of reactive pairs of substrates is based on selection concepts used in the directed evolution of catalytic RNA and DNA^{12,13} (Fig. 1b). We covalently linked each pool B substrate to its corresponding oligonucleotide by a linker containing a biotin group and a disulphide bond (Fig. 1b and Supplementary Information). After incubation under a set of chosen reaction conditions, followed by cleavage of the disulphide bonds, only pool A sequences remain covalently linked to biotin. Streptavidin affinity selection of the resulting solution separates biotinylated from non-biotinylated sequences. In contrast to many existing reaction discovery screens^{1,5}

Ex. 1010, 545; POR, 24

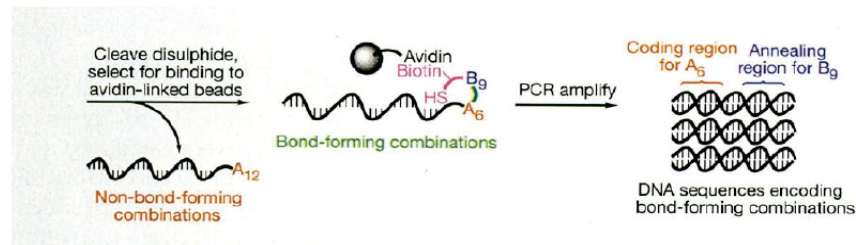


The Petition explicitly relies on Kanan's streptavidin affinity selection as teaching claim 1(d)'s selecting step

Petition

(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.

Pet, 34-35



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There is no dispute that a “cis-reactive cell” (CRC) of the '848 patent requires at least two “interactors”

'848 Patent, claim 1

b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two nucleic acid moieties, wherein the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;

EX1001, claim 1; POR, 21

'848 Patent

As used herein, the term “interactor” refers to at least one MOI coupled with at least one NAM.

As used herein, the term “Cis Reactive Cell” (CRC) refers to an association of at least two interactor moieties, joined by an associated oligonucleotide. In a specific embodiment a CRC comprises two interactors.

EX1001, 9:35-37; POR, 21

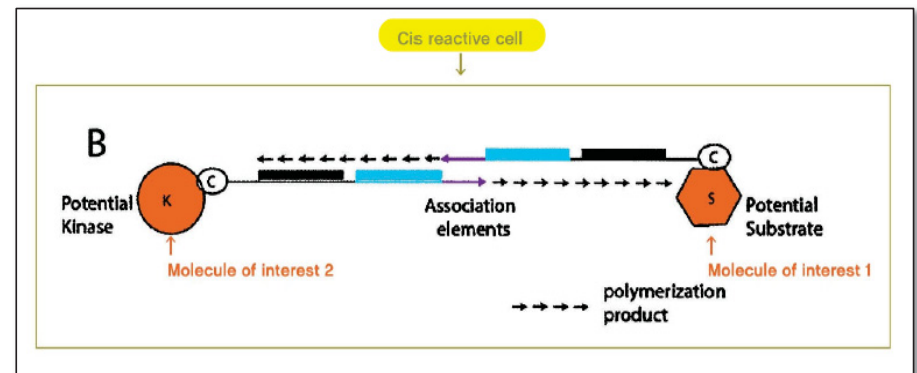
Dr. Nelson

Q: Do [you] agree that a cis-reactive cell of the '848 patent requires at least two interactors [bound] in proximity to one another by an associated oligonucleotide?

A: “In the context of the '848 patent, that is my understanding, that is correct.”

EX2009, 39:8-13; POR, 21

Dr. Nelson



EX1005, ¶49; POR, 21



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There is no dispute that an “interactor” of the ’848 patent requires a “molecule of interest” (MOI) coupled with a “nucleic acid moiety” (NAM)

’848 Patent, claim 1

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;

EX1001, claim 1; POR, 21

’848 Patent

As used herein, the term “interactor” refers to at least one MOI coupled with at least one NAM.

EX1001, 9:33-34; POR, 21

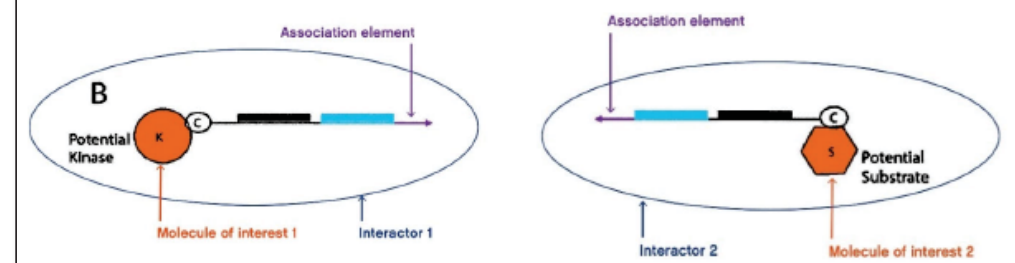
Dr. Nelson

44. 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).” Ex. 1001, 10:45-48.

EX1005, ¶144; POR, 22

Petition

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



Pet, 5



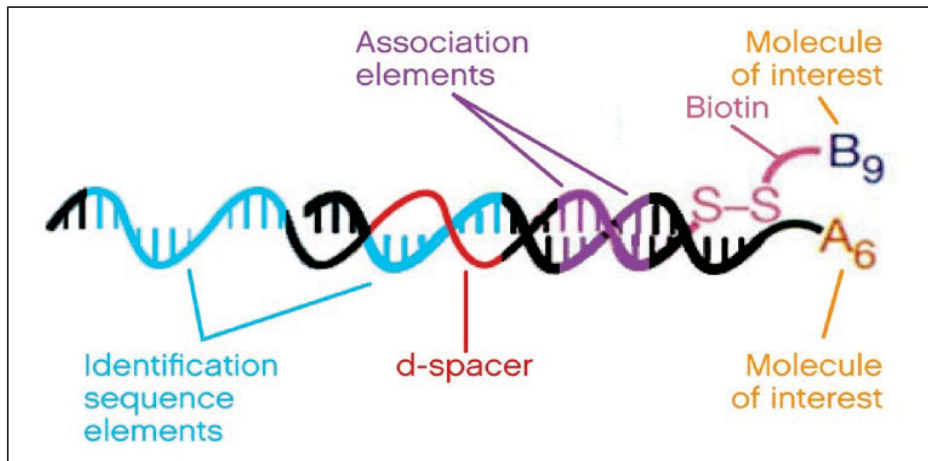
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Petitioner's proposed modified "cis-reactive cells" include Kanan's disulfide (S-S) bond

Petition

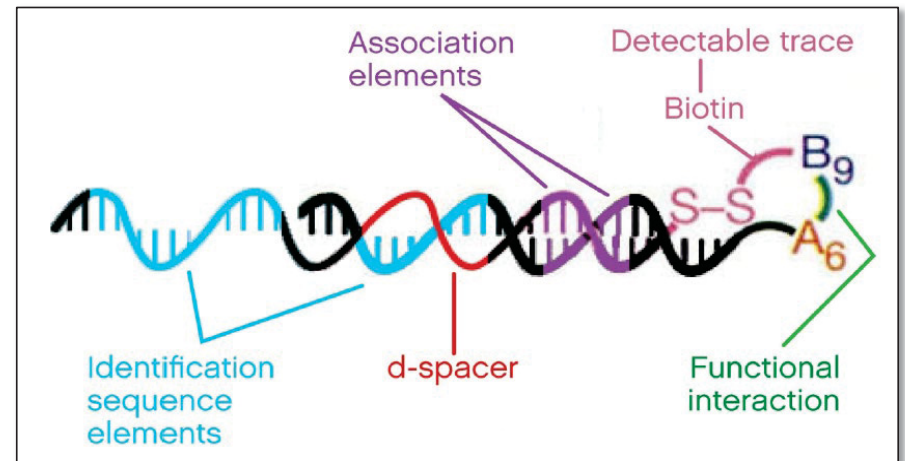
Neri. Ex. 1005, ¶¶114-115. This forms a cis-reactive cell, as shown below. And because Kanan with Neri allows for all library members to interact from two sub-



Pet, 32-33

Petition

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.



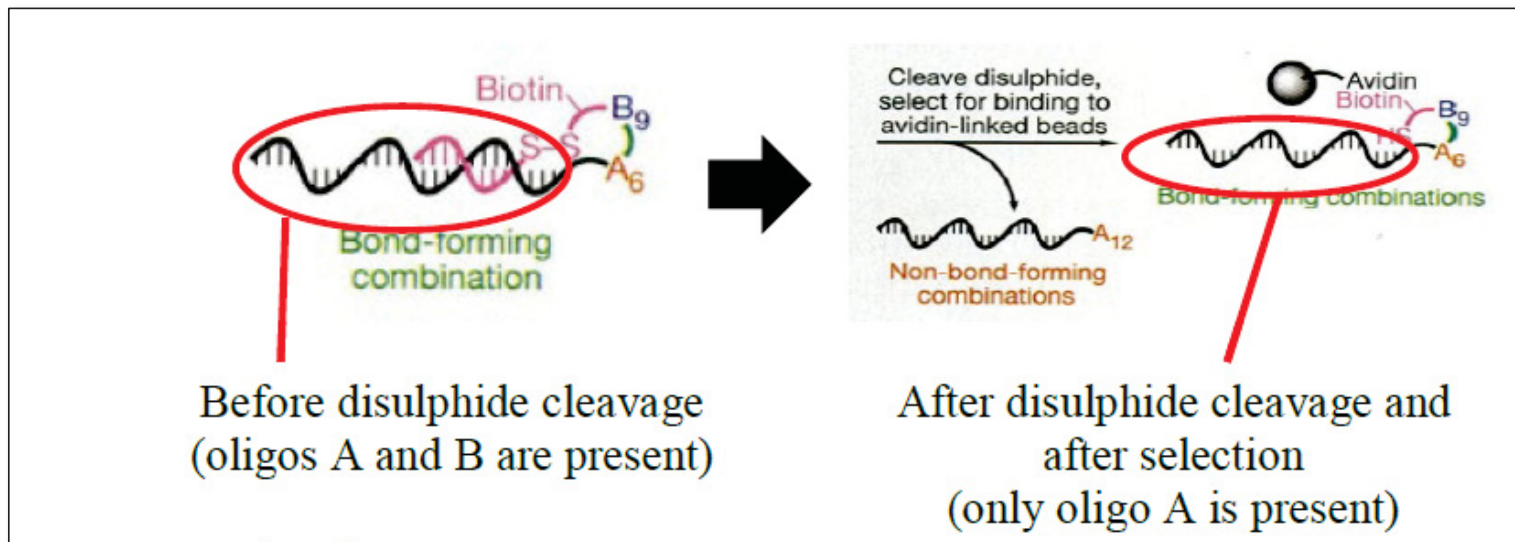
Pet, 33-34



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Kanan teaches disulfide cleavage to cleave and remove the pool B oligonucleotides

