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Paper 40
Entered: July 23, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

ARBUTUS BIOPHARMA CORPORATION,
Patent Owner.

IPR2019-00554
Patent 8,058,069 B2

Before TINA E. HULSE, CHRISTOPHER G. PAULRAJ, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

PAULRAJ, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision - *35 U.S.C. § 318(a)*
Determining No Challenged Claims Unpatentable
Denying Patent Owner's Motion to Strike
Denying Patent Owner's Motion to Exclude

I. INTRODUCTION

A. Background and Summary

This is a Final Written Decision entered pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

On January 9, 2019, Moderna Therapeutics, Inc., ("Petitioner") filed a Petition requesting institution of an *inter partes* review of claims 1–22 of U.S. Patent No. 8,058,069 B2 ("the '069 patent," Ex. 1001). Paper 1 ("Pet."). Arbutus Biopharma Co. ("Patent Owner") timely filed a Preliminary Response (Paper 7, "Prelim. Resp."). In our Institution Decision, we determined that there was a reasonable likelihood that Petitioner would prevail with respect to at least one challenged claim and, accordingly, instituted an *inter partes* review pursuant to 35 U.S.C. § 314 based on all grounds presented in the Petition. Paper 8 ("Inst. Dec."). Following institution, Patent Owner filed its post-institution Patent Owner Response (Paper 15, "PO Resp."), Petitioner filed its Reply to Patent Owner's Response (Paper 21, "Pet. Reply"), and Patent Owner filed its Sur-Reply (Paper 30, "Sur-Reply"). No motion to amend was filed in this proceeding. An oral hearing was held on April 22, 2020, and a transcript of that hearing has been entered into the record. Paper 39 ("Tr.").

For the reasons set forth below, having considered all the evidence and arguments set forth by the parties, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–22 of the '069 patent are unpatentable under 35 U.S.C. § 103. We also deny Patent Owner's Motion to Strike Petitioner's Reply (Paper 28) and Patent Owner's Motion to Exclude certain evidence (Paper 31).

B. Related Proceedings

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. *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, code (63).

C. The '069 Patent (Ex. 1001)

The '069 patent relates to lipid formulations for nucleic acid delivery and, in particular, "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. These nucleic-acid lipid particles may be used to deliver nucleic acids to cells for therapeutic techniques such as RNA interference (RNAi). *Id.* at 1:28–40. 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 [SNALPs] that advantageously impart increased activity of the encapsulated nucleic acid (e.g., an interfering

[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.

> 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, 6:6–15. 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 68:39–43. 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).

D. 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.

E. Asserted Grounds of Unpatentability

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

Claims Challenged	35 U.S.C.[2]	Reference(s)/Basis
1–22	§§ 102, 103	'196 PCT,[3] '189 Publication[4]
1–22	§ 103	'196 PCT, '189 Publication, Lin,[5] Ahmad[6]
1–22	§§ 102, 103	'554 Publication[7]

Petitioner relies upon the Declaration of Dr. Andrew S. Janoff, Ph.D., (Ex. 1008) in support of its Petition and the Declaration of Thomas J. Anchordoquy, Ph.D., (Ex. 1020) in support of its Reply.[8] Patent Owner relies upon the Declaration of David H. Thompson, Ph.D., (Ex. 2031) in support of its Patent Owner Response.

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[2] The Leahy-Smith America Invents Act ("AIA") included revisions to 35 U.S.C. §§ 102 and 103 that became effective on March 16, 2013. Because the '069 patent issued from an application filed before March 16, 2013, we apply the pre-AIA version of the statutory bases for unpatentability.

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

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

[5] 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.

[6] 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.

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

[8] Dr. Janoff unfortunately passed away on December 19, 2019 and Dr. Anchordoquy stepped in as Petitioner's declarant. Paper 25, 2.

II. ANALYSIS

A. Level of Skill in the Art

Petitioner, relying upon the testimony of Dr. Janoff, contends that a person of ordinary skill in the art ("skilled artisan" or "POSA") for the '069 patent "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). In his Reply Declaration, Dr. Anchordoquy agrees with the level of skill in the art that was previously set forth by Dr. Janoff. Ex. 1020 ¶ 25.

In its Preliminary Response, Patent Owner noted in a footnote that "[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. Patent Owner does not address the level of skill in the art in its post-institution Response. But Patent Owner's expert, Dr. Thompson, applies the definition of a person of ordinary skill in the art adopted by the Board in IPR2018-00739 as to the related '435 patent. Ex. 2031 ¶¶ 28–29. That definition is consistent with the level of skill proposed by Petitioner and its experts.

In our Institution Decision, we adopted Dr. Janoff's definition of the POSA because Dr. Janoff testified 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 because he explained 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; Inst. Dec. 11–13. We determine that this level of ordinary skill in the art is consistent with the evidence of the record, including the level of skill reflected in the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). We continue to apply that same skill level in our analysis for this Final Written Decision. We further find that the parties' experts are qualified to provide opinions about the '069 patent from the perspective of the POSA.

B. 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. *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, 51,340, 51,358 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018) (now codified at 37 C.F.R. § 42.100(b) (2019)).

Petitioner proposed a construction for "nucleic acid-lipid particle." Pet. 23. Patent Owner contends that no claim construction is necessary, but also disputes Petitioner's proffered construction of "nucleic acid-lipid particle." PO Resp. 9–10. We determine that it is not necessary to construe any claim terms 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)).

