UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOLOGIC, INC.,
Petitioner

v.

ENZO LIFE SCIENCES, INC.
Patent Owner

U.S. Patent No. 7,064,197

SYSTEM, ARRAY AND NON-POROUS SOLID SUPPORT COMPRISING FIXED OR IMMOBILIZED NUCLEIC ACIDS

PETITION FOR *INTER PARTES* REVIEW

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Ex. 1016	Excerpt from File History of EP Patent 0117440 (Enzo November 3, 1997, Submission).
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Ex. 1018	Aotsuka et al., "Measurement of anti-double stranded DNA Antibodies in major immunoglobulin classes." *Journal of Immunological Methods*, 28, 149-62 (1979).

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Ex. 1019	P. T. Gilham, "Immobilized Polynucleotides and Nucleic Acids," published in *Immobilized Biochemicals and Affinity Chromatography* (R. B. Dunlap (ed.)), 1974 (Ex. 1019) ("Gilham").
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I. Introduction

Petitioner Hologic, Inc. ("Hologic") requests *inter partes* review ("IPR") of claims 17, 19, 25, 105, 106, 113, 114, 116, 119, 120, 128, 129, 130, 131, 150, 151,152, 154, 178, 180, 185, 186, 187, and 189 ("the challenged claims") of U.S. Patent No. 7,064,197 ("the '197 Patent") (Ex. 1001) assigned to Enzo Life Sciences, Inc. ("Patent Owner" or "Enzo") (Reel 17133, Frame 718) under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.100 *et seq. See* Ex. 1027 (USPTO assignment record.) This Petition demonstrates there is a reasonable likelihood that Petitioner will prevail in proving, by a preponderance of the evidence, that the challenged claims of the '197 patent are unpatentable over prior art not considered during prosecution. The challenged claims of the '197 patent should be found unpatentable and canceled.

II. Grounds for Standing

Petitioner certifies that the '197 Patent is available for IPR and that the Petitioner is not barred or estopped from requesting IPR challenging the '197 Patent on the grounds identified. *See* 37 C.F.R. § 42.104(a). Specifically: (1) Petitioner is not the owner of the '197 Patent; (2) Petitioner is not barred or estopped from requesting IPR; and (3) this Petition is being filed not more than one year after Petitioner was served with a complaint alleging infringement of the '197 Patent.

III. Mandatory Notices Under 37 C.F.R. § 42.8(b)

A. Real Party–In–Interest

Hologic and Gen-Probe Incorporated are the real parties-in-interest.

IV. Related Matters

Petitioner identifies the following judicial proceedings in which the '197 Patent has been asserted as related matters. "DED" stands for District of Delaware.

Caption	Number	Dist.	Filed
Enzo Life Sciences, Inc. v. Hologic, Inc.	1-15-cv-00271	DED	Mar. 27, 2015
Enzo Life Sciences, Inc. v. Siemens Healthcare Diagnostics, Inc.	1-12-cv-00505	DED	Apr. 20, 2012
Enzo Life Sciences, Inc. v. Affymetrix, Inc.	1-12-cv-00433	DED	Apr. 6, 2012
Enzo Life Sciences, Inc. v. Agilent Technologies Inc.	1-12-cv-00434	DED	Apr. 6, 2012
Enzo Life Sciences, Inc. v. Illumina Inc.	1-12-cv-00435	DED	Apr. 6, 2012
Enzo Life Sciences, Inc. v. Abbott Laboratories et al.	1-12-cv-00274	DED	Mar. 6, 2012
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Enzo Life Sciences, Inc. v. Life	1-12-cv-00105	DED	Jan. 30, 2012

Caption	Number	Dist.	Filed
Technologies Corporation			
Enzo Life Sciences, Inc. v. Roche Molecular Systems Inc. et al.	1-12-cv-00106	DED	Jan. 30, 2012

Petitioner has requested *inter partes* review of claims 1, 6, 8, 9, 12, 13, 14, 15, 16, 27, 31, 32, 33, 34, 38, 41, 61, 62, 63, 64, 68, 69, 70, 72, 73, 74, 78, 79, 100, 101, 191, 192, 193, 194, 195, 212, 213, 218, 219, 222, 225, 226, 227, 230, 233, and 236 of the '197 Patent in another petition (Case No. IPR2016-00820) filed on March 30, 2016.

V. Lead and Back-up Counsel; Electronic Service

Lead counsel is M. Paul Barker (Reg. No. 32, 013), paul.barker@finnegan.com, (650)849-6620. Backup counsel are Arpita Bhattacharyya (Reg. No. 63,681), arpita.bhattacharyya@finnegan.com, (617)646-1676 and Thomas L. Irving (Reg. No. 28,619), tom.irving@finnegan.com, (202)408-4082. Petitioner consents to electronic service of all documents at hologicipr@finnegan.com.

VI. Fee Payment

The required fees are submitted under 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office may charge such fees to Deposit Account No. 06–0916.

VII. Statement of Precise Relief Requested

A. Claims for Which Review Is Requested[1]

Petitioner requests IPR and cancelation of claims 17, 19, 25, 105/17, 105/19, 106/17, 106/19, 113/17, 113/19, 114/17, 114/19, 116/17, 116/19, 119/17, 119/19, 120/17, 120/19, 128/17, 128/19, 129/17, 129/19, 130/17, 130/19, 131/17, 150, 151,152, 154, 178/25, 180/25, 185/25, 186/25, 187/25, and 189/25 of the '197 Patent under 35 U.S.C. § 311.

B. Statutory Grounds of Challenge

The challenged claims are unpatentable and should be canceled in view of the following prior art references and grounds of unpatentability:

Prior Art References	
Ref. 1:	Falk Fish and Morris Ziff, "A Sensitive Solid Phase Microradioimmunoassay For Anti-Double Stranded DNA Antibodies," *Arthritis and Rheumatism,* Vol. 24, No. 3 (March 1981) ("Fish") (Ex. 1006).

[1] Taking guidance from M.P.E.P. § 2287(III) (which discusses how to treat multiple dependent claims in reexamination proceedings), Petitioner represents the challenged multiple dependent claims as "x/y" where x is the dependent claim number and y is the claim from which x depends.

Prior Art References	
Ref. 2:	Barbara E. Noyes and George R. Stark, "Nucleic Acid Hydribization Using DNA Covalently Coupled to Cellulose," *Cell,* vol. 5, 301-310 (July 1975) ("Noyes") (Ex. 1007).
Ref. 3:	A. C. Van Prooijen-Knegt, et al. "In Situ Hybridization of DNA Sequences in Human Metaphase Chromosomes Visualized by an Indirect Fluorescent Immunocytochemical Procedure." *Experimental Cell Research* 141, 397-407 (October 1982) ("VPK") (Ex. 1008).
Ref. 4	U.S. Patent No. 5,572,892 (patented March 30, 1971) ("Metzgar") (Ex. 1009)
Ref. 5	K. B. Ramachandran and D. D. Perlmutter, "Effects of Immobilization of the Kinetics of Enzyme-Catalyzed Reactions. I. Glucose Oxidase in a Recirculation Reactor System," Biotechnology and Bioengineering, Vol. XVIII, 669-684 (1976) ("Ramachandran") (Ex. 1028)
Ref. 6	Sato et al., "Cell Surface Charge and Cell Division in *Escherichia coli* after X radiation." Radiation Research 87, 646-656 (1981) ("Sato") (Ex. 1034).

Ground	Grounds of Unpatentability
1	Claims 17, 19, 25, 105/17, 105/19, 106/17, 106/19, 114/17, 114/19, 116/17, 116/19, 119/17, 119/19, 128/17, 128/19, 129/17, 129/19, 150,152, 178/25, 180/25, 186/25 and 187/25 are anticipated by Fish under 35 U.S.C. § 102(b).
2	Claims 130/17, 130/19, 131/17, 151, and 154 are obvious under 35 U.S.C. § 103(a) in view of Fish.
3	Claims 120/17, 120/19 and 189/25 are obvious under 35 U.S.C. § 103(a) based on Fish in view of Metzgar and further in view of Sato.
4	Claims 113/17, 113/19 and 185/25 would have been obvious under 35 U.S.C. § 103(a) based on Fish in view of Gilham.
5	Claim 17, 19, 25, 105/17, 105/19, 106/17, 106/19, 114/17, 114/19, 119/17, 119/19, 120/17, 120/19, 128/17, 128/19, 129/17, 129/19, 131/17, 150, 151, 152, 178/25, 180/25, 186/25, and 189/25 would have been obvious under 35 U.S.C. § 103(a) based on VPK in view of Metzgar.
6	Claims 113/17, 113/19, 116/17, 116/19, 130/17, 130/19, 154, 185/25, and 187/25 are obvious under 35 U.S.C. § 103(a) based on Noyes in view of VPK and further in view of Metzgar and Ramachandran.

C. Level of Ordinary Skill in the Art at the Time of the Claimed Invention

The ’197 Patent has a purported effective filing date of January 27, 1983, based on the filing date of Application No. 06/461,469—the earliest application in the priority chain of the ’197 Patent. A continuation-in-part (CIP) application was purportedly filed on May 9, 1985 (the “1985 CIP Application”). As discussed below, none of the claims of the ’197 Patent challenged in this IPR is entitled to the January 27, 1983 filing date. Petitioner, however, in a great abundance of caution, advances separate grounds in view of both of the 1983 and 1985 dates.

The application field for the ’197 patent is nucleic acid chemistry, including techniques for attaching nucleic acids to other moieties like solid supports or labels.. A person having ordinary skill in this field (POSITA) as of both the 1983 and the 1985 filing dates would have (i) possessed or would have been actively pursuing an advanced degree in organic chemistry and/or biochemistry, (ii) attained at least two years of experience in a chemistry or biochemistry laboratory and would have been familiar with nucleic acid chemistry, and (iii) have been knowledgeable of conventional techniques for attaching nucleic acids to other moieties like solid supports or labels. See Ex. 1002 at ¶21. This level of skill of the POSITA would have applied to all obviousness analyses in this Petition. Furthermore, all conclusions regarding obviousness apply as of the January 27,

1983, and May 9, 1985 filing dates, as well as one year prior to each date (January 27, 1983, and May 9, 1984).