Dr. Pentelute



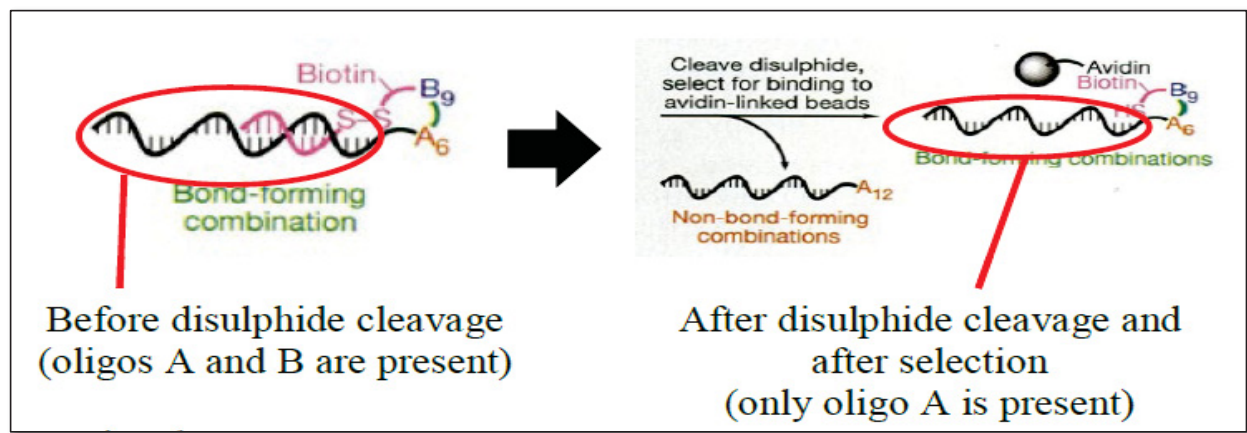
EX2008, ¶117; POR, 26-27



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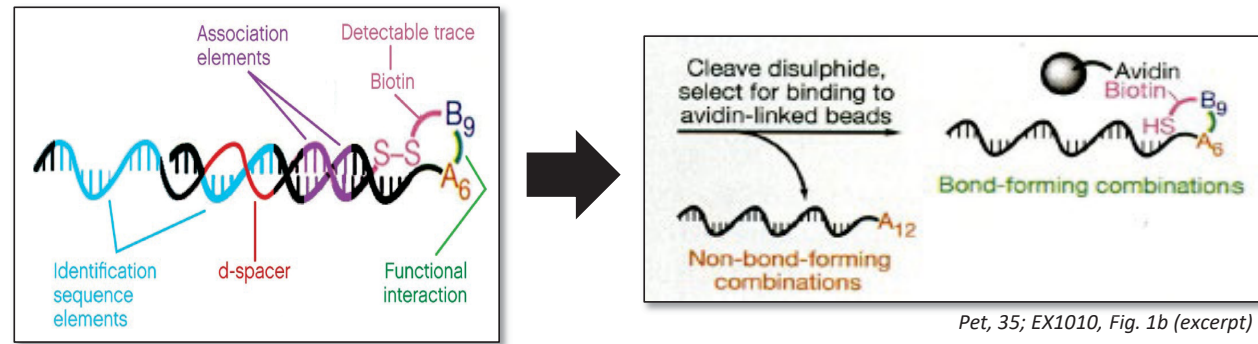
Petitioner's modified method fails to teach or suggest selecting all cis-reactive cells exhibiting the detectable trace because the complexes "selected" in Kanan's method are not CRCs

Kanan
(annotated by
Dr. Pentelute)



EX2008, ¶117; POR, 26-27

Petition



Pet, 35; EX1010, Fig. 1b (excerpt)

**GROUND 1:
Petitioner's Reply introduces a new theory for
claim 1(d)'s selecting step**



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Petitioner's new theory: "selecting' can be a process"

Reply

PO ignores that "selecting" can be a process, consistent with the dependent claims and the specification's disclosure of "selecting" procedures. *Id.*, 19:1-20:46. PO's view

Reply, 5

Dr. Nelson (reply declaration)

"Selections for Bond-Formation," *see* Ex. 1013, 8. This confirms that Kanan's selection is a process that begins prior to the cleavage of the disulfide bond of the pool B oligonucleotides. Ex. 1013, 7-8.

EX1051, ¶124; *PO Sur-Reply*, 5



Petitioner's new theory: Kanan's selection begins prior to S-S cleavage

Dr. Nelson (1st declaration)

A POSA would have understood that the use of the biotin-streptavidin capture would allow selection of only the CRCs with bond-forming combinations, i.e., demonstrate the detectable trace, because only those combinations would have the linked biotin with affinity for streptavidin-linked magnetic particles, as shown above in Fig. 1.b. Therefore, in my opinion, Kanan discloses selecting all cis-reactive cells exhibiting the detectable trace.

EX1005, ¶124

Dr. Nelson (reply declaration)

This confirms that Kanan's selection is a process that begins prior to the cleavage of the disulfide bond of the pool B oligonucleotides. Ex. 1013, 7-8.

EX1051, ¶124



Petitioner's new construction of "selecting" ignores the express language of the claims

'848 Patent

The invention claimed is:

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

- a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;
- b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two nucleic acid moieties, wherein the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;
- c. subjecting the plurality of cis-reactive cells to conditions which stimulate a desired functional interaction having a detectable trace;
- d. selecting all cis-reactive cells exhibiting the detectable trace; and
- e. subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis that permits detection of the at least two identification sequence elements.

EX1001, claim 1; PO Sur-Reply 8

2. The method of detecting functional interactions between at least two molecules of interest as recited in claim 1, wherein selecting all cis-reactive cells exhibiting the detectable trace is accomplished via selective separation or selective detection of the cis-reactive cells.

EX1001, claim 2; PO Sur-Reply 8

3. The method of detecting functional interactions between at least two molecules of interest as recited in claim 2, wherein selecting all cis-reactive cells exhibiting the detectable trace is accomplished by affinity purification.

EX1001, claim 3; PO Sur-Reply 8

19. The method of detecting functional interactions between at least two molecules of interest as recited in claim 2, wherein the selective detection comprises labeling the cis-reactive cells with an affinity reagent.

EX1001, claim 19 (as corrected in Certificate of Correction); PO Sur-Reply 8



The specification describes selecting CRCs consistent with the claim language

'848 Patent

To detect functional interactions in a pool of CRCs the CRCs which display functional interactions must be selected for detection and/or analysis. It will be appreciated by one of ordinary skill in the art that this step will be modified according to the nature of the functional interaction that is being investigated. As used herein, a “filter” or a “filtering process” is the means employed to selectively separate the desired CRCs. Nonlimiting examples of filters for functional interac-

EX1001, 19:41-48; PO Sur-Reply, 8

'848 Patent

Following functional activation the secondary library is filtered for CRCs which contain MOIs that have been altered by the activation. Selection of positive (that is, altered) CRCs can be done by, e.g., affinity purification of the library of CRCs with respect to a modification introduced by an enzymatic reaction. The CRCs are then identified by the sequence

EX1001, 6:41-46; PO Sur-Reply, 8



The '848 patent file history is consistent with the claim language

'848 Patent original claims

1. A method of detecting affinity interactions between at least two molecules of interest, the method comprising:
 - a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety comprising an identification sequence element and at an association element;
 - b. promoting an association between at least two nucleic acid moieties from different interactors to form a plurality of unique associated oligonucleotides, wherein each nucleic acid moiety may form more than one unique associated oligonucleotide, and wherein each unique associated oligonucleotide comprises at least two identification sequence elements derived from the at least two nucleic acid moieties;
 - c. selecting the plurality of unique associated oligonucleotides; and
 - d. subjecting the selected associated oligonucleotides to an analysis that permits detection of the at least two identification sequence elements.

EX1002, 64; PO Sur-Reply, 9

20. A method of detecting functional interactions between at least two molecules of interest, the method comprising:
 - a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;
 - b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two nucleic acid moieties, wherein the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;
 - c. subjecting the plurality of cis-reactive cells to conditions which stimulate a desired functional interaction having a detectable trace;
 - d. selecting all cis-reactive cells exhibiting the detectable trace;
 - e. subjecting the associated oligonucleotides from the cis-reactive cells selected in (d) to an analysis that permits detection of the at least two identification sequence elements.

EX1002, 68; PO Sur-Reply, 9



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Petitioner mischaracterizes the '848 patent to fit its new construction

Reply

encompassed within the plain and ordinary meaning of the claim terms. For example, the specification describes various ways of “selecting,” such as selective amplification with PCR and oligonucleotide tag array paired with labelled affinity reagents (*e.g.*, Ex.1001, 19:7-9, 20:31-39, 30:56-67), which PO’s construction improperly excludes.

Reply, 2

'848 patent

Filtering and Selection

Affinity Interactions

The selection in the affinity embodiment of the inventive methods primarily concerns elimination of interactors which are not associated with any other interactors and maintaining the associated interactors. This can be achieved in several ways. One way is to perform selective amplification of associated NAMs, for example, with PCR, wherein there is one primer on each NAM so that only joined NAMs will produce amplification products. This approach might necessitate two

EX1001, 19:1-11; PO Sur-Reply, 8-9

PO Sur-Reply, 9



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Petitioner mischaracterizes a microarray embodiment in the '848 patent

Reply

encompassed within the plain and ordinary meaning of the claim terms. For example, the specification describes various ways of “selecting,” such as selective amplification with PCR and oligonucleotide tag array paired with labelled affinity reagents (*e.g.*, Ex.1001, 19:7-9, 20:31-39, 30:56-67), which PO’s construction improperly excludes.

Reply, 2

'848 patent

Another example of a suitable filtering process is conditional detection. The CRCs can be hybridized to a DNA oligonucleotide tag array where all possible combinations of identification sequences in the library are present. The different combinations of associated NAMs are spatially separated by the hybridization. To identify which NAM combinations represent a CRC with a positive interaction pair the array with the CRCs can be stained with a labelled affinity reagent specific for the interaction. However this approach requires

EX1001, 20:31-39; PO Sur-Reply, 9-10



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Petitioner mischaracterizes the '848 patent's Example 5

Reply

encompassed within the plain and ordinary meaning of the claim terms. For example, the specification describes various ways of “selecting,” such as selective amplification with PCR and oligonucleotide tag array paired with labelled affinity reagents (*e.g.*, Ex.1001, 19:7-9, 20:31-39, 30:56-67), which PO's construction improperly excludes.