C. Overview of the Prior Art

Petitioner relies primarily upon the following prior art teachings in its challenge.

1. The '196 PCT (Ex. 1003)

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 the same components). In describing how embodiments are made, the '196 PCT also states that preferred embodiments are charge neutralized. *Id*. ¶ 14.

The '196 PCT further provides detailed descriptions of the components of SNALPs. *See* Ex. 1003 ¶¶ 86–107. Concerning the preferred makeup of the disclosed SNALPs, the '196 PCT states the following about the amount of cationic lipid included as part of the particle:

> 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.

Id. ¶ 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." *Id.* ¶ 91.

With regard to 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. The '189 Publication (Ex. 1004)

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 the content of the SNALP).

The '189 Publication describes embodiments wherein the siRNA is fully encapsulated in the nucleic acid-lipid particle. *Id*. ¶ 14. In particular, the '189 Publication discloses, as an example, the "2:40 formulation" that "was prepared using a Direct Dilution process" and discusses the formulations efficacy during tests. *Id.* ¶¶ 351–391. The formulation comprises 10% molar distearoylphosphatidylcholine (DSPC) (a non-cationic phospholipid), 48% molar cholesterol, 2% PEG-CDMA (a conjugated lipid), and 40% 1,2-DiLinoleyloxy-N, N-dimethylaminopropane (DLinDMA) (a cationic lipid). *Id*. ¶ 351.

3. Lin (Ex. 1006)

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 TE 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_{II}^{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^C_α complex with such large mole fractions of DOPC. In principle, extremely large mole fractions of neutral helper lipid may be incorporated within an L^C_α 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^C_α 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^C_{II} complexes always transfect much more efficiently than lamellar L^C_α complexes. Our work has led us to redesigned L^C_α complexes, which easily compete with the high TE of H^C_{II} complexes, even in the presence of large mole fractions of order 0.70 DOPC (Fig. 4 *A*, DOSPA/DOPC complexes).

Id. at 3314–15.

4. Ahmad (Ex. 1007)

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 TE 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. *Id.* at 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 of Ahmad is depicted below.

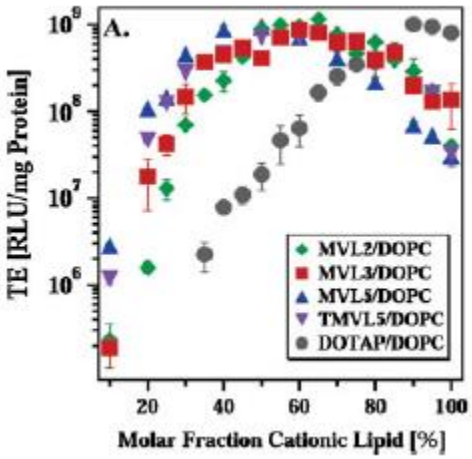

Figure 3A, above, plots the TE data as a function of the molar fraction of cationic lipid. In interpreting Figure 3A shown above, Ahmad finds that

> [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.

Id.

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. *Id.* 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* with ρ_{chg}. 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 σ_M 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.

5. The '554 Publication (Ex. 1005)

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. The '554 Publication 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 '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.* ¶ 14. 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.* In response to this, the '554 Publication states that:

> The present application compounds, composition and method 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 examples of serum-stable formulations, e.g., the "L053" and "L054" formulations, as follows:

> In one embodiment, the invention features a serum-stable formulated molecular composition comprising a biologically active molecule (e.g., a [short interfering nucleic acid (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. Table IV, a portion of which is reproduced below, identifies various lipid nanoparticle formulations, including the applicable compositions and molar ratios for such formulations.

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 (partial). The partially reproduced table above identifies the applicable compositions and molar ratios for the L051, L053, and L053 formulations, which are four-component particles containing a cationic lipid, a phospholipid, cholesterol, and a conjugated lipid. The L051 formulation has a composition of CLinDMA/DSPC/Chol/PEG-n-DMG at a molar ratio of 48/40/10/2. The L053 and L054 formulations both have a composition of DMOBA/DSPC/Chol/PEG-n-DMG at molar ratios of 30/20/48/2 and 50/20/28/2 respectively.

D. Patentability Analysis

1. Legal Standards

a. Anticipation

"For a claim to be anticipated, each claim element must be disclosed, either expressly or inherently, in a single prior art reference, and the claimed arrangement or combination of those elements must also be disclosed, either expressly or inherently, in that same prior art reference." *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332–33 (Fed. Cir. 2010). "Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983). The requirement that the prior art elements themselves be "arranged as in the claim" means that claims cannot be "treated . . . as mere catalogs of separate parts, in disregard of the part-to-part relationships set forth in the claims and that

give the claims their meaning." *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1459 (Fed. Cir. 1984). "[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).

"[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). "The concept of 'inherent disclosure' does not alter the requirement that all elements must be disclosed in an anticipatory reference in the same way as they are arranged or combined in the claim." *Therasense*, 593 F.3d at 1332.

