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Paper No. 8
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

ARBUTUS BIOPHARMA CORPORATION,
Patent Owner.

Case IPR2019-00554
Patent 8,058,069 B2

Before CHRISTOPHER G. PAULRAJ, JACQUELINE T. HARLOW and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

HARLOW, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Petitioner, Moderna Therapeutics, Inc., filed a Petition (Paper 1, "Pet."), requesting *inter partes* review of claims 1–22 of U.S. Patent No. 8,058,069 B2 (Ex. 1001, "the '069 patent"). Patent Owner, Arbutus Biopharma Corporation, timely filed a Preliminary Response (Paper 7, "Prelim. Resp.").

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." For the reasons stated below, we determine that there is a reasonable likelihood that Petitioner would prevail with respect to at least one challenged claim. We hereby institute *inter partes* review of the challenged claims on all the grounds of unpatentability asserted in the Petition.

A. Related Matters

Petitioner filed petitions seeking *inter partes* review of two additional patents held by Patent Owner in IPR2018-00680, challenging U.S. Patent No. 9,404,127 B2, and IPR2018-00739 ("the '739 IPR"), challenging U.S. Patent No. 9,364,435 B2 ("the '435 patent")).[1] Pet. 4; Paper 4, 2–3. The Board instituted review in each proceeding on September 11, 2018.

[1] Patent Owner explains that Protiva Biotherapeutics, Inc., identified as the patent owner in IPR2018-00680 and IPR2018-00739, previously "existed as a wholly-owned subsidiary of Arbutus Biopharma Corporation," and was "amalgamated into Arbutus Biopharma Corporation in January 2018." Paper 4, 2.

See IPR2018-00680 (Paper 13); IPR2018-00739 (Paper 15). The '435 patent at issue in the '739 IPR is a continuation of the '069 patent challenged here. Ex. 1002, (63).

B. The '069 Patent

The '069 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 '069 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 5:44–51. The '069 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 5:51–61.

The '069 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." Ex. 1001, 5:61–6:3. In characterizing the 1:57 SNALP and 1:62 SNALP formulations, the '069 patent explains that these are "target formulations, and [] the amount of lipid (both cationic and non-cationic) present and the amount of lipid conjugate present in the formulation may vary." *Id*. at 68:35–39. In this regard, the '069 patent explains that the 1:57 SNALP formulation usually includes 57 mol % ± 5 mol % cationic lipid and 1.5 mol % ± 0.5 mol % lipid conjugate, with non-cationic lipid making up the balance of the formulation. *Id*. at 68:39–44. Similarly, the 1:62 SNALP formulation typically includes 62 mol % ± 5 mol % cationic lipid and 1.5 mol % ± 0.5 mol % lipid conjugate, with non-cationic lipid making up the remainder. *Id*. at 68:44–48.

The '069 patent describes several studies comparing the efficacy of siRNA encapsulated in different SNALP formulations. For example, in a study examining siRNA SNALP formulations directed at silencing Eg5, a kinesin-related protein critical for mitosis in mammalian cells (Ex. 1001, 68:55–62), the '069 patent reports that the 1:57 SNALP formulation "was among the most potent inhibitors of tumor cell growth at all siRNA concentrations tested" (*id*. at 70:19–22). Similarly, in a test of SNALP formulations targeting apolipoprotein B ("ApoB"), a protein associated with hypercholesterolemia (*id*. at 70:55–59), the '069 patent explains that the 1:57 SNALP formulation "was the most potent at reducing ApoB expression in vivo" (*Id*. at 72:21–23). The '069 patent also reports experimental results indicating that the ApoB 1:57 SNALP formulation "was more than 10 times as efficacious as the 2:30 SNALP [a prior art SNALP composition] in

mediating ApoB gene silencing in mouse liver at a 10-fold lower dose" (*id.* at 73:64–67), and that the "1:57 and 1:62 SNALP formulations had comparable ApoB silencing activity in vivo" (*id.* at 74:51–53).

C. Challenged Claims

Petitioner challenges claims 1–22 of the '069 patent. Claim 1, the sole independent claim of the '069 patent, is illustrative, and is reproduced below:

> 1. A nucleic acid-lipid particle comprising:
>
> (a) a nucleic acid;
>
> (b) a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the particle;
>
> (c) a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from 4 mol % to 10 mol % of the total lipid present in the particle and the cholesterol or derivative thereof comprises from 30 mol % to 40 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, 91:23–35.

D. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 5):

Claims	Basis	References
1–22	§§ 102 and 103	'196 PCT[2] and '189 Publication[3]
1–22	§ 103	'196 PCT, '189 Publication, Lin,[4] and Ahmad[5]
1–22	§§ 102 and 103	'554 Publication[6]

Petitioner also relies on the Declaration of Dr. Andrew S. Janoff, Ph.D. (Ex. 1008) to support its challenge.

[2] MacLachlan et al., WO 2005/007196 A2, published Jan. 27, 2005 ("'196 PCT"). Ex. 1003.

[3] MacLachlan et al., US 2006/0134189 A1, published Jun. 22, 2006 ("'189 Publication"). Ex. 1004.

[4] 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. 1006.

[5] Ahmad et al., *New Multivalent Cationic Lipids Reveal Bell Curve for Transfection Efficiency Versus Membrane Charge Density: Lipid-DNA Complexes for Gene Delivery*, 7 J. GENE MED. 739–48 (2005) ("Ahmad"). Ex. 1007.

[6] Chen et al., US 2006/0240554 A1, published Oct. 26, 2006 ("'554 Publication"). Ex. 1005.

II. ANALYSIS

A. Patent Owner's Request for Denial under 35 U.S.C. § 314(a)

Patent Owner argues that the Petition should be denied under 35 U.S.C. § 314(a). Prelim. Resp. 3–4. Section 314(a) states that

> [t]he Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.

Under § 314(a), the Director has discretion to deny institution of an *inter partes* review. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2140 (2016) ("[T]he agency's decision to deny a petition is a matter committed to the Patent Office's discretion."). We consider several non-exclusive factors when determining whether to deny institution under § 314(a), including

> 1. whether the same petitioner previously filed a petition directed to the same claims of the same patent;
>
> 2. whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;
>
> 3. whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition;
>
> 4. the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;
>
> 5. whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent;

> 6. the finite resources of the Board; and
>
> 7. the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

General Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha, Case IPR2016-01357, slip op. at 15–16 (PTAB Sept. 6, 2017) (Paper 19) (precedential). Our discretionary determination of whether to institute review also takes into account guidance in the Office Patent Trial Practice Guide, August 2018 Update, 83 Fed. Reg. 39,989 (August 13, 2018) ("Trial Practice Guide Update"), https://go.usa.gov/xU7GP. In particular, the Trial Practice Guide Update states

> [t]here may be other reasons besides the "follow-on" petition context where the "effect . . . on the economy, the integrity of the patent system, the efficient administration of the Office, and the ability of the Office to timely complete proceedings," 35 U.S.C. § 316(b), favors denying a petition even though some claims meet the threshold standards for institution under 35 U.S.C. §§ 314(a), 324(a).

