Trials@uspto.gov
571-272-7822

Paper No. 52
Date: September 28, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOLOGIC, INC. and BECTON, DICKINSON AND COMPANY,
Petitioners,

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*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a)

I. INTRODUCTION

The original sole Petitioner in this *inter partes* review, Hologic, Inc. ("Hologic") 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 ("the challenged claims") 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."). In an October 4, 2016, Decision, we granted the Petition. Paper 8 ("Inst. Dec.").

During trial, Becton, Dickinson and Company ("Becton") was joined as co-petitioner. Paper 32. Hologic and Becton are hereafter referred to collectively as "Petitioners."

Patent Owner filed a Patent Owner Response (Paper 24, "PO Resp."), to which Petitioners filed a Reply (Paper 38, "Reply"). Both sides filed Motions to Exclude. *See* Papers 43, 45. Both sides requested a hearing for oral arguments, and a consolidated hearing for this *inter partes* review and Case IPR2016-00822 was held June 1, 2017. A transcript of the hearing appears in the record. *See* Paper 51 ("Tr.").

As discussed below, Petitioners have shown by a preponderance of the evidence that all of the challenged claims are unpatentable.

A. Related Matters

Co-petitioner Hologic successfully petitioned for two *inter partes* reviews of claims of the '197 patent—the instant proceeding and Case IPR2016-00822. Co-petitioner Becton also filed two petitions for *inter*

partes reviews of the ’197 patent, along with motions to join the already instituted Hologic-petitioned *inter partes* reviews. *See* IPR2017-00172; IPR2017-00181. Becton’s petitions were denied, but Becton was joined as co-petitioner in this proceeding and as well as in Case IPR2016-00822. *See* Paper 32; IPR2016-00822, Paper 31.

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 23, 1.

B. The ’197 Patent

The ’197 patent relates generally to the detection of genetic material by polynucleotide or oligonucleotide probes. Ex. 1001, 1:23–24, 5:43–46. The ’197 patent refers to the genetic 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. In the challenged claims, the analyte is either "single-stranded nucleic acid" (claims 1, 6, 12, 13, 27), "DNA or RNA" (claims 8, 15), or "nucleic acid" (claims 9, 14). "Analytes in a biological sample are preferably denatured into single-stranded form, and then directly fixed to a suitable solid support." *Id*. at 5:61–63. 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 1 reciting a "non-porous solid support"). To obtain fixation (or binding) to the non-porous solid support, the '197 patent teaches treating the surface of the support with a chemical such as polylysine. *Id*. at 11:37–39.

> 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

Petitioners challenge 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 the '197 patent. 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. Grounds of Unpatentability Tried

We instituted trial on the following grounds of unpatentability:

References	**Basis**[1]	**Claims Challenged**
Fish (Ex. 1006)[2]	§ 102(b)	1, 6, 8, 9, 12–16, 27, 32–34, 41, 61–63, 69, 70, 72–74, 79, 100, 191, 193, 194, 212, 213, 219, 222, 225–227, 230, 233, and 236

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, enacted September 16, 2011, amended 35 U.S.C. §§ 102 and 103. AIA § 3(b)–(c). Their amendment became effective eighteen months later on March 16, 2013. *Id*. at § 3(n). Because the application from which the '197 patent issued was filed before March 16, 2013, any citations herein to 35 U.S.C. §§ 102 and 103 are to their pre-AIA versions.

[2] Falk Fish, et al., "A Sensitive Solid Phase Microradioimmunoassay For

References	Basis[1]	Claims Challenged
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
Noyes (Ex. 1007),[6] VPK, and Ramachandran (Ex. 1028)[7]	§ 103(a)	16, 38, 64, 78, 101, 195, 218, 222, and 230

Inst. Dec. 26; *see also* Paper 10 (errata to Institution Decision).

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).

[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).

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)).

There are two major claim construction disputes in this case. They regard the meaning of "fixed or immobilized" and "hybridizable form." These limitations are recited by all challenged independent claims. At institution, we adopted express constructions that the parties had stipulated to for both limitations, but that was not the end of the matter. Inst. Dec. 8–9. The parties now dispute what their stipulated constructions encompass.

1. "fixed or immobilized"

All of the challenged independent claims recite "fixed or immobilized." For example, claim 1 recites "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)." (Emphasis added).

Prior to institution, the parties agreed that "fixed or immobilized" means "bound." Pet. 11; Prelim. Resp. 13 n.3; *see also* Ex. 1010, 13–15 (*Markman* order applying same construction). In our Institution Decision, we applied that agreed-upon meaning. Inst. Dec. 8. Although neither side opposes that construction post-institution, a dispute remains as to whether "fixed or immobilized" encompasses only that which is directly bound or additionally that which is indirectly bound. *See, e.g.,* Pet. 48 (mapping VPK's disclosure of indirect binding to the "fixed or immobilized" limitation); PO Resp. 55–57 (Patent Owner arguing that VPK's indirect binding does not meet the "fixed or immobilized" limitation); Reply 20–21 (Petitioners arguing the opposite).

This remaining dispute can be resolved by resorting to the specification, in light of which the limitation must be read. The specification states:

> Analytes in a biological sample are preferably denatured into single-stranded form, and then directly fixed to a suitable solid support. Alternatively, the analyte may be directly fixed to the support in double-stranded form, and then denatured. *The present invention also encompasses indirect fixation of the analyte*, such as in in situ techniques where the cell is fixed to the support and sandwich hybridization techniques where the analyte is hybridized to a polynucleotide sequence that is fixed to the solid support.

Ex. 1001, 5:61–6:2 (emphasis added). This excerpt unequivocally demonstrates two things. First, the applicants considered indirect fixation to be within the scope of their invention, and they so informed the public. Second, the applicants considered the term "fixation" to include both direct fixation and indirect fixation in the absence of an explicit reference to the

former or latter. Critically, the independent claims recite an analyte that merely "is fixed or immobilized" without specifying that the fixation or immobilization must be direct or indirect. *See, e.g.*, *id.* at 13:63–67 (claim 1). Accordingly, we construe "fixed or immobilized" as meaning bound, whether directly or indirectly.

Further intrinsic evidence supports our construction via the doctrine of claim differentiation and application of 35 U.S.C. § 112 ¶5 (now § 112(e)). Claim 16, which is in multiple dependent form, is reproduced below:

> 16. The non-porous solid support of claims 1, 2, 12, 13, 14, 15 or 4, wherein said fixation or immobilization is not to a cell fixed in situ to said non-porous solid support.

Each of the claims from which claim 16 depends is an independent claim that recites "fixed or immobilized." By statute, claim 16 must specify a further limitation beyond each claim from which it depends. *See* 35 U.S.C. § 112 ¶5 ("A claim in multiple dependent form shall contain a reference, in the alternative only, to more than one claim previously set forth and then specify a further limitation of the subject matter claimed."). The only limitation specified by claim 16 is that "said fixation or immobilization is not to a cell fixed in situ to said non-porous solid support." Hence, for claim 16 to comply with 35 U.S.C. § 112 ¶5, the further limitation that it specifies (i.e., "said fixation or immobilization is not to a cell fixed in situ to said non-porous solid support") must *not* be a limitation of the claims from which it alternatively depends. In other words, the "fixed or immobilization" limitation of each of claims 1, 2, 12, 13, 14, 15 and 4 must encompass fixation or immobilization that is to a cell fixed in situ to said non-porous solid support. This type of claim differentiation is the strongest type to

which the doctrine applies.

> In the most specific sense, "claim differentiation" refers to the presumption that an independent claim should not be construed as requiring a limitation added by a dependent claim. Thus, the claim differentiation tool works best in the relationship between independent and dependent claims.

Curtiss-Wright Flow Control Corp. v. Velan, Inc., 438 F.3d 1374, 1380 (Fed. Cir. 2006) (citations omitted).

Thus, in light of the specification and claim differentiation, we construe "fixed or immobilized" to mean bound, whether directly or indirectly.

2. "hybridizable form"

All of the independent claims that are challenged recite "hybridizable form." For example, claim 1 recites "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)." (Emphasis added).

Prior to institution, the parties agreed 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). In our Institution Decision, we gave it the

[8] Patent Owner's proffered construction additionally added 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. *See* Ex. 1001, 2:22–29.

agreed-upon meaning. Inst. Dec. 8–9. Although neither side opposes that construction post-institution, a dispute remains as to the meaning of the construction to which the parties agreed and we adopted. *See, e.g.*, Pet. 25 (mapping Fish's ssDNA bound to poly-L-lysine ("PLL")-treated plastic to the hybridizable form limitation); PO Resp. 11 ("Fish fails to disclose sufficient information regarding the various factors and conditions that affect hybridization to allow a POSITA to determine whether any bound ssDNA would be capable of hybridizing with other nucleic acids."); Reply 8 ("Enzo argues Fish discloses no hybridization conditions, although the challenged claims lack such a requirement.").

We maintain our construction that "hybridizable form" means "capable of binding through Watson-Crick base pairing." However, in response to Patent Owner's post-institution arguments for patentability over the Fish-based grounds, we provide some clarifications.

a) The Limitation "hybridizable form" is not Synonymous with the Limitation "single-stranded"

The limitation "hybridizable form" pertains to the form of the recited analyte (i.e., "single-stranded nucleic acid" in independent claims 1, 6, 12, 13, and 27; "DNA or RNA" in independent claims 8 and 15; and "nucleic acid" in independent claims 9 and 14) when it is fixed or immobilized to the non-porous solid support. This means that the analyte must be bound to the solid support in a manner that renders it capable of binding to a complementary sequence through Watson-Crick base pairing. To be so capable, the analyte must be single-stranded *and* have bases available for base-pairing.

Patent Owner argues that something more must be required of "hybridizable form" because otherwise "every 'single-stranded' nucleic acid necessarily exists in 'hybridizable form.'" PO Resp. 13. Patent Owner elaborates as follows:

> [Petitioner's declarant, Norman Nelson, Ph.D.,] simply assumes that ***any*** single-stranded nucleic acid is capable of Watson-Crick base pairing—and therefore hybridization—regardless of existing conditions. In fact, Dr. Nelson testified that he could not think of a single example of a single-stranded nucleic acid bound to a solid support that would not be capable of Watson-Crick base pairing. (Nelson Tr. [Ex. 2017] 39:15–41:1.) Petitioner's inherency argument reads out the language "in hybridizable form," contravening even the broadest reasonable construction which must attribute some meaning to that claim language. Thus, Dr. Nelson's opinions not only lack any supporting analysis or facts, they erroneously render the claim limitation "hybridizable form" meaningless. *Haemonetics Corp. v. Baxter Healthcare Corp.*, 607 F.3d 776, 781 (Fed. Cir. 2010).

PO Resp. 13. Patent Owner's argument is not persuasive.

We are not applying our construction of "hybridizable form" in a manner that would render meaningless "single-stranded," which is an additional limitation of some but not all of the challenged claims.[9] Patent Owner's own declarant, Dr. Buck, testified that whether a single-stranded nucleic acid bound to a solid support is in hybridizable form depends on its

[9] Independent claims 1, 6, 12, 13, and 27 recite a "single-stranded nucleic acid," but independent claims 8 and 15 merely recite "DNA or RNA" and independent claims 9 and 14 merely recite "nucleic acid."

"attachment methodology and chemistry." Ex. 2042 ¶94. Dr. Buck elaborated as follows:

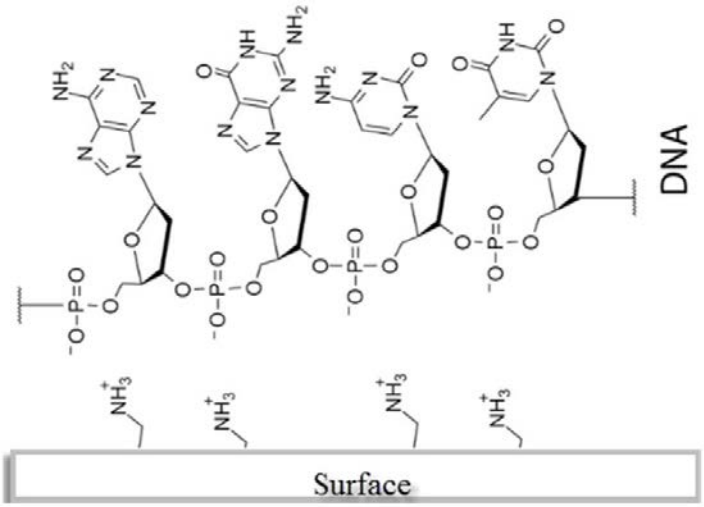
> For example, the way in which a single-stranded nucleic acid is bound to a solid support will have a large impact on whether or not that nucleic acid is capable of hybridizing with a complementary sequence. A single-stranded nucleic acid may be bound to a support in a way that renders it incapable of hybridizing with a complementary nucleic acid strand.

Id. at ¶95. In other words, if, for example, a single-stranded nucleic acid were bound to a solid support via all of its bases, the bases would not be available to pair with a complimentary sequence of bases on a probe. Thus, despite being single-stranded, the nucleic acid, with its bases bound to the solid support, would not be in a form that renders it capable of further binding through Watson-Crick base pairing. Hence, the nucleic acid would not be fixed or immobilized in "hybridizable form" despite being single-stranded.[10]

In contrast to this example, in the '197 patent, the analyte is bound to the solid support via its phosphate backbone, thus making the bases available for potential base-pairing. Ex. 2042 ¶189. Dr. Buck, Patent Owner's declarant, prepared an illustration of this configuration in his declaration, which illustration is reproduced below.

---

[10] Although Petitioner's declarant, Dr. Nelson, could not identify a way to bind a single-stranded nucleic acid to a solid support in a form that would not be capable of Watson-Crick base pairing (Ex. 2017, 40:8–41:1), Patent Owner's declarant, Dr. Buck, testified that such a form could exist. Ex. 2042 ¶¶94–95.



Ex. 2042 ¶189. Dr. Buck's illustration, reproduced above, depicts the "binding interaction [that] occurs between the negatively charged phosphate backbone of the nucleic acid strand and the positively charged amines on the gamma-aminopropyltriethoxysilane-treated surface" of the solid support. *Id*. (Dr. Buck statement after citing Ex. 1001, 8:48–52; 8:65–9:2).

Accordingly, our construction of "hybridizable form" as "capable of binding through Watson-Crick base pairing" does not render meaningless the term "single-stranded."

b) The Limitation "hybridizable form" Modifies the Recited Analyte, Not Unclaimed Aspects of the Surrounding Environment

Whether a recited analyte is fixed or immobilized in "hybridizable form" depends on the form of the recited analyte as bound to the support, but not on unclaimed aspects of the surrounding environment (e.g., temperature, pH, concentration, etc.)—termed "factors and conditions" by Patent Owner. *See* PO Resp. 9, 11.

Patent Owner argues that the challenged claims require the presence of certain "factors and conditions affecting hybridization" to satisfy the

"hybridizable form" limitation. *See, e.g.*, PO Resp. 9–10 ("Fish does not disclose sufficient information about the various factors and conditions affecting hybridization for a POSITA to determine whether the ssDNA in the Fish experiments would hybridize if complementary DNA were present."). But, the challenged claims do not require actual hybridization; they require only the *capability* to hybridize. And that capability, per the claim language, is met by the "form" of the recited analyte, and not by extraneous factors and conditions such as a solution in which the analyte may be present.

