Trials@uspto.gov
571-272-7822

Paper 45
Entered: April 16, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

____

MODERNATX, INC.,
Petitioner,

v.

CUREVAC AG,
Patent Owner.

____

Case IPR2017-02194
Patent 8,383,340 B2

____

Before JAMES T. MOORE, SUSAN L. C. MITCHELL, and
KRISTI L. R. SAWERT, *Administrative Patent Judges.*

SAWERT, *Administrative Patent Judge.*

FINAL WRITTEN DECISION

Determining Claims 1–26 Unpatentable in *Inter Partes* Review
35 U.S.C. § 318(a) and 37 C.F.R. 42.73

Dismissing Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying Petitioner's Motion to Exclude
37 C.F.R. § 42.64(c)

Granting Petitioner's Motion to Seal
37 C.F.R. §§ 42.14 and 42.54

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–26 ("the challenged claims") of U.S. Patent No. 8,383,340 B2 ("the '340 patent," Ex. 1001). We have jurisdiction under 35 U.S.C. § 6, and enter this Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner has shown, by a preponderance of the evidence, that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e).

A. Procedural History

ModernaTX, Inc. ("Petitioner") filed a Petition (Paper 3, "Pet.") requesting *inter partes* review under 35 U.S.C. § 311. Petitioner supported its Petition with the Declaration of David Hornby, Ph.D. (Ex. 1002). CureVac AG ("Patent Owner") filed a Preliminary Response (Paper 7, "Prelim. Resp."). Patent Owner supported its Preliminary Response with the Declaration of František Švec, Ph.D. (Ex. 2001).

On April 18, 2018, pursuant to 35 U.S.C. § 314(a), we partially instituted trial to determine whether: claims 1, 3–4, 6–19, and 21–26 are unpatentable under 35 U.S.C. § 103 for obviousness over Zhang[1] and Lloyd[2]; claim 2 is unpatentable under 35 U.S.C. § 103 for obviousness

[1] Y. Clare Zhang et al., *Antisense Inhibition: Oligonucleotides, Ribozymes and siRNAs*, *in* 106 METHODS IN MOLECULAR MEDICINE: ANTISENSE THERAPEUTICS 11–34 (M. Ian Phillips ed., 2005) ("Zhang," Ex. 1038).

[2] Linda L. Lloyd et al., *Rigid polymerics: the future of oligonucleotide analysis and purification*, 1009 J. CHROMATOGR. A 223–30 (2003) ("Lloyd," Ex. 1005).

over Sullenger[3] in view of Lloyd; claim 5 is unpatentable under 35 U.S.C. § 103 for obviousness over Zhang in view of Lloyd and Polymer Laboratories Catalog[4]; and claim 20 as unpatentable under 35 U.S.C. § 103 for obviousness over Zhang in view of Lloyd and Gjerde II.[5] Paper 9, 25 ("Institution Decision" or "Inst. Dec.").

On April 27, 2018, in response to the Supreme Court's decision in *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348 (2018), we modified our institution decision "to include review of all challenged claims and all grounds presented in the Petition," thus adding to the trial the ground of unpatentability of claims 1–5, 8, 10–22, and 26 under 35 U.S.C. § 102 for anticipation by Gjerde I.[6] Paper 11, 2. Neither party requested any changes to the schedule or further briefing. *See* Paper 10.

Patent Owner filed a Response (Paper 20, "PO Resp."). In addition to the Declaration of Dr. Švec (Ex. 2001) previously submitted, Patent Owner supported its Response with the Declaration of Mariola Fotin-Mleczek, Ph.D. (Ex. 2012), the Declaration of Moritz Thran, Ph.D. (Ex. 2013), the Declaration of Alexander Schwenger, Ph.D. (Ex. 2014), and a second

---

[3] Bruce A. Sullenger and Eli Gilboa, *Emerging clinical applications of RNA*, 418 NATURE 252–58 (2002) ("Sullenger," Ex. 1039).

[4] Polymer Laboratories, CHROMATOGRAPHY PRODUCTS FROM POLYMER LABORATORIES, ISSUE 3 (2004–2005) ("Polymer Laboratories Catalog," Ex. 1024).

[5] Douglas T. Gjerde et al., U.S. Patent No. 6,066,258 (issued May 23, 2000) ("Gjerde II," Ex. 1006).

[6] Douglas T. Gjerde et al., U.S. Patent No. 6,576,133 B2 (issued June 10, 2003) ("Gjerde I," Ex. 1004).

Declaration of Dr. Švec (Ex. 2016). Petitioner filed a Reply (Paper 27 (confidential version), Paper 28 (public version), "Reply"). In addition to the Declaration of Dr. Hornby (Ex. 1002) previously submitted, Petitioner supported its Reply with a second Declaration of Dr. Hornby (Ex. 1070). Petitioner also filed a combined Motion for Entry of a Modified Protective Order and Motion to Seal (Paper 29), and a Motion to Exclude Evidence (Paper 32, "Pet. Mot.").

On our authorization (Paper 30), Patent Owner filed a Sur-reply (Paper 36, "Sur-reply"). Patent Owner also filed a Motion to Exclude Evidence (Paper 37, "PO Mot."). Each party filed an Opposition to the other's Motion to Exclude (Paper 40, "Pet. Opp."; Paper 39, "PO Opp."), and Replies (Paper 42, "Pet. Opp. Reply"; Paper 41, "PO Opp. Reply").

An oral hearing was held on February 7, 2019. Paper 43. A transcript of the hearing is included in the record. Paper 44 ("Tr.").

B. Related Proceedings

Petitioner and Patent Owner report no related proceedings under 37 C.F.R. § 42.8(b)(2). Pet. 64; Paper 5, 1; Paper 13, 1.

C. The '340 Patent

The '340 patent, titled "Method of Purifying RNA on a Preparative Scale by Means of HPLC," issued on February 26, 2013. Ex. 1001, [54], [45]. The '340 patent relates to a method for purifying RNA on a preparative scale by high-performance liquid chromatography ("HPLC") using a porous reversed phase—namely, porous non-alkylated polystyrenedivinylbenzene ("PSDVB")—as the stationary phase. Ex. 1001, Abstract, 19:57–62 (claim 1). The '340 patent explains that prior

researchers purified RNA by HPLC using non-porous alkylated PSDVB as the stationary phase. *Id.* at 1:35–37. But that purification method only led to "analytical quantities of the RNA up to at most 1000 ng" (1 µg). *Id.* at 1:53–55.

The '340 patent states that "[t]he object of the present invention is here to improve a method of this type" and that "[t]his is achieved according to the invention by a method for purifying RNA on a preparative scale, which is distinguished in that the RNA is purified by means of HPLC using a porous reversed phase as stationary phase." *Id.* at 1:56–62. The '340 patent states that "a significant factor" to the disclosed invention "is therefore that a porous reversed phase is used." *Id.* at 1:62–64.

The '340 patent teaches that the disclosed method "results in preparative RNA purification." *Id.* at 3:14–15. "This differs from an analytical HPLC method," the '340 patent continues, in that in an analytical method, a "distinctly smaller quantity is introduced and separated." *Id.* at 3:17–19. In contrast, "relatively large quantities of RNA are purified" in a preparative method. *Id.* at 3:20–23. The '034 patent sets forth quantities in the range of 0.5 mg to 1.5 mg or more per a single HPLC run as "relatively large quantities." *Id.* at 3:23–28.

The '340 patent teaches that the stationary phase may be provided in the form of beads or as a polymerized block. *Id.* at 6:65–7:1. In both cases, the stationary phase is "porous," which the '340 patent describes as "characterized by pores." *Id.* at 7:1–3. Pore sizes of 1000 Å to 5000 Å are preferred. *Id.* at 7:21–23. The '340 patent teaches that "stationary reversed phases which are not porous" result in the buildup of "excessively high

pressures" "such that preparative purification of the RNA by means of HPLC is possible only with great difficulty, if at all." *Id.* at 12:3–10.

The '340 patent provides several examples of RNA purification using HPLC with a porous non-alkylated PSDVB matrix as the stationary phase. *See id.* at 14:12–18:55 (Examples 1–7). The '340 patent states that the porous non-alkylated PSDVB matrix is "a conventional commercial product." *Id.* at 14:20–23. The examples of purified RNA are in amounts of 100 µg (Example 3) to 3 mg (Example 5). *Id.* at 15:40–16:9, 16:51–17:20.

D. The Challenged Claims

Of the challenged claims, claim 1 is the only independent claim and is illustrative of the claimed subject matter:

> 1. A method for purifying RNA on a preparative scale,
>
> wherein the RNA is purified by HPLC or low or normal pressure liquid chromatography using a porous reversed phase as stationary phase and a mobile phase, wherein the porous reversed phase is a porous non-alkylated polystyrenedivinylbenzene.

Ex. 1001, 19:57–62.

Dependent claims 2 to 26 add limitations relating to RNA type and size (claims 2–4), reversed phase particle size and pore size (claims 5–7), reversed phase structure (claim 8), chromatography column characteristics (claim 9), chromatography type (claims 10 and 26), mobile phase characteristics (claims 11–19), and methods of applying the mobile phase (claims 20–25). *Id.* at 19:64–22:29.

E. The Instituted Grounds of Unpatentability

We instituted an *inter partes* review of claims 1–26 of the ’340 patent on the following grounds of unpatentability.

Claim(s)	Basis	Reference(s)
1–5, 8, 10–22, and 26	35 U.S.C. § 102	Gjerde I
1, 3–4, 6–19, and 21–26	35 U.S.C. § 103	Zhang and Lloyd
2	35 U.S.C. § 103	Sullenger and Lloyd
5	35 U.S.C. § 103	Zhang, Lloyd, and Polymer Labs. Catalog
20	35 U.S.C. § 103	Zhang, Lloyd, and Gjerde II

Inst. Dec. 25; Paper 11, 2.

II. EVIDENTIARY MOTIONS

Petitioner and Patent Owner each filed a motion to exclude certain evidence. We address Patent Owner’s motion first and then turn to Petitioner’s motion.

A. Patent Owner’s Motion to Exclude

Patent Owner moves to exclude Exhibits 1048 and 1050, as well as portions of Exhibit 1002. PO Mot. 2. Exhibit 1048 is titled “International Laboratory News.” Exhibit 1050 is titled “Product Literature Request Form.” Exhibit 1002 is the Declaration of Dr. Hornby. Patent Owner moves to exclude Exhibits 1048 and 1049 under various provisions of the Federal Rules of Evidence (“FRE”), and to exclude paragraphs 53 and 54 of Dr. Hornby’s Declaration under FRE 702 and 703. *Id.* at 3–9. Because we do not rely on any of Exhibit 1048, Exhibit 1050, or paragraphs 53 and 54 of Exhibit 1002, we dismiss Patent Owner’s motion as moot.

B. Petitioner's Motion to Exclude

Petitioner moves to exclude portions of Exhibits 2001, 2012, 2013, 2014, and 2016. Pet. Mot. 1. Exhibits 2001 and 2016 are Dr. Švec's first and second Declarations, respectively, Exhibit 2012 is Dr. Fotin-Mleczek's Declaration, Exhibit 2003 is Dr. Thran's Declaration, and Exhibit 2014 is Dr. Schwenger's Declaration. Petitioner moves to exclude portions of these exhibits as irrelevant and prejudicial under FRE 402 and 403. *Id.* at 1–2. Petitioner also moves to exclude Exhibits 2012 and 2013 in their entireties as containing improper expert testimony under FRE 702. *Id.* at 3–4. Patent Owner opposes. *See generally* PO Opp.

1. Testimony not cited in the Patent Owner Response

Petitioner moves to exclude certain paragraphs of Dr. Švec's Declarations, Dr. Fotin-Mleczek's Declaration, Dr. Thran's Declaration, and Dr. Schwenger's Declaration as inadmissible under FRE 401, 402, and 403. Pet. Mot. 1–3. Petitioner argues that, because Patent Owner did not cite to those paragraphs in its Preliminary Response or Patent Owner Response, the testimony fails the test for relevance under FRE 401 and is thus inadmissible under FRE 402 (as irrelevant), or should be excluded under FRE 403 (as wasteful). *Id.* Petitioner cites to *SK Innovation Co., Ltd. v. Celgard, LLC*, Case IPR2014-00679, slip op. at 49 (Paper 58) (PTAB Sept. 25, 2015) as supporting exclusion of information not relied on with particularity during the proceeding. *Id.* at 3.

We do not agree. In *SK Innovation*, the Board excluded entire exhibits—not portions thereof—that a party did not cite during the course of the proceeding. *See* Paper 58 at 49. Here, Patent Owner cites to and relies

upon each declaration exhibit that Petitioner seeks to exclude in its Patent Owner Response. Accordingly, *SK Innovation* is distinguishable and therefore we deny Petitioner's motion as to those declarations.

2. Testimony from witnesses

Next, Petitioner moves to exclude the entirety of Dr. Fotin-Mleczek's and Dr. Thran's declarations under FRE 702. *Id.* at 3–7. Petitioner argues that the testimony lacks the scientific, technical, or other specialized knowledge that FRE 702 requires. *Id.*

We deny Petitioner's request to exclude the entirety of Dr. Fotin-Mleczek's and Dr. Thran's declarations because Petitioner's arguments go to the weight we should accord those declarants' testimony and credibility, not to the admissibility of the declarations. *See, e.g.*, *Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*, Case CBM2012-00002, slip op. at 70 (Paper 66) (PTAB Jan. 23, 2014) ("the Board, sitting as a non-jury tribunal, is well-positioned to determine and assign appropriate weight to the evidence presented in this trial"). Accordingly, we deny Petitioner's motion as to those declarations.

3. Summary as to Petitioner's motion

For the reasons explained above, we deny Petitioner's motion to exclude.

III. PATENTABILITY ANALYSIS

We have reviewed the parties' respective briefs as well as the relevant evidence discussed in those papers. For the reasons that follow, we determine that Petitioner has shown by a preponderance of the evidence that all claims of the '340 patent as challenged are unpatentable under 35 U.S.C. § 103(a) for obviousness. In particular, we determine that this case is one

that falls within the Supreme Court's characterization of obviousness as entailing an improvement that is no "more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

A. Principles of Law

To prevail in its challenges to the patentability of all claims of the '340 patent, Petitioner must demonstrate by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). "In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid. Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). That burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made." 35 U.S.C. § 103(a) (2006); *see also KSR*, 550 U.S. at 406. The question of obviousness is resolved on the basis of underlying factual determinations including the scope and content of the prior art, any differences between the claimed

subject matter and the prior art, the level of ordinary skill in the art; and objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A petitioner cannot satisfy its burden of proving obviousness by employing "mere conclusory statements." *Magnum Oil*, 829 F.3d at 1380. Moreover, a decision on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

B. Level of Ordinary Skill in the Art

We begin with the level of ordinarily skill in the art. The person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention. *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Petitioner asserts, and Patent Owner does not dispute, that the relevant "time of the invention" in this case is December 22, 2006—the effective filing date of the application leading to the '340 patent. *See* Pet. 14; *see generally* PO Resp.

Petitioner asserts that an ordinarily skilled artisan at the time of the invention "would have had a Ph.D. in biochemistry, molecular biology, or a related discipline, with at least two years of experience in nucleic acid manipulation." Pet. 14–15 (citing Ex. 1002 ¶ 28). Patent Owner asserts that "[t]he education and experience levels may vary between POSAs, with some having a bachelor of science degree plus five years or more of relevant work experience, or with others holding more advanced degrees—e.g., Ph.D.—

while having fewer years of experience." PO Resp. 15 (citing Ex. 2001 ¶ 32).

At institution, we found that the prior art itself was sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. Inst. Dec. 6. For this Decision, we maintain that the prior art demonstrates the appropriate level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect appropriate level of ordinary skill in art). Nevertheless, for completeness, we also find that an ordinarily skilled artisan would have had a Ph.D. in a discipline related to liquid chromatography, such as chemistry (including analytical, physical, and polymer chemistry), biochemistry, and molecular biology. We agree with Patent Owner that, in some cases, the ordinarily skilled artisan may have had less formal education, e.g., a bachelor's degree, but more relevant work experience, e.g., five or more years in a laboratory setting. We also find that an ordinarily skilled artisan would have had skills and/or knowledge related to the use of HPLC to purify polymers such as nucleic acids. Ex. 1002 ¶ 27; Ex. 2001 ¶ 32.