Trial Practice Guide Update 10–11. We additionally construe our rules to "secure the just, speedy, and inexpensive resolution of every proceeding." 37 C.F.R. § 42.1(b); *Deeper, UAB v. Vexilar, Inc.*, Case IPR2018-01310, slip op. at 42 (PTAB Jan. 24, 2019) (Paper 7) (informative).

Patent Owner acknowledges that the '739 IPR is directed to a different patent than is challenged in this proceeding. Prelim. Resp. 4. Nevertheless, Patent Owner contends that exercise of our discretion to deny institution is warranted here because the'069 patent and the previously challenged '435 patent are related, "have similar, although not identical claims," and face challenges based on the same prior art. *Id.* Patent Owner

further contends that Petitioner knew of the prior art asserted in the '739 IPR, benefited from Patent Owner's filings and the Board's rulings in that case, and cannot justify the ten month delay between the filing of the petition in the '739 IPR and its filing of this Petition. *Id.* at 6–7. Patent Owner additionally asserts that "re-litigating the issues of the '739 IPR" is an inefficient use of the Board's resources, and the potential overlap between this Decision and the forthcoming final decision in the '739 IPR militate in favor of denial. *Id.* at 8–9 (emphasis omitted). Patent Owner concludes by arguing that the Petition is deficient because it does not address various arguments and evidence presented in the '739 IPR, and that it was filed in an attempt to harass Patent Owner. *Id.* at 9–12.

Certain of Patent Owner's concerns regarding the overlap between this proceeding and the '739 IPR resonate. For example, we recognize that it would have been more efficient for the parties and the Board had the two petitions been concurrently filed. But such efficiencies, as well as Patent Owner's additional concerns, are outweighed in this case by the fact that the instant proceeding challenges a different patent, reciting claims of different scope, than are addressed in the '739 IPR. For example, the sole independent claim of the '069 patent includes specific requirements for cationic lipid, phospholipid, and cholesterol content not present in the sole independent claim of the '435 patent. *Compare* Ex. 1001, 91:23–35 *with* Ex. 1002, 89:55–63. We are unaware of, and Patent Owner does not identify, any decision by the Board relying on a previously filed petition concerning one patent as a basis for denying institution under § 314(a) of a subsequent petition challenging a second (albeit, related) patent. In addition,

the fact that the sole independent claim of the '069 patent is narrower than that of the previously challenged '435 patent defuses Patent Owner's arguments that the Petition should have more thoroughly addressed the evidence of record in the '739 IPR, and that the instant Petition was filed only to harass Patent Owner (Prelim. Resp. 8–12).

Not only is this Petitioner's first challenge to the '069 patent, but neither Patent Owner nor Petitioner identifies any other challenge to the '069 patent before the Board. *Cf. Valve Corp. v. Elec. Scripting Prods., Inc.*, Case IPR2019-00062, -00063, -00084, Paper 11 (Apr. 2, 2019) (precedential) (exercising discretion to deny institution of follow-on petition filed by a party having a "significant relationship" with the party that filed the first petition against the challenged patent, and where there was complete overlap in the challenged claims between the petitions). Nor do the parties apprise us of litigation concerning the '069 patent in another forum. To the contrary, Patent Owner represents that "there is no underlying district court dispute over the '069 patent." Prelim. Resp. 11; *cf. NHK Spring Co., Ltd. v. Intri-Plex Techs., Inc.*, Case IPR2018-00752, Paper 8 (Sept. 12, 2018) (precedential) (recognizing the advanced state of a co-pending district court proceeding involving the same petitioner asserting the same prior art relied on in its petition for *inter partes* review as an additional factor weighing in favor of discretionary denial under § 314(a)).

Accordingly, because this *inter partes* review represents the first challenge to the '069 patent before the Board or elsewhere, based on a balanced assessment of the circumstances of this case, we decline to exercise our discretion to deny institution under § 314(a).

B. Level of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art ("skilled artisan" or "POSITA") "would have specific experience with lipid particle formation and use in the context of delivering therapeutic nucleic acid 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. 6 (citing Ex. 1008 ¶¶ 29–32). Petitioner further asserts that "[t]his level of skill is representative of the authors/inventors of prior art cited herein." *Id.* (citing Ex. 1008 ¶¶ 29–32).

Patent Owner limits its response to a footnote, stating, "[e]ach of the petition challenges are additionally flawed for being based on an improper, if not indeterminable, proffered level of skill. Indicative of impermissible hindsight, the petition equates the level of skill of the artisan with the level of skill of the artisans of the '069 patent." Prelim. Resp. 15, n.2.

As an initial matter, we note that the level of ordinary skill proposed in the Petition differs somewhat from the level of skill identified by Dr. Janoff, as well as from that advanced by Petitioner in the '739 IPR. *Compare* Pet. 6 *with* Ex. 1008 ¶ 31 *and* '739 IPR, Paper 2, 5. In particular, the Petition asserts that a skilled artisan would have "specific experience with lipid particle formation and use in the context of delivering *therapeutic nucleic acid payloads*" (Pet. 6 (emphasis added)), while Dr. Janoff and the petition in the '739 IPR state that such an artisan "would have specific experience with lipid particle formation and use in the context of delivering

therapeutic payloads" (Ex. 1008 ¶ 31 (emphasis added); '739 IPR, Paper 2, 5). Petitioner does not explain the discrepancy.

For purposes of this decision, we adopt Dr. Janoff's formulation of the level of ordinary skill as set forth above. Dr. Janoff testifies that he is familiar with the technology at issue and the state of the art at the earliest priority date for the '069 patent, and explains that he arrived at his definition of the level of ordinary skill in the art in light of his "review of the '069 patent, its file history, and [his] knowledge of the field of the art." Ex. 1008 ¶¶ 30–31. We note, however, that our institution decision is unaffected by whether we include a requirement that the skilled artisan's experience with lipid particle formation and use in the context of delivering therapeutic payloads must further include experience particular to therapeutic nucleic acid payloads.