VIII. Summary of the Prosecution History of the '197 Patent and the State of the Art

A. Hybridizable Nucleic Acids Bound to Solid Supports

As the POSITA would have known, two strands of nucleic acids hybridize to one another through hydrogen bonding between complementary nucleotides (bases) that naturally pair with one another. Ex. 1002 ¶24. Under the Watson-Crick base pairing model, the nucleotide "A" pairs with the nucleotide "T" on the opposite strand, and the nucleotide "C" pairs with the nucleotide "G" on the opposite strand. *Id*. In RNA molecules, "T" is replaced by "U" to form an "A-U" base pair.

More than a year before the January 27, 1983, filing date of the first application, multiple techniques were available to the POSITA for binding single stranded nucleic acids in a hybridizable form to many different types of solid supports. Ex. 1002, ¶25. Exemplary uses of hybridizable single-stranded nucleic acids bound to solid supports included identifying biological materials in samples and separating biological materials from samples. Ex. 1002, ¶25.

B. Specification of the '197 Patent

The '197 Patent describes non-porous solid supports with fixed or immobilized nucleic acids, and systems and arrays comprising such non-porous

solid supports. Ex. 1001, Title and Abstract. The ’197 Patent discusses non-porous solid supports such as “glass, or alternatively, plastic, polystyrene, polyethylene, dextran, polypropylene, and like.” Ex. 1001, 6:2-6; 12:39-45. The ’197 Patent also identifies conventional microtiter well plates as non-porous solid supports to which nucleic acids can be fixed. *Id*. at 12:54-58. The patent also discusses glass plates having “an array of depressions or wells” (*id*. at 8:65-9:5), and polystyrene plates (*id*. at 11:56-58; 12:7-26) as solid supports to which nucleic acids may be bound (fixed or immobilized). Although not required by any of the challenged claims, Patent Owner also argued that the ’197 Patent describes treatment of the solid supports with amine providing compounds, epoxy compounds, and acid solutions to fix or immobilize nucleic acids. Ex. 1011 at pp 40-41 (providing citations to the application for support); Ex. 1001 at Abstract (note that the Abstract discussing the three groups was not added until November 8, 2005 (Ex. 1024 at pp. 50 and 52)). The ’197 Patent also explains that polynucleotide analyte sequences fixed or immobilized to the solid supports may be hybridized to complementary polynucleotide or oligonucleotide probes. *See e.g.,* Ex. 1001 at 5:61-6:9; 6:15-27; 8:65-9:5. Although not required by any of the challenged claims, the hybridizing probe may have a label capable of generating a soluble signal, and hybridization of the probe to the analyte may be detected or quantified using the soluble signal. *Id*. at 1:23-32; 6:15-32; 8:65-9:12.

This Petition will show that the non-porous solid supports and arrays claimed in the '197 Patent previously had been disclosed in prior art not considered during prosecution of the applications leading to the '197 Patent, for example, in Fish (Ex. 1006), Noyes (Ex. 1007), VPK (Ex. 1008), Gilham (Ex. 1019), Metzgar (Ex. 1009), Ramachandran (Ex. 1028) and Sato (Ex. 1034). Ex. 1002 at ¶25. The prior art shows every limitation of the challenged claims, including the limitations added to secure allowance of the patent.

C. Summary of Prosecution History

The challenged claims in this Petition ("the array claims") had a very long prosecution history. The array claims faced many rounds of office action rejections under 35 U.S.C. § 112, ¶. *See, e.g.,* Ex. 1022, pp. 6-9; Ex. 1014, pp. 4-8. However, the array claims did not face prior art based rejections. *Id.* After Patent Owner submitted multiple expert declarations to overcame the § 112 rejections, the Examiner allowed the claims. *See, e.g.,* Ex. 1003, pp. 95-126 *(*providing voluminous attorney arguments and referring to expert declaration to overcome §112 rejections); Ex. 1013 at pp. 79-85 (referring to the Waldrop, Stavrianopoulos, and Kirtikar declarations for overcoming new matter rejections of the array claims). The Examiner incorrectly failed to recognize prior art that showed arrays comprising non-porous solid supports with nucleic acids attached in a hybridizable form thereto.

IX. Claim Construction

In an IPR, an unexpired patent's claims receive the "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). Unless otherwise noted, Petitioner proposes that the claim terms of the '197 Patent be given their ordinary and customary meanings in the art. Petitioner, however, construes the following terms according to the intrinsic evidence and traditional canons of claim construction. Petitioner uses these constructions in its grounds for unpatentability. *See* 37 C.F.R. § 42.104(b)(4).

A. "Non-Porous Solid Support"

All challenged independent claims, i.e., claims, 17, 19, and 25, recite the term "non-porous solid support." Ex. 1001 (claims). This term should be given its ordinary and customary meaning in the art. And as admitted by the Patent Owner, certain solid supports were known in the art to be non-porous. For example, the '197 patent states that a polynucleotide can be fixed "to a non-porous solid support, such as a conventional microtiter well . . . ." Ex. 1001, 12:54-61. Similarly, when arguing that its counterpart European patent application disclosed non-porous solid supports—despite failing to mention the word "non-porous"—Patent Owner repeatedly asserted that containers in which reactions take place in solution, such as the disclosed wells, must be non-porous. Ex. 1016, pp. 6-7.

Also, the Patent Owner readily admitted that the prior art technique of in-situ hybridization was performed on glass slides, which necessarily are non-porous. Ex. 1026 at pp. 5 and 7 (The Examiner argued that "a transparent non-porous solid support is embodied by glass slides," as disclosed by Langer's in-situ technique (p. 5), and the Patent Owner admitted that Langer et al. disclosed an in-situ hybridization method that was performed on "nonporous solid supports that are transparent or translucent." (page 7)). And in its Opening Claim Construction Brief in the related litigations, the Patent Owner noted that "non-porous" is a commonly understood term—citing the Examiner's understanding "that glass slides are 'reasonably interpreted as the commonly utilized non-porous microscope type slides which are well known in the art.'" Ex. 1023, pp. 8-9 (citing Ex. 1022 (11-26-2004 Office Action, p. 10)).

Thus, the ordinary and customary meaning of "non-porous solid support" should apply, which includes conventional laboratory equipment such as microtiter wells and glass slides. In the related litigations involving the '197 Patent, the district court construed the term "non-porous" to mean "having no pores." Ex. 1010, pp. 5-7. If adopted here, that construction would not change the conclusions in this Petition, because the prior art applied in this Petition shows conventional microtiter wells and glass slides, which the Petitioner admits are encompassed by the claim language "non-porous solid support."

B. "Hybridizable form"

The term "hybridizable form" is recited in all of the challenged independent claims as a property of the fixed or immobilized single strand. This term should be construed as "capable of binding through Watson-Crick base pairing." This construction is supported by the specification of the '197 Patent, which states that "[p]olynucleotide sequence-based detection techniques are characterized by a sequence of steps comprising the non-covalent binding of a labelled polynucleotide sequence or probe to a complementary sequence of the analyte [which can be fixed] under hybridization conditions in accordance with the Watson-Crick base pairing of adenine (A) and thymine (T), and guanine (G) and cytosine (C), and the detection of that hybridization." Ex. 1001, 2:22-34 (emphasis added). In the related litigations involving the '197 Patent, the defendants and the Patent Owner agreed that the term "hybridizable form" should be construed as "capable of binding through Watson-Crick base pairing." Ex. 1010, p. 10.

Furthermore, the Patent Owner successfully asserted during the claim construction phase of the related litigations, that when "two nucleic acids strands [are] hybridized to each other," "the claims and specification do not require, or disclose, that [the] two strands hybridize 'throughout their entire length.'" Ex. 1023, pp. 13-14, citing several passages of the '197 patent that support that position, including the passage quoted above. Petitioner agrees with the Patent

Owner's assertion that a POSITA , especially in view of the '197 Patent's specification and claims, would understand that the immobilized nucleic acid strand does not have to hybridize along its entire length in order to be considered "hybridizable." Ex. 1002, ¶24.

C. "Array"

The term "array" is recited in all of the challenged independent claims of the '197 Patent. Petitioner proposes that this term be construed as "an orderly grouping or arrangement."

The specification uses the term "array" only in the context of "glass plates" having "an array of depressions or wells." Ex. 1001, 8:65-9:2. The specification provides no further guidance for construing this term. During prosecution, however, Patent Owner argued that "[t]he everyday meaning of array is an orderly grouping or arrangement." Ex. 1003, p. 116. Therefore, Petitioner proposes that the term "array" be construed as "orderly grouping or arrangement." In the related litigations, the district court similarly construed the term "array" to mean "an orderly grouping or arrangement." Ex. 1010, pp. 13-14.

X. The Challenged Claims of the '197 Patent Are Unpatentable

Pursuant to 37 C.F.R. § 42.104(b)(4), Section X of this Petition now explains how the challenged claims of the '197 Patent are unpatentable under the asserted grounds. Petitioner's supporting evidence, and the relevance of the

evidence to the challenges raised, are also identified in Section X, pursuant to 37 C.F.R. § 42.104(b)(5). The supporting evidence includes an expert declaration from Petitioner's Expert, Dr. Norman Nelson (Ex. 1002). Dr. Nelson's declaration includes claim charts that explicitly refer to and quote passages from the prior art references to show where the elements of the claims can be found in the prior art.

A. Ground 1: Claims 17, 19, 25, 105, 106, 114, 116, 119, 128, 129, 150, 152, 178, 180, 186, and 187 are anticipated by Fish

The '197 Patent was filed on June 7, 1995, and claims priority to U.S. Application No. 06/461,469, filed on January 27, 1983. Fish was published March 1981 (Ex. 1006). As discussed in Section IX.D.1, *infra*, Petitioner disputes Patent Owner's priority claim to the application filed in 1983. Nevertheless, since Fish was published more than a year prior to the purported effective filing date (January 27, 1983) of the '197 Patent, it is prior art to the '197 Patent under § 102(b).

