

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALAMAR BIOSCIENCES, INC.,
Petitioner

v.

OLINK PROTEOMICS AB,
Patent Owner

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

DECLARATION OF DR. BRADLEY L. PENTELUTE

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I, Bradley L. Pentelute, hereby declare as follows.

I. INTRODUCTION

1. I have been retained as an expert witness on behalf of Olink Proteomics AB (“Patent Owner,” “PO,” or “Olink”) for the above-captioned *inter partes* review (IPR). I am being compensated for my time in connection with this IPR at my standard consulting rate. My compensation is not dependent upon my opinions, my testimony, or the outcome of this case.

2. I understand that this declaration is being submitted in an IPR proceeding involving U.S. Patent No. 7,883,848 to Olink issued on February 8, 2011 (“the ’848 patent”) (EX1001), which resulted from U.S. Patent Application No. 11/483,825 (“the ’825 application”), filed on July 10, 2006, which claimed priority to U.S. Provisional Application No. 60/697,415 filed on July 8, 2005. I understand that the ’848 patent claims a priority date of July 8, 2005. I refer to this date throughout this declaration.

3. In preparing this declaration, I have reviewed and I am familiar with the ’848 patent and each of the documents cited herein, in light of general knowledge in the art before July 8, 2005. In formulating my opinions, I have relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, I have also considered the viewpoint of a person of ordinary skill in the art (“POSA”) (i.e., a person of ordinary skill in the field of Chemistry, Organic

Chemistry, Biochemistry, Biotechnology, Molecular Biology, or a related discipline, as defined further below in Section VIII) prior to July 8, 2005.

II. MY BACKGROUND AND QUALIFICATIONS

4. I am currently a Full Professor in the Department of Chemistry at the Massachusetts Institute of Technology (MIT), an Extramural Member of the Koch Institute for Integrative Cancer Research at MIT, an Associate Member of the Broad Institute of MIT and Harvard, and a Member of the Center for Environmental Health Sciences at MIT. In addition, I am a co-founder, CEO, and board Member of Amide Technologies (Cambridge, MA) and a co-founder of New Frontier Bio (Beverly, MA). I also serve as Scientific Advisor for Decoy Therapeutics (Cambridge, MA), as an Associate Editor for Scientific Reports (Nature), and as a member of the Nominating Committee of the American Peptide Society.

5. Before becoming a Full Professor, I was an Associate Professor (from 2016 to 2021) and previously an Assistant Professor (from 2011 to 2016) in the Department of Chemistry at MIT. I also was a Visiting Professor at the Tokyo Institute of Technology (Tokyo, Japan) in 2019-2020, and at the Osaka University (Osaka, Japan) in 2015-2018. I co-founded Tegrigen Therapeutics (Cambridge, MA) in 2021 and Resolute Bio (Beverly, MA) in 2018. I also served as Ad Hoc Grant Reviewer for the National Institutes of Health (NIH) and for National

Science Foundation (NSF), and as a Committee Member of the Safety Culture in Academic Research Laboratories of The National Academies.

6. From 2008 to 2011, I was a Postdoctoral Fellow in the Department of Microbiology and Molecular Genetics at Harvard Medical School in Professor John Collier's Lab, where my research work focused on how infectious agents infiltrate cells at the molecular level. I have also been a Senior Scientist at Ethos Pharmaceuticals from January to September 2008.

7. I received my Ph.D. in Organic Chemistry from the University of Chicago, where I was a graduate student in Professor Stephen Kent's Lab. I also hold a Master of Science degree in Chemistry also from the University of Chicago, and a Bachelor of Science degree in Chemistry and a Bachelor of Arts degree in Psychology both from the University of Southern California.

8. I have over 25 years of experience in the field of Organic Chemistry, Chemical Biology, Biotechnology, and Molecular Biology. My work has been published in more than 150 peer-reviewed scientific articles that have been collectively cited more than 10,000 times. I am also an Inventor of over 50 U.S. and International Patents and Patent Applications.

9. I have taught undergraduate and graduate level courses at MIT and presented more than 450 invited lectures, conference presentations, seminars, or workshops in the area of Organic Chemistry, Chemical Biology, Biotechnology,

Molecular Biology, and on my own research.

10. My research is at the intersection of chemistry, biology, and engineering, and integrates a deep investigation and knowledge of molecular science with of state-of-the-art engineering, automation, and machine learning. I focus on discovering and inventing new chemistries (e.g., protein modification chemistries) and binders (e.g., protein inhibitors), platforms for the efficient synthesis and delivery into cells of molecules and macromolecules (e.g., amino acids, peptides, proteins, and oligonucleotides); and flow technologies for the rapid production of molecules, macromolecules, and biopolymers. In addition, my work includes the generation of molecular data for the establishment of systems for the training of algorithms; for example, for the design of new molecules with new functions.

11. A major area of my research focuses on the development of novel and improved molecular encoding techniques. Technologies such as DNA-encoded libraries have transformed the process of drug discovery by enabling the rapid synthesis of vast collections of molecules. I have invented and developed a molecular encoding technology based on the use of abiotic peptides as carriers of information for the encoding of molecular synthesis, which builds upon and improves DNA-encoded libraries.

12. Another major area of my research focuses on the investigation of

molecular interactions and on the discovery and invention of new molecular binders. This area includes combining the combinatorial peptide libraries generated with the novel molecular encoding techniques that I developed with affinity selection platforms, which I also developed, to study protein-ligand interactions. For example, I developed a platform technology that utilizes size exclusion-based enrichment from pools of synthetic peptides and liquid chromatography-tandem mass spectrometry-based peptide sequencing to identify high-affinity binders to protein targets.

13. During my career I supervised over 100 Research Scientists, Postdoctoral Researchers, Technical Associates, Research Specialists, and Ph.D., M.D./Ph.D., Master of Science, and Undergraduate Students, most of whom now hold outstanding professional positions as Co-founders of Biotechnological Companies, Senior Scientists, Assistant and Associate Professors, and Executive Directors.

14. I have received grant funding to continually support my research from multiple organizations including the National Institutes of Health (NIH), Defense Advanced Research Projects Agency, and the National Science Foundation.

15. Throughout my career, I have received multiple awards and honors, including the David Ginsburg Memorial Colloquium Award from the Technion University, Israel (2023); the Rao Makineni Lectureship from the American

Peptide Society (2021); the Eli Lilly Award in Biological Chemistry (2018); the Bristol-Myers Squibb Innovation Award (2017); the Amgen Young Investigator Award (2016); the Novartis Early Career Award in Organic Chemistry (2015); the Sloan Research Fellowship in Chemistry (2015); the National Science Foundation Career Award (2014); the Sontag Distinguished Scientist Award (2013); the Young Chemical Biologist Award from the International Chemical Biology Society (2013); the Damon Runyon-Rachleff Innovation Award (2013); the Vallee Foundation Travel Award (2012); the Collier Award at the Gordon Conference on Microbial Toxins and Pathogenicity (2010); A Student Travel Award from the Australian Peptide Society (2006); the University of Southern California Chemistry Alumni Award for Outstanding Undergraduate Research (2003); and the Renaissance Scholar Distinction from the University of Southern California (2003). I was also named as a finalist for the Blavatnik Award (2018).

16. My *curriculum vitae* is attached to this declaration as Exhibit 2010 and contains additional details on my education, honors and awards, publication, professional activities, and qualifications to provide expert opinions in this matter.

III. SUMMARY OF OPINIONS

17. In preparing this declaration, I have reviewed the declaration of Dr. Norman C. Nelson, Ph.D. (EX1005) and all the evidence cited therein. I have also reviewed the references cited in my present Declaration. As detailed below, I

disagree with Dr. Nelson's arguments that claims of the '848 patent would have been obvious in view of the prior art.

18. Dr. Nelson alleges that the combination of Kanan (EX1010) and Neri (EX1011) would have rendered obvious claims 1-15 and 17-20 of the '848 Patent (Ground 1), and that the combination of Kanan, Neri, and Famulok (EX1012) would have rendered obvious claim 16 of the '848 Patent (Ground 2). Dr. Nelson also argues that the combination of Baez (EX1003) and Landegren (EX1004) would have rendered obvious claims 1-8 and 11-12 of the '848 Patent (Ground 3), and that the combination of Baez, Landegren, and Freskgard (EX1009) would have rendered obvious claims 14-15 of the '848 Patent (Ground 4). As discussed in detail throughout this declaration, I disagree with Dr. Nelson for several reasons.

19. First, Dr. Nelson's proposed combination of Kanan and Neri does not teach or suggest all of the elements of the challenges claims. I understand that legally, this is a fundamental flaw in Dr. Nelson's obviousness analysis. The addition of the Famulok reference in Ground 2 does not cure these deficiencies, as Dr. Nelson's arguments in Ground 2 depend on the same flawed analysis he presents in Ground 1. Second, a POSA would have understood that combining Kanan and Neri as Dr. Nelson proposes would encounter fundamental technical defects, resulting in unreliable readout data due to false-positive and false-negative results. Accordingly, a POSA would not have been motivated to combine Kanan

and Neri (or to further combine Kanan and Neri with Famulok as in Ground 2) with a reasonable expectation of success in view of fundamental technical defects, e.g., increased likelihood of false-negative and false-positive results.

20. Third, I disagree with Dr. Nelson’s opinions regarding Grounds 3 and 4 because the combination of Baez and Landegren do not teach or suggest all of the elements of the challenged claims. As with Grounds 1 and 2, I understand that this is a fundamental flaw in Dr. Nelson’s obviousness analysis. The addition of the Freskgard reference in Ground 4 does not cure these deficiencies, as Dr. Nelson’s arguments in Ground 4 depend on the same flawed analysis he presents in Ground 3. Fourth, I further disagree with Dr. Nelson’s opinions because a POSA would not have been motivated to combine Baez and Landegren with a reasonable expectation of success in view of Landegren’s discouragement of using solid-phase assays—the same types of solid-phase assays taught in Baez and Freskgard, and relied upon by Dr. Nelson.

IV. LIST OF DOCUMENTS CONSIDERED

In formulating my opinions, I have reviewed all the references and documents cited herein, including those listed below.

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

Exhibit No.	Description
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	Curriculum Vitae of Norman C. Nelson, Ph.D.
1007	Complaint in Olink v. Alamar, 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., Reaction Discovery enabled by DNA-templated synthesis and in vitro selection, 431 NATURE 545–49 (2004) (“Kanan”)
1011	U.S. Application No. 04/0014090 (“Neri”)
1012	Famulok, Bringing picomolar protein detection into proximity, 20 Nature Biotechnology 448–49 (2002) (“Famulok”)
1013	Kanan et al., Reaction Discovery enabled by DNA-templated synthesis and in vitro selection, Supplementary Information, 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, Immunoassays, 71 Analytical Chemistry 294–304 (1999)
1017	Reen, Enzyme-Linked Immunosorbent Assay (ELISA), 32 METHODS IN MOLECULAR BIOLOGY 461–66 (1994)

Exhibit No.	Description
1018	Sano et al., Immuno-PCR: Very Sensitive Antigen Detection by Means of Specific Antibody- DNA Conjugates, 258 SCIENCE 120–122 (1992)
1019	Gullberg et al., Cytokine detection by antibody-based proximity ligation, 101 PNAS 8420–24 (2004)
1020	Fredriksson et al., Protein detection using proximity-dependent DNA ligation assays, 20 Nature Biology 473–77 (2002)
1021	Brenner & Lerner, Encoded combinatorial chemistry, 89 PNAS 5381–83 (1992)
1022	Needels et al., <i>Generation and screening of an oligonucleotideencoded synthetic peptide library</i> , 90 PNAS 10700–04 (1993)
1023	Pelletier & Sidhu, Mapping protein-protein interactions with combinatorial biology methods, 12 CURRENT OPINIONS IN BIOTECHNOLOGY 340–47 (2001)
1024	Li & Liu, DNA-Templated Organic Synthesis: Nature’s Strategy for Controlling Chemical Reactivity Applied to Synthetic Molecules, 43 Angewandthe Chemie International Edition 4848–70 (2004)
1025	Guille & Kneale, Methods for the Analysis of DNA-Protein Interactions, 8 MOLECULAR BIOLOGY 35–52 (1997)
1026	U.S. Patent No. 6,692,918 (“Kurn”)
1027	Reischl & Kochanowski, Quantitative PCR, 3 MOLECULAR BIOLOGY 55–71 (1995)
1028	Wilton, Dideoxy Sequencing of DNA, ENCYCLOPEDIA OF LIFE SCIENCES 1–16 (2002)
1029	AMERSHAM BIOSCIENCES, MEGABACE 4000 INSTRUMENT ADMINISTRATOR’S GUIDE VERSION 3.2 (2002)

Exhibit No.	Description
1030	Heather & Chain, The sequence of sequences: The history of sequencing DNA, 107 GENOMICS 1–19 (2016)
1031	Evans, Sanger sequencing: past successes and current applications, CYTIVA, https://www.cytivalifesciences.com/en/us/news-center/sangersequencing-past-and-present-10001 (last accessed August 16, 2024)
1032	Winter et al., Making Antibodies by Phage Display Technology, 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”)
2002	Wei Feng et al., NULISA: A Proteomic Liquid Biopsy Platform with Attomolar Sensitivity and High Multiplexing, 14 NATURE COMMUNICATIONS 7238 (2023) (“Feng”)
2009	Deposition Transcript of Norman C. Nelson (June 3, 2025)
2010	<i>Curriculum Vitae</i> of Bradley L. Pentelute Ph.D.
2011	Mullis et al., “Specific enzymatic amplification of DNA in vitro: the polymerase chain reaction,” Cold Spring Harb Symp Quant Biol, 51:263-73 (1986)
2012	Sambrook et al., <i>Molecular Cloning, A Laboratory Manual</i> (3rd edition), Cold Spring Harbor Laboratory Press (2001)

V. STATE OF THE ART BEFORE JULY 8, 2005

21. As the '848 patent explains, the human genome contains tens of thousands of genes, which encode tens of thousands of proteins and peptides. EX1001, 1:32-35. The number of proteins and peptides in the human body is further increased by processes such as alternative splicing and post-translational modifications. EX1001, 1:32-35. Hundreds of thousands of biomolecules in the human body, including the myriad of proteins and peptides encoded by the human genome, constantly interact with each other in highly complex molecular networks.

22. The discovery and investigation of molecular interactions and networks is important for the understanding of physiological and pathological process.

23. Before July 8, 2005, persons of ordinary skill in the art desired techniques and methods for the discovery and investigation of molecular interactions and networks that possessed a high degree of accuracy and sensitivity, and ideally resolved molecular interactions in a high throughput fashion for more than one set of interacting biomolecules at the same time. However, techniques and methods at the time were limited in one or more aspects.

24. The application of Enzyme-Linked Immunosorbent Assays (ELISA) and Protein Microarrays was limited because both techniques required at least one of the tested molecules to be known and linked to the solid phase. Therefore, only

one member of the interaction could be resolved in a high throughput fashion.

EX1001, 2:23-24; EX1007, 461. The number of molecules that could be assayed in a single experiment was further limited by spatial constraints. For example, ELISAs could be conducted in multiwell plates, wherein each well of the plate contained one of the tested molecules linked to its surface. Protein microarrays were known to be physically limited in the number of different molecules that could be tested. As explained in the '848 patent, the spatial constraints “limit[] the capacity of information extraction per experiment.” EX1001, 2:14-15. In addition, the required immobilization on a solid surface “potentially can disturb the interaction and/or the protein conformation.” EX1001, 2:19-22.

25. Yeast two hybrid systems and display techniques (*e.g.*, phage display and ribosome display) both required cloning of each molecule to be tested, which made the process laborious and costly, especially on large scale. Molecules were tested as part of fusion constructs, which could affect their binding properties. The application of these techniques was further limited because “they [could] perform high throughput of [only] one of the interaction partners.” EX1001, 2:66-67.

26. DNA-templated synthesis (DTS), discussed in detail below, was designed for the investigation of a limited subset of molecular interactions, *i.e.*, chemical bond-forming reactions. The aim of DTS was to increase the relative local concentration of chemical compounds (“reactants”) in solution to facilitate

chemical bond formation. EX1001, 3:29-36. In addition, as discussed in more detail below, DTS employed a detection method that was non-combinatorial, which limited the number of pairs of reactants that could be tested in a single experiment, and each interaction had to be “predicted” in advance. EX1001, 3:46-55.

27. Other methods employing encoded combinatorial synthesis had been used for the synthesis of compounds in drug discovery screening. These techniques are discussed in detail below. Briefly, in encoded combinatorial synthesis, nucleic acid hybridization brings two or more molecules together to form a combined molecular entity, which is then tested for interaction with a target bound to a solid phase in a biopanning assay. *See e.g.*, EX1011, ¶¶83-84.

28. Immuno PCR (iPCR) was an improvement on the ELISA platform, whereby detection was by amplification of a nucleotide sequence instead of by an enzymatic reaction. EX1018, Abstract. This increased the sensitivity of the assay, but did not overcome the limitations of the ELISA discussed above.

29. Proximity Ligation Assay (PLA), is discussed in detail below. Briefly, the PLA methods that had been developed before July 8, 2005, required the tested molecules to be known and required a pair of aptamers or antibodies binding each tested molecule (or analyte); that is, the methods were applicable only to the detection of known biomolecules for which at least two binding agents were

available. This imposed limitations of the types of molecules that could be detected. For example, PLA as known before July 8, 2005, was “difficult to adapt the method to small organic molecules or even small peptides.” EX1012, 449.

VI. OVERVIEW OF THE '848 PATENT

A. Background

30. The invention of the '848 patent “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, 5:26-28. The invention of '848 patent overcame the limitations of the prior art techniques because it allowed to resolution of molecular interactions in a high throughput fashion for more than one of the interacting molecules at once and with a high degree of sensitivity.

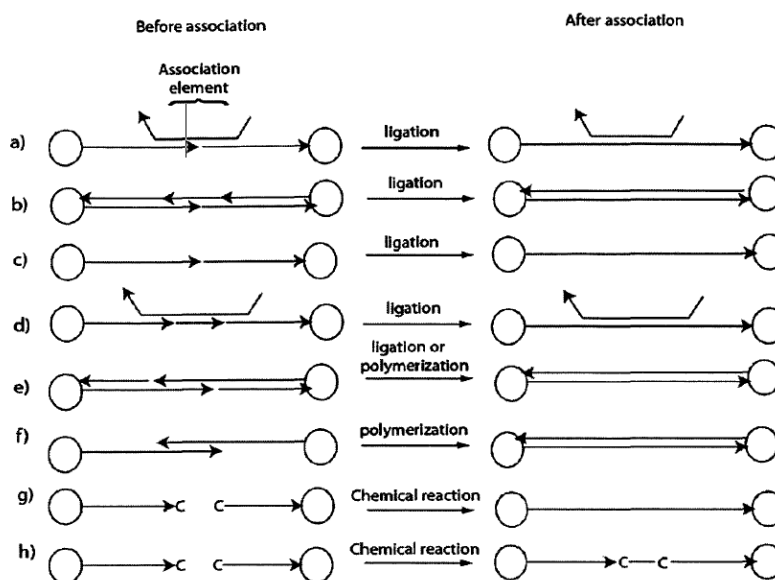
31. The '848 patent discloses “methods for detecting affinity-based interactions and functional-based interactions, and the relative strength of those interactions between molecules of interest.” EX1001, 1:10-14. “Libraries of interactors are constructed wherein the interactors comprise at least one 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.” EX1001, 1:15-19.