Concerning Patent Owner's assertion that "the petition equates the level of skill of the artisan with the level of skill of the artisans of the '069 patent" (Prelim. Resp. 15, n.2), we observe that the Petition and Dr. Janoff state only that "[t]his level of skill is representative of the authors/inventors of prior art cited herein" (Pet. 6 (quoting Ex. 1008 ¶ 31)), and do not characterize the level of skill exhibited by the inventors of the '069 patent itself. Furthermore, based on the record before us, we find that the level of ordinary skill in the art articulated by Dr. Janoff is consistent with that reflected in the prior art of record. *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 (Fed. Cir. 1985)).

C. Claim Construction

Based on the filing date of the Petition, we apply the same claim construction standard used in federal district court, which includes construing the claim in accordance with the ordinary and customary meaning of the claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent. 37 C.F.R. § 42.100(b); 83 Fed. Reg. 51358 (Oct. 11, 2018) (amending the claim construction standard for trial proceedings before the Board).

The parties here disagree regarding the proper construction of the claim term "nucleic acid-lipid particle." While acknowledging that it was reached applying a different standard (i.e., broadest reasonable interpretation), Petitioner contends that, as in the '739 IPR institution decision, "nucleic acid-lipid particle" should be construed here to mean "a particle that comprises a nucleic acid and lipids, in which the nucleic acid *may be* encapsulated in the lipid portion of the particle." Pet. 23 (emphasis added). Patent Owner responds that Petitioner's proffered construction is too broad, and asserts instead that "the claimed nucleic acid-lipid particle *necessarily* includes a nucleic acid encapsulated in the lipid portion of the particle." Prelim. Resp. 17 (emphasis added). Patent Owner acknowledges, however, that construing "nucleic acid-lipid particle" is not required for this Decision because its arguments against institution do not rely on a construction of that term requiring encapsulation of the recited nucleic acid. Prelim. Resp. 17 ("Regardless of whether the Board construes 'nucleic

acid-lipid particle' as a SNALP as indicated by Petitioner's expert; as a lipid particle with an encapsulated nucleic acid; or under the broad construction advanced by the Petitioner, the petition fails to show that there is a reasonable likelihood that the Petitioner would prevail on any of the grounds of challenge.").

At this stage in the proceeding, we determine that the term "nucleic acid-lipid particle" does not require express construction to resolve the issues before us. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (noting that "we need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'") (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). As highlighted above, Patent Owner does not, at this stage, join the question of whether Petitioner's asserted grounds of unpatentability teach or suggest a nucleic acid encapsulated in the lipid portion of the nucleic acid-lipid particle. *See generally,* Prelim. Resp. In addition, the Petition identifies disclosure of "a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery" by each of the '196 PCT and the '189 Publication (Ex. 1003 ¶ 2; Ex. 1004 ¶ 182) as supporting certain of its unpatentability arguments. Pet. 32. Thus, were we to agree with Patent Owner and construe "nucleic acid-lipid particle" to require encapsulation of the nucleic acid within the lipid, our determination, set forth in Part II.D.3., below, that Petitioner has established a reasonable likelihood of prevailing on its assertion that each of the '196 PCT and the '189 Publication render claim 1 unpatentable would not change. To the

extent the parties raise patentability arguments turning on whether the '069 patent requires encapsulation of the nucleic acid within the lipid particle during trial, we urge them to further brief the issue in their post-institution briefs, and we will revisit whether the term needs to be construed after consideration of the full record. But for purposes of this Decision, it is unnecessary to construe "nucleic acid-lipid particle," as our determination to institute *inter partes* review remains unchanged regardless of whether we apply Petitioner's or Patent Owner's proposed construction.

D. Anticipation or Obviousness Based on '196 PCT or '189 Publication

Petitioner contends that claims 1–22 are anticipated or rendered obvious by each of the '196 PCT and the '189 Publication. Pet. 31–49. Petitioner explains that it presents its arguments based on the '196 PCT and '189 Publication together "because the '189 publication is substantively similar to the '196 PCT, the primary difference being that it also discloses testing relating to the admitted prior art 2:40 formulation." *Id.* at 31 (citing Ex. 1004 ¶¶ 350–391; Ex. 1008 ¶ 108). To support its contentions, Petitioner cites to Dr. Janoff's declaration testimony (Ex. 1008).

Patent Owner responds that neither the '196 PCT nor the '189 Publication discloses the recited concentration ranges for phospholipids, and contends that Petitioner relies improperly on hindsight to arrive at the claimed phospholipid range. Prelim. Resp. 18–23. Patent Owner also argues that Petitioner fails to articulate a rationale for arriving at the claimed proportions of the various components recited in the challenged claims. *Id.* at 23–29. Finally, Patent Owner asserts that evidence of

unexpected results and objective indicia of nonobviousness developed during trial in the '739 IPR support denial of institution here. *Id.* at 32–48.

1. Overview of '196 PCT

The'196 PCT describes "compositions and methods for the therapeutic delivery of a nucleic acid by delivering a serum-stable lipid delivery vehicle encapsulating the nucleic acid to provide efficient RNA interference (RNAi) in a cell or mammal." Ex. 1003 ¶ 2. More particularly, the '196 PCT discloses "using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." *Id.* ¶¶ 2, 10.

In describing one embodiment, the '196 PCT states that the nucleic acid-lipid comprises a cationic lipid, a non-cationic lipid, a conjugated lipid, a bilayer stabilizing component for inhibiting aggregation of particles, and a siRNA. *Id.* ¶¶ 11, 85 (describing SNALP with same components). In describing how embodiments are made, the '196 PCT also states that preferred embodiments are charge neutralized. *Id.* ¶ 15.

The '196 PCT further provides detailed descriptions of the components of stable nucleic acid-lipid particles. *See* Ex. 1003, ¶¶ 86–107. Concerning the preferred makeup of the disclosed SNALP, the '196 PCT states the following about the amount of cationic lipid in the SNALP.

> The cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle, preferably from about 5% to about 45% of the total lipid present in said particle. In certain preferred embodiments, the cationic lipid comprises from about 5% to about 15% of the total lipid present in said particle. In other preferred embodiments, the cationic lipid comprises from about 40% to about 50% of the total lipid

> present in said particle. Depending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied and the delivery efficiency of a particular formulation can be measured using an endosomal release parameter (ERP) assay. For example, for systemic delivery, the cationic lipid may comprise from about 5% to about 15% of the total lipid present in said particle and for local or regional delivery, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle.

Ex. 1003 ¶ 88.