"Anticipation" under 35 U.S.C. § 102 requires disclosure of each and every claim limitation in a single prior art reference, either explicitly or inherently. *In re Omeprazole Patent Litigation*, 483 F.3d 1364, 1371 (Fed.Cir. 2007). Even if a prior art reference lacks an express disclosure of a claim limitation, it may nonetheless anticipate by inherency. *In re Cruciferous Sprout Litig*., 301 F.3d 1343, 1349 (Fed.Cir. 2002). The Federal Circuit has explained that "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single

anticipating reference." *Verizon Services Corp. v. Cox Fibernet Virginia*, *Inc*., 602 F.3d 1325, 1337 (Fed. Cir. 2010) (internal citations and quotation marks omitted); *Continental Can Co. v. Monsanto Co*., 948 F.2d 1264, 1268 (Fed.Cir.1991). Thus, inherent anticipation "requires that the missing descriptive material is 'necessarily present,' not merely probably or possible present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp*., 295 F.3d 1292, 1295 (Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (emphasis added). "A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations." *Eli Lilly & Co. v. Barr Labs.*, 251 F.3d 955, 970 (Fed. Cir. 2001).

Here, Fish explicitly or inherently discloses every limitation of claims 17, 19, 25, 105, 106, 114, 116, 119, 128, 129, 150, 152, 178, 180, 186, and 187 of U.S. Patent No. 7,064,197.

1. Independent claims 17, 19, and 25

The challenged independent claims have many common limitations, as shown below, which are addressed jointly to avoid repetition.

Claim 17, which is exemplary of all of the challenged independent claims, recites: "An array comprising various single-stranded nucleic acids fixed or immobilized in hybridizable form to a non-porous solid support."

The preambles of all of the challenged independent claims in this Petition recite an "array." The challenged independent claims further recite that the "array" comprises single-stranded nucleic acids "fixed or immobilized in hybridizable form to a non-porous solid support." Indeed, the only distinction between claims 17 and 19 is that claim 17 recites that the "array" comprises "*various* single-stranded nucleic acids …," whereas claim 19 recites that the "array" comprises "single-stranded nucleic acids …." (Emphasis added.) As discussed below, the prior art here shows various types of single-stranded DNA fixed or immobilized to a non-porous solid support, and thus it addresses both the "various single-stranded nucleic acids" and "single-stranded nucleic acids" limitations in claims 17 and 19, respectively. Claim 25 adds the terms "wells or depressions"—reciting "non-porous solid support having wells or depressions."

There are no other differences between the challenged independent claims. Thus, all of these claims can easily be addressed with one description of the prior art. As shown below, Fish discloses every limitation of independent claims 17, 19, and 25.

a. **"Array"**

The preamble of independent claims 17, 19, and 25 recite an "array." Fish discloses microtitration trays having a plurality of wells arranged in rows. Ex. 1006, p. 536, left col., first full ¶. The microtitration tray of Fish is an "array," as

recited in claims 17, 19, and 25, because the wells in the microtitration trays provide an orderly grouping or arrangement of nucleic acids bound to the surface of the wells in the trays. Ex. 1002, ¶37. In fact, the '197 Patent uses the term "array" only in the context of "glass plates" having "an array of depressions or wells." Ex. 1001, 8:65-9:2. Nowhere does the '197 Patent discuss any other form of orderly grouping or arrangement of nucleic acids on a non-porous solid support. Thus, Fish discloses an "array" as recited in claims 17, 19, and 25.

b. **"A non-porous solid support," or "[a] non-porous solid support having wells or depressions."**

Claims 17 and 19 recite a "non-porous solid support," and claim 25 recites "a non-porous solid support having wells or depressions." Fish discloses these limitations. Specifically, Fish discloses polyvinyl microtitration trays having rows of wells and DNA is bound (immobilized) in the wells to detect antibodies that bind to the immobilized DNA. Ex. 1006, Abstract; p. 536, left col., first two full ¶¶. Microtitration trays made of polyvinyl (a type of plastic) are non-porous. Ex. 1002, ¶¶41, 42. In fact, the '197 patent identifies conventional microtiter wells as being non-porous when it discloses that polynucleotides can be fixed "to a non-porous solid support, such as a conventional microtiter well . . . ." Ex. 1001, 12:54-57.

That understanding is consistent with assertions by the Patent Owner in counterpart European application No. 84100836.0-2106 (EP Patent No. 0107440).

When arguing that its counterpart European patent application disclosed non-porous solid supports or systems—despite failing to mention the word "non-porous"—the Patent Owner asserted that containers in which reactions take place in solution, such as the disclosed wells, must be non-porous. Ex. 1029 (12-28-94 submission), pp. 15-16 (After discussing the lack of the term "non-porous" in the specification (p. 15), the Patent Owner argued "[t]he claimed method requires the presence of a soluble signal. Accordingly, by necessity, this requires the presence of a solution which, in turn, requires a container or system that is non-porous." (p. 16). Patent Owner later asserted that "[a] support or system…to which DNA is bound, being a depression or a well and allowing the determination of the DNA whereby washing steps and substrate reactions…are performed in the support/system ***must*** be non-porous.") (Emphasis added). Ex. 1016, p. 6.

Thus, consistent with the conventional understanding—and confirmed by the Patent Owner's own assertions—the polyvinyl microtitration trays of Fish are a "non-porous solid support," as well as a "non-porous solid support having wells or depressions," and thus Fish shows that limitation of all of the independent claims.

c. **"single-stranded nucleic acid"/ "various single-stranded nucleic acid" "fixed or immobilized in hybridizable form to said non-porous solid support"**

The challenged independent claims recite that either "single-stranded nucleic acids" (claim 19), or "various single-stranded nucleic acids" (claims 17 and 25),

are "fixed or immobilized in hybridizable form to said non-porous solid support." Fish shows immobilizing various single strands of DNA—a mixture of poly-dA and poly-dC, or denatured calf thymus DNA—on poly-l-lysine (PLL) coated microtitration tray wells. Ex. 1002, ¶46; Ex. 1006, p. 534, left col., first full ¶; p. 536, left col., first two full ¶; Figure 1 (Description).

The data in Fish confirm that the single-stranded DNA (polydA + poly DC, as well as the denatured calf thymus DNA) was bound to the PLL coated wells. For example, Fig. 1 at p. 539 of Ex. 1006 shows the results of nuclease S1 treatment of the three different types of immobilized DNA. Ex. 1002, ¶47. S1 digests single-stranded DNA but not double-stranded DNA. Ex. 1002, ¶47; Ex. 1006, p. 538, right col., ¶1. The empty and black bars in Fig. 1 show the amount of antibody bound to the DNA in the wells without S1 treatment (-) and with S1 treatment (+), respectively. Ex. 1002, ¶47; Ex. 1006, p. 539 Fig. 1. Dr. Nelson states that "[a]fter addition of serum to the wells and the anti-DNA antibodies in the serum are allowed to bind to the immobilized DNA, the wells are washed to remove antibodies that are not bound to the immobilized DNA and those that remain bound to the DNA are detected with a second, labeled anti-Ig antibody that bind to remaining antibodies." Ex. 1002, ¶47, Ex. 1006, p. 536, left col., third full ¶ and ¶ bridging the cols.; p.538, right col., first ¶ .

The data show that in the wells having bound double-stranded poly dA-T for

both patients (O.N. and B.E.), there was virtually no difference in binding with or without S1 treatment. *Id. (see* the first row for each patient "poly dA-dT," which shows approximately equal length empty and black bars (equal anitibody binding) extending to about 200). That is the expected result for double-stranded DNA, because S1 does not digest double-stranded DNA and all of the immobilized DNA would still be available for binding after S1 treatment. Ex. 1002, ¶48.

But for both patients, there was significantly less antibody binding with S1 treatment than without S1 treatment in the wells with immobilized single-stranded poly DA + poly dC and in the wells with immobilized single-stranded denatured DNA. *Id (see* the second and third row for each patient "poly dA + dC" and "denatured DNA", which show shorter black bars (S1 treated) than empty bars (no S1 treatment). That is the expected result for single-stranded DNA because S1 digests single-stranded DNA, so after S1 treatment less immobilized single-stranded DNA would be available for antibody binding. Ex. 1002, ¶48.

Those results prove that single-stranded DNA must have been immobilized to the PLL coated wells; otherwise the DNA would have been washed away during the experiment and there would have been no difference in antibody binding with or without S1 treatment. *Id*.

Fish also reports antibody binding to the immobilized single-stranded DNA in Figures 3 and 4. Ex. 1002, ¶ 51; Ex. 1006, p. 539, left col., first full paragraph;

p. 540, right col.– Fig. 3; p. 541, left col.–Fig. 4. Fish describes measures to block non-specific antibody binding directly to the surface of wells, which allowed them to conclude that the reported data in Figs. 3 and 4 show antibodies binding to immobilized single-stranded DNA. Ex. 1002, ¶51; Ex. 1006, p. 537, left col., fourth line under Table 2, through the paragraph bridging the cols. on p. 537.

The single-stranded DNA is fixed or immobilized to the microtitration trays by the amine groups provided on the surface by the PLL coating. Ex. 1002, ¶55; *see also* Ex. 1006, p. 534, left col., first 14 lines (discussing that PLL facilitates binding of DNA to plastic surfaces). Also, Dr. Nelson states that "[i]t is known that the amine groups of PLL form non-covalent bonds with nucleic acids via ionic interactions between the positive charges of the amine groups and the negative charges of the phosphate groups in the DNA backbone." Ex. 1002, ¶55, citing articles to support that assertion.

Fish does not expressly disclose that the fixed or immobilized ssDNA would be "in hybridizable form," because the Fish assay did not involve hybridization of such ssDNA. But the single-stranded DNA that was immobilized in the microtitration tray wells in Fish necessarily was capable of binding through Watson Crick base pairing. Ex. 1002, ¶66. It is important to note that nucleic acid "in hybridizable form" simply means that the nucleic acid is capable of binding through Watson Crick base pairing—not that it actually is so paired. (As noted

above, Enzo agreed to this construction in the related litigations (Ex. 1010, p. 10.)