Reply, 2

'848 patent Example 5

b. Association and selection by ligation and PCR

A total volume of 5 µl comprising 100 pM of the thiolated (NAM-Thiol-D5, NAM-Thiol-E5, NAM-Thiol-A3, NAM-Thiol-B3 and non thiolated oligonucleotides (NAM B5, NAM, C5, NAM F5, NAM C3, Nam D3, NAM E3) is mixed to constitute a final volume of 50 µl comprising 1xPCR buffer (available from Invitrogen, Norway), 5 pmol of each PCR primer (FWDprime, REWprime), 1.5 U Taq platinum (available from Invitrogen, Norway), 3 mM MgCl₂, 80 mM ATP, 100 nM of the oligonucleotide LigA, 200 nM dNTP and 1 U T4 DNA ligase. The mixture is incubated at 95 C for 2 min and then cycled 30 times between 60 C and 95 C.

EX1001, 30:56-67

Experimental Design

The application of resolving pair wise reacted groups within an interactor library is exemplified. Formation of a covalent bond is interrogated within a library. Dimerization of thiol groups serves as an example. Oligonucleotides with thiol groups will dimerize pairwise if mixed and subsequently allowed to react. Five oligonucleotides with association elements in the 3' end and 5 oligonucleotides with association elements in the 5' end are employed. Two of the 3' arms and 2 of the 5' arms are equipped with thiol groups. Subsequent to dimerization interacting MOI are identified by association of the respective NAMs by ligation (FIG. 5a). The ligation joins the two tag motifs encoding the thiol groups. The ligated product can also serve as amplification template for PCR, enabling selective amplification of the ligated NAMs. Subse-

EX1001, 30:18-23; PO Sur-Reply, 10



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The '848 patent need not claim all embodiments in the specification



“Specifically, and most importantly for this case, we have repeatedly explained that ‘[a]lthough reluctant to exclude an embodiment, this court must **not allow the disclosed embodiment to “outweigh the language of the claim, especially when the court’s construction is supported by the intrinsic evidence.”**”

SIMO Holdings Inc. v. Hong Kong uCloudlink Network Tech. Ltd., 983 F.3d 1367, 1379 (Fed. Cir. 2021); *PO Sur-Reply*, 12

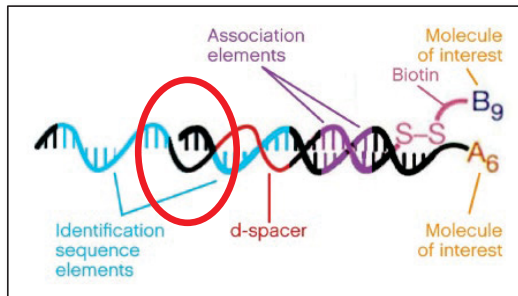
“*Oatey* itself thus recognizes that **we should not infer that any particular embodiment is included in a claim when there is probative evidence that sufficiently indicates the contrary.**”

SIMO Holdings Inc. v. Hong Kong uCloudlink Network Tech. Ltd., 983 F.3d 1367, 1378 (Fed. Cir. 2021); *PO Sur-Reply*, 12

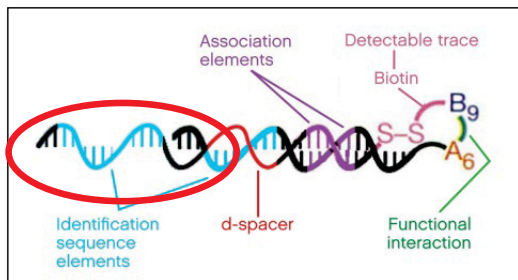


Petitioner introduces substantively revised versions of figures originally presented in the Petition

Petition

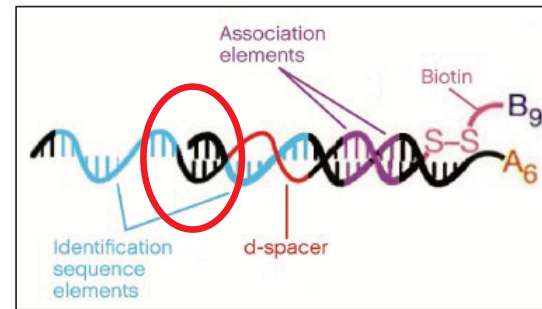


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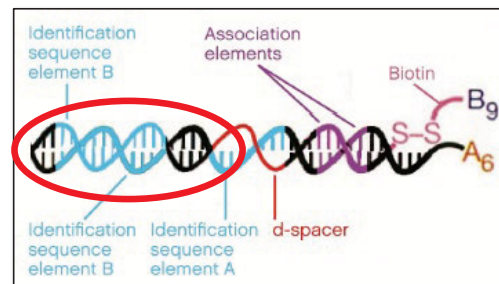


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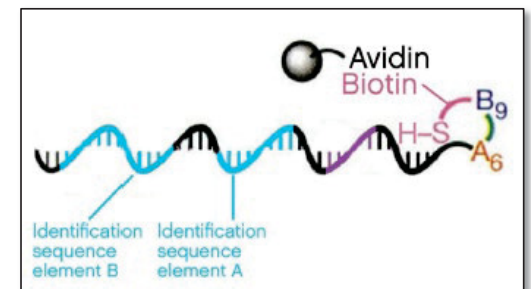
Reply



Reply, 16



Reply, 4



Reply, 9



Petitioner requires the Board to search through the record to find support for its new figures

Reply

Ex.1051, ¶¶7-11 (each figure component is described and/or illustrated in Pet., 19-23, 27-33, 43-44 and Ex.1005, ¶¶105-106, 114-115, 180-184; Ex.2009, 163:3-22; 165:12-20; 167:1-168:24; 169:8-12) (after PO raised alleged discrepancy, Dr. Nelson

Reply, 5

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

Reply, 9

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

Reply, 16

PO Sur-Reply, 6-7



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Petitioner is obligated to make its case *in the Petition*



“Unlike district court litigation — where parties have greater freedom to revise and develop their arguments over time and in response to newly discovered material — the expedited nature of IPRs bring with it an **obligation for petitioners to make their case in their petition** to institute. While the Board's requirements are strict ones, they are requirements of which petitioners are aware when they seek to institute an IPR.”

Intelligent Bio-Sys. v. Illumina Cambridge, 821 F.3d 1359, 1369 (Fed. Cir. 2016); *PO Sur-Reply*, 1, 5-6

“Rather than explaining how its original petition was correct, Continental's subsequent arguments amount to an entirely new theory of prima facie obviousness absent from the petition. **Shifting arguments in this fashion is foreclosed by statute, our precedent, and Board guidelines..**”

Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc., 853 F.3d 1272, 1286 (Fed. Cir. 2017); *PO Sur-Reply*, 2, 6

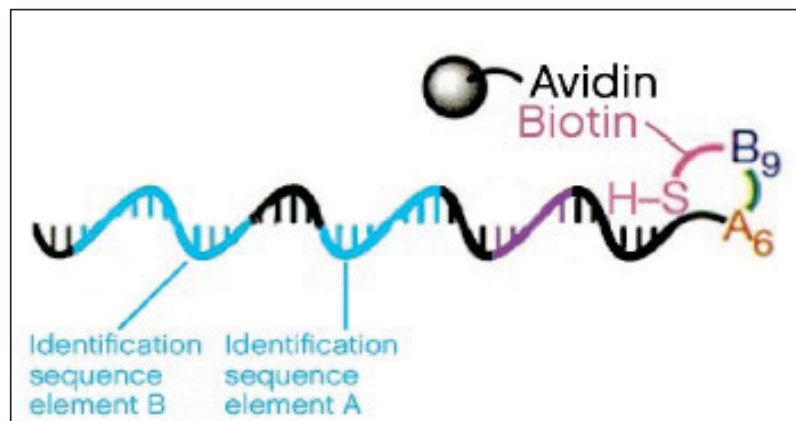


Even under Petitioner's new theory, Kanan and Neri do not teach or suggest claim 1(d)

Dr. Nelson (reply declaration)

30. A depiction of how the bond-forming combination of the Kanan/Neri design after polymerization, *id.*, ¶¶ 181-182, and the selection process, *id.*, ¶ 122; Ex. 1013, 8, as described in my First Declaration, would be visualized as follows:

EX1051, ¶30



EX1051, ¶30; PO Sur-Reply, 13



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GROUND 1:
The Petition fails to demonstrate that Kanan and Neri
teach or suggest claim 1(e)'s analysis step



No associated oligonucleotides from the CRCs selected in step (d) can be analyzed in step (e)

'848 Patent

1. A method of detecting functional interactions between at least two molecules of interest, the method comprising:
 - a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;
 - b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two nucleic acid moieties, wherein the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;
 - c. subjecting the plurality of cis-reactive cells to conditions which stimulate a desired functional interaction having a detectable trace;
 - d. selecting all cis-reactive cells exhibiting the detectable trace; and
 - e. subjecting the associated oligonucleotides **from the cis-reactive cells selected in step (d)** to an analysis that permits detection of the at least two identification sequence elements.

EX1001, claim 1; POR 6-7

Dr. Pentelute

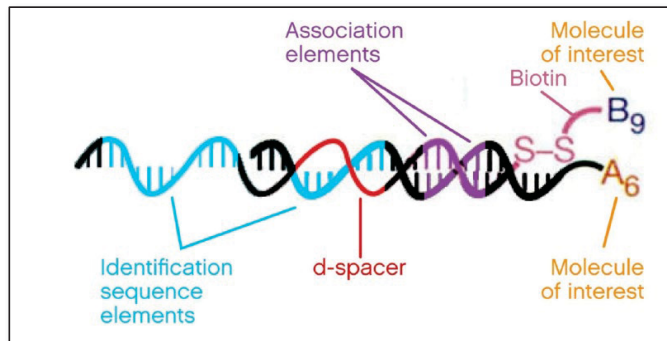
the B oligonucleotides are uncoupled from the B substrates. For the same reason, **there can be no alleged “associated oligonucleotides from the cis-reactive cells selected in step (d)”** to subject to “an analysis” in step (e), **because there are no alleged CRCs to be selected in step (d).** What is more, as I explained above, there is no longer any alleged “associated oligonucleotide” at all.