This is not to say that a solution's temperature, pH, solute, solvent, etc. cannot affect whether an analyte will ultimately hybridize through Watson-Crick base pairing. It is merely to say that we look to the form of the recited analyte, rather than other unspecified factors or conditions of the surrounding environment, in determining whether that analyte is hybridizable. As such, the challenged claims are not limited by any particular hybridization factors or conditions. For example, the concentration of complimentary probes within a solution surrounding an analyte may affect whether or how quickly the analyte hybridizes with a complimentary probe, but the concentration of complimentary probes does not affect the status of whether the analyte is in a "hybridizable form."

In light of the specification and the parties' stipulation (*see* Pet. 14; Prelim. Resp. 12), we construe "hybridizable form" as meaning that the recited analyte is bound to the non-porous solid support in a form that renders it capable of binding through Watson-Crick base pairing, which, in turn, means that it has bases available for base-pairing.

B. Ground 1: Anticipation by Fish

Petitioners contend that claims 1, 6, 8, 9, 12–16, 27, 32–34, 41, 61–63, 69, 70, 72–74, 79, 100, 191, 193, 194, 212, 213, 219, 222, 225–227, 230, 233, and 236 are anticipated by Fish.

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.[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. *Id*.

Fish next describes the same procedure but using single-stranded DNA ("ssDNA") either in the form of: (1) a mixture of synthetic

[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.

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 the following:

> [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 the Challenged Independent Claims

The challenged independent claims (namely, claims 1, 6, 8, 9, 12–15, and 27) are of similar scope, and none of their differences is material in light of the Fish teachings on which Petitioners rely. Further, all of Patent Owner's arguments for patentability of the challenged independent claims

---

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

are common to all of the challenged independent claims. *See* PO Resp. 2–22. Accordingly, for the challenged independent claims, we address explicitly only claim 1.

Independent claim 1 recites, in both the preamble and the body of the claim, a "non-porous solid support." Fish meets 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 unrebutted testimony of Dr. Nelson. Ex. 1002 ¶¶38, 40–42.

Claim 1 recites a "non-porous solid support comprising one or more amine(s), hydroxyl(s) or epoxide(s) thereon." Fish meets this limitation because it discloses treating the microtitration tray with poly-L-lysine (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."). Indeed, the '197 patent itself describes treating the surface of the non-porous solid support with polylysine to facilitate fixation of single-stranded DNA thereto. Ex. 1001, 11:37–39.[13]

Claim 1 recites "at least one *single-stranded* nucleic acid fixed or immobilized . . . to said non-porous solid support via said one or more

[13] The '197 patent refers to "polylysine" (PPL) generally, without specifying poly-L-lysine (PLL). Ex. 1001, 11:37–39. However, the '197 patent applicants touted the use of "poly-L-lysine" specifically during the prosecution history. *See, e.g.*, Ex. 1003, 97; *see also* Tr. 54:10–15 (counsel for Patent Owner agreeing that polylysine (per the '197 patent) and poly-L-lysine (per Fish) are both polylysines.).

amine(s), hydroxyl(s) or epoxide(s)." (Emphasis added.) Fish discloses wells of 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: "[T]he 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."). In fact, Fish explicitly refers to "**Single stranded DNA coated trays**" (Ex. 1006, 536, left col. ¶2) and "single-stranded nucleic acids, bound to the PLL treated plastic, . . ." (Ex. 1006, 538, right col. ¶1). Fish meets this limitation.

Patent Owner argues that Fish does not meet this limitation because "Fish does not describe any experiments that tested, let alone confirmed, whether single-stranded nucleic acids actually bound to the disclosed PLL-coated wells." PO Resp. 4 (citing Ex. 2042 ¶¶67–71, 76, and 77). But that is a straw man argument. The fact that Fish researchers may not have performed testing to confirm that ssDNA was bound to the PLL-coated wells does not negate that they nonetheless *described* ssDNA bound to PLL-coated wells. *See* 35 U.S.C. § 102(a)–(b) ("A person shall be entitled to a patent unless — (a) the invention was known or used by others in this country, or patented *or described* in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or (b) the invention was patented *or described* in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.") (emphasis added).

Further, and as we stated in the Institution Decision:

> [I]t 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.").

Inst. Dec. 13. Patent Owners have not presented any argument or evidence post-institution that would change our reading of Fish.

Petitioners have persuaded us that Fish teaches the limitation of claim 1 of "at least one single-stranded nucleic acid fixed or immobilized . . . to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s)" and the similar corresponding limitations of the other challenged independent claims.

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)." (Emphasis added.) Petitioners argue that Fish inherently discloses the "hybridizable form" limitation. Pet. 29. More specifically, Petitioners argue that the bound ssDNA in Fish is in "hybridizable form" because it "necessarily was capable of binding through Watson-Crick base pairing." *Id*. at 25 (citing Ex. 1002 ¶¶62, 64).

In addition to the cited testimony, Petitioners also rely on certain "admissions made by the Patent Owner." *Id*. (citing Ex. 1002 ¶¶62, 64). Dr. Nelson, Petitioner's declarant, explains the alleged admissions, with citations to the prosecution history of the '197 patent, as follows:

> the Patent Owner asserted that its single sentence disclosure of PLL coating as "the lynchpin[] of DNA microarray technology" that uses PLL to immobilize single-stranded DNA to solid supports in such arrays. Ex. 1003, pp. 96–97[.] The Patent Owner further asserted that its one sentence disclosure of coating a solid support with PLL, which included 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 single-stranded DNA using a PLL coated non-porous solid support results in an immobilized single-stranded DNA that necessarily will hybridize under appropriate hybridization conditions. Thus, the immobilized single-stranded DNA in Fish necessarily will be in hybridizable form according to the Patent Owner's own assertions.

Ex. 1002 ¶62.

It is true that the '197 patent describes, via a single sentence, PLL as an acceptable surface treatment for its invention. Ex. 1001, 11:37–39. It is also true that, during the prosecution of the '197 patent, Patent Owner touted that it invented the use of PLL to coat non-porous solid supports with ssDNA. Ex. 1003, 96–98. For example, Patent Owner argued to the Examiner the following:

> To recap, prior efforts to bind nucleic acids to non-porous materials were plagued by: 1) poor binding

> capacity and uniformity; 2) suppression of hybridization capability; and 3) nonspecific binding leading to high background (noise) signal. Applicants overcame these obstacles in large part *by developing surface treatments* that enabled nucleic acids for the first time to be specifically and uniformly fixed to the surfaces of non-porous solid supports in quantities sufficient to exhibit favorable kinetics. The uniformity of these non-porous solid supports, which stands in contrast to the nooks and crannies of porous supports in the prior art, allows for hybridization and detection of different nucleic acids under the same or similar hybridization and detection conditions.

Id. at 98 (emphasis added; footnotes omitted). Notably, the surface treatment that Patent Owner most touted was PLL. *See, e.g., id*. at 97 ("The advantages of the poly-L-lysine chemistry are that it requires no DNA modification, it is extremely cheap and, once perfected, it provides a highly consistent performance.") (quoting "Drs. Sean Grimmond and Andy Greenfield's Chapter 2, entitled 'Expression Profiling with cDNA Microarrays: A User's Perspective and Guide,' submitted in the above-captioned Application with Applicants' Communication of May 8, 2003.").

We find Petitioner's arguments regarding Patent Owner's admissions persuasive. Fish teaches binding the ssDNA to a non-porous solid support using PLL, which Patent Owner admits results in ssDNA being bound thereto in hybridizable form.

Nevertheless, Patent Owner argues that "no disclosure exists to establish that those bound nucleic acids [in Fish] were fixed in 'hybridizable form,' much less sufficient evidence to establish inherency." PO Resp. 10 (citing *Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1383 (Fed.

Cir. 2009); *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)). *Agilent* held that "[t]he very essence of inherency is that one of ordinary skill in the art would recognize that a reference unavoidably teaches the property in question." 567 F.3d at 1383. *Oelrich* similarly held that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." 666 F.2d at 581.

Patent Owner misapplies the law of inherency to argue, erroneously, that Petitioners were required to prove "that any bound nucleic acids in Fish would unavoidably hybridize to other nucleic acids." *See* PO Resp. 10. But, as discussed above, actual hybridization is not a requirement of any challenged claim. Thus, Petitioners are not required to prove that the ssDNA would "unavoidably hybridize" under the conditions present in Fish (or under any specific set of conditions).[14] Rather, the claims recite

---

[14] At oral argument, counsel for Patent Owner argued:

> [T]he petitioner's argument boils down in some respects to as long as you are doing or attempting to do a nucleic acid attachment that somehow, anyhow, involves poly-l-lysine, then it's necessarily going to result in a hybridizable form. And again, that's just not scientifically true. You could include, for example, nucleases in your attachment buffer. You could put all sorts of caustic acids or bases or something in there that are going to result in a nucleic acid that's not binding in hybridizable form. So there's no support for the assertion that including PLL in any manner in a nucleic acid attachment protocol is going to result in a nucleic acid being attached in hybridizable form.

Tr. 41:14–24. However, the Federal Circuit has held "that a product would be inherently anticipated where it was a natural result of the prior art process, even when it would be possible to prevent the formation of the

"hybridizable form," which the parties have stipulated means "*capable* of binding through Watson-Crick base pairing." (Emphasis added). Hence, what is required of Petitioners is proof that the ssDNA in Fish unavoidably has the capability to bind through Watson-Crick base pairing. Under our claim construction, the focus of this inquiry is on the form of the ssDNA when it is fixed or immobilized to the solid support, rather than the surrounding "conditions" in which that ssDNA might be present.

Petitioners have proven that such a capability is the inherent result of ssDNA being fixed or immobilized *to PLL-treated plastic*. Petitioners have proven this via Dr. Nelson's testimony, as well as the specification of the '197 patent and its prosecution history. *See* Ex. 1002 ¶64 (Dr. Nelson testifying that "the immobilized ssDNA in Fish necessarily is capable of hybridizing because it will hybridize when complementary DNA is present in appropriate hybridization conditions"); Ex. 1001, 11:37–39 ("Another technique for improving the fixing or uniformity of the plastic surface for fixing DNA involves treatment of the surface with polylysine (PPL)."); Ex. 1003, 96–98 (Patent Owner touting, during the prosecution of the '197 patent, its invention of using PLL to coat non-porous solid supports with ssDNA).

Petitioners have, therefore, shown that Fish anticipates independent claims 1, 6, 8, 9, 12–15, and 27.

---

product through 'extraordinary measures.'" *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 961 (Fed. Cir. 2014).

3. Application of Fish to the Challenged Dependent Claims

Each of 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 depends directly from at least one of the challenged independent claims. Patent Owner's only argument for these dependent claims is that they "are not anticipated by Fish at least because Petitioner did not establish that those claims' respective independent claims are anticipated by Fish." PO Resp. 22. That argument is not persuasive because Petitioner, in fact, has shown Fish anticipates the challenged independent claims, as discussed above.

As discussed below, Petitioners adequately show how the additional limitations recited in these claims are taught by Fish, as discussed next. *See* Pet. 30–33.

Dependent claims 32, 72, 226, and 227 recite that "said nonporous solid support comprises glass or plastic." Fish discloses supports having "plastic surfaces" and "polyvinyl surfaces" and also "polyvinvyl microtitration tray." Ex. 1006, Abstract, left col. ¶1, right col. ¶2; Ex. 1002 ¶68 (polyvinyl is plastic). Thus, Fish anticipates claims 32, 72, 226, and 227.

Dependent claims 33, 73, and 212 recite 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, claims 41, 225, and 233 recite that "said non-porous solid support" comprises "a plate or plates, a well or wells, a microtiter well or microtiter wells, or a depression or depressions." Fish meets these limitations because it discloses a non-porous solid support that has wells.

Ex. 1006, 536, left col., ¶1 ("Twenty-five microliter aliquots of the PLL solution were introduced into each well of a V-shaped polyvinyl microtitration tray."). Thus, Fish anticipates claims 33, 41, 73, 212, 225, and 233.

Dependent claims 34, 74, and 213 recite that the non-porous solid support is "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, 536, left col. ¶¶1–2, 539, Fig. 1 (caption). Thus, Fish anticipates claims 34, 74, and 213.

Dependent claims 61, 100, and 191 recite that "said nucleic acid is DNA." Fish discloses binding of ssDNA to PLL-coated microtitration trays. Ex. 1006, 536, left col. ¶¶1–2, 539, Fig. 1 (caption). Thus, Fish anticipates claims 61, 100, and 191.

Dependent claims 62, 69, and 193 recite that "said single-stranded nucleic acid is unlabeled." Fish does not describe, let alone require, that the single-stranded DNA is labelled. *See, e.g.*, Ex. 1006, 536, left col. ¶2 (discussing binding of poly-dA and poly-dC to the PLL-coated microtitration trays without describing the poly-dA or pol-dC as labelled). Thus, Fish anticipates claims 62, 69, and 193.

Dependent claims 63, 70, and 194 recite that "more than one single-stranded nucleic acid" is fixed or immobilized on the "non-porous solid support." Fish discloses binding two different single-stranded nucleic acids—poly-dA and poly-dC—on the PLL-coated microtitration trays. Ex. 1006, 536, left col. ¶2. Thus, Fish anticipates claims 63, 70, and 194.

Dependent claims 79, 219, and 236 recite that "the fixation or immobilization" to the non-porous solid support "is non-covalent." Dr.

Nelson testified that the binding of ssDNA to PLL-coated microtitration trays in Fish is non-covalent. Ex. 1002 ¶75. According to Dr. Nelson, 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.* As such, Fish necessarily discloses non-covalent binding of the single-stranded DNA to the PLL-coated microtitration trays.[15] Dr. Nelson's testimony is consistent with the '197 patent's use of polylysine to facilitate the fixation or immobilization of ssDNA to a solid support, and testimony offered by Dr. Buck, Patent Owner's declarant. *See* Ex. 1001, 11:37–39; Ex. 2042 ¶189. Although Dr. Buck's explanation expressly pertained to using gamma-aminopropyl-triethoxysilane as the surface treatment, the '197 patent states that polylysine can be used (Ex. 1001, 11:37–39), and the inventors touted "the advantages" of the latter surface treatment during prosecution of the '197 patent. Ex. 1002, 97. Petitioners have shown that Fish anticipates claims 79, 219, and 236.

C. Ground 2: Obviousness in View of Fish

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

---

[15] Dr. Nelson further testified that, although the ssDNA and the amine groups of the PLL potentially could bind covalently, they would only do so if the amine groups and/or the ends of the DNA strands are functionalized to cause covalent bonding. Ex. 1002 ¶75. Dr. Nelson noted that Fish does not disclose functionalizing either the PLL or the DNA strands. *Id*.

