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Paper 8
Date: October 4, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOLOGIC, INC.,
Petitioner,

v.

ENZO LIFE SCIENCES, INC.,
Patent Owner.

Case IPR2016-00822
Patent 7,064,197 B1

Before MICHAEL J. FITZPATRICK, ZHENYU YANG, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

FITZPATRICK, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Petitioner, Hologic, Inc., filed a Petition to institute an *inter partes* review of claims 17, 19, 25, 105, 106, 113, 114, 116, 119, 120, 128–131, 150–152, 154, 178, 180, 185–187, and 189 of U.S. Patent No. 7,064,197 B1 (Ex. 1001, "the '197 patent") pursuant to 35 U.S.C. § 311(a). Paper 3 ("Pet."). Patent Owner, Enzo Life Sciences, Inc., filed a Preliminary Response pursuant to 35 U.S.C. § 313. Paper 7 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). Upon consideration of the Petition, and for the reasons explained below, we determine that the information presented shows a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged. *See* 35 U.S.C. § 314(a). We grant the Petition to institute an *inter partes* review.

A. Related Matters

Petitioner has filed an additional petition to institute an *inter partes* review of the '197 patent, in which it challenges other claims of the patent. *See* IPR2016-00820.

The parties identify the following lawsuits as involving the '197 patent: *Enzo Life Sciences, Inc. v. Hologic, Inc.*, No. 1:15-cv-271 (D. Del.); *Enzo Life Sciences, Inc. v. Siemens Healthcare Diagnostics, Inc.*, No. 1:12-cv-505 (D. Del.); *Enzo Life Sciences, Inc. v. Affymetrix, Inc.*, No. 1:12-cv-433 (D. Del.); *Enzo Life Sciences, Inc. v. Agilent Technologies Inc.*, No. 1:12-cv-434 (D. Del.); *Enzo Life Sciences, Inc. v. Illumina Inc.*, No. 1:12-cv-435 (D. Del.); *Enzo Life Sciences, Inc. v. Abbott Laboratories et al.*, No.

1:12-cv-274 (D. Del.); *Enzo Life Sciences, Inc. v. Becton Dickinson and Company et al.*, No. 1:12-cv-275 (D. Del.); *Enzo Life Sciences, Inc. v. Life Technologies Corp.*, No. 1:12-cv-105 (D. Del.); and *Enzo Life Sciences, Inc. v. Roche Molecular Systems Inc. et al.*, No. 1:12-cv-106 (D. Del.). Pet. 2–3; Paper 6, 1–2.

B. The '197 Patent

The '197 patent relates generally to the detection of genetic material by polynucleotide probes. Ex. 1001, 1:23–24. The '197 patent refers to the material to be detected as an analyte. *Id*. at 1:37–39. An analyte may be present in a biological sample such as a clinical sample of blood, urine, saliva, etc. *Id*. at 5:47–50. If an analyte of interest is present in a biological sample, it is fixed, according to the invention of the '197 patent, in hybridizable form to a solid support. *Id*. at 5:58–60. The '197 patent states that it is preferred, and all of the challenged claims require, that the solid support be non-porous. *Id*. at 6:2–6; *e.g., id*. at 15:51–53 (claim 17 reciting a "non-porous solid support").

> Chemically-labeled probes are then brought into contact with the fixed single-stranded analytes under hybridizing conditions. The probe is characterized by having covalently attached to it a chemical label which consists of a signaling moiety capable of generating a soluble signal. Desirably, the polynucleotide or oligonucleotide probe provides sufficient number of nucleotides in its sequence, e.g., at least about 25, to allow stable hybridization with the complementary nucleotides of the analyte. The hybridization of the probe to the single-stranded analyte with the resulting formation of a double-stranded or duplex hybrid is then detectable by means of the signalling moiety of the chemical label which is attached to the probe portion of the resulting hybrid. Generation of the soluble signal

> provides simple and rapid visual detection of the presence of the analyte and also provides a quantifiable report of the relative amount of analyte present, as measured by a spectrophotometer or the like.

Id. at 6:15–32.

C. The Challenged Claims

Petitioner challenges claims 17, 19, 25, 105, 106, 113, 114, 116, 119, 120, 128–131, 150–152, 154, 178, 180, 185–187, and 189. Pet. 1. Independent claims 17, 19, and 25 are illustrative and reproduced below.

> 17. An array comprising various single-stranded nucleic acids fixed or immobilized in hybridizable form to a non-porous solid support.
>
> 19. An array comprising single-stranded nucleic acids fixed or immobilized in hybridizable form to a non-porous solid support.
>
> 25. An array comprising various single-stranded nucleic acids fixed or immobilized in hybridizable form to a non-porous solid support having wells or depressions.

