No. 19-_____

In the Supreme Court of the United States

ENZO LIFE SCIENCES, INC.,

Petitioner,

v.

BECTON, DICKINSON AND COMPANY,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

In 2006, the Patent Office issued petitioner's patent under a statutory scheme that guaranteed that an issued patent is presumed valid in adversarial proceedings until a challenger proves that it is invalid by clear and convincing evidence. Years later, the Leahy-Smith America Invents Act ("AIA") eliminated that guarantee by creating, for the first time, an adversarial proceeding that allows a challenger to obtain revocation of a patent by merely a preponderance of the evidence: *inter partes* review. Unlike any previous administrative process for reexamining a patent, *inter partes* review requires full participation by the challenger and operates as an adjudication on the relative strength of the parties' disputed arguments. The AIA expressly subjected patents that issued before its enactment to that new regime.

Does the application of *inter partes* review to a patent that issued before the enactment of the AIA violate the Due Process Clause because it retroactively diminishes vested rights by lowering the burden of proof required to revoke a patent in an adversarial proceeding?

PARTIES TO THE PROCEEDINGS

The parties to the proceedings include those listed on the cover. The United States intervened below.

Hologic, Inc. was a petitioner in the agency proceedings and an appellee below, but was dismissed from the appeal prior to judgment. The court of appeals amended the caption of the case to list only Becton, Dickinson and Company as appellee and the United States as intervenor. Hologic, Inc. is no longer involved in the proceedings relevant to this petition.

CORPORATE DISCLOSURE STATEMENT

Enzo Life Sciences, Inc. is a wholly owned subsidiary of Enzo Biochem, Inc., a publicly traded company.

RELATED PROCEEDINGS

The following federal cases and agency proceedings are directly related to this petition:

- *Hologic, Inc. and Becton, Dickinson and Company v. Enzo Life Sciences, Inc.*, Case IPR2016-00820, Patent Trial and Appeal Board. Final written decision filed Sept. 28, 2017.
- *Hologic, Inc. and Becton, Dickinson and Company v. Enzo Life Sciences, Inc.*, Case IPR2016-00822, Patent Trial and Appeal Board. Final written decision filed Oct. 2, 2017.
- *Enzo Life Sciences, Inc. v. Becton, Dickinson and Company*, Nos. 2018-1232, 2018-1233, United States Court of Appeals for the Federal Circuit. Judgment entered Aug. 16, 2019.

Further, U.S. Patent No. 7,064,197 is also involved in the following proceedings:

- *Enzo Life Sciences, Inc. v. Hologic, Inc.*, No. 1:15-cv-00271-LPS-CJB, United States District Court for the District of Delaware. Case terminated on Apr. 24, 2019 pursuant to stipulation of dismissal.
- *Enzo Life Sciences, Inc. v. Becton, Dickinson & Co.*, No. 1:12-cv-00275-LPS, United States District Court for the District of Delaware. Case stayed as to the '197 patent by order entered July 31, 2017.
- *Enzo Life Sciences, Inc. v. Roche Molecular Systems, Inc. et al.*, No. 1:12-cv-00106-LPS, United States District Court for the District of Delaware. Case stayed as to the '197 patent by order entered Aug. 2, 2017.
- *In re Rabbani, et al.*, *Ex Parte* Reexamination Control No. 90/014,270, United States Patent and Trademark Office.
- *In re Rabbani, et al.*, *Ex Parte* Reexamination Control No. 90/014,272, United States Patent and Trademark Office.

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No. 19-____

ENZO LIFE SCIENCES, INC.

v.

BECTON, DICKINSON AND COMPANY

PETITION FOR A WRIT OF CERTIORARI

Enzo Life Sciences, Inc. ("Enzo") respectfully petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a–18a) is unreported but is available at 780 F. App'x 903. The opinions of the Patent Trial and Appeal Board (Pet. App. 19a–81a, 82a–143a) are unreported but are available at 2017 WL 4339646 and 2017 WL 4407743. The order denying rehearing and rehearing en banc (Pet. App. 144a–145a) is unreported.

JURISDICTION

The court of appeals entered judgment on August 16, 2019. A timely petition for rehearing and rehearing en banc was denied on December 4, 2019. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

Pursuant to 28 U.S.C. § 2403(a), the court of appeals certified to the Attorney General the fact that the constitutionality of an Act of Congress was drawn into question.

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

The Due Process Clause of the Fifth Amendment to the United States Constitution provides: "No person shall * * * be deprived of life, liberty, or property, without due process of law."

Section 6(c)(2)(A) of the Leahy-Smith America Invents Act, Pub. L. No. 112-19, 125 Stat. 284, 304 (2011) provides: "The amendments made by subsection (a) shall take effect upon the expiration of the 1-year period beginning on the date of the enactment of this Act and shall apply to any patent issued before, on, or after that effective date."

35 U.S.C. § 316(e) provides: "In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence."

35 U.S.C. § 282 (2006) provides, in pertinent part: "A patent shall be presumed valid. * * * The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity."

These provisions and 35 U.S.C. §§ 311, 315 are set out in Appendix E. Pet. App. 146a–154a.

INTRODUCTION

This case presents the retroactivity question that the Court expressly reserved two Terms ago in *Oil States Energy Services, LLC* v. *Greene's Energy Group, LLC*, 138 S. Ct. 1365, 1379 (2018) (No. 16-712). Although the Court had no occasion then to address the Fifth Amendment because the parties there did not invoke it, that question of law is now presented. The court of appeals held that the retroactive application of *inter partes* review ("IPR") to U.S. Patent No. 7,064,197 ("Enzo's Patent"), which issued before the enactment of the Leahy-Smith America Invents Act ("AIA"), does not violate the Fifth Amendment. That decision not only applied the wrong analysis by conflating the Due Process and Takings Clauses, it also conflicts with this Court's Due Process Clause precedents. The Due Process Clause forbids subjecting patents that issued before the enactment of the AIA ("pre-AIA patents") to IPR, because the retroactive application of IPR to pre-AIA patents eviscerates a vested right—the presumption of validity that vested in such patents at the time of issuance. Indeed, the AIA upended the settled expectations that Enzo had in its intellectual property long after Enzo had disclosed its inventions for the benefit of society in exchange for a patent with certain vested rights pursuant to the law at the time it issued.

This Court should clarify the due process test for retroactive legislation that diminishes property rights. This Court should hold that the AIA's retroactive application of IPR to pre-AIA patents violates the Due Process Clause by expressly authorizing the Patent Office to revoke patents without the statutory protection of the presumption of validity—a substantive right that vested when the patents issued. The Court should grant the petition and reverse.

STATEMENT

Enzo is the owner of a patent that issued in 2006 bearing the statutorily-secured presumption of validity under 35 U.S.C. § 282 (2006). That presumption requires that a challenger bear the burden of proof to show that a patent is invalid by clear and convincing evidence in an adversarial proceeding. *Microsoft Corp.* v. *i4i Ltd. P'ship*, 564 U.S. 91, 95, 100–07 (2011). When Enzo's Patent issued, a challenger had to go to district court, where he would face the heightened burden, or to the Patent Office where he had limited ability to participate, in a non-adversarial *ex parte* reexamination. No alternative adversarial proceeding existed to challenge the validity of Enzo's Patent.

In 2011, as part of the most sweeping changes to patent law in sixty years, Congress created a novel regime for revoking patents called *inter partes* review. To make it easier to attack patents through IPR so that IPR would be an attractive alternative to litigation for challengers, the AIA fixed a preponderance standard that was lower than the burden in district court. 35 U.S.C. § 316(e). *For the first time*, the presumption of validity and its heightened standard did not apply in an adversarial, adjudicative proceeding for patent revocation. Because IPR is a substitute for litigation, and can actually moot co-pending litigation involving alleged infringement or invalidity, the AIA has eviscerated the presumption of validity. It is now possible—and common—for adversaries to secure revocation of a patent without any agency, judge, or jury applying the clear-and-convincing standard to decide the challenged claims' validity.

Regardless of whether it might be constitutionally permissible for Congress to reserve a prospective right of review via IPR for later-issued patents, the statute is also retrospective, expressly reaching back to cover patents

that issued before the AIA's enactment. When the IPR provisions first took effect in September 2012, therefore, pre-AIA patents accounted for about 90% of all unexpired utility patents subject to attack via IPR. See *U.S. Patent Statistics Chart, Calendar Years 1963–2018*, U.S. Patent & Trademark Office, https://www.uspto.gov/web/offices/ac/ido/oeip/taf/us_stat.htm [https://perma.cc/F4AQ-V9EX]. That backward-facing impact on pre-AIA patents continues. For the first 6 years of IPR, pre-AIA patents have accounted for about 62.5 percent of all petitions. Saurabh Vishnubhakat, *The Mixed Case for a PTAB Off-Ramp*, 18 Chi.-Kent J. Intell. Prop. 514, 519 (2019).

Thus, the brunt of the IPR provisions was felt by patent-holders, like Enzo, whose patent rights had vested *before* the AIA's sweeping changes. This case arises from IPR proceedings that found Enzo's Patent unpatentable—decided in a new adversarial, adjudicative proceeding that does not apply the statutory presumption of validity.

I. BACKGROUND

A. The Presumption of Validity

The Patent Act of 1952 provides that an issued patent "shall be presumed valid." 35 U.S.C. § 282 (2006). By its own terms, section 282 places the "burden of establishing invalidity" on the "party asserting such invalidity." *Id.*

The presumption had long been a feature of the common law. Section 282 codifies the longstanding concept. *Microsoft Corp.* v. *i4i Ltd. P'ship*, 564 U.S. 91, 101 (2011). Consistent with the common law, section 282's "burden" not only determines *which* party must show invalidity, but also by how much. *Id.* at 102. "The common-law presumption * * * reflected the universal understanding that a preponderance standard of proof was too 'dubious' a basis

to deem a patent invalid." *Id.* (citing and discussing *Radio Corp. of Am.* v. *Radio Eng'g Labs.*, 293 U.S. 1, 8 (1934)). Thus, the substance of the presumption is really its concomitant standard of proof: a party asserting invalidity must prove invalidity by "clear and convincing evidence." *Microsoft*, 564 U.S. at 95.

Inventors engage in the "patent bargain" against the legal backdrop of the presumption. When an inventor has devised a new and useful invention, he faces a decision: whether to seek patent protection based on the legal regime that then exists, or to keep his invention a trade secret. *Kewanee Oil Co.* v. *Bicron Corp.*, 416 U.S. 470, 480 (1974). If the inventor seeks a patent, he surrenders secrecy. He must describe the invention to enable others to make use of it. 35 U.S.C. § 112. In return, after meeting other requirements of patentability, he receives a patent on the condition that, when his limited monopoly expires, the invention is irrevocably dedicated to the public. *Sears, Roebuck & Co.* v. *Stiffel Co.*, 376 U.S. 225, 230 (1964). The entire patent system is built around this *quid pro quo* because it facilitates the ultimate goal of "bring[ing] new designs and technologies into the public domain through disclosure." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 151 (1989).

