Trials@uspto.gov
571-272-7822

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 IPR2016-00820
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 1, 6, 8, 9, 12–16, 27, 31–34, 38, 41, 61–64, 68–70, 72–74, 78, 79, 100, 101, 191–195, 212, 213, 218, 219, 222, 225–227, 230, 233, and 236 of U.S. Patent No. 7,064,197 B1 (Ex. 1001, "the '197 patent") pursuant to 35 U.S.C. § 311(a). Paper 1 ("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* IPR2016-00822.

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 1, 6, 8, 9, 12–16, 27, 31–34, 38, 41, 61–64, 68–70, 72–74, 78, 79, 100, 101, 191–195, 212, 213, 218, 219, 222, 225–227, 230, 233, and 236. Pet. 1. Of the challenged claims, claims 1, 6, 8, 9, 12–15, and 27 are independent. The remainder of the challenged claims all depend directly from at least one of the challenged independent claims, with several of them in multiple dependent form.

Claim 1 is illustrative and reproduced below.

> 1. A non-porous solid support comprising one or more amine(s), hydroxyl(s) or epoxide(s) thereon, wherein at least one single-stranded nucleic acid is fixed or immobilized in hybridizable form to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s).

D. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

References	**Basis**[1]	**Claims Challenged**
Fish (Ex. 1006)[2]	§ 102(b)	1, 6, 8, 9, 12–16, 27, 31–34, 41, 61–63, 68–70, 72–74, 79, 100, 191–194, 212, 213, 219, 222, 225–227, 230, 233, and 236
Fish	§ 103(a)	31, 64, 68, 101, 192, and 195
Fish and Gilham (Ex. 1019)[3]	§ 103(a)	38, 78, and 218
VPK (Ex. 1008)[4]	§ 102(a) and (b)	1, 6, 8, 9, 12–15, 27, 31, 32, 34, 61–63, 68–70, 72, 74, 79, 100, 191–193, 194, 213, 219, 226, 227, and 236
VPK and Metzgar (Ex. 1009)[5]	§ 103(a)	33, 41, 73, 212, 225, and 233

[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] P. T. Gilham, "Immobilized Polynucleotides and Nucleic Acids," *Immobilized Biochemicals and Affinity Chromatography*, 173–85 (1974).
[4] 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),[6] VPK, and Ramachandran (Ex. 1028)[7]	§ 103(a)	16, 38, 64, 78, 101, 195, 218, 222, and 230

Pet. 6–7; *see also id*. at 40 (asserting that VPK is prior art under § 102(a) as well as § 102(b)).

As an initial matter, we acknowledge Patent Owner's assertion that "Petitioner failed to present any evidence" that its non-patent references (i.e., Fish, 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. 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 Immobilized Biochemicals" held November 7–9, 1973. Ex. 1019, second page after cover ("Library of Congress Cataloging

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[5] U.S. Patent No. 3,572,892, issued Mar. 30, 1971.
[6] Barbara E. Noyes, et al., "Nucleic Acid Hybridization Using DNA Covalently Coupled to Cellulose," *Cell*, vol. 5, 301–10 (July 1975).
[7] 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).

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. "non-porous solid support"

All of the independent claims that are challenged recite a "non-porous solid support." Neither party proposes an express construction. *See* Pet. 12 (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.

2. "fixed or immobilized in hybridizable form"

All of the independent claims that are challenged recite "fixed or immobilized [] in hybridizable form."

The parties agree that "fixed or immobilized" means "bound." Pet. 11; Prelim. Resp. 13 n.3; *see also* Ex. 1010, 13–15 (*Markman* order applying same construction). We give it the agreed-upon meaning.

The parties agree that "hybridizable form" means "capable of binding

through Watson-Crick base pairing." Pet. 14 (citing Ex. 1001, 2:22–34); Prelim. Resp. 12[8]; *see also* Ex. 1010, 5 (*Markman* order applying same construction). We give it the agreed-upon meaning.

B. Ground 1: Anticipation by Fish

Petitioner asserts that claims 1, 6, 8, 9, 12–16, 27, 31–34, 41, 61–63, 68–70, 72–74, 79, 100, 191–194, 212, 213, 219, 222, 225–227, 230, 233, and 236 are anticipated by Fish. Pet. 6.

Anticipation requires that "each and every element as set forth in the 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.[9] Synthetic double-stranded

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[8] Patent Owner's construction additionally adds that the Watson-Crick base pairing would be "to a complementary nucleic acid sequence." Prelim. Resp. 12. This additional language, however, is superfluous, as it merely describes what Watson-Crick base pairing inherently requires.