All of the remaining claims that are challenged depend directly from at least one of independent claims 17, 19, and 25, with several of them in multiple dependent form.

D. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

References	**Basis**[1]	**Claims Challenged**
Fish (Ex. 1006)[2]	§ 102(b)	17, 19, 25, 105, 106, 114, 116, 119, 128, 129, 131, 150, 152, 178, 180, 186, and 187
Fish	§ 103(a)	130, 131, 151, and 154
Fish, Metzgar (Ex. 1009),[3] and Sato (Ex. 1034)[4]	§ 103(a)	120 and 189
Fish and Gilham (Ex. 1019)[5]	§ 103(a)	113 and 185
VPK (Ex. 1008)[6] and Metzgar	§ 103(a)	17, 19, 25, 105, 106, 114, 119, 120, 128, 129, 131, 150–152, 178, 180, 186, and 189

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, took effect on March 18, 2013. Because the application from which the '197 patent issued was filed before that date, our citations to 35 U.S.C. §§ 102 and 103 are to their pre-AIA version.
[2] Falk Fish, et al., "A Sensitive Solid Phase Microradioimmunoassay For Anti-Double Stranded DNA Antibodies," *Arthritis and Rheumatism*, Vol. 24, No. 3, 534–43 (March 1981).
[3] U.S. Patent No. 3,572,892, issued Mar. 30, 1971.
[4] Sato et al., "Cell Surface Charge and Cell Division in Escherichia coli after X irradiation," Radiation Research 87, 646–56 (1981).
[5] P. T. Gilham, "Immobilized Polynucleotides and Nucleic Acids," *Immobilized Biochemicals and Affinity Chromatography*, 173–85 (1974).
[6] 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*, Vol. 141, 397–407 (Oct. 1982).

References	Basis[1]	Claims Challenged
Noyes (Ex. 1007),[7] VPK, Metzgar, and Ramachandran (Ex. 1028)[8]	§ 103(a)	113, 116, 130, 154, 185, and 187

Pet. 6; *see also* Pet. 29–30 (arguing that Fish anticipates claim 131 despite not listing claim 131 in its identification of the ground on page 6 of the Petition).

As an initial matter, we acknowledge Patent Owner's assertion that "Petitioner failed to present any evidence" that several of the references (namely, Fish, Sato, Gilham, VPK, Noyes, and Ramachandran) "were publicly accessible printed publications." Prelim. Resp. 6. We disagree, and find on this record that Petitioner has made a sufficient showing that each of these references qualify as prior art printed publications. For example, Fish appears to be an article from the journal *Arthritis and Rheumatism* and bears a "March 1981" publication date on the cover of the volume as well as the cover page of the article. Ex. 1006, cover page and 534. Sato appears to be an article from the journal *Radiation Research* and bears a publication date of 1981. Ex. 1034, 646. Gilham appears to be an article published in a book titled *Immobilized Biochemicals and Affinity Chromatography*, which includes a copyright date of 1974 and an indication that it contains most of the papers presented in a "Symposium on Affinity Chromatography and

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[7] Barbara E. Noyes, et al., "Nucleic Acid Hybridization Using DNA Covalently Coupled to Cellulose," *Cell*, vol. 5, 301–10 (July 1975).
[8] K. B. Ramachandran, et al., "Effects of Immobilization of the Kinetics of Enzyme-Catalyzed Reactions. I. Glucose Oxidase in a Recirculation Reactor System," *Biotechnology and Bioengineering*, Vol. XVIII, 669–84 (1976).

Immobilized Biochemicals" held November 7–9, 1973. Ex. 1019, second page after cover ("Library of Congress Cataloging in Publication Data"). VPK appears to be an article from the journal *Experimental Cell Research* and is dated October 1982. Ex. 1008, cover page. Noyes appears to be an article from the journal *Cell* and is dated July 1975. Ex. 1007, 301. Finally, Ramachandran appears to be an article from the journal *Biotechnology and Bioengineering* and is dated 1975. Thus, each of these references bears a date prior to the earliest possible effective filing date for the challenged claims (i.e., Jan. 27, 1983). *See* Ex. 1001, 1:19; 35 U.S.C. § 120. Moreover, the references are either journal articles or excerpts from a book, and thus appear to have been publicly disseminated. Petitioner has made sufficient showing that these documents qualify as prior art printed publications. After institution, Patent Owner may, if it chooses to do so, continue to challenge the sufficiency or admissibility of the evidence. *See* 35 U.S.C. § 311(b); 37 C.F.R. § 42.64(b).