We disagree with Petitioner, however, that the ordinarily skilled artisan also must have had at least two years of experience in all types of nucleic acid "manipulation." *See* Pet. 14–15. For example, Petitioner presents little to no evidence that the ordinarily skilled artisan in liquid chromatography purification techniques must also be skilled in nucleic acid "identification" techniques (such as polymerase chain reaction and Southern blots), and/or in the chemical synthesis of nucleic acids. Ex. 1002 ¶ 27. Instead, we find that the ordinary skilled artisan's knowledge, experience,

and understanding of liquid chromatography—including HPLC instrumentation, columns, mobile phases, stationary phases, and purification techniques—is paramount to the subject matter at issue. Ex. 2001 ¶ 33.

We otherwise find no substantive differences between the parties' respective proposed definitions of a person of ordinary skill, and find that the outcome of this case would be the same regardless of which definition is used. Finally, we consider each parties' declarants—Dr. Hornby and Dr. Švec—qualified to opine from the perspective of an ordinary artisan at the time of the invention. *See* Ex. 1003 (curriculum vitae of Dr. Hornby); Ex. 2002 (curriculum vitae of Dr. Švec).

C. Broadest Reasonable Interpretation

Having defined the ordinarily skilled artisan, we now turn to the claim terms in dispute in this review. For petitions filed before November 13, 2018,[7] the Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b) (2017); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must

---

[7] *See Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board*, 83 FED. REG. 51340 (Oct. 11, 2018) (amending 37 C.F.R. § 100(b) effective November 13, 2018) (to be codified at 37 C.F.R. pt. 42).

be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history.”). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Technologies* in the context of an *inter partes* review). We determine that, to resolve whether Petitioner has met its burden to show that the challenged claims are unpatentable, we need interpret only three claim terms: “for purifying RNA on a preparative scale,” “porous reversed phase,” and “wherein the RNA has a size of up to 100 to 10000 nucleotides or base pairs.”

1. “for purifying RNA on a preparative scale”

The parties dispute whether the preamble of claim 1, “for purifying RNA on a preparative scale,” is limiting. Petitioner argues that the preamble is a statement of intended use and, therefore, is non-limiting. Pet. 15–17; Reply 20–22. Alternatively, Petitioner contends that, if the Board concludes that the preamble should be construed, the phrase “on a preparative scale” should “mean purifying at least 100 μg RNA.” Pet. 17. Patent Owner disagrees that the preamble is non-limiting, but generally agrees with Petitioner that “on a preparative scale” requires purification “of at least 100 μg RNA.” PO Resp. 16–20.

"In general, a preamble limits the invention if it recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (quotation omitted). "Conversely, a preamble is not limiting where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention." *Id.* The inquiry as to whether a preamble is limiting is fact-specific and determined on a case-by-case basis. *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989). Upon review of the entire record, we determine that the preamble phrase "for purifying RNA on a preparative scale" is limiting. Although we recognize the general rule that a preamble generally does not limit the claims, *e.g., Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002), that general rule does not apply in this case.

First, we find that the phrase "for purifying RNA on a preparative scale" is not merely a statement of purpose, "but rather discloses a fundamental characteristic of the claimed invention that is properly construed as a limitation of the claim itself." *Poly-Am., L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004). In *Poly-America*, the Federal Circuit held that the preamble phrase "blown-film textured liner" was limiting because "[t]he specification is replete with references to the invention as a 'blown-film' liner, including the title of the patent itself and the 'Summary of the Invention.'" *Id.* The court also noted that "[t]he phrase is used repeatedly to describe the preferred embodiments," and the preamble language "is restated in each of the patent's seven claims." *Id.* Thus, the

court concluded that "the inventor considered that the 'blown-film' preamble language represented an important characteristic of the claimed invention." *Id.*

Similarly here, the written description of the '340 patent repeatedly characterizes a fundamental characteristic of the claimed invention as purifying RNA on a preparative, versus an analytical, scale. *See* Ex. 1001, 3:20–23 ("In contrast [to analytical HPLC method], a preparative HLPC method should be understood to mean an HPLC method in which relatively large quantities of RNA are purified."); *see also, e.g.*, *id.* at Abstract ("The application describes a method for the preparative purification of RNA . . . ."), 1:19–21, 1:59–60, 3:14–19, 3:51–52, 8:49–56, 9:15–16, 11:20–22, 13:15–16, 15:1–3. This fundamental characteristic is included in the title of the patent, "Method for Purifying RNA on a Preparative Scale by Means of HPLC," *id.* at [54], as well as the only independent claim, from which all claims of the '340 patent depend either directly or indirectly, *id.* at 19:57–62; *see also* 35 U.S.C. § 112 ¶ 4 ("A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers."). Given that preparative scale RNA purification is replete within the written description of the '340 patent, included in the title, recited in every claim, and described as a fundamental characteristic of the claimed invention, we conclude that "for purifying RNA on a preparative scale" is limiting.

Second, we agree with Patent Owner that the preamble "for purifying RNA on a preparative scale" is also limiting because it provides antecedent basis for "the RNA" found later in claim 1. *See* PO Resp. 18. "When

limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention." *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003). Petitioner argues that the preamble is not limiting because "reference to 'the RNA' later in claim 1 'does not necessarily convert the entire preamble into a limitation, particularly one that only states the intended use of the invention.'" Pet. 16 (quoting *TomTom, Inc. v. Adolph*, 790 F.3d 1315, 1323 (Fed. Cir. 2015)).[8] But we do not determine that the preamble is limiting solely because "RNA" provides antecedent basis for "the RNA." Instead, we find that the preamble provides antecedent basis for a later-recited term *and* describes a fundamental characteristic of the claimed invention. Thus, *TomTom* is distinguishable.

Moreover, we do not read *TomTom* as requiring us to parse this particular preamble into limiting and non-limiting portions. In *TomTom*, the Federal Circuit held that the lower court erred in determining that it had to construe a second, unrelated portion of the preamble ("generating and updating data for use in") because it had construed a first portion of the preamble ("at least one mobile unit"). *Id.* at 1323. But here, Petitioner does not persuade us that "for purifying RNA" and "on a preparative scale" are unrelated; nor could it because, as explained above, the specification repeatedly describes the purification of RNA on a preparative scale as a fundamental characteristic of the invention.

[8] Petitioner also appears to argue that "RNA" in the preamble cannot provide antecedent basis for "the RNA" in the body of the claim because "[t]he preamble does not specify a type of RNA." Reply 22. We find no support in the law or in the facts of this case for this argument.

Finally, we reject Petitioner's argument that the preamble is not limiting because it "does not result in a manipulative difference in the steps of the claim." Reply 21–22. The written description of the '340 patent states that the invention is achieved by "using a porous reversed phase as [the] stationary phase[9]." Ex. 1001, 1:59–62. This porous reversed phase is recited in claim 1, thus resulting in a manipulative difference in the steps of the claim over the prior art. *Id.* at 19:59–60. Specifically, the prior art Azarani[10] used a non-porous reversed phase as the stationary phase, and could purify only "analytical quantities of RNA." *Id.* at 1:35–37, 53–55.

Petitioner argues that Azarani only "*happened* to be performed on an analytical scale," and therefore "does not necessitate that the claims be narrowly construed to be preparative scale methods." Reply 21 (emphasis added). We are not persuaded by Petitioner's argument, however, because Petitioner cites to no evidence or expert testimony that Azarani's method was capable of preparative scale RNA purification. *Id.* The '340 patent, in contrast, states that "only analytical quantities of the RNA up to at most 1000 ng (1 μg or 0.001 mg) can be separated and analysed with [Azarani's]

[9] In HPLC, high pressure is applied to force a liquid mobile phase containing a mixture of components through a stationary phase packed in a column. *See, e.g.*, Ex. 1033, 675, 728–39. Generally, components "that are strongly *retained* by the stationary phase move only slowly with the flow of mobile phase" (and thus elute later from the column), whereas components "that are weakly held by the stationary phase travel rapidly" (and thus elute earlier from the column). *Id.* at 675 (emphasis in original).

[10] Arezou Azarani and Karl H. Hecker, *RNA analysis by ion-pair reversed-phase high performance liquid chromatography*, 29(2)(e7) NUCLEIC ACID RES. 1–9 (2000) ("Azarani," Ex. 1008).

method." Ex. 1001, 1:53–55; *see also id.* at 3:19–20 (stating that quantities of 8 ng to 1000 ng were introduced into the HPLC column). The '340 patent's characterization of the prior art is supported by Table 1 of Azarani, which describes injection of 8 to 1000 ng of MS2 RNA. Ex. 1008, 6 (Table 1). Thus, we have no reason to doubt that Azarani's method was capable only of analytical purification of RNA due to the use of a non-porous reversed phase.

As noted above, the parties generally agree that "on a preparative scale" requires purification of "at least 100 μg RNA." Pet. 17; PO Resp. 16. We agree with the parties that "on a preparative scale" means at least 100 μg RNA. In this regard, the '340 patent defines "a preparative HPLC method" as "mean[ing] an HPLC method in which relatively large quantities of RNA are purified." Ex. 1001, 3:14–30. And the '340 patent provides several examples of HPLC RNA purification of amounts from 100 μg to 3 mg, and refers to each purification as "on a preparative scale." *Id.* at 14:52–55 (1.5 mg), 15:33–35 (200 μg), 16:3–8 (100 μg), 16:41–43 (250 μg), 17:14–16 (3 mg), 18:3–10 (1.5 mg), 18:47–49 (200 μg).

Finally, we note that Patent Owner proposes that we interpret the full preamble, "[a] method for purifying RNA on a preparative scale," as "purifying *and collecting for downstream use* at least 100 μg of RNA." PO Resp. 16 (citing Ex. 1001, 16:3–8) (emphasis added). We decline to add "and collecting for downstream use" to the preamble. Patent Owner points us to no language in the written description of the '340 patent supporting this addition. *Id.*

For all the above reasons, we determine that the preamble "for purifying RNA on a preparative scale" is limiting. We give "[a] method for purifying RNA" its plain and ordinary meaning, and together with "on a preparative scale," interpret the preamble as "a method for purifying at least 100 μg RNA." We need not address the parties' respective arguments about the prosecution history of the application leading to the '340 patent in detail.[11]

2. "porous reversed phase"

In the Institution Decision, we interpreted "porous reversed phase" as "characterized by pores" that allow the RNA "molecules to get inside the pores of the matrix." Inst. Dec. 10 (quoting Ex. 1001, 7:1–3, 50–54). Patent Owner argues that "porous reversed phase" means "characterized by pores

---

[11] Petitioner alleges in the introduction to its Reply that Patent Owner "used the broad explicit definition of 'porous' when it *sought* broad patent protection" during prosecution. Reply 3 (emphasis in original). But the citations to the prosecution history that Petitioner provides do not show that Patent Owner offered or relied on a specific definition of "porous" to obtain the '340 patent. *See id.* at 22 (citing Ex. 1021, 676–77). Instead, the prosecution history merely provides a restatement of the claim element. Ex. 1021, 676–77.

Moreover, we note that Patent Owner distinguished the "porous" reversed phase of the claims from the "superficially porous" reversed phase of Bidlingmeyer. *Id.* Bidlingmeyer explains that superficially porous particles (i.e., a microparticulate silica having a solid core and a thin porous shell) "avoids the problem of macromolecules sticking inside the pores," "as opposed to completely porous particles." Ex. 1011 ¶ 86. Thus, Bidlingmeyer further supports our finding that RNA enters and is retained by a "porous" stationary phase, *see infra*, and that this understanding of "porous" is well known in the art.

where the size of the pore depends on the size of the RNA to be separated to allow the RNA molecules being separated to get inside the pores of the matrix." PO Resp. 22. Alternatively, Patent Owner argues that "[i]t is irrelevant whether or not the term 'porous reversed phase' includes a limitation to pore size." PO Resp. 15.

Petitioner argues that our interpretation is unreasonable, and reads into the claim a limitation linking pore size to RNA size. Reply 19–20. Petitioner argues that the '340 patent explicitly defines the term "porous" as "mean[ing] that the beads or the block are characterized by pores." *Id.* at 19 (quoting Ex. 1001, 7:1–3). Petitioner also argues that the '340 patent only references "a possibility" that RNA enters the pores, and that the pore size of the reversed phase "may" be selected according to the size of the RNA to be purified. *Id.* at 19–20 (quoting Ex. 1001, 7:45–54). For these reasons, Petitioner argues, "porous reversed phase" should be interpreted as "a reversed phase characterized by pores." *Id.* at 19.

The broadest reasonable interpretation "is an interpretation that corresponds with what and how the inventor describes his invention in the specification, i.e., an interpretation that is 'consistent with the specification.'" *In re Smith Int'l, Inc.*, 871 F.3d 1375, 1383 (Fed. Cir. 2017) (quoting *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997)). Upon consideration of the entire record, we determine that an ordinarily skilled artisan would understand a "porous reversed phase" as one in which the RNA molecules can enter the pores of the stationary phase. *See* Inst. Dec. 8–10. Thus, we interpret "porous reversed phase" as a nonpolar

stationary phase characterized by pores in which the RNA molecules can enter and be retained during the chromatography process.

To begin, the ’340 patent states that the invention relates to a method for preparative purification of RNA which uses a “porous reversed phase” as the stationary phase.[12] Ex. 1001, Abstract; *see also id.* at 6:58–59 (“In the method according to the invention, a reversed phase is used as the stationary phase for HPLC purification.”). The ’340 patent states that the stationary-phase material packed in the HPLC column “may be provided in bead form or as a polymerized ‘block’, i.e., a block which fills a substantial part of the chromatography column.” *Id.* at 6:65–7:1. The ’340 patent then states that, “[i]rrespective of its precise nature, the polymeric stationary phase is porous in its nature, which means that the beads or the block are characterized by pores.” *Id.* at 7:1–3. The ’340 patent then lists preferred particle sizes and pore sizes for RNA purification. *See id.* at 7:4–12 (preferred particle sizes), 21–27 (preferred pore sizes).

We are not persuaded by Petitioner’s argument that the broadest reasonable interpretation of porous is complete with “characterized by pores.” Reply 19–20. This is because, when read and understood in its entirety, the ’340 patent makes clear that the disclosed method’s ability to

---

[12] Historically, HPLC was performed with a polar stationary phase and a nonpolar mobile phase. *Id.* at 739–40. This type of chromatography is now referred to as “normal-phase chromatography.” *Id.* at 740. In “reversed-phase chromatography,” the stationary phase is nonpolar and the mobile phase is polar. *Id.*; *see also* Ex. 1001, 6:59–64 (“For chromatography with reversed phases, a nonpolar compound serves as the stationary phases [sic] and a polar solvent . . . serves as the mobile phase for elution.”).

separate—and thus purify—RNA depends on two factors: retention of the RNA on the stationary phase by hydrophobic interactions created by the reversed phase,[13] and diffusion of the RNA molecules into the pores of the stationary phase.

Specifically, the '340 patent states that "the retention of the RNA molecules and the separation *not only depends* on the interaction of the (reversed) phase but also on the possibility of molecules to get inside the pores of the matrix *and thus provide a further retention effect*." Ex. 1001, 7:50–54 (emphases added). Put differently, in the claimed method, RNA is retained on the stationary phase by both hydrophobic interactions and by diffusion of the RNA into the pores of the stationary phase. For this reason, the '340 patent teaches that, as a general matter, a pore size of 1000 Å to 5000 Å may be used to separate RNA of up to 15,000 nucleotides from other components of a sample mixture, but that "the pore size of the reversed phase may also be selected in dependence of the size of the RNA to be separated," i.e., a larger pore size may be used to separate larger RNA

[13] It is well known in the art that reversed phase chromatography relies on hydrophobic interactions between the analyte (e.g., RNA) and the stationary phase as a mechanism of separation. Ex. 2003, 6. Specifically, hydrophobic analytes exhibit more affinity for the hydrophobic, nonpolar stationary phase than for the polar mobile phase, and thus are retained on the stationary phase, and elute less quickly than hydrophilic analytes. Ex. 1101 ¶ 26. The '340 patent's description of reversed-phase chromatography is consistent with the art, stating that "the various [HPLC] techniques . . . operate on the principle of hydrophobic interactions which result from repulsive forces between a relatively polar solvent, the relatively non-polar analyte, and the non-polar stationary phase (reversed phase principle)." Ex. 1001, 2:16–20.

molecules, whereas a smaller pore size may be used to separate smaller RNA molecules. *Id.* at 7:46–50.