[9] Unless otherwise noted, our citations to paragraphs of non-patent

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. *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.").

"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[10] 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-

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references are numbered starting with the first full paragraph of a respective page or column.

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

> 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 the Challenged Independent Claims

The challenged independent claims (namely, claims 1, 6, 8, 9, 12, 13, 14, 15, and 27) are of similar scope, and none of their differences is material in light of the Fish teachings on which Petitioner relies. Accordingly, we address explicitly only independent claim 1.[11]

Independent claim 1 recites, in both the preamble and the body of the claim, a "non-porous solid support." Fish appears to meet this limitation because Fish uses microtitration trays that are polyvinvyl (Ex. 1006, 536, left col. ¶1), which material is plastic and non-porous according to the testimony of Norman Nelson, Ph.D. Ex. 1002 ¶¶38, 40, 68.

Claim 1 recites a "non-porous solid support comprising one or more amine(s), hydroxyl(s) or epoxide(s) thereon." Fish appears to meet this

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[11] Even if the claims were materially different, it would be proper nonetheless to address a single claim and, assuming that Petitioner has established a reasonable likelihood of prevailing with respect to that claim (which Petitioner has), institute on all challenged claims. *See* 35 U.S.C. § 314(a) (requiring, for institution, "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."). By Rule, this standard is to be applied on a ground-by-ground basis. *See* 37 C.F.R. § 42.108(c) ("*Inter partes* review shall not be instituted for a ground of unpatentability unless the Board decides that the petition supporting the ground would demonstrate that there is a reasonable likelihood that at least one of the claims challenged in the petition is unpatentable.").

limitation because it discloses treating the microtitration tray with PLL (Ex. 1006, 536, left col. ¶¶1–2), which provides amine groups on the surface of the tray. Ex. 1002 ¶42; Ex. 1017, 1, right col. ¶2 ("Non-terminated DNA has also been spotted onto amine functionalized surfaces such as PLL."), 2, left col. ¶1 ("PLL, APS and PAMAM all present amine functional groups suitable for interaction with DNA.").

Claim 1 recites "at least one single-stranded nucleic acid." Fish appears to meet this limitation because it discloses wells of ssDNA (i.e., the mixture of poly-dA and poly-dC as well as the denatured calf thymus DNA). Ex. 1006, 536, left col. ¶¶1–2.

Claim 1 recites that the single-stranded nucleic acid is "fixed or immobilized in hybridizable form to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s)." Fish appears to meet these limitations. First, 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; *see also* Ex. 1002 ¶53 (Dr. Nelson: "[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.").

Patent Owner argues that the Fish experiment was "***not designed*** to determine whether single-stranded nucleic acids bound to PLL-coated wells." Prelim. Resp. 13–14. But, that is not relevant to whether or not Fish discloses single-stranded nucleic acids bound to the PLL-coated wells of the microtitration tray, which Fish explicitly does. *See* Ex. 1006, 538, right col.

¶1 (stating that "single-stranded nucleic acid" was "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. 22–23. Because S_1 digests ssDNA, the difference in binding proves that there was ssDNA there to be digested. *Id*. at 23.

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. 25 (citing Ex. 1002 ¶¶62, 64). 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 ¶64.

"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. 2001 [declaration of Gregory Buck, Ph.D.] ¶ 72.) 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. 2001 ¶ 72.)
>
> 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 complementary strands of ssDNA under suitable conditions, the bound ssDNA is necessarily capable of binding through Watson-Crick base pairing. *See* Ex. 1002 ¶64.

There is a reasonable likelihood Petitioner would prevail in showing that independent claims 1, 6, 8, 9, 12, 13, 14, 15, and 27 are anticipated by Fish.

3. Application of Fish to the Challenged Dependent Claims

Each of claims 16, 31–34, 41, 61–63, 68–70, 72–74, 79, 100, 191–194, 212, 213, 219, 222, 225–227, 230, 233, and 236 depends directly from at least one of the challenged independent claims. Except with respect to claims 3, 68, and 192, Petitioner adequately shows how the additional limitations recited in these claims are taught by Fish. *See* Pet. 30–33.

Each of claims 31, 68, and 192 recites that the fixed or immobilized "nucleic acid comprises a nucleic acid sequence complementary to a nucleic acid sequence 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. 31 (emphasis added). Per Petitioner's own argument, this additional limitation is not satisfied by Fish.