The disclosure of a broader range for a genus in the prior art does not necessarily anticipate a narrower claimed range for a particular species. "If the prior art discloses its own range, rather than a specific point, then the prior art is only anticipatory if it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over the ranges." *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015); s*ee Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 998–1000 (Fed. Cir. 2006) (determining that prior art's disclosure of a 100 to 500 °C temperature range and a 0.001 to 1.0 percent molar ratio range did not constitute a "specific disclosure" of claims requiring a temperature range of 330 to 450

°C and a molar ratio range of 0.1 to 5.0 percent). In some instances, an overlapping range disclosed in the prior art may be sufficient to anticipate a claim when the narrower claimed range is not shown to be "critical" to the invention, i.e., that the invention would not operate differently across the broader range disclosed in the prior art. *Ineos*, 783 F.3d at 869–871; *see also ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012).

b. Obviousness

A patent claim is unpatentable under 35 U.S.C. § 103 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). In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), the Supreme Court set out a framework for assessing obviousness under § 103 that requires consideration of four factors: (1) the "level of ordinary skill in the pertinent art," (2) the "scope and content of the prior art," (3) the "differences between the prior art and the claims at issue," and (4) "secondary considerations" of nonobviousness such as "commercial success, long felt but unsolved needs, failure of others, etc." *Id.* at 17–18; *KSR*, 550 U.S. at 407.

"A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art," and "such overlap creates a presumption of obviousness." *E.I. Dupont De Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) ("*Dupont*") (citing *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003)). The *Dupont* court recognized four different ways by which this presumption may be rebutted. "First, a modification of a process parameter may be patentable if it 'produce[s] a new and unexpected result which is different in kind and not merely in degree from the results of the prior

art.'" *Id.* (citing *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)). "Second, and relatedly, a patentee may rebut the presumption of obviousness by showing that the prior art taught away from the claimed range." *Id.* (citing *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006)). "Third, a change to a parameter may be patentable if the parameter was not recognized as 'result-effective.'" *Id.* (citing *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012)). "Fourth, [the] disclosure of very broad ranges may not invite routine optimization." *Id.* (citing *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011)).

"The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of . . . ranges is the optimum combination." *Peterson*, 315 F.3d at 1330. "[W]here 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." *Aller*, 220 F.2d at 456. However, the parameter to be optimized must have been recognized by those skilled in the art to be a "result-effective variable." *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). "While the absence of any disclosure regarding the relationship between the variable and the affected property may preclude a finding that the variable is result-effective, the prior art need not provide the exact method of optimization for the variable to be result-effective." *Applied Materials, Inc.*, 692 F.3d at 1297. Rather, "[a] recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective." *Id.* Moreover, where multiple result-effective variables are combined, "[e]vidence that the variables interacted in an unpredictable or unexpected way could render the combination nonobvious." *Id.* at 1298 (citing *KSR*, 550 U.S. at 421).

2. Ground 1: Anticipation or Obviousness in View of the '196 PCT or the '189 Publication

Under Ground 1, Petitioner contends that claims 1–22 are anticipated or rendered obvious by each of the '196 PCT and the '189 Publication. Pet. 31–49. As it is dispositive to our conclusions here, we focus our analysis on independent claim 1. We address both the anticipation and obviousness challenges together below.

As discussed above, the '196 PCT and '189 Publication each generally disclose nucleic acid-lipid particles containing a cationic lipid component within a broad range of 2–60% of the total lipid present in the particle. Ex. 1003 ¶ 88; Ex. 1004 ¶ 9. The references disclose that a non-cationic lipid component is present within a broad range of 5–90% of the total lipid present. Ex. 1003 ¶ 91; Ex. 1004 ¶¶ 10, 152. The '196 PCT also discloses a bilayer stabilizing component, which may be a conjugated lipid, with the broadest range of 0.5–50%, and the '189 Publication more particularly discloses a PEG-lipid conjugate within a range of 0.5–20%. Ex. 1003 ¶ 22; Ex. 1004 ¶¶ 11, 152. Each of these references also discloses examples of non-cationic lipids that include phospholipids and cholesterol. Ex. 1003 ¶ 89; Ex. 1004 ¶ 159. And the references disclose that, if cholesterol is included as a non-cationic lipid, it may be present within a broad range of about 10–60% of the total lipid present. Ex. 1003 ¶ 91; Ex. 1004 ¶¶ 12, 152.

Petitioner does not point to any express disclosure of a phospholipid range in either the '196 PCT or the '189 Publication. Petitioner, however, contends that "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%," and "[t]he 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(e)), namely 0%-19.5%." Pet. 39. Petitioner contends that "[g]iven the

breadth of the claimed ranges for the phospholipid and cholesterol, these disclosures are sufficiently specific to anticipate the claimed ranges." *Id.* Petitioner also contends that "[g]iven the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious." *Id.* Petitioner contends that the overlapping ranges creates a presumption of obviousness under *Dupont*. *Id.* at 32. Petitioner summarizes a scenario in which the claimed ranges overlap the prior art ranges in the following table:

	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. at 39. Petitioner's table above identifies the claimed ranges for each lipid component and the amounts or ranges in the prior art disclosures that Petitioner contends overlaps the claimed ranges.

We have considered the arguments and evidence presented and determine that Petitioner has not met its burden with respect to its Ground 1 challenges. In particular, we determine that the teachings of the '196 PCT and '189 Publication do not anticipate or otherwise render obvious a nucleic acid-lipid particle containing each of the recited lipid components within the claimed ranges, including specifically a phospholipid range of 4–10%.[9]

[9] The Board reached a similar conclusion with respect to a dependent claim requiring a phospholipid range of 3–15% for the related '435 patent that was challenged in the '739 IPR. *See* IPR2018-00739, Paper 51 at 30–32, 35–37. Although the challenged claims of the '069 patent are different from those considered by the Board in the '739 IPR—insofar as the claims here require *both* phospholipid and cholesterol and recite a slightly narrower phospholipid range—Petitioner's basic argument as to why the prior art satisfies the phospholipid range requirement is the same. We reach our conclusions here based on the evidence and arguments presented in this proceeding.