II. ANALYSIS

A. Claim Construction

"A claim in an unexpired patent that will not expire before a final written decision is issued shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). Pursuant to that standard, the claim language should be read in light of the specification, as it would be interpreted by one of ordinary skill in the art. *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010). Thus, we generally give claim terms their ordinary and customary meaning. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("The

ordinary and customary meaning is the meaning that the term would have to a person of ordinary skill in the art in question." (internal quotation marks omitted)).

Our construction of the challenged claims is based on the current record and, thus, could change during trial, in light of new arguments and evidence.

1. "array"

Each of independent claims 17, 19, and 25 recites an "array."[9] The parties agree that "array" should be construed to mean "an orderly grouping or arrangement." Pet 14; Prelim. Resp. 22 (proposing same construction but doing so while also construing surrounding claim language); *see also* Ex. 1010, 8 (*Markman* order applying same construction). We give it the agreed-upon meaning.

2. "fixed or immobilized in hybridizable form"

Each of independent claims 17, 19, and 25 recites "fixed or immobilized in hybridizable form."

The parties agree that "fixed or immobilized" means "bound." Pet. 9; Prelim. Resp. 13 n.2; *see also* Ex. 1010, 13–15 (*Markman* order applying same construction). We give it the agreed-upon meaning.

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[9] The recitation of "array" appears only in the preambles of these claims. Neither party explicitly addresses whether the preambles are limiting or not. *See, e.g.*, *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305–06 (Fed. Cir. 1999) (preamble may or may not be limiting).

The parties agree that "hybridizable form" means "capable of binding through Watson-Crick base pairing." Pet. 13 (citing Ex. 1001, 2:22–34); Prelim. Resp. 11[10]; *see also* Ex. 1010, 5 (*Markman* order applying same construction). We give it the agreed-upon meaning.

3. "non-porous solid support"

Each of independent claims 17, 19, and 25 recites "a non-porous solid support." Neither party proposes an express construction. *See* Pet. 11 (Petitioner arguing that it should be given its ordinary meaning in the art); *see generally* Prelim. Resp. In a related lawsuit, the court construed "non-porous" to mean "having no pores" and "solid support" to mean a "solid structure." Ex. 1010, 5–6. The court's constructions accurately restate what the claim language means in the context of the '197 patent. However, we find it unnecessary to expressly construe this claim language. We give "non-porous solid support" its ordinary meaning, in light of the specification, as it would be interpreted by one of ordinary skill in the art.

B. Ground 1: Anticipation by Fish

Petitioner asserts that claims 17, 19, 25, 105, 106, 114, 116, 119, 128, 129, 131, 150, 152, 178, 180, 186, and 187 are anticipated by Fish. Pet. 6, 29–30.

Anticipation requires that "each and every element as set forth in the

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[10] Patent Owner's construction additionally adds that the Watson-Crick base pairing would be "to a complementary nucleic acid sequence." Prelim. Resp. 11. This additional language, however, is superfluous, as it merely describes what Watson-Crick base pairing inherently requires.

claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987).

1. Disclosure of Fish

Fish describes a "sensitive solid phase microradioimmunoassay . . . for measurement of antidouble stranded DNA (dsDNA) antibodies." Ex. 1006, Abstract. Fish notes "the capacity of poly-L-lysine (PLL) to facilitate the binding of pure dsDNA to plastic surfaces." *Id*. Fish describes an experiment in which "[t]wenty-five microliter aliquots of the PLL solution were introduced into each well of a V-shaped polyvinyl microtitration tray." *Id*. at 536, left col. ¶1.[11] Synthetic double-stranded DNA ("dsDNA") in the form of a double-stranded copolymer of deoxyadenosine and deoxythymidine ("poly dA–dT") was introduced into the wells of alternating rows, and certain washing and incubation steps were performed to the entire tray. *Id*.

Fish next describes the same procedure but using single stranded DNA ("ssDNA") either in the form of: (1) a mixture of synthetic homopolymers of deoxyadenosine ("poly-dA") and deoxycytidine ("poly-dC") or (2) denatured calf thymus DNA. *Id*. at 536, left col. ¶2; *id*. at 539, Fig. 1 (caption: "PLL treated microtitration wells were coated with various preparations of double-stranded and single-stranded DNA.").

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[11] Unless otherwise noted, our citations to paragraphs of non-patent references are numbered starting with the first full paragraph of a respective page or column.