EX2008, ¶120; POR, 29



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The Petition does not explain if, when, or how a POSA would have allegedly implemented a polymerization step



Pet, 33

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

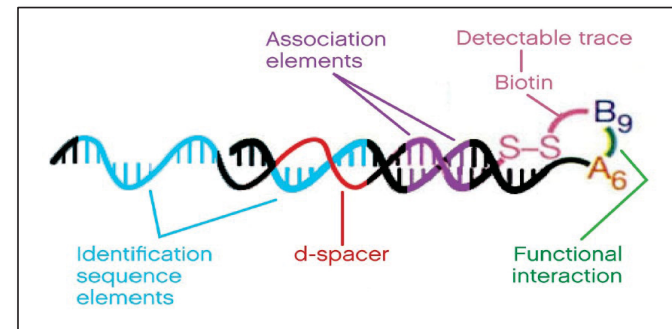
Pet, 33

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

Pet, 34

(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."

Pet, 35



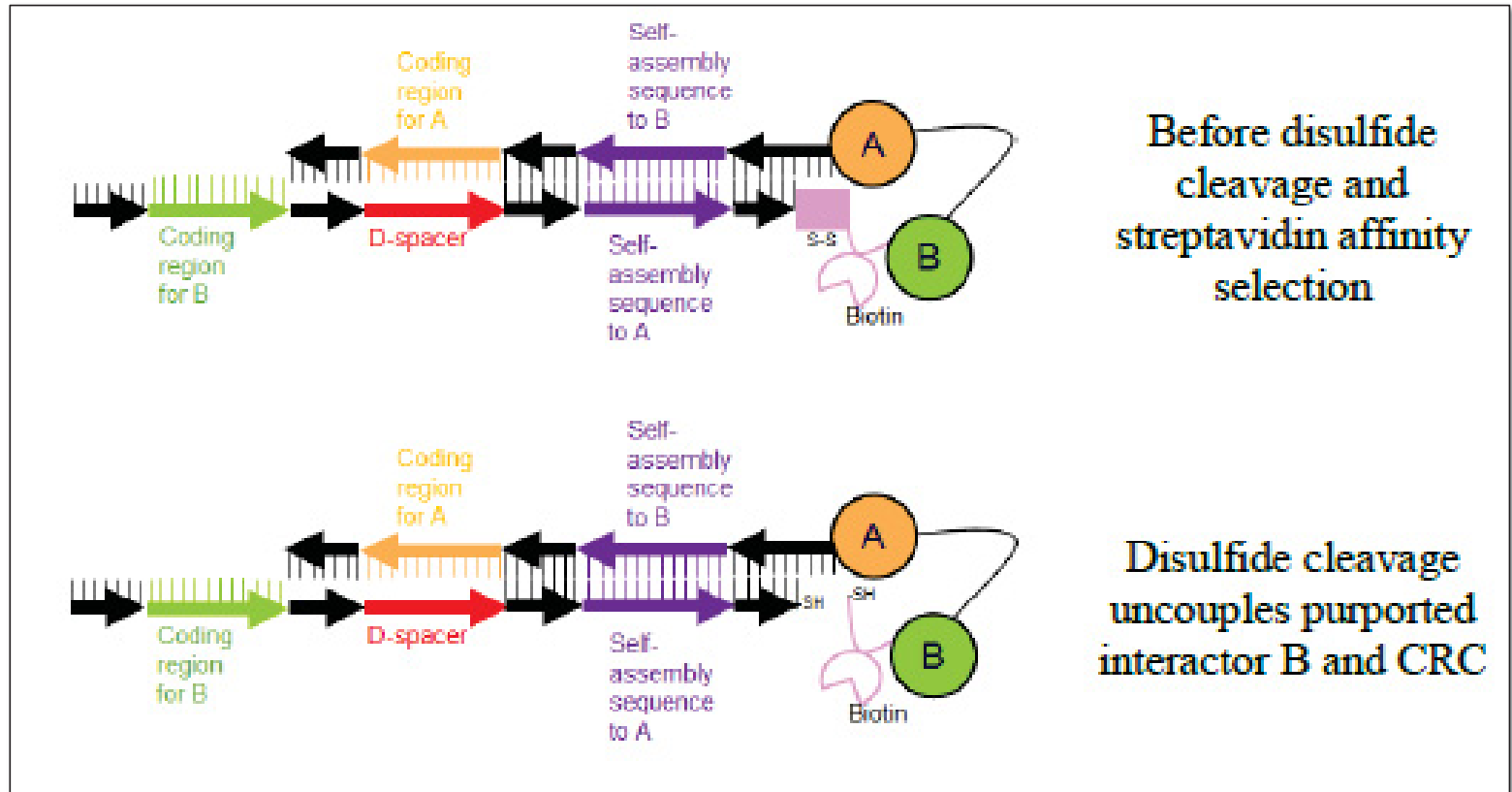
Pet, 34



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Kanan teaches cleavage and removal of pool B oligonucleotides, resulting in removal of a purported identification sequence element before step (e)

Dr. Pentelute



EX2008, ¶125; POR, 31-32

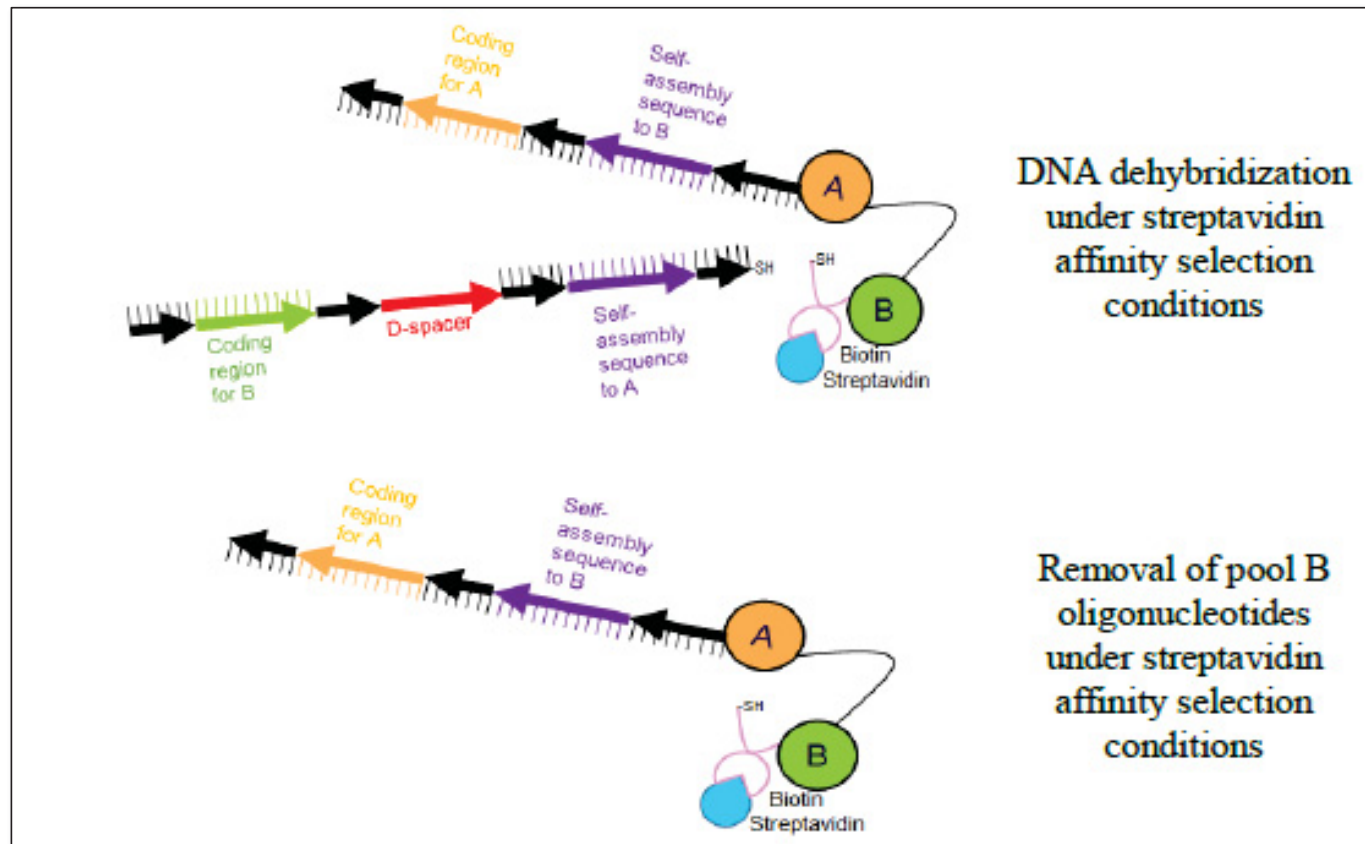


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35

Kanan teaches cleavage and removal of pool B oligonucleotides, resulting in removal of a purported identification sequence element before step (e)

Dr. Pentelute



EX2008, ¶125; POR, 31-32



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Reference to polymerization in the Petition is vague and conclusory

Petition

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 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.*

Pet, 20-21

Dr. Nelson at ¶182 (discussing claim 17)

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. A POSA would have been motivated to create this double-coding code taught in Neri to increase the specificity of the test. With polymerization, one of the interactors will not only contain its coding region but will also contain the anticodon of the other interactor. Further, encoding the anticodon of the interactor would allow identification of a multistep interaction, if desired. A POSA would have also known it would have been obvious to modify the linkage of the DNA to the substrate so that pool A is attached by the 3' end and pool B is attached by the 5', or vice versa, as desired.

EX1005, ¶182; Pet, 20-21



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Petitioner's conclusory assertions should be rejected



“To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The **petitioner must instead articulate specific reasoning**, based on evidence of record, to support the legal conclusion of obviousness.”

In re Magnum Oil Tools Int'l, Ltd., 829 F.3d 1364, 1380 (Fed. Cir. 2016); *PO Sur-Reply*, 14

“Absent some articulated rationale, a finding that a combination of prior art would have been ‘common sense’ or ‘intuitive’ is no different than merely stating the combination ‘would have been obvious.’ Such a **conclusory assertion with no explanation is inadequate** to support a finding that there would have been a motivation to combine.”

In re Van Os, 844 F.3d 1359, 1361 (Fed. Cir. 2017); *POR*, 33



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Neri teaches performing polymerization after biopanning

Dr. Nelson (first declaration)

182. 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. A POSA would have been motivated to create this

EX1005, ¶182; Pet, 20-21

Dr. Nelson (first deposition)

Q: And this step, this DNA polymerase reaction in paragraph 30, Neri says that this takes place after the biopanning method; is that right?