A claim is unpatentable "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). "Obviousness is a question of law based on underlying facts." *MobileMedia Ideas LLC v. Apple Inc.*, 780 F.3d 1159, 1167 (Fed. Cir. 2015), *cert. denied*, 136 S. Ct. 270 (2015). The underlying facts include (i) the scope and content of the prior art, (ii) the differences between the prior art and the claimed invention, (iii) the level of ordinary skill in the field of the invention, and (iv) any relevant objective considerations of nonobviousness that are presented. *Id.* (citing *Graham v. John Deere*, 383 U.S. 1, 17–18 (1966)). An additional underlying fact is whether there was a reason to combine prior art teachings when so asserted.[16] *Id.*

1. Claims 31, 68, and 192 as Obvious Over Fish

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." Petitioners argue that 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

[16] In other grounds, discussed below, Petitioners propose combining prior art teachings from multiple references.

same). Patent Owner argues that "Fish does not disclose a hybridization assay for the detection of nucleic acids. The purpose of Fish was the detection of anti-dsDNA antibodies and Fish provides no indication that the protocols described could be applicable to nucleic acid detection techniques involving hybridization." PO Resp. 24 (citations omitted).

We are persuaded by Petitioner, and not by Patent Owner. Petitioners' obviousness challenge is not premised on Fish teaching hybridization assays or that its technology could be applied to techniques involves hybridization. Rather, Petitioners' obviousness challenge is premised on the fact that 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." Ex. 1002 ¶78. What Petitioners rely on Fish for is its teaching of how to fix ssDNA to a PLL-treated non-porous solid support such that ssDNA is capable of binding to a complimentary genetic sequence through Watson-Crick base pairing. Pet. 35 ("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. Fish also inherently discloses that the fixed or immobilized nucleic acids are 'in hybridizable form.'").

Patent Owner also argues that a person of ordinary skill in the art "would have had no expectation that the methods described in Fish would result in the successful fixation of nucleic acids in hybridizable form." PO Resp. 25 (citing Ex. 2042 ¶¶92–117). The cited testimony spans twenty-five

paragraphs and seventeen pages of Dr. Buck's declaration and, for that reason alone, is not probative for that which it is cited. *Cf.* 37 C.F.R. § 42.104(b)(5) ("The Board may exclude or give no weight to the evidence where a party has failed to state its relevance or to identify specific portions of the evidence that support the challenge."). Additionally, the testimony is based on an erroneous interpretation of "hybridizable form." *See*, *e.g.*, Ex. 2042 ¶93 (interpreting "hybridizable form" as requiring certain "hybridizing conditions"). It is therefore not persuasive.

Patent Owner also argues that evidence of secondary considerations support non-obviousness of "the challenged claims." PO Resp. 67. The proffered evidence, however, is not probative of non-obviousness of claims 31, 68, and 192, let alone any other challenged claims.

Patent Owner argues commercial success based on $49.5 million in royalties collected from third-party defendants in settled litigation involving only the '197 patent. PO Resp. 67. But, Patent Owner does not provide any frame of reference for determining the significance of the royalty sum. *Cf. Vandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1567 (Fed. Cir. 1984) ("appellants failed to show how sales of the patented device compared to sales of their previous model, or what percentage of the market their new model commanded"). Moreover, Patent Owner does not link the settlement royalties to the inventions of claims 31, 68, and 192, as opposed to the inventions of their respective base claims—independent claims 1, 6, and 27—which are anticipated by Fish. *See J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) ("asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art").

Patent Owner also argues "at the time of the invention, experts were skeptical as to whether it was possible to attach nucleic acids to a non-porous solid support in hybridizable form." PO Resp. 67 (citing Ex. 2042 ¶¶239–41). But, as discussed above, the asserted prior art (Fish) taught this limitation.

Petitioners have shown that claims 31, 68, and 192 would have been obvious in view of Fish.

2. Claims 64, 101, and 195 as Obvious Over Fish

Claims 64, 101, and 195 recite that the fixed or immobilized "nucleic acid is RNA." With supporting testimony from Dr. Nelson, Petitioners explain 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 (citing Ex. 1002 ¶79). Dr. Nelson testified that it "would have been obvious to a person of ordinary skill in the art that the DNA immobilization technique disclosed in Fish could be used for binding RNA." Ex. 1002 ¶79. Dr. Nelson based his opinion on the similarity in the chemical structures of DNA and RNA. *Id*. In addition, we conclude that common sense would have led a person of ordinary skill in the art to contemplate adapting technology for binding ssDNA to a surface to applications of binding RNA to a surface. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

Patent Owner asserts that "Fish teaches away from the use of RNA." PO Resp. 27. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from

following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Patent Owner's purported explanation for teaching away is as follows:

> First, as explained above, Fish does not describe a successful method for fixing ssDNA in hybridizable form. (Ex. 2042 ¶¶ 92–117.) Second, to the extent any ssDNA was bound to the PLL-coated wells in Fish, Fish does not describe the chemistry involved in attaching DNA to a PLL-coated surface, so a POSITA would have had no basis to determine whether or not that chemistry could be applicable to RNA. (Ex. 2042 ¶ 134.) Thus, a POSITA would have had no reason to expect that Fish's methods would be successful when applied to RNA.

PO Resp. 27. Patent Owner's first point is erroneous—as discussed above, Fish does describe a successful method for fixing ssDNA in hybridizable form. Patent Owner's second point also is not persuasive. The fact that Fish does not explain that PLL could be used to fix RNA does not constitute discouragement from so using PLL. Fish does not teach away from using its fixation technology to fix RNA. *See Gurley*, 27 F.3d at 553.

It is also true that "a reference may teach away from a use when that use would render the result inoperable." *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1381 (Fed. Cir. 2007). Patent Owner appears to invoke this law, albeit without citing it, in arguing that "RNA could not be substituted for the DNA used in Fish to satisfy its intended purpose." PO Resp. 27. Patent Owner reasons that Fish is directed to the detection of dsDNA antibodies, and that such antibodies are not detectable using RNA. *Id*. This argument is not persuasive, however, because Petitioners' proposed

modification of the prior art is to use Fish's fixation technology to fix RNA to a surface, not to substitute RNA into Fish to improve Fish's detection of dsDNA antibodies. *See* Reply 10 (citing Ex. 1002 ¶79).

Petitioners have shown that claims 64, 101, and 195 would have been obvious in view of Fish.[17]

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

Petitioners contend 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

[17] As discussed above, Patent Owner offers secondary considerations evidence. *See* PO Resp. 67. However, for the same reasons identified above for claims 31, 68, and 192, Patent Owner's secondary considerations evidence is not probative of claims 64, 101, and 195 being non-obviousness.

sequences. *Id*.

Petitioners argue 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.

Patent Owner argues against obviousness by attacking the references individually. *See* PO Resp. 29 ("Gilham involves the reaction of RNA with aminoethylcellulose, a ***porous*** material, in aqueous solution with a carbodiimide activating agent for use in affinity chromatography. Gilham provides no evidence that this reaction could be performed on any other support, much less a non-porous solid support.") (citations omitted), 29–30 ("[A]s Fish does not disclose the chemistry by which nucleic acids are allegedly bound to the PLL-coated wells, a POSITA would not have known how to adjust the Fish protocol to bind nucleic acids by the periodate oxidation of 3' terminal cis diol group in RNA."), 30 ("Because Fish is directed to the use of dsDNA in detecting antibodies, RNA could not be used in the Fish experiments and the resulting combination would not satisfy the intended purpose of Fish."), 32 ("Fish is directed to the use of dsDNA in detecting anti-dsDNA antibodies, so the authors of Fish would not have been motivated to use RNA, which the chemistry used in Gilham requires."). However, such arguments are inapposite. *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.").[18]

Petitioners have shown that claims 38, 78, and 218 would have been obvious in view of Fish and Gilham.

E. Ground 4: Anticipation by VPK

Petitioners contend 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

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. Petitioners assert 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), Petitioners point 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*

[18] In this case, Petitioner bears the burden of persuasion to show that the challenged claims are unpatentable. 35 U.S.C. § 316(e). Regardless of who bears the burden to prove patentability/unpatentability in any particular proceeding, *Merck's* holding is applicable here because it speaks generally to the absence of probative value in attacking references individually when obviousness over a combination of references is at issue. *Merck*, 800 F.2d at 1097.

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), Petitioners argue 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, Petitioners argue that 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*.

Patent Owner argues that VPK is not prior art under either § 102(a) or (b). With respect to § 102(a), Patent Owner argues that the invention (as claimed in the challenged claims) was conceived and reduced to practice before VPK was published in October 1982. PO Resp. 39–54. With respect to § 102(b), Patent Owner argues that the challenged claims are entitled to the benefit of the '469 application's January 1983 filing date, which is not more than one year after VPK's October 1982 publishing. PO Resp. 33–39.

For the reasons explained below, we determine that VPK is prior art under at least § 102(b) and do not reach whether it is also prior art under § 102(a).

Pursuant to 35 U.S.C. § 120, "in 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." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1326 (Fed. Cir. 2008). The '197 patent references a chain of continuation and continuation-in-part applications that originates with the '469 application. The question before us is whether the '469 application contains a written description of the challenged claims. We conclude that it does not.

Each of the challenged claims recites, or incorporates by reference, a "non-porous solid support." Petitioners argue that the '469 application does not provide a written description of this limitation. Pet. 42–45. To do so, the '469 application "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (quoting *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989) (brackets added by *Ariad*)). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351.

As argued by Petitioners and not disputed by Patent Owner, the '469 application does not include the term "non-porous solid support." *See generally* Ex. 1004; Pet. 42; PO Resp. 32–39. Petitioners point out that the '469 application discloses "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.'" Pet. 42 (citing Ex. 1004, 24:14–22, 30:5–7, 52:31–37). Petitioners argue that the '469 "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." *Id*. (citing *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1346 (Fed. Cir. 2005); *see also id*. at 43 (citing *Purdue Pharma LP v. Faulding Inc*., 230 F.3d 1320, 1327 (Fed. Cir. 2000)).

In response, Patent Owner argues that the '469 application "discloses many examples of non-porous solid supports," yet Patent Owner identifies only the three examples that Petitioners concede are disclosed. *See* PO Resp. 35. Patent Owner further argues that "[t]hose examples, placed in the context of the entire description of the 1983 [i.e., '469] Application, would have indicated to a POSITA that the inventors had possession of the entire genus of non-porous solid supports." *Id*. In particular, Patent Owner relies on "fours aspects" of the '469 application. *Id*. We address each below,

Patent Owner describes the first "aspect" it relies on as follows:

> *First*, the 1983 Application describes that each of its examples of nonporous solid supports functions in the same way: to support a nucleic acid strand in hybridizable form ***on the surface*** of that example. (Ex. 1004, 24:14–22, 27:16–19, 29:1–12, 30:5–14, 31:29–32:1, 52:31–37; *see also* Ex. 2042 ¶ 156.) The fixation of the genetic material to the ***surfaces*** of those exemplary solid supports indicates that those solid supports are all non-porous—otherwise, the genetic material could, at least in part, be ***inside*** the support (*i.e.*, in a pore). (Ex. 2042 ¶¶ 156, 160–161.)

PO Resp. 35–36. In this argument, Patent Owner cites exclusively to examples of non-porous solid supports (*see* Ex. 1004, 24:14–22, 27:16–19, 29:1–12, 30:5–14, 31:29–32:1, 52:31–37) and assigns significance to the

fact that the '469 application does not mention any binding inside those supports "(i.e., in a pore)." PO Resp. 36. But it is a truism that there cannot be internal binding in those examples because such materials do not have pores. Thus, the absence of any discussion of internal binding as to those materials is insignificant. Patent Owner's argument is merely another way of pointing out that the '469 application discloses three solid support materials that happen to be non-porous.

Patent Owner describes the second "aspect" it relies on as follows:

> *Second*, a POSITA would have recognized from the 1983 Application that a non-porous solid support of ***many*** shapes can support a nucleic acid strand in hybridizable form on its surface. Dr. Dollie Kirtikar, one of the named inventors of both the 1983 Application and the '197 Patent, testified during prosecution that the chemistry of affixing a nucleic acid to glass or plastic would work the same way for any appropriately surface-treated glass or plastic, regardless of its shape. (Ex. 2002 ¶¶ 2, 7–8.) The specific geometry of the non-porous solid support, whether a well, depression, plate, cuvette, or tube, was not crucial to the practice of that invention. (*Id.* ¶¶ 8, 11; Ex. 2042 ¶¶ 157–159.)

PO Resp. 36 (footnote omitted). This argument is not probative of Patent Owner's contention that the '469 application provides written description support for the later-added "non-porous solid support" limitation. It merely speaks to the insignificance, in Patent Owner's view, of the shape of non-porous solid supports. Moreover, it relies on testimony from the inventor provided in 2003, and that testimony does not purport to interpret the disclosure of the '469 application, let alone from the perspective of a person of ordinary skill in the art as of 1983. *See* Ex. 2002.

Patent Owner describes the third "aspect" it relies on as follows:

> *Third*, a POSITA would understand from the 1983 Application that "glass plates provided with an array of depressions or wells," "polystyrene plates," "cuvettes," "glass tubes," and "polystyrene surfaces or wells" all function to prevent liquid from flowing through them, distinguishing those non-porous supports from porous materials, which permit liquid to flow through their pores. (Ex. 2042 ¶¶ 160–161.) For example, the 1983 Application describes depositing labeled nucleic acid probes, which would have been in solution, in the well of a glass plate for hybridization. (Ex. 1004, 24:19–22.)

PO Resp. 36–37. This argument is not probative of Patent Owner's contention that the '469 application provides written description support for the later-added "non-porous solid support" limitation. It merely demonstrates, unremarkably, that a person of ordinary skill in the art would know that non-porous materials do not leak.

Patent Owner describes the fourth "aspect" it relies on as follows:

> *Finally*, the specification of the 1983 Application describes "solid supports" generally, indicating that the inventors did not intend to limit their invention to the examples disclosed. (Ex. 1004, 1:11–15.) The 1983 Application also states, "[a]s will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations, modifications, and substitutions are possible in the practice of this invention, without departing from the spirit or scope thereof." (Ex. 1004, 35:1–5.)

Id. at 37. This argument is not probative of Patent Owner's contention that the '469 application provides written description support for the later-added "non-porous solid support" limitation. The '469 application discloses the

concept of "a solid support" (*see* Ex. 1004, 1:11) and it discloses examples of solid supports as discussed above. However, it does not disclose the concept of a "non-porous solid support" or otherwise "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *See Ariad*, 598 F.3d at 1351.

Petitioners have demonstrated by a preponderance of the evidence that the '469 application does not provide written description support for the challenged claims. Thus, because the challenged claims are not entitled to the benefit of the '469 application's filing date, VPK qualifies as prior art to the challenged claims under 35 U.S.C. § 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, 12–15, and 27) are of similar scope, and none of their differences is material in light of the VPK teachings on which Petitioners rely. Indeed, all of Patent

Owner's arguments for patentability of the challenged independent claims are common to all of the challenged independent claims. *See* PO Resp. 54–57. Accordingly, for the challenged independent claims, 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 meets 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 meets this limitation because it treats the glass slides with 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 is fixed or immobilized in hybridizable form to said non-porous solid support." VPK teaches chromosomes that are indirectly bound to the aminoalkylsilane-treated glass slides and then denatured into ssDNA, which is in hybridizable form, as evidenced by subsequent hybridization. Ex. 1008, 397 ("Summary"), 398 right col. ¶1, 399 left col. ¶¶2–3, 401 ¶ bridging left and right cols. and Figs. 2 and 3, 401–03 ¶ bridging pages 401 and 403, 403 left col. ¶¶1–4, 405 left col. ¶–right col. ¶1; Ex. 1002 ¶¶91–92. Patent Owner does not dispute that VPK teaches this binding. PO Resp. 55–57. Patent Owner argues, however, that VPK does not meet the limitation in question because the chromosomes in VPK are not bound *directly* to the aminoalkylsilane-treated glass slides. *See, e.g.*, PO Resp. 55–56 ("In VPK, the metaphase chromosomes (comprising nucleic acids) are contained inside

the nucleus . . . As a result, any binding that occurs between the cell and the glass slide does not involve the metaphase chromosomes."). Patent Owner's argument is inapposite in light of our construction of "fixed or immobilized" as meaning bound, whether directly or indirectly.