The strength of the proof required to invalidate a patent is part of the inventor's calculus. An inventor weighs the loss of secrecy over his invention against the value of a patent—which derives from the ability to enforce the right to exclude others from making or using the invention. If an inventor knows that the patent he would receive could be revoked upon merely "dubious" evidence, he might reasonably choose secrecy instead of disclosure. As this Court has recognized, inventors view the heightened standard of proof as "an essential component" of the "incentives for inventors to disclose their innovations to

the public in exchange for patent protection." See *Microsoft*, 564 U.S. at 112. The presumption of validity is a statutory promise about what an inventor receives in an issued patent, which induces inventors to engage in the patent bargain.

B. Pre-AIA Proceedings for Challenging the Validity of an Issued Patent

For hundreds of years in the United States, since the establishment of the American patent system, there existed only one adversarial proceeding available to challenge the validity of issued patents: litigation in courts. See *Oil States*, 138 S. Ct. at 1383–84 (Gorsuch, J., dissenting). Administrative proceedings that allow the U.S. Patent Office to reconsider an earlier grant are a relatively recent invention that Congress first introduced forty years ago.

1. In 1980, Congress created *ex parte* reexamination—a process for the Patent Office to review its previous decision to grant a patent. 35 U.S.C. § 301. Third parties, such as an accused infringer, could at most file a request that the Patent Office reexamine the patent in light of prior art "bearing on the patentability" of an issued patent. 35 U.S.C. § 301(a). If the Patent Office determines that the request raises a "substantial new question of patentability," the agency can begin a proceeding between the Patent Office and the patent owner. § 303(a).

The conduct of an *ex parte* reexamination follows "the procedures established for initial examination" of a patent. § 305. In other words, reexamination is like patent prosecution: the examiner writes "office actions" potentially informing the applicant of a reason for rejection, and the applicant or his attorney submits written responses overcoming those reasons or amending the language of

the claims. See § 132. Reexamination may result in the challenged claims surviving without change, being reissued with amendments, or being cancelled.

Third parties, including any adversary who successfully triggered the proceedings, have no right to participate in the proceedings and no right to seek judicial review. See §§ 305–306. Thus, *ex parte* reexamination is not, nor has it been, a substitute for litigation. In addition, reexamination is fundamentally different from litigation because it allows the Patent Office to consider whether a past grant was proper in light of new information, but the agency does not adjudicate disputes between parties.

Based on the premise that reexamination is dissimilar to litigation, the Federal Circuit held, in *Patlex Corp.* v. *Mossinghoff*, 758 F.2d 594 (Fed. Cir. 1985), that reexamination did not violate the Fifth Amendment despite its retrospective nature in applying to patents that had issued before its creation. *Id.* at 600–03. The Federal Circuit also held, as a matter of statutory interpretation, that the presumption of validity is not applicable in reexamination proceedings because reexamination is a mechanism for the agency to fix its own potential errors. *In re Etter*, 756 F.2d 852, 855–59 (Fed. Cir. 1985) (en banc).

2. In 1999, Congress created a second iteration of reexamination, styled *inter partes* reexamination. American Inventors Protection Act of 1999 ("AIPA"), Pub. L. No. 106-113, tit. IV, §§ 4601–4608, 113 Stat. 1501, 1501A-567 to 1501A-572 (codified at 35 U.S.C. §§ 311–318 (2006)). *Inter partes* reexamination gave third parties "greater opportunities to participate in the Patent Office's reexamination proceedings as well as in any appeal of a Patent Office decision." *Cuozzo Speed Techs., LLC* v. *Lee*, 136 S. Ct. 2131, 2137 (2016).

Inter partes reexamination was still fundamentally an examination, not an adversarial or litigation-style proceeding. The statute allowed a third party "one opportunity to file written comments" when the patent owner responded to the examiner (*e.g.*, by amending the claims or distinguishing the invention from the prior art). 35 U.S.C. § 314 (2006). The procedural rules did not permit a third party to participate like it could in litigation—they provided no ability to conduct discovery, argue at hearings, or present witnesses. *Inter partes* reexamination coexisted with litigation and was not an alternative to a district court action.

Unlike *ex parte* reexamination, Congress decided ***not*** to make *inter partes* reexamination retroactive. That is, only patents issuing from original applications filed on or after the statute's enactment date of November 29, 1999 could be attacked in *inter partes* reexamination. AIPA § 4608, 113 Stat. at 1501A-572 (codified at 35 U.S.C. § 311 note (2006)). Thus, patentees were on notice of, and their patents were issued with, an express condition reserving the Government's right to conduct *inter partes* reexamination.

C. *Inter Partes* Review and Other AIA Trials

Congress made sweeping changes to patent law with the enactment of the AIA in 2011. Pub. L. No. 112-29, 125 Stat. 284 (2011). In addition to shifting to a first-inventor-to-file system, the AIA created a regime of post-issuance proceedings for adjudicating disputes over patentability. It added three new adversarial proceedings in which challengers could participate fully: *inter partes* review ("IPR"), post-grant review ("PGR"), and covered business method review ("CBM"). AIA § 6, 125 Stat. at 299–313; *id.* § 18, 125 Stat. at 329–31. The Patent Office calls these proceedings "AIA trials." See, *e.g.*, 77 Fed. Reg. at 48,756–57.

Unlike the earlier reexamination proceedings, AIA trials do not follow the same basic procedures as initial examination. Instead, as their name suggests, they were designed to be adjudications where the agency weighs the relative strength of the parties' arguments. The statute further assembled a new agency tribunal—the Patent Trial and Appeal Board ("Board")—to conduct AIA trials.[1] See generally AIA § 7, 125 Stat. at 313–15.

1. *Inter partes* review allows parties to challenge a patent, on the basis that an earlier publication or patent renders the patent invalid for anticipation or obviousness. See AIA § 6(a), 125 Stat. at 299–304; 35 U.S.C. § 311.

Congress intended IPR to be a litigation-style proceeding. The House Judiciary Committee noted that the bill "converts *inter partes* reexamination *from an examinational to an adjudicative proceeding*." H.R. Rep. 98, pt. 1, 112th Cong., 1st Sess. 46 (2011) ("House Rep.") (emphasis added). In justifying these changes, the committee observed that reexamination had not been an "effective and efficient alternative" to district court litigation. *Id.* at 45. The purpose of making IPR an "adjudicative" proceeding was so that it would be an "alternative" to court.

Consequently, the conduct of an IPR looks more like going to court than going to the Patent Office for examination of a patent application. The statute enabled discovery (including depositions of witnesses), the use of experts and declarants, protective orders, and oral hearings. 35 U.S.C. § 316(a); 37 C.F.R. §§ 42.1–42.74. The implementing regulations even adopt the Federal Rules of Evidence.

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[1] The Federal Circuit recently held that the appointment of the Board's administrative patent judges is unconstitutional under the Appointments Clause. *Arthrex, Inc.* v. *Smith & Nephew, Inc.*, 941 F.3d 1320, 1325 (Fed. Cir. 2019). As of the date of this petition, that appeal is ongoing.

37 C.F.R. § 42.62. Unlike *ex parte* reexamination, any party to an IPR dissatisfied with the Board's decision may appeal to the Federal Circuit. 35 U.S.C. § 319.

Congress made two other decisions to make IPR an "alternative" to litigation. *First*, IPR expressly "appl[ies] to any patent issued *before*, on, or after" the effective date of September 16, 2012. AIA § 6(c)(2)(A), 125 Stat. at 304 (emphasis added). In the legislative record, the sole mention of making IPR applicable to pre-AIA patents is a bullet in the committee report, stating that the AIA would "repeal" the "1999 limit" (which accompanied *inter partes* reexamination, *supra* p. 9). House Rep. at 47. Instead, "all patents can be challenged in inter partes review." *Id.* This made IPR available to attack the validity of millions of issued patents—many of which (like Enzo's Patent) issued from pre-1999 applications and had never been subject to *any* adversarial proceeding at the Patent Office. See *U.S. Patent Statistics Chart, Calendar Years 1963–2018*, *supra*.

Second, unlike a patent challenger in district court subject to the clear-and-convincing evidence standard, an IPR petitioner need prove unpatentability by only a preponderance of the evidence to secure the revocation of a patent. 35 U.S.C. § 316(e). The House Judiciary Committee listed this lower burden of proof among other supposed "improvements" to the proceeding. House Rep. at 47. Although the AIA did not change the statutory presumption of validity in § 282 or the clear-and-convincing standard for proving invalidity in district court proceedings, an accused infringer may avoid that heightened standard by initiating a parallel IPR before the Board.

2. The two other types of AIA trials, PGR and CBM, allow a wider scope of challenges but are limited to narrower sets of patents. In those trials, a challenger may

assert nearly any basis that an issued patent is unpatentable. See 35 U.S.C. § 321(b) (allowing "any ground that could be raised under" 35 U.S.C. § 282(b)(2)–(3)). Thus, almost any invalidity defense that a district court litigant could have asserted under § 282 is also available in PGR and CBM proceedings.

Congress made PGR available *only prospectively* for post-AIA patents. AIA § 6(f)(2)(A), 125 Stat. at 311; see also 35 U.S.C. § 100 note (2012) (defining post-AIA patents as those issuing from any application with any claim that has an effective filing date on or after March 16, 2013). Owners of post-AIA patents therefore acquire their patents with the express condition that the patents may be challenged and revoked in PGR proceedings. Thus, PGR does not face the same retroactivity concerns as IPR.

Congress made CBM available as a transitional program for "covered business method patents." Congress also made CBM retroactive—applicable to patents that issued before the enactment of the AIA. AIA § 18(a)(2), 125 Stat. at 330 (providing that CBM regulations "shall apply to any covered business method patent issued before, on, or after that effective date"). CBM is currently scheduled to sunset in September 2020. See AIA § 18(a)(3), 125 Stat. at 330–31.

3. During the consideration of the AIA, opponents specifically objected to "provisions in the bill that apply retroactively," because unlike the majority of the AIA's reforms (such as the transition to a first-inventor-to-file system) that apply going forward, these provisions "apply[] to patents granted more than a decade ago." House Rep. at 162 (statement of Rep. John Conyers, Jr., dissenting views). On the floor of the House, Rep. Schock argued that the CBM provisions were unfairly "retroac-

tive" especially when applied to patents "that [had] undergone initial scrutiny, review, and have even been upheld in court." 157 Cong. Rec. H4496 (daily ed. June 23, 2011). On the floor of the Senate, Sen. Pryor expressed concerns that the CBM provisions would allow an agency to review "patents whose claims ha[d] been found valid both through previous reexaminations by the PTO and jury trials," as patent claims that had already withstood review "should be considered presumptively valid." 157 Cong. Rec. S5428 (daily ed. Sept. 8, 2011).

