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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

PROTIVA BIOTHERAPEUTICS, INC.,
Patent Owner.

Case IPR2018-00739
Patent 9,364,435 B2

Before SHERIDAN K. SNEDDEN, SUSAN L. C. MITCHELL, and RICHARD J. SMITH, *Administrative Patent Judges*.

MITCHELL, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

Determining Claims 1–6, 9, 12, 14, and 15
Unpatentable in *Inter Partes* Review
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Determining Claims 7, 8, 10, 11, 13, and 16–20
Not Unpatentable in *Inter Partes Review*
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Denying Patent Owner's Motion to Amend
35 U.S.C. § 316(d) and 37 C.F.R. § 42.121

I. INTRODUCTION

This is a final written decision in *inter partes* review of claims 1–20 of U.S. Patent No. 9,364,435 B2 (Ex. 1001, "the '435 patent") entered 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 claims 1–6, 9, 12, 14, and 15 of the '435 patent are unpatentable under 35 U.S.C. § 102. *See* 35 U.S.C. § 316(e). We also determine that Petitioner has not shown by a preponderance of the evidence that claims 7, 8, 10, 11, 13, or 16–20 are unpatentable.

Because we have found only some of the challenged claims unpatentable, we address Patent Owner's contingent Motion to Amend concerning proposed substitute claims for those unpatentable claims, which are proposed substitute claims 21–26, 29, 32, 34, and 35. We also find that Patent Owner's proposed substitute claims 21–26, 29, 32, 34, and 35 are unpatentable. Therefore, we deny Patent Owner's Motion to Amend.

A. Procedural History

Moderna Therapeutics, Inc. ("Petitioner")[1] filed a Petition to institute an *inter partes* review of claims 1–20 (the "challenged claims") of the '435 patent. Paper 2 ("Pet."); *see* 35 U.S.C. §§ 311–319. Petitioner relied upon the Declaration of Andrew S. Janoff, Ph.D. to support its challenge.

[1] Petitioner states that the name of its parent has been changed to Moderna, Inc., and that Moderna, Inc.'s intellectual property matters are now conducted under the name of ModernaTX, Inc., which is a fully-owned subsidiary of Moderna, Inc. Paper 46, 2.

See generally Pet. Protiva Biotherapeutics, Inc. ("Patent Owner")[2] filed a Preliminary Response to the Petition. Paper 12 ("Prelim. Resp.").

Pursuant to 35 U.S.C. § 314(a), on September 12, 2018, we instituted an *inter partes* review of challenged claims 1–20 (Paper 15, "Inst. Dec." or "Institution Decision") instituting *inter partes* review of all challenged claims under all asserted grounds. Inst. Dec. 33. Patent Owner filed a Response (Paper 24, "PO Resp.") supported by the Declaration of David H. Thompson, Ph.D (Ex. 2009). Petitioner filed a Reply (Paper 28, "Reply") supported by a second Declaration of Dr. Janoff (Ex. 1021), and Patent Owner filed an authorized Sur-reply (Paper 34, "Sur-reply"). *See* Papers 16, 19 (authorizing Patent Owner's Sur-Reply).

Patent Owner filed a contingent motion to amend (Paper 26 (corrected), "Mot.") supported by a Declaration of Dr. Thompson (Ex. 2040), which Petitioner opposed (Paper 29, "Opposition to Motion to Amend") with a supporting Declaration of Dr. Janoff (Ex. 1020). Patent Owner filed a Reply to Petitioner's opposition. Paper 33, "Reply Opp."

At the request of both parties, we held an oral hearing on June 6, 2019, and the transcript of that hearing has been entered into the record. Paper 49 ("Tr.").

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[2] According to Patent Owner, Protiva Biotherapeutics, Inc. ("Protiva") existed as a wholly-owned subsidiary of Arbutus Biopharma Corporation and was amalgamated into Arbutus Biopharma Corporation in January 2018. Paper 14, 2. Patent Owner identifies Arbutus Biopharma Corporation (fka "Tekmira"), Genevant Sciences, Ltd., and its fully owned subsidiaries: Genevant Sciences Holding, Ltd., Genevant Sciences Corporation, Genevant Sciences, Inc., and Genevant Sciences, GmbH, as the real parties in interest. *Id*.

B. Related Proceedings

Patent Owner identifies the following related matters:

Moderna Therapeutics, Inc. v. Protiva Biotherapeutics, Inc., IPR2018-00680 regarding U.S. Patent No. 9,404,127 B2; and European Patent Office Opposition proceedings regarding EP 2 279 254. Paper 14, 2.

C. The '435 Patent (Ex. 1001)

The '435 patent relates to "stable nucleic acid-lipid particles (SNALP) comprising a nucleic acid (such as one or more interfering RNA), methods of making the SNALP, and methods of delivering and/or administering the SNALP." Ex. 1001, Abstract. The '435 patent states that "[t]he present invention is based, in part, upon the surprising discovery that lipid particles comprising from about 50 mol % to about 85 mol % of a cationic lipid, from about 13 mol% to about 49.5 mol % of a non-cationic lipid, and from about 0.5 mol % to about 2 mol % of a lipid conjugate provide advantages when used for the in vitro or in vivo delivery of an active agent, such as a therapeutic nucleic acid (e.g., an interfering RNA)." *Id.* at 5:55–62. The '435 patent further states that

> the present invention provides stable nucleic acid-lipid particles (SNALP) that advantageously impart increased activity of the encapsulated nucleic acid (e.g., an interfering RNA such as siRNA) and improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described. Additionally, the SNALP of the invention are stable in circulation, e.g., resistant to degradation by nucleases in serum and are substantially non-toxic to mammals such as humans.

Id. at 5:62–6:5.

The '435 patent identifies specific SNALP formulations that encapsulate siRNA as the nucleic acid, such as the 1:57 SNALP and the 1:62

SNALP, and states that "the Examples herein illustrate that the improved lipid particle formulations of the invention are highly effective in downregulating the mRNA and/or protein levels of target genes." *Id*. at 6:5–30.

D. Illustrative Claim

Petitioner challenges claims 1–20 of the '435 patent. Claim 1 is illustrative and reproduced below:

> 1. A nucleic acid-lipid particle comprising:
> (a) a nucleic acid;
> (b) a cationic lipid comprising from 50 mol % to 85 mol % of the total lipid present in the particle;
> (c) a non-cationic lipid comprising from 13 mol % to 49.5 mol % of the total lipid present in the particle; and
> (d) a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol % to 2 mol % of the total lipid present in the particle.

Ex. 1001, 89:55–63.

Claim 1 is the only independent claim, and claims 2–20 are directly or indirectly dependent on claim 1. *Id*. at 89:55–92:22.

E. The Instituted Grounds of Unpatentability

We instituted the instant trial based on the following grounds of unpatentability. Inst. Dec. 5, 33.

Reference[s]	Basis	Claims challenged
WO 2005/007196 A2[3] and US 2006/0134189 A1[4]	§ 103	1–20
'196 PCT, '189 Publication, Lin,[5] and Ahmad[6]	§ 103	1–20
US 2006/0240554 A1[7]	§§ 102 and 103	1–20

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person having ordinary skill in the art ("POSITA") "would have specific experience with lipid particle formation and use in the context of delivering therapeutic payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience." Pet. 5 (citing Ex. 1007 ¶¶ 31–32). Petitioner further states that "[t]his level of skill is representative of the inventors on the '435 patent and authors/inventors of prior art cited herein." *Id.* at 6. We

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[3] Ian MacLachlan et al., WO 2005/007196 A2, published Jan. 27, 2005 ("'196 PCT"). Ex. 1002.
[4] Ian MacLachlan et al., US 2006/0134189 A1, published June 22, 2006 ("'189 Publication"). Ex. 1003.
[5] Alison J. Lin et al., *Three-Dimensional Imaging of Lipid Gene-Carriers: Membrane Charge Density Controls Universal Transfection Behavior in Lamellar Cationic Liposome-DNA Complexes*, 84 BIOPHYSICAL J. 3307–16 (2003) ("Lin"). Ex. 1005.
[6] Ayesha Ahmad et al., *New Multivalent Cationic Lipids Reveal Bell Curve for Transfection Efficiency Versus Membrane Charge Density: Lipid-DNA Compleses for Gene Delivery*, 7 J. GENE MED. 739–48 (2005) ("Ahmad"). Ex. 1006.
[7] Tongqian Chen et al., US 2006/0240554 A1, published Oct. 26, 2006 ("'554 Publication"). Ex. 1004.

applied that description for purposes of our Institution Decision. Inst. Dec. 7.

Patent Owner objects to Petitioner's proffered definition for two reasons. PO Resp. 9–10 (citing Ex. 2009 ¶¶ 22–24). First, Patent Owner objects to Petitioner's equating the level of ordinary skill with the level of skill of the inventors of the '435 patent. *Id.* According to Patent Owner, "the petition has improperly assumed a much higher level of skill than that of a person of ordinary skill in the art ("POSITA")." *Id.* at 10 (citing Ex. 1007 ¶ 31; 2009 ¶¶ 22–24; Ex. 2028, 44:8–12). Patent Owner further states that "[b]ecause the petition sets the level much higher, to that of the inventors, Petitioner has failed to conduct an appropriate analysis." *Id*. at 10 (citing Ex. 2009 ¶¶ 23–24).

As an initial matter, we did not rely on Petitioner's statement that the proposed level of skill is representative of the inventors on the '435 patent in our Institution Decision, and we do not rely on it for purposes of this Decision. *See* Inst. Dec. 6. We do not view Petitioner's statement regarding the proposed level of ordinary skill as representative of the inventors on the '435 patent as part of Petitioner's proposed level of ordinary skill in the art.