32. A molecule of interest (MOI) can be any molecule “about which interactive information is desired.” EX1001, 8:53-55, 10:51-59. To construct a library, each MOI is coupled with at least one nucleic acid moiety (NAM). EX1010, 8:55. Each NAM “comprises at least one unique identification nucleic acid sequence” (“identification sequence element”) that is uniquely coupled with a specific MOI, so that detection of the identification sequence element indicates that the specific MOI is involved in the interaction. EX1001, 8:43-45. Each “NAM also comprises at least one element which enables association with other NAMs” (“association element”). EX1001, 8:45-47. This “association element” allows NAMs coupled with MOIs to associate and form “associated oligonucleotides.” Thus, an “associated oligonucleotide,” which results from the association of NAMs, comprises the identification sequence elements of the component NAMs. EX1001, 9:49-50. Therefore, the qualitative and quantitative analysis of “associate oligonucleotides” provides a read-out of the interactions between the MOIs to which the component NAMs are coupled. EX1001, 20:49-21:4.

33. The coupling of at least one MOI with at least one NAM forms an “interactor,” and the “association of at least two interactors [] joined by an associated oligonucleotide” forms a “cis-reactive cell” (or “CRC”). EX1001, 9:33-38. The association between NAMs can be covalent or non covalent. EX1001, 9:50-52. Figure 5 of the ’848 patent (reproduced below) shows exemplary

associations between NAMs.

Figure 5



EX1001, Figure 5.

34. The '848 patent explains that "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 (emphasis added). The molecular interactions that can be detected according to the methods of the '848 patent include functional interactions, which may include affinity interactions. EX1001, 1:10-14, 14:23-26. The '848 patent also explains that, unlike prior art PLA methods, the invention of the '848 patent is not limited to exclusively detecting pre-defined targets or using molecule with pre-defined affinities. EX1001, 4:48-53. To detect functional interactions, a library of

interactors is prepared as discussed above, then a “secondary library of [CRCs]” is formed. EX1001, 15:65-66. In each case, a plurality of CRCs is formed, wherein each CRC “comprises at least two interactors bound in proximity to one another by an associated oligonucleotide formed from the association between at least two [NAMs].” EX1001, 41:44-47. The CRCs are subjected to conditions that stimulate “a desired functional interaction having a detectable trace.” EX1001, 41:44-47.

35. The ’848 patent teaches that “CRCs which display functional interactions must be selected for detection and/or analysis.” EX1001, 19:41-43. Filtering processes, including affinity purification, are employed during the process to “selectively separate the desired CRCs.” EX1001, 19:46-54. This selection step can be modified “according to the nature of the functional interaction that is being investigated.” EX1001, 19:44-46. “Downstream of the filtering process of CRCs the compositions of associated NAMs are detected and/or quantified.” EX1001, 19:55:57. As explained above, the analysis of associated oligonucleotides provides a read-out of the interactions between the MOIs to which the component NAMs are coupled. EX1001, 20:49-59. Such analysis can be an assay suitable for the analysis of nucleic acids, such as microarray, PCR, or sequencing. EX1001, 20:61-21:43.

B. Prosecution history of the ’848 patent

36. I am not an expert in the patent examination process. However, I have

reviewed the patent prosecution history '848 patent to understand how it came to be issued, and I include a brief summary of that history herein.

37. During prosecution, claims 20-22 and 24-47 (directed to methods of detecting functional interactions) were allowed. EX1002, 316. Then-pending claims 3 and 21 were rejected as indefinite for reciting the term “enhancement.” EX1002, 307-308. Claims 1-12, 15-17, and 19 (directed to methods of detecting affinity interactions) were rejected as allegedly not novel over Thisted et al (“Thisted,” WO 2005/026387 A1). EX1002, 308-314. Claims 13 and 14 were rejected as allegedly obvious over Thisted in view of Guille et al (“Guille,” Molecular Biotechnology 8(1):35-52, August 1997). EX1002, 314-315. Claim 18 was rejected as allegedly obvious over Thisted in view of US Pat. No. 6,692,918 (“Kurn”). EX1002, 315-316.

38. The Applicant responded by amending the claims, canceling claims 1-19 and 38-43. EX1002, 504-505. Claim 21 was amended to no longer recite “enhancement,” and claim 22 was amended to recite that “selecting...is accomplished *by* affinity purification” (emphasis added). EX1002, 504-505. Claims 44 and 45 were added, each depending from claim 21 (and therefore including all of the features of claim 21). Claims 44 and 45 recited “wherein the selective detection comprises labeling the cis-reactive cells with an affinity reagent” and “wherein the selective detection comprises introducing a modified

molecule wherein the modification permits the selective detection,” respectively.

EX1002, 503-504.

39. The Examiner allowed the claims 20-37, 44, and 45 (now issued claims 1-20) and included an Examiner’s amendment replacing step designations in claim 1 such as “a.” with designations of the format “a)”. EX1002, 522.

According to the Examiner, the claims were allowable because, e.g., neither “the closest prior art cited in the Office action” nor “another body of close prior art” (Liu, EX1038) “suggest[ed] the formation of an ‘associated oligonucleotide.’”

EX1002, 523. Independent claim 1 is copied below:

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

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

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

EX1001, 41:37-58.

VII. OVERVIEW OF PETITIONER'S ASSERTED ART

A. Kanan (EX1010)

40. Kanan is a research article published on September 30, 2004, in the journal *Nature*. Kanan also includes Supplementary Information (EX1013; “Kanan’s Supplementary Information”). EX1010, 549. Kanan’s Supplementary Information contains a description of the experimental procedures of Kanan, e.g., the steps to synthesize the pool A and pool B members and a step-by-step description of the experimental methods for reaction discovery.

41. Kanan describes a method “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.” EX1010, Abstract. The method of Kanan leverages DNA annealing to organize many substrates in a single solution into DNA sequence-programmed pairs. EX1010, 545.

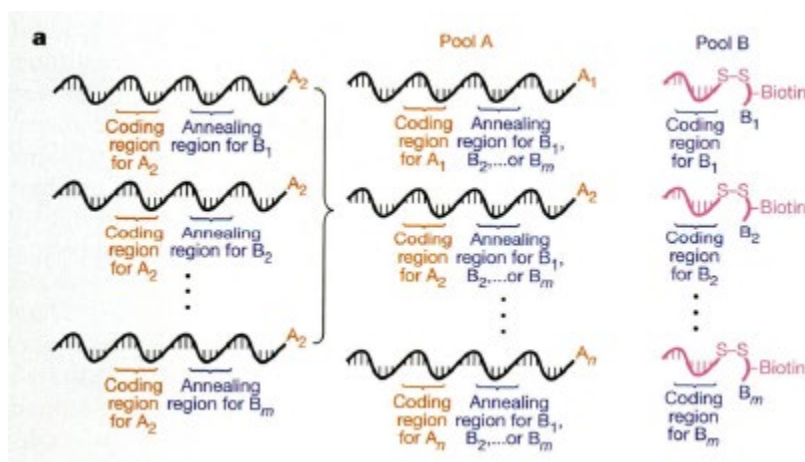
42. Briefly, Kanan discloses preparing two pools of DNA-linked “substrates” (*i.e.*, small molecules), which Kanan calls “pool A” and “pool B,” in which each small molecule was linked to an oligonucleotide. EX1010, 545.

43. Kanan discloses that each small molecule in “pool B” (*e.g.*, small molecules B₁, B₂, . . . B₉, *etc.*) was covalently linked to the 3’ end of an oligonucleotide containing a “coding region” for the specific small molecule in pool B, that is a sequence of nucleotides unique to the specific member of pool B (*e.g.*, B₉), which uniquely identifies that specific small molecule (*e.g.*, B₉). EX1010, 545. Kanan further states that each small molecule of pool B was linked to its respective oligonucleotides via a “linker containing a biotin group and a disulphide bond.” EX1010, 545. As explained below, the biotin molecule is the basis for the isolation of pairs of small molecules that form a covalent bond (*e.g.*, A₆-[covalent bond]-B₉, as depicted in Figure 1b of Kanan reproduced below), and the disulphide bond is an essential component of Kanan’s methods because it allows the oligonucleotide to be cleaved from the B small molecule. Disulphide cleavage is required for the isolation of pairs of small molecules that have formed a covalent bond and for the correct read-out of the “coding regions” for the identification of the two small molecules in the covalent bond-forming pair. All of Kanan’s methods require a *cleavable disulphide bond* that permits biotin-mediated separation of bond-forming and non-bond-forming small molecules, as described

in more detail below.

44. According to Kanan, each small molecule in “pool A” (*e.g.*, small molecules $A_1, A_2, \dots A_9$, *etc.*) was covalently linked to the 5' end of an oligonucleotide containing two regions: (i) a “coding region” for the specific small molecule in pool A, that is a sequence of nucleotides unique to the specific member of pool A (*e.g.*, A_6), which uniquely identifies that specific small molecule (*e.g.*, A_6); and (ii) an “annealing region” that is a sequence of nucleotides complementary to the “coding region” for a specific small molecule in pool B (*e.g.*, B_9). EX1010, 545.

45. Figure 1a of Kanan (reproduced below) shows the structure of exemplary pool A and B members.



EX1010, 546 (“S-S” indicates the disulphide bond).

46. Kanan’s Supplementary Information provides a detailed description of the procedure followed to synthesized the pool A and the pool B members,

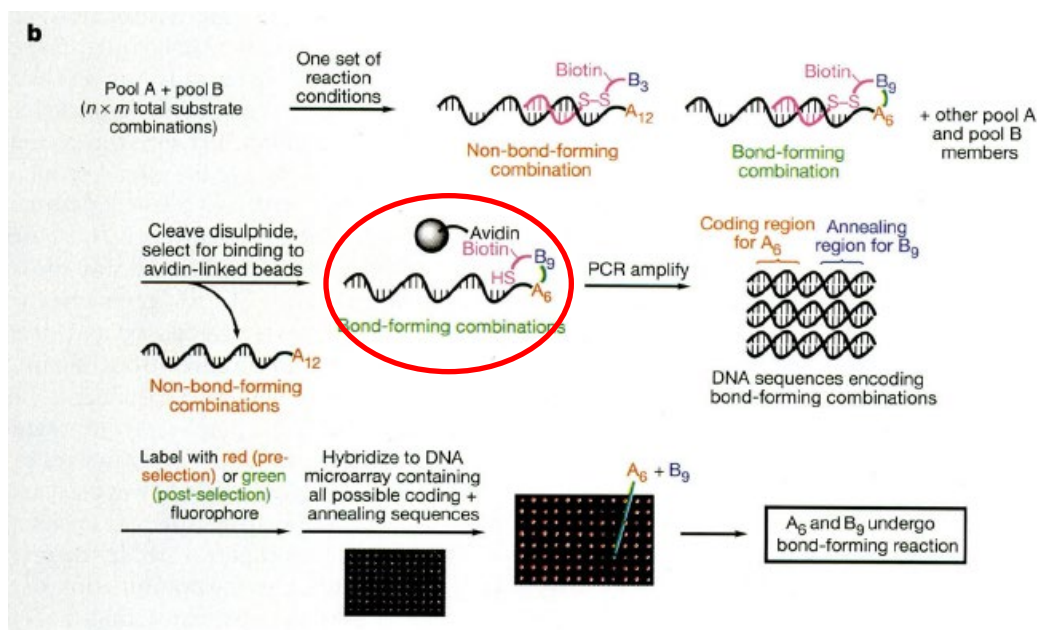
including the step-by-step protocol for the “Preparation of Pool A DNA-linked Substrate,” “Modular Assembly of Pool A Members,” and “Preparation of Pool B.” EX1013, 2-7.

47. When a pool A containing n small molecule substrates and a pool B containing m small molecule substrates 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.” EX1010, 545. Accordingly, “[o]nly substrates linked to complementary oligonucleotides experience effective molarities in the millimolar range.” EX1010, 545.

48. As explained in Kanan, the single aqueous solution was then incubated “under a set of chosen reaction conditions” to allow pool A and pool B members experiencing effective molarities in the millimolar range to react. EX1010, 545. Subsequently, Kanan discloses that the reactive pairs were separated from the non-reactive pairs according to the following procedure. After incubation under the chosen reaction conditions, Kanan states that the next step is cleavage of the disulphide bond. EX1010, 545; EX1013, 8. Kanan teaches that the cleavage of the disulphide bond must take place before the selection of reactive pairs such that after cleavage, “only pool A sequences encoding bond formation between a pool A and a pool B substrate remain covalently linked to biotin.” EX1010, 545. After cleavage of the disulphide bond, Kanan discloses a streptavidin selection step that

separates the bond-forming pairs from the non-bond-forming pairs, because only if the pool A and the pool B small molecules formed a covalent bond, a pool A nucleotide is bound to biotin via a bridging pool B molecule. Kanan explains that the streptavidin beads, to which the biotin molecules were attached, are then washed with water, formamide solutions, and heated at 65 °C and then at 90 °C. EX1013, 8. During this process, the hybridized oligonucleotides are separated. EX1013, 8. This separation is needed to obtain single stranded pool A oligonucleotides that then can be subjected to polymerase reaction and analyzed on microarrays. EX1013, 8. Kanan teaches that the pool A oligonucleotides contain both the “coding region” that uniquely identifies the A small molecule and the sequence complementary to the “coding region” that uniquely identifies the B small molecule in each covalently bonded pair. Therefore, analysis of the pool A oligonucleotides results in the identification of both the A and the B small molecules in the covalently bonded pair.

49. Figure 1b of Kanan (reproduced below) depicts the experimental procedure.



EX1010, 546. “S-S” indicates a disulphide bond, and “HS” indicates one end of the cleaved disulphide bond. As shown circled above, the molecules “selected” in Kanan’s streptavidin-affinity selection step only comprise the oligonucleotides from pool A.

50. As explained in Kanan and in the ’848 patent, the method of Kanan requires the synthesis of a pool A oligonucleotide for each binding pair to be tested for covalent-bond formation. A pool A oligonucleotide must be synthesized for binding to each one of the pool B members because it is the complementarity between the “annealing region” in the pool A oligonucleotide and the “coding region” in each pool B oligonucleotide that allows the hybridization of the two oligonucleotides. In this sense the “combination of molecules in DTS is not combinatorial” because not every pool A molecule can hybridize to any pool B

molecule. EX1001, 3:66-67. After selection, Kanan teaches identifying the bond-forming pairs by “amplification of the selected sequences by ... [PCR] followed by DNA microarray analysis.” EX1010, 545, Fig. 1b.

B. Neri (EX1011)

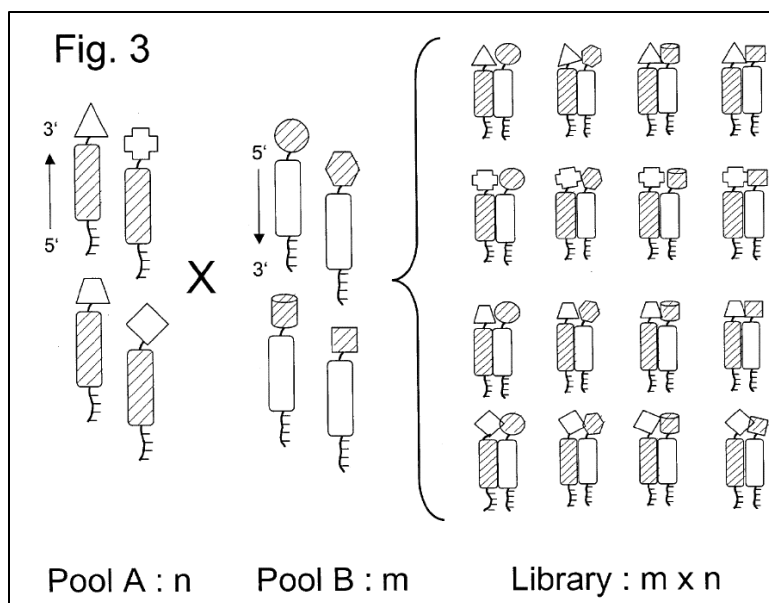
51. Neri is U.S. Patent Application Publication (No. 2004/0014090) (“Neri”) titled “Encoded Self-Assembling Chemical Libraries (ESACHEL)” (EX1011), published on January 22, 2004.

52. Neri describes a method for generating “self-assembling libraries of organic molecules.” EX1011, ¶5. According to Neri, the libraries are generated by “combinatorial self-assembly of smaller sub-libraries,” and the self-assembly is mediated by annealing of complementary oligonucleotides linked to each member of the sub-libraries.” EX1011, ¶5. Thus, Neri’s methods creating libraries comprising combinations of test molecules. Neri discloses that these libraries of test molecules are screened for binding to targets of interest. EX1011, ¶5. Neri explains that this method is relevant in the field of drug discovery, as “the isolation of specific binders against a relevant biological target typically represents the starting point in the process which leads to a new drug.” EX1011, ¶6.

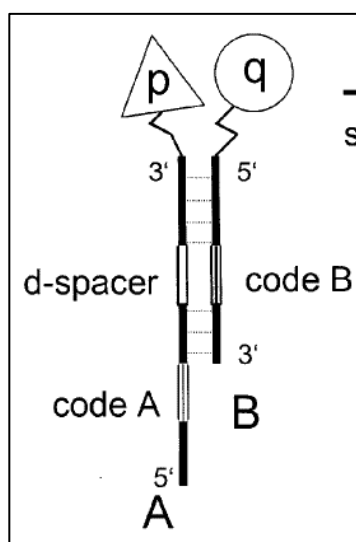
53. Specifically, Neri discloses the synthesis of chemical compounds comprising a moiety (e.g., those designated “p” or “q” in Neri) linked to an oligonucleotide, wherein the oligonucleotide comprises a “self-assembly

sequence” (“oligomerization domain”) and (optionally) a unique “sequence tag” (or “code”). EX1011, ¶¶40-45. Neri teaches that two (or more) sub-libraries of chemical compounds can be synthesized where each member of the first sub-library (“pool A”) is formed by linking each A moiety to an oligonucleotide comprising a self-assembly sequence, common to all the members of pool A, and a distinctive DNA sequence unique for each one of the molecules of pool A; and each member of the second sub-library (“pool B”) is formed by linking each B moiety to an oligonucleotide comprising a self-assembly sequence, common to all the members of pool B, and a distinctive DNA sequence unique for each one of the molecules of pool B. EX1011, ¶¶48-56.

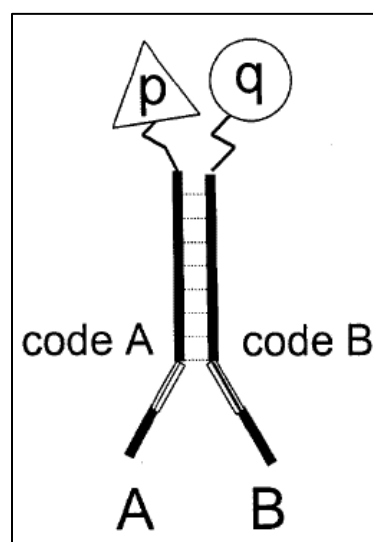
54. Neri explains that the self-assembly sequence common to all the members of pool A and the self-assembly sequence common to all the members of pool B are complementary and their hybridization allows for the heterodimerization of pool A and pool B chemical compounds. EX1011, ¶57. The heterodimerization of pool A and pool B chemical compounds, generates a combination of molecules (*i.e.*, an A molecule + a B molecule), which can then be tested for binding of combinations of moieties (e.g., combinations of p and q) to a specific target. Neri depicts the self-assembly of pool A and pool B library members in Figures 3, 5, and 7, reproduced below:



EX1011, Figure 3.



EX1011, Figure 5 (excerpted).



EX1011, Figure 7 (excerpted).

In the figures above, Neri depicts hybridization of the A and B oligonucleotides as horizontal lines. EX1011, Figs. 5, 7.