Dr. Nelson explains that the single-strands of DNA immobilized via the amine groups of PLL in Fish necessarily were capable of binding through Watson Crick base pairing in view of admissions made by Patent Owner, as well as publications showing hybridization of PLL immobilized ssDNA to another strand in conventional microarrays employing solid supports coated with PLL. Ex. 1002, ¶64, 66.

For example, Diehl discloses arrays in which ssDNA was immobilized to non-porous solid supports by PLL coatings. Ex. 1002, ¶57; Ex. 1021, ¶ bridging pp. 1-2. Dr. Nelson explains that after complementary labeled DNA was added to the array, the strong fluorescent signals shown for positive spots on the array (see Fig. 1 of Diehl at p. 2) show that the immobilized ssDNA hyridized to complementary strands. *Id*. Thus, the ssDNA immoblized with PLL on the arrays necessarily was hybridizable.

Diehl did not follow the exact protocol when attaching the ssDNA using PLL. If there would have been any impact on the capability of the ssDNA to hybridize caused by those differences, Diehl's treatment would have negatively impacted that capability rather than improved it.

For example, Dr. Nelson explains that the Diehl used, relative to Fish, a higher concentration of PLL to coat the wells. Ex. 1002, ¶¶58, 59 (citing Ex. 1032

and Ex. 1033). Use of a higher concentration of PLL could result in an increased amount of amines on the surface, creating more interactions between the DNA and the surface amines. Ex. 1002, ¶61. If increased interactions of the ssDNA with the surface of the support occur along the length of the ssDNA, that could result in interference with the immobilized ssDNA's capability of interacting and hybridizing with its complementary strand. Ex. 1002, ¶61. An increase in interactions with surface amines certainly would not improve the opportunity for immobilized ssDNA to hybridize to a complementary strand. Ex. 1002, ¶61.

As discussed above, Fish's data showed that the lower concentration of PLL successfully immobilized the ssDNA to the wells. Once the ssDNA was immobilized, a lower concentration of amines on the surface (compared to Diehl) could not interfere with the hybridization capability of the ssDNA. *Id*. Thus, the different concentration used by Diehl does not bring into question the capability of the ssDNA immobilized on the microtitration wells in Fish to bind through Watson Crick base pairing. Ex. 1002, ¶62.

Diehl, furthermore, crosslinked the ssDNA to the support by UV irradiation. Ex. 1010, p. 2, left col., first ¶. As Dr. Nelson explains, crosslinking of the DNA creates stronger covalent bonds between the immobilized ssDNA and the solid support. Ex. 1002, ¶63. If that difference had any effect on the capability of the immobilized ssDNA to hybridize, it would have been a negative effect. *Id*. The

non-covalent bonds between the ssDNA and the solid support in Fish allow the immobilized ssDNA to more freely interact with a complementary sequence than the covalent bonds in Diehl. *Id*. Thus, the fact that the immobilized ssDNA in Diehl hybridized to complementary strands, despite conditions that could decrease that from happening, shows that the immoblized ssDNA in Fish was capable of hybridizing through Watson Crick base pairing.

Moreover, the Patent Owner touted its single sentence disclosure of PLL coating as "the lynchpin[] of DNA microarray technology" that uses PLL to immobilize ssDNA to such arrays. Ex. 1003, pp. 96-97 The Patent Owner went on to assert that its one sentence disclosure of coating with PLL—including no specific concentration or conditions—"allows for hybridization and detection of different nucleic acids under the same or similar hybridization and detection conditions." *Id*. at 98. Thus, the Patent Owner admits that attaching a ssDNA using a PLL coated non-porous solid support results in an immobilized ssDNA that necessarily will hybridize under appropriate hybridization conditions. Accordingly the immobilized ssDNA in Fish necessarily will be in hybridizable form.

The Patent Owner also asserted during prosecution that the one sentence discussing coating with PLL—without any mention of specific conditions—disclosed fixation of "polynucleotide in a hybridizable form" to a non-porous solid support. Ex. 1025, p. 52, first two paragraphs (citing Ex. 1011 at pp. 40-41 (Charts

7 and 8, submitted on October 3, 2002)). The Patent Owner thus asserted that the specification's one sentence concerning PLL treatment provides disclosure of fixation of a polynucleotide in hybridizable form to a non-porous solid support. The Patent Owner cannot now credibly assert that conditions different than those used by Fish are necessary to immobilize ssDNA via reactive amine groups provided by PLL coating.

Moreover, the challenged independent claims 17, 19, and 25 recite that the immobilized DNA is in "hybridizable form," i.e., the nucleic acid is *capable of* hybridization to complementary sequences. Thus, this limitation only applies to the capability of the immobilized ssDNA to hybridize. It has been shown that the immobilized ssDNA in Fish necessarily is capable of hybridizing because it will hybridize when complementary DNA is present in appropriate hybridization conditions. None of the challenged claims requires the solid support or the system to be in appropriate hybridization conditions. Thus, Fish need not show appropriate hybridization conditions to anticipate the claims. The testing conditions (e.g., buffers, pH, temperature, etc.) used for the antibody binding experiments in Fish are not relevant to the analysis. Rather, Fish shows single-stranded DNA appropriately immobilized on a non-porous solid support that is capable of hybridizing. Fish need show nothing more.

Accordingly, immobilized and hybridizable single-stranded DNA is

"necessarily present" on the PLL coated microtitration tray wells of Fish. *Trintec,* 295 F.3d at 1295; *see also Schering Corp. v. Geneva Pharmaceuticals,* 339 F.3d 1373, 1377 (Fed. Cir. 2003) (discussing that "recognition by a person of ordinary skill in the art before the critical date of the [patent at issue] is not required to show anticipation by inherency. The district court therefore did not err in allowing for later recognition of the inherent characteristics of the prior art [] patent."). Accordingly, Fish inherently discloses that the fixed or immobilized nucleic acids are "in hybridizable form," as required by all of the independent claims.

2. Dependent claims 105, 106, 114, 116, 119, 128, 129, 150, 152, 178, 180, 186, and 187.

a. **Claims 105 and 178**

Claims 105 and 178 additionally recite that "said non-porous solid support comprises glass or plastic." The microtitration tray (the "non-porous solid support") disclosed by Fish is made of polyvinyl, which is plastic. Ex. 1002, ¶70. Thus, Fish anticipates these claims.

b. **Claims 106 and 119**

Claim 106 additionally recites that "said non-porous solid support" comprises "a plate or plates, a well or wells, a microtiter well or microtiter wells, a depression or depressions, a tube or tubes, *or* a cuvette or cuvettes." (Emphasis added.) Similarly, claim 119 recites that "said non-porous solid support" comprises "a well or wells, a microtiter well or microtiter wells, *or* a depression or

depressions." (Emphasis added.). Fish discloses that the microtitration tray (the "non-porous solid support") comprises one or more "wells" arranged into rows on the tray. Ex. 1006, p. 536, left col., first full ¶. Since claims 106 and 119 recite "a microtiter well or microtiter wells" in the alternative, Fish anticipates these claims.

c. **Claims 114 and 186**

Claims 114 and 186 additionally recite that "said fixation or immobilization to said non-porous solid support is non-covalent." The binding of single-stranded DNA to the PLL-coated microtitration trays in Fish necessarily is non-covalent. Ex. 1002, ¶77. The binding to the PLL-coated surface is via the amine groups provided by PLL, which have a positive charge, and the amine groups ionically interact with the negative charges on the DNA to form ionic (i.e., non-covalent) bonds between the amine groups and the DNA. *Id.* The DNA and the amine groups of the PLL would bind covalently only if the amine groups and/or the ends of the DNA strands are functionalized to cause covalent bonding. *Id*. Fish does not disclose functionalizing either the PLL or the DNA strands. *Id*. Accordingly, Fish inherently discloses non-covalent binding of the single-stranded DNA to the PLL-coated microtitration trays. Thus, Fish anticipates these claims.

d. **Claims 116 and 187**

Claims 116 and 187 additionally recite that "said fixation or immobilization [of nucleic acid] is not to a cell fixed in situ to said non-porous solid support." Fish

discloses attaching ssDNA to the poly-L-lysine coated microtitration trays without a cell. Ex. 1002, ¶69; Ex. 1006, p. 534, left col., first ¶; p. 536, left col., first two full ¶; Figure 1 (Description). Therefore, Fish anticipates claims 116 and 187.

e. **Claims 128 and 150**

Claims 128 and 150 additionally recite that "said nucleic acid is DNA." Fish discloses binding of single-stranded DNA to PLL-coated microtitration trays. Ex. 1002, p. 536, left col., first two full ¶; Figure 1 (Description). Thus, Fish anticipates these claims.

f. **Claim 129 and 152**

Claims 129 and 152 additionally recite that "said single-stranded nucleic acid is unlabeled." Fish does not disclose labeling of the single-stranded DNA, and therefore, it follows *ipso facto* that the single-stranded DNA bound to the PLL-coated microtitration trays are unlabeled. *See, e.g.,* Ex. 1006, p. 536, left col., second full ¶ (discussing binding of poly-dA and poly-dC to the PLL-coated microtitration trays). Thus, Fish anticipates these claims.

g. **Claim 131**

Claim 131 additionally recites that the fixed or immobilized "nucleic acids comprise nucleic acid sequences complementary to nucleic acid sequences of interest sought to be identified, quantified or sequenced." Fish discloses binding of poly-dA to PPL-coated microtitration tray wells. Ex. 1006, p. 536, left col., ll., ¶3. Poly-dA is complementary to poly-dT, which may be a sequence of interest sought

to be identified, quantified or sequenced. The claims only recite the property of immobilized strand—its complementarity to another strand, and do not require the presence of the complementary strand. Thus, Fish anticipates this claim.

h. **Claim 180**

Dependent claim 180 additionally recites that the non-porous solid support has been "treated with a surface treatment agent, a blocking agent, or both." Fish discloses surface treatment of microtitration trays with PLL prior to immobilization of DNA. Ex. 1006, p. 536, left col., first two full ¶¶. Thus, Fish anticipates this claim.