For the amount of non-cationic lipid content of the SNALP, the '196 PCT states that "[t]he non-cationic lipid typically comprises from about 5% to about 90% of the total lipid present in said particle, preferably from about 20% to about 85% of the total lipid present in said particle." Ex. 1003 ¶ 91. For the bilayer stabilizing component such as a conjugated lipid, the '196 PCT states the following.

> Typically, the bilayer stabilizing component is present ranging from about 0.5% to about 50% of the total lipid present in the particle. In a preferred embodiment, the bilayer stabilizing component is present from about 0.5% to about 25% of the total lipid in the particle. In other preferred embodiments, the bilayer stabilizing component is present from about 1% to about 20%, or about 3% to about 15% or about 4% to about 10% of the total lipid in the particle. One of the ordinary skill in the art will appreciate that the concentration of the bilayer stabilizing component can be varied depending on the bilayer stabilizing component employed and the rate at which the liposome is to become fusogenic [i.e. has the ability to fuse with membranes of a cell].

Id. ¶ 93. The '196 PCT also states that "[b]y controlling the composition and the concentration of the bilayer stabilizing component, one can control the rate at which the bilayer stabilizing component exchanges out of the

liposome and, in turn, the rate at which the liposome becomes fusogenic." *Id.* ¶ 94.

2. Overview of '189 Publication

The '189 Publication describes "nucleic acid-lipid particles comprising siRNA molecules that silence ApoB expression and methods of using such nucleic acid-lipid particles to silence ApoB expression." Ex. 1004, Abstract. In describing these nucleic acid-lipid particles, the '189 Publication states that they may comprise an siRNA molecule that silences ApoB expression, a cationic lipid, a non-cationic lipid, and a conjugated lipid that inhibits aggregation of particles. *Id.* ¶ 8. In describing the relative weight percentages of the content of the nucleic acid-lipid particles, the '189 Publication states:

> The cationic lipid may comprise from about 2 mol % to about 60 mol %, about 5 % mol % to about 45 mol %, about 5 mol % to about 15 mol%, about 30 mol % to about 50 mol % or about 40 mol % to about 50 mol % of the total lipid present in the particle.
>
> . . . The non-cationic lipid comprises from about 5 mol % to about 90 mol % or about 20 mol % to about 85 mol % of the total lipid present in the particle.
>
> . . . The conjugated lipid that prevents aggregation of particles may comprise from about 0 mol % to about 20 mol %, about 0.5 mol % to about 20 mol %, about 1 mol % to about 15 mol %, about 4 mol % to about 10 mol %, or about . . . 2 mol % of the total lipid present in said particle.

Id. ¶¶ 9–11; *see id.* ¶¶ 150–181 (describing content of SNALP). The '189 Publication describes embodiments wherein the siRNA is fully encapsulated in the nucleic acid-lipid particle. *Id.* ¶ 14.

3. Analysis

Given the substantial similarity between the references, and because the parties address Petitioner's unpatentability challenges based on the '196 PCT and the '189 Publication together, we do as well.

Petitioner asserts that claim 1 is anticipated or rendered obvious by each of the '196 PCT and the '189 Publication.[7] For example, Petitioner contends that the disclosure by each reference of "compositions and methods for silencing gene expression by delivering nucleic acid-lipid particles comprising a siRNA molecule to a cell" (Ex. 1003, Abstract; Ex. 1004, Abstract) teaches or suggests "[a] nucleic acid-lipid particle" (Ex. 1001, 91:23) as recited in the preamble of claim 1. Pet. 32 (citing Ex. 1008 ¶ 110).

Petitioner likewise asserts that the claim 1(a) requirement for "a nucleic acid" (Ex. 1001, 91:24) is satisfied by the disclosure in the '196 PCT and the '189 Publication that "the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery" (Ex. 1003 ¶ 2; Ex. 1004 ¶ 182). Pet. 32 (citing Ex. 1008 ¶ 111).[8]

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[7] Petitioner also details how each limitation of dependent claims 2–22 is met by the disclosures of the '196 PCT and the '189 Publication. *See* Pet. 41–49. At this stage of the proceeding, Patent Owner has not addressed the dependent claims individually for any of the asserted grounds. *See generally*, Prelim. Resp. Accordingly, we focus our analysis on claim 1.

[8] Although Petitioner adopts its own numbering scheme to identify the various elements of claim 1 (*see, e.g.*, Pet. 32), we adhere to the numbering set forth in claim 1 itself (*see* Ex. 1001, 91:24–35).

Element (b) of claim 1 calls for "a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the particle." Ex. 1001, 91:25–26. Petitioner asserts that the '196 PCT and the '189 Publication disclose this claim element because each reference teaches that the cationic lipid typically makes up 2% to about 60% of the total lipid present in a nucleic acid-lipid particle, and preferably 40% to about 50%. Pet. 32–33 (citing Ex. 1003 ¶ 88; Ex. 1004 ¶ 152). According to Petitioner, "[g]iven the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range," and, "[g]iven the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious." Pet. 33 (citing Ex. 1008 ¶ 112; *E.I. DuPont de Nemours & Company v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018)).

Petitioner further contends that the '196 PCT incorporates by reference, and the '189 Publication directly references, U.S. Patent No. 5,264,618 ("the '618 patent"; Ex. 1017),[9] which discloses nucleic acid-lipid particles consisting of greater than 50 mol % cationic lipid. Pet. 33, 34.[10] Petitioner avers that an ordinarily skilled artisan "would have had a reasonable expectation that the nucleic-acid lipid particles could be successfully formulated with cationic lipid [in] the 50 mol% to 65 mol% range, especially given the disclosure in the '618 patent of various

[9] Felgner et al., U.S. Patent No. 5,264,618, issued Nov. 23, 1993 (Ex. 1017).

[10] The Petition inadvertently identifies the '618 patent as Ex. 1016. *See, e.g.*, Pet. 33, 34. The '618 patent is Ex. 1017.

formulations containing over 50% cationic lipid." *Id.* at 34 (citing Ex. 1017, 34:54–35:23).

Petitioner also asserts that "[t]he testing in the '069 patent cannot overcome the presumption of obviousness as it is insufficient to show alleged 'unexpected results' with regard to the prior art for the entire claimed range." Pet. 34. According to Petitioner, the testing is deficient because it "dealt with only a single formulation of lipid species" (*id.*), and the examples in the '069 patent indicate that variation of the cationic lipid used in nucleic acid-lipid particles impacts their transfection efficiency (*id.* at 34–38). For example, Petitioner reasons that

> the *in vivo* testing in Example 3 shows that even minor variations in lipid percentages appeared to impact efficacy. [Ex. 1008] ¶ 114. Specifically, Samples 2 and 12 from Table 4 contain the exact same lipid species in the respective ratios 2/40/10/48 and 1/40.4/10.1/48.5. Ex. 1001, Table 4. According to Figure 2, these slight variations in lipid proportions lead to apparently different transfection efficiencies. *Id.*, Fig. 2; [Ex. 1008] ¶ 114. A POSITA would expect that similar minor variations in lipid proportions within the claimed range might lead to similar variations in transfection efficiency. [Ex. 1008] ¶ 114.