As to the anticipation challenge under this Ground, there is no dispute that neither the '196 PCT nor the '189 Publication recites any range specifically for a phospholipid component that falls within or overlaps the claimed 4–10% range. Petitioner also does not rely upon an inherent anticipation theory to argue that the phospholipid range is necessarily satisfied by the prior art disclosures. Nonetheless, Petitioner contends that a POSA would have understood that the claimed phospholipid range is satisfied because the references disclose a broader range of 5–90% for non-cationic/neutral lipids and identify phospholipids as one of the disclosed species of non-cationic/neutral lipids. Pet. Reply 5. We are unpersuaded by this contention.

Here, the 5–90% range for non-cationic lipids generally disclosed in the '196 PCT and '189 Publication is considerably broader than the 4–10% range claimed specifically for phospholipids. Moreover, the references each disclose more preferred ranges for the non-cationic lipids that do not overlap with the claimed phospholipid range. Ex. 1003 ¶ 91 (disclosing a preferred range of 20–85% for the non-cationic lipid); Ex. 1004 ¶ 152 (disclosing more preferred amounts of 10–85%, 20–80%, 30–70%, 40–60%, and 48% for the non-cationic lipid). Petitioner does not contend that the amount of phospholipid would not be considered "critical" to the claimed invention such that the broader prior art range may nonetheless anticipate the narrower claimed range. *See Ineos*, 783 F.3d at 869. To the contrary, Petitioner acknowledges that having too much phospholipid "will inhibit release of the payload upon contact with the endosome." Pet. Reply 21–22. As discussed further below in addressing Petitioner's optimization arguments, the evidence of record does not suggest the claimed nucleic acid-lipid particle would operate in the same manner if the phospholipid amount was adjusted

across the entirety of the 5–90% range disclosed in the '196 PCT and '189 Publication.[10]

As to the obviousness challenge under this Ground, we are not persuaded by Petitioner's contention that the claims are presumed *prima facie* obvious in light of the overlapping ranges disclosed in the prior art such that the burden of production shifts to Patent Owner. As stated above, neither the '196 PCT nor the '189 Publication explicitly discloses a phospholipid range. And while Petitioner derives an overlapping phospholipid range by making certain assumptions about the other lipid components of the particle, nothing in *Dupont* or any other Federal Circuit decision we are aware of suggests that a presumption of obviousness applies under the circumstances presented here, *i.e.*, when one of the claimed ranges for one of the expressly claimed sub-components of the claimed composition is not necessarily disclosed based on broader ranges for other components disclosed in the prior art.[11] To the contrary, the Federal Circuit has only applied the presumption where the overlapping range is expressly disclosed, not where an overlap might be assumed based on other motivating factors. *See Galderma Labs., L.P. v. Tolmar*, Inc., 737 F.3d 731, 738 (Fed. Cir. 2013) (noting that burden of production shifts to

[10] Although Petitioner has also pointed to the '189 Publication's disclosure of the 2:40 formulation that included 10% phospholipid, the amounts of cholesterol (48%) and cationic lipid (40%) in that formulation do not satisfy the claim requirements, and thus the 2:40 formulation cannot anticipate the claims. Ex. 1004 ¶ 351.

[11] We recognize that a prior art range that is not expressly disclosed may nonetheless be satisfied by necessary implication in some circumstances. For example, a reference that expressly discloses a four-component nucleic acid-lipid particle containing 60% cationic lipid, 20–30% cholesterol, 0.5–6% conjugated lipid, with the balance of the lipid content being phospholipid, necessarily implies an overlapping phospholipid range of 4–19.5%. But that is not the situation presented by Petitioner in this case.

patentee "where there is a range *disclosed in the prior art*, and the claimed invention falls within that range") (emphasis added); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006) ("Where a claimed range overlaps with a range *disclosed in the prior art*, there is a presumption of obviousness.") (emphasis added). We, therefore, do not find a presumption of obviousness to be appropriate in this case. As explained below, Petitioner's motivations and assumptions for choosing amounts of the various lipid components from the broadly disclosed ranges in the prior art to arrive at an overlapping phospholipid range are not necessarily well-founded. Furthermore, as also explained below, even if a presumption could apply here, it is rebutted because we find nothing in the cited evidence indicating that the amount of phospholipid in a nucleic acid-lipid particle was recognized in the prior art as a result-effective variable.

Petitioner arrives at a phospholipid range of 0–19.5% by first assuming that the skilled artisan would have selected a cationic lipid amount of 60%, cholesterol in the amount 20–40%, and PEG in the amount of 0.5–25%. Pet. 39. Petitioner, however, does not explain sufficiently why a POSA would have chosen those particular amounts of the other non-phospholipid components from the broader ranges disclosed in the references. Indeed, Petitioner's assumption of PEG in an amount up to 25% is contradictory to the maximum amount of 20% for the PEG-lipid conjugate disclosed in the '189 Publication. Ex. 1004 ¶ 152. Although Petitioner indicates that a POSA would have been motivated to maximize the cationic lipid amount in order to increase transfection efficiency, there is no persuasive reason provided as to why the amounts of the remaining lipid components (and in particular the phospholipid) would have necessarily overlapped with the claimed ranges. The '196 PCT and '189 Publication only identify phospholipid as an *optional* example of a non-cationic lipid, and we find nothing in the references that suggests that a particle with all four claimed lipid components was necessary or desirable.