B. Ground 2: Claims 130, 131, 151, and 154 are obvious under 35 U.S.C. § 103(a) in view of Fish.

Obviousness is a conclusion of law based on the factual inquiries set forth in *Graham v. John Deere Co*., 383 U.S. 1, 17-18 (1966), which include consideration of (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed subject matter as a whole, (3) the level of skill in the art, and (4) objective evidence of nonobviousness. *KSR Int'l Co. v Teleflex Inc*., 550 U.S. 398, 421 (2007). The obviousness analysis looks to the state of the art that existed at the time the invention was made. *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965). "An obviousness finding [is] appropriate where the prior art 'contained *detailed enabling methodology* for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting

that it would be successful.'" *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O'Farrell,* 853 F.2d 894, 902 (Fed. Cir. 1988)). "Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *O'Farrell,* 853 F.2d at 903–04. In an obviousness analysis, one "must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* 550 U.S. at 417. Applying a known technique to improve a product "is obvious unless its actual application is beyond" the level of ordinary skill in the art. *Id*.

As explained in Section X.A, *supra*, Fish expressly or inherently discloses every element of independent claims 17, 19, and 25, and many of the challenged dependent claims. Petitioner shows in Section X.A, *supra*, why claim 131 is anticipated by Fish. If, however, the panel disagrees that claim 131 is anticipated by Fish, this claim would at least have been obvious to a POSITA in view of Fish, as explained below. Similarly, although Fish does not explicitly disclose all of the limitations of claims 130, 151, and 154, these claims would have been obvious to a POSITA in view of Fish.

a. **Claim 131**

Claim 131 recites that the fixed or immobilized "nucleic acids comprise nucleic acid sequences complementary to nucleic acid sequences of interest sought to be identified, quantified or sequenced." As discussed previously in Section

IX.A, Fish discloses binding of ssDNA to PLL-coated microtitration wells ("the non-porous solid support"). Fish also inherently discloses that the fixed or immobilized nucleic acids are "in hybridizable form." *See* Section X.A, *supra*.

A POSITA would have reasonably expected from the disclosure of Fish that the ssDNA immobilized to the PLL-coated wells would hybridize, i.e., form Watson-Crick base pairs, with complementary nucleotide sequences added in solution to the microtitration wells. Ex. 1002, ¶73. A POSITA would have also known that hybridization of nucleic acids to complementary strands can be used to identify, detect, or quantify target (analyte) sequences by binding the target sequences to a substrate and introducing complementary probe sequences labeled with signaling moiety that would hybridize with the target sequences. *Id*. Indeed, the background of the '197 Patent discloses that detection techniques for detecting substances in samples based on nucleic acid hybridization "[have] become a routine practice in clinical, diagnostic, and analytical laboratories." Ex. 1001, 2: 9-16. The '197 Patent also discusses that nucleic acid hybridization-based detection were known to involve non-covalent binding of labeled probe sequences to complementary analyte sequences of interest, including techniques in which one of the strands is fixed to a solid support—similar to immunoassay-based detection techniques. *Id.* at 2:17-52. Thus, claims 31, 68, and 192 are obvious in view of Fish.

Here, a POSITA would have had a reason to use ssDNA immobilized on non-porous microtitration well to detect a complementary sequence of interest for detection in view of the admitted prior hybridization detection methods. Ex. 1002, ¶80. And as asserted above, there would have been a reasonable expectation that it would work. Here, the array of claim 131 is no more than predictable use of prior art elements according to their established functions." *See KSR*, 550 U.S. at 417. Thus, claim 131 would have been obvious in view of Fish.

b. **Claims 130 and 154**

Claims 130 and 154 recite that the fixed or immobilized "nucleic acids is/are RNA." Fish discloses binding of ssDNA to PLL-coated microtitration wells ("the non-porous solid support") via amine reactive groups provided on the surface of the microtitration wells by the PLL coating. Ex. 1002, ¶81. A POSITA would have readily expected from the disclosure of Fish that the DNA immobilization technique disclosed in Fish could be used for binding RNA. Ex. 1002, ¶81. This is because both DNA and RNA are negatively charged, and therefore, both would bind ionically with the positive charges of the amine reactive groups of the PLL coating. *Id.* Also, there is nothing special about attaching a single-strand of RNA instead of DNA. *Id*. Thus, claims 130 and 154 would have been obvious to POSITA based on the teachings of Fish.

c. **Claim 151**

Claim 151 recites that fixed or immobilized nucleic acids comprise "a gene sequence or pathogen sequence." Fish discloses binding of ssDNA to PLL-coated microtitration wells ("the non-porous solid support") via amine reactive groups provided on the surface of the microtitration wells by the PLL coating. Ex. 1002, ¶82. A POSITA would have readily expected from the disclosure of Fish that the DNA immobilization technique disclosed in Fish could be used for binding gene sequences to the PLL-coated microtitration tray wells because genes are DNA. Ex. 1002, ¶82. Similarly, a pathogen sequence can be DNA. *Id*. There is nothing special about attaching gene sequences or pathogen sequences instead of DNA to a non-porous solid support. *Id*. Thus, claim 151 would have been obvious to a POSITA based on the teachings of Fish.

C. Ground 3: Claims 120 and 189 are obvious under 35 U.S.C. § 103(a) based on Fish in view of Metzgar and further in view of Sato.

Claims 120 and 189 recite that "said non-porous solid support comprises one or more hydroxyls." As explained in Section IX.A, *supra*, Fish expressly or inherently discloses every element of independent claims 17, 19, and 25, and many of the challenged dependent claims. Claims 120 and 189 would have been obvious based on Metzgar in view of Sato. Metzgar issued as a patent on Mar 30, 1971, and therefore, Metzgar is prior art to the '197 Patent under § 102(b). Similar, Sato was

published in 1981, and therefore, Sato is also prior art to the '197 Patent under § 102(b).

Fish discloses binding of ssDNA to PLL-coated polyvinyl microtitration tray wells ("the non-porous solid support") via amine reactive groups provided on the surface of the microtitration wells by the PLL coating, as discussed above. The polyvinyl microtitration trays do not comprise one or more hydroxyl groups. However, a POSITA would have readily expected from the disclosure of Fish that the procedure for immobilization of nucleic acids described in Fish could be performed on glass slides. Glass slides necessarily include hydroxyl groups. Ex. 1002, ¶83. It is important to consider that the claims do not require any use of the hydroxyl groups—only that they are present on the solid support. Indeed, microscope glass slides having wells or depressions similar to the microtitration trays of Fish were common at the time of invention of the '197 Patent. Ex. 1002, ¶83. Metzgar specifically discloses microscope slides made of glass and having "depressions or wells on the top surface thereof." Ex. 1009, Abstract; 2:28-30; Figure 1. Many laboratory experiments, for example, experiments that involve visualization of radioactive or nonradioactive signals under a microscope glass slides. Ex. 1002, ¶83.

Therefore, a POSITA would have been motivated, with a reasonable expectation of success, to perform the nucleic acid immobilization procedure

described in Fish on easy-to-use, non-porous supports, such as the glass slides having wells or depressions, as disclosed in Metzgar. *Id*. A POSITA would also have reasonably expected that glass slides could be treated with PLL to provide amine reactive groups on the surface, which could then be used bind nucleic acids. Ex. 1002, ¶83. Indeed, Sato discloses treatment of glass slides with PLL prior to fixing cells on the slides, thus indicating that PLL treatment of glass slides a known and routine practice. Ex. 1002, ¶83; Ex. 1034, p. 647, last ¶.

Accordingly, a POSITA would have readily and reasonably expected to treat glass slide with PLL and immobilize nucleic acids thereon. Ex. 1002, ¶83. Here, the use of the glass slides which have one or more hydroxyl groups is no more than predictable use of prior art elements according to their established functions." See *KSR*, 550 U.S. at 417. Accordingly, a POSITA would have been motivated to combine the teachings of Fish and Metzgar to arrive at the claimed invention in claims 120 and 189. Thus, those claims would have been obvious.

D. Ground 4: Claims 113 and 185 would have been obvious under 35 U.S.C. § 103(a) based on Fish in view of Gilham.

As explained in Section X.A, *supra*, Fish expressly or inherently discloses each and every element of independent claims 17, 19, and 25, and many of the challenged dependent claims. Gilham further discloses the limitations in dependent claims 113 and 185. Since Gilham was published in 1974, Gilham is prior art to the '197 Patent under §102(b).

Claims 113 and 185 recite that "said fixation or immobilization to said non-porous solid support is covalent." Gilham explicitly discloses various chemistries for covalently linking polynucleotides to solid matrices. Ex. 1019, p. 173. For example, Gilham discloses covalent binding of RNA to aminoethylcellulose solid supports through the reactivity of the 3'-terminal cis diol moiety of the RNA to the amine group of the cellulose support. Ex. 1002, ¶81; Ex. 1019, p. 174 (Table I) (covalent binding at the polynucleotide terminal by periodate oxidation of 3'-terminals of RNA); p. 175, second ¶. Moreover, Gilham discloses that "[c]ovalent immobilization via the periodate oxidation of the 3'-terminals of polynucleotides has also been used for the isolation of complementary polynucleotides." *Id*., p. 179, first ¶. Gilham goes on to state that such immobilized RNA provides a new approach to study complementary sequences. *Id*.

As discussed above, Fish discloses coating of microtitration trays with PLL to provide amine reactive groups on the surface of the microtitration trays. *See* Section IX.A.1, *supra.* A POSITA would have readily and reasonably expected that the amine reactive groups on the PLL coating of the microtitration wells of Fish (like the amine group on the cellulose substrate of Gilham) can be utilized to covalently bind RNA through periodate oxidation of the 3'-terminal diol group of the RNA and subsequent reduction with sodium borohydride, as discussed in Gilham. Ex. 1002, ¶86; Ex 1019, p. 175.