Neither the House nor the Senate specifically debated the retroactivity of the IPR provisions.

II. FACTS AND PROCEDURAL HISTORY

1. Founded in 1979 by Dr. Elazar Rabbani, Enzo sought to develop groundbreaking nucleic acid detection technology, using an interdisciplinary team of chemists and molecular biologists. From those efforts, Enzo filed, in 1983, the first patent application in a chain that eventually issued as U.S. Patent No. 7,064,197, claiming nucleic acid detection techniques involving non-porous solid supports. C.A. App. 112. The patented techniques can be used to diagnose disease by detecting the presence or quantity of certain genetic material, such as nucleotide sequences in a sample being tested, using non-radioactive detection.

Enzo's Patent issued on June 20, 2006, more than five years before the enactment of the AIA. C.A. App. 112–29. From 2006 to 2012, Enzo's Patent could be revoked or invalidated in only two proceedings: (1) *ex parte* reexamination (which did not allow adversaries to be involved beyond an initial request for the Patent Office to take a second look), and (2) district court litigation (where the presumption of validity governs). Because the patent ap-

plication that became Enzo's Patent was filed before November 29, 1999, C.A. App. 112, it was never subject to *inter partes* reexamination.[2]

2. After Enzo filed suit for infringement against Hologic, Inc. ("Hologic") and Becton, Dickinson and Company ("BD") in district court,[3] Hologic filed two petitions for *inter partes* review in 2016, availing itself of the AIA's new regime. Pet. App. 20a, 83a; C.A. App. 137–206, 3790–3860. Hologic argued that most of the claims of Enzo's Patent are unpatentable over prior art references. See Pet. App. 23a–25a, 86a–88a. The Board instituted trial on both petitions and allowed BD to join as co-petitioner.[4] Pet. App. 20a, 83a.

In IPR2016-00820, the Board found that Hologic and BD proved, by a preponderance of the evidence, that all the challenged claims are unpatentable. Pet. App. 80a. In IPR2016-00822, the Board found that Hologic and BD proved, by a preponderance of the evidence, that all the challenged claims are unpatentable. Pet. App. 142a.

3. Enzo appealed. Enzo argued that the Board had erred in its findings of anticipation, obviousness, and the status of a reference as prior art. Pet. App. 8a–17a. Enzo further argued that the application of IPR to Enzo's Pa-

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[2] As explained above (p. 9), *inter partes* reexamination applied only prospectively to patents issuing from applications filed on or after the enactment date of the American Inventors Protection Act of 1999. 35 U.S.C. § 311 note (2006).

[3] *Enzo Life Sciences, Inc.* v. *Hologic, Inc.*, No. 1:15-cv-00271-LPS-CJB (D. Del. filed Mar. 27, 2015); *Enzo Life Sciences, Inc.* v. *Becton, Dickinson & Co.*, No. 1:12-cv-00275-LPS (D. Del. filed Mar. 6, 2012).

[4] BD did not initially file its own petition for IPR within one year of being sued. See 35 U.S.C. § 315(b) (providing time bar for district court defendants).

tent is unconstitutional under the Fifth Amendment because it retroactively eviscerated rights that vested at issuance. See Pet. App. 18a; Enzo C.A. Br. 59–61; Enzo C.A. Reply Br. 25–30.[5] BD[6] responded to the constitutional issue. BD C.A. Br. 65–68. The Government intervened to defend the constitutionality of applying IPR to pre-AIA patents. Pet. App. 2a; see generally Gov't C.A. Br. A panel of the Federal Circuit heard oral argument on July 9, 2019. See Pet. App. 17a.

After oral argument, a different panel of the Federal Circuit held that the retroactive application of IPR did not violate the Takings Clause in *Celgene Corp.* v. *Peter*, 931 F.3d 1342 (Fed. Cir. July 30, 2019). The Government filed a notice of supplemental authority in this case, citing *Celgene*. Gov't Notice of Suppl. Authority, D.I. 87 (Aug. 1, 2019). Enzo responded, explaining that the Takings Clause (at issue in *Celgene*) is distinct from "the Due Process Clause, the basis of Enzo's constitutional challenge." Enzo Notice of Suppl. Authority, D.I. 88 (Aug. 14, 2019).

4. A panel of the Federal Circuit affirmed. Pet. App. 2a. The panel upheld the Board's findings of unpatentability on substantial evidence review. Pet. App. 6a, 11a–12a, 15a–17a. Regarding constitutionality, the panel construed Enzo's Fifth Amendment argument as a Takings Clause challenge. See *id.* at 18a.

In one paragraph, the panel dismissed Enzo's concerns. The panel asserted without analysis that the same

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[5] See also Notice of Appeal at 2, *Hologic, Inc.* v. *Enzo Life Scis., Inc.*, Case IPR2016-00820 (P.T.A.B. Nov. 29, 2017) (raising the issue "whether *inter partes* review is unconstitutional as applied to the '197 patent because the enactment of the *inter partes* review statutes retroactively impaired Enzo's vested rights in the '197 patent, which rights vested when the '197 patent issued in 2006").

[6] The original petitioner, Hologic, withdrew. Pet. App. 6a.

issue had already been addressed in *Celgene*: "the retroactive application of IPR to the '197 patent, which issued before the enactment of the AIA, is *not an unconstitutional taking* under the Fifth Amendment." Pet. App. 18a (emphasis added). The opinion ignored due process and did not address Enzo's vested rights arguments. See generally Pet. App. 1a–18a.

6. Enzo timely petitioned for rehearing and rehearing en banc, highlighting that the panel failed to address Enzo's Due Process Clause arguments and that the Due Process Clause and the Takings Clause provide distinct protections. Enzo Pet. for Reh'g & Reh'g En Banc, D.I. 94 (Oct. 30, 2019). However, the Federal Circuit denied Enzo's petition on December 4, 2019. Pet. App. 145a.

REASONS FOR GRANTING THE PETITION

Serious questions about the constitutionality of retroactively subjecting pre-AIA patents to *inter partes* review have existed since the AIA's enactment over 8 years ago. This case presents that important constitutional question, which this Court expressly deferred in *Oil States Energy Services, LLC* v. *Greene's Energy Group, LLC*, 138 S. Ct. 1365 (2018) (No. 16-712):

> Oil States does not challenge the retroactive application of inter partes review, even though that procedure was not in place when its patent issued. Nor has Oil States raised a due process challenge. Finally, our decision should not be misconstrued as suggesting that patents are not property for purposes of the Due Process Clause or the Takings Clause.

Id. at 1379. Faced with IPR proceedings against its own pre-AIA patent, Enzo has maintained all along that the retroactive application of IPR violates the vested rights

doctrine—a prohibition on certain forms of retroactive legislation that is grounded in the Due Process Clause. Academics, practitioners, inventors, and industry participants that depend on patent rights have all questioned the unfair retroactivity of IPR.[7] But the court of appeals rejected Enzo's argument. The time has therefore come for the Court to answer the question.

Allowing the Federal Circuit's decision to stand would give Congress carte blanche to enact retroactive substantive changes affecting previously granted property rights, such as shortening the term of a patent long after it issued. And it would empower the Government to stack the deck against property owners by making it easier for an owner's adversary to invoke the Government's powers to take away what the Government had already given.

This is an important question, and this case presents the ideal vehicle to address it. The Court should grant the petition.

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[7] See, *e.g.*, Brief of Biotechnology Innovation Org. (BIO) & Ass'n of Univ. Tech. Managers (AUTM) as Amici Curiae in Support of Pet'r, *Oil States*, 2017 WL 3888208, at *30–32; Brief of 3M Company et al. as Amici Curiae in Support of Neither Party, *Oil States*, 2017 WL 3888218, at *7–8 ("Congress may not change the fundamental nature of that right once vested by an issued patent. * * * Private property that is vested thus comes with settled expectations that cannot be disturbed by retroactive changes to the nature of the right."); Vishnubhakat, *supra*, at 521; Gregory Dolin & Irina D. Manta, *Taking Patents*, 73 Wash. & Lee L. Rev. 719 (2016) (arguing that the retroactive application of IPR may violate the Takings Clause).

I. THE RETROACTIVE APPLICATION OF *INTER PARTES* REVIEW TO PRE-AIA PATENTS VIOLATES THE DUE PROCESS CLAUSE VESTED RIGHTS DOCTRINE

A. The Due Process and Takings Clauses Provide Distinct Protections for Property Rights.

The court below erred by relying on a Takings Clause case to reject Enzo's due process arguments. Its holding was premised entirely on Enzo's due process challenge being the same "issue" that had been decided below in *Celgene Corp.* v. *Peter*, 931 F.3d 1342 (Fed. Cir. 2019). See Pet. App. 18a. In that earlier case, the Federal Circuit rejected a Takings Clause challenge to the retroactive application of IPR to pre-AIA patents, focusing on whether a taking had occurred at all. *Celgene*, 931 F.3d at 1358–63. *Celgene* did not analyze due process. See *id.* Although Enzo alerted the Court to the difference between Enzo's argument (grounded in the Due Process Clause) and Celgene's argument (grounded in the Takings Clause) both before and after the panel opinion, *supra* pp. 15–16, the full court of appeals allowed the holding to stand.

The due process and the just-compensation provisions of the Fifth Amendment offer distinct protections. As this Court explained in *Lingle* v. *Chevron U.S.A. Inc.*, 544 U.S. 528 (2005), whether legislation passes muster under a due process analysis "is logically prior to and distinct from the question whether a regulation effects a taking." *Id.* at 543; see also *id.* at 540–41 (reviewing "substantially advances" test "derived from due process"). The Takings Clause "does not bar government from interfering with property rights, but rather requires compensation in the event of * * * a taking." *Id.*; *Knick* v. *Township of Scott*, 139 S. Ct. 2162, 2170 (2019). By con-

trast, the Due Process Clause acts as a prohibition on unreasonable, arbitrary, or capricious action; "[n]o amount of compensation can authorize such action." *Lingle*, 544 U.S. at 543. In other words, if a government action violates due process, it is void; if the action is a taking, the remedy is compensation.

In advancing its constitutional challenge below, Enzo cited this Court's older cases that prohibited retroactively eviscerating vested rights. While those cases did not specifically identify which clause of the Fifth Amendment applied, they show that the vested rights doctrine is grounded in due process: after all, the Court invoked due process remedies to invalidate retroactive legislation. See, *e.g.*, *Choate* v. *Trapp*, 224 U.S. 665, 673–74 (1912) (citing "the provisions of the 5th Amendment"); *Ward* v. *Bd. of Cty. Comm'rs*, 253 U.S. 17, 20 (1920) (citing the Fifth Amendment). For instance, in *Choate*, the Court declared that the tax-exemption rights in grants of land were "protected from repeal," remanding for an injunction barring enforcement of the new legislation. 224 U.S. at 678–79. That disposition—voiding the legislation rather than remanding to determine whether adequate compensation had been paid for the Government's intrusion on the granted property right—is a due process holding.