Second, Patent Owner objects to Petitioner's definition of a person of ordinary skill because it is indeterminable. PO Resp. 10. Patent Owner bases this contention on its characterization of Dr. Janoff's testimony during cross-examination. *Id.* Patent Owner states that Dr. Janoff "repeatedly indicat[ed] that Petitioner's own definition is 'too vague' to understand." *Id.* (citing Ex. 2028, 33:6–14, 34:7–35:25, 36:1–37:5). Although Dr. Janoff may not have been as responsive to some questions during his deposition as may have been appropriate, *see* PO Resp. 4–8, what Dr. Janoff said in the cited portions of his testimony was that the *questions* from Patent Owner's

counsel were "too vague." *See* Ex. 2028, 3:36–14, 34:7–35:25, 36:1–37:5. The cited portions of Dr. Janoff's testimony indicate that, rather than specifically asking about Petitioner's proposed definition of a person having ordinary skill in the art, Dr. Janoff was asked questions about his work experience. *Id.*; *see, e.g., id.* at 33:7–8, 35:7–8 ("Do you have specific experience working with lipid particles?" "Do you have any experience with any therapeutic payload?").

Although Patent Owner cites to Dr. Thompson's testimony in support of its objections to Petitioner's definition, it does not expressly proffer its own definition of a person of ordinary skill in the art. PO Resp. 9–10 (citing Ex. 2009 ¶¶ 22–24). Dr. Thompson states that "Dr. Janoff has not simply applied a slightly higher level of skill in the art in setting forth his opinions in his declaration, but has assumed a much higher level of skill than that of a person of ordinary skill in the art." Ex. 2009 ¶ 24. Dr. Thompson, however, does not proffer what he considers to be an appropriate level of ordinary skill in the art. *See generally* Ex. 2009.

Accordingly, we find on the record as a whole that a person of ordinary skill in the art would have specific experience with, and/or be generally familiar with, lipid particle formation and use in the context of delivering therapeutic payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience. We also find on this record that both Dr. Janoff and Dr. Thompson are ones of at least ordinary skill in the art under this standard. *See* Ex. 1007 ¶¶ 8–22; Ex. 1018 (*curriculum vitae* of Dr. Janoff); Ex. 2009 ¶¶ 1–6; Ex. 2010 (*curriculum vitae* of Dr. Thompson).

We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163–64 (Fed. Cir. 1985)).

B. Claim Construction

For petitions filed before November 13, 2018, [8], the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Only terms in controversy must be construed and only to the extent necessary to resolve the controversy.

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[8] The Petition was filed March 5, 2018. Paper 2. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42).

Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed. Cir. 1999).

As in our Decision on Institution, because Patent Owner substantively challenges the proposed construction of the term "nucleic acid-lipid particle" and relies on its narrower definition of the term in its arguments addressing the grounds asserted, we address the construction of that term, but find that we need not construe any other terms addressed by Petitioner for the purpose of reaching our institution decision. We again note, however, that Petitioner provides the same definition for "cationic lipid" as the express definition set forth in the specification of the '435 patent, namely, "any of a number of lipid species that carry a net positive charge at a selected pH, such as physiological pH (e.g., pH of about 7.0)." *Compare* Pet. 24, *with* Ex. 1001, 12:59–61.

nucleic acid-lipid particle

In our Decision on Institution, we expressly defined the term "nucleic acid-lipid particle. *See* Inst. Dec. 7–11. In construing this claim term when read in light of the Specification of the '435 patent, we stated that it should not be limited to the definition of a stable nucleic acid-lipid particle or SNALP and that it should not be limited to *in vivo* use. *See* Inst. Dec. 9–10. We concluded that:

> Our preliminary construction of "nucleic acid-lipid particle" at this stage of the proceeding and for purposes of this decision is derived from the express definition of "lipid particle" as set forth in the '435 patent that generally describes use of such a lipid particle to deliver nucleic acid as an active or therapeutic agent where the nucleic acid may be encapsulated in the lipid to protect it from enzymatic degradation. At this stage of the proceeding, we define "nucleic acid-lipid particle" as "a particle that comprises a nucleic acid and lipid, in which the nucleic acid

> may be encapsulated in the lipid portion of the particle." *See* Ex. 1001, 11:14–22.

Inst. Dec. 10–11.

Patent Owner asserts that our proposed construction is too broad "at least to the extent [that it encompasses] lipid particles lacking any encapsulated nucleic acid." PO Resp. 11. Patent Owner asserts that a "nucleic acid-lipid particle" when read in light of the Specification of the '435 patent requires that the nucleic acid be encapsulated in the lipid particle. *Id*. at 11–12. Patent Owner's reasoning is as follows.

> A "nucleic acid-lipid particle" expressly includes a nucleic acid. According to the '435 patent, "nucleic acids, when present in the lipid particles of the present invention, are resistant in aqueous solution to degradation with a nuclease." EX1001, 11:51–54. The '435 patent describes nucleic acid encapsulation in the lipid particle as conferring resistance to such enzymatic degradation. EX1001, 11:20–22; *see also* EX2007, 4:15–19; 22:40–45; 23:1–3; 23:27–29; 26:35–37. A "lipid particle" "*may* [include a nucleic acid] encapsulated in the lipid portion of the particle, thereby protecting it from enzymatic degradation." EX1001, 11:14–22. A "nucleic acid-lipid particle," however, *does* include a nucleic acid encapsulated in the lipid portion of the particle, thereby protecting it from enzymatic degradation. EX1001, 11:23–31, 11:51–54; *see also* EX2009 ¶39.

PO Resp. 11–12 (emphasis in original).

In short, Patent Owner asserts that we should construe "nucleic acid-lipid particle" as a SNALP. *Id*. at 12–13 (citing testimony of Dr. Janoff and Dr. Thompson and the Specification of the '435 patent). Patent Owner concludes, however, that whichever construction we choose as the broadest reasonable construction, "the petition fails to establish the unpatentability of claims 1–20." PO Resp. 13.

Petitioner responds that Patent Owner is trying inappropriately to import "serum stable" and "systemic use" limitations into the claims to limit the claims to a SNALP. *See* Reply 3–5.

We find that our construction of "nucleic acid-lipid particle" is the broadest reasonable construction in light of the Specification of the '435 patent. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs.,* 136 S. Ct. at 2142. For instance, the '435 patent identifies a "stable nucleic acid-lipid particle" or SNALP as an example of a "nucleic acid-lipid particle," *see, e.g.*, Ex. 1001, 3:38–39 (stating "nucleic acid-lipid particle (e.g., SNALP)"), 3:47–48, 3:57–58, 4:4–8, 4:12–13, 4:17–19, 27:43–45, and the term "nucleic acid-lipid particle" is broader than a SNALP.

The Specification of the '435 patent states that a SNALP *requires* the nucleic acid to be fully encapsulated within the lipid. *See* Ex. 1001, 11:23–30. A "lipid particle" with a nucleic acid as a therapeutic agent, i.e., a nucleic acid-lipid particle, however, *may* have the nucleic acid "encapsulated in the lipid, thereby protecting the agent [or nucleic acid] from enzymatic degradation." *Id*. at 11:14–22 (defining "lipid particle"). Encapsulation, or more specifically, full encapsulation of the nucleic acid is not required according to the Specification of the '435 patent.

In fact, "lipid encapsulated" as defined in the Specification of the '435 patent "can refer to a lipid particle that provides an active agent or therapeutic agent, such as a nucleic acid (e.g., an interfering RNA), with full encapsulation, partial encapsulation, or both. In a preferred embodiment, the nucleic acid is fully encapsulated in the lipid particle (e.g., to form an SPLP, pSPLP, SNALP, or other nucleic acid-lipid particle)." *Id*. at 11:59–64. The Specification of the '435 patent expressly states that only "[i]n some

embodiments, the nucleic acid is fully encapsulated in the lipid particle." *Id*. at 27:43–47.

Dr. Thompson attempts to shoehorn the statement that nucleic acids, when in the lipid particles, "are resistant in aqueous solution to degradation with a nuclease," to require a "nucleic acid-lipid particle" as required by the claims to be a SNALP. *See* PO Resp. 11–12; Ex. 2009 ¶¶ 39–45 (stating in paragraph 45 that "there is no meaningful distinction between a nucleic acid-lipid particle and a SNALP in the context of the '435 patent"). Although we do not question that the '435 patent touts SNALPs as the focus of the '435 patent, *see* Ex. 1001, Abst., the claims are not limited to SNALPs when the claims are read in light of the Specification of the '435 patent.

Accordingly, we construe "nucleic acid-lipid particle" as "a particle that comprises a nucleic acid and lipids, in which the nucleic acid may be encapsulated in the lipid portion of the particle." *See* Ex. 1001, 15:52–63.[9] This is the same construction that we applied for purposes of the Institution Decision. Inst. Dec. 10–11.

We determine that we need not expressly construe any undisputed terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'") (*quoting Vivid Techs.,* 200 F.3d at 803).

[9] We also continue to find that "nucleic acid-lipid particle" is not limited to *in vivo* use for the same reasons that we gave in our Decision on Institution. *See* Inst. Dec. 10.

C. Principles of Law

As set forth above, we instituted trial on all of Petitioner's challenges to the claims of the '435 patent on anticipation and obviousness grounds. Dec. 18; Pet. 7. The following principles of law guide our analysis of the asserted grounds.

1. Anticipation

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc*., 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). "A reference anticipates a claim if it discloses the claimed invention 'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (internal citation and emphasis omitted). Moreover, "it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968); *see Eli Lilly & Co. v. Los Angeles Biomedical Res. Inst. at Harbor-UCLA Medical Ctr*., 849 F.3d 1073, 1074–75 (Fed. Cir. 2017).

"Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. . . . Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art." *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (citing *Titanium Metals Corp. v. Banner,* 778 F.2d 775, 780, 782 (Fed. Cir. 1985).

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Id*. (citing *Titanium Metals,* 778 F.2d at 782). "It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art." *Titanium Metals,* 778 F.2d at 782 (emphasis added).

2. Obviousness

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007).
The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish

obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party who petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

> 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.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles. First, we address the anticipation and obviousness ground involving the '554 Publication as it is dispositive of

many of the challenged claims. For the claims for which the '554 Publication does not either anticipate or render them obvious, we address the remaining grounds.

D. Anticipation by or Obvious Over the '554 Publication

Petitioner asserts that claims 1–20 of the '435 patent are unpatentable as anticipated by or obvious over the '554 Publication. Pet. 51–64. With regard to its anticipation challenge, Petitioner points to a specific formulation taught in the '554 Publication of a nucleic acid-lipid particle using the L054 formulation as described in Figure 16 with siRNA for reducing HBsAg levels. *Id*. at 52. Petitioner also points to a more general discussion in the '554 Publication which it admits "does not disclose exactly the same ranges of lipid components from claim 1 of the '435 patent explicitly, [but] it discloses encompassing and overlapping ranges and specific examples falling within the claimed ranges with sufficient specificity to anticipate." *Id.* at 51.

Patent Owner responds that the L054 formulation is not a nucleic acid-lipid particle as set forth in the claims, and the prior art ranges are not sufficiently specific to anticipate the challenged claims. PO Resp. 39–46. Patent Owner also asserts that "Petitioner does not provide any showing that the '554 Publication would have taught or suggested the use of nucleic acid–lipid particles with high levels of cationic lipids and low levels of conjugated lipids." *Id*. at 47.

We have reviewed the complete record before us, including the parties' explanations and supporting evidence presented during this trial. We determine that given the evidence on this record, Petitioner has shown

by a preponderance of the evidence that claims 1–6, 9, 12, 14, and 15 are anticipated by the ’554 Publication.

1. ’554 Publication (Ex. 1004)

The ’554 Publication involves lipid nanoparticles that transfect or deliver biologically active molecules, such as siRNA, to relevant cells and/or tissues in a subject to prevent, inhibit, or treat diseases, conditions, or traits in a cell, subject, or organism. Ex. 1004, Abst., ¶¶ 16–20. The ’554 Publication notes that cationic lipids may be used to transport foreign nucleic acids into cells because such lipids “interact with nucleic acids through one end and lipid or membrane systems through another.” *Id*. ¶ 5. The ’554 Publication also identifies two structurally different complexes comprising nucleic acid and cationic lipid: a lamellar structure in which the nucleic acid monolayers sandwiched between cationic lipid bilayers, and an inverted hexagonal structure “in which nucleic acid molecules are encircled by cationic lipid in the formation of a hexagonal structure.” *Id*. ¶ 13. The inverted hexagonal structure exhibits greater transfection efficiency, but has very poor stability as compared to the lamellar complex. *Id*. The ’554 Publication concludes that converting the complexes to an inverted hexagonal structure using a suitable helper lipid or a co-surfactant, however, is not suitable for delivery in biological systems. *Id*.

Therefore, the ’554 Publication identifies a “need to design delivery agents that are serum stable, i.e. stable in circulation, that can undergo structural transformation, for example from lamellar phase to inverse hexagonal phase, under biological conditions.” *Id*. ¶ 14. In answer to this need, the ’554 Publication states that:

> The present application provides compounds, compositions and methods for significantly improving the

> efficiency of systemic and local delivery of biologically active molecules. Among other things, the present application provides compounds, compositions and methods for making and using novel delivery agents that are stable in circulation and undergo structural changes under appropriate physiological conditions (e.g., pH) which increase the efficiency of delivery of biologically active molecules.

Id. ¶ 15.

The '554 Publication describes a particular embodiment, the L054 formulation. The '554 Publication states:

> In one embodiment, the invention features a serum-stable formulated molecular composition comprising a biologically active molecule (e.g., a siNA molecule), a cationic lipid, a neutral lipid, and a PEG-conjugate, in which the cationic lipid is DMOBA, the neutral lipid is distearoylphosphatidylcholine (DSPC), and the PEG conjugate is PEG-DMG. In another embodiment, the composition further comprises cholesterol or a cholesterol derivative. This is known as formulation L053 or L054 (see Table IV).

Id. ¶ 140.

The L054 formulation was utilized in two evaluations, one of a formulated siNA composition in models of chronic HBV infection, and a second of a formulated siNA composition in an in vitro HCV replicon model of HCV infection. *See id*. ¶¶ 393, 400, 595, 603. The L054 formulation's use in the chronic HBV infection model showed an example of in vitro efficacy of siNA nanoparticles in reducing HBsAg levels in HepG2 cells. *Id*. ¶ 395. The L054 formulation's use in the in vitro HCV replicon model of HCV infection showed an "example of formulated siNA L053 and L054 (Table IV) nanoparticle constructs targeting viral replication in a Huh7 HCV replicon system in a dose dependent manner." *Id*. ¶ 400.

The formulation for L054 is shown in Table IV of the '554 Publication as set forth below.

TABLE IV

Lipid Nanoparticle (LNP) Formulations

Formulation #	Composition	Molar Ratio
L051	CLinDMA/DSPC/Chol/PEG-n-DMG	48/40/10/2
L053	DMOBA/DSPC/Chol/PEG-n-DMG	30/20/48/2
L054	DMOBA/DSPC/Chol/PEG-n-DMG	50/20/28/2

Id. at Table IV; ¶ 92 ("In one embodiment, the molar ratio of DMOBA:DSPC:cholesterol:PEG-DMG are 50:20:28:2 respectively, this composition is generally referred to herein as formulation L054.").

2. Analysis

Petitioner principally relies on the L054 formulation disclosed in the '554 Publication to establish that the challenged claims are anticipated. *See* Pet. 51–64. We begin our analysis with the only independent claim, claim 1, as Patent Owner's arguments focus on the limitations of this claim.

a. Claim 1

Petitioner points to the L054 formulation as disclosed in the '554 Publication as providing an example of the nucleic acid-lipid particle with the components as set forth in claim 1 within the claimed ranges. *See* Pet. 52–56.

Dr. Janoff testifies as follows concerning this specific example.

> The '554 publication also includes various specific formulations, including formulation L054, which contains 50% cationic lipid (DMOBA), 48% non-cationic lipid (CHol/DSPC), and 2% conjugate lipid (PEG-n-DMG). Ex. 1004, Table 4. This formulation was tested, for example, with siRNA for reducing HBsAg levels. *See id.*, Fig. 16. The disclosed nucleic

> acid-lipid particles meet all of the limitations in claim 1 of the '435 patent.

Ex. 1007 ¶ 99; *see id*. ¶¶ 144–152.

"It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art." *Titanium Metals,* 778 F.2d at 782 (emphasis added) (citing *In re Petering*, 301 F.2d 676, 682 (CCPA 1962)); *KSR*, 550 U.S. at 406. Here, it appears that the L054 formulation is a composition that is covered by claim 1 because it contains all of the components required by claim 1 within the claimed ranges.

Patent Owner asserts that the L054 is a lipid mixture, that may be used to make particles, but is not a particle itself. PO Resp. 39–40. Petitioner counters that the '435 patent similarly uses input formulations in describing the nucleic acid-lipid particles of the invention, which Dr. Thompson confirmed. Reply 13–14; Ex. 1019, 162:9–14.

We agree with Petitioner that the '435 patent describes nucleic acid-lipid particles in terms of mole percent of the formulation's composition, not the particle, just as in the '554 Publication. *See, e.g.,* Ex. 1001, 69:50–70:15 (Table 2 showing formulation composition in mole percent); Ex. 1004, Table IV (showing composition of L054 formulation in molar ratio); *see also* Ex. 1021 ¶ 27 (Dr. Janoff explaining that using lipid percentages in the formulations for a nucleic acid-lipid particle "was accepted practice in the field."); Ex. 1019, 162:9–14 (Dr. Thompson stating that he did not recall any description of cationic lipid analysis after particle formulation in the '435 patent). The '435 patent describes the resultant nucleic acid-lipid particle not in terms of mole percent of its components, but in terms of its size, poly-

dispersity, and percent encapsulation of the drug. *See, e.g.*, Ex. 1001, 69:50–70:15.

We do not agree with Patent Owner's conclusion that the final particle products of the L054 formulation all fall outside of the claimed range, and therefore, not anticipate claim 1. Dr. Thompson testifies that cholesterol-based detergents identified for use with the detergent dialysis methods described in the '554 Publication would skew the molar ratio of lipids in the finished particles relative to the starting materials because less cholesterol would be incorporated in the finished particles. Ex. 2009 ¶ 113. Dr. Thompson concludes that:

> In the L054 example, while the lipid formulation is listed as 50/20/28/2, the molar fractions of the same lipids in the resulting particle would be expected [to] be different and presumably outside the scope of the challenged claims. The L054 lipid mixture has cationic lipid content and conjugated lipid content that are at the edge of the claimed ranges. Because L054 has cationic lipid content and conjugated lipid content on the edge of the claimed range, even small differences in incorporation of components will result in lipid particles that are outside the claimed range of cationic lipid content and conjugated lipid content. For example, if cholesterol is not quantitatively incorporated, see above, particles derived from the L054 lipid mixture would have more than 2 mol % conjugated lipid.

Id. ¶ 115.