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 meets 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.").

Petitioners have shown that VPK anticipates independent claims 1, 6, 8, 9, 12–15, and 27.

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. Patent Owner argues that these dependent claims are not anticipated by VPK because Petitioners did not establish that those claims' respective independent claims are anticipated by VPK. PO Resp. 57. That argument is not persuasive because Petitioner, in fact, has shown VPK anticipates the challenged independent claims, as discussed above.

As discussed below, Petitioners adequately show how VPK meets the additional limitations recited in these dependent claims. *See* Pet. 49–51.

a) Claims 31, 68, and 192

Dependent 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." VPK discloses in situ hybridization and related procedures to "allow identification and localization of specific DNA sequences in human chromosomes by fluorescence microscopy." Ex. 1008, 397 ("Summary"). It further explains that "[w]ith this method the genes coding for 18S and 28S ribosomal RNA (rRNA) were localized on human metaphase chromosomes by in situ hybridization of 18S or 28S rRNA followed by an immunocytochemical incubation with specific anti-RNA–DNA hybrid antiserum." *Id*.; *see also id*. at 401 ¶ bridging left and right cols.

Patent Owner argues that VPK does not teach the limitation in question because, although VPK discloses a nucleic acid sequence complimentary to a sequence of interest, it discloses it only as a probe and not as part of a nucleic acid that is "fixed or immobilized" to the non-porous solid support. PO Resp. 57–59. Patent Owner's argument is not persuasive. At institution, we held: "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)." Inst. Dec. 22. No further argument or evidence has been presented post-institution that would persuade us to change that construction. Thus, VPK anticipates claims 31, 68, and 192.

b) Claims 32, 72, 226, and 227

Dependent claims 32, 72, 226, and 227 recite that "said non-porous solid support comprises glass or plastic." VPK discloses immobilization of metaphase chromosomes on glass slides. Ex. 1008, 398 right col. ¶1. Thus, VPK anticipates these claims.

c) Claims 34, 74, and 213

Dependent claims 34, 74, and 213 recite that the non-porous solid support is "treated with a surface treatment agent, a blocking agent, or both." VPK discloses treatment of glass slides with aminoalkylsilane prior to immobilization of metaphase chromosomes on the glass slides. Ex. 1008, 398 right col. ¶¶1–2. Thus, VPK anticipates these claims.

d) Claims 61, 100, and 191

Dependent claims 61, 100, and 191 recite that "said nucleic acid is DNA." The metaphase chromosomes in VPK are DNA. *See, e.g.*, Ex. 1008, 397 ("Summary" referring to "specific DNA sequences in human chromosomes"). Thus, VPK anticipates these claims.

e) Claims 62, 69, and 193

Dependent claims 62, 69, and 193 recite that "said single-stranded nucleic acid is unlabeled." VPK does not describe, let alone require, that the denatured metaphases chromosomes are labelled. *See generally* Ex. 1008. In fact, VPK implies that such *single-stranded* DNA is unlabeled, as VPK teaches labeling by using labeled antibodies. *Id*. at 400 right col. ¶¶1–3. Thus, VPK anticipates claims 62, 69, and 193.

f) Claims 63, 70, and 194

Dependent claims 63, 70, and 194 recite that "more than one single-stranded nucleic acid" is fixed or immobilized on the "non-porous solid support." VPK discloses using human lymphocytes, which would have 46 chromosomes, and explicitly discloses in situ hybridization of multiple "human lymphocyte metaphase chromosomes." Ex. 1008, 401 ¶2; *see also id*. at 402 Figs. 2 and 3. Thus, VPK anticipates claims 63, 70, and 194.

g) Claims 79, 219, and 236

Dependent claims 79, 219, and 236 recite "wherein said fixation or immobilization to said non-porous . . . solid support is non-covalent." Petitioners argue that this limitation is inherently disclosed by VPK because "[t]he binding of chromosomes to the aminoalkylsilane-treated glass slides necessarily would be non-covalent." Pet. 51 (citing Ex. 1002 ¶101). Petitioners provide an adequate explanation why this is so, with supporting testimony from Dr. Nelson. *Id*. (citing Ex. 1002 ¶101). Patent Owner does not dispute that the binding in VPK is non-covalent. PO Resp. 60. We find VPK anticipates claims 79, 219, and 236.

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

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

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

Dependent 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, dependent claims 41, 225, and 233 recite that the non-porous solid support "comprises 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. Petitioners present 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 (citing Ex. 1002 ¶112).

Patent Owner does not dispute that Metzgar teaches glass slides having wells or depressions. PO Resp. 66. Patent Owner, however, does dispute Petitioner's proffered reason for why a person of ordinary skill in the art would have combined that teaching of Meztgar with the teachings of VPK. Patent Owner's argument is as follows:

> In the [Institution] Decision, the Board concluded that Petitioner presents an adequate reason for why a POSITA would perform the in situ procedure of VPK on the glass slides having wells or depressions as taught by Metzgar: "in order to analyze multiple samples or analytes simultaneously on the same glass slide." (Decision, 23 (citing Pet. 57.)

> However, the record now available to the Board shows that, to the contrary, a support with wells or depressions would not serve the intended purpose of VPK's hybridization to a cell fixed *in situ*, which is to identify and locate a nucleic acid sequence of interest on the chromosomes within a cell.

PO Resp. 66 (citing (Ex. 1008, "3"; Ex. 2042 ¶¶234–36.)).

Patent Owner's argument is conclusory and not sufficiently developed in the Patent Owner Response. *See* PO Resp. 66. In the testimony to which Patent Owner cites, however, some detail is provided in that Dr. Buck states that "a non-porous support comprising wells or depressions would be pointless for *in situ* hybridization, as the cell in situ by itself provides a defined area in which the target nucleic acids reside." Ex. 2042 ¶235. In view of this cited testimony, Patent Owner's argument appears to be that a person of ordinary skill in the art would be interested in the chromosomes of only a single cell or the cells of only a single source or donor. That premise is not supported by Patent Owner. And, as Petitioners argue in their Reply, it "fails to address [Petitioners'] position that there would have been motivation to use Metzgar's glass slides to analyze multiple cell samples simultaneously on the different wells or depressions of Metzgar's glass slide." Reply 23 (citing Ex.1002 ¶112).

Petitioners have shown that claims 33, 41, 73, 212, 225, and 233 would have been obvious over VPK and Metzgar.[19]

---

[19] As discussed above, Patent Owner offers secondary considerations evidence. *See* PO Resp. 67. However, for the same reasons identified above for claims 31, 68, and 192, Patent Owner's secondary considerations evidence is not probative of claims 33, 41, 73, 212, 225, and 233 being non-obviousness.

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

Petitioners contend 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. Each of these claims depends from at least one of independent claims 1, 6, and 27. Claims 16, 222, and 230 add that "said fixation or immobilization is not to a cell fixed in situ to said non-porous solid support." Claims 38 and 78 add that "said fixation or immobilization to said non-porous solid support is covalent," and claim 218 similarly add that "said fixation or immobilization to said non-porous glass or non-porous plastic solid support is covalent." Claims 64, 101, and 195 add that "said nucleic acid is RNA."

1. Disclosure of Noyes and Ramachandran

Noyes discloses covalent (and direct) bonding 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, and Ramachandran to Claims 16, 38, 64, 78, 101, 195, 218, 222, and 230

Petitioners argue that a person of ordinary skill in the art would have

combined the relied-upon teachings of Noyes, VPK, and Ramachandran and map those teachings to claims 16, 38, 64, 78, 101, 195, 218, 222, and 230. Pet. 52–55. As for the reason to combine the prior art teachings, Petitioner asserts that a person of ordinary skill in the art would have: (1) "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"; (2) "readily understood that nucleic acids can be covalently bound to the glass slides of VPK by first modifying the surface of the glass slides with aryl amines, which can be diazotized and covalently linked to nucleic acid strands"; (3) "readily and reasonably expected to use the procedure disclosed in Ramachandran to convert the alkylamines on the glass slides of VPK to arylamines"; and (4) "reasonably expected to covalently bind nucleic acids to the glass slides of VPK by diazotizing the arylamines as taught by Noyes." Pet. 52–53 (citing Ex. 1002 ¶¶105–07).

Claims 16, 222, and 230 recite that "said fixation or immobilization is not to a cell fixed in situ to said non-porous solid support." With respect to these claims, Petitioner argues that a person of ordinary skill in the art

> would have been motivated, with a reasonable expectation of success, to immobilize the DNA or RNA of Noyes *directly* on easy-to-use, non-porous supports, such as the alkylamine-treated glass slides disclosed in VPK, by first converting the alkylamines to arylamines (as in Ramachandran), diazotizing the arylamines (as in Noyes) and then binding the single stranded DNA and RNA to the arylamines (as in Noyes).

Pet. 54 (citing Ex. 1002 ¶108). We find that Petitioner has articulated

sufficient reasoning, as quoted above, why a person of ordinary skill in the art would have combined the asserted prior art in a manner that falls within the scope of claims 16, 222, and 230, including the requirement that the fixation or immobilization is "not to a cell fixed in situ" to the non-porous solid support.

Claims 38, 78, and 218 recite that "said fixation or immobilization to said non-porous [] solid support is covalent." With respect to these claims, Petitioner argues that a person of ordinary skill in the art

> would have been motivated, with a reasonable expectation of success, to immobilize DNA or RNA on easy-to-use, non-porous supports, such as the alkylamine-treated glass slides of VPK, by first converting the alkylamines to arylamines (as in Ramachandran), diazotizing the arylamines (as in Noyes) and then *covalently* binding the single stranded DNA and RNA to the arylamines (as in Noyes).

Pet. 55 (citing Ex. 1002 ¶109). We find that Petitioner has articulated sufficient reasoning, as quoted above, why a person of ordinary skill in the art would have combined the asserted prior art in a manner that falls within the scope of claims 38, 78, and 218, including the requirement that the fixation or immobilization to the non-porous solid support "is covalent."

Claims 64, 101, and 195 recite that "said nucleic acid is RNA." With respect to these claims, Petitioner argues that a person of ordinary skill in the art "would have readily and reasonably expected to immobilize RNA on the glass slides of VPK by using the procedures disclosed by Noyes and Ramachandran." Pet. 55 (citing Ex. 1002 ¶110). We find that Petitioner has articulated sufficient reasoning, as quoted above, why a person of ordinary

skill in the art would have combined the asserted prior art in a manner that falls within the scope of claims 64, 101, and 195, including the requirement that the bound nucleic acid "is RNA."

In opposition to Petitioner's challenge, Patent Owner presents two arguments, both of which are directed to all of claims 16, 38, 64, 78, 101, 195, 218, 222, and 230. Patent Owner argues that Petitioner has not shown (1) that the asserted prior art meets the "hybridizable form" limitation common to all of claims 16, 38, 64, 78, 101, 195, 218, 222, and 230 or (2) that the prior art would have been combined by a person of ordinary skill in the art in the manner asserted by Petitioner. PO Resp. 60–65.

With respect to the "hybridizable form" limitation, Patent Owner argues that, in the asserted combination, any nucleic acids that covalently bind to the glass surface would do so via certain bases, specifically guanine, thymine, and uracil, "rendering those bases unavailable to bind to the corresponding Watson-Crick bases of a second nucleic acid through hybridization," which "would hinder or prevent hybridization entirely." PO Resp. 62 (citing Ex. 2042 ¶¶226–27). On its face, this argument is equivocal, as Patent Owner argues, in the alternative, that hybridization of such nucleic acids would be *hindered but not prevented*. *Id*. The testimony of Dr. Buck that Patent Owner relies on for this argument is equally equivocal. *See* Ex. 2042 ¶227 ("Therefore, covalent attachment of multiple bases to a solid support could hinder or even prevent hybridization entirely.").

Moreover, Dr. Buck's testimony cites exclusively to Noyes, yet Noyes does not support his ultimate conclusion that the combination would lack covalently bound nucleic acids in "hybridable form." *See* Ex. 2042 ¶¶226–

27 (citing Ex. 1007, 1, 2, 4, 6). In fact, as pointed out by Petitioner, Noyes "shows successful hybridization of RNA and ssDNA covalently bound to cellulose via primary aryl amino groups that have been diazotized." Reply 24 (citing Ex.1002 ¶104). The testimony of Dr. Nelson on which Petitioners rely is supported by Noyes. *See* Ex. 1002 ¶104 (citing Ex. 1007, 301 left col. ("Summary"), right col. ¶2, 303, 304 ¶1). We are persuaded that the asserted combination would meet the "hybridizable form" limitation and all other limitations of claims 16, 38, 64, 78, 101, 195, 218, 222, and 230.

Patent Owner next argues that a person of ordinary skill in the art would not combine the prior art teachings as asserted by Petitioners because doing so "would impermissibly destroy the objectives of the references." PO Resp. 62. But, Patent Owner's examples of how the objectives of the references would be destroyed are not commensurate with the combination Petitioners assert. For example, Patent Owner argues that the asserted combination would destroy "the objective of VPK" because VPK seeks "[t]o provide visual 'identification and localization of specific DNA sequences in human chromosomes by fluorescence microscopy'" which requires that the chromosomes remain intact inside the cells. *Id*. at 62–63 (citing Ex. 1008, 12; Ex. 2042 ¶216.).[20] But, in this ground, Petitioners do not rely on VPK for its chromosome-intact DNA sequencing. In this ground, Petitioners rely on VPK merely for its aminoalkylsilane-treated glass slides. *See* Pet. 52–53.

[20] Although Patent Owner did not cite to page 397 of Exhibit 1008, that page is where the language Patent Owner quotes is found. *See* PO Resp. 62–63; Ex. 1008, 397 (Summary).

Petitioners have shown that claims 16, 38, 64, 78, 101, 195, 218, 222, and 230 would have been obvious Noyes, VPK, Metzgar, and Ramachandran.

III. MOTIONS TO EXCLUDE

Petitioners moved to exclude the following evidence introduced by Patent Owner: Exhibits 2035 and 2037–2041 in their entirety; paragraphs 3–10, 12, 14, 16, and 17 of Exhibit 2043; and paragraphs 146 and 165–181 of Exhibit 2042. Paper 45, 1. Collectively, this evidence is relied on by Patent Owner to prove that VPK is not prior art under 35 U.S.C. § 102(a). As discussed above, we do not reach that issue, as Petitioners have shown that VPK is prior art under § 102(b). Accordingly, this Decision does not rely on any of the evidence Petitioners seek to exclude. Petitioners' Motion to Exclude is, therefore, moot.