The ’340 patent’s characterization of the “porous reversed phase” as a stationary phase having pores in which the RNA can enter and be retained is consistent with, and supported by, the weight of the extrinsic record evidence. For example, Snyder describes “porous column-packing materials” as containing pores, and states that “[s]ample molecules move into and out of these pores by diffusion.” Ex. 2004, 20. *See also, e.g.*, Ex. 1005, 225 (discussing increasing “the pore size of the HPLC media” so that “the larger oligonucleotides can permeate the porous structure”); Ex. 1011 ¶ 86 (discussing the ability of macromolecules to stick inside the pores of porous particles); Ex. 1013, 1:24–30 (describing the “slow diffusional mass transfer of solutes into and out of the stagnant mobile phase present in the pores of the [porous stationary phase] separation medium”); Ex. 2008, 86 (stating that, in retention chromatography, “the walls of the pores provide the large surface area needed for retention”).

Moreover, Polymer Laboratories Catalog—which Petitioner offers as evidence of the commercially available PLRP-S column used in the Examples of the ’340 patent—confirms that the porous stationary phase media provides both “[a]ccessibility and high permeability of the molecules to the internal surface of the porous particle,” while maintaining “[t]he underlying hydrophobic retention characteristics of the PLRP-S media.” Ex. 1024, 100. Thus, we find that an ordinarily skilled artisan reading “porous reversed phase” in light of the specification would understand that, consistent with the art, the pores allow for entry of RNA.

Our interpretation of "porous reversed phase" is also informed by the '340 patent's characterization of "nonporous" reversed phases. Specifically, the '340 patent distinguishes "porous" from "nonporous" reversed phases by teaching that the use of a "porous reversed phase as [the] stationary phase" in HPLC was "a significant factor" in achieving RNA purification on a preparative scale. Ex. 1001, 1:59–64. The prior art Azarani performed ion-pair reversed-phase HPLC with a nonporous alkylated PSDVB stationary phase, but could purify only "analytical quantities of RNA." *Id.* at 1:35–37, 53–55. The '340 patent explains that "stationary reversed phases which are not porous" result in the buildup of "excessively high pressures" "such that preparative purification of the RNA by means of HPLC is possible only with great difficulty, if at all." *Id.* at 12:3–10. The use of a porous reversed phase, on the other hand, avoids the elevated pressures described in Azarani and provides "preparative separation . . . in a particularly favorable manner." *Id.* at 7:28–34.

Again, the '340 patent's explanation of the difference between "porous" (as allowing RNA entry) and "nonporous" (as not allowing RNA entry) is consistent with the extrinsic evidence of record. For example, Gjerde I defines "nonporous" as "denot[ing] a bead which has surface pores having a diameter that is *less than* the size and shape of the smallest RNA molecule in the mixture in the solvent medium," and thus, "essentially exclude[] the RNA molecules being separated from entering the bead." Ex. 1004, 20:66–21:6 (emphasis added). *See also* Ex. 1013, 13:12–17 (defining "non-porous" to include surface micropores having a diameter that

is *less than* the size and shape of the smallest polynucleotide fragment in the separation . . . solvent" (emphasis added)).

We are not persuaded by Petitioner's argument that the '340 patent's use of the terms "possibility" and "may" compels a different result. *See* Reply 19–20. In our view, this argument elevates form over substance. The '340 patent—when read and understood in its entirety and in the context of knowledge in the art—makes clear that the "porous reversed phase" retains RNA not only via hydrophobic interactions between the RNA and the stationary phase, but also through the diffusion of the RNA into the pores of the stationary phase. Nor are we persuaded by Petitioner's argument that the patentee has acted as its own lexicographer. Reply 19. A patentee acts as a lexicographer when it "use[s] terms in a manner *other than* their ordinary meaning." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (emphasis added). Here, as explained above, the '340 patent uses "porous" (and "nonporous") in a manner consistent with the art of record.

For similar reasons, we are not persuaded by Dr. Hornby's testimony on the meaning of "porous reversed phase." *See* Ex. 1070 ¶¶ 39–43. Dr. Hornby's testimony fails to consider the '340 patent as a whole and the knowledge that the ordinarily skilled artisan brings to bear when reading that patent—instead focusing on the presence or absence of certain isolated words in a conclusory manner. For example, Dr. Hornby relies on the absence of the word "trap" as evidence that RNA does not necessarily enter into the pores. *Id.* ¶ 41. But this approach is inconsistent with the knowledge in the art that molecules move into and out of a porous stationary phase by diffusion, Ex. 2004, 20, as well as with Petitioner's own exhibits,

which describe a "nonporous" stationary-phase material as excluding molecules from entering the pores. Ex. 1004, 21:25–27; Ex. 1006, 9:23–33.

We also disagree with Dr. Hornby's characterization of the '340 patent as not requiring or "even elaborat[ing] on selecting [a] particular pore size for a particular RNA size." Ex. 1070 ¶ 42. As explained above, the '340 patent provides both general and specific guidance on pore sizes "suitable to separate a RNA from other components of a mixture" based on the size of the RNA molecule. Ex. 1001, 7:36–8:2. Moreover, Petitioner's own reference Lloyd evidences that selecting a pore size "depend[ing] on the size of the oligonucleotide to be separate/purified" is routine in the art. Ex. 1005, 225; *see also id.* (explaining that purifying "smaller oligonucleotides requires small pore sizes," and that, "as the chain length increases[,] larger pore size materials will be required").

Dr. Hornby's testimony on this issue is also inconsistent with his previously published work. In a 2009 publication, Dr. Hornby explained that the term "nonporous" is "a term which can be misleading at times." Ex. 2025, 46. This is because "most polymers have pores as part of their structures" but are still called "nonporous" "because the pores of the particle matrix do not form part of the separation process." *Id.* Put differently, Dr. Hornby explains, an ordinarily skilled artisan would understand that a technically porous "material may still be termed *'nonporous' if the RNA cannot enter the bead matrix*, but only interact[s] with the extended surface of the bead." *Id.* (emphasis added). We view Dr. Hornby's previous explanation as supportive of, and consistent with, our interpretation of "porous" as allowing RNA entry into the bead, and "nonporous" as not

allowing RNA entry. We do not find Dr. Hornby's current testimony on the meaning of "porous reversed phase" credible in light of the evidence of record. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) ("[C]onclusory, unsupported assertions by experts as to the definition of a claim term are not useful to a court.").

3. "wherein the RNA has a size of up to 100 to 10000 nucleotides or base pairs"

Claim 4 depends from claim 1 and recites "wherein the RNA has a size of up to 100 to 10000 nucleotides or base pairs." Ex. 1001, 20:56–57. Patent Owner argues that, when read in view of the written description of the '340 patent, this phrase means that "the RNA has a size *of* 100 to 10000 nucleotides or base pairs." PO Resp. 20 (emphasis added); *see also* Sur-reply 16–17. Patent Owner argues that the written description describes an embodiment in which "the RNA to be purified has a size up to 15000 nucleotides . . . , *in particular 100 to 10000* . . . nucleotides or base pairs." *Id.* (quoting Ex. 1001, 4:54–61 (emphasis added)). In response, Petitioner argues that Patent Owner's construction "reads 'up to' out of the claim[]." Reply 16.

We agree with Petitioner. First, claim 4, by its own terms, recites "of up to." Replacing "of up to" with "of," as Patent Owner suggests, improperly reads "up to" out of the claim. *See Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1254 (Fed. Cir. 2010) ("Claim construction begins and ends in all cases with the actual words of the claim." (quotation omitted)). Second, although we acknowledge that the '340 patent expresses a preference for "100 to 10000" nucleotides or base pairs, claim 4 unambiguously recites "of up to 100 to 10000." We give full effect

to each of those words. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so.").

For these reasons, we agree with Petitioner that claim 4 recites an upper limit for the size of the RNA (i.e., up to 100 to 10,000 nucleotides or base pairs), but does not recite a lower limit. Reply 16. This interpretation is also supported by the '340 patent, which discloses the purification of RNA having sizes as small as 20 to 30 nucleotides via the disclosed method. *See* Ex. 1001, 4:64–67 ("20–30 nucleotides may also be separated this way").

D. Overview of Asserted References

Before turning to Petitioner's asserted grounds of unpatentability, we provide an overview of the asserted references.

1. Gjerde I

Gjerde I discloses a "matched ion polynucleotide chromatography" method for size-based segregation of a mixture of RNA molecules. Ex. 1004, Abstract. The method includes applying RNA to non-polar reverse phase media and eluting the RNA molecules with a mobile phase that includes a counterion reagent and an organic component. *Id.* Gjerde I teaches that the method can be used in segregating RNA molecules having lengths from 100 to 20,000 nucleotides. *Id.*

Gjerde I teaches that the separation media includes beads and monolithic columns. "The surface can be porous, but preferably any surface pores are of a size which excludes the smallest RNA molecule being analyzed." *Id.* at 7:45–48. As for beads, Gjerde I teaches that "the beads which are operable in RNA segregation as described herein have a pore size

which essentially excludes the RNA molecules being separated from entering the bead." *Id.* at *Id.* at 20:66–21:3. Gjerde I teaches that a "pretreatment of a porous bead to render it nonporous can be effected with any material which will fill the pores in the bead structure." *Id.*at 14–16. Gjerde I teaches that "pores having dimensions that allow movement of the RNA into the interconnected pore structure and into the bead impair the segregation of RNA molecules." *Id.* at 21:21–25.

Gjerde I explains that monoliths "contain polymer separation media which have been formed inside a column as a unitary structure having through pores or interstitial spaces which allow eluting mobile phase and analyte to pass through and which provide the non-polar separation surface." *Id.* at 7:60–64. Gjerde I again states that "[t]he surface can be porous, but is preferably non-porous." *Id.* at 23:32–33. "As with beads," Gjerde I continues, "the pores contained in the rod must be compatible with RNA molecules and not trap the material." *Id.* at 23:34–36.

Gjerde I provides an example preparation of a non-polar organic polymer monolith chromatography column. *Id.* at 31:25–61 (Example 10). Gjerde I states that PSDVB is polymerized in a chromatography tube, and that, following polymerization, the column is washed with tetrahydrofuran "thereby creating through-pores in the otherwise solid polymer monolith." *Id.*

2. Zhang

Zhang provides an overview of the state of the art of gene therapy using antisense inhibition. Ex. 1038, Abstract. Zhang notes that antisense inhibition includes not only the use of antisense oligonucleotides, but also

the use of small interfering RNAs (siRNAs). *Id.* Zhang states that "[w]ith the discovery of RNA interference (RNAi) and development in delivery of these gene drugs, more preclinical and clinical investigations are anticipated to take place in the near future to finally fulfill the promise of antisense therapeutics in humans." *Id.*

3. Lloyd

Lloyd evaluated "[a] family of rigid macroporous HPLC materials" "for the analysis and purification of a range of . . . oligonucleotides." Ex. 1005, Abstract. The aim of Lloyd's work was to "demonstrate the feasibility of using" certain polystyrenedivinylbenzene columns (called "PLRP-S") "for the analysis and purification of oligonucleotides." *Id.* at 224.

Lloyd analyzed a 25-base pair double-stranded DNA ladder to determine the separation range for four pore sizes of PLRP-S media (100 Å, 300 Å, 1000 Å, and 4000 Å) using ion-pair reversed-phase HPLC. *Id.* at 225, 228. Lloyd found that the 100 Å PLRP-S media could resolve up to 50–75 bp, the 300 Å up to 250–300 bp, the 1000 Å up to 400–450 bp, and 4000 Å up to at least 500 bp. *Id.* Because rapid and economical oligonucleotide purification requires high resolution and high capacity, Lloyd also studied the resolving ranges and capacity of the four PLRP-S columns. *Id.* Lloyd teaches that a "typical 20mer oligonucleotide was . . . chosen to look at capacity, frontal loading analysis, as a function of media pore size." *Id.* Lloyd states that the results shown in Figures 1–3 evidence "good mass transfer characteristics and the ability to use virtually the entire column for preparative/process work." *Id.*

Lloyd states that there is "much interest in the use of oligonucleotides as therapeutic agents, for example antisense therapy against viral infections or for enhanced cancer therapies." *Id.* at 227. Indeed, Lloyd continues, "[t]here is a requirement to produce large quantities of well-defined oligonucleotides in an economic and timely fashion for clinical trials." *Id.* Lloyd teaches that "[r]eversed-phase ion-pair chromatography is an obvious choice, as excellent selectively and high capacity, as has been demonstrated above, is achieved." *Id.*; *see also id.* at 228 ("From the previous data it is clear that ion-pair reversed-phase HPLC can be used for the analysis and purification of oligonucleotides.").

4. Sullenger

Sullenger provides an overview of RNA therapeutics as an emerging area of medical research. Ex. 1039, Abstract. Sullenger states that "the RNA therapeutic developing pipeline is burgeoning and the next generation of RNA-based therapies is quickly making its way through pre-clinical studies." *Id.* at 257. For example, Sullenger explains that specific active immunotherapy of cancer, which involves transfecting dendritic cells with mRNA "is emerging as a promising modality for treating cancer recurrence." *Id.* at 256; *see also id.* at 257 (describing mRNA-based immunotherapy as possibly "constitut[ing] a highly effective and broadly applicable treatment for patients with recurring cancer.").

5. Polymer Laboratories Catalog

The Polymer Laboratories Catalog discloses "PLRP-S columns for biomolecule analysis," having a range of pore sizes which "enables high capacity/high resolution separations from the smallest peptide to the largest

protein." Ex. 1024, 99. The Catalog discloses that "PLRP-S is a rigid macroporous styrene/divinylbenzene (PS/DVB) HPLC phase." *Id.* at 84. The Catalog discloses that the columns provide "[e]asy [s]cale-up" for preparative HPLC, stating that "[s]eparations developed on an analytical scale column can be transferred to a preparative scale column with minimal method re-development." *Id.* at 101. The Catalog states that the PLRP-S columns are "ideal for oligonucleotide analysis," and are available in pore sizes from 100 Å to 4000 Å. *Id.* at 105. The Catalog states that "[t]he small pore PLRP-S 100Å resolves up to 50-75 bp, the 300Å 250-300 bp, the 1000Å 400-450 bp and the 4000Å in excess of 500 bp." *Id.*

6. Gjerde II

Gjerde II teaches non-polar polymeric separation media, including beads and monoliths, for chromatographic separation of mixtures of polynucleotides. Ex. 1006, Abstract. Gjerde II teaches that the media "can be used in the separation of RNA or of double- or single-stranded DNA." *Id.* at 9:54–55. Gjerde II provides an Example wherein four fragments of DNA were separated under isocratic conditions using nonporous PSDVB as the stationary phase. *Id.* at 23:44–24:5 (Example 4).

E. Anticipation of the Challenged Claims

Petitioner contends that claims 1–5, 8, 10–22, and 26 are unpatentable as anticipated by Gjerde I. *See* Pet. 18–37. Petitioner states that this ground of unpatentability "is presented in view of Petitioner's position that the 'preparative scale' language in the claim 1's preamble is not limiting." *Id.* at 18. Patent Owner argues that "Petitioner has conceded that Gjerde I does not disclose preparative HPLC," and that, because the preamble should be

given patentable weight, "Gjerde I does not anticipate the present claims." PO Resp. 21. We agree with Patent Owner for the following reasons.