55. Neri does not disclose evaluating the interaction (e.g., covalent chemical reaction) between the moieties (labeled “p” and “q” in the figures above)

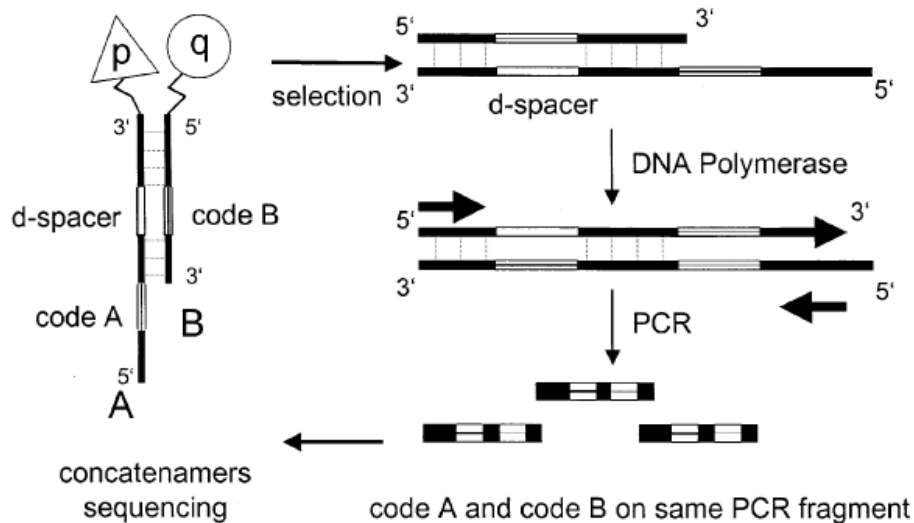
linked to the oligonucleotides of pool A and pool B, but instead describes a strategy for generating combinations of molecules derived from the assembly of the molecules through the linked oligonucleotides (*i.e.*, an A molecule + a B molecule), and then testing the A-B pairs of molecules for binding of their combinations of moieties (e.g., p and q) to a separate target having no nucleic acid attached thereto.

56. Neri discloses that target-binding members of the library (*i.e.*, an A molecule + a B molecule) are assayed by a “biopanning” method, in which the self-assembled A and B library members are panned across an immobilized target molecule to identify binding properties between the library and the target molecule. EX1011, ¶¶31, 59, 72, 83-84, 144, claim 19. Neri explains that its biopanning method can be performed by “exposing the library to the target protein on [a] bead, followed by the physical removal of the bead from the library solution, followed by judicious washing of the bead, to reduce the amount of non-specific binders on the bead.” EX1011, ¶59 *see also*, EX1011, Abstract, ¶¶31, 72, 83-84, 144, claim 19. Neri’s biopanning process is a selection process that achieves “physical separation of the complex between ESACHEL members and the target molecule, from the pool of non-bound ESACHEL members” by “immobilizing the target molecule of a solid support (e.g. a plastic tube, a resin, magnetic beads, etc.).” EX1011, ¶84.

57. In Neri's embodiment depicted in Figure 5, Neri discloses that "[t]he oligonucleotides of sub-library A bear chemical entities at the 3' end. Towards the 3' extremity, the DNA sequence is designed to hybridize to the DNA sequences at the 5' extremity of oligonucleotides of sub-library B. The hybridization region is interrupted by a small segment. In sub-library A, this small segment is conveniently composed of phosphodiester backbone without bases (termed d-spacer []); in sub-library B, the corresponding short segment will have unique sequence for each member of the sub-library (therefore acting as 'code' for the sub-library B). By contrast, oligonucleotides of sub-library A have their distinctive code towards the 5' extremity." EX1011, ¶29.

58. Figure 5 of Neri is copied below:

Fig. 5



EX1011, Figure 5.

59. Neri discloses that after biopanning, the “[o]ligonucleotides of sub-library B remain stably annealed to the oligonucleotides of sub-library A.” EX1011, ¶70. Neri states that the “shorter” oligonucleotide (“B” in Figure 5 of Neri reproduced above) “can work as a primer for a DNA polymerase reaction on the template A.” EX1011, ¶70. According to Neri, DNA polymerization will generate a DNA segment “carrying both code A and code B,” and this DNA segment “can be amplified (typically by PCR), using primers which hybridize at the constant regions of the DNA segment.” EX1011, ¶70. DNA “segments” derived from different pairs of “p” and “q” moieties and generated as described above can be linked together in concatamers, which can then be “read” by sequencing to identify the members of the binding pairs. EX1011, ¶71.

60. Neri’s prophetic Example 3 relates to the libraries of Figure 5. In Example 3, Neri discloses annealing of the oligonucleotides of pool A and B and subsequent PCR. EX1011, ¶¶111]-119.

C. Famulok (EX1012)

61. Famulok, “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” (EX1012) was published in May 2002 in Volume 20 in the journal *Nature Biotechnology*. Famulok is a commentary on the research article “Protein detection

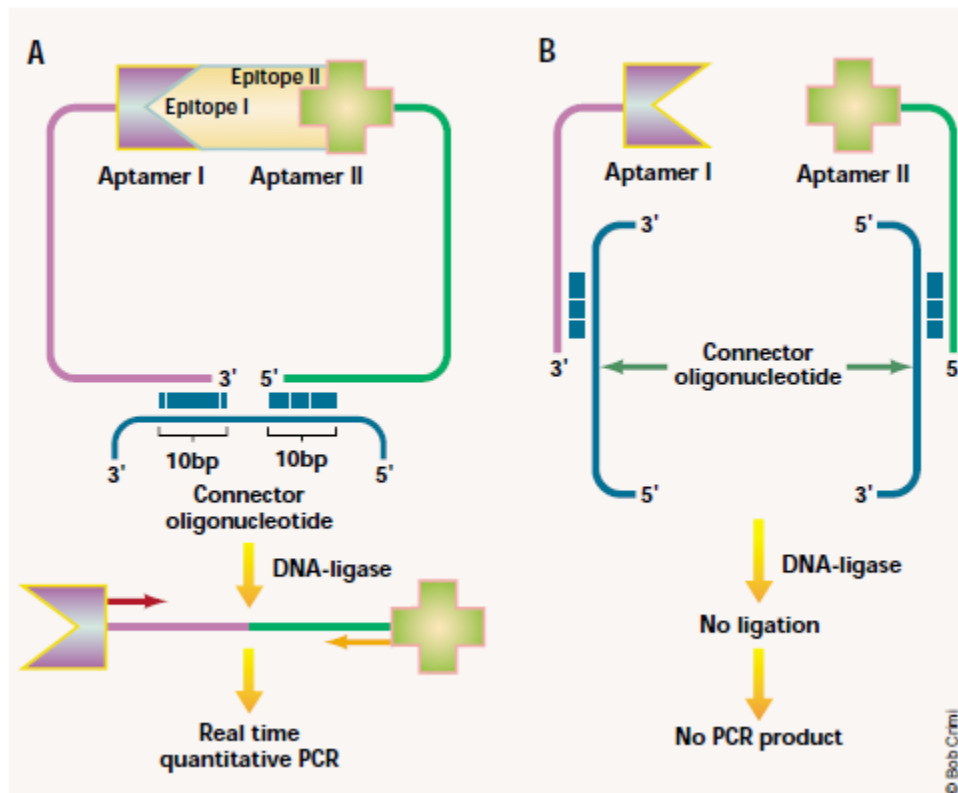
using proximity-dependent DNA ligation assays” by Fredriksson *et al.*, published in the same Volume of the journal Nature Biotechnology (EX1020; “Fredriksson”). As discussed below, Famulok’s disclosures are very similar to those of Fredriksson. This makes sense, because Famulok is a commentary on Fredriksson.

62. Famulok describes and comments on the technology disclosed in Fredriksson: Proximity Ligation. EX1012, 448. Fredriksson discloses using a pair of aptamers for the detection of proteins. EX1012, 448. Aptamers are single-stranded oligonucleotides that fold into a definite architectures and once folded, are capable of binding specific targets such as proteins. Fredriksson further discloses adding to each aptamer “a different DNA-sequence extension that does not interfere with its folding and is not required for target recognition.” EX1012, 448. According to Fredriksson, this DNA-sequence extension functions as a “molecular tag” that can be used to identify the specific aptamer and thereby the specific target bound by the aptamer.

63. Fredriksson explains that, when two aptamers, each containing a specific DNA-sequence extension, bind to a same target, the ends of the DNA-sequence extensions come “into close spatial proximity.” EX1012, 448. Fredriksson teaches that a “splint” (or “connector”) oligonucleotide, complementary to the ends of both the DNA-sequence extensions, is then hybridized with the two ends, which are “subsequently ligated together by a T4

DNA ligase.” EX1012, 448. The ligated nucleic acid molecules can then be used
“as a PCR template and the amplified PCR product can be monitored and
quantified under real-time PCR conditions, whereas no signal is obtained with
unligated [DNA-sequence extensions].” EX1012, 448.

64. Figure 1 of Famulok (reproduced below) depicts Fredriksson’s
proximity ligation assay.



EX1012, 449.

65. Famulok further notes that “the fact that two different epitopes will
have to be bound, regardless whether antibodies or aptamers are used, would make
it difficult to adapt the method to small organic molecules or even small peptides.”

EX1012, 449.

D. Baez (EX1003)

66. Baez is a U.S. Patent (No. 6,511,809) titled “Method for the Detection of an Analyte by Means of a Nucleic Acid Reporter” (EX1003) published on January 28, 2003.

67. Baez describes “[a] process . . . for the detection of an analyte utilizing a nucleic acid label as a reporter.” EX1003, Abstract. The method of Baez “relates to immune assays” and leverages “nucleic acid amplification as a reporting mean of the detection of an analyte.” EX1003, 1:12-15.

68. Baez explains that in its methods, “the analytes contain at least two reporter conjugate binding sites.” EX1003, 13:33-34. Baez also discloses that when an analyte is to be immobilized on a solid surface, the analyte must also comprise and additional binding site to bind to a “capture reagent” on the solid surface (typically an antibody). EX1003, 11:14-18.

69. Specifically, Baez teaches using a pair of molecules (*e.g.*, a pair of antibodies), which are both capable of binding to a same analyte (“a binding pair”), conjugated with a “nucleic acid-label.” EX1003, 7:48-57. Baez uses the term “reporter conjugate” to refer to such conjugates “comprising a ‘nucleic acid-label’ coupled to a member of a binding pair.” EX1003, 7:48-57. Baez explains that, when the two reporter conjugates are bound to the same analyte, their nucleic acid

labels come into “spatial proximity” and can then be joined to form a single nucleic acid molecule. EX1003, 11:21-24. The single nucleic acid molecule can then be amplified by, e.g., PCR. EX1003, 11:21-24.

70. Baez discloses methods that use a solid-phase support comprising “immobilized streptavidin or avidin.” EX1003, 17:24-27; *see also*, EX1003, 17:52-54, claims 2, 12.

71. Figure 2 of Baez (reproduced below and annotated for illustrative purposes) depicts a pair of “reporter conjugates” bound to an analyte immobilized on a solid support.

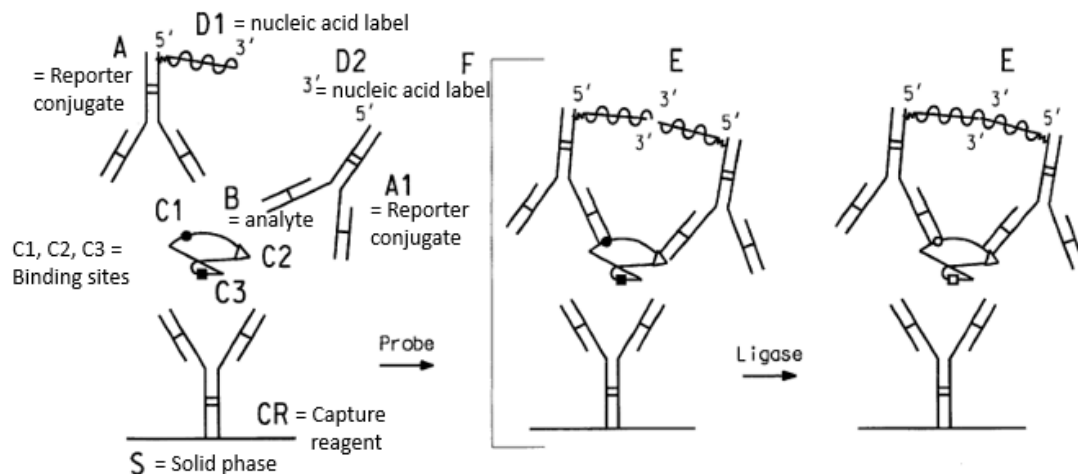


FIG. 2

EX1003, Figure 2

E. Landegren (EX1004)

72. Landegren is a PCT Publication (No. WO01/61037) titled “Methods

and Kits for Proximity Probing” (“Landegren”) (EX1004), published on August 23, 2001.

73. Landegren discloses a “rapid and convenient assay for the detection and/or quantification of one or several analytes in solution using so called proximity probes.” EX1004, Abstract. A proximity probe comprises a binding moiety (*e.g.*, an antibody or a nucleic acid, such as an aptamer) and a nucleic acid. EX1004, 3. Landegren teaches that when two proximity probes bind “pair wise” to an analyte, the two nucleic acids come into proximity, such proximity promotes a “detectable interaction” (*i.e.*, the two nucleic acids are linked to form a single nucleic acid molecule), which is then “detected in a secondary step” (*i.e.*, the single nucleic acid is amplified by PCR and thereby detected). EX1004, 3. This detection step does not involve sequencing of the nucleic acids.

74. Landegren discloses that its methods are performed in solution-phase, which, according to Landegren, are advantageous over solid-phase assays. For example, Landegren states that “[a]ssays that use a solid phase require considerable time and effort for the analysis.” EX1004, 1. Landegren further discloses that in solid-phase assays, “[t]he binding of reagents and analytes to the surface is a time consuming process and the washing steps must be precisely and reproducibly controlled between samples to give exact results.” EX1004, 1. Further, “[s]olid phase assays are also more difficult to automate than homogenous

assays.” EX1004, 1. Landegren’s solution-phase assays, however, provide the “ability to detect and quantify one or several analytes in solution in a homogenous one tube assay with high sensitivity and specificity” and can be “performed in solution without the need of a solid phase.” EX1004, Abstract.

F. Freskgard (EX1009)

75. Freskgard is a PCT Publication (WO 2005/003778) titled “A Method For Identifying A Synthetic Molecule Having Affinity Towards A Target” (EX1009), published on January 13, 2005. EX1009, (43), (54).

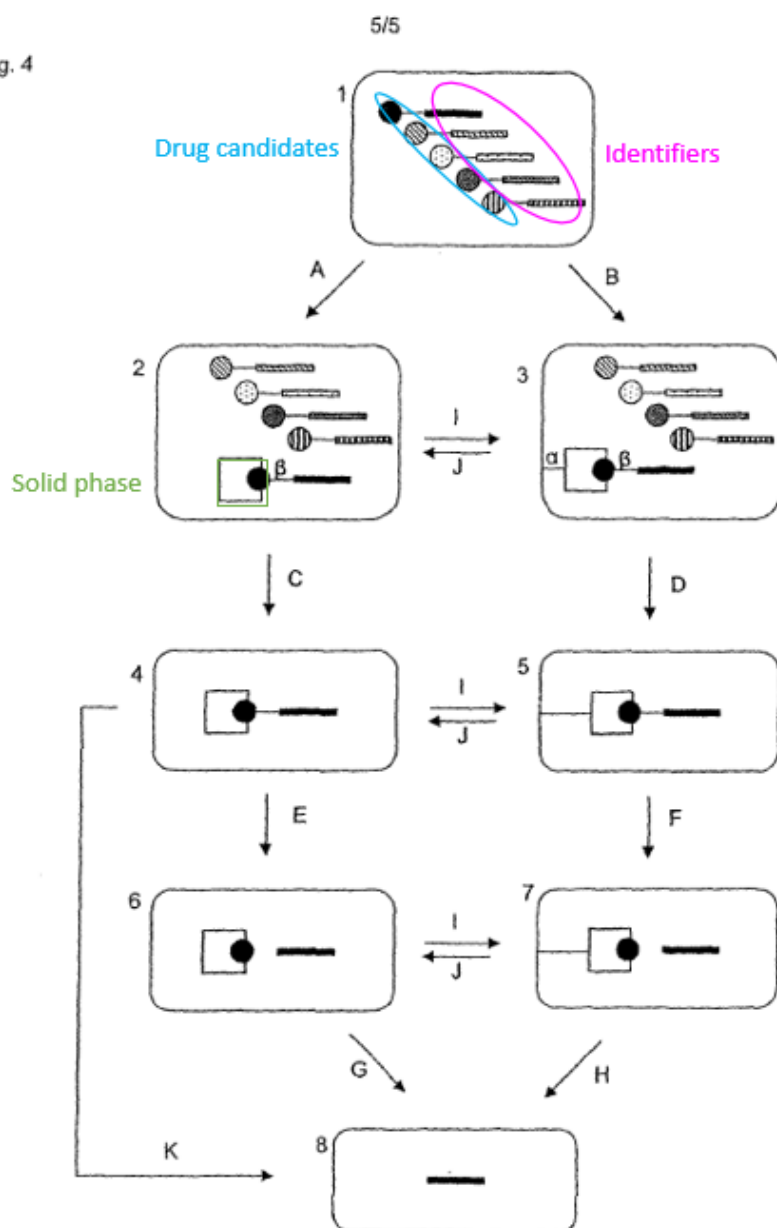
76. Freskgard discloses “a method of identifying from a library a synthetic molecule having affinity towards a target.” EX1009, 1:10-13. The method of Freskgard can be used in drug discovery to select “lead compounds,” which are usually “small organic molecules that demonstrate a desired biological activity on a target.” EX1009, 1:19-34.

77. In the method of Freskgard, a library of complexes, wherein each complex is formed by a drug candidate and an “identifier,” is produced. EX1009, 43:6-14. According to Freskgard, each identifier contains a specific nucleic acid sequence that uniquely identifies the drug candidate to which it is linked. EX1009, 35:31-33. The library is then “subjected” to a target in a panning method, in which complexes containing drug candidates that have affinity for the target bind to the target. EX1009, 43:6-44:15. The target (with any complex bound to it) is

immobilized on a solid phase either before or after being incubated with the complexes. EX1009, 43:6-44:15. The non-bound complexes are then washed away. EX1009, 43:6-44:15. The target-complex aggregates are recovered, the “identifiers” are separated from the drug candidate, and amplified and decoded “by sequencing the identifier.” EX1009, 2:30-31.

78. A detailed depiction of the method of Freskgard is provided in Figure 4 (reproduced below and annotated for illustrative purposes).

Fig. 4



EX1009, Figure 4 (annotated).

VIII. LEGAL BASIS FOR MY ANALYSIS

A. Person of ordinary skill in the art

79. I understand that patent law analyses are performed from the viewpoint of a person of ordinary skill in the art (“POSA”) at the relevant priority

date. I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, who thinks along conventional wisdom in the art, and is a person of ordinary creativity. A POSA for the '848 patent, as of July 2005, would have had an advanced degree, such as a Ph.D. in Chemistry, Organic Chemistry, Biochemistry, Biotechnology, Molecular Biology, or a related discipline, with about 2 years of experience in laboratory research involving small molecule, proteins, nucleic acid chemistry, and hybridization techniques. A POSA would have had familiarity with high throughput assays, such as screening and sequencing techniques. A POSA could also be a person with a lower level of formal education and more years of technical or professional experience.

80. I have reviewed the definition of a POSA in Dr. Nelson's declaration. EX1005, ¶¶23-26. Dr. Nelson's definition of a POSA is similar to my own, and I would have reached the same conclusions in my declaration had I applied Dr. Nelson's definition.