"Half of the nucleic acid coated wells were subjected to nuclease S_1 digestion." *Id*. at 538, right col. ¶1; *see also id*. at 539, Fig. 1. S_1 nuclease digests ssDNA but not dsDNA. *Id*. at 538, right col. ¶1. The measured attachment/activity of the anti-DNA antibody in the wells is shown in the right-hand column of Figure 1 of Fish. *Id*. at 539, Fig. 1. According to Fish, the results demonstrated that:

> [N]uclease S_1 treatment had no effect on the binding of SLE Ig[12] to poly dA–dT coated wells, thus indicating that this DNA preparation was indeed wholly double-stranded. On the other hand, the binding of [SLE] Ig to heat-denatured DNA was almost completely abolished by the enzymatic digestion. This positive control for the nuclease S_1 activity suggests that single-stranded nucleic acid, bound to PLL treated plastic, remains susceptible to the hydrolytic activity of the enzyme.

Id. at 538, right col. ¶1.

2. Application of Fish to Independent Claims 17, 19, and 25

Independent claims 17 and 25 recite "[a]n array comprising various single-stranded nucleic acids." Independent claim 19 recites the same language except that it omits the word "various." Fish discloses such arrays because it discloses wells of ssDNA (i.e., the mixture of poly-dA and poly-dC as well as the denatured calf thymus DNA) arranged in rows. Ex. 1006, 536, left col. ¶¶1–2. Patent Owner argues that this limitation (assuming the preamble is limiting) is not met by Fish because "a microtitration tray is not itself an array." Prelim. Resp. 22. This argument is not persuasive. Fish

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[12] The anti-DNA antibody employed was plastic systemic lupus erythematosus patient serum Immunoglobulin, or SLE Ig. Ex. 1006, 534, Abstract.

explicitly describes rows of wells on the tray, which are sufficient to constitute an orderly grouping or arrangement.

Claims 17 and 19 recite a "non-porous solid support," and claim 25 recites "a non-porous solid support having wells or depressions." Fish appears to meet these limitations because Fish uses microtitration trays that are polyvinvyl (Ex. 1006, 536), which material is plastic and non-porous according to the testimony of Norman Nelson, Ph.D. Ex. 1002 ¶¶41, 42.

Claims 17, 19, and 25 recite that the single-stranded nucleic acids are "fixed or immobilized in hybridizable form to said non-porous solid support." Fish appears to meet this limitation because it discloses ssDNA (i.e., the mixture of poly-dA and poly-dC as well as the denatured calf thymus DNA) bound to the PLL-coated wells of the microtitration tray. Ex. 1006, 536, left col. ¶¶1–2, 539, Fig. 1. Patent Owner argues that Fish does not disclose this limitation because its experiment was "***not designed*** to determine whether single-stranded nucleic acids bound to PLL-coated wells." Prelim. Resp. 13. That is not relevant to whether or not Fish discloses the limitation, which Fish explicitly does. *See* Ex. 1006, 538, right col. ¶1 (referring to "single-stranded nucleic acid" as "bound to PLL treated plastic").

In any event, it appears that the Fish researchers had no need to make such a determination because they already knew that ssDNA would bind to the PLL-coated wells, as they were relying on such binding to carry out their experiment. *See* Ex. 1006, 536, left col. ¶2 ("**Single stranded DNA coated trays.** A mixture of poly-dA (5 μg/ml) and poly-dC (5 μg/ml) in Tris buffer was introduced into PLL-coated microtitration trays as described previously

[with respect to the synthetic dsDNA]."), 538, right col. ¶1 ("This positive control for the nuclease S 1 activity suggests that single-stranded nucleic acid, bound to PLL treated plastic, remains susceptible to the hydrolytic activity of the enzyme.").

Petitioner offers additional evidence that the ssDNA binds to the PLL-coated wells, as the Fish researchers explicitly recognized. Specifically, Petitioner notes that, in Figure 1 of Fish, the ssDNA samples that were treated with S_1 showed less binding of SLE Ig than identical ssDNA samples that were not exposed to S_1. Pet. 20–21. Because S_1 digests ssDNA, the difference in binding proves that there was ssDNA there to be digested. *Id*. at 21.

Petitioner argues that the bound ssDNA in Fish is in "hybridizable form" because it "necessarily was capable of binding through Watson Crick base pairing." Pet. 22 (citing Ex. 1002 ¶66). In the cited testimony, Dr. Nelson testifies that this is so because the bound ssDNA "will hybridize when complementary DNA is present in appropriate hybridization conditions." Ex. 1002 ¶66.