"[T]he petitioner is master of its complaint." *SAS*, 138 S. Ct. at 1355. Here, Petitioner premises its ground of unpatentability for anticipation on its view that the preamble is not limiting, and makes no separate argument in the Petition that the claims are also unpatentable for anticipation by Gjerde I even if the preamble is limiting. *See* Pet. 19–21. For example, in its claim chart, Petitioner fails to map the language of the preamble to any teachings in Gjerde I. *Id.* at 19; *see also* Ex. 1002 ¶ 80 (same). Dr. Hornby also testifies that he "was asked to assume that the preamble of claim 1 is not limiting," and, for that reason, states that "Gjerde I does not have to disclose purification on a preparative scale." Ex. 1002 ¶ 81.

Because we determine that the preamble is limiting, *supra* § III.C.2., Gjerde I must teach preparative-scale purification to anticipate. *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994). Petitioner makes no such argument, and thus fails to demonstrate by a preponderance of the evidence that claims 1–5, 8, 10–22, and 26 are unpatentable as anticipated by Gjerde I. *See SAS Inst.*, 138 S. Ct. at 1358 (stating that "the petition [is] the centerpiece of the proceeding both before and after institution").

F. Obviousness of Claims 1, 3, 4, 6–19, and 21–26 Over Zhang and Lloyd

Petitioner contends that claims 1, 3, 4, 6–19, and 21–26 are unpatentable as obvious over Zhang and Lloyd. *See* Pet. 37–52. For the reasons explained below, we agree with Petitioner.

1. Limitations of the challenged claims

Petitioner contends that the prior art discloses or suggests each element of the challenged claims. *See* Pet. 37–61. Petitioner presents a claim chart mapping the language of claim 1 to the disclosures of Zhang and Lloyd, *id.* at 38–40, and arguments mapping the language of dependent claims 3, 4, 6–19, and 21–26 to the disclosures of the Zhang and Lloyd, *id.* at 45–52. We have reviewed Petitioner's claim chart and arguments and, for the reasons articulated below, find that a preponderance of the evidence supports Petitioner's contentions.

a. Claim 1

The preamble of claim 1 recites "[a] method for purifying RNA on a preparative scale." Ex. 1001, 19:57. As explained above, we interpret the preamble as "a method for purifying at least 100 μg RNA." *Supra* § III.C.1.

Lloyd discloses a feasibility study of PLRP-S columns "for the analysis and purification of oligonucleotides" via ion-pair reversed-phase HPLC. Ex. 1005, 224. Lloyd does not expressly define whether the purification of "oligonucleotides" includes both RNA and DNA, or only DNA. *See generally id.* Petitioner argues, and Dr. Hornby testifies, however, that an ordinarily skilled artisan would understand "oligonucleotides" to include both DNA and RNA. Pet. 42; Ex. 1002 ¶ 158. We agree.

To begin, Lloyd states that "purity is essential" for many "*oligonucleotide* applications," such as "antisense therapies." Ex. 1005, 223 (emphasis added). Lloyd states further that there is "much interest in the use of *oligonucleotides* as therapeutic agents, for example antisense therapy against viral infections and for enhanced cancer therapies." *Id.* at 227

(emphasis added). An ordinarily skilled artisan wanting to understand the scope of "oligonucleotides" in Lloyd would have been aware of Zhang. *See In re Nilssen*, 851 F.2d 1401, 1403 (Fed. Cir. 1988) (hypothetical person of ordinary skill in the art is presumed to know all prior art). Zhang teaches that antisense therapies comprise both DNA and RNA oligonucleotides.

Specifically, Zhang teaches that antisense oligonucleotides (AS-ODNs), ribozymes, and small interfering RNAs (siRNAs) are all examples of "antisense strategies for gene therapy." Ex. 1038, 11 (stating that "antisense strategies for gene therapy have expanded from antisense oligonucleotides (AS-ODNs) solely, to the addition of ribozymes and, more recently, to the inclusion of small interfering RNAs (siRNAs)"). Zhang teaches that ribozymes are "naturally occurring RNA molecules," the smallest of which comprises 30 to 40 nucleotides. *Id.* at 18. Zhang teaches further that "[t]he specificity of ribozymes make them very attractive as therapeutics" for certain diseases such as cancer, *id.* at 22, and for the treatment of viral infections, *id.* at 23. As to siRNAs, Zhang teaches that these molecules are double-stranded RNAs of approximately 21 nucleotides. *Id.* at 25. Zhang teaches further that siRNAs are a promising antisense therapy for such viruses as HIV, hepatitis B and C, papillomavirus, herpesvirus, rotavirus, and influenza virus. *Id.* at 26.

Taken together then, an ordinarily skilled artisan reading Lloyd would have understood that the antisense therapies against cancer and viral infections described in Lloyd comprise RNA oligonucleotides, such as the ribozymes and siRNAs described in Zhang. Thus, Lloyd's disclosure of the PLRP-S column "for the analysis and purification of oligonucleotides" via

ion-pair reversed-phase HPLC teaches a method for purifying RNA, as claimed. Ex. 1005, 224.

Lloyd also discloses that, for antisense therapies, "[t]here is a requirement to produce *large quantities* of well-defined oligonucleotides in an economic and timely fashion for clinical trials." *Id.* at 227 (emphasis added). We agree with Petitioner that an ordinarily skilled artisan would have understood "large quantities" as preparative-scale quantities, i.e., at least 100 µg of RNA. Pet. 41 n.4. Specifically, Dr. Hornby testifies that Lloyd's method has "high capacity," Ex. 1002 ¶ 159 (quoting Ex. 1005, 225, 227). Dr. Hornby also testifies that an ordinarily skilled artisan would have understood from the prior art that antisense therapies would require "doses between '0.1 mg/kg and 100 mg/kg body weight/day of active ingredients.'" *Id.* ¶ 154 (quoting Ex. 1051, 94:14–21). We credit Dr. Hornby's testimony on this issue, which is supported by the evidence of record. *See* Ex. 1051, 94:14–21 (disclosing doses of siRNAs); Ex. 1047, 203 (stating that "preparative separation methods must be created and scaled up to support AO [antisense oligonucleotide] manufacture for therapeutic use"), 204 (stating that "kilograms are required for AO drug clinical trials").

For these reasons, we agree with Petitioner that Lloyd, combined with Zhang, teaches a method for purifying RNA on a preparative scale, as claimed. As to the remaining limitations of claim 1, Lloyd teaches the use of ion-pair reversed-phase HPLC for the analysis and purification of oligonucleotides, using a PLRP-S column having a porous reversed phase as the stationary phase and using a mobile phase. *See* Ex. 1005, 223 (Abstract); *id.* at 228 ("From the previous data it is clear that ion-pair

reversed phase HPLC can be used for the analysis and purification of oligonucleotides."); *id.* at 223–225 (describing PLRP-S as a porous reversed phase having pore sizes of from 100 Å to 4000 Å); *id.* at 226 (Figure 1) (specifying mobile-phase eluent "A" comprising 0.1 M TEAA and eluent "B" comprising 0.1 M TEAA in 50% acetonitrile)).

Finally, as to "a porous non-alkylated polystyrene-divinylbenzene," Lloyd teaches using a PLRP-S column as the stationary phase, which Lloyd describes as "poly(styrene-divinylbenzene) reverse-phase material." *Id.* at 224. As shown by other record evidence, a skilled artisan would have understood that PLRP-S, which is manufactured by Polymer Laboratories, is a porous non-alkylated PSDVB. *See* Ex. 1024, 84 ("PLRP-S HPLC media is inherently hydrophobic and reproducible, and does *not require a bonded alkyl chain*, e.g.[,] C8, C18, to confer hydrophobicity." (emphasis added)).[14]

b. Claims 3, 4, 6–19, and 21–26

Having decided that the combination of Lloyd and Zhang teaches or suggests each and every limitation of claim 1, we turn to the dependent claims. We find that Petitioner also shows, by a preponderance of the evidence, that Lloyd and Zhang account for the limitations in dependent claims 3, 4, 6–19, and 21–26. Pet. 45–52. We have also reviewed Dr. Hornby's claim charts and find that a preponderance of the evidence supports his contention that the cited references collectively disclose or suggest each and every limitation of claims 3, 4, 6–19, and 21–26. Ex. 1002 ¶ 167 (claims 3 and 4) (citing Ex. 1005, 223 (Abstract), 225; Ex. 1038, 18,

[14] There appears to be no dispute in this case that Lloyd's PLRP-S column is a porous, non-alkylated PSDVB. *See generally* PO Resp.

25); *id.* ¶ 172 (claims 6 and 7) (citing Ex. 1005, 225); *id.* ¶ 177 (claim 8) (citing Ex. 1005, 224 (as evidenced by Ex. 1028, 118 (describing PLRP-S as in "rigid, spherical" "bead form")); *id.* ¶ 182 (claim 9) (citing Ex. 1005, 225); *id.* ¶ 187 (claim 10) (citing Ex. 1005, 224, 227); *id.* ¶ 192 (claim 11) (citing Ex. 1005, 225, 226 (Figure 1)); *id.* ¶ 197 (claims 12–14) (citing Ex. 1005, 226 & Figure 1); *id.* ¶ 202 (claim 15 and 16) (citing Ex. 1005, 226 (Figure 1)); *id.* ¶ 207 (claim 17) (citing Ex. 1005, 226 (Figure 1)); *id.* ¶ 212 (claim 18 and 19) (citing Ex. 1005, 226 (Figure 1)); *id.* ¶ 219 (claims 21 and 22) (citing Ex. 1005, 226 (Figure 1)); *id.* ¶ 224 (claims 23–25) (citing Ex. 1005, 226 (Figure 1)); *id.* ¶ 230 (claim 26) (citing discussion as to claim 1).

We therefore adopt the teachings set forth in the claim charts as mapped to the limitations of the challenged claims as our own findings.

c. Analysis of Patent Owner's arguments

Patent Owner disputes that Zhang and Lloyd teach or suggest the purification of RNA on a preparative scale. PO Resp. 25–32. As to RNA purification, Patent Owner asserts that Zhang "merely teaches the concept that antisense therapeutics can be used in gene therapies"—not methods of purification—and that, in any event, "[t]he oligonucleotides (AS-ODNs) disclosed by Zhang are DNA oligonucleotides." *Id.* at 25, 35–37. Patent Owner also asserts that Lloyd does not teach RNA purification because Lloyd "in fact only teaches the purification of DNA oligonucleotides," "the term 'RNA' is not mentioned at all in Lloyd," and "Lloyd does not provide any examples of RNA separation." *Id.* at 25–26 (citing Ex. 2015, 152:5–154:7; Ex. 1005, 227; Ex. 2015 at 89:7–9; 90:2–4). We do not agree.

As an initial matter, that Zhang does not teach "purification" of oligonucleotides is irrelevant. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (non-obviousness based on a combination of references cannot be established by attacking references individually). Petitioner relies on the combination of Zhang and Lloyd here to show that an ordinarily skilled artisan would have understood that Lloyd's disclosure of a method for purifying "oligonucleotides" for, e.g., antisense therapies, relates to the purification of both DNA and RNA. Pet. 42; Ex. 1002 ¶ 158. And, for the reasons explained above, we agree. *Supra* § III.F.1.a.

As to the "antisense oligonucleotides (AS-ODNs)" disclosed in Zhang, Patent Owner is correct that these oligonucleotides are DNAs. *See* Ex. 2021, 4 (describing AS-ODNs as "synthetically made, single-stranded short sequences of DNA bases"). But this fact does not defeat Petitioner's obviousness ground, because Petitioner also relies on ribozymes and siRNAs as reading on the preamble of claim 1. *See* Pet. 38–40 (claim chart). And ribozymes and siRNAs are, in fact, RNA oligonucleotides as Zhang shows. *See* Ex. 1038, 18 (describing ribozymes as "naturally occurring RNA molecules," the smallest known of which is 30 to 40 nucleotides), 25 (describing siRNAs as "approx[imately] 21 nt [nucleotide]" double-stranded RNAs); *see also* Ex. 1035, G–17 (under definition of "oligomer," referring to a short polymer of nucleotides as an "oligonucleotide").[15]

[15] Other record evidence also supports Petitioner's argument that an ordinarily skilled artisan would understand that antisense therapeutics include RNA oligonucleotides such as ribozymes and siRNAs. *See* Ex. 1061 (describing ribozymes as "catalytically active ONs [oligonucleotides] that

Finally, as to the disclosure of Lloyd, we acknowledge that Lloyd only *exemplifies* the separation and purification of a DNA oligonucleotides. Ex. 1005, 225–26, 227–28. Specifically, in one experiment, Lloyd used a PLRP-S column to separate a 25-base pair double-stranded DNA ladder via ion-pair reversed-phase HPLC to test for resolution of various DNA fragments. *Id.* at 225–26. In another experiment, Lloyd used a PLRP-S column to separate two phospho thioate (PS) DNA oligonucleotides (an 18-mer and an 20-mer) from a phospho diester (PO) contaminant "to assess the feasibility of reversed-phase ion-air chromatography for the analysis and purification of the[] therapeutic agents." *Id.* at 227–28. But Patent Owner's argument that Lloyd does not teach or suggest each and every element of claim 1 because Lloyd does not recite the term RNA represents an overly narrow view of the prior art. *See, e.g.*, Sur-reply, 6–7. Taking account of the record as a whole, the preponderance of the evidence supports Petitioner's argument that an ordinarily skilled artisan would have understood that Lloyd's teachings were applicable to both DNA and RNA purification for the reasons stated above.[16] *Supra* § III.F.1.a.

---

not only bind, but can also cleave, their target RNA," and describing siRNAs as "21–31-mer" molecules).

[16] Lloyd's teaching of oligonucleotide purification as encompassing both DNA and RNA purification is also supported by her citation to a previous RNA-related publication when using the term "oligonucleotides." Ex. 1002 ¶ 158. Specifically, Lloyd cites to "Lloyd 1991" as reporting "anion-exchange separation of *oligonucleotides*." Ex. 1005, 224 (citing Ex. 1037) (emphasis added). Lloyd 1991 describes the use of anion-exchange HPLC for the purification of synthetic oligonucleotides, including "[o]ligomers of poly(rA), poly(rC), and RNA." Ex. 1037, 207 (Abstract).

Patent Owner argues next that Lloyd does not teach "preparative purification," but rather only expresses a general desire to produce large quantities of oligonucleotides. PO Resp. 26. Patent Owner points out that Lloyd only analyzed DNA oligonucleotides on an analytical scale, and argues that Lloyd does not provide adequate information for an ordinarily skilled artisan to "assess the feasibility of using these methods to purify oligonucleotides on a preparative scale." *Id.* at 26–27. Dr. Švec also testifies that tests for determining "dynamic loading capacity is not preparative purification," and tests for "determining the resolution of a column is not preparative purification." Ex. 2016 ¶¶ 24–28.

Although we acknowledge that none of Lloyd's experiments constitute actual examples of the preparative purification of RNA or DNA, we do not agree with Patent Owner's argument. Instead, we are of the view that Lloyd reasonably teaches or suggests the preparative purification of RNA using reversed-phase HPLC and a PLRP-S column as the stationary phase. Specifically, Lloyd expressly recognizes the "interest in the use of oligonucleotides as therapeutic agents, for example antisense therapy against viral infections." Ex. 1005, 227. Thus, Lloyd continues, "[t]here is a requirement to produce *large quantities* of well-defined oligonucleotides in an economic and timely fashion for clinical trials." *Id.* (emphasis added). Lloyd then states that "reversed-phase ion-pair chromatography is an *obvious choice*, as excellent selectivity and high capacity, as has been demonstrative above, is achieved." *Id.* (emphasis added). Lloyd points to PLRP-S as an HPLC packing material that is mechanically rigid, stable to temperature and pH in a range of defined pore sizes, and made of "high-

performance poly(styrene-divinylbenzene)-based reversed phase." *Id.* at 224.

Put differently, Lloyd suggests to the ordinarily skilled artisan to use a PLPR-S column in ion-pair reversed-phase chromatography to produce large quantities (i.e., preparative amounts) of oligonucleotides. In our view, this disclosure is a sufficient teaching or suggestion of preparative purification as claimed, which is all the law requires. *See, e.g.*, *Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 727 (Fed. Cir. 2002) ("[O]bviousness does not require the prior art to reach expressly each limitation exactly. Rather, obviousness may render a claimed invention invalid where the record contains a suggestion or motivation to modify the prior art teaching to obtain the claimed invention."); *see also Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness."). Moreover, we are persuaded by and credit Dr. Hornby's testimony that "Dr. Švec's view of Lloyd's teachings is too narrow" because "it considers only what Lloyd demonstrated experimentally." Ex. 1070 ¶ 56.