First, the mole percentage of cationic lipid is at the low end of the range as set forth in claim 1. Therefore, any loss of the other lipid components, such as cholesterol, should result in a higher mole percentage of cationic lipid, which would be within claim 1's range of 50 mol % to 85 mol % of the total lipid present in the particle. *See* Ex. 1019:17–23

(Dr. Thompson stating that the cationic component is the most retained during particle formation).

Second, Dr. Thompson does not definitively testify that the nucleic acid-lipid particle that is formed from the L054 formulation would fall outside of the claimed range. Although Dr. Thompson agrees that the ranges of the L054 formulation overlap with the ranges in claim 1 of the '435 patent for the required components, *see* Ex. 1020, 219:1–7, he testifies that the final formulation of the particles may be different from that of the formulation, *see id*. at 219:9–24. Dr. Thompson also testifies that in formulating the particles, he would find, as a first approximation, a bell curve for the lipid percentages of the particles, *see id*. at 220:8–221:6, and a broad distribution for the fabrication method used in the '554 Publication, *see id*. at 222:12–23.

When questioned further about this bell curve or dispersion of lipid percentages of the particles, Dr. Thompson testified as follows.

> Q: So would you have also hypothesize[d] that some of the particles in the dispersion would have greater than 50 percent cationic lipid?
>
> . . . .
>
> A: In a population of particles, there may be a X percent of particles that fall within the range. Are those the functional particles that give rise to the modest function that's reported? Who knows. The experiment was not done in a rigorous way. So it's – it's not an answerable question with any precision.
>
> You know, I can – just as the authors opine, I opine as well that the – that the particles that are being produced here are – are, have a much broader distribution than – than particles produced by other more controlled methodologies.

Id. at 224:6–21 (objection to form and foundation omitted).

With regard to whether the mole percentage of conjugated lipid would change from the formulation to the particle, Dr. Thompson discussed how

the cholesterol content would be the most difficult to control, that losing cholesterol would cause the conjugate lipid concentration to go up, but Dr. Thompson would not confirm that none of the particles produced by the L054 formulation process would have less than 2 mole percent of conjugated lipid. *See id*. at 224:23–23. Dr. Thompson stated instead that "[t]he composition can change as a function of the formulation process." *Id*. at 226:22–23.

Based on Dr. Thompson's testimony that formulation of particles using the L054 formulation according to the processes set forth in the '554 Publication would result in a distribution of particles in terms of lipid mole percentage content, ostensibly with some particles having more cationic lipid content and less conjugated lipid content, we find Dr. Thompson's opinion that no particles formed using the L054 formulation would be within the mole percentage ranges for lipids as required by claim one is speculative, and thus, not accorded weight.

Dr. Thompson's concern about the broader range of a distribution of particles formed by the processes as described in the '554 Publication is not that no particle within the distribution would be within claim 1's required ranges, but seems to be a practical one involving a researcher's view that "usually you're not focused on those minor components of the distribution. It's the heart of the distribution that you're, that is – that's where your drug is, that's where your activity most likely lies." Dr. Thompson concludes that:

> In my analysis I was considering largely the method of formulation and the likelihood that that method of formulation would deliver the particles of specified composition, and it's my opinion that that is the wrong technique and unreliable in producing particles of a – with controlled composition.

Id. at 228:14–20.

Anticipation, however, does not require that all of the formed particles from the L054 formulation, or even the majority of them, be within the claimed ranges as required by claim 1. Anticipation merely requires that a composition within the claimed ranges be disclosed. *See Titanium Metals*, 778 F.2d at 782. We find that the L054 formulation discloses such a composition.[10]

Patent Owner relies on its narrow definition of nucleic acid-lipid particle as requiring particles that encapsulate the nucleic acid. PO Resp. 41–43. We are not persuaded by this argument as we have stated that we do not find "nucleic acid-lipid particle" as used in the challenged claims to be so limited. *See supra* Section II.B.[11]

Because we find that claim 1 is anticipated by the L054 formulation, we decline to address Petitioner's other challenges to this claim. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding that a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *see also Beloit Corp. v. Valmet Oy*, 742 F.2d 1421, 1423 (Fed.

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[10] Patent Owner also relies on testimony from Dr. Janoff and statements in the '435 patent concerning input versus final lipid-to-drug ratios. PO Resp. 40 (citing Ex. 1001, 79:40–80:9). As Dr. Janoff testifies, however, such a change in ratio of total lipid content to drug content may be a result of one or both of those components changing from input to final product. *See* Ex. 2028, 155:1–158:14. This evidence does not establish how particular ranges for the individual lipid components from a starting formulation would change, if at all, in the final particle.

[11] We also agree with Petitioner that the '554 Publication discusses encapsulation of the nucleic acid in relation to the L054 formulation. *See* Reply 14–15; Ex. 1004 ¶¶ 11, 136, 317, 400; Ex. 1021 ¶ 28; *see also* Ex. 1004 ¶ 140 (referring to L054 formulation as a "serum-stable formulated molecular composition").

Cir. 1984) (holding that once a dispositive issue is decided, there is no need to decide other potentially dispositive issues); *see also SZ DJI Tech. Co., LTD. v. Drone-Control, LLC*, Case IPR2018-00207, slip op. at 30–33 (Paper 44) (PTAB June 11, 2019) (discussing basis for declining consideration of other grounds when all challenged claims are shown to be unpatentable); *cf. In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (not reaching other grounds of unpatentability after affirming the anticipation ground).

b. Dependent Claims

Claims 2 through 20 depend either directly or indirectly on claim 1, which we have found to be anticipated. *See* Ex. 1001, 89:64–67, 90:54–92:22. Petitioner sets forth how these dependent claims are also either anticipated or rendered obvious by the '554 Publication supported by the testimony of Dr. Janoff. *See* Pet. 56–64; Ex. 1007 ¶¶ 153–172.

Patent Owner responds that none of dependent claims 2–20 is anticipated or rendered obvious. *See* PO Resp. 48–52. Patent Owner specifically addresses claims 5–8, 11, and 16–20.[12]

Although we agree with Patent Owner that the Petition regarding the patentability of the challenged dependent claims based on the '554 Publication is not a model of clarity, we find that Petitioner has sufficiently shown that dependent claims 2–6, 9, 12, 14, and 15 are anticipated by the '554 Publication. We also find, however, that Petitioner has failed to show by a preponderance of the evidence that claims 7, 8, 10, 11, 13, and 16–20 would have been either anticipated or obvious over the '554 Publication.

[12] Patent Owner includes claim 14 in the heading for claims 16 through 20, but does not specifically discuss claim 14. *See* PO Resp. 52. Therefore, we view the inclusion of claim 14 as an inadvertent error.

(i) *Anticipated Dependent Claims 2–6, 9, 12, 14 and 15*

Petitioner cites to the L054 formulation as an example teaching the additional limitations of dependent claims 2 through 6, 9, 12, 14 and 15. *See* Pet. 56–58, 60–62 (citing Ex. 1004 ¶¶ 395, Table IV; Ex. 1007 ¶¶ 153–157, 161, 164). For instance, claim 2 defines the nucleic acid of claim 1 as including an interfering RNA. *See* Ex. 1001, 89:64–67. Petitioner points to the siRNA for reducing HBsAG levels as described in Figure 16 that uses the L054 formulation as one example of such a nucleic acid-lipid particle. Pet. 56. For claim 3, Petitioner cites the same example as teaching that the nucleic acid of claim 2 is further defined as a small interfering RNA or siRNA. *See* Pet. 57.

Dependent claim 4 narrows the range for cationic lipid to 50 mol % to 65 mol % of the total lipid present in the particle. Ex. 1001, 90:58–60. Petitioner refers to its discussion of claim 1 in which it states that "the L054 formulation tested in Figure 16 contains 50% cationic lipid (DMOBA)." Pet. 53, 57. Dependent claim 5 defines the non-cationic lipid as a mixture of a phospholipid and cholesterol or a derivative of them. Ex. 1001, 61–63. Petitioner again points to the L054 formulation as an example of such a particle. Petitioner states "[f]or example, the L054 formulation tested in Figure 16 contains 48% non-cationic lipid (cholesterol and DSPC)." Pet. 58 (citing Ex. 1001, Table IV; Ex. 1007 ¶ 156).

Dependent claim 6 further defines the phospholipid of claim 5 as including DSPC, which is one of the non-cationic lipids in the L054 formulation. *See* Ex. 1001, 64–67; Ex. 1004, Table IV. Petitioner also points to an express statement in the '554 Publication that teaches suitable

neutral lipids include the two non-cationic lipids set forth in claim 6 and mixtures of those lipids. Pet. 60 (citing Ex. 1004 ¶ 85).

Dependent claim 9 further defines the conjugated lipid as a polyethyleneglycol (PEG)-lipid conjugate. Ex. 1001, 91:7–9. Petitioner provides that "the L054 formulation tested in Figure 16 contains 2% conjugate lipid (PEG-n-DMG)." Pet. 60 (citing Ex. 1001, Table IV; Ex. 1007 ¶ 161). Claim 12 narrows that range for the conjugated lipid set forth in claim 1 to 1 mol % to 2 mol % of the total lipid present in the particle. Ex. 1001, 91:18–21. Petitioner refers to its explanation of claim 1 in which it references the L054 formulation tested in Figure 16 that contains 2% conjugate lipid (PEG-n-DMG). Pet. 55, 61–62.

Dependent claim 14 further requires a pharmaceutically acceptable carrier with the nucleic acid-lipid particle of claim 1. Ex. 1001, 92:1–3. Petitioner points to express teachings in the '554 Publication that the "pharmaceutical carrier is generally added following formulated siNA composition formation. Thus, after the formulated siNA composition is formed, the formulated siNA composition can be diluted into pharmaceutically acceptable carriers such as normal saline." Pet. 62 (quoting Ex. 1004 ¶ 502; Ex. 1007 ¶ 166).