B. Obviousness

81. I understand that a claim is unpatentable as obvious if the differences between the claimed invention and the asserted prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made. Similarly, a claim is invalid as obvious if a prior art reference, or two or more prior art references in combination, disclose expressly or inherently every

claim limitation so as to render the claim as a whole obvious to a POSA at the time the invention was made.

82. I understand that obviousness is ultimately a question of law based on a determination of a number of factual issues. Those factual issues relate to: (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention as a whole, (3) the level of ordinary skill in the art at the time the invention was made, and (4) objective indicia of nonobviousness that reflect, for example, the contemporaneous response to the invention at the time, such as commercial success, long-felt need, failure of others, industry-wide praise, and unexpected results.

83. I understand that care must be taken to avoid the impermissible use of hindsight in an obviousness analysis. I understand that it is improper to use the invention as a plan or template for hindsight reconstruction of bits and pieces of the prior art to form the invention.

84. It is my further understanding that a patent claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. There must be a reason why it would have been obvious to modify and/or combine the prior art to arrive at the claimed invention. I understand that the patent challenger has the burden to show that a POSA in the relevant field had a reason to combine the elements in the manner

claimed when asserting obviousness in view of a combination of references.

85. I understand that there is no suggestion or motivation to make a modification to a prior art reference if the proposed modification would render the prior art unsatisfactory for its intended purpose. I also understand that an obviousness allegation cannot be supported by a combination of references that would require a substantial reconstruction and redesign of the elements shown in the primary reference or a change in the basic principle under which the primary reference was designed to operate.

86. I understand that where there is a reason to modify or combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of success in doing so. I also understand that conclusory statements lacking factual substantiation are insufficient for evaluating reasonable expectation of success as part of an obviousness determination. Instead, I understand that the Petitioner must articulate a basis on which it concludes that it would have been obvious to make the claimed invention.

87. I have been informed that objective factors concerning nonobviousness, also known as “objective indicia” or “secondary considerations,” may be probative nonobviousness. I have been informed that objective indicia can include such factors as commercial success, long-felt need, failure of others, industry praise, and unexpected results. I have also been informed that, in order for

the objective indicia to have weight, there must be a nexus between the evidence of the objective indicia and the claim as a whole. I understand that, without nexus, evidence of objective indicia does not support a finding of non-obviousness. I further understand that evidence of objective indicia will have no weight if the evidence is related to an unclaimed feature or features found in the prior art.

IX. CLAIM CONSTRUCTION

88. I understand that terms of the claims generally are given their ordinary and customary meaning in light of the claim language, specification, and prosecution history—that is, the meaning that the term would have to a POSA in question at the time of the invention. This is the standard I have applied here.

89. The '848 patent provides specific descriptions of several claim terms. The ordinary and customary meanings of these terms in light of the claim language, the specification, and prosecution history are provided below.

90. **Molecule of interest (MOI):** Claim 1 recites the term “molecules of interest” in the preamble (detecting functional interactions between at least two molecules of interest) and in step (a) when forming interactors by “coupling each molecule of interest with at least one nucleic acid moiety.” According to the specification:

the term ‘molecule of interest’ (MOI) refers to a molecule about which interactive information is desired.... Examples of suitable MOIs include, but are not limited to, whole proteins, protein domains,

peptides, peptoids, functional enzymes, low molecular weight compounds, small molecules, polymers, non-proteinaceous cellular products, virus particles, cells metabolites, lipids, carbohydrates, nucleic acids, inorganic compounds or combinations thereof.

EX1001, 8:53-62. Thus, a POSA would understand that an MOI is a molecule about which interactive information is desired. I understand that Dr. Nelson agrees that an MOI is a molecule about which interactive information is desired. EX2009, 34:22-35:20; EX1005, ¶45.

91. **Nucleic acid moiety (NAM):** Claim 1 recites the term “nucleic acid moiety” in step (a), reciting that the nucleic acid moiety is coupled to a molecule of interest and comprises “an identification sequence element and an association element.” According to the specification:

the term nucleic acid moiety (NAM) refers to a nucleic acid molecule which is coupled to at least one molecule of interest (MOI). A NAM comprises at least one unique identification nucleic acid sequence so that detection of that sequence infers involvement of the coupled MOI. A NAM also comprises at least one element which enables association with other NAMs.

EX1001, 8:41-52. Thus, a POSA would understand that a NAM of the '848 patent is coupled to an MOI, and further comprises an identification sequence element and an association element. I understand that Dr. Nelson agrees that a NAM is coupled to an MOI, and that a NAM further comprises an identification sequence

element and an association element. EX2009, 36:4-37:6; EX1005, ¶46.

92. **Interactor:** Claim 1 recites the term interactor as being formed by “coupling each molecule of interest with at least one nucleic acid moiety....” According to the specification, “the term ‘interactor’ refers to at least one MOI coupled with at least one NAM.” EX1001, 9:33-34. Thus, a POSA would understand that an interactor requires an MOI coupled to at least one NAM. I understand that Dr. Nelson agrees that an interactor requires an MOI coupled to at least one NAM. EX2009, 37:12-38:8; EX1005, ¶44.

93. **Cis-reactive cell (CRC):** Claim 1 recites the term cis-reactive cell in step (b) and states that 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.” According to the specification, “the term ‘Cis Reactive Cell’ (CRC) refers to an association of at least two interactor moieties, joined by an associated oligonucleotide.” EX1001, 9:35-37. Thus, a POSA would understand that a CRC requires at least two interactors. I understand that Dr. Nelson agrees that a CRC requires at least two interactors bound in proximity to one another. EX2009, 38:18-39:20; EX1005, ¶49.

94. **Selecting all cis-reactive cells.** Claim 1(d) recites, “selecting all cis-reactive cells exhibiting the detectable trace.” EX1001, 41:53-54. Claim 1(b)

recites forming a plurality of cis-reactive cells, and claim 1(c) recites subjecting the cis-reactive cells to conditions that stimulate a desired functional interaction.

EX1001, 41:39-52. The 848 patent specification states that, “[t]o detect functional interactions in a pool of CRCs *the CRCs* which display functional interactions must be selected for detection and/or analysis.” EX1001, 19:41-43. Thus, a POSA would understand that “selecting all cis-reactive cells” in step 1(d) refers to selecting from the CRCs that formed in step (b) all CRCs exhibiting a detectable trace achieved in step (c). I understand that Dr. Nelson agreed that the selecting step (d) requires selecting cis-reactive cells. EX2009, 43:15-24.

95. Claim terms not addressed above are also given their ordinary and customary meaning.

X. DR. NELSON FAILS TO DEMONSTRATE THAT ANY OF THE CHALLENGED CLAIMS IS UNPATENTABLE AS OBVIOUS OVER THE CITED ART.

A. Dr. Nelson fails to demonstrate that the challenged claims would have been obvious over Kanan in view of Neri and further in view of Famulok.

96. Dr. Nelson states that “[w]hile Kanan does not teach self-assembly of all library members or the use of discrete identification sequences separate from the association region on each interactor, 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.” EX1005, ¶82. Further, Dr. Nelson argues that

“[a] POSA would have been motivated to combine the teachings of Kanan and Neri with the teachings of Famulok because the splint oligonucleotide disclosed in Famulok would create a DNA strand that does not rely on polymerization to encode the anticodon of the shorter library member to the sequence of the longer library member.” EX1005, ¶177.

97. I disagree. As I articulate below, the proposed combination of Kanan and Neri (or further in view of Famulok) does not teach or suggest all the elements of the challenged claims. As discussed below, Kanan’s methods require disulphide cleavage and removal of the oligonucleotides from the pool B library members, eliminating the alleged interactors and CRCs and precluding the ability to select any CRCs. Further, POSA would have understood that the reference combination proposed by Dr. Nelson has fundamental technical defects that yield false positive and false negative results. In view of those technical defects, a POSA would not have been motivated to combine the teachings of Kanan and Neri (or Kanan, Neri, and Famulok) as Dr. Nelson proposes, and would not have had a reasonable expectation of success in doing so.

1. Dr. Nelson fails to demonstrate that the combination of Kanan and Neri teaches or suggests all of the elements of the challenged claims.

a. The combination of Kanan and Neri does not teach or suggest claim 1 step (d) “selecting all cis-reactive cells exhibiting the detectable trace”.

98. Claim 1 of the '848 patent in step (a) recites “forming a plurality of interactors by coupling each molecule of interest with at least one nucleic acid moiety.” EX1001, 41:39-41. As I explained above at ¶92, an “interactor” is formed by the *coupling* of at least one “molecule of interest” (“MOI”) with at least one “nucleic acid moiety” (“NAM”). Thus, each “interactor” requires (i) a “MOI” *coupled* with (ii) a “NAM.” Dr. Nelson acknowledges that “[t]he 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).*’” EX1005, ¶44. I understand that Dr. Nelson further testified at deposition that “interactors comprise at least two distinct parts which are coupled, one part is the molecule of interest and one part is the nucleic acid moiety.” EX2009, 37:12-22. Indeed, in multiple instances Dr. Nelson refers to “interactors [formed] by coupling each molecule of interest with a nucleic acid moiety.” *See e.g.*, EX1005, ¶¶48, 88-90, 106. I understand that at his deposition, Dr. Nelson did not dispute the meaning of these terms. EX2009, 34:22-38:8.

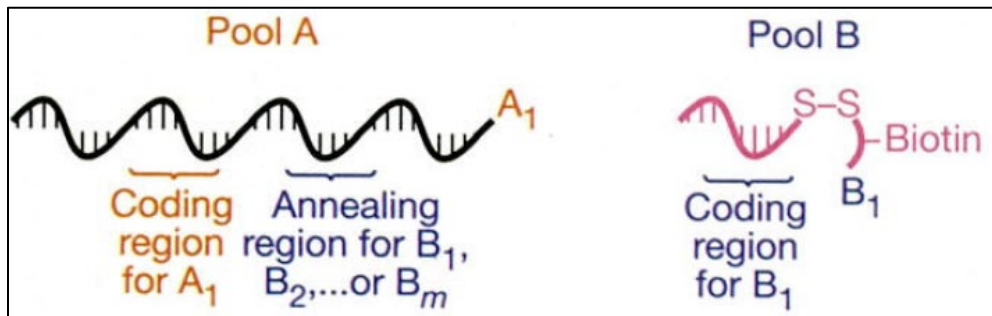
99. Claim 1 of the '848 patent in step (b) recites “forming a plurality of

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....” EX1001, 41:43-49. As I explained above at paragraph 33, the “association of at least two interactors [] joined by an associated oligonucleotide” forms a “Cis Reactive Cell” (or “CRC”). EX1001, 9:33-38. Thus, *a CRC contains at least two interactors, and each interactor contains “at least one MOI coupled with at least one NAM.”* EX1001, 9:33-34. As explained in the ’848 patent “coupled with” means linked to and “[p]referably the coupling between the MOI and the NAM is covalent and stable or at least of high affinity.” EX1001, 11:28-29. Dr. Nelson acknowledges that “[t]he creation of CRCs through the [a]ssociation of interactors is a key feature of the current invention....” EX1005, ¶40. Dr. Nelson further explains that “[i]n Figure 4(B) of the ’848 Patent, ‘[l]ibrary morphology after *association of the interactors to construct CRCs* is illustrated.’” EX1005, ¶108. I understand that, at his deposition, Dr. Nelson did not dispute the meaning of cis-reactive cells. EX2009, 38:18-39:20 (“a cis-reactive cell of the ’848 patent requires at least two interactors [bound] in proximity to one another....”).

100. Claim 1 of the ’848 patent in step (d) recites “selecting all cis-reactive cells exhibiting the detectable trace...” EX1001, 41:53-54. As Dr. Nelson agrees, step (d) requires selecting *CRCs* from the *CRCs* that were formed in step (b). “The

[] interactors [are] ‘permitted to interact and equilibrate, creating a secondary library of ‘cis reactive cells’ (CRCs) . . . Once the CRC library is constructed the functional interaction [] is stimulated . . . Next ‘*the CRCs* which display functional interactions *must be selected* for detection and/or analysis.’” EX1005, ¶¶49-51.

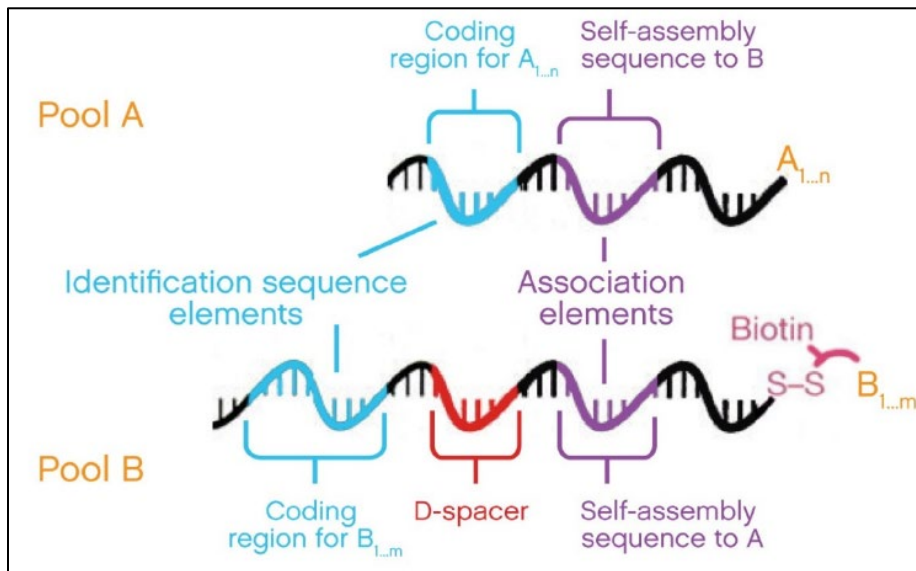
101. Kanan teaches linking each substrate of pool B to its respective oligonucleotide *via* a “linker containing a biotin group and a disulphide bond.” EX1010, 545. Kanan, in Figure 1 (reproduced below), depicts the structure of an exemplary molecule B designated “B₁,” and of an exemplary molecule A designated “A₁,” coupled with their respective nucleic acid moieties.



EX1010, Figure 1.

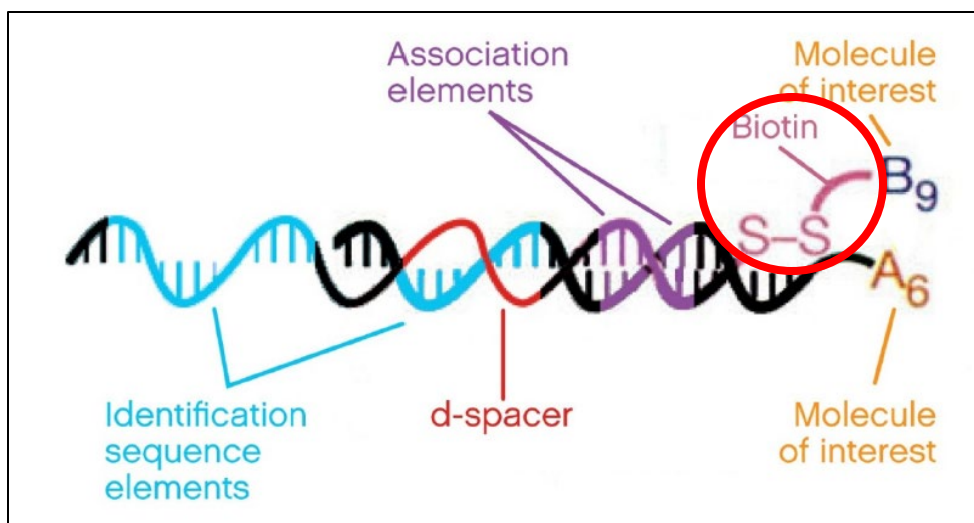
102. Dr. Nelson agrees with me that “Kanan teaches each pool B substrate is linked ‘to its corresponding oligonucleotide by *a linker* containing a biotin group and *disulphide bond*.’” EX1005, ¶119 (emphasis added). According to Dr. Nelson, “[a] POSA would have known that the self-assembly sequence, ‘*dspacer*,’ and identification elements as taught in Neri could have been readily applied to oligonucleotides taught in Kanan.” EX1005, ¶105. Dr. Nelson also “included a

figure[] to represent the library members in Kanan with the additional elements of Neri.” EX1005, ¶114. The figure that Dr. Nelson created is reproduced below and shows that, in his proposed combination of Kanan and Neri, a disulphide bond links a pool B polynucleotide and a pool B substrate (the latter designated as “B_{1...m}” in the figure below).



EX1005, ¶114.

103. Dr. Nelson goes on to explain that, when combining Kanan with Neri, “the association elements (self-assembly sequences) [] would allow all interactors to interact” to form CRCs. EX1005, ¶115. Dr. Nelson provides a figure to show “a cis-reactive cell formed by interactors from the pool A and pool B library members in Kanan combined with the additional elements of Neri.” EX1005, ¶115. Dr. Nelson’s figure is reproduced below and clearly shows that in pool B a disulphide bond (shown as “S-S”) couples a substrate of pool B to its oligonucleotide.



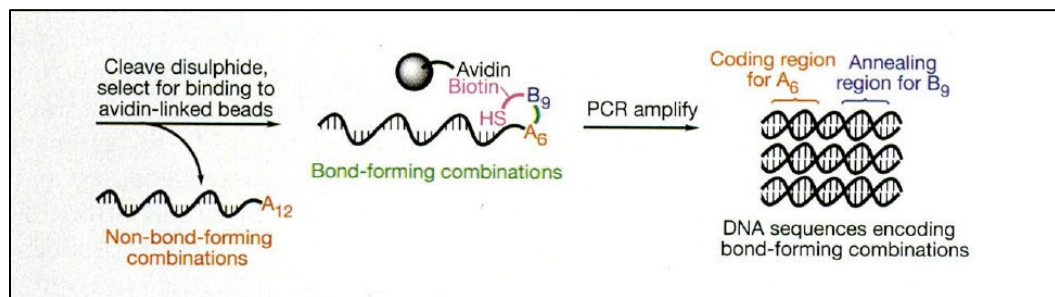
EX1005, ¶115 (annotated, circle added).

104. Thus, in Dr. Nelson’s alleged CRC of Kanan and Neri, in one of the two alleged interactors (the alleged interactor comprising substrate B and its oligonucleotide, in Dr. Nelson’s figure above) a disulphide bond couples the substrate with its oligonucleotide, *per* Kanan.

105. In his description of step (c), Dr. Nelson explains that “Kanan teaches subjecting the CRCs, such as those generated from the combination of Kanan and Neri, to conditions that stimulate a desired functional interaction with a detectable trace,” and that the incubation is “followed by *cleavage of the disulphide bonds.*” EX1005, ¶119 (emphasis added).

106. Thus, the *cleavage of the disulphide bond in step (c) uncouples the linkage between the substrate and its oligonucleotide* in one of the alleged interactors of the alleged CRC (again, the alleged interactor comprising substrate B and its oligonucleotide, in Dr. Nelson’s figure above). In other words, the cleavage

of the disulphide bond *destroys an alleged interactor* of pool B in step (c), because the cleavage of the disulphide bond *uncouples* the pool B substrates from the pool B oligonucleotides. Thus, in the combination of Kanan and Neri, the destruction of one of the alleged B interactors, in step (c), also destroys the alleged CRCs containing it, because a CRC must contain at least two interactors. This is evidence in Kanan's Figure 1b, copied below.



EX1010, Figure 1b. As shown above, Kanan teaches first “cleav[ing] disulphide,” and *then* “select for binding to avidin-linked beads” as two separate steps. EX1010, Figure 1b.

107. I understand from Dr. Nelson's declaration testimony that he agrees that the cleavage of the disulphide bond precedes the selection step in the combination of Kanan and Neri. In his description of step (d), Dr. Nelson relies only on Kanan for teaching the selection step. “Kanan teaches selecting the CRCs, such as those generated from the combination of Kanan and Neri . . . A POSA would have understood that the use of biotin-streptavidin capture would allow selection of only the CRCs with bond-forming combinations, i.e., demonstrate a

detectable trace.” EX1005, ¶122.