The Federal Circuit's decision ought to be set aside because of this error.

B. The Federal Circuit's Decision Contravenes This Court's Precedents Forbidding the Retroactive Diminishment of Vested Property Rights.

The Federal Circuit erred in upholding the constitutionality of the retroactive application of IPR to pre-AIA patents. Due process forbids subsequent changes in law

from diminishing or eviscerating vested rights in a government grant. Patents are property for purposes of the Due Process Clause. *Oil States*, 138 S. Ct. at 1379. For utility patents, the burden of proof required to revoke a patent in an adversarial proceeding is a vested right because burdens of proof are substantive law. *Medtronic, Inc.* v. *Mirowski Family Ventures, LLC*, 571 U.S. 191, 199 (2014) ("The assignment of the burden of proof is a rule of substantive law." (quoting *Dir., Office of Workers' Comp. Programs* v. *Greenwich Collieries*, 512 U.S. 267, 271 (1994))). Therefore, retroactively subjecting Enzo's Patent to IPR vitiated a vested right.

1. When the Government grants property rights, the substantive provisions of statutes that define the terms of the grant are "vested property right[s] arising out of a law of Congress and protected by the Constitution of the United States," "which Congress could not repeal consistently with the Fifth Amendment." *Ward*, 253 U.S. at 20–21.

Land patents are a historical example. When the Government granted land patents bearing statutory tax exemptions, the Supreme Court upheld those tax exemptions as vested rights that could not be diminished by subsequent legislation. *Id.* (citing *Choate*, 224 U.S. at 665; *Gleason* v. *Wood*, 224 U.S. 679 (1912); *English* v. *Richardson*, 224 U.S. 680 (1912)). Because the tax exemption was among the bundle of rights transferred to the patent-holder along with title to the land, the Government could not later deprive the patent-holder of that right. *Choate*, 224 U.S. at 673–74 ("The patent issued in pursuance of those statutes gave * * * as good a title to the exemption as it did to the land itself. Under the provisions of the 5th Amendment there was no more power to deprive him of the exemption than of any other right in the property.").

The Court drew a distinction between statutory provisions that "fram[e]" a general legislative scheme, and provisions that define the terms of an exchange or transfer. See *Choate*, 224 U.S. at 674. The former category could be repealed at any time even if a person had taken actions in reliance on the statutory framework, because there had been nothing given or received "in exchange for the offer," "no consideration moving from one to the other." *Id.* at 674–75. But the latter category, which defines the substance of what the government had given away, became "vested property right[s] which could not be abrogated by statute." *Id.* at 678–79. Thus, a substantive statutory provision defining the grant does not "stand[] on a different footing from the grant of the land itself"—it is itself a property interest of the patent-holder. See *id.* at 674.

These principles equally apply to utility patents. *McClurg* v. *Kingsland*, 42 U.S. (1 How.) 202, 206 (1843). In considering the effect of a repeal of a statute that created certain patent rights, this Court held that subsequent legislation "can have no effect to impair the right of property then existing in a patentee, or his assignee, according to the well-established principles of this court." *Id.* (citing *Soc'y for Propagation of Gospel in Foreign Parts* v. *Town of New Haven*, 21 U.S. (8 Wheat.) 464, 493–94 (1823)).[8] Thus, a holder of an issued utility patent owns a bundle of rights, defined by the unique claims that set out the technological realm of his exclusive rights, see 35 U.S.C. § 112(b), along with the substantive statutory provisions that governed the terms of the patent at the time of issuance.

[8] As explained in section II, *infra*, these land patent and vested-rights precedents have never been overruled.

2. Under the vested rights doctrine, the presumption of validity is a property interest.

The burden of proof required to revoke a patent in an adversarial proceeding is not a mere procedural provision; it is substantive law. In *Medtronic*, this Court acknowledged "settled case law" that "the burden of proof is a substantive aspect of a claim." 571 U.S. at 199 (quoting *Raleigh* v. *Ill. Dep't of Revenue*, 530 U.S. 15, 20–21 (2000)) (internal quotation marks omitted). Like other substantive provisions—*e.g.*, the temporal term of a patent, 35 U.S.C. § 154, or the exclusive rights to make, use, sell, and import the invention, § 271—the burden of proof is one of the many vested rights to which a patent-holder takes title once the Patent Office issues him a patent. Congress could no more retroactively shorten the term of a patent than it could eviscerate an issued patent's presumption of validity.

In short, the right to a clear and convincing burden of proof in adversarial proceedings against Enzo's Patent is a property interest that vested when the patent issued. The Due Process Clause therefore forbids subsequent statutory enactments from depriving Enzo of that vested right.

3. The AIA deprived Enzo of that vested burden of proof by subjecting Enzo's Patent to IPR where unpatentability may be established by a mere preponderance of the evidence. See 35 U.S.C. § 316(e). The AIA avoided doing so outright—Congress did not literally repeal the presumption—but the AIA undercuts the presumption by creating a new, parallel path where it does not apply. After enactment of the AIA, parties (like BD in this case) can and do avail themselves of adversarial IPRs to challenge patents, circumventing the higher burden of proof in district court.

IPR permits accused infringers, like BD, to pursue trials before the Board as a substitute for trials before a court. For example, BD submitted expert testimony, cross-examined Enzo's witness, objected to testimony or exhibits, and participated in oral argument—all hallmarks of adversarial litigation available in IPR. See, *e.g.*, 37 C.F.R. pt. 42. These procedures were not available in an agency proceeding before the AIA created IPR.

In the end, BD established unpatentability by only a preponderance of the evidence (Pet. App. 80a, 142a), when it would have faced a higher bar in litigation. Moreover, the Federal Circuit reviewed the Board's decision under the substantial evidence standard. This relatively deferential review incorporates the burden of proof used by the Board. *OSI Pharms., LLC* v. *Apotex, Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019). Because of the lower burden of proof at the Board, the court of appeals is more likely obligated to affirm the findings in spite of contrary evidence in the record. See *id.* (observing that a decision could be affirmed if the standard below were a preponderance standard even if the same record would require reversal had the standard of proof been "clear and convincing evidence"). Thus, the existence of judicial review of IPR proceedings does not ameliorate the consequences to a patent owner in facing a lower burden of proof in the forum of first impression.

Successful IPR petitioners, like BD, may then assert collateral estoppel in district court litigation. *E.g.*, *XY, LLC* v. *Trans Ova Genetics*, 890 F.3d 1282, 1294 (Fed. Cir. 2018). Even aside from collateral estoppel, a successful IPR leads to cancellation of the claims. 35 U.S.C. § 318(b). Under current Federal Circuit case law, cancellation of claims moots concurrent litigation involving those claims. *Fresenius USA, Inc.* v. *Baxter Int'l, Inc.*, 721 F.3d 1330, 1332 (Fed. Cir. 2013).

This common scenario shows the evisceration of the presumption of validity—a vested patent right—due to retroactive IPR. Like Enzo in this case, a patent owner may sue for infringement in court, but find its patent revoked in a proceeding that bypasses the clear and convincing evidence standard. IPR has rendered the heightened burden of proof to revoke a patent a dead letter.

4. Because the retroactivity of the IPR provisions eviscerates the vested presumption of validity, this Court should hold that the retroactive application of IPR to pre-AIA patents is unconstitutional under the Due Process Clause.

II. THIS COURT SHOULD CLARIFY WHEN THE DUE PROCESS CLAUSE PROTECTS AGAINST RETROACTIVE LEGISLATION THAT DIMINISHES PROPERTY RIGHTS

This Court should grant the petition to answer a critical question that its precedents have left unclear: When, if ever, does the Due Process Clause prevent legislative retroactivity? The Government argued below that retroactive legislation will survive so long as there is a rational basis. Gov't C.A. Br. 25–29. Although it is true that this Court has applied a rational basis test to tax and economic legislation, the Government's position ignores this Court's earlier, still-valid precedents showing that legislation affecting granted property is analyzed differently.

The two lines of precedent suggest that different tests apply to different types of legislation. First, where the retroactivity affects discrete, identifiable property interests, particularly the vested rights in a past grant from the Government, this Court has regarded the Fifth Amendment as an outright prohibition on retroactive diminishment. See, *e.g.*, *McClurg*, 42 U.S. at 206. Second, when property is not at stake, retroactivity is prohibited

only if it creates such unfairness that the legislation is essentially arbitrary. The rational basis cases are more recent, but they have *never* overruled the earlier vested rights precedents. Granting this petition would allow the Court to clarify the analytical framework.

Beginning in the late twentieth century, this Court began to rebuff retroactivity challenges to tax legislation and legislation arising from Congress's interstate commerce powers. Those cases involved new legislation attaching monetary liability to past acts. *E.g.*, *Usery* v. *Turner Elkhorn Mining Co.*, 428 U.S. 1, 15–20 (1976) (upholding retroactive legislation requiring employers to pay benefits to former employees); *Pension Benefit Guar. Corp.* v. *R.A. Gray & Co.*, 467 U.S. 717, 728–34 (1984) (upholding retroactivity of pension plan legislation that reached back to the 5-month timeframe when Congress had been debating the prospective provision). Both in *Usery* and *Pension Benefit*, the Court explained that its application of a rational basis test arose from the "presumption of constitutionality" for "legislative Acts adjusting the burdens and benefits of economic life." *Usery*, 428 U.S. at 15; *Pension Benefit*, 467 U.S. at 729 (citing "strong deference accorded legislation in the field of national economic policy"); see also *United States* v. *Carlton*, 512 U.S. 26, 30 (1994) (equating the due process test for retroactive tax statutes with the test for economic legislation). The test for retroactivity in this sphere is solely "that the retroactive application of a statute is supported by a legitimate legislative purpose furthered by rational means." *Pension Benefit*, 467 U.S. at 729.

Nevertheless, none of these due process cases involved rights that had previously been *conveyed, issued, or granted* by the Government pursuant to a statutory scheme. That distinction is key: the challengers in those cases did not hold any identifiable property interest.