Patent Owner moved to exclude the following evidence introduced by Petitioners: paragraphs 3 and 5 of Exhibit 1037 and "Attachment A" appended to Exhibit 1037. Paper 43, 3. This evidence is cited by Petitioners in their Reply to support their reliance, in the Petition, on Exhibits 1021 and 1032. *See* Reply 7 n.1. This Decision does not rely on Exhibit 1037 (or Exhibits 1021 and 1032). Thus, Patent Owner's Motion to Exclude is also moot.

IV. CONCLUSION

Petitioners have shown by a preponderance of the evidence that all of the challenged claims of the '197 patent are unpatentable.

V. ORDER

Accordingly, it is

ORDERED that 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 are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is dismissed as moot;

FURTHER ORDERED that Petitioners' Motion to Exclude is dismissed as moot; and

FURTHER ORDERED that, because this Decision is final, a party to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

For Petitioner:

M. Paul Barker
Paul.barker@finnegan.com

Jamie Wisz
Jamie.wisz@wilmerhale.com

Arpita Bhattacharyya
Arpita.bhattacharyya@finnegan.com

Heather Petruzzi
Heather.petruzzi@wilmerhale.com

For Patent Owner:

Kevin McNish
kmcnish@desmaraisllp.com

Trials@uspto.gov
571-272-7822

Paper 48
Date: October 2, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOLOGIC, INC. and BECTON, DICKINSON AND COMPANY,
Petitioners,

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*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a)

I. INTRODUCTION

The original sole Petitioner in this *inter partes* review, Hologic, Inc. ("Hologic"), 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 ("the challenged claims") 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."). In an October 14, 2016, Decision, we granted the Petition. Paper 8 ("Inst. Dec.").

During trial, Becton, Dickinson and Company ("Becton") was joined as co-petitioner. Paper 31. Hologic and Becton are hereafter referred to collectively as "Petitioners."

Patent Owner filed a Patent Owner Response (Paper 19, "PO Resp.") to which Petitioners filed a Reply (Paper 33, "Reply"). Both sides filed Motions to Exclude. *See* Papers 39, 41. Both sides requested a hearing for oral arguments, and a consolidated hearing for this *inter partes* review and Case IPR2016-00820 was held June 1, 2017. A transcript of the hearing appears in the record. *See* Paper 47 ("Tr.").

As discussed below, Petitioners have shown by a preponderance of the evidence that all of the challenged claims are unpatentable.

A. Related Matters

Co-petitioner Hologic successfully petitioned for two *inter partes* reviews of claims of the '197 patent—the instant proceeding and Case IPR2016-00820. Co-petitioner Becton also filed two petitions for *inter partes* reviews of the '197 patent, along with motions to join the already

instituted Hologic-petitioned *inter partes* reviews. *See* IPR2017-00172; IPR2017-00181. Becton's petitions were denied, but Becton was joined as co-petitioner in this proceeding and as well as in Case IPR2016-00820. *See* Paper 31; IPR2016-00820, Paper 32.

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 22, 1.

B. The '197 Patent

The '197 patent relates generally to the detection of genetic material by polynucleotide or oligonucleotide probes. Ex. 1001, 1:23–24, 5:43–46. The '197 patent refers to the genetic 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. In the challenged independent claims, the recited analytes are

"single-stranded nucleic acids." *Id*. at cls. 17, 19, and 25. "Analytes in a biological sample are preferably denatured into single-stranded form, and then directly fixed to a suitable solid support." *Id*. at 5:61–63. 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 cl. 17 (reciting a "non-porous solid support"). To obtain fixation (or binding) to the non-porous solid support, the '197 patent teaches treating the surface of the support with a chemical such as polylysine. *Id*. at 11:37–39.

> 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

Petitioners challenge 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 challenged claims, several of which are in multiple dependent form, depend directly from at least one of independent claims 17, 19, and 25.

D. Grounds of Unpatentability Tried

We instituted trial on 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, 150, 152, 178, 180, 186, and 187

[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

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

Inst. Dec. 26.

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).

[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).

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)).

In our Institution Decision, we expressly construed three terms, recited in each of independent claims 17, 19, and 25: "array"; "fixed or immobilized"; and "hybridizable form." First, we construed "array" to mean "an orderly grouping or arrangement," as both sides had proposed. Inst. Dec. 8; *see also* Pet. 14; Prelim. Resp. 22; Ex. 1010, 8. Second, we construed "fixed or immobilized" to mean "bound," as both sides had proposed. Inst. Dec. 8; *see also* Pet. 9; Prelim. Resp. 13 n.2; Ex. 1010, 13–15. Third, we construed "hybridizable form" to mean a form "capable of binding through Watson-Crick base pairing," as both sides had proposed. Inst. Dec. 9; *see also* Pet. 13; Prelim. Resp. 11; Ex. 1010, 5.

The parties now dispute what their stipulated constructions of "array" and "hybridizable form" encompass. Accordingly, we provide additional

clarification below.

1. "array"

All of the challenged independent claims recite an "array." For example, claim 17 recites: "An *array* comprising various single-stranded nucleic acids fixed or immobilized in hybridizable form to a non-porous solid support." (Emphasis added).[9]

Prior to institution, the parties agreed that an "array" is "an orderly grouping or arrangement." Pet. 14; Prelim. Resp. 22. In our Institution Decision, we applied that agreed-upon meaning. Inst. Dec. 8. For example, we found "Fish explicitly describes rows of wells on the tray, which are sufficient to constitute an orderly grouping or arrangement." *Id*. at 11–12.

Although neither side opposes our construction post-institution, a dispute remains as to what that construction encompasses. For example, to meet this term in the Fish-based grounds, Petitioners cite to Fish's disclosure

---

[9] The term "array" appears in claims 17, 19, and 25 in their preambles only, and, thus, is not necessarily a limitation. *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). However, Petitioners do not argue that "array" is not a limitation and, by mapping the asserted prior art to it, Petitioners imply that it is a limitation. *See, e.g.*, Pet. 17–18. Petitioners bear "the burden of proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e). Also, their Petition must explain "[h]ow the challenged claim is to be construed" and "[h]ow the construed claim is unpatentable under the statutory grounds identified." 37 C.F.R. § 42.104(3)–(4). The Petition does not explain how the claims are unpatentable having their preambles construed as non-limiting. Accordingly, for purposes of this Decision, we treat "array" as a limitation of the challenged claims.

of microtitration trays having a plurality of wells arranged in rows. *See, e.g.*, Pet. 17 (citing Ex. 1006, 536 left col. ¶1).[10] Patent Owner responds, citing cross-examination testimony of Petitioners' declarant, that an array requires an orderly grouping or arrangement of nucleic acids, such that the whereabouts of each nucleic acid is known. *See* PO Resp. 20 ("Dr. Nelson explained that in the context of nucleic acid analysis in the early 1980s, an 'array' would comprise an 'orderly arrangement ***of nucleic acids***,' meaning a 'pattern' in which 'the whereabouts of each nucleic acid is known.'") (citing Ex. 2117, 43:3–13, 44:17–45:12, 46:7–14).

Thus, Petitioners apply the term "array" as satisfied by, for example, an orderly arrangement *of wells*, whereas Patent Owner applies the term "array" as requiring an orderly arrangement *of nucleic acids* (and further such that the whereabouts of each nucleic acid is known). The '197 patent uses the term consistent with Petitioners' application and inconsistent with Patent Owner's application. *See* Ex. 1001, 8:66–67 (referring to "an array *of wells or depressions*," not an array of nucleic acids) (emphasis added); *see also id*. at Abstract ("Nucleic acids are fixed or immobilized to non-porous solid supports (substrates), and include systems containing *such supports and arrays* with fixed or immobilized nucleic acids."). The cross-examination testimony on which Patent Owner relies (i.e., Ex. 2117, 43:3–13, 44:17–45:12, 46:7–14) does not appear to account for this intrinsic evidence.

---

[10] 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.

Accordingly, we reject Patent Owner's application of the term "array" as requiring an orderly grouping or arrangement of nucleic acids, such that the whereabouts of each nucleic acid is known. The term "array" as used in the challenged claims includes an orderly grouping or arrangement of wells or depressions. Other language in the challenged claims ultimately requires the array to comprise single-stranded nucleic acids. *See*, *e.g.* Ex. 1007, cl. 19 ("An array comprising single-stranded nucleic acids fixed or immobilized in hybridizable form to a non-porous solid support."). But, the term "array" itself does not require an orderly grouping or arrangement of nucleic acids.

2. "hybridizable form"

All of the challenged independent claims recite "hybridizable form." For example, claim 17 recites: "An array comprising various single-stranded nucleic acids fixed or immobilized in *hybridizable form* to a non-porous solid support." (Emphasis added).

Prior to institution, the parties agreed that "hybridizable form" means "capable of binding through Watson-Crick base pairing." Pet. 13 (citing Ex. 1001, 2:22–34); Prelim. Resp. 11[11]; *see also* Ex. 1010, 5 (*Markman* order applying same construction). In our Institution Decision, we gave it the agreed-upon meaning. Inst. Dec. 8–9. Although neither side opposes

[11] Patent Owner's proffered construction additionally added 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. *See* Ex. 1001, 2:22–29.

that construction post-institution, a dispute remains as to the meaning of the construction to which the parties agreed and we adopted. *See, e.g.*, Pet. 23 (mapping Fish's ssDNA bound to poly-L-lysine ("PLL")-treated plastic to the hybridizable form limitation); PO Resp. 10 ("Fish fails to disclose sufficient information regarding the various factors and conditions that affect hybridization to allow a POSITA to determine whether any bound ssDNA would be capable of hybridizing with other nucleic acids."); Reply 8 ("Enzo also focuses on hybridization conditions, even though its claims lack such a requirement.").

We maintain our construction that "hybridizable form" means "capable of binding through Watson-Crick base pairing." However, in response to Patent Owner's post-institution arguments for patentability over the Fish-based grounds, we provide some clarifications.

a) The Limitation "hybridizable form" is not Synonymous with the Limitation "single-stranded"

The limitation "hybridizable form" pertains to the form of the "single-stranded nucleic acids" as fixed or immobilized to the non-porous solid support. This means that single-stranded nucleic acids must be bound to the solid support in a manner that renders them capable of binding to complementary sequences through Watson-Crick base pairing. To be so capable, single-stranded nucleic acids must be single-stranded *and* have bases available for base-pairing.

Patent Owner argues that something more must be required of "hybridizable form" because otherwise "every 'single-stranded' nucleic acid necessarily exists in 'hybridizable form.'" PO Resp. 12. Patent Owner elaborates as follows:

> [Petitioners' declarant, Norman Nelson, Ph.D.,] simply assumes that ***any*** single-stranded nucleic acid is capable of Watson-Crick base pairing—and therefore hybridization—regardless of existing conditions. In fact, Dr. Nelson testified that he could not think of a single example of a single-stranded nucleic acid bound to a solid support that would not be capable of Watson-Crick base pairing. (Nelson Tr. [Ex. 2117] 39:15–41:1.) Petitioner's inherency argument reads out the language "in hybridizable form," contravening even the broadest reasonable construction which must attribute some meaning to that claim language. Thus, Dr. Nelson's opinions not only lack any supporting analysis or facts, they erroneously render the claim limitation "hybridizable form" meaningless. *Haemonetics Corp. v. Baxter Healthcare Corp*., 607 F.3d 776, 781 (Fed. Cir. 2010).

PO Resp. 12. Patent Owner's argument is not persuasive.

We are not applying our construction of "hybridizable form" in a manner that would render meaningless "single-stranded." Patent Owner's own declarant, Dr. Buck, testified that whether a single-stranded nucleic acid bound to a solid support is in hybridizable form depends on its "attachment methodology and chemistry." Ex. 2142 ¶94. Dr. Buck elaborated as follows:

> For example, the way in which a single-stranded nucleic acid is bound to a solid support will have a large impact on whether or not that nucleic acid is capable of hybridizing with a complementary sequence. A single-stranded nucleic acid may be bound to a support in a way that renders it incapable of hybridizing with a complementary nucleic acid strand.

Id. at ¶95; *also compare id*. at ¶238, *with id*. at ¶239.

In other words, if, for example, a single-stranded nucleic acid were bound to a solid support via all of its bases, the bases would not be available to pair with a complimentary sequence of bases on a probe. Thus, despite being single-stranded, the nucleic acid, with its bases bound to the solid support, would not be in a form that renders it capable of further binding through Watson-Crick base pairing. Hence, the nucleic acid would not be fixed or immobilized in "hybridizable form" despite being single-stranded.[12]

Accordingly, our construction of "hybridizable form" as "capable of binding through Watson-Crick base pairing" does not render meaningless the term "single-stranded."

b) The Limitation "hybridizable form" Modifies Single-Stranded Nucleic Acids, Not Unclaimed Aspects of the Surrounding Environment

Whether single-stranded nucleic acids are fixed or immobilized in "hybridizable form" depends on the form of the single-stranded nucleic acids when bound to the support, but not on unclaimed aspects of the surrounding environment (e.g., temperature, pH, concentration, etc.)—termed "factors and conditions" by Patent Owner. *See* PO Resp. 9–12.

Patent Owner argues that the challenged claims require the presence of certain "factors and conditions affecting hybridization" to satisfy the "hybridizable form" limitation. *See, e.g.*, PO Resp. 9 ("Fish does not disclose sufficient information about the various factors and conditions

[12] Although Petitioners' declarant, Dr. Nelson, could not identify a way to bind a single-stranded nucleic acid to a solid support in a form that would not be capable of Watson-Crick base pairing (Ex. 2117, 40:8–41:1), Patent Owner's declarant, Dr. Buck, testified that such a form could exist. Ex. 2142 ¶¶94–95, 239.

affecting hybridization for a POSITA to determine whether the ssDNA in the Fish experiments would hybridize if complementary DNA were present."). But, the challenged claims do not require actual hybridization; they require only the *capability* to hybridize. And that capability, per the claim language, is met by the "form" of the single-stranded nucleic acids when bound to the support, and not by extraneous factors and conditions such as a solution in which the single-stranded nucleic acids may be present.

This is not to say that a solution's temperature, pH, solute, solvent, etc. cannot affect whether single-stranded nucleic acids will ultimately hybridize through Watson-Crick base pairing. It is merely to say that we look to the form of single-stranded nucleic acids, rather than other unspecified factors or conditions of the surrounding environment, in determining whether those single-stranded nucleic acids are hybridizable. As such, the challenged claims are not limited by any particular hybridization factors or conditions. For example, the concentration of complimentary probes within a solution surrounding single-stranded nucleic acids may affect whether or how quickly the single-stranded nucleic acids hybridize with complimentary probes, but the concentration of complimentary probes does not affect the status of whether the single-stranded nucleic acids are in "hybridizable form."

In light of the specification and the parties' stipulation (*see* Pet. 13; Prelim. Resp. 11), we construe "hybridizable form" as meaning that the single-stranded nucleic acids are bound to the non-porous solid support in a form that renders them capable of binding through Watson-Crick base pairing, which, in turn, means that they have bases available for base-pairing.

B. Ground 1: Anticipation by Fish

Petitioners contend that claims 17, 19, 25, 105, 106, 114, 116, 119, 128, 129, 150, 152, 178, 180, 186, and 187 are anticipated by Fish.