108. At his deposition, I understand that Dr. Nelson confirmed that Kanan’s disulphide cleavage precedes the selection step:

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

A Uh-huh.

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

A Avidin, but that is correct.

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

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

EX2009, 62:19-63:7.

109. I agree with Dr. Nelson on this point. In Kanan, cleavage of the disulphide bond is required for the isolation of pairs of substrates that form a covalent bond, and such cleavage must take place *before* streptavidin affinity selection of the bond-forming pairs. This is because, upon cleavage of the disulphide bond “only pool A sequences encoding bond formation between a pool A and pool B substrate remain covalently linked to biotin,” EX1010, 546, enabling

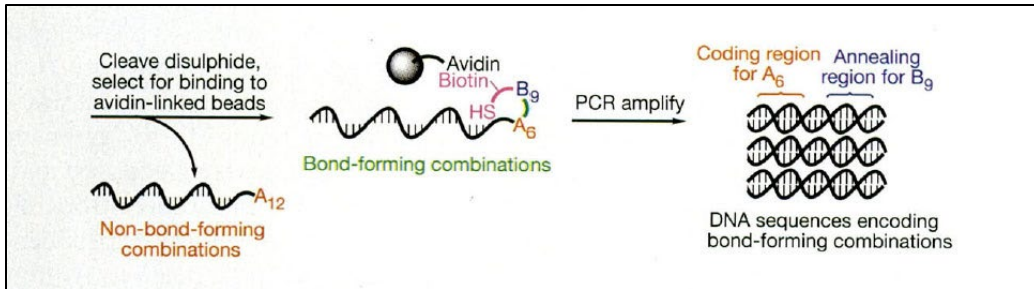
selection of covalent bond-forming pairs through streptavidin affinity selection.

110. Kanan's Supplementary Information confirms the order of steps in Kanan's methods:

[a]fter the reaction . . . the solution was diluted with 20 μ L of H₂O and passed through a gel filtration microcentrifuge column . . . To the eluant was added 150 μ L of a 0.1 M aqueous solution of tris(2-carboxyethyl)phosphine hydrochloride in 1.0 M sodium phosphate, pH 8.0 to *effect disulfide cleavage*. After 1 h at 25 °C, this solution was added to a 20 pmol binding-capacity aliquot of streptavidin-linked magnetic particles.

EX1013, 8. I understand that Dr. Nelson confirmed at his deposition that Kanan's Supplemental Information also teaches performing disulphide cleavage before any selection step. EX2009, 72:10-73:16.

111. Dr. Nelson's analysis confirms that there are no longer any CRCs to select in step (d) because to illustrate the workflow of the combination of Kanan and Neri, Dr. Nelson reproduced in his declaration Figure 1 of Kanan. EX1005, ¶122. Figure 1 of Kanan (reproduced below) shows that the disulphide bond linking the B substrates to their respective nucleic acids is *cleaved (uncoupled from the substrate B) before the streptavidin selection step*.



EX1010, 546.

112. Further, for step (d) Dr. Nelson states “the biotin-streptavidin capture would allow selection of only . . . bond-forming combinations . . . because *only those combinations would have the linked biotin* with affinity for streptavidin-linked magnetic particles.” EX1005, ¶124; *see also, id.*, ¶119. Thus, the disulphide bond *must be cleaved before streptavidin selection*, otherwise all pairs (bond-forming pairs and non-bond-forming pairs) would *contain the biotin that is subsequently selected using streptavidin or avidin for analysis*.

113. Thus, a POSA would have understood that when subjecting Dr. Nelson’s proposed modified cis-reactive cells to the workflow of the Kanan and Neri combination, streptavidin affinity selection (to select only bond-forming combinations) would take place *after* disulphide bond cleavage. Since cleavage of the disulphide bond in step (c), as I explained above, *destroys* the alleged CRCs formed in step (b) by uncoupling the B oligonucleotides from the B substrates, the alleged CRC formed in step (b) cannot be selected in step (d), simply because there are no longer any alleged CRCs to select.

114. Further, as discussed above, Kanan's Supplementary Information confirms that oligonucleotide cleavage in Kanan's methods occurs *before* the streptavidin affinity selection. The protocol in Kanan's Supplementary Information also indicates steps that a POSA would understand remove a nucleic acid from pool B after disulphide cleavage and binding to streptavidin-linked magnetic particles:

To the eluant was added...[a reducing agent] to effect disulfide cleavage. After 1 h...this solution was added to...streptavidin-linked magnetic particles.... The supernatant was removed.... *The particles were rinsed once with 200 μ L H_2O , and once with [NaCl, Tris, and EDTA at pH 7.5] ("washing buffer") The particles were then resuspended in...95% formamide-5% 10 mM EDTA and incubated at 65 °C for 10 min.... Fifteen μ L of this eluant was *diluted with 60 μ L of H_2O and added to a fresh aliquot of streptavidin particles.... [T]he supernatant was removed and the particles were rinsed with H_2O and washing buffer as above.... The particles were resuspended in 95% formamide-5% 10 mM EDTA and incubated at 90 °C for 10 min.... [T]his eluant was *diluted with 35 μ L H_2O and passed through a gel filtration spin column.... This solution was used directly in PCR reactions for microarray analysis.*"**

EX1013 8 (emphasis added).

115. I understand that Dr. Nelson acknowledged at deposition that low ionic strength/salt concentrations and formamide are each factors which separate

strands of DNA into individual strands. Dr. Nelson testified regarding the mechanism by which low concentrations of ions (e.g., in water) denature DNA:

Q What type of conditions would you say would potentially cause a hybridized pair of nucleic acids to become unhybridized?

A The main factors affecting the stability of a nucleic acid hybrid are the *ionic strength* of the solution and the temperature thereof. So high temperature or *low salt can cause disruption of the duplex*.

Q Anything else other than ionic strength or temperature that might cause a disruption of the duplex?

A Yes. There are a variety of other factors. Other -- for example, other components of the solution, such as denaturing components. *Formamide is a solution that tends to denature or break apart the double strands*. And other chemical compounds that are in the solution of the DNA that can decrease the stability of the duplex.

Q I think you mentioned ionic strength may be a factor; is that right?

A Yes. Uh-huh.

Q How does ionic strength affect hybridization of nucleic acids?

A Basically, *you need counter-ions to the negative charge in the phosphate groups*. So, classically, sodium is used as a counter-ion to bind with the negative charge of the phosphate group to minimize repulsion of the two strands. Magnesium is another component that is used to do the same function.

Q And so *is it fair to say that without these counter-ions, the strands start to repel each other to do a negative charge?*

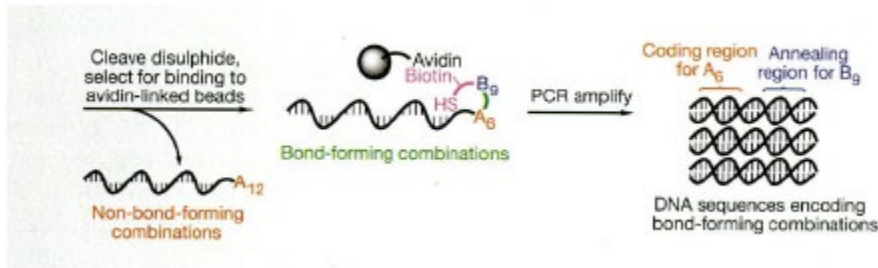
A Well, it depends on what else is in the solution. But generally speaking, that would be a reasonable statement.

EX2009, 29:19-31:2 (emphasis added).

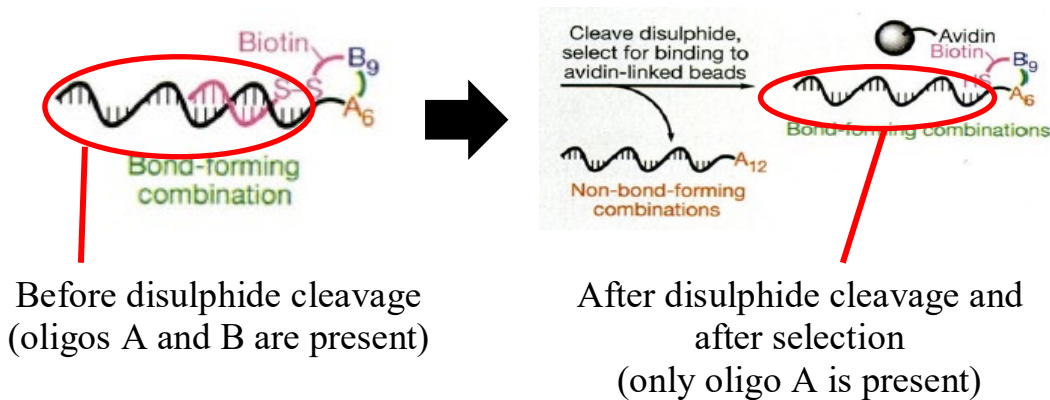
116. As to “what else is in the solution,” in my opinion a POSA would have known that water has a low ionic strength/low salt concentration unless otherwise specified. That is, it is customary for the disclosure of “water” or “H₂O” to refer to water without additional components (e.g., salts), or with negligibly low amounts of additional components (e.g., as minor, negligible contaminants). A POSA would understand that a solution with salts would be referred to by the salt, e.g., a solution of pure water with sodium chloride added to a concentration of 1 mM would be referred to as a sodium chloride solution, not as “water.” Therefore, Kanan’s disclosure of steps involving water or H₂O would be understood to refer to water having negligible or no ions (i.e., water having low ionic strength). Accordingly, as I note above, a POSA would have understood that Kanan’s water and formamide wash steps would remove the pool B DNA segment that is no longer coupled to its substrate after the disulphide cleavage step. EX1013, 8.

117. Dr. Nelson’s Declaration further confirms that the uncoupled B oligonucleotides are physically separated from the complexes before, or at most

during, the selection step. To illustrate the selection step, in his Declaration, Dr. Nelson reproduced a portion of Kanan's Figure 1, EX1005, ¶122, which clearly shows that, not only the disulphide bond is cleaved (the cleaved disulphide bond is shown as "HS"), but also that the oligonucleotides bound to the streptavidin beads are single-stranded:



EX1010, 546. Below I provide an annotated excerpt of Kanan's Figure 1b depicting the cleavage and removal of the B oligonucleotides in Kanan's method:



EX1010, Fig. 1b.

118. This confirms that not only the alleged CRCs are destroyed upon cleavage of the disulphide bond, but they are further destroyed once the oligonucleotide of pool A and the oligonucleotide of pool B are separated in Kanan's method. As I explained above, (i) a POSA would understand that a CRC

must contain at least two interactors, (ii) and each interactor must contain at least one MOI *coupled with* at least one NAM. By cleaving the oligonucleotides in pool B via disulphide cleavage, Kanan's methods uncouple the alleged B interactors and thus destroy the alleged CRCs by eliminating one of the two interactors.

Additionally, for CRCs, the interactors must be "bound in proximity to one another *by an associated oligonucleotide*," which is formed by the "association of NAMs."

EX1001, 41:43-49, 9:44-47. In the Kanan and Neri combination, upon dissociation, the oligonucleotides are no longer hybridized (i.e., associated). If the oligonucleotides are not associated, there cannot be an alleged associated oligonucleotide that binds the alleged interactors in proximity. Thus, the alleged interactors cannot form an alleged CRC, which means that there cannot be any alleged CRCs. A POSA following the modified Kanan and Neri method would not have selected any CRCs at all, due to Kanan's disulphide cleavage requirement.

119. For at least these reasons, the combination of Kanan and Neri fails to teach or suggest at least step (d) of claim 1 of the '848 patent which requires selecting cis-reactive cells.

b. Kanan and Neri do not teach or suggest claim 1 step (e)'s "subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis...."

120. Step (e) of claim 1 requires "subjecting *the associated oligonucleotides from the cis-reactive cells selected in step (d)* to an analysis..."

EX1001, 41:55-56. As discussed above, in the combination of Kanan and Neri, no alleged “cis-reactive cells” can be selected in step (d) because the alleged CRCs are destroyed before any selection step when the disulphide bond is cleaved and 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.

c. Dr. Nelson fails to show that Kanan and Neri teach step (e)’s “detection of the at least two identification sequence elements.”

i. Kanan’s methods remove the pool B oligonucleotides, which removes an identification sequence element and leaves only one identification sequence element remaining for analysis.

121. Step (e) of claim 1 requires “subjecting the associated oligonucleotides from the cis-reactive cells selected in step (d) to an analysis that *permits detection of the at least two identification sequence elements.*” EX1001, 41:55-58.

122. In his discussion of step (e), Dr. Nelson’s argues:

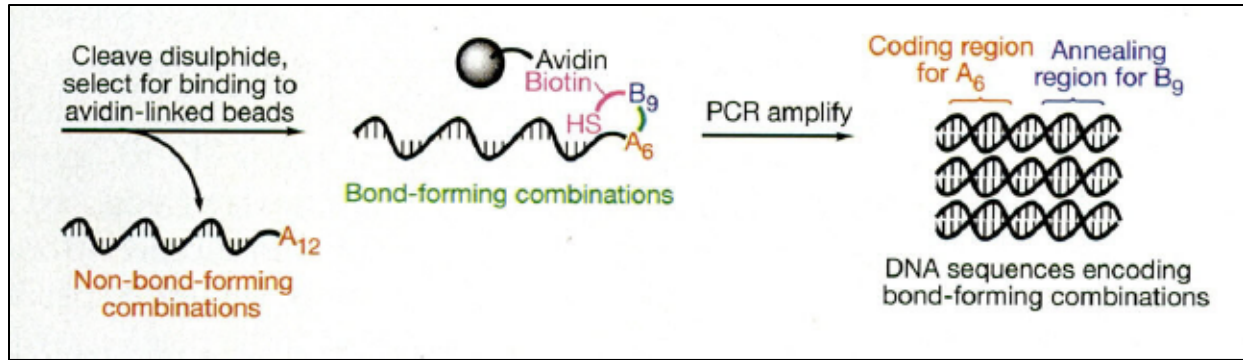
Kanan in view of Neri teaches subjecting the selected CRCs from step (d) to an analysis that permits detection of the at least two identification sequence elements. Kanan teaches that the bond-forming pairs are

amplified by PCR and analyzed with microarray analysis . . . the detection of the bond-forming substrate products permits the detection of the at least two identification sequence elements in the combination of Kanan with Neri because it is the resulting nucleic acid, which includes the two identification sequence elements of Neri, that is detected and corresponds to each unique substrate.

EX1005, ¶¶126-27.

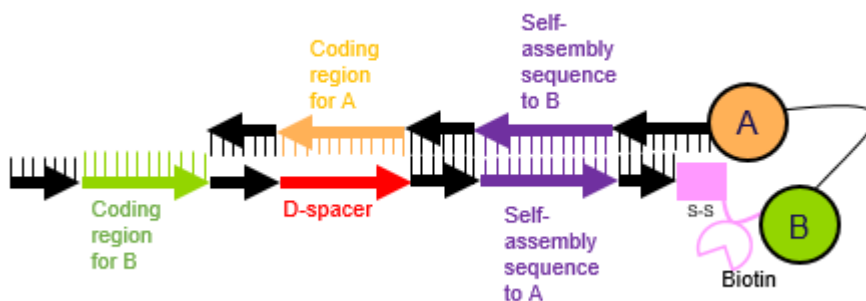
123. While Dr. Nelson states “it is the resulting nucleic acid, which includes the two identification sequence elements of Neri, that is detected” (EX1005, ¶127), Dr. Nelson does not explain how, in the combination of Kanan and Neri, the “nucleic acid, which includes the two identification sequence elements of Neri,” is formed. Thus, Dr. Nelson provides only the above conclusory statement without explaining when and how the resulting nucleic acid, which purportedly includes the two identification sequence elements of Neri is formed.

124. As discussed above, Kanan’s methods require *cleaving and removing* the pool B oligonucleotides, which would have comprised one of the two identification sequence elements in Dr. Nelsons proposed combination. EX1010, 545-546, Fig. 1. See Kanan Figure 1, where the B₉-A₆ bond-forming pair that is analyzed contains only the A oligonucleotide:

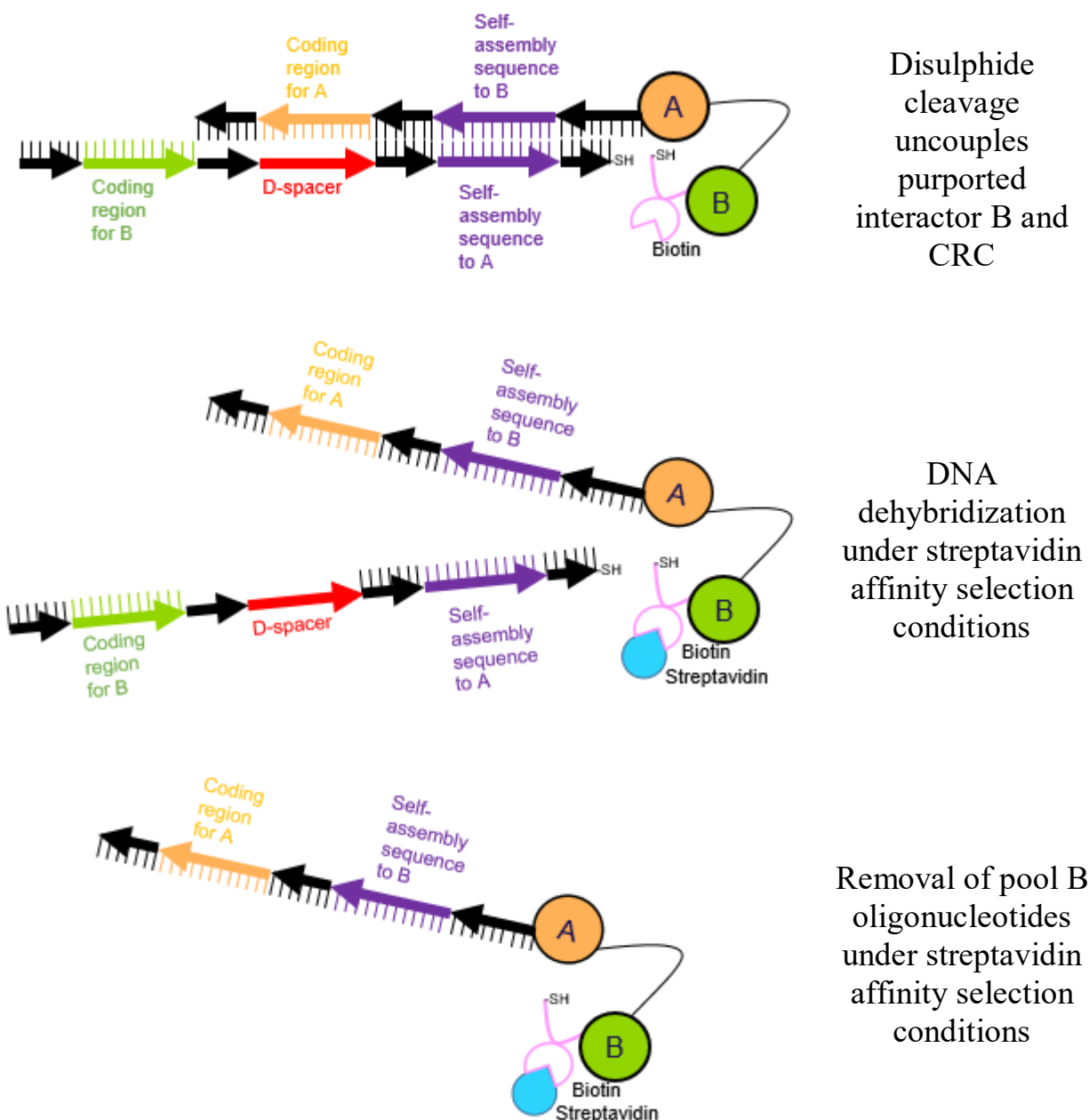


EX2009, 64:4-65:12.