Challenges to retroactive taxes stand in a different class from challenges to retroactive modifications to statutory rights in a patent grant. "Tax legislation is not a promise, and a taxpayer has no vested right in the Internal Revenue Code." *Carlton*, 512 U.S. at 33; *Choate*, 224 U.S. at 674–75 (distinguishing a general tax scheme that could be repealed because the legislature "was not making promises," from a vested tax exemption in a granted land patent). By contrast, a utility patent is a conveyance of a bundle of rights secured by a bargain with the Government—and the public—based on the law then in effect. A patent-holder accordingly has vested property rights that due process protects.[9]

This Court's precedents lack clear guidance on the proper analytical framework for assessing challenges to retroactive legislation. In particular, this Court's fragmented opinions in *Eastern Enterprises* v. *Apfel*, 524 U.S. 498 (1998), invalidated retroactive legislation but provided no clarity on the correct analysis to arrive at that decision. Four Justices held that the retroactive provision violated the Takings Clause, *id.* at 504 (plurality opinion), while five Justices argued that the proper frame for analysis was the Due Process Clause, see *id.* at 539 (Kennedy, J., concurring in the judgment and dissenting in part); *id.* at 554–56 (Breyer, J., dissenting) ("The question involved—the potential unfairness of retroactive liability—finds a natural home in the Due Process Clause."). Justice Kennedy urged that "[a]ccepted principles forbidding retroactive legislation" under the Due Process Clause were "sufficient to dispose of the case," because the challenged

[9] Petitioner's argument should not be read to suggest that inventors or patent owners have a generalized vested right in the Patent Act—only that the issuance of a particular patent is a legally significant event at which time substantive rights, such as the presumption of validity, vest.

law had a severe retroactive effect and undermined the stability of investment and confidence in law. *Id.* at 547, 549 (Kennedy, J.). In his dissenting opinion in which three other Justices joined, Justice Breyer observed that "the Due Process Clause can offer protection against legislation that is unfairly retroactive * * * for as courts have sometimes suggested, a law that is fundamentally unfair because of its retroactivity is a law that is basically arbitrary." *Id.* at 556 (Breyer, J.). As no single opinion garnered a majority, *Eastern Enterprises* provided no clear answer on the proper test for determining whether retroactive legislation is constitutional.

This case presents an opportunity to clarify the uncertainty in this Court's retroactivity precedents. The Court should adopt a clear, categorical rule between retroactivity affecting statutorily-defined property rights (which is prohibited), and retroactivity affecting only generalized economic interests (which, while disfavored, need only survive rational basis review).

III. WHETHER PATENT LAW MAY BE CHANGED RETROACTIVELY IS VITALLY IMPORTANT FOR INVENTORS AND THE ADVANCEMENT OF INNOVATION

Deciding the question presented is vitally important for inventors, both those who earned pre-AIA patents and those who may become patent applicants and owners in the future.

For the millions of inventors whose pre-AIA patents are now more vulnerable to attack, and therefore, more difficult to enforce than they were before the creation of IPR, retroactivity has directly diminished the value of their patents. Some estimates have quantified a drop in the average value of an American patent by 58 percent from 2013 to 2018 due to the AIA's changes to patent law.

The Trouble with Patent-Troll-Hunting, The Economist, Dec. 14, 2019, at 60; Dolin & Manta, *supra* note 7, at 791–92 (reporting that "the value of patents has dropped by two-thirds since and because of the AIA," attributable to a "putative infringer's knowledge that all patents have been significantly weakened through tinkering with their scope and the abolition of the robust presumption of validity"). While quantifying the economic effect of IPR alone is difficult, the impact on patent owners is real. And because the effects sweep across all patents, they not only affect nonpracticing entities (so-called "patent trolls"), but also harm practicing biotechnology firms like Enzo that rely on the patent system to protect their innovations.

Retroactive changes, like undermining the presumption of validity in pre-AIA patents, upend the benefit of the patent bargain for these inventors and patent owners. When they made the decision to surrender the secrecy of their inventions in exchange for patent protection, they did so with the reasonable expectation that the rights and benefits of a patent available at the time would remain constant for the life of the patent. Cf. *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 739 (2002) ("Fundamental alterations in these rules risk destroying the legitimate expectations of inventors in their property.").[10] This Court has recognized that inven-

[10] With the exception of IPR, Congress had respected those expectations. For example, when it altered the length of the patent term in 1994—to be 20 years from a patent's earliest effective filing date instead of 17 years from issuance—Congress took care not to diminish the term of issued patents. See Uruguay Round Agreements Act, Pub. L. No. 103-465, sec. 531, § 154(c)(1), 108 Stat.

tors' reliance interests are a potent policy rationale supporting stability in patent law. That rationale undergirds the presumption of validity itself. See *Microsoft*, 564 U.S. at 108 (citing Brief for the United States as Amicus Curiae at 33, *Microsoft* (No. 10-290)). Lowering the bar for establishing invalidity to a preponderance standard significantly diminishes the value of already issued patents by making it more difficult for owners to enforce their patents against accused infringers. Even the Government once agreed:

> [T]he preponderance standard would diminish the expected value of patents and would reduce future inventors' incentives to innovate and to disclose their inventions to the public. And with respect to *existing* patents, a repudiation of the heightened standard that has historically governed infringement suits would alter the patent bargain by reducing the value of the rights that inventors have received in exchange for disclosing their innovations.

Brief for the United States as Amicus Curiae Supporting Respondents at 28, *Microsoft*, 564 U.S. 91 (No. 10-290), 2011 WL 991991 (emphasis in original).

Countless inventors in the future will also face the decision between exploiting an invention in secret, and forgoing secrecy by disclosing their inventions to the public in exchange for a patent, thereby advancing innovation. The Government's ability to upset their reliance interests by enacting retroactive changes later, and cancelling a pa-

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4809, 4984–85 (1994). And when the AIA transitioned the patent system to a first-inventor-to-file system, it did so only prospectively for later-filed patent applications. See AIA § 3(n), 125 Stat. at 293 (codified at 35 U.S.C. § 100 note).

tent upon only a mere preponderance in a contested proceeding, may very well deter inventors from participating in the patent system.

Under the Federal Circuit's holding in this case, virtually no retroactive change concerning patent rights would be limited by the Fifth Amendment under the Federal Circuit's holding. For example, the term of a patent is determined by statute. 35 U.S.C. § 154. Under the vested rights doctrine that Enzo invokes, the term—a substantive provision of law—is fixed once the patent issues. It is a vested right, part and parcel of the granted patent. But, between *Celgene* and the Federal Circuit's rejection of vested rights arising out of statutory grants, Congress could retroactively diminish the term of issued patents by subsequent legislation, contrary to this Court's precedents. Uncertainty about what future "reforms" might do to granted patents injures present patent-holders, disincentivizes inventors from participating in the patent system, and harms the "Progress of Science and useful Arts" that the patent system is meant to promote. See U.S. Const., art. I, § 8, cl. 8.

The retroactivity question has real consequences. Certiorari should be granted to address this important issue.

IV. DESPITE THE FEDERAL CIRCUIT'S CURSORY TREATMENT, THIS CASE PRESENTS AN IDEAL VEHICLE FOR RESOLVING THE RETROACTIVITY QUESTION THAT THE COURT RESERVED IN *OIL STATES*

The parties in this case and the Government have thoroughly briefed the Due Process Clause retroactivity issue below. This case presents an ideal vehicle for the

vested rights issue: While other parties have raised challenges to the retroactive application of IPR, those other cases currently ripe for review either focused on the Takings Clause,[11] concerned patents that issued *after* the enactment of the AIA,[12] or conceded that rational basis review is the governing test.[13] Enzo, by contrast, has maintained its vested rights theory since its notice of appeal.

The only remaining question in this case is the pure legal question of constitutionality under the Due Process Clause. There are no additional factual issues, or the application of law to fact, that remain. That procedural history makes this case an ideal vehicle to address the pure question presented—despite the fact that the Federal Circuit barely considered Enzo's serious constitutional question. Like in *Oil States*, where this Court granted certiorari even though the Federal Circuit summarily affirmed and ignored the petitioner's constitutional challenge, 639 F. App'x 639 (Fed. Cir. 2016) (per curiam), the Federal Circuit's avoidance of difficult constitutional issues with the patent system is not a bar to this Court's review.

The present case exemplifies the problems with the IPR regime and the Federal Circuit's approach to thorny questions of constitutionality. This Court's intervention is urgently needed.

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[11] See *Celgene*, 931 F.3d 1342, 1357–63.

[12] *Arthrex, Inc.* v. *Smith & Nephew, Inc.*, 935 F.3d 1319, 1331 (Fed. Cir. 2019).

[13] Petition for Writ of Certiorari, *Collabo Innovations, Inc.* v. *Sony Corp.*, No. 19-601, 2019 WL 5856141, at *32 (analyzing due process issue under "arbitrary and irrational" test).

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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MARCH 3, 2020

APPENDIX

APPENDIX A — OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT, FILED AUGUST 16, 2019

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-1232, 2018-1233

ENZO LIFE SCIENCES, INC.,

Appellant,

v.

BECTON, DICKINSON AND COMPANY,

Appellee,

UNITED STATES,

Intervenor.

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00820, IPR2016-00822.

August 16, 2019, Decided

Before LOURIE, O'MALLEY, and CHEN, Circuit Judges.

LOURIE, *Circuit Judge.*

Appendix A

Enzo Life Sciences, Inc. appeals from two final written decisions of the United States Patent and Trademark Office ("PTO") Patent Trial and Appeal Board ("the Board") holding various claims of U.S. Patent 7,064,197 ("the '197 patent") unpatentable as anticipated or obvious. *See Hologic, Inc. v. Enzo Life Scis., Inc.*, No. IPR2016-00820, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646 (P.T.A.B. Sept. 28, 2017) ("*'820 Decision*"); *Hologic, Inc. v. Enzo Life Scis., Inc.*, No. IPR2016-00822, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743 (P.T.A.B. Oct. 2, 2017) ("*'822 Decision*"). The PTO intervened to defend the constitutionality challenge to *inter partes* review ("IPR") proceedings as applied to patents issued before the enactment of the America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284 (2011). For the following reasons, we *affirm*.

BACKGROUND

Deoxyribonucleic acid ("DNA") and ribonucleic acid ("RNA") are nucleic acids made of a series of nucleotides. A nucleotide is composed of a sugar, a phosphate, and a nitrogenous base. DNA has four nitrogenous bases: adenine (A), guanine (G), cytosine (C), and thymine (T). RNA also has the bases adenine (A), guanine (G), and cytosine (C), but contains uracil (U) instead of thymine (T). A polynucleotide refers to multiple nucleotides linked together in a chain. Two strands of polynucleotides can bind to one another, *i.e.*, hybridize, through hydrogen bonding between complementary nucleotides known as Watson-Crick base pairing: bases T or U pair with A, and G pairs with C. A strand of nucleotides that is not

hybridized to another strand is said to be single-stranded, while two strands hybridized to each other are said to be double-stranded.