Dependent claim 15 further requires contacting a cell with the nucleic acid-lipid particle of claim 1 to introduce the nucleic acid into the cell. Ex. 1001, 92:4–7. Petitioner states that this additional limitation is met in part by referring back to its discussion of claim 1. With reference to the nucleic acid-lipid particles of claim 1, Petitioner states that "[o]ne example of such particles with siRNA for reducing HBsAg levels using the L054 formulation are described in Figure 16," and quotes the '554 Publication as stating, "FIG. 16 shows a non-limiting example of in vitro efficacy of siNA

nanoparticles in reducing NBsAg levels in Hep G2 cells . . . treated with formulated active siNA L053 and L054 nanoparticles . . . ." Pet. 52.

We find that Petitioner has shown that the L054 formulation anticipates claims 2 through 6, 9, 12, 14, and 15 by the L054 formulation and its use in experiments as referenced above as taught in the '554 Publication. As set forth by Petitioner, the L054 formulation not only meets the limitations of claim 1, but also the additional limitations of dependent claims 2 through 6, 9, and 12 arranged as in the claim as set forth above. Also, the '554 Publication expressly states that formulated siNA compositions, such as L054, may be diluted into a pharmaceutical carrier such as saline, thus anticipating claim 14. Also, the use of the L054 nanoparticles to show in vitro efficacy of siNA nanoparticles in reducing HBsAg levels in HepG2 cells anticipates claim 15.

Patent Owner specifically responds to Petitioner's arguments concerning claims 5 and 6. PO Resp. 48–49. Patent Owner states, with respect to claim 5, it cannot be anticipated because the L054 formulation does not anticipate claim 1. *Id*. at 48. Because we have found that claim 1 is anticipated by the L054 formulation, this argument is not persuasive. Patent Owner's argument concerning claim 6 refutes an obviousness analysis. Because we find that claim 6 is anticipated by the L054 formulation, we also are not persuaded by this argument.

(ii) Dependent Claims 7, 8, 10, 11, 13, and 16–20 are not Unpatentable Over the '554 Publication

We agree with Patent Owner that Petitioner has failed to establish that dependent claims 7, 8, 10, 11, 13, and 16–20 are unpatentable. Petitioner offers an anticipation challenge to claims 7, 8, 10, 13, and 16–20 based on the teachings of the '554 Publication. Pet. 58–64. Petitioner also challenges

claims 7, 8, and 11 based on obviousness over the '554 Publication. *Id*. at 58–62. Finally, Petitioner sets forth an obviousness challenge to claims 7, 8, 10, 11, 13, and 16–20 based on the teachings of the '196 PCT and the '189 Publication. Pet. 42–48. We determine that Petitioner has not shown by a preponderance of the evidence on any of these challenges that these dependent claims are unpatentable.

Although we did not need to reach the following arguments in determining the unpatentability of claim 1, we will reach these arguments here as they relate to the dependent claims. *See* Pet. 52–56. The '554 Publication discloses several different ranges for each lipid component, some of which touch or overlap the claimed ranges, some of which do not. *See* Ex. 1004 ¶¶ 116–118, 313. As Patent Owner states, Petitioner cites these different ranges for the different lipid components of claim 1 as set forth in paragraphs 116, 118, and 313 of the '554 Publication without demonstrating how all of these ranges for the different components relate to each other with sufficient specificity to anticipate claim 1. *See* Pet. 52–55; PO Resp. 44–45. Therefore, we find that claim 1, that recites ranges of each lipid component, is not anticipated by the teaching of these ranges. *See Atofina v. Great Lakes Chem. Corp*, 441 F.3d 991, 999 (Fed Cir. 2006).

In sum, the only basis on which we conclude that claim 1, or any claim that depends on claim 1, is anticipated is by the L054 formulation that has lipid components in the claimed ranges for claim 1. This informs our discussion of the remaining dependent claims set forth below.

Alleged Anticipation of Dependent Claims 7 and 8

For dependent claims 7 and 8, which provide specific ranges for the phospholipid and cholesterol components of the nucleic acid-lipid particle, respectively, claim 7, which depends from claim 5, requires the phospholipid

to be 3–15 mol % of the total lipid present. Ex. 1001, 91:1–3. Claim 8, which also depends from claim 5, requires the cholesterol to be from 30–40 mol % of the total lipid present in the particle. *Id.* at 4–6. Petitioner sets forth an anticipation and obviousness challenge from the teachings of the '554 Publication for each of claims 7 and 8. *See* Pet. 58–60.

For claim 7, Petitioner points to a range for the total amount of neutral lipid component, 20–85 mol %, as compared to a range for the cholesterol component of 20 to 45 mol %, when it is present, and concludes a range for phospholipid is 0–40 mol %. Petitioner states that

> [n]ot only does the disclosed range encompass the claimed range, when combined with a cationic lipid proportion in the 60% range and cholesterol in the 20–40% range, the range for the phospholipid is decreased to 0%-20%. Given the breadth of the claimed range for the phospholipid, these disclosures are sufficiently specific to anticipate the claimed range.

Pet. 58–59 (citing Ex. 1007 ¶ 158).

Patent Owner responds that no range for phospholipid is disclosed in the '554 Publication. PO Resp. 49.

We agree with Patent Owner that Petitioner fails to show that claim 7 is anticipated by the teachings of the '554 Publication. As Patent Owner points out, Petitioner points to no affirmative teaching in the '554 Publication of a specific range for the amount of phospholipid in the nucleic acid-lipid particle. *See* Pet. 58–59. Petitioner makes some assumptions about the various other components in the particle, and then calculates a range for the phospholipid that encompasses the claimed range based on those assumptions and assuming that the phospholipid makes up the balance of the non-cationic lipid in the particle. *Id.* Petitioner makes no mention of the conjugated lipid component that is also required by the claim or why one

of skill in the art would choose 60 mol % for the cationic lipid component. *Id*. We determine that Petitioner has failed to show that the claimed range for the phospholipid is taught by the '554 Publication. *See Atofina v. Great Lakes Chem. Corp*, 441 F.3d 991, 999 (Fed Cir. 2006). Therefore, we determine that Petitioner has failed to show that claim 7 is anticipated by the teachings of the '554 Publication.

For claim 8, Petitioner cites to a range for cholesterol, from 20 to 45 % of the total lipid present, which encompasses the claimed range, and also references a specific formulation that has an amount of cholesterol within the claimed range. Pet. 59–60. Petitioner concludes that "[g]iven the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range." Pet. 60 (citing Ex. 1007 ¶ 160).

Patent Owner responds that Petitioner has offered no relationship between the disclosure mapped for claim 8 to that mapped for claims 1 and 5 from which claim 8 depends. PO Resp. 49. We agree. As we stated above, Petitioner offers no particular embodiment with overlapping ranges for each component of the nucleic acid-lipid particle for claim 8 that includes the limitations of claims 1 and 5 from which claim 8 depends. Therefore, we determine that Petitioner has failed to show that claim 8 is anticipated by the teachings of the '554 publication.

Alleged Anticipation of Dependent Claim 10

Claim 10 adds the requirement that the PEG-lipid conjugate comprise a PEG-DAG conjugate, a PEG-DAA conjugate, or a mixture of these. Ex. 1001, 91:10–13. Petitioner points to a disclosure in the '554 publication of PEG-DAG conjugates and states that "[b]ecause one of the listed species of PEG-lipid conjugates is disclosed, this element is anticipated." Pet. 60–61 (citing Ex. 1004 ¶ 86; Ex. 1007 ¶ 162).

Similar to claim 8, Petitioner fails to show any relationship between the disclosure of the PEG-DAG conjugate that teaches the additional requirement for claim 10 to any disclosure that teaches the limitations of claims 1 and 9 from which claim 10 depends. For example, paragraph 86 of the '554 publication cited by Petitioner refers to suitable PEG-DAG conjugates, but does not indicate that the PEG-lipid conjugate in the claimed combination may be the described PEG-DAG conjugates. Therefore, we determine that Petitioner has failed to show that claim 10 is anticipated by the teachings of the '554 Publication.

Alleged Anticipation of Dependent Claim 13

Dependent claim 13 requires the nucleic acid to be fully encapsulated in the nucleic acid lipid particle of claim 1. Ex. 1001, 91:22–24. Petitioner asserts that the '554 Publication teaches that "encapsulation of anionic compounds using cationic lipids is essentially quantitative due to electrostatic interaction." Pet. 62 (quoting Ex. 1004 ¶ 11). From this teaching, Dr. Janoff concludes that a person or ordinary skill would understand that full encapsulation only requires "an excess of cationic lipid with regard to the nucleic acid for electrostatic interaction." *Id*. (citing Ex. 1007 ¶ 165).

It is not readily apparent, however, from the L054 formulation and the discussion concerning this formulation that the nucleic acid lipid particle is fully encapsulated. *See* Ex. 1004 ¶¶ 87, 89, 92, 140, 395, 400, 595, 603. Although the L054 formulation is said to be serum stable, *see* Ex. 1004 ¶ 140, there is no mention of whether the nucleic acid is fully encapsulated within the lipid particle. *See* Ex. 1004 ¶¶ 87, 89, 92, 140, 395, 400, 595, 603. Other examples described in the '554 Publication do expressly describe encapsulation of the nucleic acid in the lipid particle, although

without identifying the extent of the encapsulation. *See, e.g.*, Ex. 1004 ¶¶ 397 (describing L051 nanoparticle "encapsulated active siNA molecules), 398 (same), 408 (same for L077, L069, L080, L082, L083, L060, L061, and L051). Also, Dr. Janoff does not discuss what would be considered an excess of cationic lipid as compared to the amount of nucleic acid that would yield a nucleic acid-lipid particle that fully encapsulates the nucleic acid or whether the L054 formulation would provide such an excess of cationic lipid. *See* Ex. 1007 ¶ 165.