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. 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. *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 the following:

> [N]uclease S_1 treatment had no effect on the binding of SLE Ig[13] 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 the Challenged Independent Claims

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 the same because it discloses microtitration trays having wells of ssDNA (i.e., the mixture of poly-dA and poly-dC and also the denatured calf thymus DNA) arranged in rows. Ex. 1006, 536, left col. ¶¶1–2. Patent Owner argues that "a container by itself cannot meet the 'array' limitation of the challenged claims." PO Resp. 20. This argument is not persuasive. The containers of

---

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

Fish to which Petitioners cite have "rows" of "wells," and, thus, an orderly grouping or arrangement of wells. Ex. 1006, 536, left col. ¶¶1–2.

Claims 17 and 19 recite a "non-porous solid support," and claim 25 recites "a non-porous solid support having wells or depressions." Fish meets these limitations because its microtitration trays are polyvinvyl (Ex. 1006, 536, left col. ¶1), which material is plastic and non-porous according to unrebutted testimony of Norman Nelson, Ph.D. Ex. 1002 ¶¶38, 40–42.

Claims 17, 19, and 25 recite "*single-stranded* nucleic acids fixed or immobilized . . . to a non-porous solid support." (Emphasis added). Fish 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 ¶55 (Dr. Nelson: "[T]he 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."). In fact, Fish explicitly refers to "**[s]ingle stranded DNA coated trays**" and "single-stranded nucleic acids, bound to the PLL treated plastic." Ex. 1006, 536, left col. ¶2, 538, right col. ¶1. Fish meets this limitation.

Patent Owner argues that Fish does not meet this limitation because "Fish does not describe any experiments that tested, let alone confirmed, whether single-stranded nucleic acids actually bound to the disclosed PLL-coated wells." PO Resp. 4 (citing Ex. 2142 ¶¶ 68–91). But that is a straw man argument. The fact that the Fish researchers may not have performed testing to confirm that ssDNA was bound to the PLL-coated wells does not negate that they nonetheless *described* ssDNA bound to PLL-coated wells. *See* 35 U.S.C. § 102(a)–(b) ("A person shall be entitled to a patent unless —

(a) the invention was known or used by others in this country, or patented *or described* in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or (b) the invention was patented *or described* in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.") (emphasis added).

Further, and as we stated in the Institution Decision:

> [I]t 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.").

Inst. Dec. 12–13. Patent Owners have not presented any argument or evidence post-institution that would change our reading of Fish.

Petitioners have persuaded us that Fish teaches the limitation of claims 17, 19, and 25 of "single-stranded nucleic acids fixed or immobilized . . . to a non-porous solid support."

Claims 17, 19, and 25 recite "single-stranded nucleic acids fixed or immobilized *in hybridizable form* to a non-porous solid support." (Emphasis added). Petitioners argue 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 addition to the cited testimony, Petitioners also rely on certain "admissions made by the Patent Owner." *Id*. at 23 (citing Ex. 1002 ¶¶62, 64). Dr. Nelson, Petitioners' declarant, explains the alleged admissions, with citations to the prosecution history of the '197 patent, as follows:

> [T]he Patent Owner asserted that its single sentence disclosure of PLL coating as "the lynchpin[] of DNA microarray technology" that uses PLL to immobilize single-stranded DNA to solid supports in such arrays. Ex. 1003, pp. 96–97[.] The Patent Owner further asserted that its one sentence disclosure of coating a solid support with PLL, which included 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 single-stranded DNA using a PLL coated non-porous solid support results in an immobilized single-stranded DNA that necessarily will hybridize under appropriate hybridization conditions. Thus, the immobilized single-stranded DNA in Fish necessarily will be in hybridizable form according to the Patent Owner's own assertions.

Ex. 1002 ¶64.

It is true that the '197 patent describes, via a single sentence, PLL as an acceptable surface treatment for its invention. Ex. 1001, 11:37–39. It is also true that, during the prosecution of the '197 patent, Patent Owner touted that it invented the use of PLL to coat non-porous solid supports with ssDNA. Ex. 1003, 96–98. For example, Patent Owner argued to the Examiner the following:

> To recap, prior efforts to bind nucleic acids to non-porous materials were plagued by: 1) poor binding capacity and uniformity; 2) suppression of hybridization capability; and 3) nonspecific binding leading to high background (noise) signal. Applicants overcame these obstacles in large part *by developing surface treatments* that enabled nucleic acids for the first time to be specifically and uniformly fixed to the surfaces of non-porous solid supports in quantities sufficient to exhibit favorable kinetics. The uniformity of these non-porous solid supports, which stands in contrast to the nooks and crannies of porous supports in the prior art, allows for hybridization and detection of different nucleic acids under the same or similar hybridization and detection conditions.

Id. at 98 (emphasis added; footnotes omitted). Notably, the surface treatment that Patent Owner most touted was PLL. *See, e.g.*, *id*. at 97 ("The advantages of the poly-L-lysine chemistry are that it requires no DNA modification, it is extremely cheap and, once perfected, it provides a highly consistent performance.") (quoting "Drs. Sean Grimmond and Andy Greenfield's Chapter 2, entitled 'Expression Profiling with cDNA Microarrays: A User's Perspective and Guide,' submitted in the above-captioned Application with Applicants' Communication of May 8, 2003.").

We find Petitioners' arguments regarding Patent Owner's admissions persuasive. Fish teaches binding the ssDNA to a non-porous solid support using PLL, which Patent Owner admits results in ssDNA being bound thereto in hybridizable form.

Nevertheless, Patent Owner argues that "no disclosure exists to establish that those bound nucleic acids [in Fish] were fixed in 'hybridizable form,' much less sufficient evidence to establish inherency." PO Resp. 9

(citing *Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1383 (Fed. Cir. 2009); *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)). *Agilent* held that "[t]he very essence of inherency is that one of ordinary skill in the art would recognize that a reference unavoidably teaches the property in question." 567 F.3d at 1383. *Oelrich* similarly held that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." 666 F.2d at 581.

Patent Owner misapplies the law of inherency to argue, erroneously, that Petitioners were required to prove "that any bound nucleic acids in Fish would unavoidably hybridize to other nucleic acids." *See* PO Resp. 9. But, as discussed above, actual hybridization is not a requirement of any challenged claim. Thus, Petitioners are not required to prove that the ssDNA would "unavoidably hybridize" under the conditions present in Fish (or under any specific set of conditions).[14] Rather, the claims recite

---

[14] At oral argument, counsel for Patent Owner argued:

> [T]he petitioner's argument boils down in some respects to as long as you are doing or attempting to do a nucleic acid attachment that somehow, anyhow, involves poly-l-lysine, then it's necessarily going to result in a hybridizable form. And again, that's just not scientifically true. You could include, for example, nucleases in your attachment buffer. You could put all sorts of caustic acids or bases or something in there that are going to result in a nucleic acid that's not binding in hybridizable form. So there's no support for the assertion that including PLL in any manner in a nucleic acid attachment protocol is going to result in a nucleic acid being attached in hybridizable form.

"hybridizable form," which the parties have stipulated means "*capable* of binding through Watson-Crick base pairing." (Emphasis added). Hence, what is required of Petitioners is proof that the ssDNA in Fish unavoidably has the capability to bind through Watson-Crick base pairing. Under our claim construction, the focus of this inquiry is on the form of the ssDNA when it is fixed or immobilized to the solid support, rather than the surrounding "conditions" in which that ssDNA might be present.

Petitioners have proven that such a capability is the inherent result of ssDNA being fixed or immobilized *to PLL-treated plastic*. Petitioners have proven this via Dr. Nelson's testimony, as well as the specification of the '197 patent and its prosecution history. *See* Ex. 1002 ¶66 (Dr. Nelson testifying that "the immobilized ssDNA in Fish necessarily is capable of hybridizing because it will hybridize when complementary DNA is present in appropriate hybridization conditions"); Ex. 1001, 11:37–39 ("Another technique for improving the fixing or uniformity of the plastic surface for fixing DNA involves treatment of the surface with polylysine (PPL."); Ex. 1003, 96–98 (Patent Owner touting, during the prosecution of the '197 patent, its invention of using PLL to coat non-porous solid supports with ssDNA).

Petitioners have, therefore, shown that Fish anticipates independent claims 17, 19, and 25.

Tr. 41:14–24. However, the Federal Circuit has held "that a product would be inherently anticipated where it was a natural result of the prior art process, even when it would be possible to prevent the formation of the product through 'extraordinary measures.'" *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 961 (Fed. Cir. 2014).

3. Application of Fish to the Challenged Dependent Claims

Each of claims 105, 106, 114, 116, 119, 128, 129, 150, 152, 178, 180, 186, and 187 depends from at least one of the challenged independent claims. Patent Owner's only argument for these dependent claims is that they "are not anticipated by Fish at least because Petitioner[s] did not establish that those claims' respective independent claims are anticipated by Fish." PO Resp. 20–21. That argument is not persuasive because Petitioners, in fact, have shown Fish anticipates the challenged independent claims, as discussed above.

As discussed below, Petitioners adequately show how the additional limitations recited in these claims are taught by Fish. *See* Pet. 27–30.

Claims 105 and 178 recite that "said non-porous solid support comprises glass or plastic." Fish discloses supports having "plastic surfaces" and "polyvinyl surfaces" and also "polyvinyl microtitration tray." Ex. 1006, Abstract, left col. ¶1, right col. ¶2; Ex. 1002 ¶68 (polyvinyl is plastic). Thus, Fish anticipates claims 105 and 178.

Claim 106 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." 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." Fish meets these limitations because it discloses a non-porous solid support that has wells. Ex. 1006, 536, left col., ¶1 ("Twenty-five microliter aliquots of the PLL solution were introduced into each well of a V-shaped polyvinyl microtitration tray."). Thus, Fish anticipates claims 106

and 119.

Claims 114 and 186 recite that "said fixation or immobilization to said non-porous solid support is non-covalent." Dr. Nelson testified that the binding of ssDNA to PLL-coated microtitration trays in Fish is non-covalent. Ex. 1002 ¶77. According to Dr. Nelson, 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.* As such, Fish necessarily discloses non-covalent binding of the single-stranded DNA to the PLL-coated microtitration trays.[15] Dr. Nelson's testimony is consistent with the '197 patent's use of polylysine to facilitate the fixation or immobilization of ssDNA to a solid support, and testimony offered by Dr. Buck, Patent Owner's declarant. *See* Ex. 1001, 11:37–39; Ex. 2142 ¶238. Although Dr. Buck's explanation expressly pertained to using gamma-aminopropyl-triethoxysilane as the surface treatment, the '197 patent states that polylysine can be used (Ex. 1001, 11:37–39), and the inventors touted "the advantages" of the latter surface treatment during prosecution of the '197 patent. Ex. 1002, 97. Petitioners have shown that Fish anticipates claims 114 and 186.

Claims 116 and 187 recite that "said fixation or immobilization [of the

[15] Dr. Nelson further testified that, although the ssDNA and the amine groups of the PLL potentially could bind covalently, they would only do so if the amine groups and/or the ends of the DNA strands are functionalized to cause covalent bonding. Ex. 1002 ¶77. Dr. Nelson noted that Fish does not disclose functionalizing either the PLL or the DNA strands. *Id*.

single-stranded nucleic acids] is not to a cell fixed in situ to said non-porous solid support." Fish meets this limitation because no cells are involved in the microradioimmunoassay discussed therein. *See generally* Ex. 1006. Fish discloses ssDNA (i.e., the mixture of poly-dA and poly-dC as well as the denatured calf thymus DNA) directly bound to the PLL-coated wells of the microtitration tray. *Id*. at 536, left col. ¶¶1–2, 539, Fig. 1; *see also* Ex. 1002 ¶55 (Dr. Nelson: "[T]he 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."). In fact, Fish explicitly refers to "**[s]ingle stranded DNA coated trays**" and "single-stranded nucleic acids, bound to the PLL treated plastic." Ex. 1006, 536, left col. ¶2, 538, right col. ¶1. Petitioners have shown that Fish anticipates claims 116 and 187.

Claims 128 and 150 recite that "said nucleic acids [are] DNA." Fish discloses binding of ssDNA to PLL-coated microtitration trays. Ex. 1006, 536, left col. ¶¶1–2, 539, Fig. 1 (caption). Thus, Fish anticipates claims 128 and 150.

Claims 129 and 152 recite that "said single-stranded nucleic acids are unlabeled." Fish does not describe, let alone require, that the single-stranded DNA is labelled. *See, e.g.,* Ex. 1006, 536, left col. ¶2 (discussing binding of poly-dA and poly-dC to the PLL-coated microtitration trays without describing the poly-dA or pol-dC as labelled). Thus, Fish anticipates claims 129 and 152.

Claim 180 recites that the non-porous solid support is "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, 536, left col. ¶¶1–2, 539, Fig. 1 (caption). Thus, Fish anticipates claim 180.

C. Ground 2: Obviousness in View of Fish

Petitioners contend that dependent claims 130, 131, 151, and 154 would have been obvious over Fish. Each of these claims depends from at least one of the challenged independent claims.

A claim is unpatentable "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). "Obviousness is a question of law based on underlying facts." *MobileMedia Ideas LLC v. Apple Inc.*, 780 F.3d 1159, 1167 (Fed. Cir. 2015), *cert. denied*, 136 S. Ct. 270 (2015). The underlying facts include (i) the scope and content of the prior art, (ii) the differences between the prior art and the claimed invention, (iii) the level of ordinary skill in the field of the invention, and (iv) any relevant objective considerations of nonobviousness that are presented. *Id.* (citing *Graham v. John Deere*, 383 U.S. 1, 17–18 (1966)). An additional underlying fact is whether there was a reason to combine prior art teachings when so asserted.[16] *Id.*

1. Claims 131 as Obvious Over Fish

Claim 131 recites that the fixed or immobilized "nucleic acids

[16] In other grounds, discussed below, Petitioners propose combining prior art teachings from multiple references.

comprise nucleic acid sequences complementary to nucleic acid sequences of interest sought to be identified, quantified or sequenced." Petitioners argue that 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). Patent Owner responds that "Fish does not disclose a hybridization assay for the detection of nucleic acids. The purpose of Fish was the detection of anti-dsDNA antibodies and Fish provides no indication that the protocols described could be applicable to nucleic acid detection techniques involving hybridization." PO Resp. 22 (citations omitted).

We are persuaded by Petitioner, and not by Patent Owner. Petitioners' obviousness challenge is not premised on Fish teaching hybridization assays or that its technology could be applied to techniques involving hybridization. Rather, Petitioners' obviousness challenge is premised on the fact that 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." Ex. 1002 ¶80. What Petitioners rely on Fish for is its teaching of how to fix ssDNA to a PLL-treated non-porous solid support such that ssDNA is capable of binding to a complimentary genetic sequence through Watson-Crick base pairing. Pet. 32 ("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.'").

Patent Owner next argues that a person of ordinary skill in the art "would have had no expectation that the methods described in Fish would result in the successful fixation of nucleic acids in hybridizable form." PO Resp. 23 (citing Ex. 2142 ¶132). That argument is not persuasive because Fish discloses binding ssDNA to PLL-coated wells of a microtitration tray. Ex. 1006, 536, left col. ¶¶1–2, 539, Fig. 1; *see also id*. at 536, left col. ¶2 ("**Single stranded DNA coated trays**"), 538, right col. ¶1 ("single-stranded nucleic acids, bound to the PLL treated plastic"). Further, the cited testimony is based on an erroneous interpretation of "hybridizable form." *See, e.g.*, Ex. 2142 ¶132 (interpreting "hybridizable form" as requiring certain "hybridizing kinetics"). It too is not persuasive.