"The very essence of inherency is that one of ordinary skill in the art would recognize that a reference unavoidably teaches the property in question." *Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1383 (Fed. Cir. 2009). Patent Owner, citing *Agilent*, argues that Fish does not inherently teach ssDNA in hybridizable form, stating:

> Whether a given nucleic acid is capable of hybridizing depends upon multiple factors, including the type of nucleic acid, the type of solid support, the way that the nucleic acid is bound to a support, and hybridization conditions. (Ex. 2101

> [declaration of Gregory Buck, Ph.D.] ¶ 73.) In order to determine whether a given nucleic acid bound to a solid support is capable of hybridization, experimental evidence showing that this bound nucleic acid does actually hybridize is necessary. (Ex. 2101 ¶ 73.)
>
> However, Petitioner does not—because it cannot—identify any evidence that hybridization actually occurred in any of Fish's experiments.

Prelim. Resp. 15. Patent Owner's argument is not commensurate with the claim language, which does not require actual hybridization. The claims require only that the bound ssDNA be in "hybridizable form." As the parties agree, "hybridizable form" means the ssDNA is *capable* of binding through Watson-Crick base pairing. Petitioner adequately has shown that because the bound ssDNA in Fish would hybridize with complimentary strands of ssDNA under suitable conditions, the bound ssDNA is necessarily capable of binding through Watson-Crick base pairing. *See* Ex. 1002 ¶66.

There is a reasonable likelihood Petitioner would prevail in showing that independent claims 17, 19, and 25 are anticipated by Fish.

3. Application of Fish to Dependent Claims 105, 106, 114, 116, 119, 128, 129, 131, 150, 152, 178, 180, 186, and 187

Each of claims 105, 106, 114, 116, 119, 128, 129, 131, 150, 152, 178, 180, 186, and 187 depends directly from at least one of independent claims 17, 19, and 25. As explained below, except with respect to claim 131, Petitioner adequately shows how the additional limitations recited in these claims are taught by Fish.

Claims 105 and 178 add that "said non-porous solid support comprises glass or plastic." The microtitration tray disclosed by Fish is

made of polyvinyl (Ex. 1006, 536, col. 1 ¶1), which Dr. Nelson testifies is plastic. Ex. 1002 ¶70; *see also* Ex. 1006, Abstract (implying that plastic is used, noting "the capacity of poly-L-lysine (PLL) to facilitate the binding of pure dsDNA to plastic surfaces").

Claim 106 adds 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." Similarly, claim 119 adds that "said non-porous solid support" comprises "a well or wells, a microtiter well or microtiter wells, or a depression or depressions." Fish discloses a non-porous solid support that comprises wells. Ex. 1006, 536, col. 1 ¶1.

Claims 114 and 186 add that "said fixation or immobilization to said non-porous solid support is non-covalent." Petitioner argues that the binding of ssDNA to the PLL-coated wells in Fish is ionic and, thus, non-covalent. Pet. 28 (citing Ex. 1002 ¶77). At this stage of the proceeding, we credit Dr. Nelson's testimony to that effect.

Claims 116 and 187 add that "said fixation or immobilization [of the single-stranded nucleic acids] is not to a cell fixed in situ to said non-porous solid support." Fish appears to meet this limitation because no cells are involved in the microradioimmunoassay discussed therein. *See generally* Ex. 1006.

Claims 128 and 150 add that "said nucleic acids [are] DNA." Fish discloses the use of DNA. *See*, *e.g.*, Ex. 1006, 539, Fig. 1 ("PLL treated microtitration wells were coated with various preparations of double-stranded and single-stranded DNA.").

Claims 129 and 152 add that "said single-stranded nucleic acids are unlabeled." Fish appears to meet this limitation because it does not mention whether the mixture of poly-dA and poly-dC or the denatured calf thymus was labeled or not. *See Upsher-Smith Labs., Inc. v. Pamlab, LLC*, 412 F.3d 1319, 1322–23 (Fed. Cir. 2005) (holding that if a reference discloses everything a claim affirmatively requires, a prima facie case of anticipation exists). Further, Patent Owner has not argued or shown that the ssDNA in Fish was labeled.

Claim 131 adds 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." Petitioner argues that this limitation is met by Fish because it discloses poly-dA, which "is complementary to poly-dT, which *may* be a sequence of interest sought to be identified, quantified or sequenced." Pet. 29–30 (emphasis added). Per Petitioner's own argument, this additional limitation is not satisfied by Fish.

Claim 180 adds that the non-porous solid support has been "treated with a surface treatment agent, a blocking agent, or both." Fish appears to meet this limitation by its use of PLL. *See*, *e.g.*, Ex. 1006, 539, Fig. 1 ("PLL treated microtitration wells were coated with various preparations of double-stranded and single-stranded DNA.").