Finally, we are not persuaded by Patent Owner's argument that the combination of Zhang and Lloyd fails to teach or suggest the subject matter of claim 4. PO Resp. 56. We note that Patent Owner's argument is conditioned on its position that claim 4 "should be read to mean [that] the RNA has a size of 100 to 1000 nucleotides or base pairs." *Id.* As explained above, however, that interpretation of claim 4 is unreasonable because it improperly reads "up to" out of the claim. *Supra* § III.C.3. Lloyd expressly teaches that the 100 Å-sized pores of the PLRP-S media could resolve up to

50–75 bp, the 300 Å up to 250–300 bp, the 1000 Å up to 400–450 bp, and 4000 Å up to at least 500 bp, and thus teaches the subject matter of claim 4. Ex. 1005, 223, 225.

2. Motivation to combine the prior art references and reasonable expectation of success

Even "[i]f all elements of the claims are found in a combination of prior art references," "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

a. Motivation to combine

Petitioner contends, and Dr. Hornby testifies, that an ordinarily skilled artisan would have been motivated to combine the teachings of Lloyd with Zhang. Pet. 42–43; Ex. 1002 ¶¶ 160–62. Specifically, Petitioner contends that Zhang evinces that large quantities of RNA were needed to perform "more preclinical and clinical investigations" into antisense therapies "in the near future." *Id.* at 42 (quoting Ex. 1038, 11, 22). Petitioner contends that an ordinarily skilled artisan looking for methods for obtaining large quantities of RNA would look to the teachings of Lloyd. *Id.* (citing Ex. 1002 ¶¶ 160–61). Petitioner contends that "Lloyd specifically teaches that its HPLC method using PLRP-S media is especially suited for purifying 'oligonucleotides [for use] as therapeutic agents, for example antisense

therapy.'" *Id.* at 43 (quoting Ex. 1005, 227). And Petitioner contends that "Lloyd expressly teaches that its method should be used to purify large quantities of antisense oligonucleotides, stating that '[r]eversed-phase ion-pair chromatography is an obvious choice' for antisense purification because of its "excellent selectivity and high capacity.'" *Id.* (quoting Ex. 1005, 227).

Upon review of the complete record, we agree with Petitioner that the record establishes by a preponderance of the evidence that an ordinarily skilled artisan would have been motivated to combine the teachings of Lloyd and Zhang.

i. Analysis of Petitioner's arguments

To begin, we find that the record supports, by a preponderance of the evidence, Petitioner's explanation that, before the '340 patent's earliest effective filing date, there was a known need in the art for skilled artisans to produce large quantities of purified RNA for antisense therapy. *See* Pet. 42–43. Specifically, Zhang explains that "antisense strategies for gene therapy" include not only antisense oligonucleotides (AS-ODNs), but also ribozymes and siRNAs—i.e., RNA oligonucleotides. Ex. 1038, 11. Zhang explains that "[t]he specificity of ribozymes makes them very attractive as therapeutics" for certain diseases, *id.* at 22, and that one "area where ribozyme therapy holds much promise is as antiviral agents," *id.* at 23. Zhang also explains that preliminary tests with siRNAs have "displayed high efficiency in inhibiting viral infection and replication," *id.* at 26, and that these therapeutics represent "a promising therapeutic approach for gene therapy." Zhang explains "more preclinical and clinical investigations" on these drugs "are anticipated in the near future to finally fulfill the promise of antisense therapy in humans." *Id.* at 11.

Lloyd also evinces that there was “much interest in the use of oligonucleotides as therapeutic agents, for example antisense therapy against viral infections or for enhanced cancer therapies,” before the effective filing date of the ’340 patent. Ex. 1005, 227. But, Lloyd explains, “[t]here is a requirement to produce large quantities of well-defined oligonucleotides in an economic and timely fashion” to carry out clinical trials on these antisense therapeutic agents. *Id.* Lloyd further explains that “purity is essential” for “antisense therapies.” *Id.* at 223.

Zhang and Lloyd make clear, then, that ordinarily skilled artisans understood, before December 22, 2006, that large amounts of purified RNA oligonucleotides were needed to perform preclinical and clinical investigations on potential antisense therapeutics. Indeed, as Petitioner persuasively explains, a preponderance of other record evidence is consistent with, and supports, the teachings of Zhang and Lloyd. *See* Pet. 42–43; *see also, e.g.*, Ex. 1039, 257 (“In the past five years, a number of clinical trials have been initiated to begin to evaluate the safety and efficacy of a variety of innovated RNA-based therapeutic strategies. . . . [T]he breadth of clinical indications that one can foresee treating with this new claims of therapeutic agents is remarkable.”); Ex. 1051, 94:20–21 (teaching that a “pharmaceutically effective dose” for siRNAs is “an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients”); Ex. 1049 ¶¶ 204 (accord), 354–55 (describing patient dosages from 10 to 300 mg/m^2/day for the ribozyme therapeutic agent ANGIOZYME™); Ex. 1047, 203 (teaching that “preparative separation methods must be created and scaled up to support AO [antisense oligonucleotide] manufacture for

therapeutic use"), 204 (teaching that "[h]igh-purity oligonucleotides are required for . . . antisense drug applications" and that, in terms of quantity, "kilograms are required for AO drug clinical trials"). For these reasons, we agree with Petitioner that an ordinarily skilled artisan would have had a need to purify RNA oligonucleotides, and would have known that "preparative" amounts of those RNA oligonucleotides would be necessary. *See* Pet. 42–43 (citing, e.g., Ex. 1002 ¶¶ 154, 160–161).

We also agree with Petitioner that the record shows, by a preponderance of the evidence, that a skilled artisan would have been prompted to use Lloyd's disclosed method and column to purify the needed preparatory amounts of RNA oligonucleotides. Pet. 43. Specifically, Lloyd teaches that high-purity oligonucleotides are essential for antisense therapies, but that conventional methods for oligonucleotide purification have many drawbacks. *See* Ex. 1005, 223–24 (discussing polyacrylamide gel electrophoresis (PAGE) and anion-exchange HPLC). Lloyd notes that ion-pair reversed-phase HPLC "has been proposed as an alternative" to conventional purification methods, but explains that this type of HPLC suffers from two disadvantages: decreasing resolution with increasing oligonucleotide length, and mass transfer restrictions within the porous particles that reduces the loading capacity of the column and the efficiency of separation. *Id.* Although acknowledging that the use of non-porous particles has been used in an attempt to overcome mass transfer limitations, Lloyd suggests that "[a]n alternative approach is to look at the pore size and structure of the HPLC material." *Id.* at 224.

To wit, Lloyd teaches that "advances in the production of rigid polymeric particles" have made it "now possible to produce reversed-phase and ion-exchange particles that are mechanically rigid and stable to temperature and pH in a range of defined pore sizes." *Id.* Lloyd teaches that these HPLC packings are "expected . . . to exhibit improved mass transfer characteristics for the larger oligonucleotides" as compared to older, non-porous silica-based particles. *Id.* Lloyd then introduces two columns that are "small particle size" and "high-performance poly(styrene-divinylbenzene)-based": "PLRP-S" for reversed-phase HPLC and "PL-SAX" for anion-exchange HPLC. *Id.*

Next, Lloyd provides experimental results "aim[ed]" at "demonstrat[ing] the feasibility of using" these columns "for the analysis and purification of oligonucleotides." *Id.* Lloyd reports that ion-pair reversed-phase chromatography using the PLRP-S column exhibited "excellent selectivity and high capacity." *Id.* at 227. Lloyd also reports that the results shown in Figure 2 indicate "good mass transfer characteristics and the ability to use virtually the entire column volume for preparative/process work." *Id.* at 225. Given these results, Lloyd states that "[r]eversed-phase ion-pair chromatography is an obvious choice" "to produce large quantities of well-defined oligonucleotides in an economic and timely fashion for clinical trials." *Id.*; *see also id.* at 228 ("From the previous data it is clear that ion-pair reversed-phase HPLC can be used for the analysis and purification of oligonucleotides."); Ex. 1002 ¶ 162.

In sum, we find that Zhang and Lloyd demonstrate a need in the art to purify large amounts of RNA for use in, for example, clinical trials for

antisense therapeutics. We also find that Lloyd suggests a finite number of high-performance PSDVB-based columns, PLRP-S and PL-SAX, and further that Lloyd suggests ion-pair reversed-phase chromatography as "an obvious choice" for obtaining preparative amounts of high-purity oligonucleotides. Thus, we agree with Petitioner that an ordinarily skilled artisan "would have had reason to select Lloyd's method to purify Zhang's antisense RNA." Pet. 43. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.").

ii. Analysis of Patent Owner's arguments

We have carefully considered Patent Owner's arguments and evidence, but remain persuaded that Petitioner has provided sufficient reason with rational underpinning for combining Lloyd and Zhang. *See* PO Resp. 32–41.

First, Patent Owner argues that Petitioner's reliance on Zhang's "AS-ODNs for the contention that Zhang would motivate a POSA to look to Lloyd is misplaced," because Zhang's "antisense oligonucleotides" are DNAs. *See* PO Resp. 35–37. Again, although Zhang's AS-ODNs are DNA oligonucleotides, Zhang also teaches that RNA oligonucleotides—i.e., ribozymes and siRNAs—are promising antisense therapeutics for cancer and viral inventions, and, as such, large amounts of these RNAs are needed for preclinical and clinical investigations. Ex. 1038, 11–12, 22–23, 25–26. As we explained above, an ordinarily skilled artisan would have looked to Lloyd for a method of preparing those antisense therapeutics.

Moreover, in contrast to Patent Owner's suggestion otherwise, we do not read the Petition as relying exclusively on Zhang's teachings about AS-ODNs for providing a motivation to combine. Petitioner argued in its Petition that "[a] POSA would have had a reason to purify large amounts of Zhang's antisense RNA," and then specifically identified Zhang's "antisense RNA" as "e.g., antisense oligonucleotides, ribozymes, or small interfering RNAs." Pet. 42–43. Although Petitioner's characterization of Zhang's AS-ODNs as antisense RNAs is unsupported by the record evidence, Petitioner's characterization of ribozymes and siRNAs as antisense RNAs is supported. *See* Ex. 1038, 11 (stating that "antisense strategies for gene therapy have expanded from antisense oligonucleotides (AS-ODNs) solely, to the addition of ribozymes and, more recently, to the inclusion of small interfering RNAs (siRNAs)"), 18, 22–23 (stating that ribozymes are "naturally occurring RNA molecules," the specificity of which "make them very attractive as therapeutics" for the treatment of cancer and viral infections), 25 (stating that siRNAs are double-stranded RNAs of approximately 21 nucleotides that are a promising antisense therapy for such viruses); *see also* Ex. 1061 (describing ribozymes as "[a]ntisense-oligonucleotides (AS-ONs)" that "pair with their complementary mRNA").

Second, Patent Owner argues that "Lloyd teaches away from the use of the methods described in her Figure 1 for attempting preparative scale purification, undermining the very reason being proffered for the combination of Zhang and Lloyd: the desire to purify RNA on a preparative scale." PO Resp. 38. Patent Owner points to the following quotation from Lloyd as evidence that Lloyd teaches away from using ion-pair reversed-

phase HPLC for oligonucleotide purification in favor of anion-exchange HPLC:

> From the previous data it is clear that ion-pair reversed-phase HPLC can be used for the analysis and purification of oligonucleotides. . . . Whilst this is often acceptable for analytical and small-scale preparative work, as the quantity requirement increases so the production costs increase and a process may become un-economical. **An alternative purification strategy is required.**

PO Resp. 38 (quoting Ex. 1005, 228) (emphasis in PO Resp.). We disagree.

As Patent Owner's quotation shows, Lloyd teaches that ion-pair reversed-phase HPLC is acceptable for "small-scale *preparative* work." Ex. 1005, 228 (emphasis added). Dr. Hornby testifies without challenge—and we credit his testimony—that an ordinarily skilled artisan would consider purification of 100 μg of RNA "small-scale preparative work." Ex. 1002 ¶ 75; Ex. 1070 ¶ 70. Thus, Lloyd does not teach away from the subject matter within the scope of claim 1.

In addition, to the extent Lloyd suggests switching from ion-pair reversed-phase HPLC to anion-exchange HPLC, Lloyd only does so because "production costs increase" as desired quantities increase, and the process becomes "un-economical." Ex. 1005, 228. It is well-settled, however, that lack of economic feasibility is not a teaching away. *See In re Farrenkopf*, 713 F.2d 714, 718 (Fed. Cir. 1983) ("That a given combination would not be made by business[wo]men for economic reasons does not mean that persons skilled in the art would not make the combination because of some technological incompatibility. Only the latter fact would be relevant.").

Third, Patent Owner argues that, at the time of the invention disclosed in the '340 patent, the art as a whole "taught that porous separation media was not ideal for purifying RNA and instead [taught that] one should use non-porous." PO Resp. 39. Patent Owner argues that Gjerde I would discourage the ordinarily skilled artisan from using a porous stationary phase because Gjerde I teaches that a porous stationary phase "hinders the separation of RNA." *Id.* at 40; *see also* Sur-reply 10. And so, Patent Owner argues, "to have an operable separation," Gjerde I teaches "us[ing] a non-porous stationary phase." *Id.* at 40 (citing Ex. 2001 ¶ 143; Ex. 2016 ¶ 50; Ex. 1004, 20:66–21:3). Patent Owner also asserts that Dr. Hornby's own publications teach using a nonporous stationary phase. *Id.* at 40–41 (citing Ex. 2024, 1377; Ex. 2025, 45, 82–83, 87).

We disagree that the art as a whole teaches away. Gjerde I discloses a "matched ion polynucleotide chromatography" method for size-based segregation of a mixture of RNA molecules. Ex. 1004, Abstract. As we explained in our Institution Decision, an ordinarily skilled artisan would have understood that Gjerde I's stationary-phase media (i.e., beads and monolithic columns) is "non-porous," even though Gjerde I uses the term "porous." Inst. Dec. 15–17; *see also* Ex. 2025, 46 (Dr. Hornby's previous publication discussing the confusion around the term "nonporous"). Specifically, in the context of beads, Gjerde I defines "nonporous" as "denot[ing] a bead which has surface pores having a diameter that is less than the size and shape of the smallest RNA molecule in the mixture in the solvent medium used therein." Ex. 1004, 21:3–6. And when describing its monolith column, Gjerde I states that, "[a]s with beads, the pores contained

in the rod must be compatible with RNA molecules and not trap the material." Ex. 1004, 23:34–36 (emphasis added).

Thus, as we explained above in connection with claim construction, we interpret Gjerde I's stationary-phase media as "non-porous," because this is how an ordinarily skilled artisan would have interpreted that media from Gjerde I's disclosure. Dr. Hornby's previous publications also describe the use of non-porous stationary phases for RNA purification. *See* Ex. 2024, 1377 (referring to "the unique separation properties of a non-porous polystyrene-divinylbenzene polymer bead that has been functionalised with C18 alkyl groups" for RNA/DNA chromatography"); Ex. 2025,[17] 45 ("The best RNA separations have been performed on nonporous resins . . . .").