A: That's what -- I mean, I read the same words as you. That's what Neri says in paragraph 30.

EX2009, 110:17-21; POR, 34

Neri

[0030] After biopanning, oligonucleotides of sub-library B remain stably annealed to oligonucleotides of sub-library A, and can work as primers for a DNA polymerase reaction on the template A. The resulting DNA segment, carrying

EX1011, [0030]; POR, 33

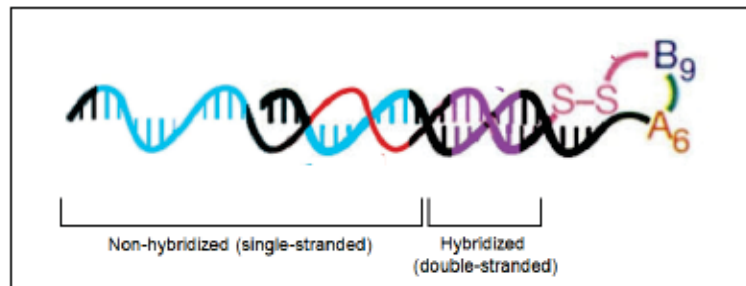


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Polymerization is incompatible with Petitioner's presented design

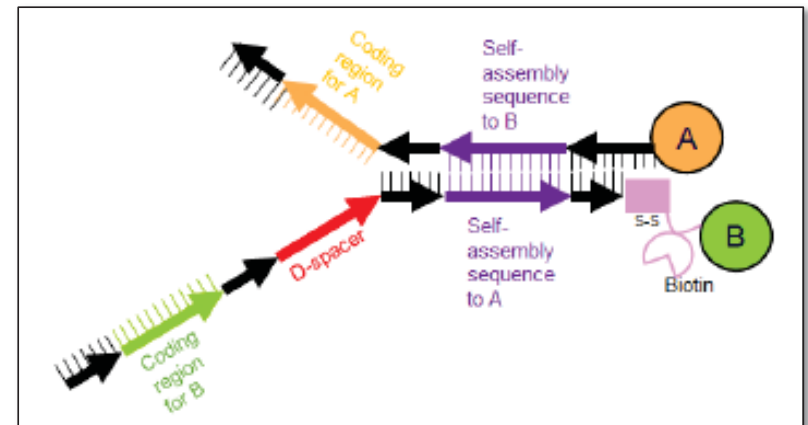
Dr. Pentelute

the Critical Region is presented. Accordingly, as Dr. Nelson presents it in his Declaration, there is no hybridization in the region at issue. I have annotated this region in the figure below:



EX2008, ¶140; POR, 40

Dr. Pentelute



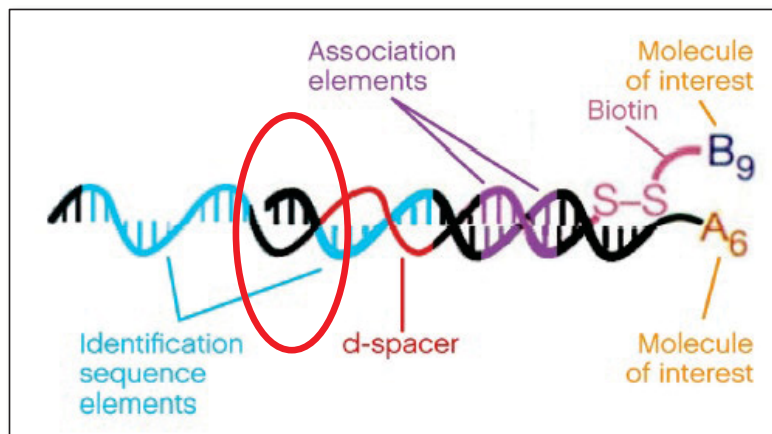
EX2008, ¶142; POR, 41



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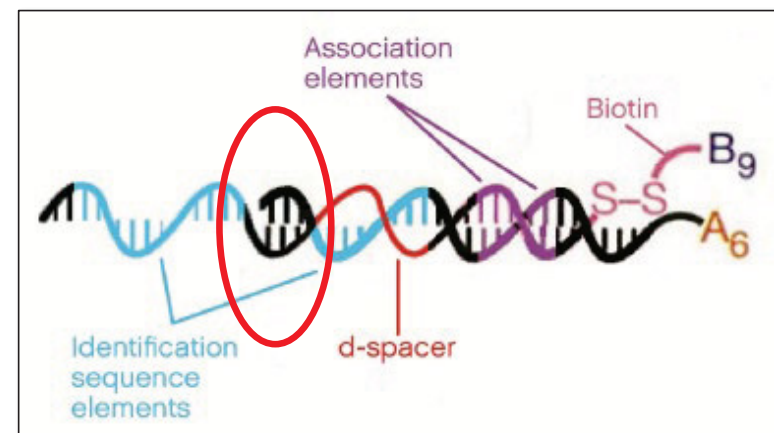
Dr. Nelson revised his figures to introduce a second hybridization region

Dr. Nelson (first declaration)



EX1005, ¶115; Pet, 33

Dr. Nelson (reply declaration)



EX1051, ¶157; Reply, 16

Dr. Nelson: the second hybridization region would have been a universal complementary region

Dr. Nelson

Q: All right. So, in this design that you have in figure -- or on page 63, where the black region is hybridized, are the sequences in the strand B and strand A the same sequence such that any member of pool A can hybridize to any member of pool B at this black region?

A: Those are primer binding sites. So those would be -- they're referred to as the primer binding site. And those are constant. So those would be the same for all pool members.

EX2009, 167:22-168:6; POR, 43

Dr. Nelson

Q: Is it your opinion that this hybridization that should be depicted in this figure [on page 67], according to you, is the same hybridization for all of pool A and pool B because they're primer binding sites?

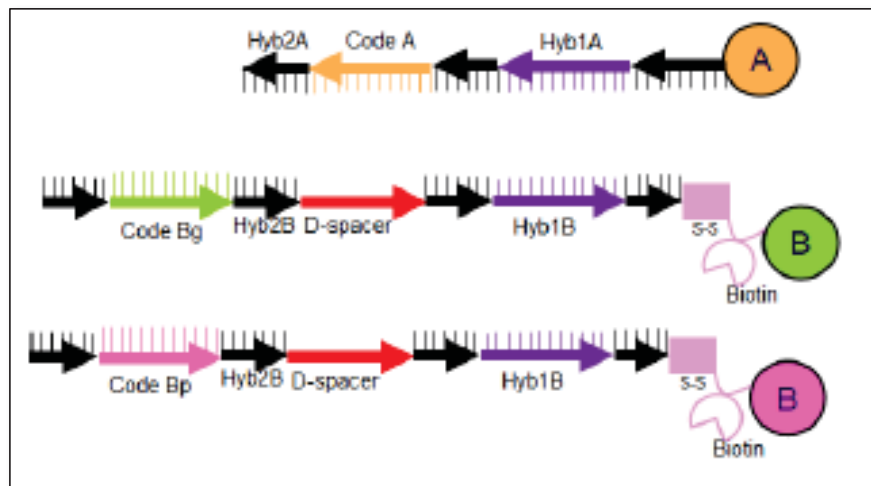
A: In this example, yes.

EX2009, 169:8-12; POR, 43

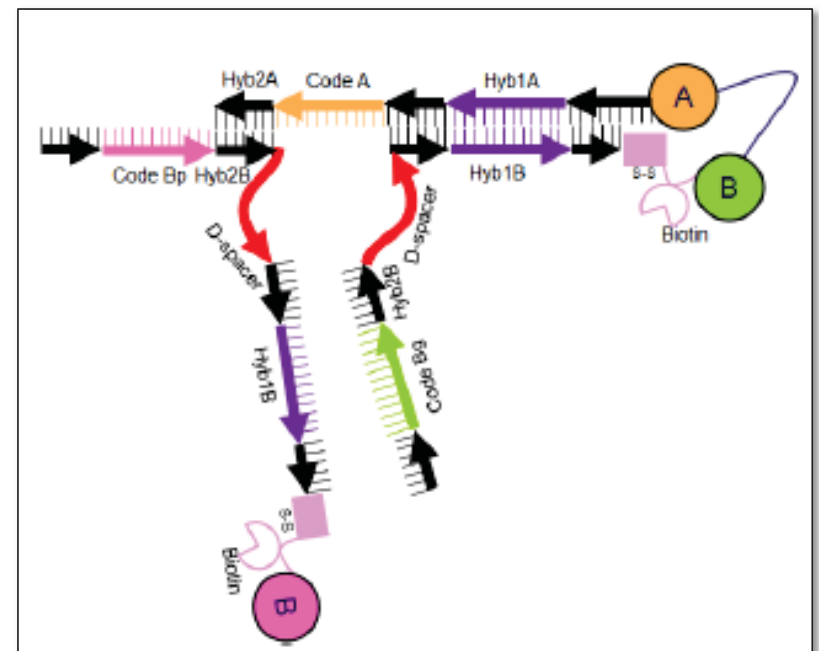


Petitioner's revised theory would have been expected to yield both false positive and false negative results