There is a reasonable likelihood Petitioner would prevail in showing that dependent claims 16, 32–34, 41, 61–63, 69, 70, 72–74, 79, 100, 191, 193, 194, 212, 213, 219, 222, 225–227, 230, 233, and 236—but not claims 31, 68, and 192—are anticipated by Fish.

C. Ground 2: Obviousness in View of Fish

Petitioner contends that dependent claims 31, 64, 68, 101, 192, and 195 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).[12]

Claims 31, 68, and 192 recite that the fixed or immobilized "nucleic acid comprises a nucleic acid sequence complementary to a nucleic acid sequence 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 claims 31, 68, and 192." Ex. 1002 ¶78; *see also* Pet. 36 (citing the same). We find this testimony persuasive.

Claims 64, 101, and 195 recite that the fixed or immobilized "nucleic acid is RNA." 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. 37.

There is a reasonable likelihood Petitioner would prevail in showing

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[12] 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.

that dependent claims 31, 64, 68, 101, 192, and 195 would have been obvious over Fish.

D. Ground 3: Obviousness in View of Fish and Gilham

Petitioner contends that dependent claims 38, 78, and 218 would have been obvious over Fish and Gilham. Pet. 6. These claims recite "wherein 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 ¶81 (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. 39. We find this reasoning

adequate.

There is a reasonable likelihood Petitioner would prevail in showing that dependent claims 38, 78, and 218 would have been obvious over Fish and Gilham.

E. Ground 4: Anticipation by VPK

Petitioner contends that claims 1, 6, 8, 9, 12–15, 27, 31, 32, 34, 61–63, 68–70, 72, 74, 79, 100, 191–193, 194, 213, 219, 226, 227, and 236 are anticipated by VPK.

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. 39–40.

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. *Id*. at 40; *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. 40–45. 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. 37–44. 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

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 blood culture cells with metaphase chromosomes to aminoalkylsilane-treated glass slides. Ex. 1008, 398, right col. ¶1, 401, Figs. 2 and 3; *see also* Ex. 1002 ¶¶89–91. 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 ¶92.

3. Application of VPK to the Challenged Independent Claims

The challenged independent claims (namely, claims 1, 6, 8, 9, 12, 13, 14, 15, and 27) are of similar scope, and none of their differences is material in light of the VPK teachings on which Petitioner relies. Accordingly, we address explicitly only independent claim 1.

Independent claim 1 recites, in both the preamble and the body of the claim, a "non-porous solid support." VPK appears to meet this limitation because it uses glass slides, which are non-porous solid supports. Ex. 1008, 398, right col. ¶1; Ex. 1002 ¶88.

Claim 1 recites a "non-porous solid support comprising one or more amine(s), hydroxyl(s) or epoxide(s) thereon." VPK appears to meet this limitation because it treats the glass slides aminoalkylsilane, which provides alkyamines on the surface of the glass slides. Ex. 1008, 398, right col. ¶¶1–2; Ex. 1015, 334; Ex. 1002 ¶89.

Claim 1 recites "at least one single-stranded nucleic acid [that] is fixed or immobilized in hybridizable form to said non-porous solid support." VPK appears to meet this limitation because the chromosomes are bound to the aminoalkylsilane-treated glass slides and then denatured into ssDNA, which is a hybridizable form. Ex. 1008, 398, right col. ¶1, 399, left col. ¶¶2–3, 401, Figs. 2 and 3; Ex. 1002 ¶¶89–92. Patent Owner argues that VPK does not meet this limitation because the chromosomes are not bound directly to the aminoalkylsilane-treated glass slides. Prelim. Resp. 45–46. Instead, in VPK, the chromosomes are indirectly bound to the slides, as they are contained within blood culture cells that are directly bound to the slides. *Id*. Neither the explicit language of the claim ("fixed or immobilized") nor

the parties' agreed-upon construction for it ("bound") requires a direct connection.

Claim 1 recites that the single-stranded nucleic acid is fixed or immobilized to the non-porous solid support "via said one or more amine(s), hydroxyl(s) or epoxide(s)." VPK appears to meet this limitation because Dr. Nelson testifies that the alkylamines on the glass slides in VPK "have a positive charge and they ionically interact with the negative charges on the cell surface to form ionic (i.e., non-covalent) bonds between the alkylamine groups and the cellular material." Ex. 1002 ¶91; *see also* Ex. 1001, 8:57–60 ("The resulting treated glass surface will now have available alkylamine thereon suitable for immobilizing or fixing any negatively charged polyelectrolytes applied thereto.").