For these reasons, we determine that Petitioner has not shown by a preponderance of the evidence that claim 13 is anticipated by the '554 Publication.

Alleged Anticipation of Dependent Claims 16–20

Claims 16–20 require *in vivo* delivery or administration of a nucleic acid-lipid particle of claim 1 to a mammalian subject. *See* Ex. 1001, 92:8–23. Petitioner points to several disparate paragraphs of the '554 Publication as teaching the additional limitations of claims 16–20 relating to the *in vivo* delivery or administration of the claimed lipid particle to a mammalian subject to treat a disease or disorder such as a viral infection, liver disease, or cancer. *See* Pet. 63–64.

For instance for claim 16, Petitioner points to the definition of "subject" in the '554 Publication, which includes a mammal or mammalian cells, to establish that such *in vivo* delivery or administration to a mammalian subject of claim 1's nucleic acid-lipid particle is taught. *See* Pet. 63 (citing Ex. 1007 ¶ 168). Petitioner also points to particular embodiments to establish the additional limitations relating to *in vivo* delivery and administration as taught in claims 17–20. *See* Pet. 63–64 (citing Ex. 1004 ¶¶ 21, 274, 275, 310). None of these embodiments,

however, relates to the L054 formulation, which we have found anticipates claim 1's nucleic acid lipid particle.

The '554 Publication does not teach that every formulation described for a lipid particle is suitable for *in vivo* delivery or administration to a mammalian subject. For instance, the '554 Publication describes its invention as featuring

> compositions, and methods of use for the *study, diagnosis*, and treatment of traits, diseases and conditions that respond to the modulation of gene expression and/or activity in a subject or organism. . . . Such novel cationic lipids, microparticles, nanoparticles and transfection agents are useful, for example, in providing compositions to prevent, inhibit, or treat diseases, conditions, or traits *in a cell*, subject or organism.

Ex. 1004, Abst. (emphasis added).

The L054 formulation is only shown to be used *in vitro* to treat cells, *id*. ¶¶ 395, 400, 595, 603, and Petitioner does not point to any teaching indicating that the L054 formulation may be appropriate for systemic use. Therefore, we determine that Petitioner has failed to show that claims 16–20 are anticipated by the '554 Publication.

Alleged Obviousness of Dependent Claims 7, 8, and 11 over the '554 Publication

For claims 7 and 8, Petitioner relies on *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003) to establish even a slight overlap in ranges renders them obvious. *See* Pet. 58–60. As we discussed previously for claim 7, Petitioner makes assumptions concerning the disclosed ranges for the other components of a lipid particle, but can point to no particular range for the phospholipid that overlaps the range required by claim 7. *Id*. at 59; PO Resp. 49; Ex.2009 ¶¶ 148–150. Also, Petitioner has not shown how achieving the claimed range for the phospholipid would be accomplished by

mere optimization or routine experimentation. *Id.*; *Peterson*, 315 F.3d at 1330.

Petitioner points to disclosure in the '554 Publication that encompasses the claimed range for cholesterol as required by claims 8, and points to a particular example that has the amount of cholesterol within the claimed range without referring to any other of the required components of the lipid particle or ranges for those components. Pet. 59–60; PO Resp. 49–50; Ex. 2009 ¶¶ 151–155. Again, Petitioner has not shown how achieving the claimed range for cholesterol as required by claim 8 would be accomplished by mere optimization or routine experimentation. *Id*.

Challenged claim 11 depends from claim 10, which we found was no anticipated by the '554 Publication. For Petitioner's obviousness challenge based on the '554 Publication, it asserts that the PEG-DAA conjugates required by claim 11 "could be used in lieu of . . . PEG-DAG conjugates . . ." required by claim 10. Pet. 61. Patent Owner points out that the '554 Publication does not disclose PEG-DAA conjugates at all, and questions the interchangeability of PEG-DAG and PEG-DAA conjugates. PO Resp. 50-51. Because we did not find claim 10 to be anticipated, and Petitioner makes no obviousness challenge to claim 10 based on the '554 Publication, we find Petitioner's argument concerning the obviousness of claim 11 to be unpersuasive.

We determine that Petitioner has failed to establish by a preponderance of the evidence that claims 7, 8, or 11 would have been obvious over the '554 publication.

Alleged Obviousness of Dependent Claims 7, 8, 10, 11, 13, and 16–20 over the '196 PCT and the '189 publication

Petitioner's obviousness challenge for dependent claims 7, 8, 10, 11, 13, and 16–20 under ground 1 fairs no better. *See* Pet. 42–48.[13] For these dependent claims, Petitioner states where the limitation added by the dependent claim is taught in the asserted references, but does not address the relationship between the different ranges for the components of the particles or any reason why one of skill in the art would combine these teachings with those that allegedly taught the limitations of the claims from which the claim at issue depends. *See id*.; PO Resp. 14–32. Petitioner also does not address whether one of skill in the art would have a reasonable expectation of success in making the claimed combination. Pet. 42–48; PO Resp. 14–32. For none of these claims does Petitioner discuss how the subject matter of each claims as a whole would have been obvious in light of the teachings of the asserted art. *Id*.; PO Resp. 14–15 (stating that petition fails to acknowledge that concentrations of different lipid components are highly interdependent).

We find that Petitioner has not shown by a preponderance of the evidence that claims 7, 8, 10, 11, 13, or 16–20 are unpatentable would have been obvious over the '196 PCT and the '189 Publication.

E. Objections and Other Arguments

Patent Owner also filed a Notice of Objection to Petitioner's Demonstrative Exhibits. Paper 48. Patent Owner's objections are presented

[13] Claims 1 and 4 are the only two claims specifically addressed in ground 2. Because we have determined that these claims are anticipated, we need not address this ground here. Pet. 48–51.

as general categories of objections with identification of Petitioner's slides that it contends fall within those broad categories. *Id.* at 1. However, the Board will not sort through multiple slides in an effort to discern what particular information is subject to Patent Owner's general objection. Nevertheless, we overrule Patent Owner's objections to Petitioner's demonstrative exhibits (slides), at least because demonstrative exhibits are not evidence, and we rely on evidence in the trial record in reaching our Decision. *See* Office Patent Trial Practice Guide, August 2018 Update, 21, 83 Fed. Reg. 39,989 (Aug. 13, 2018) ("Demonstrative exhibits used at the final hearing are aids to oral argument and not evidence").

Patent Owner asserts that the testimony of Dr. Janoff should be accorded no weight. *See* PO Resp. 4–8. Patent Owner argues that, according to Dr. Janoff's testimony, his declaration is "based on the petition," and thus constitutes attorney argument. *Id.* at 4–5 (citing Ex. 1007 ¶¶ 5–7, 27; Ex. 2028, 26:12–27:5, 91:18–92:20, 92:21–93:11). Patent Owner argues further about the conduct of Dr. Janoff and Petitioner's counsel during cross-examination, contending that it was "disruptive and prejudicial," and that "[s]uch conduct is particularly prejudicial in the context of the present proceeding, as Patent Owner has repeatedly raised issues as to the lack of clarity in the petition materials." *Id.* at 6–7 (citing multiple excerpts from Ex. 2028).

Petitioner responds that Dr. Janoff testified that "he was aware of the Petition when executing his declaration," and also "testified unequivocally that the opinions in his declaration are his opinions in the matter." Reply 24 (citing Ex. 2028, 89:4–92:20, 26:12–18). Petitioner further responds that "[t]he transcript illustrates that counsel for Patent Owner repeatedly asked questions devoid of any context and without reference to either Dr. Janoff's

declaration or the '127 patent," but that "Dr. Janoff, nonetheless, provided answers to the extent possible." *Id.* at 24–25 (citing multiple excerpts from Ex. 2028).

We decline to exercise the extraordinary remedy of according "no weight" to Dr. Janoff's testimony based on the contention that Dr. Janoff's testimony is attorney argument because it is based on the Petition. PO Resp. 4–8. Similarly, although Dr. Janoff may not have been as responsive to some questions during his deposition as may be appropriate, we decline to accord "no weight" to his entire testimony (*see* id.), particularly given that some questions appear vague, or lacking context or proper foundation. *See, e.g.,* Ex. 2028, 35:7–8, 29:19–20, 56:24–57:17; *see also* Reply 24–25.

In making the argument that "Dr. Janoff's declaration merely adopts the attorney arguments set forth in the petition," Patent Owner omits the remainder of the cited quotes from Dr. Janoff's declaration. *See* PO Resp. 4–5. All of those quotes actually state that Dr. Janoff's opinions are based on the Petition "and other documents and materials identified in this declaration" (Ex. 1007 ¶ 26) or "and the exhibits cited in the Petition as well as other documents" (*id.* ¶¶ 5–7).

F. Patent Owner's Motion to Amend

Patent Owner's contingent Motion to Amend proposes to substitute claims 21–40 for issued claims 1–20, if the latter are determined to be unpatentable. We have determined that Petitioner has shown by a preponderance of the evidence that the challenged claims 1–6, 9, 12, 14, and 15 are unpatentable as anticipated by the teachings of the '554 Publication.

Thus, we consider Patent Owner's contingent Motion to Amend concerning substitute claims for these claims.