Dr. Pentelute



EX2008, ¶150-153; POR, 44-46



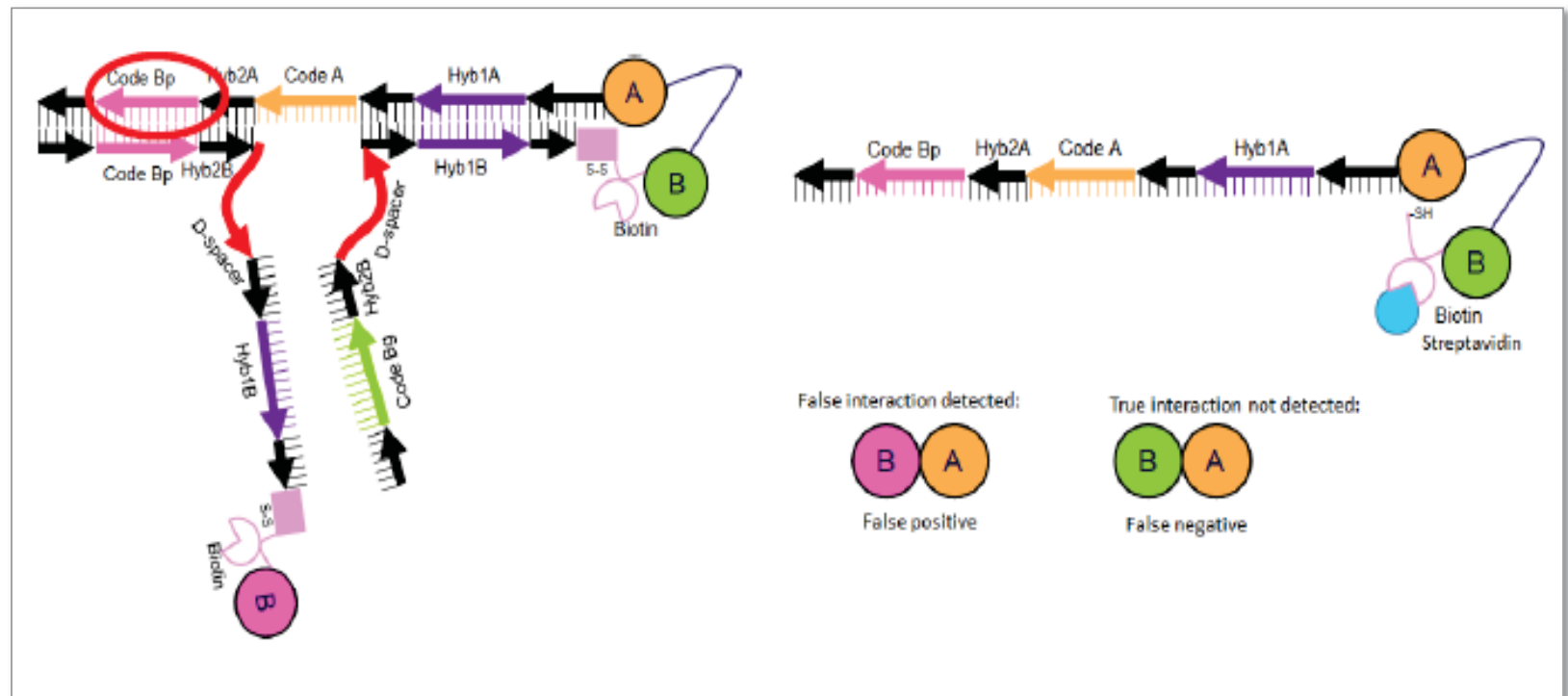
EX2008, ¶150-153; POR, 44-46



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Petitioner's revised theory would have been expected to yield both false positive and false negative results

Dr. Pentelute



EX2008, ¶150-153; POR, 44-46



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Petitioner's expert Dr. Nelson provides inconsistent testimony regarding Petitioner's belatedly proposed timing of polymerization

Dr. Nelson:
polymerization “at the time of association.”

(Ex. 1013, 8). Ex. 1005, ¶ 183. As discussed in my First Declaration, this association via polymerization would occur at the time of association, which would be prior to the functional interaction. Ex. 1005, ¶¶ 107-116, 180-184.

EX1051, ¶9; PO Sur-Reply 16

Dr. Nelson :
“polymerization [occurs] after the formation of the CRC.” - i.e., after association

derived from the at least two nucleic acid moieties.” Ex. 1001, Cl. 1. The pool A oligonucleotides being analyzed in step (e) are the product of a pool A oligonucleotide hybridizing with a pool B oligonucleotide, and the pool B identification sequence element being transferred onto the pool A oligonucleotide using polymerization after the formation of the CRC, creating a novel oligonucleotide comprised of the identification elements of the component interactors. See Ex. 1001, 16:66-17:3; Ex. 1005, ¶¶ 180-184.

EX1051, ¶42; PO Sur-Reply 16



GROUND 1:
The Petition fails to demonstrate that a POSA would have been motivated to modify Kanan and Neri with a reasonable expectation of success



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



“[O]bviousness concerns whether a skilled artisan not only *could* have made but **would have been motivated to make** the combinations or modifications of prior art to arrive at the claimed invention.”

Personal Web Techs., LLC v. Apple, Inc., 848 F.3d 987, 994 (Fed. Cir. 2017); *POR*, 47



Petitioner fails to meaningfully address the technical flaws in its proposed combination

Reply

teaching polymerization). Lastly, PO's arguments regarding unintended hybridization would not change a POSA's reasonable expectation of success because they would have had the skills to design the assay conditions to promote hybridization between the intended hybridizing regions. Pet., 11-12, 21-23; Ex.1005, ¶¶25, Ex.1051, ¶¶68-69.

Reply, 18-19

Dr. Nelson (reply declaration)

results.” Ex. 2008, ¶ 158. I disagree because this argument ignores that the Kanan/Neri design reduces unintended hybridization, as I discussed above. Dr. Pentelute also ignores that a POSA would have a reasonable expectation of success in preventing unintended hybridization because a POSA would have the skills to design oligonucleotides and the assay conditions to promote hybridization between the intended hybridizing regions.

EX1051, ¶68; Reply, 19



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Dr. Nelson wrongly believes Neri's Example 3 is a working example

Dr. Nelson (reply declaration)

Moreover, the cited prior art describes working examples and does not raise undesired hybridization as a concern. For example, the basic structure of the Kanan/Neri design is based on Neri's Figure 5 (see, e.g., Ex. 1005, ¶ 96), yet Neri does not discuss unintended hybridization after the d-spacer being a concern.

EX1051, ¶62

Dr. Nelson (reply deposition)

Q. Is it your opinion that Neri's example which refers to figure 5, is a working example?

A. Again, I'm a scientist and I don't know the formal legal definition of working example. It says example 3 here, and that's an example or a working example -- I've just always used the term "working example." So to me they're interchangeable, but that's just my scientific opinion.

EX2013, 263:11-19

Neri

Example 3

[0111] This example illustrates one of the many possible decoding methodologies, for ESACHEL embodiments as described in FIG. 1 and in Example 2.

[0112] The decoding strategy, schematically depicted in FIG. 5, is based on the principle that, after biopanning of desired ESACHEL binding specificities, PCR fragments are generated, each of which carries the code of pairs of sub-library members, whose combination was rescued in the biopanning experiment, therefore allowing the identification of the corresponding heterodimerized chemical entities.

[0118] As an example of model oligonucleotides A and B which can be used for the generation of a PCR product, which carries both code A and B, is provided below:

typeB oligo

Chemical entity B-5'-GCA TAC CGG AAT TCC CAG CAT AAT GAT CGC TAT CGC TGC-3'

typeA oligo (d=d-spacer element)

5'-CGT CAG CTC GAA TTC TCC ATA TAT GCA GCG ATA GCG ATC DDD DDD CTG GGA ATT CCG GTA TGC-3'-chemical entity A

EX1011, Example 3



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PO Sur-Reply, 17-19

GROUND 2:
The Petition fails to demonstrate Kanan, Neri, and Famulok
teach or suggest all the elements of claim 16



In Petitioner's proposed combination, Neri's interactors are associated by hybridization, not ligation

'848 Patent, claim 16

16. The method of detecting functional interactions between at least two molecules of interest as recited in claim 1, wherein association is via ligation.

EX1001, claim 16; POR, 6-7

Dr. Nelson

Q And those two strands A and B oligonucleotides in Figure 7 are hybridized together here? Is that what's depicted in the figure?

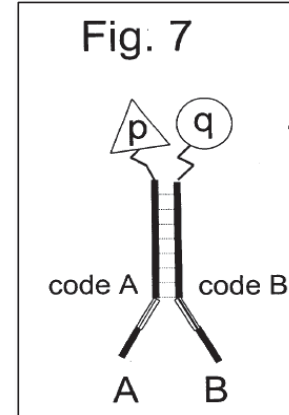
A That is to the best of my recollection at this time, yes.

EX2009, 130:23-131:2

Neri

[0032] FIG. 7: A PCR-based method for ESACHEL deconvolution: Sub-libraries A and B form a heteroduplex, flanked by unique sequences coding for the different library members and by constant DNA segments at the termini.

EX1011, [0032]; POR, 51



EX1011, Fig.7; POR, 53



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Petitioner mischaracterizes the '848 patent Figure 5

Reply

because it excludes embodiments from the specification. For example, Figure 5 provides examples of association via ligation and discloses embodiments with association between NAMs before ligation. Ex.1001, Fig. 5; Ex.2008, ¶33; Ex.1051, ¶¶70-72. Thus, PO is incorrect that Kanan/Neri/Famulok fail to teach claim 16.

Reply, 19

'848 Patent

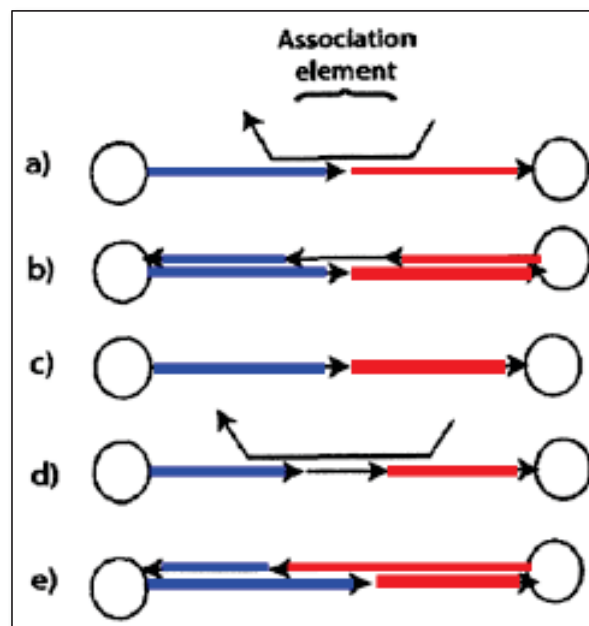


Fig 5a, b, c, d:
no hybridization
between
interactors

PO Sur-Reply, 20

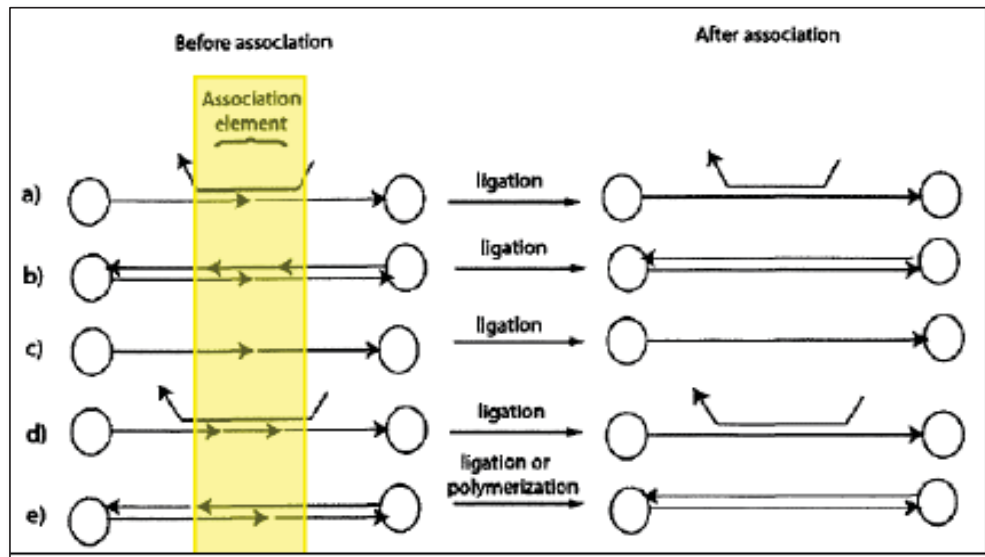
Fig 5e: {
Ligation takes place **at the**
hybridization/association site