Pet. 36. Petitioner, therefore, asserts that an ordinarily skilled artisan "would have no reason to believe that the alleged unexpected advantages of a 50–65% proportion of DLinDMA would be applicable to all cationic lipids" (*Id.* at 38 (citing Ex. 1008 ¶ 117)).

Element 1(c) of the '069 patent requires

> a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from 4 mol % to 10 mol % of the total lipid present in the particle and the cholesterol or derivative thereof comprises

> from 30 mol % to 40 mol % of the total lipid present in the particle.

Ex. 1001, 91:27–32. Petitioner asserts that the '196 PCT and the '189 Publication each "teach that the non-cationic lipids may include a phospholipid and cholesterol." Pet. 38 (citing Ex. 1003 ¶ 89; Ex. 1004 ¶ 159). Petitioner further contends that each reference discloses that the lipid component of the nucleic acid-lipid particle is from about 20% to about 85% non-cationic lipid, and that when present, cholesterol makes up from about 20% to about 45% of the total lipid. Pet. 38 (citing Ex. 1003 ¶ 91; Ex. 1004 ¶ 152).

According to Petitioner,

> [n]ot only do the disclosed ranges encompass the claimed ranges, when combined with a cationic lipid proportion at the high end of the disclosed range (i.e., 60%), the available range for cholesterol is decreased to 20–40%. [Ex. 1008] ¶ 119. The range for the other non-cationic lipid (e.g., a phospholipid) is also decreased to the portion not filled with cholesterol (or PEG conjugate as described below in Claim 1[d]), namely 0%–19.5%. *Id.*

Pet. 39. Petitioner summarizes this scenario in a table, reproduced below.

	Cationic Lipid	Cholesterol	Phospholipid	PEG
'069 claims	50-65%	30-40%	4-10%	0.5-2%
Prior disclosures	60%	20-40%	0-19.5%	0.5-25%

Id.

Finally, element (d) of claim 1 recites "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, 91:33–35. Petitioner points to

disclosure in the '196 PCT that a conjugated lipid that inhibits aggregation of SNALP is present from about 0.5% to about 25% of the total lipid (Ex. 1003 ¶¶ 92–93), and disclosure in the '189 Publication that a PEG-lipid conjugate typically comprises from about 0.5 mol % to about 20 mol % of the total lipid (Ex. 1004 ¶ 152) as satisfying this claim element. Pet. 39–40.

Petitioner additionally contends that an ordinarily skilled artisan would have sought to increase fusogenicity in order to improve transfection efficiency by choosing a proportion of conjugated lipid in the 0.5%–2% range. Pet. 40 (citing Ex. 1008 ¶ 121).

Based on our review of the current record, we agree with Petitioner's characterization of the teachings of the '196 PCT and the '189 Publication, and the knowledge in the art, as well as Petitioner's assertions as to the reasonable inferences an ordinary artisan would have made from those references. We address Patent Owner's arguments below.

Turning first to Patent Owner's contention that neither the '196 PCT nor the '189 Publication discusses concentration ranges for phospholipids (Prelim. Resp. 18–19), we do not find this argument persuasive. Patent Owner's argument is predicated on the '196 PCT and '189 Publication not expressly identifying a phospholipid fraction of the total lipid. *Id.* But that argument ignores the fact that the '196 PCT and the '189 Publication each identify phospholipids and cholesterol as non-cationic lipids that may be present in the non-cationic lipid fraction. Ex. 1003 ¶ 89; Ex. 1004 ¶ 159. The references further explain that non-cationic lipid comprises from about 20% to about 85% of total lipid present in the nucleic acid-lipid particle, and that when present, cholesterol makes up from about 20% to about 45% of

the total lipid. Ex. 1003 ¶ 91; Ex. 1004 ¶ 152. Based on these disclosures, Petitioner, relying on Dr. Janoff, demonstrates that each of the '196 PCT and the '189 Publication discloses phospholipid and cholesterol concentration ranges that overlap with those recited in claim 1 of the '069 patent. Pet. 38–39 (citing Ex. 1008 ¶ 119). In addition, Petitioner points to an exemplary nucleic acid-lipid particle formulation disclosed by the '618 patent, which patent is incorporated by reference, or directly referenced, respectively, by the '196 PCT and '189 Publication, that includes both phospholipid and cholesterol fractions, in proportions consistent with Petitioner's interpretation of the prior art. *Id.* at 38.

Patent Owner's remaining arguments, concerning the potential infiltration of hindsight bias into Petitioner's reasoning, the sufficiency of Petitioner's rationale for selecting the claimed composition from the prior art ranges, and existence of evidence of unexpected results and objective indicia of nonobviousness (Prelim. Resp. 19–48) are more significant. At this stage in the proceeding, however, on the limited record before us, we determine that Petitioner has carried its burden to show a reasonable likelihood of success in establishing the unpatentability of claim 1 based on the '196 PCT and the '189 Publication.

It has long been "recognized that 'where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'" *DuPont*, 904 F.3d at 1006 (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)). Accordingly, "[a] *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior

art." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). Applying these principles in the context of an *inter partes* review, our reviewing court has explained that

> "where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence" of teaching away, unexpected results or criticality, or other pertinent objective indicia indicating that the overlapping range would not have been obvious in light of that prior art.

DuPont, 904 F.3d at 1008 (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013)). The burden of persuasion, however, remains always with the Petitioner. *See id.* at 1007 ("The factfinder then assesses that evidence, along with all other evidence of record, to determine whether a patent challenger has carried its burden of persuasion to prove that the claimed range was obvious.").