There is a reasonable likelihood Petitioner would prevail in showing that dependent claims 105, 106, 114, 116, 119, 128, 129, 150, 152, 178, 180, 186, and 187—but not claim 131—are anticipated by Fish.

C. Ground 2: Obviousness in View of Fish

Petitioner contends that dependent claims 130, 131, 151, and 154 would have been obvious over Fish. Pet. 6. In assessing obviousness, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).[13]

Claim 131 depends directly from independent claim 17 and adds 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." Petitioner's expert testifies that because it "was well known prior to 1983 that hybridization of labeled nucleotide sequences to complementary sequences can be used to identify, detect, or quantify target (analyte) sequences by binding one of the strands to a substrate and introducing labeled nucleotide sequences complementary to the bound sequence," it would have been obvious to a person of ordinary skill in the art "that the ssDNA immobilized on the microtitration tray wells of Fish can be used to detect a complementary sequence of interest, as recited in claim 131." Ex. 1002 ¶80; *see also* Pet. 33 (citing the same). We find this testimony persuasive.

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[13] Additionally, secondary considerations such as "commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy." *Graham*, 383 U.S. at 17–18. The current record, however, lacks such evidence.

Claim 130 depends directly from independent claim 17 and adds that the "nucleic acids [are] RNA." Similarly, claim 154 depends directly from independent claim 25 and adds that the "nucleic acids are RNA." Claim 151 depends directly from independent claim 25 and adds that the "nucleic acids comprise a gene sequence or pathogen sequence." Petitioner adequately explains how and why a person of ordinary skill in the art would have adapted Fish such that the subject matter of these claims would have been obvious. Pet. 33–34.

There is a reasonable likelihood Petitioner would prevail in showing that dependent claims 130, 131, 151, and 154 would have been obvious over Fish.

D. Ground 3: Obviousness in View of Fish, Metzgar and Sato

Petitioner contends that dependent claims 120 and 189 would have been obvious over Fish, Metzgar, and Sato. Pet. 6. Claim 120 depends directly from independent claim 17, and claim 189 depends directly from independent claim 25. Claims 120 and 189 additionally recite that "said non-porous solid support comprises one or more hydroxyls."

Petitioner provides testimony from Dr. Nelson (Ex. 1002 ¶83) that glass necessarily includes hydroxyl groups and identifies teachings from Metzgar and Sato to show why it would have been obvious to use glass trays, instead of polyvinyl trays, in Fish. Pet. 35–36. In particular, Petitioner notes that Metzgar discloses microscope slides made of glass and having "depressions or wells on the top surface thereof" and that Sato discloses treatment of glass slides with PLL prior to fixing cells on the slides, thus indicating that PLL treatment of glass slides was a known and

routine practice. Pet. 35 (quoting Ex. 1009, Abstract and citing Ex. 1009, 2:28–30 and Fig. 1), 36 (citing Ex. 1034, 647 ¶4). In light of these teachings, Petitioner persuasively argues, that a person of ordinary skill in the art would have been motivated "to perform the nucleic acid immobilization procedure described in Fish [which uses PLL] on easy-to-use, non-porous supports, such as the glass slides having wells or depressions, as disclosed in Metzgar." Pet. 35–36.

There is a reasonable likelihood Petitioner would prevail in showing that dependent claims 120 and 189 would have been obvious over Fish, Metzgar, and Sato.

E. Ground 4: Obviousness in View of Fish and Gilham

Petitioner contends that dependent claims 113 and 185 would have been obvious over Fish and Gilham. Pet. 6. Claim 113 depends directly from independent claim 17, and claim 185 depends directly from independent claim 25. Claims 113 and 185 additionally recite that "said fixation or immobilization to said non-porous solid support is covalent."

Gilham discloses covalently linking polynucleotides to solid matrices. Ex. 1019, 173. For example, according to Dr. Nelson, 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 ¶85 (citing Ex. 1019, 174 at Table I (covalent binding at the polynucleotide terminal by periodate oxidation of 3'-terminals of RNA), 175 ¶2). 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." Ex. 1019, 179 ¶1. Gilham goes on to state that such immobilized RNA provides "a new approach" to study complementary sequences. *Id*.

Petitioner argues that a person of ordinary skill in the art would 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." Pet. 38. We find this reasoning adequate.

There is a reasonable likelihood Petitioner would prevail in showing that dependent claims 113 and 185 would have been obvious over Fish and Gilham.