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'848 patent Figure 5 embodiments: ligation takes place at the association site

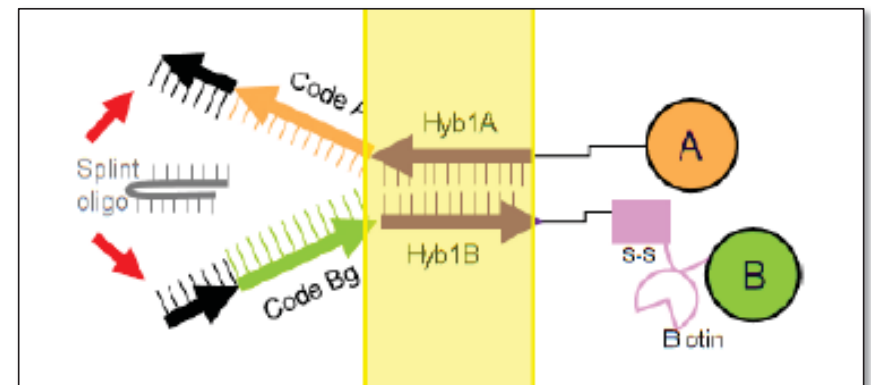
'848 patent Figure 5



PO Sur-Reply, 21; EX1001, Fig. 5

Pentelute: "Dr. Nelson's proposed combination"

EX2008, ¶169



PO Sur-Reply, 21; EX2008, ¶167



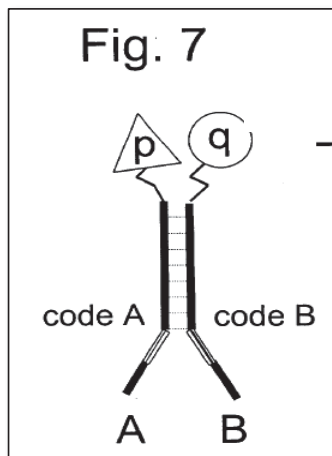
GROUND 2:
The Petition fails to demonstrate that a POSA would have been motivated to combine Kanan, Neri, and Famulok with a reasonable expectation of success



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Petitioner fails to grapple with the technical flaws presented in its art combination for Ground 2

Neri



EX1011, Fig.7; POR, 53

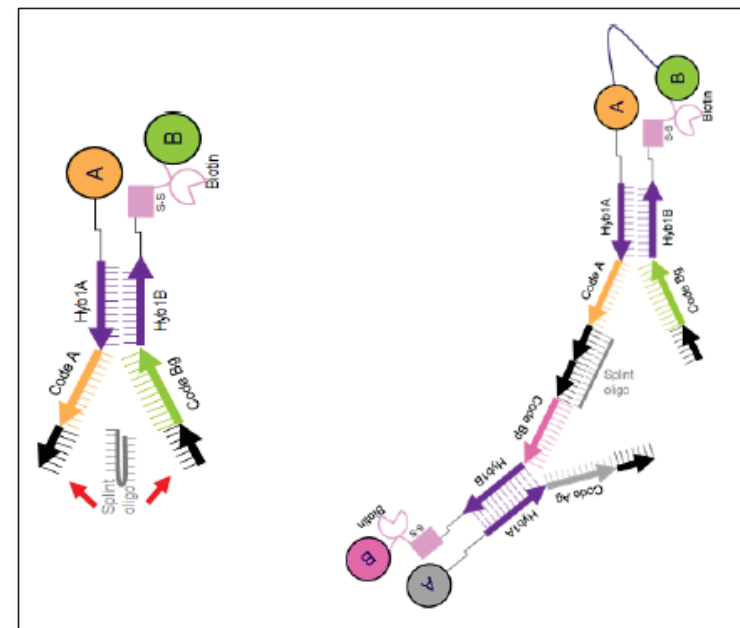
Dr. Pentelute

If the ends are unique for each A and B oligonucleotide, then a connector oligonucleotide as in Famulok would need to be made for each combination of A and B, defeating Dr. Nelson's proposed purpose for combining Kanan with Neri to make the process combinatorial and not require sequences for each combination.

If the ends are universal for each A and B oligonucleotide, then false positives and false negative results arising from binding of multiple strands would be expected as in Ground 1, but in a slightly different way....

EX2008, ¶¶166-167

Dr. Pentelute

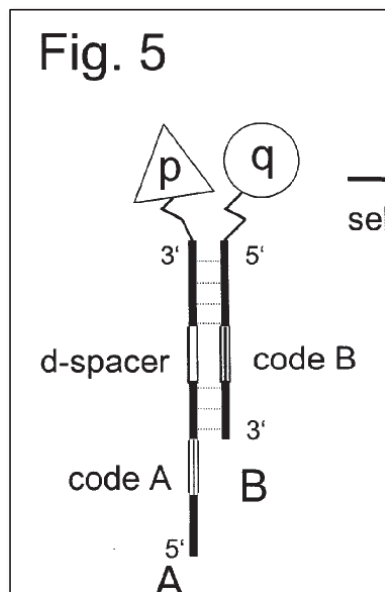


EX2008, ¶167



Petitioner's proposed ligation modification is impractical with Neri's Figure 5 design

Neri

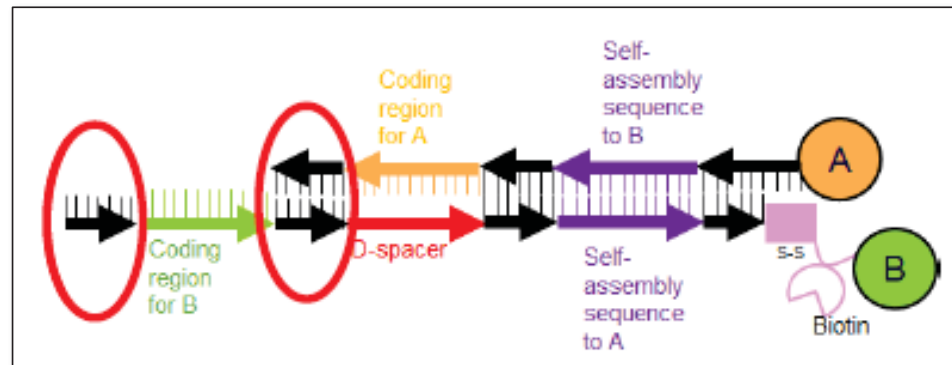


EX1011, Fig. 5

Dr. Pentelute

[A] POSA would have understood that there would be no “overhang region” in each of A and B in Petitioner’s embodiment that could be ligated using Famulok’s splint oligonucleotide methods. EX1012, Fig. 1; EX1011, Fig. 5, 7.

EX2008, ¶172



EX2008, ¶171; POR, 55



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Petitioner's conclusory assertions should be rejected



“To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The **petitioner must instead articulate specific reasoning**, based on evidence of record, to support the legal conclusion of obviousness.”

In re Magnum Oil Tools Int'l, Ltd., 829 F.3d 1364, 1380 (Fed. Cir. 2016); *PO Sur-Reply*, 14

“Absent some articulated rationale, a finding that a combination of prior art would have been ‘common sense’ or ‘intuitive’ is no different than merely stating the combination ‘would have been obvious.’ Such a **conclusory assertion with no explanation is inadequate** to support a finding that there would have been a motivation to combine.”

In re Van Os, 844 F.3d 1359, 1361 (Fed. Cir. 2017); *POR*, 33



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GROUND 3 and 4:
The Petition fails to demonstrate that Baez and Landegren
teach or suggest claim 1(a)'s forming interactors step



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Claim 1(a) requires forming a plurality of interactors

'848 Patent

The invention claimed is:

1. A method of detecting functional interactions between at least two molecules of interest, the method comprising:
 - a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;
 - b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two nucleic acid moieties, wherein the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;
 - c. subjecting the plurality of cis-reactive cells to conditions which stimulate a desired functional interaction having a detectable trace;
 - d. selecting all cis-reactive cells exhibiting the detectable trace; and
 - e. subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis that permits detection of the at least two identification sequence elements.

EX1001, claim 1



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The Petition's inconsistent claim mapping fails to show that Baez and Landegren teach claim 1(a)

Petition

MOIs = Baez's **antibody-nucleic acid conjugates**

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

Pet, 55

Interactors = Baez's **reporter conjugates**

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.

Pet, 56

Board

Notwithstanding the above, we have doubts that Petitioner is reasonably likely to prevail on Grounds 3 and 4. In particular, as we understand the Petition, Grounds 3 and 4 rest on the contention that Baez's antibody-nucleic acid conjugates are “molecules of interest” ...

However, the Petition also points to these antibody-nucleic acid conjugates as the “interactors” recited in step (a) of claim 1 ...

To the extent the antibody-nucleic acid conjugates are asserted to be the molecules of interest, the Petition fails to clearly explain what nucleic acid moiety is then coupled to it to form the interactors.

DOI, 36



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Patent Owner's District Court complaint maps NULISA differently than the Petition's mapping of Baez

Petition

MOIs = Baez's **antibody-nucleic acid conjugates**

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

Pet, 55

Interactors = Baez's **reporter conjugates**

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.

Pet, 56

PO Complaint Materials

MOIs = **matched antibody pairs**

Specifically, the matched antibody pairs of the NULISA and NULISaseq Platforms (shown in green and yellow in the figure below) are molecules of interest ...

EX1008, 1; PO Sur-Reply, 23

Interactors = **antibody and a nucleic acid**

In general, the NULISA platform, used with or without its ARGO system, uses probes consisting of an antibody and a nucleic acid. These form "a plurality of interactors."