Proposed substitute independent claim 21 is representative and is reproduced below, with additional matter being underlined and deleted material marked with double-brackets. Patent Owner proposes amending dependent claims 2–20 to reflect dependencies relative to original claims 2–20 in light of new substitute claim 21. *See* Mot. 8. According to Patent Owner, "[n]o further substantive amendments are proposed for these claims." Mot. 8.

> 21. (Substitute for claim 1) A <u>serum-stable</u> nucleic acid-lipid particle comprising:
>
> (a) a nucleic acid;
>
> (b) a cationic lipid comprising from 50 mol % to [[85]] <u>75</u> mol % of the total lipid present in the particle;
>
> (c) a non-cationic lipid comprising from [[13]] <u>23</u> mol % to 49.5 mol% of the total lipid present in the particle; and
>
> (d) a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol % to 2 mol % of the total lipid present in the particle;
>
> <u>wherein the particle is formulated such that the nucleic acid is not substantially degraded after exposure of the particle to a nuclease at 37ºC for 20 minutes</u>.

Id. at 3–4.

1. Procedural Requirements for a Motion to Amend

In an *inter partes* review, amended claims are not added to a patent as of right, but rather must be proposed as a part of a motion to amend. 35 U.S.C. § 316(d). "During an *inter partes* review instituted under this chapter, the patent owner may file 1 motion to amend the patent," and "[f]or

each challenged claim, propose a reasonable number of substitute claims." *Id.*; *see also* 37 C.F.R. § 42.121(a)(3).

Patent Owner's proposed substitute claims, however, must meet the statutory requirements of 35 U.S.C. § 316(d) and the procedural requirements of 37 C.F.R. § 42.121. *See Lectrosonics, Inc. v. Zaxcom, Inc.*, Case IPR2018-01129, slip op. at 2 (PTAB Feb. 25, 2019) (Paper 15) (precedential); Memorandum "Guidance on Motions to Amend in view of *Aqua Products*" (Nov. 21, 2017) (https://www.uspto.gov/sites/default/files/documents/guidance_on_motions_to_amend_11_2017.pdf) ("Board's Memorandum"). Although a motion to amend must comply with these requirements, a patent owner does not bear a burden to prove its proposed claims are patentable. *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1296 (Fed. Cir. 2017) (en banc) (stating Board may not place burden of persuasion on the patent owner).

Accordingly, Patent Owner must demonstrate: (1) the amendment proposes a reasonable number of substitute claims; (2) the amendment responds to a ground of unpatentability involved in the trial; and (3) the amendment does not seek to enlarge the scope of the claims of the patent or introduce new subject matter, such that the proposed substitute claims are supported in the original disclosure. *See* 35 U.S.C. § 316(d); 37 C.F.R. § 42.121. We determine that Patent Owner's Motion to Amend satisfies these procedural requirements for the reasons set forth below.

a. The Amendment Proposes a Reasonable Number of Substitute Claims

We find that Patent Owner proposes a reasonable number of substitute claims. Patent Owner proposes one substitute claim for each challenged claim, which is a presumptively reasonable number of substitute claims. *See*

37 C.F.R. § 42.121(a)(3) ("The presumption is that only one substitute claim would be needed to replace each challenged claim.").

b. The Amendment Responds to a Ground of Unpatentability Involved in the Trial

We find that Patent Owner's proposed substitute claims specifically respond to the unpatentability grounds set forth in the Petition. In two of the obviousness grounds involved in the *inter partes* review, Petitioner relies upon the teachings in the '196 PCT and the '189 Publication of nucleic acid-lipid particles that comprise a nucleic acid, and the lipid components—a cationic lipid, a non-cationic lipid, and a conjugated lipid—in mol percentage ranges that Petitioner asserts overlap with the claimed ranges. *See* Pet. 32–48; *see* Ex. 1007 ¶¶ 106–118. In the third obviousness ground, the only ground that includes an anticipation challenge, Petitioner relies upon the teachings in the '554 Publication of "encompassing and overlapping ranges and specific examples falling within the claimed ranges with sufficient specificity to anticipate." Pet. 51 (citing Ex. 1007 ¶ 143).

In response to Petitioner's challenges, Patent Owner contends that "substitute claim 21 amends independent claim 1 by reciting a narrower range for the concentration of the cationic lipid, and a narrower range for the concentration of non-cationic lipid." Mot. 3. Patent Owner additionally contends that addition of the term "serum stable" to the preamble of substitute claim 21 and addition of the phrase "wherein the particle is formulated such that the nucleic acid is not substantially degraded after exposure of the particle to a nuclease at 37ºC for 20 minutes" respond to the instituted grounds. *Id.*

Petitioner argues that the proposed substitute claims do "not respond to a ground of unpatentability involved in the trial" because the mol %

ranges for cationic lipid in the proposed substitute claims also overlap with the ranges taught by the cited prior art references. Opp. 2 (citing 37 C.F.R. § 42.121(a)(2)(i)). Petitioner contends that Patent Owner proposed narrower ranges because "it is apparently geared toward more closely aligning the claims with testing that the Patent Owner relies upon as evidence of unexpected results." *Id.* (citing Mot. 16). Petitioner also argues that proposed substitute claims 22–40 do not respond to a ground of unpatentability involved in the trial because "Patent Owner does not propose changes to dependent claims 2–20" and "[t]he proposed amendments do nothing to address that the additional limitations present in these claims are disclosed in the prior art." *Id.* at 1 n.1.

Patent Owner replies that the proposed substitute claims respond to the grounds of unpatentability because they relate to serum stability and nuclease resistance, both of which are requirements for systemic use of the claimed particles. Reply Opp. 3. Patent Owner also explains that the proposed substitute cationic lipid range of "50 mol % to 75 mol %" is outside of the range disclosed in the prior art '189 Publication, and "Petitioner does not provide a reason to increase the amount of cationic lipid." *Id.* at 3–4.

Patent Owner further contends that the proposed substitute claims are patentable over the '554 Publication because the reference discloses the use of chemically-modified RNA constructs to protect the nucleic acid from enzymatic degradation, rather than the '435 patent's protection mechanism of encapsulating the nucleic acid within the lipid portion of the particle. *Id.* (citing Ex. 1001, 22:55–62). Patent Owner also argues that the overlapping ranges "may invoke a rebuttable presumption of obviousness under the specific rationale of 'routine optimization'" but "Petitioner offers no

argument or evidence demonstrating that arriving at the claimed ranges of the lipid components was routine." *Id.* at 7–8.

Because Petitioner argues in part that the challenged claims are unpatentable because the claimed ranges of lipids overlap with the ranges taught by the prior art references, and Patent Owner attempts to address these challenges by narrowing the claimed ranges, we find that the amendment responds to a ground of unpatentability involved in the trial – the merits of which we will discuss below.

c. The Amendment Does Not Seek to Enlarge the Scope of the Claims of the Patent or Introduce New Subject Matter

We find that the written description of the '435 patent provides adequate support for the proposed substitute claims. The '435 patent claims priority to Provisional Application No. 61/045,228, filed April 15, 2008 ("the '228 provisional," Ex. 2041) "through a series of three continuation applications: U.S. Application No. 13/928,309 filed June 26, 2013, ('the '309 application,' EX2044); U.S. Application No. 13/253,917 filed October 5, 2011, ('the '917 application,' EX2043); and U.S. Application No. 12/424,367 filed April 15, 2009 ('the '367 application," EX2042)." Mot. 4.

Petitioner asserts that the proposed substitute claims "lack written description support and an enabling disclosure for the different nucleic acid payloads recited therein." Opp. 1. Petitioner contends, "the substitute claims broadly cover any nucleic acid payload—despite wide variations in potential nucleic acids and without support for anything but siRNA" and represent "Patent Owner's attempt to extend its disclosures to cover other nucleic acid payloads" because "Petitioner is an mRNA company, while Patent Owner (and its predecessors) have traditionally focused on siRNA." *Id.* at 2–3.

According to Petitioner, "Patent Owner points to testing of only siRNA payloads with a limited number of exemplar lipid components and with limited formulation processes" and admits "that changes to the payload, identity of lipid components, or production techniques can all impact the particle properties and resulting efficacy" and "the test data did not show the claimed formulations outperforming the prior art 2:40 formulation." *Id.* at 9–10 (citing Ex. 1022 ¶ 63; Ex. 1019; Ex. 1020). Petitioner explains, the '435 patent's "Background of the Invention" section discusses using siRNA for gene silencing and states that "the purpose of the invention is 'downregulating the expression of genes of interest to treat or prevent diseases and disorders such as cancer and atherosclerosis," but "[t]his is not a function of mRNA." *Id.* at 12–13 (citing Exs. 1001, 1:39–51; 1022 ¶ 70). Petitioner also explains that the '435 patent's specification identifies the nucleic acids in SNALPs as "one or more interfering RNA molecules such as siRNA, aiRNA, and/or miRNA" and "the preferred embodiments are described as having an siRNA payload: 'in preferred embodiments, the active agent or therapeutic agent comprises an siRNA.'" *Id.* (quoting Ex. 1001, 3:32–37, 14:62–17:47).

Patent Owner responds that its Motion to Amend and the original disclosure provide written description support for the use of "'nucleic acid' including mRNA." Reply Opp. 9. Specifically, Patent Owner's Motion to Amend discusses several disclosures in the '228 provisional that provide written description support for the nucleic acid limitation in challenged claim 1 and proposed substitute claim 21. Mot. 6 (citing Exs. 2041 ¶¶ 10, 19, 25–29; 2045 ¶¶ 17–18, 61, 76, 140, 307; 2040 ¶ 28). The disclosures highlighted by Patent Owner discuss encapsulation of "a nucleic acid" or an interfering RNA and merely provide siRNA as an example of a nucleic acid

by stating "(*e.g.*, the siRNA molecule)." *See* Ex. 2041 ¶¶ 10, 25–29. According to Patent Owner, "[t]he disclosure is directed to 'stable nucleic acid-lipid particles encapsulating a nucleic acid.'" Mot. 6 (citing Exs. 2041 ¶ 10; EX2045 ¶¶ 289, 329, 331; 2040 ¶ 28).