Other prior art of record shows that two and three component lipid particles were known in the art. *See*, *e.g.*, Ex. 1006, 3308 (Lin describing two component particles comprising cationic lipid and phospholipid, but lacking cholesterol or a conjugated lipid); Ex. 1010, 51, Figs. 1 and 2 (Bennet describing three component lipid particles comprising cationic lipid, phospholipid, and cholesterol, but lacking a conjugated lipid); Ex. 1005, 90, Table IV ('554 Publication describing three component lipid particles comprising cationic lipid, cholesterol, and a conjugated lipid, but lacking phospholipid). Nor does Petitioner point to any suggestion in the '196 PCT or the '189 Publication that the entirety of the broadly disclosed ranges could apply if all four claimed lipid components were to be included as part of the nucleic-acid lipid particle.

In addition to the overlapping ranges argument, Petitioner argues that adjusting the amount of the various lipid components in the particle would have been a matter of "routine optimization," and identifies reasons to optimize the amounts of cationic lipid, conjugated lipid, cholesterol, and phospholipid to arrive at the claimed amounts. Pet. Reply 7–22. With respect to the phospholipid component, Petitioner contends that a POSA would have been motivated to include a phospholipid as a bilayer stabilizing component, but would have been aware that having too much phospholipid will inhibit the release of the "payload" (i.e., the nucleic acid) upon contact with the endosome of the target cell. *Id.* at 21. Because the concentrations of the different lipid components are highly interdependent, Petitioner contends that the range of phospholipid must necessarily be decreased when a higher amount of cationic lipid is used and cholesterol is added to the mix. *Id.* at 21–22. Petitioner also points to the 2:40 formulation disclosed in the '189 Publication as the starting point for optimization. *Id.* at 7–8.

We are not persuaded by Petitioner's routine optimization argument at least as applied to the claimed phospholipid range. We have considered the testimony

of Petitioner's experts and find it unpersuasive in supporting Petitioner's routine optimization argument. Dr. Janoff did not present any arguments for why the skilled artisan would have been motivated to optimize the phospholipid component in his declaration submitted with the Petition. *See generally* Ex. 1008. At his deposition, Dr. Janoff testified that the non-cationic lipid range of 13–49.5% recited in the related '435 patent represented an "immense universe"—"some phospholipids, some not"—and "in order for a person of ordinary skill in the art to find utility because of the immense range, this would require undue experimentation, not simple optimization." Ex. 2033, 59:11–60:16.

In the expert declaration submitted with Petitioner's Reply, Dr. Anchordoquy attests that "[a]s with the conjugated lipid, a [POSA] would have been aware that having some amount of phospholipid can provide structural stability to the resulting particles, but having too much will inhibit release of the payload upon contact with the endosome." Ex. 1020 ¶ 109. Dr. Anchordoquy, however, does not support this assertion with any prior art teaching (or other persuasive evidence showing) that the amount of phospholipid was known to affect structural stability or the payload release of the nucleic acid-particle. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations" at hand "may render the testimony of little probative value in a validity determination."). Rather, Dr. Anchordoquy only cites to prior art showing that stability and delivery efficiency were general considerations to be taken into account when designing a nucleic acid-lipid particle. *Id.* ¶ 107 (citing Ex. 1005 ¶ 137; Ex. 1024, 239–40). The portions of the prior art references cited by Dr. Anchordoquy above do not mention phospholipids. Dr. Anchordoquy also notes that "[e]ach prior art reference discloses four lipid component particles that are effective in vivo which contain a phospholipid" and "[t]he disclosed phospholipid range is thus not theoretical." *Id.*

¶ 108 (citing Ex. 1003 ¶ 223; Ex. 1004 ¶¶ 289, 369; Ex. 1005, Table IV). While this may be true, there is nothing in the cited portions of those references that discloses *how* the phospholipid amount affects the properties of the nucleic acid-lipid particle.

Petitioner also cites to the deposition testimony of Patent Owner's expert Dr. Thompson as an admission that it was "known to add [phospholipid] to 'stabilize [the] complex.'" Pet. Reply 21 (citing Ex. 1025, 28:8–22). Dr. Thompson's testimony, however, is more nuanced than what is suggested by Petitioner. When asked whether DSPC and DPPC (two particular types of phospholipids) were "considered potential helper lipids for delivery particles," Dr. Thompson responded as follows:

> Those two lipids were often referred to or were thought of, at the time of the '069, were viewed as a way to stabilize the complex. So helper not in the sense that that language was typically used in the literature where helper, meaning helping the cargo to escape the endosome. That's not the property that those lipids were designed to impart in the complex. DPPC and DSPC are helping in the sense that they are helping the stability of the complex during circulation. They are providing -- by our understanding, providing the kind of serum stability that allows your, the particle to reach its target.