F. Ground 5: Obviousness in View of VPK and Metzgar

Petitioner contends that claims 17, 19, 25, 105, 106, 114, 119, 120, 128, 129, 131, 150–152, 178, 180, 186, and 189 would have been obvious over VPK and Metzgar. Pet. 6.

1. VPK is Prior Art on the Record Presented

The '197 patent claims priority to various applications, the oldest two being U.S. Patent Application Ser. No. 06/732,374 ("the '374 application"), filed on May 9, 1985, and U.S. Patent Application Ser. No. 06/461,469 ("the '469 application"), filed on January 27, 1983. Ex. 1001, 1:8–19. Petitioner asserts that VPK, which was published October 1982 (Ex. 1008, cover page), is prior art to the challenged claims of the '197 patent under both 35

U.S.C. §§ 102(a) and (b). Pet. 39.

With respect to whether VPK is prior art under § 102(a), Petitioner points out that VPK was published before the earliest filing date in the claim of priority, which is the earliest presumed invention date. Pet. 39; *see Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577 (Fed. Cir. 1996) ("Had Dr. Mahurkar not come forward with evidence of an earlier date of invention, the Cook catalog would have been anticipatory prior art under section 102(a) because Dr. Mahurkar's invention date would have been the filing date of his patent.").

With respect to whether VPK is prior art under § 102(b), Petitioner argues that the challenged claims are not adequately supported by the '469 application and, thus, not entitled under 35 U.S.C. § 120 to the benefit of its January 1983 filing date. Pet. 39–44. Accordingly, as Petitioner argues, the challenged claims are entitled to an effective filing date no earlier than that of the '374 application, which was filed in May 1985 and more than one year after VPK published in October 1982. *Id*.

In its Preliminary Response, Patent Owner argues that the challenged claims are entitled to the benefit of the January 1983 filing date, thereby disqualifying VPK as § 102(b) prior art. Prelim. Resp. 41–48. Patent Owner does not, however, argue that the claims are entitled to an even earlier *invention* date. Accordingly, on the current record, VPK is prior art under § 102(a), *see Mahurkar*, 79 F.3d at 1577, and we need not decide whether VPK is also prior art under § 102(b).

2. Disclosure of VPK and Metzgar

VPK "describes modifications of [existing] in situ hybridization and immunocytochemical procedures, permitting identification of specific DNA sequences in human chromosomes by fluorescence microscopy." Ex. 1008, 398, left col. ¶1; *see also* Ex. 1002 ¶93. It discloses binding of human metaphase chromosomes to aminoalkylsilane-treated glass slides. Ex. 1008, 398, right col. ¶1, 401, Figs. 2 and 3; *see also* Ex. 1002 ¶¶94–96. The DNA in the chromosomes is denatured, and the resulting ssDNA is then hybridized with RNA. *Id*. at 399, left col. ¶¶2–3; *see also* Ex. 1002 ¶97.

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, Fig. 1. Figure 1 of Meztgar illustrates a slide with an array of twelve wells, arranged in two rows of six. Ex. 1009, Fig. 1.

3. Application of VPK and Metzgar to the Challenged Claims

Petitioner presents an adequate reason for why a person of ordinary skill in the art would have performed the immobilization of nucleic acids and the in situ hybridization procedure described in VPK on glass slides having wells or depressions as taught by Metzgar: "in order to analyze multiple samples or analytes simultaneously on the same glass slide." Pet. 45.

Petitioner sufficiently explains how the relied-upon teachings, so combined, meet each limitation of claims 17, 19, 25, 105, 106, 114, 119, 120, 128, 129, 131, 150–152, 178, 180, 186, and 189. Pet. 46–53. We explicitly address only Patent Owner's counter-arguments.

With respect to all claims challenged on the present ground, Patent Owner argues that "Metzgar does not disclose an orderly grouping or arrangement of nucleic acids, nor does it suggest that the slides it describes could be used for nucleic acid detection or fixing nucleic acids." Prelim. Resp. 49. The fact that Metzgar does not disclose an orderly grouping or arrangement *of nucleic acids* is of no moment because the obviousness challenge is based on the combined teachings of VPK and Metzgar. *See In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references."). Similarly, a reason to use Metzgar's multiple-well slides in VPK's procedure need not be suggested by Metzgar. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007) ("The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.").