Patent Owner further contends that the '435 patent's specification provides support for the use of mRNA as a nucleic acid. Reply Opp. 9 (citing Ex. 1001 10:26–35). In fact, the specification states that "[t]he term 'nucleic acid' as used herein refers to a polymer containing at least two deoxyribonucleotides or ribonucleotides in either single- or double-stranded form and includes DNA and RNA" and further explains that "RNA may be in the form of siRNA, asymmetrical interfering RNA (aiRNA), microRNA (miRNA), mRNA, tRNA, rRNA, tRNA, viral RNA (vRNA), and combinations thereof." Ex. 1001, 10:26–36.

We find Patent Owner's examples of written description support for the nucleic acid limitation, especially as set forth in the Specification of the '435 patent, sufficient. The '435 patent's specification discusses nucleic acids broadly, but also provides examples of nucleic acids, including mRNA. Ex. 1001, 10:26–36. Thus, we find Patent Owner's proposed substitute claims satisfy the written description requirement.

2. Patentability Analysis of Proposed Substitute Claims

In accordance with *Aqua Products*, Patent Owner does not bear the burden of persuasion to demonstrate the patentability of the substitute claims presented in the Motion to Amend. Rather, ordinarily, "the petitioner bears the burden of proving that the proposed amended claims are unpatentable by a preponderance of the evidence." *Bosch Auto. Serv. Sols., LLC v. Matal*, 878 F.3d 1027, 1040 (Fed. Cir. 2017), *as amended on reh'g in part* (Mar.

15, 2018). The Board itself also may justify any finding of unpatentability by reference to evidence of record in the proceeding. *Id.* (citing *Aqua Products*, 872 F.3d at 1311 (O'Malley, J.)). Thus, the Board determines whether the proposed substitute claims are unpatentable based on the entirety of the record, including any argument made by Petitioner.

In its Opposition, Petitioner asserts that the proposed substitute claims do not remedy the unpatentability issues. Opp. 1. According to Petitioner, the proposed substitute claims are unpatentable under 35 U.S.C. § 103 as obvious over 1) the '196 PCT and the '189 Publication; and 2) the '196 PCT, the '189 Publication, Lin, and Ahmad; under 35 U.S.C. §§ 102 and 103 as anticipated by and obvious over the '554 Publication; and under 35 U.S.C. § 112 for lack of written description support and enablement. *Id.* at 8–20. We will focus our discussion on anticipation by the '554 Publication as we find this dispositive of the motion.

Petitioner contends that Patent Owner's addition of "serum-stable" to the preamble of claim 1 is non-limiting because preambles are generally considered to be non-limiting. *Id.* at 1, 3–4 (citing *Catalina Marketing Int'l, Inc. v. CoolSavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002)). According to Petitioner, a POSITA would not "consider the term 'serum-stable' limiting in the claims." *Id.* (citing Ex. 1022 ¶ 53).

Petitioner further argues that even if the preamble were considered limiting, "the cited prior art references disclose serum-stable particles at greater than 50 mol% cationic lipid" and "[e]ach of the three primary references disclose the desire for serum-stable particles." *Id.* at 4 (citing Ex. 1002 ¶¶ 2, 15–16, 120, 134; Ex. 1003, ¶¶ 182, 191, 217; Ex. 1004 ¶¶ 14–15, 158; Ex. 1022 ¶ 54). Petitioner points to disclosures in the '189 Publication and the '554 Publication that discuss a series of *in vivo*

experiments with formulations matching the cationic lipid ranges in the proposed substitute claims. *Id.* (citing Ex. 1003 ¶¶ 351–391; Ex. 1004 ¶ 408, Table IV, Fig. 29). Petitioner concludes "[a] POSITA would understand these disclosures in the context of the prior art references to disclose serum-stable particles at greater than 50 mol% cationic lipid." *Id.* (citing Ex. 1022 ¶ 54).

Petitioner additionally contends that the limitation "wherein the particle is formulated such that the nucleic acid is not substantially degraded after exposure of the particle to a nuclease at 37ºC for 20 minutes" fails to "differentiate over the prior art, given that serum-stable particles that resist nuclease degradation are disclosed in the prior art already of record." *Id.* at 1–2. According to Petitioner, the limitation "does not require the particle to be 'serum stable' as such resistance can be tested *in vitro* using a nuclease." *Id.* at 3 (citing Ex. 1020, 159). In support of this statement, Petitioner points to *in vitro* testing of the L054 formulation in the '554 Publication. *Id.* at 6 (citing Ex. 1004, Table IV). Petitioner explains that the L054 formulation (tested *in vitro*) and the L060 formulation (tested *in vivo*) both contained the cationic lipid, DMOBA, and the L060 formulation showed *in vivo* efficacy with 52 mol % DMOBA. *Id.* (citing Ex. 1004 Table IV, ¶ 408, Fig. 29; Ex. 1022 ¶ 59). Petitioner also argues that "[e]ach of the three primary references disclose nucleic acid-lipid particles that can also withstand nuclease exposure and Patent Owner's prior disclosures disclose these exact parameters." *Id.* at 7–8 (citing Ex. 1002; Ex. 1003).

Patent Owner responds that the addition of "serum-stable" to the preamble of claim 1 "reinforces that the claims require a particle in which the nucleic acid is encapsulated in the particle so as to protect the nucleic acid from enzymatic degradation" and "is tied to the added limitation of

'wherein the particle is formulated such that the nucleic acid is not substantially degraded after exposure of the particle to a nuclease at 37ºC for 20 minutes.'" *Id.* Patent Owner also contends that Petitioner's argument that the '554 Publication discloses "in vivo efficacy of a particle having 52 mol% DMOBA . . . is irrelevant as toxicity was never assessed in the '554 publication." *Id.* at 5–6.

After considering the parties' arguments and the remainder of the record, we conclude that the proposed substitute claims do not overcome the prior art references and find them unpatentable for the same reasons as discussed above.

For purposes of this analysis, we assume that "serum stable" is limiting. The L054 formulation is also within the more narrow ranges required by substitute claim 21. *Compare* Ex. 1004 ¶ 92, *with* substitute claim 21. The question becomes whether the addition of serum stability sufficient to meet the parameters of the wherein clause is sufficient to distinguish the substitute claims from the prior art.

The L054 formulation is described as serum stable. *Id.* ¶ 140. In Example 9, titled "Evaluation of Formulated siNA Compositions in Models of Chronic HBV Infection," an in vitro analysis of the activity of nanoparticle formulation L054 was performed. *Id.* ¶ 595. The '554 Publication describes adding the siNA nanoparticle formulation to wells containing HepG2 cells with media. *Id.* "The cells were incubated for 4 days, the media was then removed, and assayed for HBsAg levels. . . . FIG. 16 shows level of HBsAg from formulation (Formulations L053 and L054, Table IV) active siNA treated cells compared to untreated or negative control treated cells." *Id.*

The '554 Publication concludes that:

> In these studies, a dose dependent reduction in HBsAg levels was observed in the active formulated siNA treated cells using nanoparticle formulations L051, L053, and L054, while no reduction is observed in the negative control treated cells. This result indicates that the formulated siNA compositions are able to enter the cells, and effectively engage the cellular RNAi machinery to inhibit viral gene expression.

Id. In describing this Example, the '554 Publication states that incubation was carried out at 37º C. *Id*.

The discussion of this experiment using L054 formulation nanoparticles indicates that these particles were serum stable "such that the nucleic acid is not substantially degraded after exposure of the particle to a nuclease at 37ºC for 20 minutes." *See* Mot., Appendix A (proposed substitute claim 21). As Dr. Thompson testifies "as soon as you feed your cells, any exposed nucleic acid is shredded. Even in in vitro setting." Ex. 2019, 129:4–5; *see also id*. at 216–217 (Dr. Thompson stating that "if you have serum present, if it's not a serum stable formulation, and one that actually performs in the presence of serum, game over").

We find that proposed substitute claim 21 is unpatentable as anticipated by the '554 Publication. For the same reasons as set forth above regarding the anticipation of claims 2–6, 9, 12, 14, and 15, we also find that substitute claims 22–26, 29, 32, 34, and 35 are also anticipated. Therefore, we deny Patent Owner's Contingent Motion to Amend.

III. CONCLUSION

After reviewing the information presented in the Petition and the Patent Owner Response, as well as the evidence of record, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–6, 9, 12, 14, and 15 of the '435 patent are unpatentable as anticipated by the '554

Publication. We also determine that Petitioner has not shown by a preponderance of the evidence that claims 7, 8, 10, 11, 13, or 16–20 are unpatentable.

Because Patent Owner's Motion to Amend was contingent, we only considered the proposed substitute claims for the unpatentable claims, which are substitute claims 21–26, 29, 32, 24, and 35. We found that these proposed substitute claims are unpatentable as anticipated by the '554 Publication.

IV. ORDER

Accordingly, it is:

ORDERED that claims 1–6, 9, 12, 14, and 15 of U.S. Patent No. 9,364,435 B2 are determined to be unpatentable;

FURTHER ORDERED that claims 7, 8, 10, 11, 13 and 16–20 of U.S. Patent No. 9,364,435 B2 have not been shown by a preponderance of the evidence to be unpatentable

FURTHER ORDERED that Patent Owner's Motion to Amend is *denied*; and

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

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