Lloyd's teachings, in any event, are consistent with Gjerde I's and Dr. Hornby's. Lloyd teaches that ion-pair reversed-phase HPLC "has been proposed as an alternative" to the conventional purification methods of, e.g., PAGE, but explains that this type of HPLC "suffer[s] from oligonucleotide mass transfer restrictions within the porous particles that reduces the efficiency of the separation." Ex. 1005, 224. Lloyd then teaches that other researchers have used *non-porous* particles in ion-pair reversed-phase HPLC

[17] Patent Owner also cites to and provides quotations purportedly made by Dr. Hornby at pages 82–83 and 87 of Exhibit 2025. PO Resp. 41. We observe, however, that Exhibit 2025 ends at page 66. We were also unable to find the quotations in the 5500-page plus record, despite performing word searches, and thus cannot review the alleged evidence. In any event, Patent Owner's argument remains unpersuasive.

to overcome mass transfer limitations.[18] *Id.* Put differently, Lloyd acknowledges that some artisans follow exactly what Gjerde I and Dr. Hornby's previous publications suggest: the use of a non-porous stationary phase to prevent analyte diffusion into pores. *See* Ex. 1004, 20:66–21:3 (stating that the beads are operable in RNA segregation because they "have a pore size which essentially excludes the RNA molecules being separated from entering the bead"); Ex. 2024, 1377. Nevertheless, Lloyd explains, this approach is not optimal because capacity is low "due to the loss of the internal pore volume." Ex. 1005, 224.

Lloyd thus suggests *another* approach: "to look at the pore size and structure of the HPLC material." *Id.* Lloyd teaches that "advances in the production of rigid polymeric particles" have made it "now possible to produce reversed-phase and ion-exchange particles that are mechanically rigid and stable to temperature and pH in a range of defined pore sizes." *Id.* Lloyd then introduces a family of small particle size, high-performance PSDVB reversed-phase columns: PLRP-S and PL-SAX. *Id.* Lloyd teaches that these HPLC columns are "expected . . . to exhibit improved mass transfer characteristics for the larger oligonucleotides" as compared to older, non-porous silica-based particles, due to the PSDVB-based media's porosity. *Id.* Thus, put in context, Lloyd teaches directly *toward* the claimed invention, which uses the same porous, non-alkylated PSDVB column as Lloyd to purify RNA. *See* Ex. 1001, 14:20–23 (describing the

[18] This teaching in Lloyd is consistent with other record evidence, which shows that "[o]ne way to circumvent intraparticular diffusion is the complete elimination of the support pores resulting in stationary phases of the micropellicular configuration." Ex. 1045, 4389.

purification of mRNA using a porous, non-alkylated PSDVB matrix that is a "conventional commercial product from Polymer Laboratories").

Accordingly, we agree with Petitioner that an ordinarily skilled artisan would have understood that both porous and nonporous media were options for RNA purification. Nevertheless, we agree that the skilled artisan would have been prompted to use Lloyd's porous, non-alkylated PSDVB column, because Lloyd teaches that this column possesses certain advantages for oligonucleotide purification that the prior-art nonporous columns do not, i.e., increased capacity and selectivity. *See* Reply 11; Ex. 1070 ¶¶ 71–73; Ex. 1005, 224; *see also Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 964 (Fed. Cir. 2014) (stating that "mere disclosure of alternative preferences" does not teach away); *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("[A] given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine.").

Finally, as to dependent claims 6 and 7, we are not persuaded by Patent Owner's argument that a skilled artisan "would not think to use a column of 4000 Å for preparative purification" because "the 4000 Å column in Lloyd had issues with reduced yields." PO Resp. 56. Patent Owner cites to Dr. Hornby's deposition as evidence that "Lloyd had issues with reduced yields." PO Resp. 56–57. Although Dr. Hornby testified that the chromatogram for the 4000 Å column showed a lower sum for the areas under the curve (AUC) when compared to the chromatograms for the 100 Å, 300 Å, and 1000 Å columns, *see* Ex. 2015, 123:19–22, Patent Owner points to no testimony or evidence suggesting that the lower AUC sum is indicative

of non-preparative purification. In fact, Dr. Hornby's deposition transcript is clear that the parties were merely "eye-balling" the AUCs for the purpose of his deposition testimony. *Id.* at 117:17–22.

Moreover, Dr. Hornby did not and could not attribute the reduced AUC sums to deficiencies in the 4000 Å porous material itself. Specifically, Dr. Hornby testified during his deposition that the AUCs shown in the 4000 Å chromatogram could be lower for a number of reasons, including material getting stuck on the frits—the "little filters at the top and the bottom"—of the chromatography column, *id.* at 124:19–125:6, the chromatography operator's decision to reduce the amount of material used, *id.* at 125:8–10, the chromatography operator's decision to use "a different response range on the detector," *id.* at 125:10–13, or the use of a different scale, *id.* at 126:17–21.

For all the above reasons, we find that Petitioner has shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have been motivated to combine the teachings of Lloyd and Zhang to achieve the claimed invention.

b. Reasonable expectation of success

We next consider whether Petitioner has shown by a preponderance of the evidence that the skilled artisan would have had a reasonable expectation of success in achieving the method claimed in the '340 patent. "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). Thus, in this case, the question before us is whether the ordinarily skilled artisan would have had a reasonable

expectation that using Lloyd's porous, non-alkylated PSDVB stationary-phase column (i.e., PLRP-S) in ion-pair reversed-phase HPLC would successfully result in the claimed method of purifying at least 100 µg of RNA.

Relying on the testimony of Dr. Hornby, Petitioner argues that an ordinarily skilled artisan would have had a reasonable expectation of success "because Lloyd provides a detailed description of purifying oligonucleotides using its method." Pet. 43–44 (citing Ex. 1002 ¶¶ 163–166). Petitioner argues that Lloyd "describes instrumentation, columns, and experimental conditions, such as gradients, buffers, temperature, etc." *Id.* at 44. Petitioner argues that Lloyd separated oligonucleotides of varying sizes, and also teaches that the PLRP-S column possesses "excellent selectivity and high capacity." *Id.* (quoting Ex. 1005, 227). Petitioner also argues that information disclosed in the Polymer Laboratories Catalog would have provided the skilled artisan with a reasonable expectation of success. *Id.* And Petitioner argues that an ordinarily skilled artisan "would have reasonably expected HPLC purification techniques developed for DNA to also work for RNA." *Id.* at 44–45.

Patent Owner disagrees. PO Resp. 41–54. Patent Owner argues that Dr. Hornby's own publications show "the unique challenges associated with purifying RNA as compared to DNA," *id.* at 41–44, and that Dr. Hornby's opinion on the interchangeability of DNA and RNA is simplistic and unsupported by the record, *id.* at 53–54. Patent Owner argues that the preponderance of the evidence shows that an ordinarily skilled artisan would not have expected the claimed method to successfully purify RNA. *Id.*

at 44–48. And, relying on the Declarations of Dr. Švec, Patent Owner argues that Lloyd's data is "incomplete and unreliable," such that an ordinarily skilled artisan "would not trust the reliability of the experiment reported in Lloyd." *Id.* at 48–53 (citing Ex. 2001; Ex. 2016).

Upon consideration of the entire record, we find again that the preponderance of the evidence supports the Petitioner's position. In making our findings as to "reasonable expectation of success," we keep in mind that we cannot demand absolute certainty. *See Intelligent Bio-Sys.*, 821 F.3d at 1367 ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a certainty of success."); *see also Pfizer*, 480 F.3d at 1364 ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.").

i. Analysis of Petitioner's arguments

We find that the record supports, by a preponderance of the evidence, Petitioner's argument that Lloyd evinces that an ordinarily skilled artisan would have had a reasonable expectation of success. *See* Pet. 43–44; Ex. 1002 ¶ 164. Specifically, Lloyd describes a method for purifying oligonucleotides (which we interpret as both DNA and RNA) using ion-pair reversed-phase HPLC and a porous, non-alkylated PSDVB column (i.e., PLRP-S). Lloyd reports that ion-pair reversed-phase chromatography using the PLRP-S column exhibits "excellent selectivity and high capacity" based on experimental results. Ex. 1005, 227. For example, Lloyd reports that the results shown in Figure 2 indicate "good mass transfer characteristics and the ability to use virtually the entire column volume for preparative/process work." *Id.* at 225. Given these results, Lloyd states that "[r]eversed-phase

ion-pair chromatography is an *obvious choice*" "to produce *large quantities* of well-defined oligonucleotides in an economic and timely fashion for clinical trials." *Id.* (emphases added); *see also id.* at 228 ("From the previous data *it is clear* that ion-pair reversed-phase HPLC can be used for the analysis and purification of oligonucleotides." (emphasis added)). Thus, we agree with Petitioner that the ordinarily skilled artisan would have reasonably expected, from Lloyd's teachings, the successful purification of RNA on a preparative scale using the PLRP-S column. Ex. 1002 ¶ 164.

We find that the record also supports, by a preponderance of the evidence, Petitioner's argument that information in the Polymer Laboratories Catalog would have provided the ordinarily skilled artisan with a reasonable expectation of success in obtaining preparative-scale quantities of purified RNA. Pet. 44; Ex. 1002 ¶ 164. Specifically, the Polymer Laboratories Catalog teaches that the PLRP-S column has "outstanding chemical and physical stability." Ex. 1024, 84. The Polymer Laboratories Catalog also informs the skilled artisan that "scale-up" to preparative scale purification "is easy," that "separations developed on an analytical scale [PLRP-S] column can be transferred to a preparative scale column with minimal method re-development," and that "[t]he media offers exceptional loading capacity due to the high surface area." *Id.* at 101.

We also agree with Dr. Hornby that the ordinarily skilled artisan would have realized, based on both Lloyd and the Polymer Laboratories Catalog, that PLRP-S columns were commercially available in a range of pore sizes so as to purify oligonucleotides (including RNA) of varying lengths. Ex. 1002 ¶ 164; Ex. 1005, 225; Ex. 1024, 94. For example, the

Polymer Laboratories Catalog identifies a "new" addition to the PLRP-S product range as "a 3μm packing in 100Å and 300Å pore sizes, designed to address the area of high resolution/high speed separations." Ex. 1024, 94. The Polymer Laboratories Catalog describes this new column as "the ideal choice" and "chemically stable and physically robust." *Id.* And the Polymer Laboratories Catalog states that a "typical application area[]" for the 100Å column is "oligonucleotides," and for the 300Å column is "larger oligonucleotides." *Id.* The Polymer Laboratories Catalog also provides a description and chromatogram of a reversed-phase HPLC used to purify a 20-mer oligonucleotide. *Id.* The Polymer Laboratories Catalog identifies the column (PLRP-S 100Å 3μm), the eluents used, the gradient, the flow rate, the temperature, and the detector. *Id.*

That the '340 patent does not describe any additional or novel techniques that must be used to successfully purify RNA on a preparative scale is another factor weighing in favor of a reasonable expectation of success. *See Cubist Pharm., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1128 (Fed. Cir. 2015) (finding that it would have been obvious to use well-known purification techniques to produce a daptomycin-related substance having the claimed purity levels because, *inter alia*, "[t]he purity patent patents do not point to any additional techniques that are necessary to obtain the recited purity levels in each of the claims").

Specifically, the '340 patent unambiguously conveys that successful RNA purification results from the use of a porous, rather than nonporous, reversed phase as the stationary phase. Ex. 1001, 1:59–64. But Lloyd also suggested a porous reversed stationary phase to overcome the mass-transfer

limitations and low capacity problem of the prior-art nonporous stationary phases before the ’340 patent’s critical date, and further identified the porous stationary phase by name—PLRP-S. Ex. 1005, 224. The ’340 patent teaches that the same stationary phase was used to obtain preparative amounts of RNA as shown in Figures 5–7. *See* Ex. 1001, Fig. 5 (chromatogram labeled “PLRP-S_1000A_8µm_250x46mm_Preparativ”), Fig. 6 & Fig. 7 (chromatograms labeled “PLRP-S_4000A_8µm_250x46mm-_Preparativ”), 13:41–49 (stating that the stationary matrix has a pore size of 1000 Å or 4000 Å); 15:12–14 (identifying the stationary phase as “[a] porous, non-alkylated polystyrene/divinylbenzene matrix” that is a “conventional commercial product from Polymer Laboratories”), 15:48–50 (same), 16:18–20 (same).

In sum, we find that the prior art suggests to the skilled artisan to use ion-pair reversed-phase HPLC and a PLRP-S column for purifying oligonucleotides (including RNA), provides many of the technical details for running the HPLC, and further identifies the PLRP-S column as commercially available in multiple pore sizes. Thus, “[t]his is not a situation where the prior art gave no direction on how to reach a successful result.” *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1026 (Fed. Cir. 2018). We are also unaware of any additional techniques disclosed in the ’340 patent that could be attributed to successful RNA purification. These factors persuade us that an ordinarily skilled artisan would have had a reasonable expectation of success.

ii. Analysis of Patent Owner’s arguments

We are not persuaded by Patent Owner’s arguments and evidence to the contrary. *See* PO Resp. 41–54.

First, Patent Owner argues that an ordinarily skilled artisan would not have reasonably expected success in purifying RNA from the prior art because methods for purifying RNA present unique challenges not applicable to methods for purifying DNA. PO Resp. 41–44. In support, Patent Owner highlights passages in various publications—Exhibits 2024,[19] 2025,[20] and 2026[21]—listing Dr. Hornby as an author. *Id.*; *see also* Sur-reply, 12–13.

We address Exhibits 2024 and 2026 individually below, and find that neither weighs persuasively against a reasonable expectation of success. As to Exhibit 2025, Patent Owner points to quotations purportedly attributable to Dr. Hornby at pages 1, 6, 82, 101, and 107. PO Resp. 43. We were unable to find these quotations because Exhibit 2025, which is a chapter of a book, begins with page 37 and ends at page 66. We also could not find the quotations through word searches of the entire evidentiary record. Thus, we must disregard these quotations as evidence.

---

[19] Sakharam P. Waghmare et al., *Studying the mechanism of RNA separations using RNA chromatography and its application in the analysis of ribosomal RNA and RNA:RNA interactions*, 1216 J. CHROMATOGRAPHY A 1377–1982 (2006) (Ex. 2024).

[20] Douglas T. Gjerde et al., *RNA Separation: Substrates, Functional Groups, Mechanisms, and Control*, *in* RNA PURIFICATION AND ANALYSIS: SAMPLE PREPARATION, EXTRACTION, CHROMATOGRAPHY (2009) (Ex. 2025).

[21] Mark J. Dickman and David P. Hornby, *Enrichment and analysis of RNA centered on ion pair reverse phase methodology*, 12 RNA 691–96 (2006) (Ex. 2026).

We begin with Exhibit 2026. Patent Owner points to statements that "the extraction, isolation, and analysis of RNA is routinely more difficult in comparison to that required for DNA," and that, "[i]n approaching the problem of RNA isolation, the stability and molecular heterogeneity [of RNA] are of immediate concern." *Id.* at 42 (quoting Ex. 2026, 691). We find that, when read in context, an ordinarily skilled artisan would understand that these statements are not related to RNA purification by chromatography. Instead, as Dr. Hornby persuasively testifies, these statements relate to the difficulty of extracting RNA from, e.g., cells or tissues, and isolating RNA from proteins and DNA. Ex. 1070 ¶ 89; *see also* Ex. 2026, 691. Dr. Hornby's testimony is supported by the article's explanation that "total RNA isolation procedures use a combination of denaturing agents, acid phenol chloroform extraction followed by precipitation of the nucleic acids," as well as its description of glass filters used "to isolate and purify total RNA from cell extracts and tissues." Ex. 2026, 691 (emphases added). The article's use of "extraction, isolation, and analysis" terminology is consistent with Sambrook & Russell,[22] which shows that "total RNA" results from extraction from tissues and cells, and that total RNA can be analyzed by many methods (e.g., northern hybridization, construction of cDNA libraries, etc.). Ex. 1054, 7.3 (Fig. 7–1). Thus, the statements in Exhibit 2026 do not inform the question of reasonable expectation of success.

---

[22] Joseph Sambrook and David W. Russell, Molecular Cloning: A Laboratory Manual (3rd ed. 2001) (Exhibit 1054, "Sambrook & Russell"). As Dr. Hornby explains, and we agree, those skilled in the art consider Sambrook & Russell a "gold-standard laboratory manual[]." Ex. 1070 ¶ 90.

Next, we turn to Exhibit 2024. Here, Patent Owner points to statements that "the mechanism by which RNA is separated appears more complicated" than DNA separation, and while methods for producing large amounts of RNA by *in vitro* transcription methods have improved, "separation and purification methods still present a bottleneck" for RNA analysis. PO Resp. 42 (quoting Ex. 2024, Abstract, 1382). Although these statements are related to RNA purification, we find that they would not discourage an ordinarily skilled artisan from RNA purification via HPLC.