Applying this framework, we are satisfied that the disclosure in the prior art of overlapping ranges to the claimed invention shows a reasonable likelihood that Petitioner will prevail in establishing that at least claim 1 of the '069 patent would have been obvious to one of skill in the art. Claim 1 recites a composition with particular components in ranges of mole percent of the total amount of lipid content. Such ranges for the various lipid components are akin to the ranges of the components of the compound at issue in *Peterson*. *See* 315 F.3d at 1329. Although we recognize, as Patent Owner underscores, that the formulation of nucleic acid-lipid particles is a complex endeavor (*see* Prelim. Resp. 26–29), we nevertheless agree with Petitioner, on this record and in view of the high level of ordinary skill in the art, that optimization of the ranges of components to achieve the claimed

composition would be the "normal desire of scientists or artisans to improve upon what is already generally known." Pet. 33 (quoting *Peterson*, 315 F.3d at 1330). We likewise credit Dr. Janoff's presently unrebutted testimony that, for artisans of ordinary skill, "determining the optimal proportion of cationic lipid for a given lipid combination would be a simple matter of varying the proportion using prior art methodologies." Ex. 1008 ¶ 112; *see also* Pet. 33 (stating the same).[11]

Patent Owner's reliance on declarations prepared for, depositions taken in, and other evidence at issue in the '739 IPR does not persuade us otherwise. *See* Prelim. Resp. 26–29. To the contrary, Patent Owner's cherry picking of select portions of the record from the '739 IPR for consideration here highlights the need to evaluate Petitioner's unpatentability challenges, and Patent Owner's response to those challenges, based on a complete record developed at trial in this proceeding. Affording both parties the opportunity to more fully develop the record here, including, for example, through the submission of expert testimony by Patent Owner specific to the claims of the '069 patent (rather than those of the '435 patent), will, in this case, better allow us to apply the framework for evaluating the patentability of range claims as set forth by our reviewing court. *See DuPont*, 904 F.3d at 1007, 1008.

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[11] Although neither Petitioner nor Dr. Janoff uses the exact phrase "routine optimization," the above quotations obviate Patent Owner's concern that "Petitioner never asserts that formulating nucleic acid-lipid particles as claimed would have been a matter of routine optimization" (Prelim. Resp. 25).

The same holds true regarding Patent Owner's arguments concerning unexpected results and objective indicia of nonobviousness (*see* Prelim. Resp. 32–49). Such evidence, when present, must always be considered in determining obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983). Here, however, Petitioner has not yet had an opportunity to respond to that evidence as applied to the challenged claims of the '069 patent in this proceeding. Thus, Patent Owner's evidence is better evaluated in the context of a completed trial where the record has been fully developed.

Based on the foregoing, we conclude that Petitioner has established a reasonable likelihood that it would prevail on its assertion that claim 1 of the '069 patent is unpatentable based on each of the '196 PCT and the '189 Publication. Our decision to institute trial in view of the analytical framework applicable to the range claims at issue here, and based on the limited record before us should not be misunderstood, however, as shifting the burden of persuasion to Patent Owner for the remainder of this case. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–76 (Fed. Cir. 2016). Rather, although we recognize that prior art teaching an overlapping range may result in a "presumption of obviousness" as to that range, the ultimate burden of persuasion concerning the motivation to formulate a composition including the recited lipid components within the ranges claimed, and the obviousness of the challenged claims in view of evidence of unexpected results and objective indicia of obviousness remains with Petitioner. *DuPont*, 904 F.3d at 1007–1008 ("Importantly, the language employed in our overlapping range cases does not shift the burden of

persuasion to the patentee to prove nonobviousness by, for example, pointing to evidence of criticality or unexpected results.").

E. Obviousness Based on '196 PCT or '189 Publication with Lin and Ahmad

Petitioner contends that claims 1–22 of the '069 patent are rendered obvious by the combined teachings of the '196 PCT, Lin, and Ahmad, as well by the combined teachings of the '189 Publication, Lin, and Ahmad. Pet. 49–53. To support its contentions, Petitioner cites to Dr. Janoff's declaration testimony (Ex. 1008).

Patent Owner responds that the Petition "fails to establish that one would have been motivated to combine the disclosures of the '196 PCT or the '189 publication with those of Lin/Ahmad, or that there would have been any reasonable expectation of success in doing so." Prelim. Resp. 29.

1. Overview of Lin

Lin describes three-dimensional laser scanning confocal microscopy studies of cationic liposome-DNA ("CL-DNA") complexes to study how to enhance transfection efficiencies ("TE"). Ex. 1006, Abstract. From these studies, Lin draws the following conclusions concerning the transfection efficiencies of CL-DNA complexes for both lamellar L_{α}^{C} and inverted hexagonal H_{II}^{C} nanostructures.

> We have identified the membrane charge density of the CL-vector (i.e., the average charge per unit area of the membrane, σ_M) as a key universal parameter that governs the transfection efficiency (TE) behavior of L_{α}^{C} complexes in cells. In contrast of L_{α}^{C} complexes, H_{II}^{C} complexes exhibit no dependence on σ_M (Fig. 4 *D*). This demonstrates a structural basis (L_{α}^{C} versus $H_{I\ I}^{C}$) for the dependence of transfection

efficiency on a physical-chemical parameter (σ_M) of CL-DNA complexes. The importance of the nanostructure of CL-DNA complexes to transfection mechanisms is further underscored in confocal microscopy images showing distinct pathways and interactions with cells for H_{II}^C and L_α^C complexes and also for L_α^C complexes with low and high σ_M.

The claim that σ_M is a universal parameter for TE results from the observation that while TE magnitudes for univalent versus multivalent cationic lipids are different at the same values of the mole fraction of the neutral lipid (Fig. 4 *A*), the magnitudes are equal (within the experimental error bars), when the comparison is made at the same value of σ_M (Fig. 4 *B*). Previous work by others has typically focused on optimizing transfection efficiency as a function of increasing cationic lipid-to-DNA charge ratio. What is remarkable about what we report in this article is that all transfection efficiency measurements were done with 2 μg of plasmid DNA at a constant cationic-to-anionic charge ratio of 2.8 (chosen as it corresponded to the middle of a typical plateau region observed for optimal transfection conditions as a function of increasing cationic-to-anionic charge ratio above the isoelectric point of the complex). Thus, the nearly four orders-of-magnitude increase observed in the universal transfection curve (Fig. 4 *B*) occurs under the condition where each data point contains the same amount of cationic charge form cationic lipid and anionic charge from DNA, and the variation in σ_M is achieved simply by varying the amount of neutral lipid.