The combination of Fish with Gilham would have been obvious to a POSITA because both references teach solid supports (cellulose in Gilham and polyvinyl microtitration trays wells in Fish) with amine groups on the surface, and subsequent binding of single-stranded DNA or RNA to the solid support via the amine groups on the surface. Ex. 1002, ¶87. A POSITA would also have been motivated, with a reasonable expectation of success, to *covalently* bind RNA using the technique described in Gilham on easy-to-use, non-porous supports (such as the microtitration plates disclosed in Fish) because covalent binding provides a stronger linkage between the immobilized nucleic acids and the solid substrate. *Id*. Moreover, a POSITA would have readily understood that the amines on the PLL-treated microtitration trays of Fish can be reacted (as in Gilham) to the 3'-terminal cis diol moiety of RNAs in order to bind the RNA to microtitration trays. *Id*. Here, the solid support in claims 113 and 185 was nothing more than predictable use of prior art elements according to their established functions." See *KSR*, 550 U.S. at 417. Accordingly, it would have been obvious to a POSITA to have combined the teachings of Fish and Gilham to arrive at the claimed invention of claims 113 and 185.

E. Ground 5: Claim 17, 19, 25, 105, 106, 114, 119, 120, 128, 129, 131, 150, 151, 152, 178, 180, 186, and 189 would have been obvious under 35 U.S.C. § 102(b) based on VPK in view of Metzgar.

The '197 Patent has a purported effective filing date of January 27, 1983. The challenged claims of the '197 Patent, however, are not entitled to the January 27, 1983, effective filing date, as explained in detail below. Indeed, the challenged claims are entitled to a filing date no earlier than May 9, 1985—the filing date of the CIP application to which priority is claimed. Therefore, VPK, which was published in 1982, is §102(b) prior art to the '197 Patent. In any event, if the Board grants the challenged claims the benefit of the January 27, 1983, filing date, VPK would still be §102(a) prior art to the '197 Patent, because it was published in October 1982.

1. The Challenged Claims Are Entitled to a Priority Date No Earlier Than the Filing of the CIP Application (Appl. No. 06/732,374)

The '197 Patent is a member of a patent family initiated over 33 years ago by the filing of U.S. Application No. 06/461,469 ("the1983 application") on January 27, 1983. The patent family includes two patents (U.S. Patent No. 4,994,373 and the '197 Patent) and several abandoned applications. The priority chain of this patent family includes a continuation-in-part application (U.S. Application No. 06/732,374, "the CIP application") filed on May 9, 1985, which was abandoned during prosecution. As discussed in detail below, the challenged

claims of the ’197 Patent are not entitled to a priority date any earlier than the filing date of the CIP application, because the challenged claims are not supported by the disclosure of the 1983 application. As the Board has previously found, determining the correct priority date of a claim is appropriate for an IPR proceeding. *ButamaxTM Advanced Biofuels LLC v. Gevo, Inc*., IPR2013-00539, paper no. 33, at 12-14 (PTAB March 3, 2015).

Notwithstanding, even if priority of the 1983 application were to apply, the claims are still invalid under §§ 102(a) and 103 as discussed in detail below.

2. The legal requirements for claiming priority

In order to receive the filing date benefit of the 1983 application, the disclosure of that application must support every limitation of the claims under 35 U.S.C. § 112, first paragraph. “[I]n a chain of continuing applications, a claim in a later application receives the benefit of the filing date of an earlier application so long as the disclosure in the earlier application meets the requirements of 35 U.S.C. § 112, ¶ 1, including the written description requirement, with respect to that claim. *Technology Licensing Corp. v. Videotek, Inc*., 545 F.3d 1316, 1326 (Fed. Cir. 2008). To satisfy the written description requirement, the disclosure of an earlier-filed application must “reasonably convey[]” to one of ordinary skill in the art that, as of the filing date sought, “the inventor had possession” of the subject matter now claimed. *Ariad Pharm., Inc. v. Eli Lilly & Co*., 598 F.3d 1336,

1351–52 (Fed. Cir. 2010); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991). The test for written description, therefore, requires "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art" to determine whether the specification "show[s] that the inventor [had] actually invented," or possessed, each feature now included as a claim limitation. *Ariad Pharm*., 598 F.3d at 1351.

As will be shown in detail below, the original disclosure of the 1983 application fails to meet the written description requirement under § 112 for the challenged claims of the '197 Patent, and therefore, those claims are not entitled to the benefit of the filing date of the 1983 application under 35 U.S.C. § 120.

3. The original disclosure of the 1983 application does not provide written description support for the element "non-porous solid support."

Each of the challenged independent claims, i.e., claims 17, 19, and 25 recites a "non-porous solid support" to which nucleic acid is fixed or immobilized. The term "non-porous," however, does not appear in the original disclosure, including the original claims, of the 1983 application. That original disclosure shows fixation or immobilization of nucleic acids to many different materials that may be porous, as well as to "glass plates provided with an array of depressions or wells," "polystyrene plates," and "cuvettes." *See, e.g*., Ex. 1004 at 24:14-22; 30:5-7; 52:original claim 73. Even though polystyrene plates, cuvettes, and glass plates

with depressions or wells are indeed non-porous as admitted by the Patent Owner because they contain solutions (see discussion above in Section IX.A.1.a), the original disclosure of the 1983 application cannot support the expansive "non-porous solid support" claim limitation merely by providing three examples when the 1983 application fails to convey that the inventors contemplated the genus of all "non-porous" substrates. *See LizardTech v. Earth Resource Mapping, Inc*., 424 F.3d 1336, 1346 (Fed. Cir. 2005) (claims to a generic method of making a seamless discrete wavelet transformation (DWT) were held invalid under §112, ¶1 because the specification taught only one particular method for making a seamless DWT and there was no evidence that the specification contemplated a more generic method. Thus, disclosure of glass plates, polystyrene plates, and cuvettes alone does not reasonably convey to one of ordinary skill in the art that the inventors had possession of the generic "non-porous solid support" concept at the time of the filing of the '469 application.

Moreover, the original disclosure of the 1983 application (including the original claims) not only fails to mention the term "non-porous," but fails to discuss any benefits or significance of immobilizing nucleic acids on "non-porous" substrates. In a similar situation, the Federal Circuit found no written description support for a claimed property shared by certain disclosed embodiments, but not mentioned in the specification. "What the '360 patentees have done is to pick a

characteristic possessed by two of their formulations, a characteristic that is not discussed even in passing in the disclosure, and then make it the basis of claims that cover not just those two formulations, but any formulation that has that characteristic. This is exactly the type of overreaching the written description requirement was designed to guard against." *Purdue Pharma LP v. Faulding Inc.*, 230 F.3d 1320, 1327 (Fed. Cir. 2013).

In *Purdue*, the Patent Owner tried to add as a limitation to the claim a property that could have been calculated based on the examples. *Purdue*, 230 F.3d at 1326. The Court held that "there is nothing in the written description of Examples 1 and 3 that would suggest to one skilled in the art that the Cmax/C24 ratio is an important defining quality of the formulation, nor does the disclosure even motivate one to calculate the ratio." *Id*. Here, the 1983 application fails to convey that the inventors thought the non-porous property of certain laboratory equipment was an important generic aspect that they had invented.

The written description requirement would not be met even if a person skilled in the art would consider it obvious from the original disclosure of the '469 application that the broad genus of "non-porous" substrates could be used. *See Tech. Licensing Corp. v. Videotek, Inc*., 545 F.3d 1316, 1333-34 (Fed. Cir. 2008) Indeed, the Federal Circuit has clearly explained that the written description requirement is not met if an earlier-filed application simply renders obvious a later-

claimed invention. *Tronzo v. Biomet*, 156 F.3d 1154, 1158 (Fed. Cir. 1998) ("A disclosure in a parent application that merely renders a later-claimed invention obvious is not sufficient to meet the written description requirement and thus entitle the later claim to the filing date of the parent application; the disclosure must describe the claimed invention with all its limitations."); *Lockwood v. American Airlines, Inc*., 107 F.3d 1565, 1571-72 (Fed. Cir. 1997) ("Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed.").

Indeed, the addition of the term "non-porous" throughout the specification of the CIP application exposes the flaws with the Patent Owner's priority claim to the 1983 application. *See* Ex. 1005 at pp. 21, 26, 31, 33, and 34. The addition of the new subject matter in the CIP application—the broad concept of "non-porous" solid supports in general—confirms that the inventors had not contemplated that the broad term "non-porous solid support" was an aspect of their invention set forth in the 1983 application. Accordingly, the challenged independent claims 17, 19, and 25, along with their dependent claims, are not entitled to the benefit of the filing date of the '469 application.

4. Claims 17, 19, 25, 105, 106, 114, 119, 120, 128, 129, 131, 150, 151, 152, 178, 180, 186, and 189 would have been obvious based on VPK in view of Metzgar.

VPK discloses binding of metaphase chromosomes to surface treated glass slides, but does not explicitly disclose an "array." However, microscope glass slides having an array of wells or depressions were common at the time of invention of the '197 Patent. Ex. 1002, ¶99. Metzgar specifically discloses microscope slides made of glass and having "depressions or wells on the top surface thereof." Ex. 1009, Abstract; 2:28-30; Figure 1. It would have been obvious to a POSITA that the immobilization of nucleic acids and the in situ hybridization procedure described in VPK could be performed on glass slides having wells or depressions in order to analyze multiple samples or analytes simultaneously on the same glass slide. Ex. 1002, ¶99; see also Ex. 1009 at Abstract (discussing that microscope slides having wells or depressions "provide the technologist or clinician with a tool for rapidly screening the sera of patients or animals for a variety of viral agents ….") (emphasis added). The method of immobilization of metaphase chromosomes on alkylaminosilane treated glass slides and the in situ hydridization assay disclosed in VPK can be performed on the glass slides of Metzgar without significant modification of the procedures and with a reasonable expectation of success. Ex. 1002, ¶99.