This is because *the very next sentence* of the article, which Patent Owner omits, states: "The use of RNA chromatography not only provides an efficient means of isolating and analysing RNA species; it can also provide valuable structural information as demonstrated here." Ex. 2024, 1382. Indeed, the article goes on to say that RNA chromatography "will enable further insight in the analysis of RNA." *Id.* The article also states, "The high-resolution separation that can be achieved using RNA chromatography, on both an analytical and preparative scale, promises to bring even greater opportunities for the study of the molecular properties of RNA." *Id.* We view these statements in Exhibit 2024 as supporting, rather than undermining, the ordinarily skilled artisan's reasonable belief that RNA chromatography would be successful to obtain preparative amounts of RNA.

Second, Patent Owner relies on the teachings of Gjerde I and Lloyd as indicative of an absence of a reasonable expectation of success, and further asserts that Petitioner's evidence about the application of DNA purification methods to RNA is inapposite to RNA purification on a preparative scale. PO Resp. 44–46; Sur-reply 8–13. As to the latter assertion, Patent Owner

relies on the Declaration of Dr. Schwenger to contradict Petitioner's argument that ordinarily skilled artisans would have expected the same column to purify both DNA and RNA. PO Resp. 53–54; Sur-reply 13–14.

We do not rely on Petitioner's arguments and evidence related to whether an ordinarily skilled artisan "would have reasonably expected HPLC purification techniques developed for DNA to also work for RNA." Pet. 44–45. In our view, these arguments and evidence are unnecessary for a reasonable expectation of success given the teachings of Lloyd and the Polymer Laboratories Catalog directly toward the claimed invention. To the extent that Patent Owner repeats its argument that the "oligonucleotides" referred to in Lloyd and the Polymer Laboratories Catalog do not encompass RNA, we disagree for the same reasons discussed above with respect to the teachings of the prior art. *Supra* § III.F.1.c. (discussion of Lloyd's disclosure of "oligonucleotides").[23]

Patent Owner also challenges Petitioner's argument that HPLC was a commonly-used technique for purifying RNA, as well as Petitioner's reliance on such background references as Azarani (Ex. 1008), McFarland (Ex. 1015), Georgopoulos (Ex. 1023), Hölzl (Ex. 1044), and Taniguchi (Ex.

[23] Patent Owner asserts that Lloyd teaches disadvantages of HPLC by explaining that "the relatively small pore silica-based weak anion exchangers do not have the required resolution or sample load for preparative separations." PO Resp. 46 (quoting Ex. 1005, 224) (citing Ex. 2001 ¶ 96; Ex. 2016 ¶ 61). But this is a criticism of *anion-exchange* HPLC, not of the ion-pair reversed-phase HPLC used in the '340 patent. Ex. 1005, 224. In any event, Lloyd teaches that the *solution* to small-pore silica-based stationary phases is the family of small particle size, high-performance PSDVB reversed phase media, i.e., PLRP-S and PL-SAX. *Id.*

1053) for support. PO Resp. 45–48; Sur-reply 9–10. Although Patent Owner's assertions about the teachings of certain background references are not without some merit, we do not rely on these background references to support a reasonable expectation of success. Thus, we need not address them here.

Third, relying on the testimony of Dr. Švec, Patent Owner argues that the data presented in Lloyd "is incomplete and unreliable," and therefore an ordinarily skilled artisan could not "even determine if the Lloyd experiments were successful." PO Resp. 48–53. Dr. Švec testifies that a successful HPLC separation requires narrow and tall, symmetrical, non-overlapping, and high-capacity peaks. Ex. 2016 ¶ 30 (citing Ex. 2004, 221–23, 227, 542). According to Patent Owner, Dr. Hornby "agreed that these qualities are important to a successful chromatogram." PO Resp. 49 (citing Ex. 2015, 14:15–15:1, 31:5–32:12). Patent Owner argues that "[t]he data provided in Lloyd either fails to meet these characteristics, or fails to provide enough information to evaluate these criteria at all." *Id.* (citing Ex. 2016 ¶ 31); *see also* Sur-reply, 4.

To begin, we observe that Patent Owner's arguments, drilled down, are that Lloyd fails to provide evidence of actual success in preparative RNA purification. But the test for obviousness does not require "actual success" in the prior art. *Grunenthal GMBH v. Alkem Labs. Ltd.*, --- F.3d ----, 2019 WL 1387982, at *8 (Fed. Cir. Mar. 28, 2019) (citing *AstraZeneca LP v. Breath Ltd.*, 603 F. App'x 999, 1002 (Fed. Cir. 2015)). "[O]nly a reasonable expectation of success, not a guarantee, is needed." *Pfizer*, 480 F.3d 1364; *see also PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed.

Cir. 2014) ("The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success.").

Patent Owner's arguments relate in the main to the chromatograms shown in Figure 1 of Lloyd. As to Figure 1, Lloyd used PLRP-S columns of different pore sizes (i.e., 100 Å, 300 Å, 1000 Å, and 4000 Å) to resolve a 25-base pair double-stranded DNA ladder via ion-pair reversed-phase HPLC. Ex. 1005, 225–26. According to Lloyd, the "DNA ladder was used to determine the separation range for the four pore sizes of [the] PLRP-S media." *Id.* at 225. After running each HPLC under the "same chromatographic conditions," the individual peaks were "collected for PAGE analysis to show the size and purity of each fraction." *Id.* at 225. The results of the HPLC are shown in Figure 1, reproduced below. *Id.* at 226.

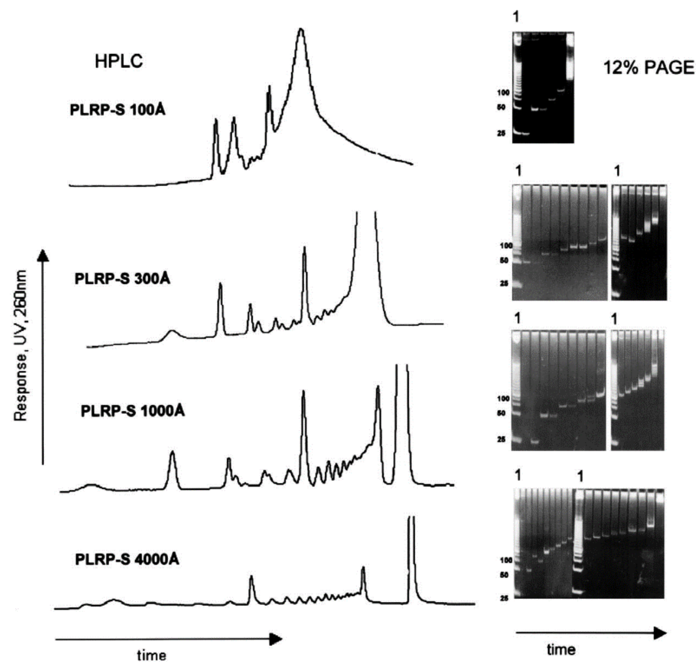

Figure 1 shows reversed-phase chromatograms of a 25-bp double-stranded DNA ladder and PAGE analysis of each peak fraction. Ex. 1005, 226 (Fig. 1).

After considering the respective testimony of Dr. Hornby and Dr. Švec about Figure 1 in light of the teachings of Lloyd, we find that Dr. Hornby's testimony is more credible because it is supported by the record evidence.

As Dr. Hornby explains, and the evidence of record supports, an ordinarily skilled artisan would have known that a DNA ladder is a mixture of DNA fragments of pre-determined sizes and concentrations—i.e., "a complex mixture of oligonucleotides." Ex. 1070 ¶ 57 (citing Ex. 1057, 1:11–43).[24] Lloyd's data shows that the PLRP-S 100 Å column successfully resolved all oligonucleotide fragments "up to 50–75 bp." Ex. 1005, 225, 226 (Fig. 1). The remaining fragments of the DNA ladder all co-eluted together, thus proving that the larger fragments were "excluded from the pores" of the PLRP-S 100 Å column. *Id.* at 225, 226 (Fig. 1); *see also* Ex. 1070 ¶ 59. The remaining chromatograms and PAGE photos show that, "[a]s the pore size of the HPLC media increases so the resolving range increases." *Id.* at 225. Specifically, the PLRP-S 300 Å column resolves individual fragments "up to 250–300 bp," the PLRP-S 1000 Å column resolves individual fragments "up to 400–450 bp," and the PLRP-S 4000 Å column resolves individual fragments "in excess of 500 bp." *Id.* at 225, 226 (Fig. 1).

Thus, we agree with and credit Dr. Hornby's testimony that an ordinarily skilled artisan would have seen from these results that the PLRP-S media was capable of achieving separation (or resolution) of a mixture of

[24] For example, as shown in the PAGE photos, Lloyd's DNA ladder contains fragments of at least 25, 50, and 100 base-pairs. Ex. 1005, 226 (Fig. 1).

oligonucleotides. Ex. 1070 ¶ 58. We also agree with and credit Dr. Hornby's testimony that the increase in the number of peaks shown in the chromatograms from the PLRP-S 100 Å column to the PLRP-S 1000 Å column "indicate[s] that better separation can be achieved with larger pore sizes." *Id.* Lloyd confirms this by stating that "[a]s the pore size of the HPLC media increases so the resolving range increases," because "the larger oligonucleotides can permeate the porous structure." Ex. 1005, 225.

Conversely, we are not persuaded by Dr. Švec's testimony that the peaks shown in the chromatograms in Figure 1 "fail to meet the characteristics of a successful separation," and thus would have dissuaded an ordinarily skilled artisan of success. *See* Ex. 2016 ¶¶ 30–31. As Dr. Hornby reasonably explains, Dr. Švec holds Lloyd to an ideal purification standard, where Lloyd was setting out to show resolution of a DNA ladder as illustrated by different peaks. Ex. 1070 ¶¶ 37–38, 57–63; *see also* Ex. 1058, 45:9–46:14 (Dr. Švec's deposition testimony acknowledging that "peaks on a chromatogram" indicate that "you have achieved separation").

None of the '340 patent's claims recite such an ideal purification standard—either in terms of purity level or degree of separation. *See* Ex. 1001, 19:55–22:29; *see also* Ex. 1070 ¶¶ 85–57. And although the claims require "preparative scale" purification of RNA, we do not import a purification standard into the *amount* of RNA (i.e., 100 μg) required by the claims. *See* Sur-reply 3–4 (arguing that "preparative" purification requires a "clean and robust separation"). In any event, the '340 patent defines "purification" broadly, meaning that "the desired RNA in a sample is separated and/or isolated from the impurities present therein," and that "after

HPLC purification the RNA is present in a purer form than in the originally introduced RNA-containing sample." Ex. 1001, 2:61–64. The '340 patent further describes purity levels as low as 70%. *Id.* at 3:10–13.

We also are not persuaded by Dr. Švec's testimony that the data presented in Figure 1 is missing critical information, *See* Ex. 2016 ¶ 31–36. As Dr. Hornby reasonably explains, the skilled artisan would not need such information as UV response axis or time axis values, the amount of sample volume injected into the HPLC column, or an identification of the chromatogram peaks to recognize that Lloyd achieved separation of the DNA fragments from a mixture of oligonucleotides. Ex. 1070 ¶ 60. Separation is illustrated by the different peaks on the chromatograms and confirmed by PAGE. Ex. 1005, 226 (Fig. 1).

For all these reasons, we are not persuaded by Patent Owner's arguments and evidence that the ordinarily skilled artisan would not have reasonably expected success in preparative RNA purification based on the data presented in Lloyd.

c. Obvious to try

In its Sur-reply, Patent Owner argues that Lloyd provides only "wishful thinking about *trying* to achieve" oligonucleotide purification. Sur-Reply 5. Patent Owner acknowledges that Lloyd states "it is clear that ion-pair reversed-phase HPLC can be used for the analysis and purification of oligonucleotides," *id.* (quoting Ex. 1005, 228), but argues that "this statement alone does not solve the problems with Lloyd's data," *id.* Given these problems, Patent Owner argues, an ordinarily skilled artisan "would not be motivated to base an attempt to purify RNA on a preparative scale based on the teaching of Lloyd." *Id.*; *see also* PO Resp. 54–56.

In *KSR*, the Supreme Court explained that a claimed invention can be obvious under an "obvious to try" analysis under certain circumstances:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 550 U.S. at 421. The Federal Circuit has since identified two instances where an obvious-to-try theory must fail: (1) when "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful"; and (2) when "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

We determine that facts of this case fall within the Supreme Court's permissible use of "obvious to try." Specifically, as discussed above, the preponderance of the record evidence shows that there was a need in the art to purify large amounts of RNA for use in, for example, clinical trials for antisense therapeutics. An ordinarily skilled artisan would have also understood that the prior-art HPLC methods using nonporous media as the

stationary phase suffered from low capacity due to the lack of the internal pore volume, and thus these methods were not the ideal solution for preparative RNA purification. Into this state of the art, Lloyd introduces a finite number of high-performance PSDVB-based columns comprising mechanically rigid and stable polymeric particles: PLRP-S and PL-SAX. Lloyd then expressly suggests using the PLRP-S column in ion-pair reversed phase HPLC as the "obvious choice" for purifying antisense therapeutics. Thus, this is not a case where the prior art gave no direction or the skilled artisan was faced with numerous possible choices.

The preponderance of the record evidence also shows that utilizing Lloyd's PLRP-S column in ion-pair reversed-phase HPLC was well within the ordinarily skilled artisan's technical grasp. The PLRP-S column was commercially available, and the Polymer Laboratories Catalog taught that "scale-up" to preparative scale purification would be "easy," due to the media's "exceptional loading capacity" and "high surface area." Thus, this is not a case where the skilled artisan had to set out on a new path with little guidance from the prior art.

3. Secondary considerations

Patent Owner presents arguments and evidence of objective indicia of nonobviousness that we must consider before reaching our conclusion on obviousness *vel non*. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). Patent Owner argues that the objective indicia of unexpected results supports the nonobviousness of the challenged claims. PO Resp. 60–62. Petitioner disputes that the claimed method produces unexpectedly superior results, and further argues that Patent Owner has established a

nexus between any unexpected results and the claimed invention. Reply 16–18.

a. Nexus

At the outset, we find that Patent Owner's proffered results, even if unexpected, can carry only little weight in our obviousness analysis. "For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quotation and emphasis omitted). Patent Owner does not allege (or even mention) a "nexus" between the claimed invention and the unexpected results. *See generally* PO Resp. 60–62. And this is not a case where we apply a presumption of nexus, because Patent Owner has not shown or alleged that the unexpected results are tied to a specific commercial product that is the invention disclosed and claimed in the '340 patent. *Id.*; *see also WBIP*, 829 F.3d at 1329 (setting forth circumstances in which the presumption of nexus applies). Thus, we find no nexus between the alleged unexpected results and the claimed invention.

b. Unexpected results

Even if we presume nexus, then we find that Patent Owner fails to show persuasively evidence of unexpected results. Patent Owner argues that "[t]he inventors of the '340 patent found that the claimed method for HPLC purification of RNA leads to a *more than 3–5 fold* increase in expression of the RNA-encoded protein compared to a non HPLC-purified RNA." PO Resp. 60. But, as Petitioner persuasively points out, Patent Owner's evidence must fail because it does not compare the alleged unexpected results to the closest prior art. Pet. 61–62; Reply 16–17.

"[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever United States, Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). Patent Owner first points to results shown in Figure 8 of the '340 patent, as "demonstrat[ing] the improvement in the expression of luciferase from RNA purified with a method according to the invention." PO Resp. 61 (citing Ex. 1001, 16:10–50). Relying on the Declaration of Dr. Fotin-Mleczek, Patent Owner argues that the "bar chart and agarose gel shown at Figure 8 show a more than five-fold increase in protein expression when the expressing-mRNA is purified using the claimed method (called 'PUREmessenger')." *Id.* (citing Ex. 2012 ¶ 25).