125. In Dr. Nelson’s proposed adaptation of Kanan, one identification sequence element is purportedly present in the pool A oligonucleotide (“Coding region for A_{1...n}”), and a second identification sequence element is purportedly present in the pool B oligonucleotide (“Coding region for B_{1...m}”). EX1005, ¶ 114. A POSA would have understood that Kanan’s disulphide cleavage and subsequent selection steps would remove the pool B oligonucleotides from the assay and thus remove the “Coding region for B_{1...m}” identification sequence element, *before* the identification step (e). I show this in the figures below:



Before disulphide
cleavage and
streptavidin
affinity selection



126. Accordingly, Dr. Nelson's proposed modification of Kanan in view of Neri does not permit detection of "the *at least two* identification sequence elements," because a POSA would have understood that Kanan's methods would have removed one of the two proposed sequence identification elements (code B)

from the system.

ii. Dr. Nelson’s passing reference to polymerization does not provide adequate information to cure these issues.

127. Dr. Nelson makes a passing reference to polymerization when discussing claim 17’s element “wherein [the] association is via polymerization. ,”

Dr. Nelson states:

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; *see also*, ¶¶177, 183.

128. Dr. Nelson’s vague description to “use the polymerization of the oligonucleotides as taught in Neri with the creation of the paired substrates in Kanan” does not give any indication about when or how a POSA would have implemented the proposed polymerization step of Neri in the combination of

Kanan and Neri. EX1005, ¶182.

129. Given no alternative explanation in Dr. Nelson’s Declaration, a POSA applying Neri’s polymerization step “as taught in Neri” (according to Dr. Nelson, EX1005, ¶182) would have performed polymerization *after* Kanan’s selection—far too late to achieve any useful data. This is because in Neri, PCR occurs *after* biopanning. *See, e.g.*, EX1011, ¶ [0030] (“*After biopanning*, oligonucleotides of sub-library B remain stably annealed to oligonucleotides of sub-library A, and can work as primers for a DNA polymerase reaction on the template A. *The resulting DNA segment, carrying both code A and code B, can be amplified (typically by PCR)....*” (emphasis added)); *id.*, ¶[0032] (“*After biopanning*, suitable pairs of primers allow the *PCR amplification* of the two strands, yielding PCR products whose sequence can be identified...” (emphasis added)); *id.*, ¶[0070] (“*After biopanning*, it is desirable to learn about the code of the binding members displaying a desired binding specificity” (emphasis added)); *id.*, ¶¶[0031]-[0032], [0071]-[0072], [0076], [0112], and [0144]; claim 19; and EX2009, 110:17-23.

130. Neri’s biopanning method is a selection method, whereby library members bound to an untagged target analyte in Neri are selected, and non-binding members are removed. *See, e.g.*, EX1011, ¶¶[0059], [0083]-[0084]. Accordingly, in Dr. Nelson’s proposed combination of Kanan and Neri, a POSA performing polymerization “as taught in Neri” would have performed analysis of sequences

only *after* biopanning, i.e., only after selection of constructs that bind to the target.

Dr. Nelson provides no explanation for why a POSA would have deviated from this order. In fact, I understand from Dr. Nelson's deposition transcript that he did not appear to have understood what biopanning means, e.g., as applied to the disclosure of Neri:

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

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

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

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

EX2009, 99:15-25.

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

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

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

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

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

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

EX2009, 103:16-104:6; *see also, id.*, 98:1-19, 100:1-25.

131. Dr. Nelson's statements are surprising given Dr. Nelson cited and relied on disclosures in Neri that refer to biopanning. *See e.g.*, EX1005, ¶83 (citing EX1011, ¶[0030]). Regardless of Dr. Nelson's understanding, a POSA would have understood that performing polymerization "after biopanning" in Neri is analogous to performing polymerization after streptavidin affinity selection in Kanan—i.e., *after disulphide cleavage and removal* of the pool B oligonucleotides. Thus, even if implementing polymerization as in Neri, the pool B oligonucleotides would have already been removed by Kanan's disulphide cleavage, preventing the ability to detect "*the at least two* identification sequence elements," as required in claim 1 step (e).

132. In addition, polymerase reaction buffers also have a composition that may cause problems for and/or not be compatible at all with the steps of the workflow of the combination of Kanan and Neri. For example, polymerase buffers can include a reducing agent to minimize polymerase oxidation and maintain

polymerase activity. Such a reducing agent could break the disulphide bond prematurely, before Kanan intended to do so with a reducing agent. For example, Goualev discloses that disulphide bonds “can be cleaved by a suitable reducing agent like DTT (dithiothreitol).” EX1036, ¶[0346]. Notably, Kanan uses the reducing agent tris(2-carboxyethyl)phosphine hydrochloride (TCEP) to intentionally cleave its disulphide bond: “To the eluant was added 150 µL of a 0.1 M aqueous solution of *tris(2-carboxyethyl)phosphine hydrochloride* in 1.0 M sodium phosphate, pH 8.0 *to effect disulfide cleavage*.” EX1013, 8. This reducing agent, known in the art as “TCEP” was commonly used to effect disulphide cleavage. For example, Goualev states that “*Disulfide linkers* can efficiently be *cleaved/reduced* by *Tris (2-carboxyethyl) phosphine (TCEP)*. TCEP selectively and completely reduces even the most stable water-soluble alkyl disulfides over a wide pH range.” EX1036, ¶[0369]; *see also, id.*, ¶[0347]. I understand that Dr. Nelson testified he was unsure of whether TCEP is a reducing agent that can cleave disulphide bonds. EX2009, 157:3-158:8.

133. A POSA would have known that polymerization conditions that might include enzyme buffer solutions with reducing agents could unintentionally and prematurely cleave the disulphide bond thereby disrupting the workflow of the combination of Kanan and Neri. Moreover, the unintentional breaking of disulphide bonds would result in destruction of the alleged interactors and CRCs

because the B substrate would no longer be coupled to pool B oligonucleotide, just like Kanan's intentional disulphide cleavage I discuss above.

2. A POSA would not have been motivated to combine Kanan with Neri as Dr. Nelson contends.

a. A POSA would know that the lack of a polymerization step would prevent identification of both MOIs.

134. As noted above, Dr. Nelson did not explain where and how the combination of the methods of Kanan and Neri includes a polymerization step to add the sequence information of an identification sequence element from one oligonucleotide onto the other oligonucleotide in a cis-reactive cell. Because Kanan and Neri combination requires breaking a disulphide bond and washing away one of the NAMs that contains one of the sequence identification elements *without polymerase extension of pool A to add the pool B identification sequence element*, only one sequence identification element would remain for analysis, e.g., microarray or sequencing. Accordingly, a POSA would understand that there would be no identification sequence element remaining that corresponds to one of the two substrates. A POSA could sequence the remaining identification sequence element to determine the identity of one of the two substrates participating in a functional interaction, but without the missing identification sequence element encoding for the other substrates, a POSA would know that the proposed method would not yield information allowing the determination of which two substrates

had a functional interaction. Therefore, a POSA would not have been motivated to modify Kanan with the disclosure of Neri as Dr. Nelson proposes.

b. A POSA would not have been motivated to include a polymerization step as Dr. Nelson proposes.

135. As I explain above, Dr. Nelson fails to explain how a POSA would modify Kanan and Neri to include a polymerization step. As I note, Neri's disclosure teaches polymerization *after* biopanning (Neri's selection step), which would suggest carrying out the polymerization step *after* the disulphide cleavage and biotin-avidin selection methods of Kanan. But this order would mean that the pool B oligonucleotide of Dr. Nelson's proposed combination is already removed before polymerization, which prevents the use of that oligonucleotide as a template to add its identification sequence element (Coding region for B_{1...m}) to the pool A strand. A POSA would have recognized multiple technical issues with this approach, and would not have been motivated to combine the references as Dr. Nelson proposes. Dr. Nelson alleges 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." EX1005, ¶ 182. However, a POSA would have understood that the Dr. Nelson's proposed approach would not "increase the specificity of the test," and Neri would instead not work at all, as explained below.

i. With Dr. Nelson's proposed construct as disclosed in his Declaration, a polymerase extension step is impractical.

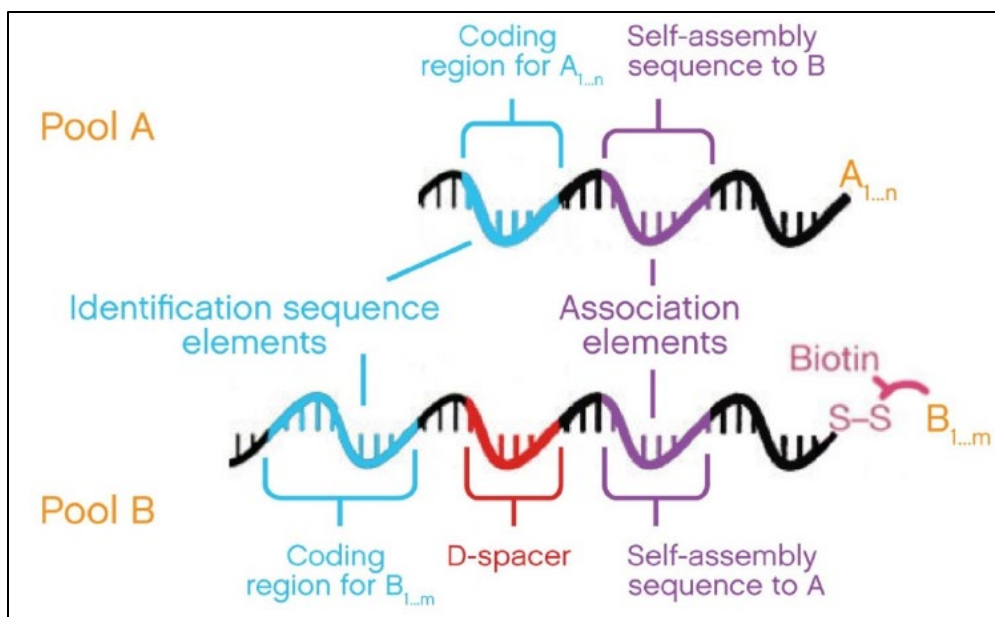
136. Even assuming that Dr. Nelson would somehow be able to explain where and how the polymerization step of Neri should be included in his combination of Kanan and Neri, the Kanan and Neri combination makes polymerase extension impractical, and a POSA, knowing this, would not have been motivated to take this approach.

137. In his declaration Dr. Nelson explains how the alleged oligonucleotides are constructed:

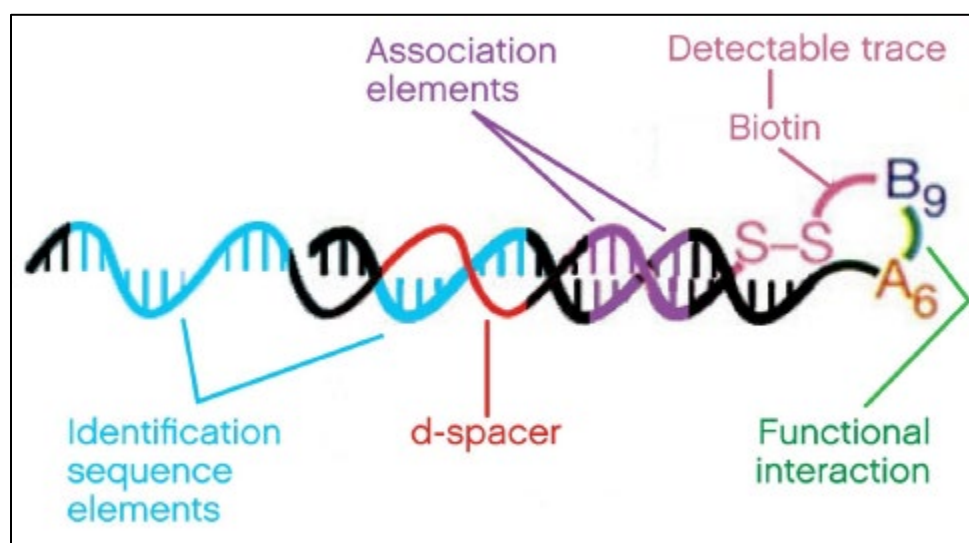
First, a POSA would have readily incorporated the self-assembly sequence taught in Neri by modifying the annealing regions of pool A and pool B library members to share common, complementary sequences to direct the hybridization of pool A members with pool B members. Second, a POSA would have readily incorporated the second identification sequence element taught in Neri to the pool B library members in Kanan by adding the "d-spacer" and identification sequence taught in Neri.

EX1005, ¶105.

138. Dr. Nelson provides the following illustrations representing the combination of Kanan and Neri:



EX1005, ¶114.

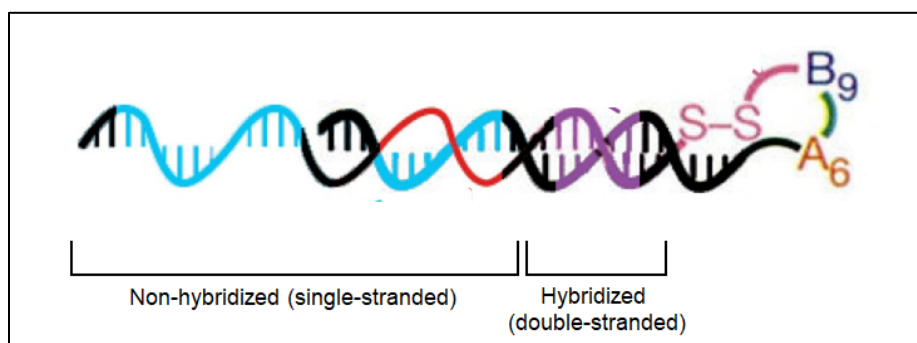


EX1005, ¶119.

139. To avoid confusion, I will refer to the black region of sequences to the left of the d-spacer in the above diagrams as the “Critical Region.” In the second diagram, this region, reproduced below, is shown with vertical lines on the pool A strand but without vertical lines on the pool B strand:



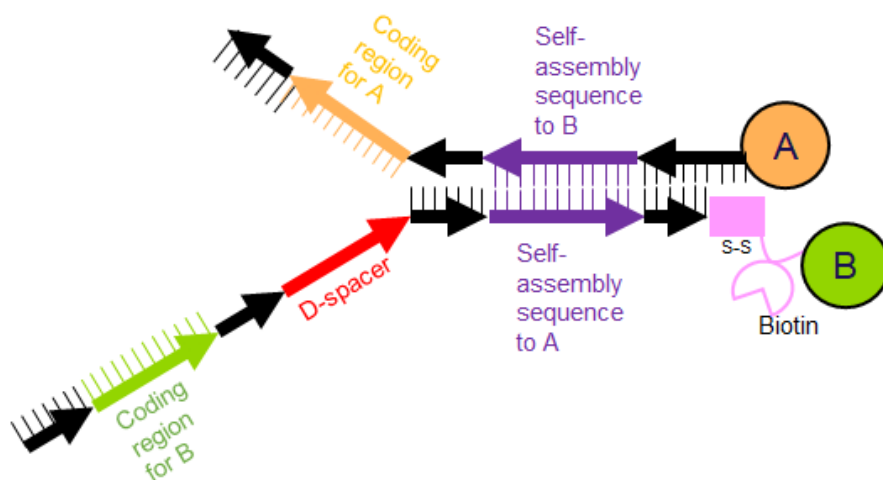
140. At his deposition, Dr. Nelson initially confirmed that, as presented, regions of his figures that show vertical lines from one but not both strands of his construct (e.g., the d-spacer region) indicate no hybridization between strands. EX2009, 87:13-88:19. Accordingly, where there are regions of his figures showing vertical lines from one strand, but not both, there is no hybridization. This is how 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:



141. As shown in the figure above, the oligonucleotides are capable of hybridizing at the “association elements” (colored in purple), but there is no hybridization between the d-spacer on the B oligonucleotide and the “identification sequence element” on the A oligonucleotide, nor at the Critical Region.

142. As to the d-spacer, this is expected because the d-spacer is abasic and having no nucleobases cannot participate in base-pairing. EX1011, ¶29. As I note

above, the Critical Region is presented in the same way: one strand is shown with vertical lines whereas the same region of the other strand is presented with no vertical lines. Accordingly, Dr. Nelson showed that the Critical Region is not a region where the two strands are or can hybridized. Indeed, a POSA would know that it is common to depict hybridization with vertical lines from each hybridized strand, and would have understood that the absence of any vertical lines in both strands of the Critical Region indicates the strands are not hybridized. *See e.g.*, EX1010, Fig. 1; EX1024, Fig. 14; EX1027, Figs. 4-5. Given that the Critical Region is not hybridized, Dr. Nelson's proposed design would take the following Y-shaped structure:



143. A POSA would have understood that, because the Critical Region is not hybridized, the pool B identification sequence element would not be added to pool A through polymerase extension using pool B as a template and the pool B strand in the Critical Region as a primer for polymerase extension. Polymerization

requires: (1) a “template” nucleic acid, to direct synthesis of a nucleic acid having a nucleotide sequence that is the reverse complement of the nucleotide sequence of the “template” nucleic acid, and (2) a “priming” nucleic acid hybridized to the “template” nucleic acid, in a way that permits polymerization to proceed by addition of nucleotides at the 3’ end of “priming” nucleic acid. EX2011, 263, 265-69; EX2012, 8.1-8.24. The “priming” nucleic acid must be “shorter” than the “template” nucleic acid, so that extension of the “priming” nucleic acid can take place using the “template” nucleic acid as a template. But, the “template” nucleic acid and the “priming” nucleic acid must be hybridized at the 3’ end of the “priming” nucleic acid. If the 3’ end of the “priming” nucleic is not hybridized to the template nucleic acid, polymerization cannot occur, because the polymerize cannot add nucleotides at the 3’ end of the “priming” nucleic acid using the “template” nucleic acid as a template.

144. For Dr. Nelson’s design to permit such polymerization such that both identification sequence elements are ultimately present on a same strand of, the “template” strand must be the B oligonucleotide, and the “priming” strand must be the A oligonucleotide. But, this configuration is incapable of polymerization if the oligonucleotides are not in the correct orientation and 3’ end of the A oligonucleotide is not hybridized on the B oligonucleotide, i.e., at the Critical Region. Rather, in Dr. Nelson’s presented design, the pool A oligonucleotide as the

Critical Region is a free-floating strand of nucleic acid, and would not be able to prime polymerization.

145. Taken together, a POSA would not have been motivated to pursue Dr. Nelson's proposed combination of Kanan and Neri in Ground 1 because there can be no polymerase extension, and after disulphide cleavage and washing away the pool B oligonucleotide containing an alleged identification sequence element, there would not be at least two identification sequence elements for detection, which would prevent a POSA from detecting functional interactions between molecules of interest. A POSA simply would not have been motivated to pursue Dr. Nelson's proposed design.

ii. Even with a polymerization step, a POSA would not have been motivated to take Dr. Nelson's newly disclosed approach.

146. I understand from Dr. Nelson's deposition transcript that he testified that his figures in his declaration are erroneous and should depict hybridization at the Critical Region. EX2009, 163:5-10, 163:24-164:4. Even if the Critical Region were hybridized, Dr. Nelson's proposed combination is still technically flawed for multiple reasons, and a POSA, knowing this, would not have been motivated to take Dr. Nelson's proposed approach.