Ex. 1025, 28:8–22. Thus, while Dr. Thompson stated that two particular phospholipids, DPPC and DSPC, "were viewed as a way to stabilize the complex," he did not state that the prior art recognized that the amount of phospholipid could be adjusted in order to impart serum stability. When pressed for other reasons people in the industry would include a phospholipid in the carrier particles, Dr. Thompson emphasized that one would need "an understanding of how all the components work together" rather than "just as a sum of a set of components." *Id.* at 29:11–30:3. And when asked to confirm that those in the industry had a "hypothesis" that phospholipids increased serum stability, Dr. Thompson noted "there were different

hypotheses of what role the components were playing," "[a]nd the measurable outcome is the result of viewing it as more than one component of the . . . formulation." *Id.* at 30:4–15. Dr. Thompson also indicated that the motivation to include a phospholipid could have been based on commercial considerations or what was readily available in the laboratory rather than any recognition in the art that it affected the stability of the particle during circulation. *Id.* at 30:16–31:5.

We thus find the testimony of the parties' experts insufficient to establish that the claimed phospholipid range in particular was a recognized result-effective variable subject to routine optimization. *See Dupont*, 904 F.3d at 1008 ("The idea behind the 'result-effective variable' analysis is . . . that a person of ordinary skill would not always be motivated to optimize a parameter 'if there is no evidence in the record that the prior art recognized that [that] particular parameter affected the result.'") (quoting *Antonie*, 559 F.2d at 620).

We have also considered, but are not persuaded by, Petitioner's argument relying upon the "2:40" formulation disclosed in the working examples as the starting point for optimization. Pet. 26; Pet. Reply 6–7. The 2:40 formulation includes 40% cationic lipid, 2% conjugated lipid, 48% cholesterol, and 10% phospholipid. Ex. 1004 ¶ 351. Petitioner does not sufficiently explain in its Petition or Reply how or why a POSA would have modified the 2:40 formulation to arrive at the claimed amounts. However, during oral argument, Petitioner's counsel argued that a POSA would have been motivated to upwardly adjust the amount of cationic lipid in order to increase transfection efficiency, maintain the amount of conjugated lipid at 2% and the amount of phospholipid at 10%, and downwardly adjust the amount of cholesterol in order to balance out the remaining lipid content. Tr. 14:9–15:25. We are not persuaded by this contention even assuming it was properly and timely presented. Although Petitioner identifies reasons to adjust each of the lipid components individually, Petitioner's optimization argument does

not take into account the interdependence of the claimed lipid components or how the adjustments would affect the nucleic acid-lipid particle as a whole. The parties are in agreement that "the concentrations of different lipid components are highly interdependent." PO Resp. 28; Pet. Reply 21.

Even if a POSA would have been primarily motivated by a desire to improve transfection efficiency by increasing the amount of cationic lipid, Petitioner does not explain why that would have prompted the POSA to maintain the same amount of conjugated lipid and phospholipid as the 2:40 formulation, while decreasing the amount of cholesterol. Indeed, if a POSA had chosen to maximize the amount of cationic lipid at 60% (the highest amount within the prior art range), maintain the amount of conjugated lipid at 2% and the phospholipid at 10%, the remaining available balance of 28% for the cholesterol component would not fall within the claimed range of 30–40%. The cited references also suggest that lower amounts of cationic lipid and higher amounts of phospholipid were acceptable. In this regard, we note that the '189 Publication also discusses a "2:30" formulation, which contained a higher amount of phospholipid (20%) and a lower amount of cationic lipid (30%) than what is required by the challenged claims. Ex. 1004 ¶ 327. The working examples demonstrated significant downregulation of the Apo-B protein using the 2:30 formulation. *See, e.g., id.* ¶ 301 (noting that treatment with a 5 mg/kg dosage using a 2:30 SNALP led to a decrease in ApoB expression as much as 88%). Petitioner does not direct us to anything in the references suggesting that the 2:40 formulation would have been considered a more appropriate starting point for optimization than the 2:30 formulation. Thus, any further adjustments to the amounts of the various lipid components in the 2:40 formulation in order to meet the claim requirements appears, on this record, to be hindsight driven.

In sum, Petitioner has not demonstrated by a preponderance of the evidence that claim 1 is anticipated by either the '196 PCT or the '189 Publication. Petitioner has also not demonstrated by a preponderance of the evidence that claim 1 is obvious based on the overlapping ranges disclosed in the '196 PCT and the '189 Publication or the 2:40 formulation disclosed in the '189 Publication.[12] Because each of dependent claims 2–22 further narrows the scope of claim 1, Petitioner has also not proven anticipation or obviousness of these dependent claims for the same reasons.

3. Ground 2: Obviousness in View of Patent Owner's Prior Disclosures and in Light of Lin and Ahmad

Under Ground 2, Petitioner asserts that claims 1–22 are obvious in view of Patent Owner's "prior disclosures" in light of Lin and Ahmad. Pet. 49–53. Petitioner relies upon the teachings of the '196 PCT and the '189 Publication, as discussed above for Ground 1, as Patent Owner's prior disclosures under this ground. Petitioner contends that:

> [t]o the extent that those disclosures alone are determined not to disclose a proportion of cationic lipid in the 50%–65% range, a [POSA] would have understood from Lin and Ahmad that such proportions of cationic lipid may increase transfection efficacy and would have been motivated to combine those disclosures with the system disclosed in the

[12] For the grounds based on obviousness, Patent Owner also contends that objective indicia, including evidence of unexpected results, long-felt need, failure of others, skepticism, and commercial success, further rebut any *prima facie* obviousness. PO Resp. 31–50. Because we have determined that Petitioner has not met its burden of showing obviousness based on the first three *Graham* factors, we need not address Patent Owner's objective indicia arguments and evidence. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("Because we agree with the district court that the Defendants failed to prove that claim 12 of the '528 patent would have been *prima facie* obvious over the asserted prior art compounds, we need not address the court's findings regarding objective evidence of nonobviousness.").