The universal TE curve for L_α^C complexes reveals a critical membrane charge density (σ^*_M) where L_α^C complexes with $\sigma_M > \sigma^*_M$ achieve high TE competitive with H_{II}^C complexes. Thus, for example, to produce a high TE of L_α^C complexes with large mole fractions of the neutral lipid requires that use of multivalent cationic lipid such as DOSPA to ensure that $\sigma_M > \sigma^*_M$. Previous to what we report here, it was thought that one could not make a high TE L_α^C complex with such large mole fractions of DOPC. In principle, extremely large mole fractions of neutral helper lipid

> may be incorporated within an L_{α}^{C} complex with the retention of high TE if the condition of $\sigma_M > \sigma^*_M$ is satisfied with the use of the appropriate multivalent cationic lipid. Recent work has shown such behavior with high TE L_{α}^{C} complexes with .80 mol fraction of DOPC and 0.20 mol fraction of a new multivalent cationic lipid, MVL5.
>
> Before what we describe in our article, it was assumed that inverted hexagonal H_{II}^{C} complexes always transfect much more efficiently than lamellar L_{α}^{C} complexes. Our work has led us to redesigned L_{α}^{C} complexes, which easily compete with the high TE of H_{II}^{C} complexes, even in the presence of large mole fractions of order 0.70 DOPC (Fig. 4 *A*, DOSPA/DOPC complexes). . . .

Id. at 3314–15.

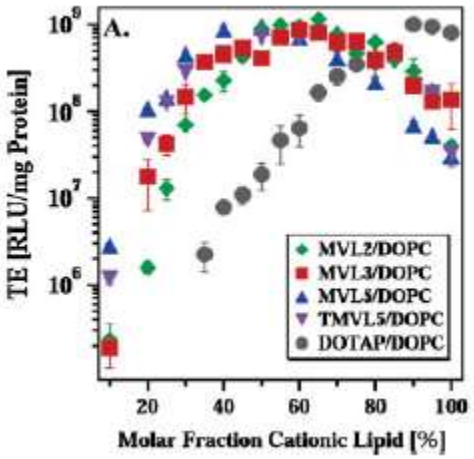
2. Overview of Ahmad

Ahmad also studied transfection efficiencies with differing membrane charge densities of CL-DNA complexes finding a universal, bell-shaped curve. Ex. 1007, 739. Ahmad found that "[t]his bell-shaped curve leads to the identification of three distinct regimes, related to interactions between complexes and cells: at low σ_M, TE increases with increasing in σ_M; at intermediate in σ_M , TE exhibits saturated behavior; and unexpectedly, at high in σ_M, TE decreases with increasing in σ_M." *Id*. Ahmad found that the intermediate, optimal regime "reflects a compromise between the opposing demands on σ_M for endosomal escape and dissociation in the cytosol." *Id*.

In studying transfection efficiency as a function of lipid composition, Ahmad transfected mouse fibroblast cells at various MVL/DOPC ratios and included data for the monovalent lipid DOTAP mixed with DOPC, a reference system. Ex. 1007, 743. As in Lin discussed above, Ahmad

prepared the complexes at a fixed lipid/DNA charge ratio of 2.8, which Lin found to be the optimum charge ratio for DOTAP/DOPC complexes. *Id*.

Figure 3A depicted below plots the TE data as a function of the molar fraction of cationic lipid.



In interpreting Figure 3A shown above, Ahmad finds that

> [f]or all cationic lipids, a maximum in TE as a function of lipid composition is observed: at 65 mol% for MVL2, 70 mol% for MVL3, 50 mol% for MVL5, 55 mol% for TMVL5, and 90 mol% for DOTAP. The optimal molar ratio results in a TE that is over two decades higher than that of the lowest transfecting complexes in these systems, and each data set fits a skewed bell-shaped curve.

Ex. 1007, 743.

In comparing the membrane charge density to a varying lipid/DNA charge ratio, as the lipid/DNA charge ratio is increased above 1, a maximum in transfection efficiency defining the optimal membrane charge density emerges, and a bell curve of efficiency is observed with the optimal membrane charge density shifting to higher values with increasing lipid/DNA charge ratio. Ex. 1007, 743. Referring to Figure 5C, Ahmad

found that the maximum TE does not change appreciably with the lipid/DNA charge ratio. *Id*. Therefore, Ahmad concludes that

> A relatively low lipid/DNA charge ratio, therefore, can be considered optimal since it allows for achievement of maximum TE with the least amount of cationic lipid. This is due to the unexpected increase of σ*m against with ρchg. Minimizing the amount of cationic lipid is desirable to reduce cost as well as potential toxic effects of the cationic lipid. In addition, achieving a given σM with fewer, more highly charged molecules should mean a smaller metabolic effort for the elimination of the lipids from the cell. This reasoning would favor multivalent over monovalent lipids. In this context, it is important to note that with the amounts of cationic lipid employed in our in vitro experiments, we find no toxic effects on the cells as judged by cell morphology and the amount of total cellular protein.

Id. at 745–46.

3. Analysis

Petitioner states that to the extent that the disclosures in the '196 PCT and the '189 Publication alone are determined not to disclose a proportion of cationic lipid required by the claims, a person of ordinary skill would have understood from Lin and/or Ahmad that such proportions of cationic lipid (above 50%) may increase transfection efficacies with the system disclosed in the '196 PCT and the '189 Publication. Pet. 49–52 (citing Ex. 1008 ¶¶ 104–105, 145–148; Ex. 1006, 3307, Fig. 4(a); Ex. 1007, 739–740, 747, Fig. 3(a)). Petitioner asserts that one of skill in the art would have been motivated to combine the teachings of the four references to arrive at the claimed invention with a reasonable expectation of success because both the Lin and Ahmad systems tested helper lipids and cationic lipids to create carrier particles for nucleic acids that are the same general carrier particles

described in the '196 PCT and the '189 Publication and such a person would have been aware that the lipid proportions used could impact transfection efficiency. Pet. 52–53 (citing Ex. 1008 ¶¶ 104, 148).

Patent Owner responds that the lipoplexes of Lin and Ahmad differ fundamentally from the nucleic acid-lipid particles described in the '196 PCT and '189 Publication, and thus, an ordinarily skilled artisan would neither have sought to combine the cited references, nor have had a reasonable expectation of success in any such combination. Prelim. Resp. 29–30. Patent Owner additionally asserts that the "central point of Lin and Ahmad was to ***reduce*** cationic lipid (and the corresponding metabolic burden/toxicity) through use of multivalent lipids (MVLs)—that is, lipids that have more positive charge per individual molecule." *Id.* at 31. According to Patent Owner, "Lin and Ahmad actually undermine Petitioner's obviousness assertion." *Id.* Patent Owner also relies on the arguments concerning unexpected results and objective indicia of nonobviousness discussed above. *Id.* at 32–49.