147. A POSA would not know when and how to include the polymerase extension and under what conditions because Dr. Nelson fails to articulate these

details. As noted above, this matters because the conditions of polymerase extension can affect the results, e.g., by causing premature disulphide cleavage or denaturation of the alleged CRC.

148. Moreover, Dr. Nelson's proposed combination would be expected to yield false negative and false positive results when attempting to detect functional interactions between molecules of interest. I understand that at his deposition, after deciding that the Critical Region is hybridized, Dr. Nelson explained that the Critical Region is the same between every combination of pool A and pool B members, i.e., any pool A member can hybridize to any pool B member at the Critical Region:

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?

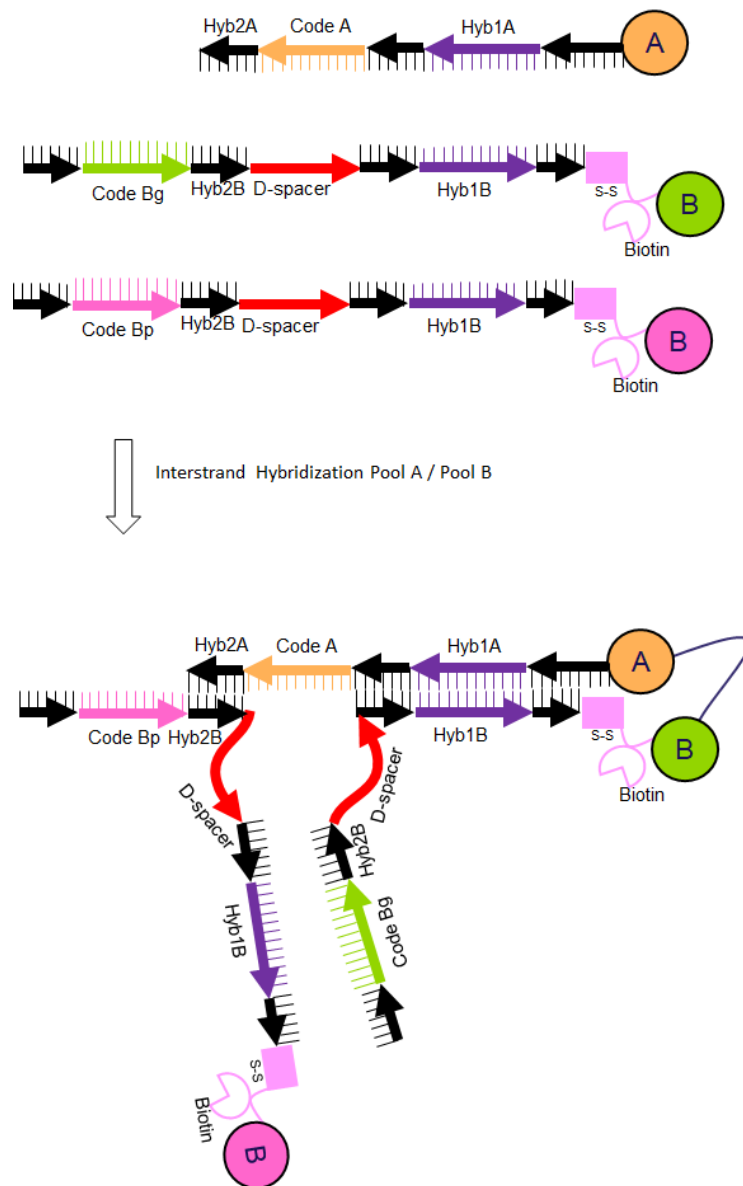
A Those are primer binding sites. So those would be -- they're referred to as the primer binding site. And those are constant. So those would be the same for all pool members.

EX2009, 167:22-168:6

149. This universal hybridization between pool members is already the case for the alleged association elements, where any pool A member can hybridize to any pool B member at their respective association elements to form an

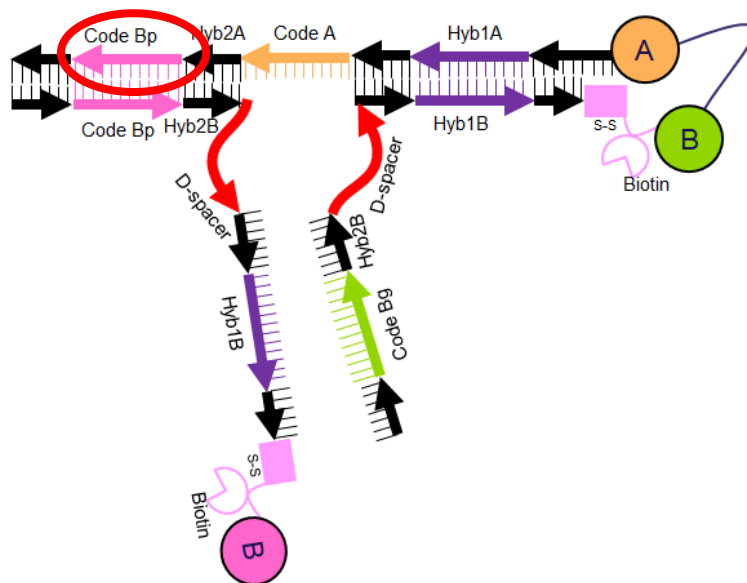
associated oligonucleotide. As a consequence, a POSA would have understood that there are *two* regions where a pool A member can bind two *any* pool B member.

150. A POSA would have also understood that the consequence of having two separate regions of pool A members that can bind to any pool B members at those same regions is that *two different pool B members can bind to the same pool A member at the same time*. This is shown in the following figure.

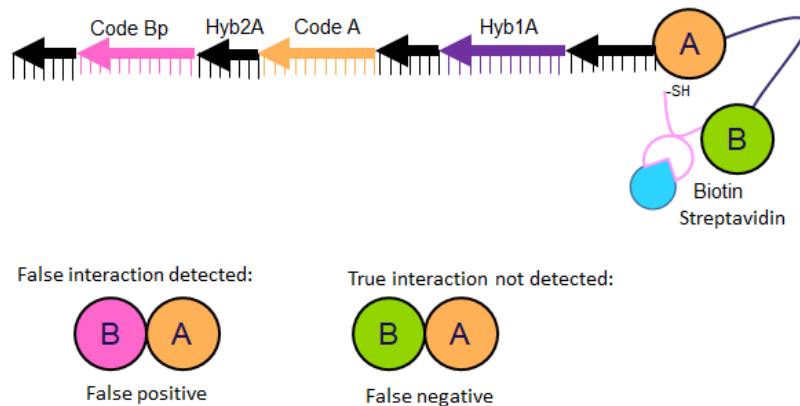


151. As shown, a POSA would have understood that two separate pool B members can bind to a single pool A member—a first pool B member binding at and around the association elements (the hybridized elements labeled “Hyb1A” and “Hyb1B” in the figures above), and a second pool B member binding in the Critical Region (the hybridized elements labeled “Hyb2A” and “Hyb2B” in the figures above). The d-spacer is a flexible region in the B oligonucleotides (EX1011, ¶29), which further contributes to the configuration shown above.

152. The POSA would have further recognized that while the substrate of the first pool B member (shown in green in the figure above) may react with the pool A substrate (shown in orange in the figures above), the alleged identification sequence element added by polymerization to the pool A member is the alleged identification sequence element of the second pool B member (labeled “Code Bp” in the figure above). This is shown in the following figure.



153. This yields both a false positive result (the impression that the second pool B substrate (shown in pink in the figure above) functionally interacted with the pool A substrate (shown in orange in the figure above)) and a false negative result (the impression that the first pool B substrate did not functionally interact with the pool A substrate). This is shown in the following figure.



154. A POSA would have known of the false positive and false negative results that would arise from Dr. Nelson's proposed combination of Kanan and Neri, and would not have been motivated to combine the references as he has described. According to Dr. Nelson, "a POSA would have been motivated to combine Kanan with Neri as Neri addresses ways to improve the method of Kanan, such as...a way to improve specificity of the binding between pool members in Kanan, and a way to more efficiently identify the bond-forming combinations in Kanan." EX1005, ¶82. And as noted above, Dr. Nelson alleges 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.” EX1005, ¶182. However, as I explain above, a POSA would have understood that the Dr. Nelson’s proposed approach would not “increase the specificity of the test,” and Neri would instead not work at all, at least because Dr. Nelson’s approach would be expected to yield false positive and false negative results arising from mismatched oligonucleotides. The effect of these mismatching events is contrary to Dr. Nelson’s stated motivation to “more efficiently identify the bond-forming combinations in Kanan” because false negative and false positive results would prevent a POSA from identifying functional interactions between substrates. For example, a POSA would not believe an experimental result suggesting a functional interaction was real or if it was a false positive without further testing. Dr. Nelson alleges that his proposed combination of Kanan and Neri would improve upon Kanan because it would “reduce the time required to synthesize the library members (substrates) of Kanan....” EX1005, ¶82. But a POSA would know that evaluating potential false positives would require even more time. Accordingly, a POSA would not have been motivated to modify Kanan as Dr. Nelson proposes because it would produce inconclusive results that just invite further experimentation.

- c. **A POSA would not have had a reasonable expectation of successfully combining Kanan and Neri as Dr. Nelson's contends because Dr. Nelson's proposal would be inoperative and/or yield false negative and false positive results preventing accurate identification of MOIs having functional interactions.**

155. A POSA would not have had a reasonable expectation of success for several reasons.

156. First, as I explained above, in Dr. Nelson's combination of Kanan and Neri, the Pool B strand is cleaved and removed from the CRC, resulting in loss of one of the identification sequence elements. The POSA thus would not have had a reasonable expectation of success in identifying a functional interaction, because following Kanan's method as Dr. Nelson's contends would not allow detection of both identification sequence elements and thus would not be efficient or useful at all. In contrast to Kanan's original method, in which both A and B coding regions are already present on the same strand and able to be detected.

157. Second, the POSA would not have reasonably expected success because Dr. Nelson's purported CRCs from the Kanan and Neri combination are structurally incapable of any polymerization due to the lack of a priming region hybridized to initiate polymerase extension; thus for this additional reason the POSA would not have expected both identification sequence elements to be present after Kanan's disulphide bond cleavage step and would be unable to analyze both elements.

158. Third, as described above, even if polymerization were possible in Dr. Nelson's purported CRC structure, the POSA would not have had a reasonable expectation of success in detecting functional interactions between two MOIs because two separate regions of the Pool A strand could hybridize to two distinct Pool B sequences and result in unreliable false positive and false negative results.

3. The addition of Famulok in Ground 2 does not cure the fatal deficiencies in Ground 1.

159. Ground 2 only challenges claim 16 (which depends from claim 1), and therefore relies on the combination of Kanan and Neri to meet all the elements of claim 1.

160. Dr. Nelson only relies on Famulok in Ground 2. Thus, Ground 2 fails to teach or suggest all the elements of the challenged claims for the same reasons discussed above for Ground 1. The addition of Famulok does not cure the deficiencies of Kanan and Neri.

161. Dr. Nelson states:

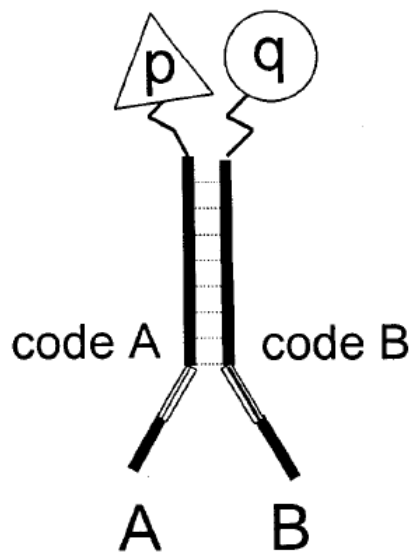
A POSA would have been motivated to combine the teachings of Kanan and Neri with the teachings of Famulok because the splint oligonucleotide disclosed in Famulok would create a DNA strand that does not rely on polymerization to encode the anticodon of the shorter library member to the sequence of the longer library member. . . A POSA would have a reasonable expectation of success in combining Kanan, Neri, Famulok because Neri teaches how to design interactors

that contain an overhang region (see EX1011, Fig. 7) that can be ligated together using the method taught in Famulok.

EX1005, ¶¶177-78.

162. Dr. Nelson fails to articulate how a POSA would have implemented Famulok's ligation technique into the combination of Kanan and Neri. However, he points to Neri Figure 7, the relevant portion of which is reproduced below:

Fig. 7



EX1011, 8.

163. In his Declaration, Dr. Nelson has failed to articulate how to combine Kanan with Neri in Ground 2. At his deposition, I understand Dr. Nelson opined that the alleged interactors in Neri's Figure 7 are associated by hybridization.

EX2009, 128:23-129:2, 130:23-131:19. He opined that a POSA combining Kanan,

Neri, and Famulok would have associated the interactors via self-assembly *hybridization* of the oligonucleotides (as taught in Neri), and *then* performed Famulok's ligation method using a splint oligonucleotide. EX2009, 134:14-135:16. Thus, in Dr. Nelson's Ground 3 combination, the purported CRCs are made from interactors *associated by hybridization* of the self-assembly region in the oligonucleotides, *not by ligation*, as required by claim 16. EX2009, 128:23-129:2, 130:23-131:19. For this additional reason, Dr. Nelson's proposed combination for Ground 3 fails to demonstrate that the combination of Kanan, Neri, and Famulok teaches or suggests all the elements of claim 16.

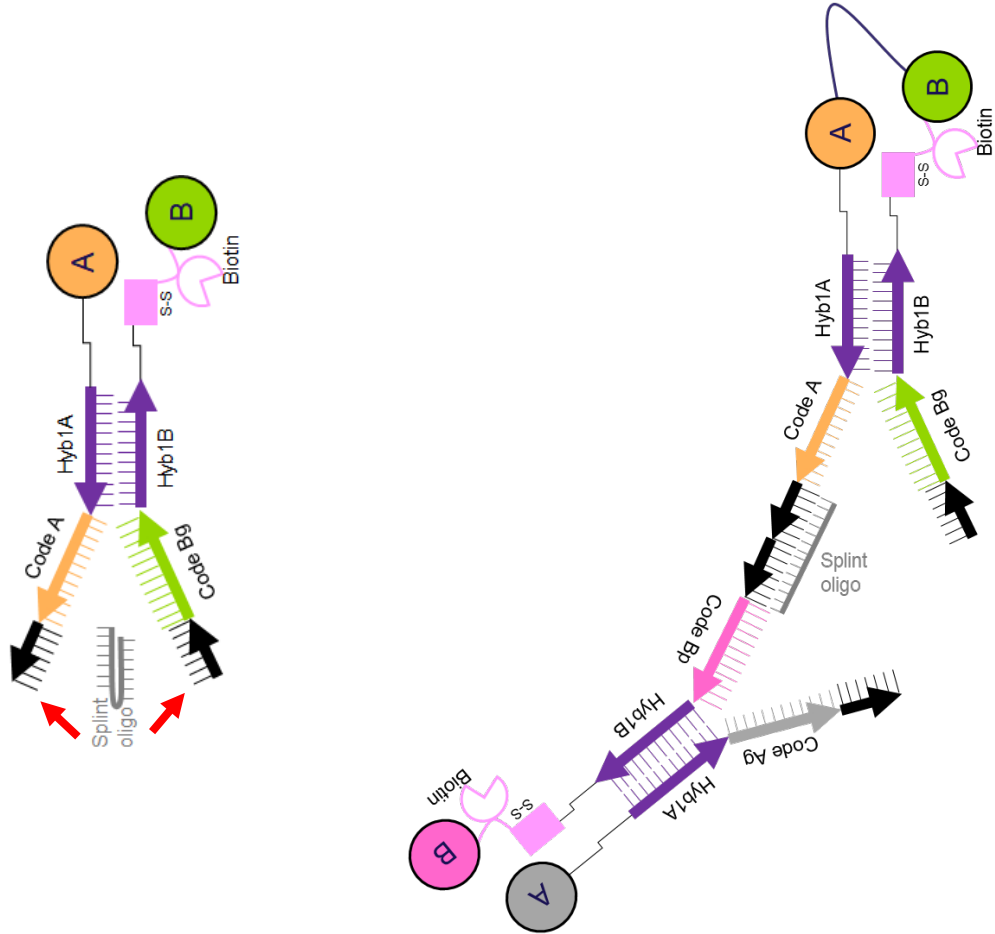
164. Regardless, Ground 2 still fundamentally relies on the methods of Kanan, which requires disulphide cleavage at a region coupling one oligonucleotide to a substrate. Dr. Nelson has not explained how Kanan and Neri would be combined, even in view of Famulok, without relying on Kanan's disulphide cleavage to select only bond-forming combinations of substrates. Accordingly, as with Ground 1, when combining with Kanan with Neri a POSA would still rely on cleavage of an alleged interactor between an alleged MOI and an alleged NAM, destroying an alleged CRC and therefore making claim 1 steps (d) and (e) (which require cis-reactive cells) impossible, as described for Ground 1.

165. As with Ground 1, a POSA also would not have been motivated to combine Kanan, Neri, and Famulok, and would not have had a reasonable

expectation of success in detection functional interactions between molecules of interest, due to the inability to detect more than one identification sequence element and determine MOIs that functionally interact, and the expectation of false negatives and false positives. Assuming Dr. Nelson intends ligation of the distal ends of the oligonucleotides (shown in black near the letters A and B in Neri Figure 7), those ends are either (1) unique for each A and B oligonucleotide, or (2) they are universal for all respective A and B oligonucleotides.

166. 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.

167. 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, as indicated in the diagram below.



168. As shown in the figure above, a POSA would have understood that a splint oligo intended to ligate the distal ends of the Neri Figure 7 structure (left) could instead ligate a pool A member of one alleged CRC with the pool B member of a completely separate alleged CRC (right). The result is that for a first CRC, a pool A substrate (shown in orange in the figure above) may functionally interact with a pool B substrate (shown in green in the figure above), but a second pool B member from a separate CRC can be ligated to the pool A member of the first CRC, resulting in the impression that the second pool B member's substrate from

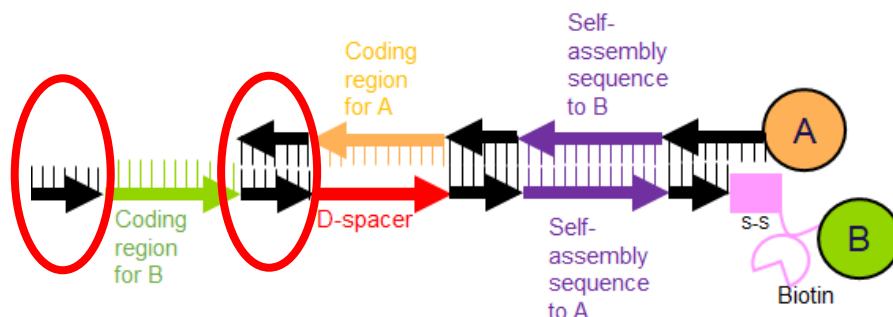
the second CRC (shown in pink in the figure above) functionally interacted with the pool A substrate from the first CRC. This is because the ligated oligonucleotides carry the alleged sequence identification element for substrate A (shown as “Code A”) and the alleged identification sequence element for the wrong substrate B (shown as “Code Bp”).

169. To be clear, this is just one simplified example demonstrating a single set of false positive and false negative results. With Dr. Nelson’s proposed combination, it is also possible that both sets of CRCs have functional interactions within their respective MOIs, but that both ends of each CRC are ligated to the strands of a separate CRC (both pool A strands ligated to pool B strands from different CRCs), rather than the simplified version above with only one set of pool A and pool B strands from different CRCs being ligated to one another. In that case, there would be *four* distinct false results instead of the two in the example above: although there are two functional interactions (between MOIs within each CRC), the ligated NAMs would have mismatched code A and code B sequences, leading to the impression that the MOIs that functionally interacted did not (two false negatives), and that MOIs that were not even part of the same CRCs did functionally interact (two false positives). The false negatives and false positives get even more complicated as additional CRCs are involved. For example, the pool A member of a first CRC could ligate to the pool B member of a second CRC,

while the pool B member of the first CRC ligates to the pool A member of yet a third CRC, and so on. Dr. Nelson provides no way to control for these false negative and false positive results.