We find that Figure 8 is not persuasive of unexpected results, because neither the '340 patent nor Dr. Fotin-Mleczek explain how (or whether) the mRNA used as a comparison was purified. For example, the '340 patent states only that "[t]he improvement of the expression of luciferase resulting from purification with the method according to the invention is shown in FIG. 8." Ex. 1001, 16:47–49. And Dr. Fotin-Mleczek states only that the comparison mRNA is "non-HPLC purified mRNA." Ex. 2012 ¶¶ 24–25. Because this information is insufficient to determine whether the claimed invention was compared with the closest prior art, we find that Patent Owner has failed to show that the results in Figure 8 constitute "unexpected results."

Next, Patent Owner points to an experiment in Dr. Thran's Declaration showing "the expression of anti-rabies antibodies in HeLa cells

following purification of the mRNA encoding the antibodies using the method of the ’340 patent.” PO Resp. 61–62 (citing Ex. 2013 ¶¶ 12–14). Patent Owner argues that Dr. Thran’s results show “about a three-fold higher expression of the encoded anti-rabies antibody compared to expression seen when the mRNA was not purified.” *Id.* Again, we do not find this evidence persuasive of “unexpected results” because we cannot determine whether Dr. Thran compared the results to the closest prior art. Dr. Thran refers to the comparison mRNA as “non-purified mRNA,” but Patent Owner provides no explanation as to whether non-purified mRNA constitutes the closest prior art to HPLC-purified mRNA. Ex. 2013 ¶ 14; PO Resp. 61–62. In any event, we are persuaded by and credit Dr. Hornby’s testimony that “a non-purified mRNA is not the closest prior art because it misses a step of ‘purifying’ RNA.” Ex. 1070 ¶ 123.

4. Conclusion as to obviousness over Zhang and Lloyd

In sum, we find that the combination of Zhang and Lloyd teach or suggest each and every element of claims 1, 3, 4, 6–19, and 21–26. We find that an ordinarily skilled artisan would have been motivated to combine Zhang and Lloyd, and would have had a reasonable expectation of success in achieving the claimed invention. We also find that Patent Owner has failed to persuasively show unexpected results. After carefully considering the arguments and evidence, therefore, we determine that the record as a whole weighs in favor of a conclusion of obviousness, especially given the disclosures of the art of record in this case and strength of the obviousness case based on the first three *Graham* factors.

Specifically, the preponderance of the record evidence shows that there was a need in the art to purify large amounts of RNA for use in, for example, clinical trials for antisense therapeutics. Thus, an ordinarily skilled artisan would have had a reason to seek out methods for purifying preparative amounts of RNA. The skilled artisan would have also understood that Lloyd suggests a finite number of high-performance PSDVB-based columns, PLRP-S and PL-SAX, for purifying antisense therapeutics, including RNA oligonucleotides in large amounts. The preponderance of the record evidence also shows that utilizing Lloyd's PLRP-S column in ion-pair reversed-phase HPLC was well within the ordinarily skilled artisan's technical grasp, and that the skilled artisan would have had a reasonable belief that the PLRP-S column could be used successfully to purify RNA on a preparative scale. For these reasons, we conclude that Petitioner has satisfied its burden of demonstrating, by a preponderance of the evidence, the unpatentability of claims 1, 3, 4, 6–19, and 21–26 of the '340 patent as obvious over Zhang and Lloyd.

G. Obviousness of Claim 2 Over Sullenger and Lloyd

Petitioner contends that claim 2 is unpatentable as obvious over Sullenger in view of Lloyd. Pet. 52–56. Petitioner also presents arguments mapping the language of dependent claim 2 to Sullenger and Lloyd. *Id.* at 52–53.

Claim 2 of the '340 patent depends from claim 1, and specifies that the RNA is "selected from among tRNA, rRNA, mRNA or whole-cell RNA, and RNA variants." Ex. 1001, 19:63–65. We agree with Petitioner that Sullenger discloses mRNA for therapeutic use, and suggests the need for

mRNA isolation for "[s]pecific active immunotherapy of cancer." Ex. 1039, 256–57. Thus, we agree with Petitioner that the combination of Sullenger and Lloyd teaches or suggests each limitation of claim 2. Pet. 52–53.

Petitioner contends, and Dr. Hornby testifies, that an ordinarily skilled artisan would have been motivated to combine the teachings of Lloyd with Sullenger. Pet. 53–55; Ex. 1002 ¶¶ 240–42. Petitioner contends that, like Zhang, Sullenger evinces the need for purified mRNA, and that an ordinarily skilled artisan would have been motivated to use Lloyd's ion-pair reversed-phase chromatography with a PLPR-S column stationary phase to produce large quantities (i.e., preparative amounts) of mRNA. Pet. 53–54 (citing Ex. 1039, 256–57; Ex. 1005, 223, 227; Ex. 1002 ¶¶ 238–242). Petitioner also contends that the skilled artisan would have had a reasonable expectation of success, "because Lloyd provides a detailed description of purifying oligonucleotides using the claimed HPLC technology." *Id.* at 55–56 (citing Ex. 1002 ¶¶ 165, 243–247; Ex. 1005, 224–25, 229; Ex. 1024, 101, 108, 123; Ex. 1017, 129).

Having considered the record, we are persuaded for the reasons stated by Petitioner, which we adopt. Pet. 52–56. We are not persuaded by Patent Owner's arguments and evidence to the contrary, which fail for the same reasons that Patent Owner's arguments and evidence fail as to the combination of Zhang and Lloyd. In particular, Patent Owner's argument that "Sullenger does not teach anything about purifying RNA" or "anything about oligonucleotides" is unpersuasive, because Petitioner relies on Sullenger to teach a need in the art to purify mRNA for clinical applications. *See* Pet. 53–55. And, as we explained above, Lloyd suggests a finite number

of high-performance PSDVB-based columns to do so, and further suggests ion-pair reversed-phase chromatography is an “an obvious choice” for obtaining preparative amounts of high-purity oligonucleotides. Ex. 1005, 225; *see also id.* at 228 (“From the previous data it is clear that ion-pair reversed-phase HPLC can be used for the analysis and purification of oligonucleotides.”).

H. Obviousness of Claim 5 Over Zhang, Lloyd, and Polymer Laboratories Catalog

Petitioner contends that claim 5 is unpatentable as obvious over Zhang in view of Lloyd and Polymer Laboratories Catalog. Pet. 56–59. Petitioner also presents arguments mapping the language of dependent claim 5 to Zhang, Lloyd, and Polymer Laboratories Catalog. *Id.* at 56–57.

Claim 5 depends from claim 1, and specifies that the “porous reversed phase has a particle size of 8 μm to 50 μm.” Ex. 1001, 20:59–60. Polymer Laboratories Catalog describes the PLRP-S columns used by Lloyd, and specifies that those columns have particle sizes within the range recited in claim 5 of the ’340 patent. Ex. 1024, 123. Thus, we agree with Petitioner that the combination of Zhang, Lloyd, and Polymer Laboratories Catalog teaches or suggests each limitation of claim 5. Pet. 56–57.

Petitioner also contends that the skilled artisan would have had a reason to combine Polymer Laboratories Catalog with Zhang and Lloyd with a reasonable expectation of success. *Id.* at 57–59. As to reason to combine, Petitioner contends that an ordinarily skilled artisan “would have had a reason to perform Lloyd’s method with the bead size disclosed in the Polymer Laboratories Catalog because Lloyd teaches using media from Polymer Labs in its method.” *Id.* at 57 (citing Ex. 1005, 225; Ex. 1002

¶¶ 256–59). Petitioner also points out that Polymer Laboratories Catalog teaches that is "PLRP-S columns are ideal for oligonucleotide analysis." *Id.* at 58 (quoting Ex. 1024, 105–106).

Petitioner contends that the skilled artisan would have had a reasonable expectation of success because, *inter alia*, "Polymer Laboratories Catalog teaches that such PLRP-S particles have 'outstanding chemical and physical stability,' have 'high pressure capability,' are 'durable and resilient for long lifetime,' are 'easily regenerated, sanitized, sterilized,' and are 'designed for reproducible scale-up,'" *id.* at 58 (quoting Ex. 1024, 86), and because "the Polymer Laboratories Catalog cites to Lloyd as evidence that its 'PLRP-S columns are ideal for oligonucleotides,'" *id.* (quoting Ex. 1024, 106); *see also* Ex. 1002 ¶¶ 260–62).

Having considered the record, we are persuaded for the reasons stated by Petitioner, which we adopt. Pet. 56–59. Patent Owner's arguments to the contrary rely on its alleged "deficiencies that exist in Lloyd," and are not persuasive for the same reasons detailed above. *See* PO Resp. 58 (arguing that the Polymer Laboratories Catalog "is simply a catalog advertising the subject matter of the Lloyd paper," and "does not remedy any of the deficiencies of Lloyd").

I. Obviousness of Claim 20 Over Zhang, Lloyd, and Gjerde II

Petitioner contends that claim 20 is unpatentable as obvious over Zhang in view of Lloyd and Gjerde II. Pet. 59–61. Petitioner also presents arguments mapping the language of dependent claim 20 to Zhang, Lloyd, and Gjerde II. *Id.* at 59–60.

Claim 20 depends indirectly from claim 1, and specifies that "the elution [of the mobile phase] proceeds isocratically." Ex. 1001, 22:7–8.

Patent Owner argues that Gjerde II uses beads that "have a pore size which essentially excludes the polynucleotides being separated from entering the beads," and are thus, non-porous. PO Resp. 59–60. Although we agree with Patent Owner on this point, Petitioner relies on Gjerde II as evidence of "isocratic" elution conditions, which were well known in the art. *See* Pet. 60–61 (citing Ex. 1006, 14:42–46, 7:57–58, 20:41–44, 23:48–52, 25:27–30; Ex. 1002 ¶¶ 266–273; Ex. 1033, 728 (describing "[a] separation that employs a single solvent of constant composition is termed an isocratic elution"); Ex. 1034, 9:12–21. Thus, we agree with Petitioner that the combination of Zhang, Lloyd, and Gjerde II teaches or suggests each limitation of claim 20. Pet. 59–60.

Petitioner also contends that the skilled artisan would have had a reason to combine Gjerde II with Zhang and Lloyd with a reasonable expectation of success. *Id.* at 60–61. As to reason to combine, Petitioner contends that an ordinarily skilled artisan would have had a reason to utilize Gjerde II's isocratic elution conditions "because Gjerde II teaches that 'by using a combination of gradient and isocratic elution conditions, the resolving power of a system can be enhanced for a particular size range of DNA.'" *Id.* at 60 (quoting Ex. 1006, 25:27–30; citing Ex 1002 ¶¶ 268–270). Petitioner also points out that Gjerde II teaches that its methods "can be used in the separation of RNA or of double- or single-stranded DNA," *id.* (quoting Ex. 1006, 9:54–55), and thus, the skilled artisan would have understood that isocratic elution conditions were suitable for RNA purification, *id.* (citing Ex. 1002 ¶ 270). Petitioner also contends that the skilled artisan would have had a reasonable expectation of success, because,

inter alia, "isocratic elutions were a well-known method in the field." *Id.* at 61 (citing Ex. 1002 ¶ 273; Ex. 1033, 728; Ex. 1034, 9:12–21).

Having considered the record, we are persuaded for the reasons stated by Petitioner, which we adopt. Pet. 59–61. In particular, we agree with Petitioner and Dr. Hornby that isocratic elution conditions were well known in the art and applicable to HPLC purification techniques. *See, e.g.*, Ex. 1034, 9:16–21 (explaining that, "for some processes, a highly precise isocratic . . . composition" may be required); *see also* Ex. 1002 ¶ 270–273. Patent Owner's arguments to the contrary are related only to the nonporous nature of Gjerde II's beads. *See* PO Resp. 59–60. Again, these arguments are not persuasive because Petitioner relies on Gjerde II as evidence of isocratic elution conditions. The preponderance of the record supports Petitioner's argument that isocratic elution conditions were routine in the art, and we find little to no persuasive evidence that applying isocratic elution conditions to Lloyd's HPLC method would have been outside the skill set of an ordinary artisan. *See* Ex. 1002 ¶ 273; Ex. 1033, 728; Ex. 1034, 9:12–21.

IV. MOTION TO SEAL AND MODIFIED PROTECTIVE ORDER

Petitioner moves to seal the non-redacted versions of Exhibit 1068, Exhibit 1070, and Petitioner's Reply (Paper 27) as confidential information. Paper 29, 1–2. Petitioner also requests that the parties' Modified Protective Order be enter. *Id.* at 2–3. For the reasons set forth below, Petitioner's motion is *granted*.

A. Standard

The record for an *inter partes* review shall be made available to the public, except as otherwise ordered, and a document filed with a motion to

seal shall be treated as sealed until the motion is decided. 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. The standard for granting a motion to seal is "good cause." 37 C.F.R. § 42.54. "There is a strong public policy for making all information filed in a quasi-judicial administrative proceeding open to the public, especially in an *inter partes* review which determines the patentability of claims in an issued patent and therefore affects the rights of the public." *Garmin Int'l v. Cuozzo Speed Techs., LLC*, IPR2012–00001, slip op. at 1–2 (PTAB Mar. 14, 2013) (Paper 34). The moving party bears the burden of showing that the relief requested should be granted. 37 C.F.R. § 42.20(c). That includes showing that the information is truly confidential, and that such confidentiality outweighs the strong public interest in having an open record. *See Garmin* at 2–3.

B. Petitioner's Motion to Seal

Petitioner seeks to seal the non-redacted versions of Exhibit 1068, Exhibit 1070, and Petitioner's Reply (Paper 27). Paper 29, 1–2. Petitioner states that Exhibit 1068 contains information relating to Dr. Fotin-Mleczek's answers to deposition questions about "ownership of CureVac stock" and "the range of integrity for RNA used in CureVac's clinical trials." *Id.* at 1. Petitioner states that Patent Owner stated during deposition that it would "like to mark the transcript confidential" and seal those portions of the deposition transcript. *Id.* Petitioner states that it has complied with Patent Owner's request by redacting portions of Exhibit 1068, as well as portions of Exhibit 1070 and Petitioner's Reply that cite to the indicated portions of Ex. 1068. *Id.* at 1–2. Petitioner has submitted both public (redacted) and confidential (non-redacted) versions of Exhibit 1068 (Ex. 1068 (non-

redacted); Ex. 1076 (redacted)), Exhibit 1070 (Ex. 1070 (non-redacted); Ex. 1075 (redacted)), and its Reply (Paper 27 (non-redacted); Paper 28 (redacted). *Id.* at 2. In reviewing these documents, we conclude that they may contain confidential information. Thus, we are persuaded that good cause exists to seal the non-redacted versions of Exhibit 1068, Exhibit 1070, and Petitioner's Reply.[25]

C. Modified Protective Order

Petitioner also seeks entry of a Modified Default Protective Order attached to its Motion to Seal as "Addendum A." Paper 29, 2–3. Petitioner states that the parties met and conferred about a protective order, and that Petitioner does not oppose Patent Owner's request for a Modified Protective Order to protect the information Patent Owner has designated as confidential. *Id.* at 2.

The Modified Protective Order is entered. The parties are reminded, however, that confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. *Office Patent Trial Practice Guide*, 77 Fed. Reg. 48,756, 48,761 (Aug. 14, 2012). This panel interprets "final judgment" to include the resolution of appellate proceedings, if any. Also, there is an expectation that information will be made public where the existence of the information is identified in a final written decision following a trial. *Id.* After final judgment in a trial, a party may file a motion to expunge confidential information from the record prior to the information becoming public. *See* 37 C.F.R. § 42.56.

---

[25] Any citations herein to these documents should be considered as to their redacted, public versions.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–26 of U.S. Patent 8,383,340 B2 have been shown to be unpatentable under 35 U.S.C. § 103 for obviousness;

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

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is denied;

FURTHER ORDERED that Petitioner's Motion To Seal and Enter the Modified Protective Order is granted; and

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

FOR PETITIONER:

Eldora Ellison
David Roadcap
Olga Partington
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
eellison-ptab@sternekessler.com
droadcap-ptab@sternekessler.com
opartington-ptab@sternekessler.com

FOR PATENT OWNER:

Teresa Rea
Deborah Yellin
CROWELL & MORING LLP
trea@crowell.com
dyellin@crowell.com