Patent Owner raises an additional argument solely with respect to claim 131. Prelim. Resp. 50–51. Claim 131 recites "said nucleic acids [which are bound to the non-porous solid support] comprise nucleic acid sequences complementary to nucleic acid sequences of interest sought to be identified, quantified or sequenced." Patent Owner argues that VPK does not teach this limitation because it "describes the opposite." Prelim. Resp. 51. More specifically, Patent Owner argues that VPK describes nucleic acid sequences within blood culture cells that are bound to glass slides that are themselves of interest but that their complementary sequences are not of

interest. *Id*. We are not persuaded by this argument. If a nucleic acid sequence is of interest, so too is its complementary sequence, because the nucleotides of the sequence have known base pairings (i.e., A with T, C with G).

There is a reasonable likelihood Petitioner would prevail in showing that dependent claims 17, 19, 25, 105, 106, 114, 119, 120, 128, 129, 131, 150–152, 178, 180, 186, and 189 would have been obvious over VPK and Metzgar.

G. Ground 6: Obviousness in View of Noyes, VPK, Metzgar and Ramachandran

Petitioner contends that dependent claims 113, 116, 130, 154, 185, and 187 would have been obvious over Noyes, VPK, Metzgar and Ramachandran. Pet. 6.

1. Disclosure of Noyes and Ramachandran

Noyes discloses covalent linkage of each of ssDNA and RNA to finely divided m-aminobenzyloxymethyl cellulose after the primary aryl amino groups have been diazotized. Ex. 1007, 301, left col. ("Summary"), right col. ¶2. Noyes also discloses hybridization of the bound ssDNA and RNA to complementary sequences. *Id*. at 301 ("Summary"), 303–05.

Ramachandran discloses treatment of non-porous glass beads with 3-amino-propyltriethoxysilane to provide alkylamines on the surface of the glass bead. Ex. 1028, 673 ¶1. Ramachandran further teaches treatment of the alkylamine glass with chloroform and ethyl alcohol to convert the alkylamines to arylamines. *Id*.

2. Application of Noyes, VPK, Metzgar and Ramachandran to the Challenged Claims

Petitioner presents an adequate reason for how and why a person of ordinary skill in the art would have combined the relied-upon teachings. Pet. 54–56. Petitioner also explains sufficiently how the relied-upon teachings, so combined, meet each limitation of claims 113, 116, 130, 154, 185, and 187. Pet. 56–57.

Patent Owner argues, with supporting testimony from Dr. Buck, that the proposed combination would not meet the "hybridizable form" limitation because "extremely reactive diazonium functional groups" would react with any available guanine (ssDNA and RNA), thymine (ssDNA and RNA), and uracil (RNA) bases, thereby preventing the ssDNA and RNA from hybridizing with complementary strands of bases. Prelim. Resp. 54–55 (citing Ex. 2101 ¶¶155–156). Although Dr. Buck's testimony supports Patent Owner's argument that the proposed combination would not meet the "hybridizable form" limitation required by all challenged claims, Petitioner has established nonetheless a reasonable likelihood of prevailing on this ground, thus justifying a trial. *See* Ex. 1008, 399, left col. ¶¶2–3 (VPK stating that the DNA in the chromosomes is denatured, and the resulting ssDNA is then hybridized with RNA.); 37 C.F.R. § 42.108 ("[A] genuine issue of material fact created by [a patent owner preliminary response's] testimonial evidence will be viewed in the light most favorable to the petitioner solely for purposes of deciding whether to institute an *inter partes* review.").

There is a reasonable likelihood Petitioner would prevail in showing

that dependent claims 113, 116, 130, 154, 185, and 187 would have been obvious over Noyes, VPK, Metzgar and Ramachandran.

III. CONCLUSION

We have considered the information presented in the Petition and Preliminary Response and determine that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. *See* 35 U.S.C. § 314(a); 37 C.F.R. § 42.108.

IV. ORDER

It is

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review of U.S. Patent No. 7,064,197 B1 is hereby instituted on the following grounds:

(1) claims 17, 19, 25, 105, 106, 114, 116, 119, 128, 129, 150, 152, 178, 180, 186, and 187 as anticipated by Fish;

(2) claims 130, 131, 151, and 154 as obvious over Fish;

(3) claims 120 and 189 as obvious over Fish, Metzgar, and Sato;

(4) claims 113 and 185 as obvious over Fish and Gilham;

(5) claims 17, 19, 25, 105, 106, 114, 119, 120, 128, 129, 131, 150–152, 178, 180, 186, and 189 as obvious over VPK and Metzgar; and

(6) claims 113, 116, 130, 154, 185, and 187 as obvious over Noyes, VPK, Metzgar, and Ramachandran.

FURTHER ORDERED that no other ground of unpatentability alleged in the Petition for any claim is authorized for this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and

37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial commences on the entry date of this decision.

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