170. Further a POSA, expecting false negatives and false positives, would not be motivated to combine Kanan, Neri, and Famulok as proposed because they would not expect useful information regarding functional interactions between molecules of interest. And finally, a POSA would not have had a reasonable expectation of success in “detecting functional interactions between at least two molecules of interest” due to the expectation of false negatives and false positives.

171. I understand that Dr. Nelson testified at his deposition that a POSA would potentially implement the embodiment of Neri’s Figure 5 in the Famulok ligation embodiment. EX2009, 137:3-8, 138:11-20. Dr. Nelson does not discuss Neri’s Figure 5 in his arguments for claim 16. EX1005, ¶¶175-179. Regardless, in my opinion, a POSA would not have expected this proposed embodiment to be useful. Assuming Dr. Nelson is relying on his proposed embodiment in which the modified CRC comprises two hybridization regions (see discussion above in Section X.A.2.b.ii), a POSA would have understood that this configuration provides no overhang region on the sublibrary members A and B to be ligated together. I show this in the figure below:



172. In the figure above, while sublibrary B has an overhang region (circled, left), the distal end of sublibrary A is (according to Dr. Nelson) purportedly hybridized to its complementary region in sublibrary B (circled, right). EX2009, 163:5-10, 163:24-164:4. Thus, 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. As Famulok discloses, “[b]inding of the aptamer pair brings the *ends of the oligonucleotide* extensions into close spatial proximity (Fig. 1A) so that a ‘splint’ oligonucleotide can *hybridize to both ends*, which are subsequently ligated together.” EX1012, 448 (emphasis added). In Dr. Nelson’s embodiment depicted above, the splint oligonucleotide would not be able to hybridize to “both ends” of the A and B oligonucleotides and thus could not facilitate their ligation. *Id.*; see also *id.*, Fig. 1; EX1020, 473 (“When pairs of probes bind PDGF-BB, the *free ends* of their sequence extensions are brought sufficiently close to hybridize together to a subsequently added connector oligonucleotide, *allowing the ends to be joined* by enzymatic DNA ligation.” (emphasis added)).

173. Even if the lack of free ligatable ends were somehow mitigated, a POSA still would not have been motivated to apply Neri's embodiment in Figure 5 to the Kanan, Neri, and Famulok combination because the resulting ligation product would include Neri's d-spacer region. EX1011, ¶[0029], Fig. 5. Neri discloses that the d-spacer is "composed of phosphodiester backbone *without bases*," which a POSA would understand to be abasic. EX1011, ¶[0029]; EX2009, 87:25-88:13. A POSA would have expected the lack of bases in the d-spacer, combined with its flexibility, to render the molecule unable to effectively bind PCR or sequencing primers and thus not provide a useful readout. This is naturally why Neri only discloses amplifying and sequencing the pool A oligonucleotides, which lack the abasic d-spacer. EX1011, ¶¶[0117]-[0119].

B. Dr. Nelson fails to demonstrate that the challenged claims would have been obvious over Baez in view of Landegren and further in view of Freskgard.

174. As I explain below, the combination of Baez and Landegren also fails to teach or suggest all of the elements from the challenged claims. This deficiency applies to both Grounds 3 and 4 because both Grounds depend on combining Baez and Landegren. Additionally, a POSA would not have been motivated to combine Baez and Landegren in the way Dr. Nelson alleges, nor would the POSA have had a reasonable expectation of success in so doing.

1. **Dr. Nelson fails to demonstrate that the combination of Baez and Landegren teaches or suggests all of the elements of the challenged claims.**
 - a. **Dr. Nelson fails to demonstrate that the combination of Baez and Landegren teaches or suggests step (a)'s forming a plurality of interactors.**

175. Dr. Nelson first states that “a POSA would have understood the antibody conjugates disclosed in Baez as a molecule of interest.” EX1005, ¶232. Baez discloses that the “antibody conjugates” (referred to as “reporter conjugates”) are comprised of an antibody probe conjugated to a nucleic acid label. EX1003, 5:51-54, Fig. 2. Thus, Dr. Nelson identifies Baez’s antibody-nucleic acid conjugates as the “molecules of interest” in his claim mapping to the ’848 patent. When discussing “interactors” of the ’848 patent, Dr. Nelson states that “a POSA would have understood the ‘reporter conjugates’ disclosed in Baez are ‘interactors.’” EX1005, ¶235. Thus, according to Dr. Nelson, the “interactors” in the combination of Baez and Landegren also are Baez’s reporter conjugates. Thus, according to Dr. Nelson, the same antibody-nucleic acid conjugate in Baez meets *both* the MOI *and* interactor claim limitations recited in claim 1.

176. However, if Baez’s antibody-nucleic acid conjugate serves as an MOI, then Dr. Nelson fails to identify any NAM that is coupled to the MOI to form a plurality of interactors, as required by claim 1 step (a).

177. I understand that the PTAB identified this same inconsistency in its

Decision instituting this IPR. Paper 7, p, 36. The Board stated that:

“[W]e 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” and that ligation of the conjugates is a “functional interaction[] between at least two molecules of interest,” as recited in the preamble of claim 1. Pet. 55; *see also id.* at 59 (describing the ligation of the nucleic acid labels and linker in Baez as “the desired functional interaction”). However, the Petition also points to these antibody-nucleic acid conjugates as the “interactors” recited in step (a) of claim 1, which are described as formed by “coupling each molecule of interest with at least one nucleic acid moiety.” *Id.* at 56. 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.

Id.

178. I agree with the Board’s conclusion regarding Grounds 3 and 4.

b. Baez and Landegren fail to teach ’848 claim 1 element (d): “selecting all cis-reactive cells exhibiting the detectable trace.”

179. Dr. Nelson also fails to demonstrate that the combination of Baez and Landegren teaches or suggests the selection step of claim 1 (d).

180. Dr. Nelson only relies on Baez for meeting the “selecting” limitation, stating that “a POSA would have understood that isolating the CRCs (ASAs)

comprising a biotin label using a streptavidin solid support structure as taught in Baez is ‘selecting’ the CRCs.” EX1005, ¶251. To support his proposition, Dr. Nelson relies on disclosures in Baez at 17:25-28 and 17:52-53. Dr. Nelson states that:

Baez discloses that the ASAs can be selected using affinity purification. This involves detecting the ASA “through the linker oligonucleotide itself.” EX1003, 17:52-53. In one example, the linker oligonucleotide is “engineered to contain a label such as biotin[.]” *Id.* at 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 or avidin. E.g., Ex. 1003, 17:25-28.

EX1005, ¶252.

181. Contrary to Dr. Nelson’s opinion, a POSA would have understood that Baez’s disclosure refers to a method of *detection*, not selection, as required in ’848 claim 1 element (d). EX1003, 17:25-28, 17:52-54.

182. Where Baez refers to biotin, it is explicitly in the context of detection, not selection. For example, Dr. Nelson relies on Baez’s disclosures in column 17, which are within a section of Baez under the header “*Detection* of Nucleic Acid Products”. EX1003, 16:65. Baez also expressly discloses that “[t]he ASA can also be *detected* through the linker oligonucleotide itself,” and that a biotin label “could be *detected* through antibody conjugates, direct fluorescence, or fluorescent energy transfer (FET), for example” (emphasis added). EX1003, 17:52-57. A POSA

would have understood that these are express disclosures of *detection*. Further, Dr. Nelson also admits that Baez’s biotin embodiment “involves *detecting* the ASA...” EX1005, ¶252 (emphasis added). In view of the disclosures of Baez, a POSA would have understood that being able to isolate amplified nucleic acid products from solution provides a means *to detect* an ASA resulting from ligation, but that there is no step involving *selecting* CRCs having a detectable trace, as required by ’848 patent claim 1 step (d).

183. Even if the biotinylated “amplified nucleic acid products” were considered a mechanism of selection (which I disagree that it is), a POSA would have understood that “selecting” such amplified nucleic acid products would not involve *selecting cis-reactive cells* as required by claim 1. Baez’s method of detecting the biotinylated amplicons, would not contain both a MOI and a NAM for each of two interactors associated by association elements, and thus does not teach selecting *all cis-reactive cells* exhibiting a detectable trace, as required by ’848 patent claim 1 step (d).

184. As I noted above, according to Dr. Nelson, the “molecules of interest” in the combination of Baez and Landegren are Baez’s antibody-nucleic acid conjugates. EX1005, ¶232. Baez’s detection of amplified nucleic acid products do not include the antibody-nucleic acid conjugates and therefore under Dr. Nelson’s theory, they cannot represent cis-reactive cells comprising associated interactors.

Dr. Nelson has not identified any disclosure in Baez that teaches *selecting* all of the CRCs with a detectable trace, as required by claim 1.

185. Accordingly, Dr. Nelson fails to show that Baez and Landegren teach or suggest every limitation of claim 1.

c. Baez and Landegren fail to teach claim 1 element (e), which requires the selection of step (d).

186. Step (e) requires “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.”

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.

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

188. When addressing claim element 1(a), Dr. Nelson states that Landegren’s disclosure of “tags” meets the “identification sequence element” of

step (a). Specifically, Dr. Nelson states that “Landegren teaches that the nucleic acid coupled to the proximity probe (i.e., conjugate) has a sequence identification element or ‘tag.’” EX1005, ¶237. I understand that Dr. Nelson confirmed his position at deposition. EX2009, 143:11-144:5.

189. When discussing claim 1 step (e), Dr. Nelson argues that detection of Baez’s PCR amplicons is sufficient to detect “the at least two identification sequence elements” from the combination of Baez and Landegren. EX1005, ¶256. Dr. Nelson states that “[a] POSA would have understood that *detection of the amplified ASA product* permits the detection of the at least two identification sequence elements because it is the resulting nucleic acid, which includes the identification sequence elements, that is amplified with PCR.” EX1005, ¶256. Accordingly, Dr. Nelson appears to rely on Landegren’s disclosure of tags to meet claim 1(a)’s identification sequence elements, and Baez’s disclosure of PCR amplicon detection to meet the same identification sequence elements in claim 1(e).

190. I disagree with Dr. Nelson’s opinion. First, a POSA would have understood that Baez’s disclosure of detecting the “amplified ASA product” would at most detect the presence of *a ligation product*, and would not have determined whether or not Landegren’s tags (Dr. Nelson’s “identification sequence elements” in Grounds 3 and 4) are indeed present in the detected ASA. *See e.g.*, EX1003,

Figs. 6-9 (showing images of agarose gels to detect amplified ASAs). Dr. Nelson provides no other technical explanation of how a POSA would have detected Landegren's tags merely by Baez's PCR amplicon detection. EX1005, ¶¶256-257.

191. Because a POSA would not consider Baez's detection of ligation products to detect the "at least two identification sequence elements," the combination of Baez and Landegren fails to teach or suggest claim 1 step (e)'s detection element.

2. A POSA would not have been motivated to combine Baez and Landegren as Dr. Nelson portrays.

a. Baez discloses that its methods reduce background noise and offer multiplex capabilities.

192. Dr. Nelson argues that a POSA would have been motivated to combine Baez and Landegren "to search for a way to reduce background signal in the assay." EX1005, ¶238. Baez, however, purports to have already met this goal. For example, Baez teaches that its methods provided "a means to reduce assay background response and to improve signal to noise ratio of binding assays." EX1003, 3:25-27. As Baez explains, its methods are "the first to apply assay principle that essentially distinguishes between analyte-specific binding reagent recognition and nonspecific reagent binding." EX1003, 3:27-30.

193. Baez discloses:

forming an analyte dependent reporter-complex (ADRC), joining the reporter labels of the (ARDC), amplifying the joining product of the

two labels and detecting the amplification product. Nucleic acid-labels are used to report analyte specific binding. Amplification is achieved by replication of the joined nucleic acid-labels. The method reduces the background signal of a binding assay, thereby, providing means of a highly sensitive analyte detection.

EX1003, 1:16-23.

194. Accordingly, Baez teaches reducing background signal by amplifying joined nucleic acid labels in its detection method. Baez repeatedly touted the successful background reduction achieved by the disclosed detection (not selection) methods: “[T]here 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. “The effect of the instant method is to provide a means of improving the ratio of the analyte-specific signal to analyte non-specific background signal, thus enhancing the ability to detect analytes at very low concentrations.” EX1003, 3:46-49.

195. Dr. Nelson also argues a POSA would have been motivated to combine Baez and Landegren to “detect and analyze multiple analytes in a single assay.” EX1005, ¶238. Baez discloses this benefit, too. Baez discloses a “multianalyte assay format,” in which “multiple analytes can be detected

simultaneously in the same assay milieu.” EX1003, 13:18-20. Baez explains that this can be achieved using “multiple specific capture reagents” in conjunction with “multiple sets of reporter conjugates, label-joining, and analyte specific amplicon amplification reagents.” *Id.*, 13:24-28. Baez also explains that “multiple solid-phase reagents, each specific for a separate analyte, could also be employed.” *Id.*, 13:29-30.

196. Thus, a POSA would not have been motivated to combine Baez with Landegren based on Dr. Nelson’s stated rationales, because Baez itself discloses that its methods already satisfy those goals. .

b. Landegren teaches *against* Dr. Nelson’s proposed use of biotinylated oligomers for solid-phase selection.

197. Dr. Nelson bases his opinions regarding the combination of Baez and Landegren on Baez’s embodiment concerning solid-phase support. EX1005, ¶252; EX1003, 17:25-28, 17:52-54. For example, Baez discloses incorporating biotinylated bases into its nucleic acid labels, which can be detected using “*immobilized* streptavidin.” EX1003, 17:25-28. A POSA would have understood that “immobilized” streptavidin refers to streptavidin being immobilized on a solid support. *Id.*; *see also*, EX1016, 2 (referring to antibodies and/or antigens “*immobilized* to a solid surface.”); EX1017, 1 (referring to immunoreactants “*immobilized* onto a solid support (microtiter plate)”); EX1038, ¶[0097] (“target molecule can be *immobilized on beads*”). Dr. Nelson also refers to Baez’s

disclosure of immobilized streptavidin as a “solid support.” EX1005, ¶251 (referring to the “*streptavidin solid support structure as taught in Baez.*”); EX2009, 150:21-151:20, 155:15-156:4.

198. In contrast to the embodiment in Baez relied upon by Dr. Nelson, Landregren teaches *against* the use of solid-phase selection and touts the benefits of its solution-phase methods:

Assays that use a solid phase require considerable time and effort for the analysis. The binding of reagents and analytes to the surface is a time consuming process and the washing steps must be precisely and reproducibly controlled between samples to give exact results. Solid phase assays are also more difficult to automate than homogenous assays.

EX1004, 1.

199. A POSA would have understood that Landegren’s solution-phase methods provide the “ability to detect and quantify one or several analytes *in solution* in a homogenous one tube assay with high sensitivity and specificity.”

EX1004, 2. A POSA would have also recognized that Landegren repeatedly and consistently discloses that its methods are designed for use in solution-phase assays, not solid-phase assays. EX1004, Abstract, 2, 5, 6, 9, 21 (claim 1), 22 (claim 8). Landegren also states that its “[p]roximity-probing provides an alternative means to screen large sets of ligand candidates *without the need for a solid phase.*”

EX1004, 16.

200. Dr. Nelson does not address Landegren's teaching against the use of solid-phase substrates or attempt to reconcile them with Baez's disclosure of using solid-phase substrates. In fact, I understand from Dr. Nelson's deposition transcript that he did not consider these disclosures in Landegren when forming the opinions in his declaration. EX2009, 48:23-49:8, 50:10-16, 53:23-55:10.

201. A POSA would not have ignored these teachings in Landegren. And in view of these disclosures, the POSA would not have been motivated to combine Landegren's solution-phase methods with Baez's methods that use solid-phase substrates. Accordingly, for this additional reason, a POSA would not have been motivated to combine Baez with Landegren as Dr. Nelson contends, because Landegren expressly teaches against such a combination.

3. A POSA would not have had a reasonable expectation of successfully combining Baez with Landegren as the Petition contends.

202. As noted above, Landegren teaches against the use of solid-phase selection: "[a]ssays that use a solid phase require considerable time and effort for the analysis. The binding of reagents and analytes to the surface is a time consuming process and the washing steps must be precisely and reproducibly controlled between samples to give exact results. Solid phase assays are also more difficult to automate than homogenous assays." EX1004, 1.

203. A POSA would not have reasonably expected success because in view of Landegren, the POSA would have expected Baez's solid-phase assays to "require considerable time and effort" and be a "time consuming process." EX1004, 1. The POSA also would have expected Baez's solid-phase assays to be "more difficult to automate." EX1004, 1.

204. Dr. Nelson does not address a POSA's reasonable expectation of success with respect to claim 1. EX1005, ¶¶231-259. Dr. Nelson's only mention of reasonable expectation of success in Grounds 3-4 is in his discussion of *claim 14*. EX1005, ¶294. Even then, Dr. Nelson's opinions only discuss the purported similarities between Baez, Landegren, and Freskgard, and does not address the conflict between Landegren's solution-phase methods and the solid-phase assays of Baez and Freskgard. EX1005, ¶294.

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

205. Dr. Nelson's Ground 4 applies solely to claims 14 and 15 of the '848 patent. Claim 14 depends from claim 1. Claim 14 requires "wherein the analysis comprises nucleic acid sequencing." Claim 15 depends from claim 14 and requires "wherein the analysis comprises sequencing by synthesis." Dr. Nelson relies on Freskgard solely for disclosure of sequencing by synthesis. EX1005, ¶¶289-96. Thus, the addition of Freskgard does not remedy the deficiencies discussed above for Ground 3, and I disagree with Dr. Nelson's opinions on Ground 4 for at least

the same reasons discussed above for Ground 3.

206. Additionally, I note that the methods taught in Freskgard include solid-phase assays. EX1009, 43:26-32. For example, Freskgard discloses that “the target may be immobilized to a solid support,” or “[p]rior to the isolation, the target bound to the potential drug candidate may be immobilized to facilitate the isolation.” EX1009, 43:18-31. Freskgard also claims a method “wherein the target is immobilized on a solid support.” EX1009, claim 20.

207. A POSA reading Freskgard would have therefore had the same concerns over combining Freskgard with Landegren and Baez in view of Landegren’s caution against using solid-phase assays. EX1004, 1, Abstract. Again, these teachings in Landegren went unaddressed in Dr. Nelson’s declaration, and I understand that he did not consider them when preparing his declaration. EX2009, 48:23-49:8, 50:10-16, 53:23-55:10.

XI. DEPENDENT CLAIMS

208. I understand that a dependent claim requires all of the limitations of the claim from which it depends. Claims 2-20 each depend directly or indirectly from claim 1. EX1001, 41:36-44:22. Therefore, I understand that claims 2-20 require all of the limitations of the “method of detecting functional interactions between at least two molecules of interest” of claim 1. Thus, the deficiencies in Dr. Nelson’s arguments and obviousness opinions for claim 1 discussed in Grounds 1

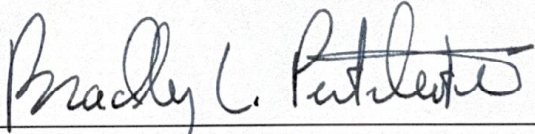
and 3 also apply to dependent claims 2-20.

CONCLUSION

In signing this declaration, I recognize that the declaration will be filed as evidence in an *inter partes* review before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required, I will appear for cross-examination within the United States during the time allotted.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on this 11th day of June, 2025.



Dr. Bradley L. Pentelute