> ’196 PCT and ’189 publication with a reasonable expectation of success.

Id. at 49.

As set forth above, we determine neither the ’196 PCT nor the ’189 Publication teach or otherwise suggest a phospholipid range of 4–10%. Petitioner does not rely upon the teachings of Lin or Ahmad to make up this for deficiency with respect to the claimed phospholipid range. We thus determine that claims 1–22 are not rendered obvious based on the additional teachings of Lin and Ahmad.

4. Ground 3: Anticipation or Obviousness in View of the ’554 Publication

Under Ground 3, Petitioner contends that claims 1–22 are anticipated or rendered obvious by the ’554 Publication. Pet. 54–67. We again focus our analysis on claim 1 as it is dispositive to our conclusions here.

As discussed above, the ’554 Publication generally discloses nucleic acid-lipid particles wherein the cationic lipid component can comprise from about 2–60% of the total lipid, the neutral (non-cationic) lipid can comprise from about 5–90% of the total lipid, the PEG conjugate can comprise from about 1–20% of the total lipid, and cholesterol can comprise from about 10–60% of the total lipid. Ex. 1005 ¶¶ 116–119, 313. Although the reference also identifies phospholipids among the examples of useful non-cationic lipids (*id.* ¶ 455), it does not teach any range specifically for the amount of phospholipid that may be included in the particle.

Petitioner’s arguments for how the phospholipid range is satisfied by the ’554 Publication are similar to those presented under Ground 1 with respect to the ’196 PCT and ’189 Publication. Pet. 57–58. Petitioner points to the more preferred range of 20–85% for the neutral lipid component and the more preferred range of 20–45% for the cholesterol component disclosed in the ’554 Publication. *Id.* at 57 (citing Ex. 1005 ¶ 313). Petitioner also points to specific formulations

discussed in the '554 Publication that include cholesterol at a 30% proportion. *Id.* (citing Ex. 1005, Table 4 (*e.g.*, L106)). Petitioner contends that "when the cationic lipid is set at the maximum disclosed (*i.e.*, 60%), the '554 publication discloses the remaining 40% can be made up of cholesterol at 20–40%." *Id.* And "[w]hen the cholesterol is less than the full remaining 40%, another non-cationic lipid (*e.g.*, a phospholipid) may be added at up to 20% (unless a PEG conjugate is also added . . . , in which case this percentage is adjusted accordingly.)" *Id.* Petitioner summarizes a scenario in which the claimed ranges overlap with the ranges disclosed in the '554 Publication in the following table:

	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. Petitioner's table above identifies the claimed ranges for each lipid component and the amounts or ranges disclosed in the '554 Publication that Petitioner contends overlaps the claimed ranges.

We have considered the arguments and evidence presented and determine that Petitioner has not demonstrated that the '554 Publication anticipates or renders obvious the challenged claims. Our reasons are similar to those discussed above with respect to Ground 1.

In particular, the '554 Publication fails to recite any range for a phospholipid component. We are also not persuaded the broader range of 5–90% (or even the more preferred range of 20–85%) for non-cationic lipids generally disclosed is sufficient to anticipate the claimed phospholipid range. As noted above, Petitioner does not allege or otherwise point to any evidence suggesting that the phospholipid range would not be critical such that a broader prior art range may nonetheless anticipate the narrower claimed range.

Furthermore, as with Ground 1, we are not persuaded that the '554 Publication teaches an overlapping phospholipid range such that the claims are *prima facie* obvious or that the adjustment of the phospholipid amount to within the claimed range would have been a matter of routine optimization. In order to arrive at an overlapping phospholipid range, Petitioner relies upon certain assumptions that are not expressly supported in the '554 Publication, e.g., by assuming that a skilled artisan would maximize the cationic lipid at 60% and balance the remaining amount with cholesterol, a conjugated lipid, and phospholipid in amounts that overlap the claimed range. But even assuming that a POSA would have been motivated to maximize the cationic lipid amount in order to increase transfection efficiency, there is no reason provided as to why the amounts of the remaining lipid components (an in particular the phospholipid) would have overlapped with the claimed ranges. In this regard, we note that most of the formulations disclosed in Table IV of the '554 Publication, including L106 identified by Petitioner, are three-component systems lacking *any* phospholipid. Ex. 1005, 90, Table IV. And for the four-component formulations that do include phospholipid, none of them include phospholipid within the claimed range. *Id.* (*e.g.*, L051 including 48% cationic lipid, 40% phospholipid, 10% cholesterol, and 2% conjugated lipid; L053 including 30% cationic lipid, 20% phospholipid, 48% cholesterol, and 2% conjugated lipid). As discussed above, Petitioner has not demonstrated that the amount of phospholipid was recognized as a result-effective variable that could have been optimized.

In sum, Petitioner has not demonstrated by a preponderance of the evidence that claim 1 is anticipated or rendered obvious by the '554 Publication. Because each of dependent claims 2–22 further narrows the scope of claim 1, Petitioner has also not proven anticipation or obviousness of these dependent claims for the same reasons.