Therefore, the use of the glass slides having an array of depressions or wells is no more than predictable use of prior art elements according to their established functions." *See KSR*, 550 U.S. at 417. Accordingly, a POSITA would have been motivated to combine the teachings of VPK and Metzgar to arrive at the claimed invention in claims 17, 19, 25, 105, 106, 114, 119, 120, 128, 129, 150, 152, 178, 180, 186, and 189. Thus, those claims would have been obvious to a POSITA.

a. **Independent claims 17, 19, and 25**

The challenged independent claims have many common limitations, as shown below, which are addressed jointly. VPK was published in October 1982 and Metzgar was published in 1971.

i. "Array"

The preamble of independent claims 17, 19, and 25 recite an "array." As discussed above, Metzgar discloses microscope slides made of glass and having "depressions or wells on the top surface thereof." Ex. 1009, Abstract; 2:28-30; Figure 1. The glass slides of Metzgar are "arrays," as recited in claims 17, 19, and 25, because the depressions or wells on the slides allow an orderly grouping or arrangement of nucleic acids bound to the surface of the wells or depressions. Ex. 1002, ¶99. In fact, the '197 Patent uses the term "array" only in the context of "glass plates" having "an array of depressions or wells." Ex. 1001, 8:65-9:2. Nowhere does the '197 Patent discuss any other form of orderly grouping or

arrangement of nucleic acids on a non-porous solid support. Thus, Metzgar discloses an "array" as recited in claims 17, 19, and 25.

ii. "A non-porous solid support," or "[a] non-porous solid support having wells or depressions."

Claims 17 and 19 recite a "non-porous solid support," and claim 25 recites "a non-porous solid support having wells or depressions." VPK and Metzgar disclose these limitations.

VPK discloses glass slides treated with aminoalkylsilane to immobilize the chromosomes on the glass slides for in situ hybridization techniques. *Id*., 397, Title and Summary; p. 398, right col., first two full ¶'s. Glass slides are non-porous. Ex. 1002, ¶93. As discussed above in Section XI(A), the Patent Owner admitted that the technique of in-situ hybridization was performed on glass slides, which necessarily are non-porous. Ex. 1026 at pp. 5 and 7. And in its Opening Claim Construction Brief in the related litigations, the Patent Owner noted that "non-porous" is a commonly understood term—citing the Examiner's understanding "that glass slides are 'reasonably interpreted as the commonly utilized non-porous microscope type slides which are well known in the art.'" Ex. 1023, pp. 3-4 (citing Ex. 1022 (11-26-2004 Office Action, p. 10)). Thus, the claim language "non-porous solid support" includes the glass slides of VPK.

The glass slide of VPK is a "non-porous solid support," as recited in claim 17, 19, and 25. Metzgar further discloses glass slides having wells or depressions.

Ex. 1009, Abstract; 2:28-30; Figure 1. The glass slide of Metzgar is a "non-porous solid support having wells or depressions," as recited in claim 25.

iii. "single-stranded nucleic acid"/ "various single-stranded nucleic acid" "fixed or immobilized in hybridizable form to said non-porous solid support"

The challenged independent claims recite that either "single-stranded nucleic acids" (claim 19), or "various single-stranded nucleic acids" (claims 17 and 25), are "fixed or immobilized in hybridizable form to said non-porous solid support."

All of these limitations are disclosed by VPK's fixation or immobilization of metaphase human chromosomes (which includes various DNA sequences) on glass slides treated with 3-amino-propyltriethoxysilane. Ex. 1002, ¶¶93-96; Ex. 1008, p. 398, right col., ll. 11-13. Although VPK shows immobilization of the chromosomes via a cell fixed in situ, the limitations of claims 17, 19, and 25 are still met because the claims do not require direct attachment of nucleic acids to the support. In fact, dependent claims 116 and 187 recite that the fixation or immobilization is *not* to a cell fixed in situ, which indicates that fixation via a cell is encompassed by the scope of claims 17, 19, and 25. The DNA sequences in the metaphase chromosomes are denatured following immobilization to the glass slide to separate the double-strands into single-strands for subsequent hybridization with ribosomal RNA (rRNA). Id. at p. 399, left col., ¶¶3-4, right col., first full ¶; see also Ex. 1002, ¶97.

The chromosomes are fixed or immobilized to the glass slides via the amine groups provided on the surface by the 3-amino-propyltriethoxysilane treatment. Ex. 1002, ¶96; see also Ex. 1001, 8:37-60 (the '197 Patent discusses that surface treatment with gamma-aminopropyltriethoxysilane provides alkylamines on the surface and improves fixation of nucleic acids on glass surfaces).

VPK also expressly discloses in situ hybridization of the immobilized chromosomal DNA to complementary ribosomal RNA (rRNA). Ex. 1002, ¶97; Ex. 1008, p. 397, Summary; p. 401, ¶ bridging the cols.; ¶ bridging pp. 401-403; p. 403, left col., first four full ¶¶ ; p. 405, first four full ¶¶ . Thus, VPK expressly discloses that the immobilized DNA is in hybridizable form.

b. Dependent claims 105, 106, 114, 119, 120, 128, 129, 131, 151, 150, 152, 178, 180, 186, and 189

i. Claims 105 and 178

Claims 105 and 178 additionally recite that "said non-porous solid support comprises glass or plastic." VPK discloses immobilization of metaphase chromosomes on glass slides. Ex. 1008, p. 398, right col., ll. 11-13. Metzgar further discloses glass slides have wells or depressions. Ex. 1009, Abstract; 2:28-30; Figure 1. A POSITA would have reasonably expected to immobilize nucleic acids on the glass slides of Metzgar according to the procedure disclosed in VPK. Ex. 1002, ¶99. Thus, claims 105 and 178 would have been obvious to a POSITA based on VPK in view of Metzgar.

ii. Claims 106 and 119

Claim 106 additionally recites that "said non-porous solid support" comprises "a plate or plates, a well or wells, a microtiter well or microtiter wells, a depression or depressions, a tube or tubes, or a cuvette or cuvettes." (Emphasis added.) Similarly, claim 119 recites that "said non-porous solid support" comprises "a well or wells, a microtiter well or microtiter wells, or a depression or depressions." (Emphasis added.). As discussed previously, Metzgar discloses glass slides have wells or depressions. Ex. 1009, Abstract; 2:28-30; Figure 1. Thus, these claims would have been obvious to a POSITA based on VPK in view of Metzgar.

iii. Claims 114 and 186

Claims 114 and 186 additionally recite that "said fixation or immobilization to said non-porous solid support is non-covalent." The binding of chromosomes to the aminoalkylsilane-treated glass slides necessarily would be non-covalent. Ex. 1002, ¶107. The alkylamines have a positive charge and they non-covalently interact with the negative charges on the chromosomes to form ionic (i.e., non-covalent) bonds between the alkylamine groups and the chromosomes. *Id*. The chromosomes and the amine groups of the treated glass would bind covalently only if the amine groups and/or the chromosomes are functionalized to cause covalent bonding. *Id*. VPK does not disclose functionalizing either the amines or the chromosomes. *Id*. Accordingly, VPK discloses non-covalent binding of the

chromosomes to the aminoalkylsilane-treated glass slides. Thus, these claims would have been obvious to a POSITA based on VPK in view of Metzgar.

iv. Claims 128 and 150

Claims 128 and 150 additionally recite that "said nucleic acid is DNA." VPK discloses fixation or immobilization of metaphase chromosomes (that include many DNA sequences) on aminoalkylsilane-treated glass slides. Ex. 1008 at Summary. Thus, these claims would have been obvious to a POSITA based on VPK in view of Metzgar.

v. Claim 129 and 152

Claims 129 and 152 additionally recite that "said single-stranded nucleic acid is unlabeled." VPK does not disclose labeling of the metaphase chromosomes (or the specific DNA sequences in the chromosomes), and therefore, it follows *ipso facto* that the DNA bound to the aminoalkylsilane-treated glass slides are unlabeled. Ex. 1002, ¶105. Thus, these claims would have been obvious to a POSITA based on VPK in view of Metzgar.

vi. Claims 120 and 189

Claims 120 and 189 additionally disclose that "said non-porous solid support comprises one or more hydroxyls." The glass slides of VPK and Metzgar necessarily include hydroxyl groups, because that is a property of glass. Ex. 1002, ¶108. The claims do not require any use of the hydroxyl groups. Thus, these claims would have been obvious to a POSITA based on VPK in view of Metzgar.

vii. Claim 151

Claim 151 additionally recites that fixed or immobilized nucleic acids comprise "a gene sequence or pathogen sequence." VPK discloses fixation or immobilization of metaphase human chromosomes (which includes various gene sequences) on glass slides treated with 3-amino-propyltriethoxysilane. Ex. 1002, ¶96; Ex. 1008, p. 398, right col., ll. 11-13. A POSITA would have readily expected from the disclosure of VPK that the chromosome immobilization techniques disclosed in VPK could be used for immobilizing gene sequences to the PLL-coated microtitration tray wells because chromosomes are made up of gene sequences. Ex. 1002, ¶82. There is nothing special about attaching gene sequences or pathogen sequences instead of chromosomes to a non-porous solid support. *Id.* Thus, claim 151 would have been obvious to a POSITA based on the teachings of VPK and Metzgar.

viii. Claim 131

Claim 131 additionally recites that the fixed or immobilized "nucleic acids comprise nucleic acid sequences complementary to nucleic acid sequences of interest sought to be identified, quantified or sequenced." VPK explicitly discloses in situ hybridization of immobilized human ribosomal DNA in metaphase chromosomes to complementary 18S and 28S rRNA to identify the sequence. Ex. 1002, ¶79; Ex. 1008, p. 401, left col., l. 13-right col. l. 3; *see also id.* at Summary.