Enzo owns the '197 patent directed to "the detection of genetic material by polynucleotide probes." '197 patent col. 1 ll. 23-24. The invention leverages hybridization techniques to detect the presence of an analyte, which may be "a DNA or RNA molecule," "a molecular complex," or "a biological system containing nucleic acids, such as a virus, a cell, or group of cells." *Id.* col. 1 ll. 39-42. A polynucleotide probe that is complementary to a target analyte will hybridize with it and is thereby used to detect that analyte's presence. *See id.* col. 2 ll. 37-63. According to the invention, the analytes to be detected are "fixed . . . in hybridizable form to [a] non-porous solid support." *Id.* col. 13 ll. 63-67; *see also id.* col. 5 ll. 58-60. The specification also discloses that a "technique for improving the fixing or uniformity of the plastic surface for fixing DNA involves treatment of the surface with polylysine." *Id.* col. 11 ll. 37-39.

Independent claim 1 is representative of the claims challenged in IPR2016-00820 ("the '820 IPR") and independent claim 17 is representative of the claims challenged in IPR2016-00822 ("the '822 IPR"):

> 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).

Id. col. 13 ll. 63-67 (emphases added).

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

Id. col. 15 ll. 51-53 (emphases added).

Hologic, Inc. filed two petitions for IPR of the '197 patent. During both proceedings, Becton, Dickinson, & Company ("Becton") moved to join as a co-petitioner, and the Board granted the motions. *See* Joinder Order at 2, *Hologic, Inc. v. Enzo Life Scis., Inc.*, No. IPR2016-00820 (P.T.A.B. Mar. 27, 2017), Paper No. 32; Joinder Order at 2, *Hologic, Inc. v. Enzo Life Scis., Inc.*, No. IPR2016-00822 (P.T.A.B. Apr. 5, 2017), Paper No. 31. The Board instituted trial on all eight grounds of unpatentability across the two IPRs, which all rely on Fish[1] or VPK[2] as the primary reference.

The Board determined that all the challenged claims were unpatentable as anticipated by Fish or rendered

1. Falk Fish & Morris Ziff, *A Sensitive Solid Phase Microradioimmunoassay for Anti-Double Stranded DNA Antibodies*, 24 Arthritis and Rheumatism 534-43 (Mar. 1981), J.A. 1266-75 ("Fish").

2. A.C. van Prooijen-Knegt et al., *In Situ Hybridiza-tion of DNA Sequences in Human Metaphase Chromosomes Visualized by an Indirect Fluorescent Immunocytochemical Procedure*, 141 Experimental Cell Research 397-407 (Oct. 1982), J.A. 1288-98 ("VPK").

obvious by Fish alone or in combination with other prior art references. *'820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646, at *11-15; *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *10-15. The Board next determined that VPK qualified as a prior art reference. *'820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646, at *15-18; *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *15-18. The Board found that the '197 patent could not claim priority from its original parent application's filing date of January 27, 1983, because that application did not provide written description support for the claimed "non-porous solid support." *See, e.g.*, '197 patent col. 13 l. 63. Instead, the Board determined that the '197 patent could only claim priority from the 1983 application's child continuation-in-part application, which was filed on May 9, 1985. VPK was publicly available as of October 1982, more than a year before the critical date of May 9, 1985, and thus qualified as prior art. *See* 35 U.S.C. § 102(b) (2006). The Board then concluded that all the challenged claims were anticipated by VPK or would have been obvious over VPK in combination with other prior art references. *'820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646, at *19-24; *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *20-23.

Enzo appeals. The PTO intervened pursuant to 35 U.S.C. § 143 to defend against Enzo's constitutionality challenge to IPRs as applied to the '197 patent because it issued on June 20, 2006, which is before the enactment of the AIA in 2011. Enzo argues that constitutes a violation of the Fifth Amendment. Before this case was argued,

Hologic moved to withdraw as a party to this appeal, and this court granted the motion. *See Enzo Life Scis., Inc. v. Becton, Dickinson & Co.*, Nos. 2018-1232, 2018-1233 (Fed. Cir. Apr. 25. 2019), ECF No. 74. Becton remains as appellee. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We review the Board's legal determinations *de novo*, and the Board's factual findings underlying those determinations for substantial evidence. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). A finding is supported by substantial evidence if a reasonable mind might accept the evidence to support the finding. *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229, 59 S. Ct. 206, 83 L. Ed. 126 (1938).

Anticipation is a question of fact that we review for substantial evidence. *In re Rambus, Inc.*, 753 F.3d 1253, 1256 (Fed. Cir. 2014). A prior art document may anticipate a claim if it describes every element of the claimed invention, either expressly or inherently. *Husky Injection Molding Sys. Ltd. v. Athena Automation Ltd.*, 838 F.3d 1236, 1248 (Fed. Cir. 2016). Whether there are inherent teachings in a prior art reference is a question of fact. *See In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995).

Obviousness is a question of law based on underlying factual findings, including "the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the pertinent art, and

any objective indicia of non-obviousness." *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007)).

I. Anticipation by Fish

The Board determined 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 in the '820 IPR and claims 17, 19, 25, 105, 106, 114, 116, 119, 128, 129, 150, 152, 178, 180, 186, and 187 in the '822 IPR were anticipated by Fish. *'820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646, at *11-12; *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *10-11. Fish teaches a microradioimmunoassay for detecting antibodies that bind to double-stranded DNA ("dsDNA"). *See* J.A. 1266. It further notes the use of poly-L-lysine ("PLL") "to facilitate the binding of pure dsDNA to plastic surfaces." *Id.* Fish also discloses experiments using single-stranded DNA ("ssDNA") in the form of a mixture of synthetic polymers deoxyadenosine ("poly-dA") and deoxycytidine ("poly-dC") or "denatured calf thymus DNA." J.A. 1268.

All of the challenged independent claims in both the '820 IPR and '822 IPR require the single-stranded nucleic acid to be "fixed or immobilized in *hybridizable form*" (the "hybridizable form limitation"). *See, e.g.*, '197 patent col. 13 l. 65, col. 15 l. 52. The Board construed "hybridizable form" to mean "*capable* of binding through Watson-Crick base pairing," adopting the parties' agreed-upon construction. *'820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL

4339646, at *5 (emphasis added).[3] The Board further clarified the construction in its final written decisions to mean that "it has bases available for base-pairing." 2017 Pat. App. LEXIS 11680, [WL] at *6.

Based on its construction, the Board found that Fish disclosed the hybridizable form limitation. The Board found that Fish teaches ssDNA bound to the PLL-coated wells. *See* 2017 Pat. App. LEXIS 11680, [WL] at *8. The Board further found that being capable of hybridizing is the inherent result of ssDNA being fixed to PLL-treated non-porous solid supports. *See* 2017 Pat. App. LEXIS 11680, [WL] at *10-11. The Board rejected Enzo's argument that Fish failed to disclose hybridization and found that "actual hybridization is not a requirement of any challenged claim." 2017 Pat. App. LEXIS 11680, [WL] at *10. The claims only recite "hybridizable form," and the Board noted that the parties' stipulated construction required that the single-stranded nucleic acid be "*capable* of binding through Watson-Crick base pairing" and did not require "actual hybridization." *Id.* (citations omitted). The Board thus concluded that the challenged claims were anticipated by Fish. 2017 Pat. App. LEXIS 11680, [WL] at *11-12.

On appeal, Enzo argues that Fish does not disclose nucleic acid hybridization, but instead describes "binding radioactively-labeled antibodies" to dsDNA. Appellant's Br. 24 (emphasis omitted). Moreover, Enzo contends, as it

3. The claim construction discussions of the two Board opinions are identical. Thus, citations regarding the Board's claim construction will only be to the *'820 Decision*.

did before the Board, that the nucleic acids in Fish did not actually hybridize in any of the experiments, and thus the finding that Fish discloses hybridization lacks substantial evidence. According to its expert, Dr. Buck, the fact that a single-stranded nucleic acid exists does not mean it is in hybridizable form. For example, Dr. Buck testified that "a nucleic acid may be 'restricted by the bonds formed between the nucleic acid and the support' or inhibited by 'entanglement of the nucleic acid strands themselves, which may form loops and coils, called secondary structures, restricting the diffusion of other nucleic acid strands available for hybridization.'" *Id.* at 25 (quoting J.A. 3630-31 ¶ 95, 5605-06 ¶ 95). Enzo also argues that Dr. Nelson, the petitioners' expert, failed to apply the modified claim construction and thus his testimony cannot constitute substantial evidence for the Board's findings.

Becton responds that the Board correctly found that Fish inherently discloses the hybridizable form limitation. Relying on Dr. Nelson's testimony, Becton argues that the positively-charged amines on the surface of the solid support coated with PLL, as disclosed in Fish, will bond with the negatively-charged phosphate groups in the DNA backbone leaving the bases free to hybridize. Becton criticizes Enzo for "deliberately sabotaging the experiment" in order to describe a situation where someone using Fish's PLL binding chemistry would not create a hybridizable single-stranded nucleic acid. Appellee's Br. 37. Becton contends that inherency cannot be defeated by "interfer[ing] with the natural result of a process." *Id.* at 38.

We agree with Becton that Fish's disclosure of a ssDNA bound to a solid support coated with PLL inherently discloses that the single-stranded nucleic acid is in hybridizable form. "A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001) (quoting *Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991)).

Here, substantial evidence supports the Board's finding that the single-stranded nucleic acid of Fish is inherently hybridizable. The Board reasonably relied on testimony from both experts that a characteristic of single-stranded nucleic acids is that their bases are available to pair with complementary bases through Watson-Crick pairing. *See '820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646, at *11 (citing J.A. 891 ¶ 64); *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *9; *see also* J.A. 874-75 ¶ 24, 891 ¶ 64 (Dr. Nelson's testimony); J.A. 3705-06 ¶ 189 (Dr. Buck's testimony). That is what a single-stranded nucleic acid does in the presence of complementary bases. Unless purposely prohibited, the binding capability is inherent in the nature of a single-stranded nucleic acid. The Board's finding that Fish's disclosure of a ssDNA fixed to a PLL-treated support inherently teaches the hybridizable form limitation is thus based on substantial evidence.

Enzo also argues that in the '822 IPR, the Board erred in finding that Fish disclosed an "array" of "single-stranded nucleic acids." *See, e.g.*, '197 patent col. 15 ll. 51-

53. All of the challenged independent claims in the '822 IPR recite an "array" of "single-stranded nucleic acids." *See, e.g., id.* The Board construed "array" to include "an orderly grouping or arrangement of wells or depressions." *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *4. The Board then found that Fish teaches this limitation because "it discloses microtitration trays having wells of ssDNA." 2017 Pat. App. LEXIS 11680, [WL] at *7 (citing J.A. 1268).

Enzo contends that Fish fails to disclose an "array" of "*single-stranded nucleic acids*." *See, e.g.*, '197 patent col. 15 ll. 51-53 (emphasis added). According to Enzo, the Board erred in reading the term "array" in isolation from "single-stranded nucleic acids," and thus erred in finding that a container with wells or depressions without any nucleic acids would meet the claim language.