We have considered the parties' arguments and evidence presented as to this ground. For the reasons set forth in Part II.D.3., above, we institute *inter partes* review based on each of the '196 PCT and the '189 Publication alone. Accordingly, because we determine that Petitioner has shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable based on Ground 1, we institute trial as to all claims and all grounds presented in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018). To the extent necessary, we will address this separate obviousness ground relying upon the additional teachings of Lin

and Ahmad in our final written decision after development of a full record during trial.

F. Anticipation or Obviousness Based on '554 Publication

Petitioner asserts that claims 1–22 of the '069 patent are anticipated or rendered obvious by the '554 Publication. Pet. 54–67. To support its contentions, Petitioner cites to Dr. Janoff's declaration testimony (Ex. 1008).

Patent Owner disagrees, relying on arguments mirroring those discussed above with regard to Ground 1. Prelim. Resp. 17–49.

1. Overview of '554 Publication

The '554 Publication discloses "novel cationic lipids, microparticles and transfection agents that effectively transfect or deliver biologically active molecules," including "short interfering nucleic acid" and "siRNA," to "relevant cells and/or tissues, such as in a subject or organism." Ex. 1005 ¶ 2. Similar to the '196 PCT and '189 Publication discussed above, the '554 Publication discloses lipid nanoparticle formulations in which the lipid component includes cationic lipid, neutral lipid, and PEG. *Id.* ¶ 313. The '554 patent further discloses that the various lipid components may be present in the following proportions:

> The cationic lipid component can comprise from about 2% to about 60%, . . . or from about 40% to about 50% of the total lipid present in the formulation. The neutral lipid component can comprise from about 5% to about 90%, or from about 20% to about 85% of the total lipid present in the formulation. The PEG-DAG conjugate can comprise from about 1% to about 20%, or from about 4% to about 15% of the total lipid present in the formulation. The cholesterol component can comprise from

> about 10% to about 60%, or from about 20% to about 45% of the total lipid present in the formulation.

Id. With regard to the neutral lipid component, the '554 Publication further explains that "[b]y 'neutral lipid' as used herein is meant any lipophilic compound having non-cationic cha[r]ge (e.g., anionic or neutral charge)." *Id.* ¶ 315.

The '554 Publication exemplifies several lipid nanoparticle formulations including cationic lipid, cholesterol, phospholipid, and PEG. For example, Formulation L054 includes the cationic lipid DMOBA, cholesterol, the phospholipid DSPC, and the PEG PEG-n-DMG present in a molar ratio of 50/20/28/2. Ex. 1005, Table 4.

2. Analysis

Because of the similarities between the '196 PCT and '189 Publication on the one hand, and the '554 Publication on the other, Petitioner's unpatentability arguments based on the '554 Publication closely mirror those discussed above in Ground 1. *Compare* Pet. 31–49 *with id.* at 54–67. Akin to its showing in Ground 1, Petitioner explains how the lipid nanoparticle formulations of the '554 Publication read on the claimed nucleic acid-lipid particles, and, of particular relevance here, identifies the proportions of total lipid in those particles attributable to cationic lipid, neutral lipid (including cholesterol), and PEG. Pet. 54–67. Relying on the ranges disclosed for each identified lipid component, Petitioner calculates that, in a scenario where cationic lipid is present in an amount at the high end of the range disclosed by the '554 Publication, the '554 Publication

teaches that the various lipid components are present in the ranges set forth in the table from the Petition reproduced below.

	Cationic Lipid	Cholesterol	Phospholipid	PEG
'069 claims	50-65%	30-40%	4-10%	0.5-2%
'554 publication	60%	20-40%	0-19%	1-20%

Id. at 58. According to Petitioner, and as illustrated by the above table, under the scenario set forth in the Petition, the '554 Publication teaches overlapping ranges for each lipid component of the nucleic acid-lipid particle recited in claim 1 of the '069 patent. *Id.*

Based on our review of the current record, we agree with Petitioner's characterization of the teachings of the '554 Publication, and the knowledge in the art, as well as Petitioner's assertions as to the reasonable inferences an ordinary artisan would have made from those references.

As with Petitioner's unpatentability assertions, Patent Owner's responsive arguments are similar to those discussed in Part II.D.3., above. Specific to this Ground, Patent Owner asserts that "the petition does not even cite to anything in the '554 publication as teaching or suggesting concentration ranges for phospholipids." Prelim. Resp. 19. We do not find this argument persuasive. As an initial matter, in describing the '554 Publication, the Petition expressly points to Formulation L054, which includes the cationic lipid DMOBA, cholesterol, the phospholipid DSPC, and the PEG PEG-n-DMG in a molar ratio of 50/20/28/2. *See* Pet. 27 (citing Ex. 1005, Table 4 (formulation L054)). Furthermore, as indicated by the definition of "neutral lipid" in the '554 Publication, and evidenced by the

phospholipid-including examples set forth in Table 4, an ordinarily skilled artisan would have recognized that the neutral lipid fraction of the disclosed lipid nanoparticles may include phospholipid. Ex. 1005 ¶ 315 (defining "neutral lipid" as "any lipophilic compound having non-cationic cha[r]ge (e.g., anionic or neutral charge)."), Table 4 (identifying numerous examples including phospholipid and cholesterol as neutral lipids); *see also* Pet. 57–58 (citing Ex. 1005 ¶¶ 313, 315, 455, Table 4; Ex. 1008 ¶¶ 157–158).

Applying the framework for analyzing range claims set forth in our discussion of Ground 1, we are satisfied that the disclosure in the '554 Publication of the overlapping ranges to the claimed invention shows a reasonable likelihood that Petitioner would prevail in establishing that at least claim 1 of the '069 patent would have been obvious to one of skill in the art. For the reasons previously discussed, in light of the allocation of the burdens of production and persuasion in range cases, we determine that Patent Owner's remaining arguments are best addressed after development of a full record during trial.

Accordingly, based on the foregoing, we conclude that Petitioner has established a reasonable likelihood that it will prevail on its assertion that claim 1 of the '069 patent is unpatentable based on the '554 Publication. We reiterate our prior admonishment, however, that the ultimate burden of persuasion remains with Petitioner.

III. CONCLUSION

For the foregoing reasons, we determine that the Petition and evidence in this record at this stage establish that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. We therefore grant the Petition and institute trial as to all challenged claims on all grounds stated in the Petition. At this juncture, we have not made a final determination with respect to the patentability of the challenged claims, nor with respect to claim construction.

IV. ORDER

Accordingly, it is hereby:

ORDERED that *inter partes* review of claims 1–22 of the '069 patent is instituted on all grounds in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial will commence on the entry date of this decision.

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