III. MOTIONS

A. Patent Owner's Motion to Strike

Patent Owner moves to strike Petitioner's Reply, in its entirety or at least certain portions, for presenting untimely arguments. Paper 28. In particular Patent Owner contends that the Reply presents a new theory that overlapping phospholipid ranges could be derived by assuming levels for cationic lipid, cholesterol, and conjugated lipid. *Id.* at 1–2. Patent Owner further contends that Petitioner's assertions of routine optimization and motivation to include optional lipids are untimely. *Id.* at 3–4. Patent Owner also contends that Petitioner's belated arguments regarding objective indicia and attempts to abandon Dr. Janoff's testimony are improper. *Id.* at 4–5. Petitioner filed an opposition to Patent Owner's Motion to Strike and Patent Owner filed a reply in support of its Motion to Strike. Paper 34; Paper 36.

"A reply may only respond to arguments raised in the corresponding . . . patent owner response." 37 C.F.R. § 42.23(b). It may be appropriate to strike arguments in a reply where the petitioner identifies new portions of a prior art reference to make a "meaningfully distinct contention" or presents an "entirely new rationale" not previously set forth in the petition. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367 (Fed. Cir. 2015); *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1370 (Fed. Cir. 2016). The Federal Circuit, however, has also cautioned that the Board should not parse the arguments on reply with "too fine a filter" and that the petitioner may appropriately use the reply to "expand" or "elaborate" on a previously argued rationale," or to otherwise respond to arguments made in patent owner's response. *Apple Inc. v. Andrea Elecs. Corp.*, 949 F.3d 697, 706 (Fed. Cir. 2020); *Chamberlain Grp., Inc. v. One World*

Techs., Inc., 944 F.3d 919, 925 (Fed. Cir. 2019); *Ericsson Inc. v. Intellectual Ventures I LLC*, 901 F.3d 1374, 1381 (Fed. Cir. 2018).

We are not persuaded that we should strike any portion of Petitioner's Reply. We agree with Patent Owner that Petitioner has appeared to shift its obviousness theory in its Reply rather than merely expand or elaborate upon the arguments presented in the Petition. For instance, with respect to the claimed phospholipid range, Petitioner originally argued that the prior art explicitly disclosed an encompassing range. Pet. 38–39, 57–58. In its Reply, Petitioner argues that adjustment of the phospholipid range would have been a matter of routine optimization since "a [POSA] would have been aware that having some amount of phospholipid can provide structural stability to the resulting particles, but having too much will inhibit release of the payload upon contact with the endosome." Pet. Reply 21–22. The Petition does not mention structural stability as a reason to optimize the phospholipid amount. Petitioner in the Reply also points to the 2:40 formulation disclosed in the '189 Publication. Pet. Reply 14–15. Although Petitioner generally discussed the 2:40 formulation in the Petition (Pet. 26), Petitioner did not previously contend that the 2:40 formulation would have been the "starting point" for optimization as argued in the Reply. Nonetheless, we also note that Patent Owner in its Patent Owner's Response specifically argued against routine optimization as a basis for obviousness and also discussed the 2:40 formulation. PO Resp. 11–12, 19–27, 36. As such, Petitioner's arguments on Reply may be considered properly responsive to Patent Owner's arguments. Furthermore, any surprise or prejudice to Patent Owner based on the allegedly new arguments is mitigated in this case because Patent Owner substantively responded to those arguments in its Sur-Reply. *See* Sur-Reply 12–21.

Even upon considering the arguments in Petitioner's Reply, we have determined that Petitioner has not met its burden of proving obviousness for the reasons set forth above. We, therefore, deny Patent Owner's Motion to Strike.

B. Patent Owner's Motion to Exclude

Patent Owner also moves to exclude Exhibit 1020 (the declaration of Dr. Anchordoquy) and portions of Exhibit 2033 (the deposition testimony of Dr. Janoff). With respect to Dr. Anchordoquy's declaration, Patent Owner argues that Dr. Anchordoquy is a zoologist, not a lipid chemist with formal training in the subject matter at hand, and thus is not qualified to provide opinion testimony in this proceeding. Paper 31, 1–7. With respect to the portions of Dr. Janoff's deposition testimony, Patent Owner argues that counsel for Petitioner improperly used an opportunity for redirect to fill in holes in Petitioner's obviousness challenge. *Id.* at 8–10. Petitioner filed an opposition to Patent Owner's Motion to Exclude. Paper 35.

We determine that Patent Owner's arguments go to the weight that should be afforded to Petitioner's expert testimony rather than the admissibility of that testimony. Accordingly, we deny Patent Owner's Motion to Exclude.

IV. CONCLUSION

Petitioner has not demonstrated by a preponderance of the evidence that claims 1–22 of the '069 patent would have been anticipated or obvious based on the challenges presented in the Petition. In summary:

Claims	35 U.S.C.	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–22	§§ 102, 103	'196 PCT, '189 Publication		1–22
1–22	§ 103	'196 PCT, '189		1–22

		Publication, Lin, Ahmad		
1–22	§§ 102, 103	’554 Publication		1–22
Overall Outcome				1–22

V. ORDER

Accordingly, it is hereby:

ORDERED that Petitioner has not demonstrated by a preponderance of the evidence that claims 1–22 of the ’069 patent are unpatentable;

ORDERED that Patent Owner’s Motion to Strike is *denied*;

ORDERED that Patent Owner’s Motion to Exclude is *denied*; and

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

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