Becton responds, and we agree, that the Board's finding was supported by substantial evidence. Fish describes supports having rows of wells coated with ssDNA. *See* J.A. 1268. The Board also credited Dr. Nelson's testimony that Table 1 in Fish provides evidence that the ssDNA bound effectively to the PLL-coated wells of the microtitration tray. *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *7 (citing J.A. 1268). That constitutes substantial evidence to support the Board's finding that Fish teaches an "array" of "single-stranded nucleic acids." *See, e.g.*, '197 patent col. 15 ll. 51-53.

Enzo does not raise any arguments with respect to any other claim limitation, nor does it separately argue the dependent claims. Thus, the dependent claims stand or fall together with the independent claims. *See In re Kaslow*, 707 F.2d 1366, 1376 (Fed. Cir. 1983). We therefore conclude that the Board did not err in finding that Fish anticipates 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 in the '820 IPR and claims 17, 19, 25, 105, 106, 114, 116, 119, 128, 129, 150, 152, 178, 180, 186, and 187 in the '822 IPR.

II. Obviousness Grounds Based on Fish

The Board determined that claims 31, 64, 68, 101, 192, and 195 in the '820 IPR and claims 130, 131, 151, and 154 in the '822 IPR would have been obvious over Fish. *'820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646, at *12-14; *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *11-14. Those claims add one of the following limitations: "wherein said nucleic acid comprises a nucleic acid sequence complementary to a nucleic acid sequence of interest sought to be identified, quantified or sequenced," *see, e.g.*, '197 patent col. 17 ll. 1-4; or "wherein said nucleic acid is RNA," *see, e.g., id.* col. 18 ll. 38-39; or "wherein said nucleic acids comprise a gene sequence or pathogen sequence," *id.* col. 22 ll. 42-43. Enzo does not separately argue the challenged dependent claims and relies on the arguments it raised for anticipation by Fish. Thus, for the same reasons that Fish anticipates the aforementioned claims, we also hold that Fish renders obvious claims 31, 64, 68, 101, 192, and 195 in the '820 IPR and claims 130, 131, 151, and 154 in the '822 IPR.

The Board next determined that claims 38, 78, and 218 in the '820 IPR and claims 113 and 185 in the '822 IPR would have been obvious over Fish and Gilham;[4] and claims 120 and 189 in the '822 IPR would have been obvious over Fish, U.S. Patent 3,572,892 ("Metzgar"), and Sato.[5] Enzo argues that the Board's findings of a motivation to combine Fish and Gilham, and Fish, Metzgar, and Sato, are not based on substantial evidence. We take the arguments asserted for each ground in turn.

A. Obviousness over Fish and Gilham

The Board determined that claims 38, 78, and 218 in the '820 IPR and claims 113 and 185 in the '822 IPR would have been obvious over Fish and Gilham. *'820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646, at *14-15; *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *14-15. The challenged claims add the limitation "wherein said fixation or immobilization to said nonporous solid support is *covalent*." *See, e.g.*, '197 patent col. 17 ll. 24-26 (emphasis added). Gilham teaches a method of covalently binding RNA to cellulous supports. *See* J.A. 1592-93. The Board found that a person of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to apply Gilham's method of covalently binding RNA to Fish's non-porous

4. P.T. Gilham, *Immobilized Polynucleotides and Nucleic Acids*, Immobilized Biochemicals and Affinity Chromatography 173-85 (1974), J.A. 1592-1604 ("Gilham").

5. Chikako Sato et al., *Cell Surface Charge and Cell Division in Escherichia coli after X Irradiation*, 87 Radiation Research 646-56 (1981), J.A. 4422-32 ("Sato").

supports, such as the microtitration plates, "because covalent binding provides a stronger linkage between the immobilized nucleic acids and the solid substrate." *'820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646, at *15 (internal citation omitted).[6]

Enzo argues that the Board failed to identify why a person of ordinary skill would have been motivated to use the covalent binding method for RNA in Gilham with the procedures for using DNA of PLL-coated plates to detect antibodies described in Fish. Moreover, according to Enzo, not only was there insufficient motivation to combine, but there would not have been an expectation of success. Enzo contends that Gilham teaches away from the use of nonporous supports like those in Fish, and that Gilham's covalent binding would likely negatively affect the nucleic acid's ability to hybridize.

Becton responds that the Board's finding of a motivation to combine Fish and Gilham was supported by subtantial evidence. We agree. Dr. Nelson, whom the Board credited, explained that both Fish and Gilham disclose nucleic acids bound to solid support surfaces with amine groups. *See* 2017 Pat. App. LEXIS 11680, [WL] at *13-14. The Board then found that a person of ordinary skill in the art would have been motivated to use the covalent binding from Gilham on Fish's non-porous solid supports. *See* 2017 Pat. App. LEXIS 11680, [WL] at *15. We also agree with Becton that Enzo's teaching away

6. The analyses of Fish and Gilham are identical in the two Board opinions. Thus, citations will only be to the *'820 Decision*.

arguments improperly attack the references individually. *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."). However, as the Board determined, it is the combined teachings of Gilham's chemistry for binding RNA in hybridizable form and Fish's methods of attaching nucleic acids to non-porous supports that render the claims obvious. *See '820 Decision*, 2017 Pat. App. LEXIS 11680, 2017 WL 4339646, at *15. Accordingly, the Board did not err in holding that claims 38, 78, and 218 in the '820 IPR and claims 113 and 185 in the '822 IPR would have been obvious over Fish and Gilham.

B. Obviousness over Fish, Metzgar, and Sato

The Board determined that claims 120 and 189 in the '822 IPR would have been obvious over Fish, Metzgar, and Sato. *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *13-14. The challenged claims add the limitation "wherein said non-porous solid support comprises *one or more hydroxyls*." *See, e.g.*, '197 patent col. 21 ll. 10-12 (emphasis added). Metzgar teaches a "multiple well tissue culture microscope slide" where the microscope slide is "glass or other transparent material." Metzgar col. 1 l. 2, col. 2 ll. 28-29. Sato discloses treating glass slides with PLL. *See* J.A. 4423. Dr. Nelson testified that "glass necessarily includes hydroxyl groups." *'822 Decision*, 2017 Pat. App. LEXIS 11681, 2017 WL 4407743, at *14 (citing J.A. 5789 ¶ 83 ("The glass slides of . . . Metzgar necessarily include hydroxyl groups, because that is a known property

of glass.")). The Board determined, based on Dr. Nelson's testimony, that a person of ordinary skill in the art would have been motivated to use the glass trays from Metzgar "as an alternative to Fish's polyvinyl trays." *Id.* (citing J.A. 5789 ¶ 83). In combination with Sato's teaching of treating glass slides with PLL, the Board concluded that the challenged claims would have been obvious over Fish, Metzgar, and Sato. *Id.*

Enzo argues that the Board failed to identify why a person of ordinary skill in the art would have been motivated to substitute glass plates for the polyvinyl microtitration trays disclosed in Fish. According to Enzo, the Board erred in failing to credit Dr. Buck's uncontested testimony that a person of ordinary skill would not combine those references because they would not work for their intended purposes.

Becton responds that substantial evidence supported the Board's finding of a motivation to combine Fish, Metzgar, and Sato, and we agree. The Board found that glass slides having wells or depressions were well-known at the time of the invention. *See id.* The Board further found, based on Dr. Nelson's testimony, that a person of ordinary skill in the art would have been motivated to immobilize nucleic acids using the methods described in Fish on the glass slides disclosed in Metzgar. *See id.* Additionally, the Board found that Sato teaches "treatment of glass slides with PLL prior to fixing cells on the slides." *Id.* The Board ultimately credited Dr. Nelson's testimony that a person of ordinary skill in the art would have been motivated to perform the nucleic

acid immobilization procedure disclosed in Fish on the glass slides in Metzgar treated with PLL as disclosed in Sato. *Id.* The Board's finding of a motivation to combine was thus based on substantial evidence. Accordingly, the Board did not err in determining that claims 120 and 189 in the '822 IPR would have been obvious over Fish, Metzgar, and Sato.

In conclusion, we determine that the Board did not err in holding that claims 1, 6, 8, 9, 12-17, 19, 25, 27, 31-34, 38, 41, 61-64, 68-70, 72-74, 78, 79, 100, 101, 105, 106, 113, 114, 116, 119, 120, 128-131, 150-152, 154, 178, 180, 185-187, 189, 191-195, 212, 213, 218, 219, 222, 225-227, 230, 233, and 236 of the '197 patent are invalid as anticipated by Fish or obvious over Fish alone or in combination with other prior art references.

III. Other Issues

Enzo argues that the Board erred in finding that VPK qualifies as prior art, and thus the claims are not unpatentable as anticipated or obvious over grounds that include VPK. Because we have determined that the Board did not err in concluding that all of the challenged claims are unpatentable on grounds based on Fish, we need not reach the arguments involving VPK. *See* Oral Arg. at 12:14-12:49, 25:58-26:11, *Enzo Life Scis., Inc. v. Becton, Dickinson & Co.*, Nos. 2018-1232, 2018-1233 (Fed. Cir. July 9, 2019), http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2018-1232.mp3.

Enzo also argues that the IPR process as applied retroactively to patents that issued before the enactment of the AIA violates the Fifth Amendment. We recently addressed this issue in *Celgene Corp. v. Peter*, No. 18-1167, 931 F.3d 1342, 2019 U.S. App. LEXIS 22517, 2019 WL 3418549, at *12-16 (Fed. Cir. July 30, 2019), which is now precedent that governs this case. *Celgene* held that "retroactive application of IPR proceedings to pre-AIA patents is not an unconstitutional taking under the Fifth Amendment." 2019 U.S. App. LEXIS 22517, [WL] at *16. Accordingly, we hold that the retroactive application of IPR proceedings to the '197 patent, which issued before the enactment of the AIA, is not an unconstitutional taking under the Fifth Amendment.

CONCLUSION

We have considered Enzo's remaining arguments but find them unpersuasive. For the foregoing reasons, we *affirm* the decisions of the Board.

AFFIRMED

APPENDIX B — FINAL WRITTEN DECISION OF THE UNITED STATES PATENT AND TRADEMARK OFFICE, PATENT TRIAL AND APPEAL BOARD, DATED 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.*

Appendix B

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.

Appendix B

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).

Appendix B

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
Fish	§ 103(a)	31, 64, 68, 101, 192, and 195
Fish and Gilham (Ex. 1019)[3]	§ 103(a)	38, 78, and 218

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 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).

Appendix B

References	Basis[1]	Claims Challenged
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), VPK,[6] 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).

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 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

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.