Thus, VPK expressly discloses that the immobilized DNA is complementary to a nucleic acid sequence of interest sought to be identified. Thus, these claims would have been obvious to a POSITA based on VPK in view of Metzgar.

ix. Claim 180

Dependent claim 180 additionally recites that the non-porous solid support has been "treated with a surface treatment agent, a blocking agent, or both." VPK explicitly discloses treatment of glass slides with aminoalkylsilane prior to immobilization of metaphase chromosomes on the glass slides. Ex. 1008, p. 398, right col., ll. 11-13. Thus, these claims would have been obvious to a POSITA based on VPK in view of Metzgar.

F. Ground 6: Claims 113, 116, 130, 154, 185, and 187 are obvious under 35 U.S.C. § 103(a) based on Noyes in view of VPK and further in view of Metzgar and Ramachandran.

Claims 113, 116, 130, 154, 185, and 187 depend from one or more of claims 17, 19, and 25. As disclosed in Section XI. D, *supra,* claims 17, 19, and 25 would have been obvious to a POSITA based on VPK in view Metzgar. As explained below, the additional limitations recited in claims 113, 116, 130, 154, 185, and 187 would have been obvious to a POSITA based on Noyes in view of VPK and further in view of Metzgar and Ramachandran. Since Noyes was published in July 1975, Noyes is prior art to the '197 Patent under §102(b). Similarly,

Ramachandran was published in 1976, and therefore, Ramachandran is also prior art to the '197 Patent under §102(b).

Noyes discloses covalent linkage of single-stranded DNA and RNA to finely divided m-aminobenzyloxymethyl cellulose after the primary aryl amino groups have been diazotized. Ex. 1007, Summary; p. 301, right col., second ¶. Noyes also discloses hybridization of the bound DNA and RNA to complementary sequences. *Id*. at Summary; p. 303; p. 304, first ¶. VPK similarly discloses binding of metaphase chromosomes to glass slides via amine groups provided by treatment of the glass slides with alkylaminosilane. Ex. 1008 at Summary; Section IX.D, *supra*. Many laboratory experiments, for example, experiments that involve visualization under a microscope, require the use of glass slides, including slides that have wells or depressions. Ex. 1002, ¶83. Therefore, a POSITA would have been motivated, with a reasonable expectation of success, to perform the nucleic acid hybridization experiments described in Noyes on easy-to-use, non-porous supports, such as the glass slides disclosed in VPK and Metzgar. *Id*.

Based on the disclosure in Noyes, a POSITA would have readily understood that nucleic acids can be covalently bound to the glass slides of VPK and Metzgar by first modifying the surface of the glass slides with aryl amines, which can be diazotized and covalently linked to nucleic acid strands. Ex. 1002, ¶113. VPK discloses treatment of glass slides with alkylaminosilane, specifically

3-amino-propyltriethoxysilane, which provides alkylamines on the surface of the glass slides. *Id*. at p. 398, right col., first full ¶; Ex. 1015, p. 334, ¶3; *see also* Ex. 1002, ¶113. A POSITA would have readily expected that the same alkylaminosilane treatment can be applied to the glass slides of Metzgar (that have wells or depressions) to get alkylamines on the surface of the glass slides. Ex. 1002, ¶113.

Ramachandran also teaches treatment of non-porous glass beads with 3-amino-propyltriethoxysilane to provides alkylamines on the surface of the glass bead. Ex. 1028, p. 673, first full ¶. Ramachandran further teaches treatment of the alkylamine glass with chloroform and ethyl alcohol to convert the alkylamines to arylamines. *Id.* A POSITA would have readily and reasonably expected to use the procedure disclosed in Ramachandran to convert the alkylamines on the glass slides of Metzgar to arylamines. Ex. 1002, ¶114. Further, a POSITA would have reasonably expected to covalently bind nucleic acids to the glass slides of Metzgar and by diazotizing the arylamines as taught by Noyes. *Id.* Here, the use of the glass slides with wells or depressions as solid supports for immobilizing nucleic acids using the technique disclosed in Noyes and Ramachandran is no more than a predictable use of prior art elements according to their established functions." *See KSR*, 550 U.S. at 417. Accordingly, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Noyes, VPK, Metzgar, and

Ramachandran to arrive at the claimed invention of claims 113, 116, 130, 154, 185, and 187.

i. Claims 116 and 187

Claims 116 and 187 additionally recite that "said fixation or immobilization [of nucleic acids] is not to a cell fixed in situ to said non-porous solid support." Noyes discloses binding of DNA or RNA *directly* to finely-divided cellulose via aryl amine groups on the surface of the cellulose particles. *See, e.g.,* Ex. 1007 at p. 301, left col. ll. 1-12 (Summary); p. 303, right col., l. 4–p. 304, left col., l. 3. A POSITA would have been motivated, with a reasonable expectation of success, to *directly* bind the DNA or RNA of Noyes on easy-to-use, non-porous supports, such as the glass slide of Metzgar, by treating the glass slides with alkylaminosilane (as taught by VPK), converting the alkylamines to arylamines (as taught by Ramachandran), diazotizing the arylamines (as taught by Noyes) and then covalently linking the single stranded DNA and RNA to the arylamines (as taught by Noyes). Ex. 1002, ¶115. Thus, these claims would have been obvious to a POSITA based on Noyes in view of VPK and further in view of Metzgar and Ramachandran.

ii. Claims 113 and 185

Claims 113 and 185 additionally recite that "said fixation or immobilization to said non-porous solid support is covalent." Noyes explicitly discloses *covalent*

linkage of DNA or RNA to diazotized aryl amines provided on the surface of finely divided cellulose. Ex. 1007, p. 301, right col., ll. 30-34; p. 306, left col., ll. 15-18. A POSITA would have been motivated, with a reasonable expectation of success, to covalently bind the DNA or RNA of Noyes on easy-to-use, non-porous supports, such as the glass slide of Metzgar, by treating the glass slides with alkylaminosilane (as taught by VPK), converting the alkylamines to arylamines (as taught by Ramachandran), diazotizing the arylamines (as taught by Noyes) and then covalently bonding the single stranded DNA and RNA to the arylamines (as in Noyes). Ex. 1002, ¶116. Thus, these claims would have been obvious to a POSITA based on Noyes in view of VPK and further in view of Metzgar and Ramachandran.

iii. Claims 130 and 154

Claims 130 and 154 recite that the fixed or immobilized "nucleic acids is/are RNA." Noyes explicitly discloses binding of RNA to finely divided cellulose via diazotized arylamine groups. Ex. 1007, Summary; p. 306, left col., first full ¶. A person of ordinary skill in the art would have readily and reasonably expected to immobilize RNA on the glass slides of Metzgar by using the procedures disclosed by VPK, Noyes and Ramachandran. Ex. 1002, ¶117. Therefore, claims 130 and 154 would have been obvious to a POSITA based on Noyes in view of VPK and further in view of Metzgar and Ramachandran.

XI. SECONDARY CONSIDERATIONS, EVEN IF CONSIDERED, FAIL TO OVERCOME THE EVIDENCE OF OBVIOUSNESS

To overcome Petitioner's prima facie obviousness case set forth above, the Patent Owner may attempt to come forward with secondary considerations of non-obviousness. For example, during prosecution of a counterpart European application (Appl. No. 92114727.8), the Patent Owner had argued that commercial success of its products embodying the claimed invention was a "clear indication of the inventive step involved in the claimed invention." Ex. 1012, pp. 7-11.

The same arguments, however, do not apply to the '197 Patent because the scope of the claims at issue in the European application is significantly different from the scope of the claims in the '197 Patent. The claims in the European application recite "generating" and "detecting" a "quantifiable signal, and further, the Patent Owner's commercial success arguments indicated that signal quantification is significant to the commercial success of its products. These commercial success arguments do not apply here, because none of the challenged claims of the '197 Patent recite generation and/or detection of "quantifiable signals." Similarly, in the U.S. prosecution, the Patent Owner submitted alleged commercial success based on array products. Ex. 1030, p. 2. It is not clear why the Patent Owner submitted the arguments, and is equally unclear that the Examiner paid any attention to them, because there was no section 103 obviousness rejection pending at the time. Ex. 1031.

Moreover, during the prosecution of the European and U.S. applications, the Patent Owner did not establish a nexus between the commercial success of its products and the merits of the claimed invention (e.g., signal quantification). *See, e.g., In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (requiring nexus between evidence of commercial success and the merits of the claimed invention).

The Federal Circuit has repeatedly held that a causal relationship, i.e., a "nexus" is required between any objective evidence of non-obviousness and the merits of the claimed invention in order for such evidence to be given substantial weight. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (finding that objective evidence that results from something that is not ''both claimed and novel in the claim,'' lacks a nexus to the merits of the invention); *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) ("To be afforded substantial weight, the objective indicia of non-obviousness must be tied to the novel elements of the claim at issue."); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (requiring nexus for evidence of licensing); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012) (requiring showing of nexus for objective evidence of copying).

Moreover, although secondary considerations must be taken into account, "they do not control the obviousness conclusion." *Newell Cos., Inc. v. Kenney Mfg. Co*., 864 F.2d 757, 768 (Fed. Cir. 1988). Where, as here, a strong prima facie

obviousness showing exists, the Federal Circuit has held that even relevant secondary considerations supported by substantial evidence may not overcome the conclusion of obviousness. *See Leapfrog Enterprises Inc. v. Fisher-Price Inc*., 485 F.3d 1157, 1162 (Fed. Cir. 2007).

Petitioner submits that the strength of the prima facie case of obviousness presented in this Petition is sufficient to overcome any evidence of secondary considerations that Patent Owner may put forward. Petitioner also reserves the right to supplement its positions regarding secondary considerations as appropriate based on the Patent Owner's potential non-obviousness positions.

XII. Conclusion

For the reasons set forth above, the challenged claims are unpatentable. Accordingly, Petitioner respectfully requests that the Board grant this Petition for inter partes review and institute trial.

Date: March 30, 2016

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(b), the undersigned certifies that on March 30, 2016, a copy of the foregoing PETITION FOR *INTER PARTES* REVIEW of U.S. Patent 7,064,197 and accompanying exhibits was served by Express Mail on the following:

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