Patent Owner also argues that evidence of secondary considerations support non-obviousness of "the challenged claims." PO Resp. 69. The proffered evidence, however, is not probative of non-obviousness of claim 131, let alone any other challenged claims.

Patent Owner additionally argues commercial success based on $49.5 million in royalties collected from third-party defendants in settled litigation involving only the '197 patent. *Id.* But, Patent Owner does not provide any frame of reference for determining the significance of the royalty sum. *Cf. Vandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1567 (Fed. Cir. 1984) ("appellants failed to show how sales of the patented device compared to sales of their previous model, or what percentage of the market their new model commanded"). Moreover, Patent Owner does not link the settlement royalties to claim 131, as opposed to the invention of claim 17, from which claim 131 depends and which is anticipated by Fish. *See J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) ("asserted

commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art").

Patent Owner further argues "at the time of the invention, experts were skeptical as to whether it was possible to attach nucleic acids to a non-porous solid support in hybridizable form." PO Resp. 69 (citing Ex. 2142 ¶¶244–46). But, as discussed above, the asserted prior art (Fish) taught this limitation.

Petitioners have shown that claim 131 would have been obvious in view of Fish.

2. Claims 130 and 154 as Obvious Over Fish

Claim 130 depends from independent claim 17 and adds that the "nucleic acids [are] RNA." Similarly, claim 154 depends from independent claim 25 and adds that the "nucleic acids are RNA." With supporting testimony from Dr. Nelson, Petitioners explain how and why a person of ordinary skill in the art would have adapted Fish such that the subject matter of claims 130 and 154 would have been obvious. Pet. 33 (citing Ex. 1002 ¶81). Dr. Nelson testified that it "would have been obvious to a person of ordinary skill in the art that the DNA immobilization technique disclosed in Fish could be used for binding RNA." Ex. 1002 ¶81. Dr. Nelson based his opinion on the similarity in the chemical structures of DNA and RNA. *Id*. In addition, we conclude that common sense would have led a person of ordinary skill in the art to contemplate adapting technology for binding ssDNA to a surface to applications of binding RNA to a surface. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

Patent Owner asserts that "Fish teaches away from the use of RNA." PO Resp. 25. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Patent Owner's purported explanation for teaching away is as follows:

> First, as explained above, Fish does not describe a successful method for fixing single-stranded DNA in hybridizable form. (Ex. 2101 ¶ 98.) Second, to the extent any single-stranded DNA was bound to the PLL-coated wells in Fish, Fish does not describe the chemistry involved in attaching DNA to a PLL-coated surface. (Ex. 2101 ¶ 98.) Thus, a POSITA would have had no reason to expect that Fish's methods would be successful when applied to RNA.

PO Resp. 25–26. Patent Owner's first point is erroneous—as discussed above, Fish does describe a successful method for fixing ssDNA in hybridizable form. Patent Owner's second point also is not persuasive. The fact that Fish does not explain that PLL could be used to fix RNA does not constitute discouragement from so using PLL. Fish does not teach away from using its fixation technology to fix RNA. *See Gurley*, 27 F.3d at 553.

It is also true that "a reference may teach away from a use when that use would render the result inoperable." *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1381 (Fed. Cir. 2007). Patent Owner appears to invoke this law, albeit without citing it, in arguing that "RNA could not be substituted for the DNA used in Fish to satisfy its intended purpose." PO Resp. 26. Patent Owner reasons that Fish is directed to the detection of dsDNA

antibodies, and that such antibodies are not detectable using RNA. *Id*. This argument is not persuasive, however, because Petitioners' proposed modification of the prior art is to use Fish's fixation technology to fix RNA to a surface, not to substitute RNA into Fish to improve Fish's detection of dsDNA antibodies. *See* Reply 11 (citing Ex. 1002 ¶79).

Petitioners have shown that claims 130 and 154 would have been obvious in view of Fish.[17]

3. Claim 151 as Obvious Over Fish

Claim 151 depends from independent claim 25 and adds that the "nucleic acids comprise a gene sequence or pathogen sequence." Petitioners argue that a person of ordinary skill in the art "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." Pet. 34 (citing Ex. 1002 ¶82). We find this reasoning sufficient. Petitioners have shown that claim 151 would have been obvious in view of Fish.

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

Petitioners contend that dependent claims 120 and 189 would have been obvious over Fish, Metzgar, and Sato. Claim 120 depends from independent claim 17, and claim 189 depends from independent claim 25.

[17] As discussed above, Patent Owner offers secondary considerations evidence. *See* PO Resp. 69. However, for the same reasons identified above for claim 131, Patent Owner's secondary considerations evidence is not probative of claims 130 and 154 being non-obviousness.

Claims 120 and 189 additionally recite that "said non-porous solid support comprises one or more hydroxyls."

Petitioners provide 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 as an alternative to Fish's polyvinyl trays. Pet. 35–36. In particular, Petitioners note 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, Petitioners persuasively argue, 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.

Patent Owner responds that claims 120 and 189 are not obvious because Petitioners' "own declarant, Dr. Nelson, admitted that the glass slide described in Metzgar ***could not be used*** in the Fish experiments—which require wells that can contain large volumes of liquid—because Metzgar's slides were specifically designed to 'facilitate the draining of liquids.'" PO Resp. 28 (citing Ex. 1009, Abstract, 1:69–72). Patent Owner's argument is not persuasive for multiple reasons. First, it does not cite to evidence that supports the assertion; specifically, it lacks a citation to the alleged admission by Dr. Nelson. *See* PO Resp. 28. Second, "[a] person of ordinary

skill is also a person of ordinary creativity, not an automaton." *KSR*, 550 U.S. at 421. If she wanted to use glass slides as taught by Metzgar but its wells were too small to perform the nucleic acid immobilization procedure described in Fish, it was within her ordinary skill and creativity to increase the well size.

Petitioners have shown that claims 120 and 189 would have been obvious over Fish, Metzgar, and Sato.[18]

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

Petitioners contend that dependent claims 113 and 185 would have been obvious over Fish and Gilham. These claims depend from at least one of the challenged independent claims and add "wherein said fixation or immobilization to said non-porous . . . solid support is covalent."

1. Disclosure of Gilham

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

[18] As discussed above, Patent Owner offers secondary considerations evidence. *See* PO Resp. 69. However, for the same reasons identified above for claim 131, Patent Owner's secondary considerations evidence is not probative of claims 120 and 189 being non-obviousness.

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*.

2. Reason to Combine the Asserted Teachings of Fish and Gilham in a Manner Encompassed by Claims 113 and 185

Petitioners argue 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.

Patent Owner argues against obviousness by attacking the references individually. *See* PO Resp. 33 ("Gilham involves the reaction of RNA with aminoethylcellulose, a ***porous*** material, in aqueous solution with a carbodiimide activating agent for use in affinity chromatography. Gilham provides no evidence that this reaction could be performed on any other support, much less a non-porous solid support.") (citations omitted), 33 ("[A]s Fish does not disclose the chemistry by which nucleic acids are allegedly bound to the PLL-coated wells, a POSITA would not have known how to adjust the Fish protocol to bind nucleic acids by the periodate oxidation of 3' terminal cis diol group in RNA."), 34 ("Because Fish is directed to the use of dsDNA in detecting antibodies, RNA could not be

used in the Fish experiments and the resulting combination would not satisfy the intended purpose of Fish."), 35 ("Fish is directed to the use of dsDNA in detecting anti-dsDNA antibodies, so the authors of Fish would not have been motivated to use RNA, which the chemistry used in Gilham requires."). However, such arguments are inapposite. *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.").[19]

Petitioners have shown that claims 113 and 185 would have been obvious in view of Fish and Gilham.[20]

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

Petitioners contend 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.

1. VPK Is Prior Art

The '197 patent claims priority to various applications, the oldest two

---

[19] In this case, Petitioners bear the burden of persuasion to show that the challenged claims are unpatentable. 35 U.S.C. § 316(e). Regardless of who bears the burden to prove patentability/unpatentability in any particular proceeding, *Merck's* holding is applicable here because it speaks generally to the absence of probative value in attacking references individually when obviousness over a combination of references is at issue. *Merck*, 800 F.2d at 1097.

[20] As discussed above, Patent Owner offers secondary considerations evidence. *See* PO Resp. 69. However, for the same reasons identified above for claim 131, Patent Owner's secondary considerations evidence is not probative of claims 113 and 185 being non-obviousness.

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. Petitioners assert 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), Petitioners point out that VPK was published before the earliest filing date in the claim of priority, which is the earliest presumed invention date. *Id*.; *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), Petitioners argue 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. 41–44. Accordingly, Petitioners argue that 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*.

Patent Owner argues that VPK is not prior art under either § 102(a) or (b). With respect to § 102(a), Patent Owner argues that the invention (as claimed in the challenged claims) was conceived and reduced to practice before VPK was published in October 1982. PO Resp. 43–58. With respect to § 102(b), Patent Owner argues that the challenged claims are entitled to

the benefit of the '469 application's January 1983 filing date, which is not more than one year after VPK's October 1982 publishing. PO Resp. 37–42.

For the reasons explained below, we determine that VPK is prior art under at least § 102(b) and do not reach whether it is also prior art under § 102(a).

Pursuant to 35 U.S.C. § 120, "in 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." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1326 (Fed. Cir. 2008). The '197 patent references a chain of continuation and continuation-in-part applications that originates with the '469 application. The question before us is whether the '469 application contains a written description of the challenged claims. We conclude that it does not.

Each of the challenged claims recites, or incorporates by reference, a "non-porous solid support." Petitioners argue that the '469 application does not provide a written description of this limitation. Pet. 41–44. To do so, the '469 application "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (quoting *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989) (brackets added by *Ariad*). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351.

As argued by Petitioners and not disputed by Patent Owner, the '469 application does not include the term "non-porous solid support." *See generally* Ex. 1004; Pet. 42; PO Resp. 36–42. Petitioners point out that the '469 application discloses "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.'" Pet. 41 (citing Ex. 1004, 24:14–22, 30:5–7, 52:31–37). Petitioners argue that the '469 "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." *Id*. at 42 (citing *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1346 (Fed. Cir. 2005); *see also id*. at 43 (citing *Purdue Pharma LP v. Faulding Inc*., 230 F.3d 1320, 1327 (Fed. Cir. 2000)).

In response, Patent Owner argues that the '469 application "discloses many examples of non-porous solid supports," yet Patent Owner identifies only the three examples that Petitioners concede are disclosed. *See* PO Resp. 38. Patent Owner further argues that "[t]hose examples, placed in the context of the entire description of the 1983 [i.e., '469] Application, would have indicated to a POSITA that the inventors had possession of the entire genus of non-porous solid supports." *Id*. at 39. In particular, Patent Owner relies on "four aspects" of the '469 application. *Id*. We address each below,

Patent Owner describes the first "aspect" it relies on as follows:

> *First*, the 1983 Application describes that each of its examples of nonporous solid supports functions in the same way: to support a nucleic acid strand in hybridizable form ***on the surface*** of that

> example. (Ex. 1004, 24:14–22, 27:16–19, 29:1–12, 30:5–14, 31:29–32:1, 52:31–37; *see also* Ex. 2142 ¶ 171.) The fixation of the genetic material to the ***surfaces*** of those exemplary solid supports indicates that those solid supports are all non-porous—otherwise, the genetic material could, at least in part, be ***inside*** the support (*i.e.*, in a pore). (Ex. 2142 ¶¶ 171.)

PO Resp. 39. In this argument, Patent Owner cites exclusively to examples of non-porous solid supports (*see* Ex. 1004, 24:14–22, 27:16–19, 29:1–12, 30:5–14, 31:29–32:1, 52:31–37) and assigns significance to the fact that the '469 application does not mention any binding inside those supports "(i.e., in a pore)." PO Resp. 39. But it is a truism that there cannot be internal binding in those examples because such materials do not have pores. Thus, the absence of any discussion of internal binding as to those materials is insignificant. Patent Owner's argument is merely another way of pointing out that the '469 application discloses three solid support materials that happen to be non-porous.

Patent Owner describes the second "aspect" it relies on as follows:

> *Second*, a POSITA would have recognized from the 1983 Application that a non-porous solid support of ***many*** shapes can support a nucleic acid strand in hybridizable form on its surface. Dr. Dollie Kirtikar, one of the named inventors of both the 1983 Application and the '197 Patent, testified during prosecution that the chemistry of affixing a nucleic acid to glass or plastic would work the same way for any appropriately surface-treated glass or plastic, regardless of its shape. (Ex. 2102 ¶¶ 2, 7–8.) The specific geometry of the non-porous solid support, whether a well, depression, plate, cuvette,

> or tube, was not crucial to the practice of that invention. (*Id.* ¶¶ 8, 11; Ex. 2142 ¶¶ 172–175.)

PO Resp. 39–40 (footnote omitted). This argument is not probative of Patent Owner's contention that the '469 application provides written description support for the later-added "non-porous solid support" limitation. It merely speaks to the insignificance, in Patent Owner's view, of the shape of non-porous solid supports. Moreover, it relies on testimony from the inventor provided in 2003, and that testimony does not purport to interpret the disclosure of the '469 application, let alone from the perspective of a person of ordinary skill in the art as of 1983. *See* Ex. 2102.

Patent Owner describes the third "aspect" it relies on as follows:

> *Third*, a POSITA would understand from the 1983 Application that "glass plates provided with an array of depressions or wells," "polystyrene plates," "cuvettes," "glass tubes," and "polystyrene surfaces or wells" all function to prevent liquid from flowing through them, distinguishing those non-porous supports from porous materials, which permit liquid to flow through their pores. (Ex. 2142 ¶¶ 176–177.) For example, the 1983 Application describes depositing labeled nucleic acid probes, which would have been in solution, in the well of a glass plate for hybridization. (Ex. 1004, 24:19–22.)

PO Resp. 40. This argument is not probative of Patent Owner's contention that the '469 application provides written description support for the later-added "non-porous solid support" limitation. It merely demonstrates, unremarkably, that a person of ordinary skill in the art would know that non-porous materials do not leak.

Patent Owner describes the fourth "aspect" it relies on as follows:

> *Finally*, the specification of the 1983 Application describes "solid supports" generally, indicating that the inventors did not intend to limit their invention to the examples disclosed. (Ex. 1004, 1:11–15.) The 1983 Application also states, "[a]s will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations, modifications, and substitutions are possible in the practice of this invention, without departing from the spirit or scope thereof." (Ex. 1004, 35:1–5.)

Id. at 40–41. This argument is not probative of Patent Owner's contention that the '469 application provides written description support for the later-added "non-porous solid support" limitation. The '469 application discloses the concept of "a solid support" (*see* Ex. 1004, 1:11) and it discloses examples of solid supports as discussed above. However, it does not disclose the concept of a "non-porous solid support" or otherwise "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *See Ariad*, 598 F.3d at 1351.