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

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."

acid bound to a solid support is in hybridizable form depends on its "attachment methodology and chemistry." Ex. 2042 ¶94. Dr. Buck elaborated as follows:

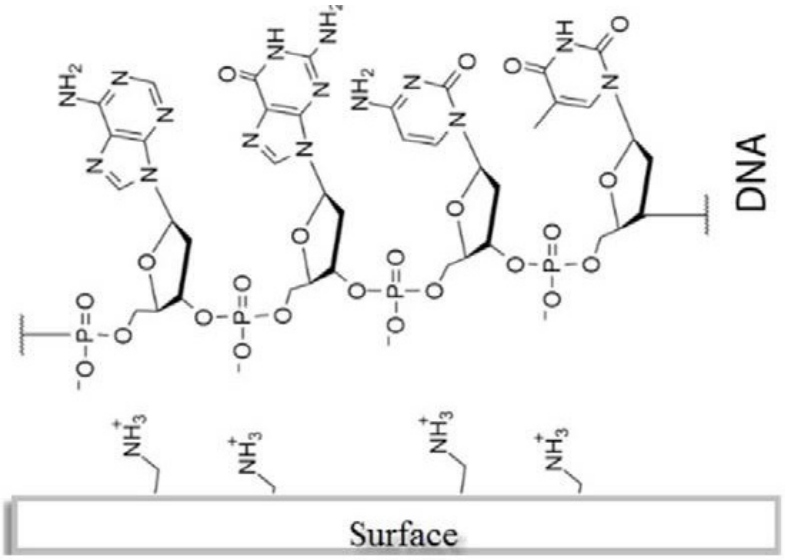
> For example, the way in which a single-stranded nucleic acid is bound to a solid support will have a large impact on whether or not that nucleic acid is capable of hybridizing with a complementary sequence. A single-stranded nucleic acid may be bound to a support in a way that renders it incapable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

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.

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.



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 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 S1 digestion." *Id.* at 538, right col. ¶1; *see also id.* at 539, Fig. 1. S1 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:

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

> [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 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

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

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 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-

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.).

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 S1 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 "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

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

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.

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.

Appendix B

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.

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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*

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

Pet. 36 (citing the 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]

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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.

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 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]

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.

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 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.

Appendix B

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.

Appendix B

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]

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

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.

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.

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.

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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).

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.

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APPENDIX C — FINAL WRITTEN DECISION OF THE UNITED STATES PATENT AND TRADEMARK OFFICE, PATENT TRIAL AND APPEAL BOARD, DATED OCTOBER 2, 2017

Case IPR2016-00822
Patent 7,064,197 B1

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.

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

FITZPATRICK, *Administrative Patent Judge.*

Appendix C

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.

Appendix C

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
Fish	§ 103(a)	130, 131, 151, and 154

1. The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, took effect on March 18, 2013. Because the application from which the '197 patent issued was filed before that date, our citations to 35 U.S.C. §§ 102 and 103 are to their pre-AIA version.

2. Falk Fish, et al., "A Sensitive Solid Phase Microradioimmunoassay For Anti-Double Stranded DNA Antibodies," *Arthritis and Rheumatism*, Vol. 24, No. 3, 534–43 (March 1981).

Appendix C

References	**Basis**[1]	**Claims Challenged**
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.

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

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

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Oxidase in a Recirculation Reactor System," *Biotechnology and Bioengineering*, Vol. XVIII, 669–84 (1976).

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.

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.

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 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'

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.

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.

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).

Appendix C

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 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"

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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.

Appendix C

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

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.

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 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.

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

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 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 "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.

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

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.

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.

Appendix C

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 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;

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.*

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 comprise nucleic acid sequences complementary to

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

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

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.

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. 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]

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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.

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 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 being U.S. Patent Application Ser. No.

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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.

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]

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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.

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" 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 amino groups have been

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.

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

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).

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 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]

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

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.

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.

APPENDIX D — DENIAL OF REHEARING OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT, FILED DECEMBER 4, 2019

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-1232, 2018-1233

ENZO LIFE SCIENCES, INC.,

Appellant,

v.

BECTON, DICKINSON AND COMPANY,

Appellee,

UNITED STATES,

Intervenor.

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00820, IPR2016-00822.

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Appendix D

Before PROST, *Chief Judge*, NEWMAN, LOURIE, DYK, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, and HUGHES, *Circuit Judges*[*].

PER CURIAM.

ORDER

Appellant Enzo Life Sciences, Inc. filed a combined petition for panel rehearing and rehearing en banc. The petition was referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on December 11, 2019.

FOR THE COURT

December 4, 2019
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

* Circuit Judges Moore and Stoll did not participate.

APPENDIX E — RELEVANT CONSTITUTIONAL AND STATUTORY PROVISIONS

U.S. Constitution
The Fifth Amendment

No person shall be held to answer for a capital, or otherwise infamous crime, unless on a presentment or indictment of a Grand Jury, except in cases arising in the land or naval forces, or in the Militia, when in actual service in time of War or public danger; nor shall any person be subject for the same offence to be twice put in jeopardy of life or limb; nor shall be compelled in any criminal case to be a witness against himself, nor be deprived of life, liberty, or property, without due process of law; nor shall private property be taken for public use, without just compensation.

Appendix E

Leahy-Smith America Invents Act,
Pub. L. No. 112-19, § 6(c)(2)(A),
125 Stat. 284, 304 (2011)

SEC. 6. POST-GRANT REVIEW PROCEEDINGS

(c) REGULATIONS AND EFFECTIVE DATE.—

(2) APPLICABILITY.—

(A) IN GENERAL.—The amendments made by subsection (a) shall take effect upon the expiration of the 1-year period beginning on the date of the enactment of this Act and shall apply to any patent issued before, on, or after that effective date.

Appendix E

35 U.S.C. 316(e)

§ 316. CONDUCT OF INTER PARTES REVIEW

(e) EVIDENTIARY STANDARDS.—In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.

Appendix E

35 U.S.C. 282 (2006)

§ 282. PRESUMPTION OF VALIDITY; DEFENSES

A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. Notwithstanding the preceding sentence, if a claim to a composition of matter is held invalid and that claim was the basis of a determination of nonobviousness under section 103(b)(1), the process shall no longer be considered nonobvious solely on the basis of section 103(b)(1). The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.

The following shall be defenses in any action involving the validity or infringement of a patent and shall be pleaded:

(1) Noninfringement, absence of liability for infringement or unenforceability,

(2) Invalidity of the patent or any claim in suit on any ground specified in part II of this title as a condition for patentability,

(3) Invalidity of the patent or any claim in suit for failure to comply with any requirement of sections 112 or 251 of this title,

(4) Any other fact or act made a defense by this title.

In actions involving the validity or infringement of a patent the party asserting invalidity or noninfringement shall give notice in the pleadings or otherwise in writing to the adverse party at least thirty days before the trial, of the country, number, date, and name of the patentee of any patent, the title, date, and page numbers of any publication to be relied upon as anticipation of the patent in suit or, except in actions in the United States Court of Federal Claims, as showing the state of the art, and the name and address of any person who may be relied upon as the prior inventor or as having prior knowledge of or as having previously used or offered for sale the invention of the patent in suit. In the absence of such notice proof of the said matters may not be made at the trial except on such terms as the court requires. Invalidity of the extension of a patent term or any portion thereof under section 154(b) or 156 of this title because of the material failure—

(1) by the applicant for the extension, or

(2) by the Director,

to comply with the requirements of such section shall be a defense in any action involving the infringement of a patent during the period of the extension of its term and shall be pleaded. A due diligence determination under section 156(d)(2) is not subject to review in such an action.

Appendix E

35 U.S.C. 311

§ 311. INTER PARTES REVIEW

(a) IN GENERAL.—Subject to the provisions of this chapter, a person who is not the owner of a patent may file with the Office a petition to institute an inter partes review of the patent. The Director shall establish, by regulation, fees to be paid by the person requesting the review, in such amounts as the Director determines to be reasonable, considering the aggregate costs of the review.

(b) SCOPE.—A petitioner in an inter partes review may request to cancel as unpatentable 1 or more claims of a patent only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications.

(c) FILING DEADLINE.—A petition for inter partes review shall be filed after the later of either—

(1) the date that is 9 months after the grant of a patent; or

(2) if a post-grant review is instituted under chapter 32, the date of the termination of such post-grant review.

Appendix E

35 U.S.C. 315

§ 315. RELATION TO OTHER PROCEEDINGS OR ACTIONS

(a) INFRINGER'S CIVIL ACTION.—

(1) INTER PARTES REVIEW BARRED BY CIVIL ACTION.—An inter partes review may not be instituted if, before the date on which the petition for such a review is filed, the petitioner or real party in interest filed a civil action challenging the validity of a claim of the patent.

(2) STAY OF CIVIL ACTION.—If the petitioner or real party in interest files a civil action challenging the validity of a claim of the patent on or after the date on which the petitioner files a petition for inter partes review of the patent, that civil action shall be automatically stayed until either—

(A) the patent owner moves the court to lift the stay;

(B) the patent owner files a civil action or counterclaim alleging that the petitioner or real party in interest has infringed the patent; or

(C) the petitioner or real party in interest moves the court to dismiss the civil action.

(3) TREATMENT OF COUNTERCLAIM.—A counterclaim challenging the validity of a claim of a patent does not constitute a civil action challenging the validity of a claim of a patent for purposes of this subsection.

(b) PATENT OWNER'S ACTION.—An inter partes review may not be instituted if the petition requesting the proceeding is filed more than 1 year after the date on which the petitioner, real party in interest, or privy of the petitioner is served with a complaint alleging infringement of the patent. The time limitation set forth in the preceding sentence shall not apply to a request for joinder under subsection (c).

(c) JOINDER.—If the Director institutes an inter partes review, the Director, in his or her discretion, may join as a party to that inter partes review any person who properly files a petition under section 311 that the Director, after receiving a preliminary response under section 313 or the expiration of the time for filing such a response, determines warrants the institution of an inter partes review under section 314.

(d) MULTIPLE PROCEEDINGS.—Notwithstanding sections 135(a), 251, and 252, and chapter 30, during the pendency of an inter partes review, if another proceeding or matter involving the patent is before the Office, the Director may determine the manner in which the inter partes review or other proceeding or matter may proceed, including providing for stay, transfer, consolidation, or termination of any such matter or proceeding.

(e) ESTOPPEL.—

(1) PROCEEDINGS BEFORE THE OFFICE.—The petitioner in an inter partes review of a claim in a patent under this chapter that results in a final written decision under

section 318(a), or the real party in interest or privy of the petitioner, may not request or maintain a proceeding before the Office with respect to that claim on any ground that the petitioner raised or reasonably could have raised during that inter partes review.

(2) CIVIL ACTIONS AND OTHER PROCEEDINGS.—The petitioner in an inter partes review of a claim in a patent under this chapter that results in a final written decision under section 318(a), or the real party in interest or privy of the petitioner, may not assert either in a civil action arising in whole or in part under section 1338 of title 28 or in a proceeding before the International Trade Commission under section 337 of the Tariff Act of 1930 that the claim is invalid on any ground that the petitioner raised or reasonably could have raised during that inter partes review.