EX1007, ¶21; PO Sur-Reply, 23



GROUND 3 and 4:
**The Petition fails to demonstrate that Baez and Landegren
teach or suggest claim 1(d)'s selecting step**



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Petitioner relies exclusively on Baez column 17 for meeting claim 1(d)'s "selecting" step

Petition

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.

Pet, 60

Baez

get electrophoresis or through other means as discussed.

Detection of Nucleic Acid Products

The detection of the ASA amplified product may be accomplished by several means including (a) direct detec-

EX1003, 16:65-67

rated into the amplified product sequences. These approaches afford several detection strategies. For example, the incorporation of biotinylated or ligand modified bases provides means of isolating the amplified nucleic acid products from solution onto a immobilized streptavidin or avidin. The addition of an avidin-signal-generating conjugate then facilitates detection. The amplified sequences may also contain signal-generating labeled bases, such as, fluorescein or digoxigenin. These can be detected directly on the solid-phase support.

EX1003, 17:23-32

through labeled antibodies specific for double-stranded DNA. The ASA can also be detected through the linker oligonucleotide itself. The linker, for example, may be engineered to contain a label such as biotin or fluorescein. Once the linker is specifically bound to the ASA, the labels could be detected through antibody conjugates, direct fluorescence, or fluorescent energy transfer (FET), for example.

EX1003, 17:52-59

POR, 60



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Baez expressly defines ASAs as a nucleic acid product

Baez

The term “analyte-specific amplicon” (ASA) refers to the nucleic acid product formed by the joining the two assay nucleic acid-labels by either the label-overlap primer approach or the label-ligation approach due to the formation of the analyte-dependent reporter-complex.

EX1003, 9:27-31; PO Sur-Reply, 24

'848 Patent

As used herein, the term “Cis Reactive Cell” (CRC) refers to an association of at least two interactor moieties, joined by an associated oligonucleotide. In a specific embodiment a

EX1001, 9:35-37; POR, 21

As used herein, the term “interactor” refers to at least one MOI coupled with at least one NAM.

EX1001, 9:33-34; POR, 21



The Petition and Reply erroneously conflate ASAs in Baez with CRCs of the '848 patent

Petition

Thus, selecting the CRCs includes Baez's isolating CRCs (ASAs in Baez) comprising a biotin label using immobilized streptavidin.

Pet, 60

Dr. Nelson (reply declaration)

To be clear, the ASA in Baez includes the complex containing two antibodies connected via the ligation of their respective nucleic acid labels, as shown in Figure 4 of Baez.

EX1051, ¶100; PO Sur-Reply 25

Reply

[T]he ASA ... is the complex with the two antibodies connected via ligation of their nucleic acid labels, shown in Baez Figure 4....

Reply, 26

Baez discloses selecting CRCs (Baez's ASAs) through affinity purification....

Reply, 27

[O]nly after the CRC (ASA in Baez) is selected is the nucleic acid portion subjected to analysis.

Reply, 27



The Reply erroneously conflates ASAs in Baez with CRCs of the '848 patent

Reply

[T]he ASA (circled) is the complex with the two antibodies connected via ligation of their nucleic acid labels, shown in Baez Figure 4:

Reply, 26

Dr. Nelson (reply declaration)

Baez's ASA's contain both a MOI (antibody) and a NAM (DNA label) for each interactor.

EX1051, ¶101

But see, Baez:

The term "analyte-specific amplicon" (ASA) refers to the nucleic acid product formed by the joining the two assay nucleic acid-labels by either the label-overlap primer approach or the label-ligation approach due to the formation of the analyte-dependent reporter-complex.

EX1003, 9:27-31; PO Sur-Reply, 24

Reply

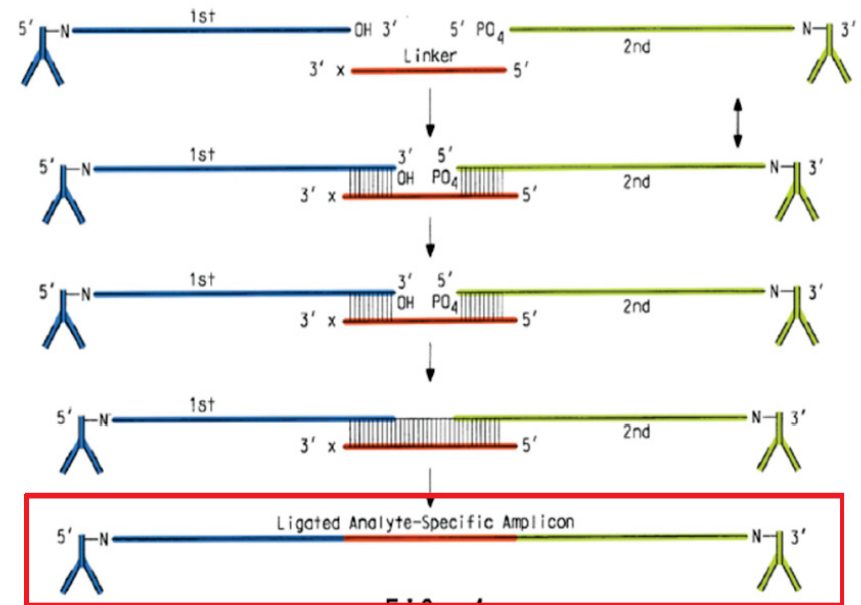


FIG. 4

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

Reply, 26



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GROUND 3 and 4:
The Petition fails to demonstrate that Baez and Landegren
teach or suggest claim 1(e)'s analysis step



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No associated oligonucleotides from the CRCs selected in step (d) can be analyzed in step (e)

'848 Patent

1. A method of detecting functional interactions between at least two molecules of interest, the method comprising:
 - a. forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety, the nucleic acid moiety comprising an identification sequence element and an association element;
 - b. forming a plurality of cis-reactive cells wherein a cis-reactive cell comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two nucleic acid moieties, wherein the associated oligonucleotide comprises at least two identification elements derived from the at least two nucleic acid moieties;
 - c. subjecting the plurality of cis-reactive cells to conditions which stimulate a desired functional interaction having a detectable trace;
 - d. selecting all cis-reactive cells exhibiting the detectable trace; and
 - e. subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis that permits detection of the at least two identification sequence elements.

EX1001, claim 1; POR, 6-7

Dr. Pentelute

187. As described above, Baez and Landegren fail to teach the selection method of step (d) at least because (1) a POSA would have understood that detection of ASAs through biotin capture is a detection step rather than a selection as claimed, and (2) a POSA would have understood that in Baez's methods, no cis-reactive cell is "selected" in Baez's ASA detection methods. Accordingly, Baez and Landegren fail to teach subjecting associated oligonucleotides from the cis-reactive cells selected in step (d) to any analysis, because there would have been no CRCs selected in Baez's method.

EX2008, 187; POR, 62



The Petition fails to demonstrate that Baez teaches claim 1(e)'s analysis step

Petition

[D]etecting the identification sequence elements includes amplifying the ASA with PCR and subsequent detection as taught in Baez.

Pet., 61

Reply

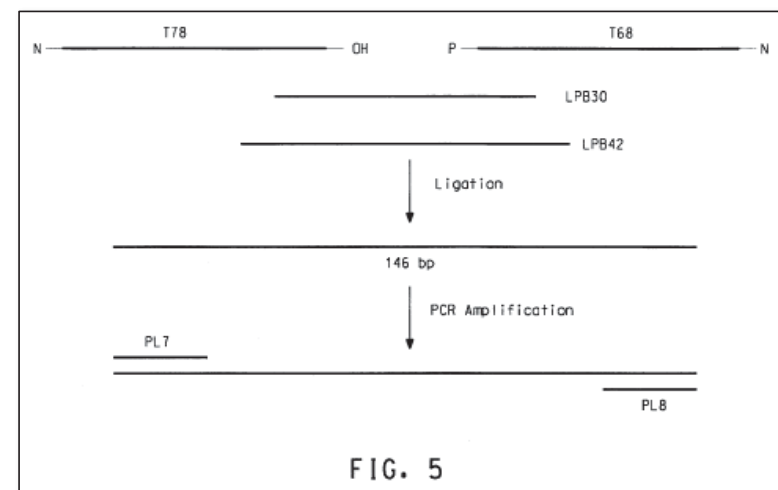
[W]hen the ligation product is detected and analyzed (step (e)), the nucleic acid includes the two identification sequence elements (Landegren's tags).

Reply, 27

Baez

other assays. One binding-pair reagent is for capturing the analyte and two are used for reporter conjugates. Third, the amplification by PCR is used to detect the product of two joined nucleic acid-label in contrast to the amplification product of a single reporter label. Fourth, the random distribution of the non-specifically bound antibodies makes

EX1003, 5:26-29



EX1003, Fig. 5



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GROUND 3 and 4:
The Petition fails to demonstrate that a POSA would have been motivated to combine Baez and Landegren (and Freskgard) with a reasonable expectation of success



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Baez purports to provide an assay with reduced background and the ability to screen multiple analytes

Petition

[A] POSA would be motivated to create an assay with reduced background signal and the ability to screen multiple analytes in a timely manner.

Pet., 53

Baez

specific binding has not been eliminated. Therefore, increased assay detection sensitivity has been limited. Thus, there is a continuing, unmet need for a means to reduce assay background response and to improve the signal to noise ratio of binding assays. The Applicant's invention is the first to apply assay principle that essentially distinguishes between analyte-specific binding reagent recognition and non-specific reagent binding.

EX1003, 3:25-30; *POR*, 64

Multianalyte Assay Format

In another preferred embodiment, multiple analytes can be detected simultaneously in the same assay milieu. This is

EX1003, 13:18-20; *POR*, 64

product of a single reporter label. Fourth, the random distribution of the non-specifically bound antibodies makes them less likely to be in close proximity to an analyte binding site to interfere with interaction and joining of nucleic acid-labels. Fifth, background is minimized, or is potentially eliminated, improving sensitivity.

EX1003, 5:33-34; *PO Sur-Reply*, 27



Petitioner fails to demonstrate that a POSA would have been motivated to combine Baez and Landegren (Ground 3) and Freskgard (Ground 4) with a reasonable expectation of success



“[O]bviousness concerns whether a skilled artisan not only *could have made* but **would have been motivated to make** the combinations or modifications of prior art to arrive at the claimed invention.”

Personal Web Techs., LLC v. Apple, Inc., 848 F.3d 987, 994 (Fed. Cir. 2017); *PO Sur-Reply*, 27



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