There is a reasonable likelihood Petitioner would prevail in showing that independent claims 1, 6, 8, 9, 12, 13, 14, 15, and 27 are anticipated by VPK.

4. Application of VPK to the Challenged Dependent Claims

Each of claims 31, 32, 34, 61, 62, 63, 68, 69, 70, 72, 74, 79, 100, 191, 192, 193, 194, 213, 219, 226, 227, and 236 depends directly from at least one of the challenged independent claims. The Petition adequately shows how Fish meets the additional limitations recited in these claims. *See* Pet. 49–51. We explicitly address only Patent Owner's counter-arguments.

Claims 31, 68, and 192 recite "said nucleic acid comprises a nucleic acid sequence complementary to a nucleic acid sequence 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. 47. More specifically, Patent Owner argues that VPK describes nucleic acid sequences within blood culture cells bound to glass slides that are themselves of interest but that their complementary sequences are not of interest. *Id*. at 47–48. 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).

Claims 79, 219, and 236 recite "wherein said fixation or immobilization to said non-porous . . . solid support is non-covalent." Patent Owner argues that VPK does not teach this limitation, repeating its argument that VPK does not disclose directly binding chromosomes to the aminoalkylsilane-treated glass slides. *Id*. at 48. As discussed above, on the present record, that argument is not persuasive.

There is a reasonable likelihood Petitioner would prevail in showing that dependent claims 31, 32, 34, 61, 62, 63, 68, 69, 70, 72, 74, 79, 100, 191, 192, 193, 194, 213, 219, 226, 227, and 236 are anticipated by VPK.

F. Ground 5: Obviousness in View of VPK and Metzgar[13]

Petitioner contends that dependent claims 33, 41, 73, 212, 225, and 233 would have been obvious over VPK and Metzgar. Pet. 7.

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[13] This Decision reverses the order of the fifth and sixth grounds presented in the Petition.

1. Disclosure of Metzgar

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.

2. Application of VPK and Metzgar to the Challenged Claims

Claims 33, 73, and 212 recite that the 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, claims 41, 225, and 233 recite that the non-porous solid support "comprises a plate or plates, *a well or wells*, a microtiter well or microtiter wells, or a depression or depressions." (Emphasis added.). Metzgar teaches the "well or wells" option of these claims. Ex. 1009, Abstract, 2:28–30, Fig. 1.

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. 57.

There is a reasonable likelihood Petitioner would prevail in showing that dependent claims 33, 41, 73, 212, 225, and 233 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 16, 38, 64, 78, 101, 195, 218, 222, and 230 would have been obvious over Noyes, VPK, Metzgar and Ramachandran. Pet. 6–7.

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. 52–54. Petitioner also explains sufficiently how the relied-upon teachings, so combined, meet each limitation of claims 16, 38, 64, 78, 101, 195, 218, 222, and 230. *Id*. at 54–55.

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, thymine, and uracil bases," thereby preventing the ssDNA and RNA from hybridizing with complementary strands of bases. Prelim. Resp. 50–51 (citing Ex. 2001 ¶¶159–160). 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 16, 38, 64, 78, 101, 195, 218, 222, and 230 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

Accordingly, 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 16, 32–34, 41, 61–63, 69, 70, 72–74, 79, 100, 191, 193, 194, 212, 213, 219, 222, 225–227, 230, 233, and 236 as anticipated by Fish;

(2) claims 31, 64, 68, 101, 192, and 195 as obvious over Fish;

(3) claims 38, 78, and 218 as obvious over Fish and Gilham;

(4) claims 1, 6, 8, 9, 12–15, 27, 31, 32, 34, 61–63, 68–70, 72, 74, 79, 100, 191–193, 194, 213, 219, 226, 227, and 236 as anticipated by VPK;

(5) claims 33, 41, 73, 212, 225, and 233 as obvious over VPK and Metzgar; and

(6) claims 16, 38, 64, 78, 101, 195, 218, 222, and 230 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.

For Petitioner:

M. Paul Barker
Paul.barker@finnegan.com

Arpita Bhattacharyya
Arpita.bhattacharyya@finnegan.com

Thomas L. Irving
tom.irving@finnegan.com

For Patent Owner:

Kevin K. McNich
kmcnish@desmaraisllp.com