Petitioners have demonstrated by a preponderance of the evidence that the '469 application does not provide written description support for the challenged claims. Thus, because the challenged claims are not entitled to the benefit of the '469 application's filing date, VPK qualifies as prior art to the challenged claims under 35 U.S.C. § 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 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 ¶¶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. Reason to Combine the Asserted Teachings of VPK and Metzgar

Petitioners argue that 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 (citing Ex. 1002 ¶99). Patent Owner disputes Petitioners' proffered reason for why a person of ordinary skill in the art would have combined that teaching of Meztgar with the teachings of VPK. Patent Owner's argument is as follows:

> In the [Institution] Decision, the Board concluded that Petitioner presents an adequate reason for why a POSITA would perform the *in situ* procedure of VPK on the glass slides having wells or depressions as taught by Metzgar: "in order to analyze multiple samples or analytes

> simultaneously on the same glass slide." (Decision, 22 (citing Pet. 45.)
>
> However, the record now available to the Board shows that, to the contrary, a support with wells or depressions would not serve the intended purpose of VPK's hybridization to a cell fixed *in situ*, which is to identify and locate a nucleic acid sequence of interest on the chromosomes within a cell.

PO Resp. 63–64 (citing (Ex. 1008, "3"; Ex. 2142 ¶¶210–12.)).

Patent Owner's argument is conclusory and not sufficiently developed in the Patent Owner Response. *See* PO Resp. 63. In the testimony to which Patent Owner cites, however, some detail is provided in that Dr. Buck states that "a non-porous support comprising wells or depressions would be pointless for *in situ* hybridization, as the cell *in situ* by itself provides a defined area in which the target nucleic acids reside." Ex. 2042 ¶211. In view of this cited testimony, Patent Owner's argument appears to be that a person of ordinary skill in the art would be interested in the chromosomes of only a single cell or the cells of only a single source or donor. That premise is not supported by Patent Owner. And, as Petitioners argue in their Reply, Patent Owner's argument does not address Petitioners' true position that there would have been motivation to use Metzgar's glass slides to analyze multiple cell samples simultaneously on the different wells or depressions of Metzgar's glass slide. Reply 21 (citing Ex. 1002 ¶112); *see also* Ex. 1002 ¶99 ("It would have been obvious . . . 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.").

Petitioners have shown that a person of ordinary skill in the art would have combined the asserted teachings of VPK and Metzgar.

4. Application of VPK and Metzgar to the Challenged Independent Claims

> The challenged independent claims are 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.

VPK teaches all of the subject matter of these claims except for an "array." In particular, VPK teaches chromosomes that are indirectly bound to aminoalkylsilane-treated glass slides and then denatured into ssDNA, which is in hybridizable form, as evidenced by subsequent hybridization. Ex. 1008, 397 ("Summary"), 398 right col. ¶1, 399 left col. ¶¶2–3, 401 ¶bridging left and right cols. and Figs. 2 and 3, 401–03 ¶ bridging pages 401 and 403, 403 left col. ¶¶1–4, 405 left col. ¶–right col. ¶1; Ex. 1002 ¶¶96–97.

The asserted combination of teachings meets the additional claim language reciting an "array" because 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; Ex. 1002 ¶99.

Patent Owner argues that the asserted combination does not teach an "array" because it does not teach "an orderly arrangement of the nucleic acids." PO Resp. 60. As discussed above, however, the meaning of "array"

in light of the specification includes an orderly grouping or arrangement of wells or depressions.

Petitioners have shown that claims 17, 19, and 25 would have been obvious over VPK and Metzgar.[21]

5. Application of VPK and Metzgar to the Challenged Dependent Claims

Each of claims 105, 106, 114, 119, 120, 128, 129, 131, 150–152, 178, 180, 186, and 189 depends from at least one of the challenged independent claims. Patent Owner argues that these dependent claims are not obvious because Petitioners did not establish that the challenged independent claims are obvious. PO Resp. 60 (citing *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988)). That argument is not persuasive because Petitioners, in fact, have shown the challenged independent claims would have been obvious over VPK and Metzgar, as discussed above.

As discussed below, Petitioners adequately show how the asserted prior art meets the additional limitations recited in these dependent claims. *See* Pet. 49–53.

Claims 105 and 178 recite that "said non-porous solid support comprises glass or plastic." Claim 106 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." Similarly, claim 119 recites that "said non-porous solid support"

[21] As discussed above, Patent Owner offers secondary considerations evidence. *See* PO Resp. 69. However, for the same reasons identified above for claim 131, Patent Owner's secondary considerations evidence is not probative of claims 17, 19, and 25 being non-obviousness.

comprises "a well or wells, a microtiter well or microtiter wells, or a depression or depressions." The asserted prior art meets these limitations because 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.

Claims 114 and 186 recite that "said fixation or immobilization to said non-porous solid support is non-covalent." The asserted prior art meets this limitation because VPK teaches treating glass slides with aminoalkylsilane, and the "binding of chromosomes to the aminoalkylsilane-treated glass slides necessarily would be non-covalent." Pet. 50 (citing Ex. 1002 ¶107). The cited testimony of Dr. Nelson is unrebutted.

Claims 120 and 189 recite "said non-porous solid support comprises one or more hydroxyls." The asserted prior art meets this limitation because VPK and Metzger teach using glass slides, which necessarily would include hydroxyl groups. Pet. 51 (citing Ex. 1002 ¶108). The cited testimony of Dr. Nelson is unrebutted.

Claims 128 and 150 recite that "said nucleic acids [are] DNA." The asserted prior art meets this limitation because the metaphase chromosomes in VPK are DNA. *See, e.g.*, Ex. 1008, 397 ("Summary" referring to "specific DNA sequences in human chromosomes").

Claim 151 recites "said nucleic acids comprise a gene sequence or pathogen sequence." The asserted prior art meets this limitation because the metaphase chromosomes in VPK necessarily include gene sequences.

Claims 129 and 152 recite that "said single-stranded nucleic acids are unlabeled." The asserted prior art meets this limitation because VPK does not describe, let alone require, that the denatured metaphases chromosomes

are labelled. *See generally* Ex. 1008. In fact, VPK implies that such *single-stranded* DNA is unlabeled, as VPK teaches labeling by using labeled antibodies. *Id*. at 400 right col. ¶¶1–3.

Claim 180 recites that the non-porous solid support is "treated with a surface treatment agent, a blocking agent, or both." The asserted prior art meets this limitation because VPK discloses treatment of glass slides with aminoalkylsilane prior to immobilization of metaphase chromosomes on the glass slides. Ex. 1008, 398 right col. ¶¶1–2.

Petitioners have shown that claims 105, 106, 114, 119, 120, 128, 129, 131, 150–152, 178, 180, 186, and 189 would have been obvious over VPK and Metzgar. [22]

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

Petitioners contend that dependent claims 113, 116, 130, 154, 185, and 187 would have been obvious over Noyes, VPK, Metzgar and Ramachandran. Each of these claims depends from at least one of independent claims 17, 19, and 25.

1. Disclosure of Noyes and Ramachandran

Noyes discloses covalent (and direct) bonding of ssDNA and RNA to finely divided m-aminobenzyloxymethyl cellulose after the primary aryl

[22] As discussed above, Patent Owner offers secondary considerations evidence. *See* PO Resp. 69. However, for the same reasons identified above for claim 131, Patent Owner's secondary considerations evidence is not probative of claims 105, 106, 114, 119, 120, 128, 129, 131, 150–152, 178, 180, 186, and 189 being non-obviousness.

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. Reason to Combine the Asserted Teachings of Noyes, VPK, Metzgar, and Ramachandran

Petitioners argue that a person of ordinary skill in the art would have combined the relied-upon teachings of Noyes, VPK, and Ramachandran and map those teachings to claims 113, 116, 130, 154, 185, and 187. Pet. 53–57. As for the reason to combine the prior art teachings, Petitioners assert that a person of ordinary skill in the art would have: (1) "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"; (2) "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"; (3) "readily and reasonably expected to use the procedure disclosed in Ramachandran to convert the alkylamines on the glass slides of Metzgar to arylamines"; and (4) "reasonably expected to covalently bind nucleic acids to the glass slides of Metzgar [sic] by diazotizing the arylamines as taught by

Noyes." Pet. 54–55 (citing Ex. 1002 ¶¶113, 114).[23]

Patent Owner responds that a person of ordinary skill in the art would not combine the prior art teachings as asserted by Petitioners because doing so "would impermissibly destroy the objectives of the references." PO Resp. 66. But, Patent Owner's examples of how the objectives of the references would be destroyed are not commensurate with the combination Petitioners assert. For example, Patent Owner argues that the asserted combination would destroy "the objective of VPK" because VPK seeks "[t]o provide visual 'identification and localization of specific DNA sequences in human chromosomes by fluorescence microscopy'" which requires that the chromosomes remain intact inside the cells. *Id*. (citing Ex. 1008, 12; Ex. 2142 ¶229–231.).[24] But, in this ground, Petitioners do not rely on VPK for its chromosome-intact DNA sequencing. In this ground, Petitioners rely on VPK merely for its aminoalkylsilane-treated glass slides. *See, e.g.*, Pet. 54 (arguing a person of ordinary skill in the art "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").

Petitioners have shown that a person of ordinary skill in the art would have combined the asserted teachings of Noyes, VPK, Metzgar, and

---

[23] Petitioners additionally cite paragraph 83 of Exhibit 1002, but it appears Petitioners intended to instead cite paragraph 112. *See* Pet. 54 (citing Ex. 1002 ¶83); *compare* Pet. 54, *with* Ex. 1002 ¶112.

[24] Although Patent Owner did not cite to page 397 of Exhibit 1008, that page is where the language Patent Owner quotes is found. *See* PO Resp. 62–63; Ex. 1008, 397 (Summary).

Ramachandran.

3. Application of Noyes, VPK, Metzgar, and Ramachandran to Claims 113, 116, 130, 154, 185, and 187

Claims 113 and 185 recite that "said fixation or immobilization to said non-porous [] solid support is covalent." With respect to these claims, Petitioners point out that Noyes discloses covalent binding and argue that a person of ordinary skill in the art

> 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)

Pet. 57 (citing Ex. 1002 ¶116). We find that Petitioners have articulated sufficient reasoning, as quoted above, why a person of ordinary skill in the art would have combined the asserted prior art in a manner that falls within the scope of claims 113 and 185, including the requirement that the fixation or immobilization to the non-porous solid support "is covalent."

Claims 116 and 187 recite 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." Petitioners point out that Noyes discloses binding of DNA or RNA directly (and, thus, not via a cell fixed in situ) to aryl amine groups on a cellulose surface and argue that a person of ordinary skill in the art

> 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).

Pet. 56 (citing Ex. 1002 ¶115). We find that Petitioners have articulated sufficient reasoning, as quoted above, why a person of ordinary skill in the art would have combined the asserted prior art in a manner that falls within the scope of claims 116 and 187, including the requirement that the fixation or immobilization to the non-porous solid support "is not to a cell fixed in situ to said non-porous solid support."

Claims 130 and 154 recite that the nucleic acids are "RNA." With respect to these claims, Petitioners point out that Noyes discloses binding RNA. Pet 57 (citing Ex. 1007, 301 left col. ("Summary"), 306 left col. ¶1). We find that Petitioners have articulated sufficient reasoning why a person of ordinary skill in the art would have combined the asserted prior art in a manner that falls within the scope of claims 130 and 154, including the requirement that the nucleic acids be "RNA."

In opposition to Petitioners' challenge, Patent Owner argues that Petitioners have not shown that the asserted prior art meets the "hybridizable form" limitation common to all of claims 113, 116, 130, 154, 185, and 187, (via their dependency on one or more of independent claims 17, 19, and 25). PO Resp. 64–66. More specifically, Patent Owner argues that, in the asserted combination, any nucleic acids that covalently bind to the glass surface would do so via certain bases, specifically guanine, thymine, and

uracil, "rendering those bases unavailable to bind to the corresponding Watson-Crick bases of a second nucleic acid through hybridization," which "would hinder or prevent hybridization entirely." PO Resp. 65–66 (citing Ex. 2142 ¶¶239–40). On its face, this argument is equivocal, as Patent Owner argues, in the alternative, that hybridization of such nucleic acids would be *hindered but not prevented*. *Id*. at 66. The testimony of Dr. Buck that Patent Owner relies on for this argument is equally equivocal. *See* Ex. 2142 ¶240 ("Therefore, covalent attachment of multiple bases to a solid support could hinder or even prevent hybridization entirely.").

Moreover, Dr. Buck's testimony cites exclusively to Noyes, yet Noyes does not support Dr. Buck's ultimate conclusion that the combination would lack covalently bound nucleic acids in "hybridable form." *See* Ex. 2142 ¶¶239–40 (citing Ex. 1007, 1, 2, 4, 6). In fact, as pointed out by Petitioner, Noyes "shows successful hybridization of RNA and ssDNA covalently bound to cellulose via primary aryl amino groups that have been diazotized." Reply 23–24 (citing Ex. 1007, 301 left col. ("Summary"), 303, 304 ¶1). We are persuaded that the asserted combination would meet the "hybridizable form" limitation and all other limitations of claims 113, 116, 130, 154, 185, and 187.

Petitioners have shown that claims 113, 116, 130, 154, 185, and 187 would have been obvious Noyes, VPK, Metzgar, and Ramachandran.[25]

---

[25] As discussed above, Patent Owner offers secondary considerations evidence. *See* PO Resp. 69. However, for the same reasons identified above for claim 131, Patent Owner's secondary considerations evidence is not probative of claims 113, 116, 130, 154, 185, and 187 being non-obviousness.

III. MOTIONS TO EXCLUDE

Petitioners moved to exclude the following evidence introduced by Patent Owner: Exhibits 2135 and 2137–2141 in their entirety; paragraphs 3–10, 12, 14, 16, and 17 of Exhibit 2143; and paragraphs 161 and 180–97 of Exhibit 2142. Paper 41, 1. Collectively, this evidence is relied on by Patent Owner to prove that VPK is not prior art under 35 U.S.C. § 102(a). As discussed above, we do not reach that issue, as Petitioners have shown that VPK is prior art under § 102(b). Accordingly, this Decision does not rely on any of the evidence Petitioners seek to exclude. Petitioners' Motion to Exclude is, therefore, moot.

Patent Owner moved to exclude the following evidence introduced by Petitioners: paragraphs 3 and 5 of Exhibit 1037 and "Attachment A" appended to Exhibit 1037. Paper 39, 3. This evidence is cited by Petitioners in their Reply to support their reliance, in the Petition, on Exhibits 1021 and 1032. *See* Reply 7 n.1. This Decision does not rely on Exhibit 1037 (or Exhibits 1021 and 1032). Thus, Patent Owner's Motion to Exclude is also moot.

IV. CONCLUSION

Petitioners have shown by a preponderance of the evidence that all of the challenged claims of the '197 patent are unpatentable.

V. ORDER

Accordingly, it is

ORDERED that 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 are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is dismissed as moot;

FURTHER ORDERED that Petitioners' Motion to Exclude is dismissed as moot; and

FURTHER ORDERED that, because this Decision is final, a party to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

For Petitioner:

M. Paul Barker
Arpita Bhattacharyya
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
paul.barker@finnegan.com
arpita.bhattacharyya@finnegan.com

Jamie T. Wisz
WILMER CUTLER PICKERING HALE AND DORR LLP
Jamie.Wisz@WilmerHale.com

For Patent Owner:

Kevin K. McNish
DESMARAIS LLP
kmcnish@desmaraisllp.com