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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

PROTIVA BIOTHERAPEUTICS, INC.,
Patent Owner.

Case IPR2018-00739
Patent 9,364,435 B2

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

MITCHELL, *Administrative Patent Judge*.

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

I. INTRODUCTION

Moderna Therapeutics, Inc. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–20 of U.S. Patent 9,364,435 B2 (the "'435 patent"). Paper 2 ("Pet."). Protiva Biotherapeutics, Inc. ("Patent Owner")[1] filed a Preliminary Response to the Petition. Paper 12 ("Prelim. Resp.").

We have authority under 35 U.S.C. § 314(a) to determine whether to institute an *inter partes* review. To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314(b) may not institute review on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). Also, in accordance with USPTO Guidance, "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." *See Guidance on the Impact of SAS on AIA Trial Proceedings* (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial).

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

Applying those standards, and upon consideration of the information presented in the Petition and the Preliminary Response, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the '435 patent. Therefore, we institute an *inter partes* review for claims 1–20 of the '435 patent.

A. Related Proceedings

Patent Owner identifies the following related matters:

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

B. The '435 Patent (Ex. 1001)

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

> the present invention provides stable nucleic acid-lipid particles (SNALP) that advantageously impart increased activity of the encapsulated nucleic acid (e.g., an interfering RNA such as siRNA) and improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as

> compared to nucleic acid-lipid particle compositions previously described. Additionally, the SNALP of the invention are stable in circulation, e.g., resistant to degradation by nucleases in serum and are substantially non-toxic to mammals such as humans.

Id. at 5:62–6:5.

The '435 patent identifies specific SNALP formulations that encapsulate siRNA as the nucleic acid, such as the 1:57 SNALP and the 1:62 SNALP, and states that "the Examples herein illustrate that the improved lipid particle formulations of the invention are highly effective in downregulating the mRNA and/or protein levels of target genes." *Id*. at 6:5–30.

C. Illustrative Claim

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

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

Ex. 1001, 89:55–63.

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

D. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. §§ 102 and 103 based on the following grounds. Pet. 5.

Reference[s]	Basis	Claims challenged
WO 2005/007196 A2[2] and US 2006/0134189 A1[3]	§ 103	1–20
'196 PCT, '189 Publication, Lin,[4] and Ahmad[5]	§ 103	1–20
US 2006/0240554 A1[6]	§§ 102 and 103	1–20

Petitioner also relies on the Declaration of Dr. Andrew S. Janoff, Ph.D. ("Janoff Declaration" or "Decl."). Ex. 1007; *see generally* Pet.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person having ordinary skill in the art ("POSITA") "would have specific experience with lipid particle formation and use in the context of delivering therapeutic payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience." Pet. 5 (citing Ex. 1007 ¶¶ 31–32). Petitioner

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

further states that "[t]his level of skill is representative of the inventors on the '435 patent and authors/inventors of prior art cited herein." *Id.* at 6.

Patent Owner contends that Petitioner's proposed level of ordinary skill should be rejected because it "equates the level of ordinary skill with knowledge possessed by the inventors themselves" who may possess exceptional skill beyond the ordinary skill requirements. Prelim. Resp. 18. Patent Owner also takes issue with a person of ordinary skill having a medical degree when the Petitioner does not address any therapeutic considerations, such as toxicity, *in vivo* aggregation, and overall systemic tolerance in the Petition. *Id*.

On this record and at this stage of the proceeding, we agree with the Petitioner's definition of a person of ordinary skill in the art as supported by the testimony of Dr. Janoff. *See* Pet. 5–6; Ex. 1007 ¶¶ 29–32. 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 '435 patent, and provides the definition of one of skill in the art as set forth above by the quoted text of Petitioner in light of his "review of the '435 patent, its file history, and [his] knowledge of the field of the '435 patent." Ex. 1007 ¶¶ 30–31. Although Dr. Janoff notes that the level of skill he defines is "representative of the inventors on the '435 patent and authors/inventors of prior art cited herein," Dr. Janoff expressly indicates that the defined level of skill is that of an ordinary artisan, not one with extraordinary skill. *Id*. ¶ 31.

We also do not agree based on the record evidence that Patent Owner's assertion that a person with a medical degree may be one of skill who is "detached from the actual concerns of those of ordinary skill in the art at the time of the invention." *See* Prelim. Resp. 18. Petitioner does not posit that someone with a medical degree alone is one of ordinary skill, but

someone that also has "specific experience with lipid particle formation and use in the context of delivering therapeutic payloads." Pet. 5; Ex. 1007 ¶ 31. We find on this record that such definition of a person with ordinary skill is appropriate in light of the concerns of those of ordinary skill at the time of the invention.

At this stage of the proceeding based on the record before us, we find that one of skill in the art "would have specific experience with lipid particle formation and use in the context of delivering therapeutic payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience," and also find on this record that Dr. Janoff is one of at least ordinary skill under this standard. *See* Ex. 1007 ¶¶ 8–22; Ex. 1018 (*curriculum vitae* of Dr. Janoff).

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

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). "Under a broadest

reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Only terms in controversy must be construed and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

Petitioner provides a proposed construction of the claim terms "nucleic acid-lipid particle" and "cationic lipid." Pet. 23–24. According to Patent Owner, "[t]he terms identified in the petition do not require construction in order to reach a decision denying institution," and "[t]he constructions proposed in the petition . . . should be rejected as being unreasonably broad and largely detached from the '435 patent specification." Prelim. Resp. 15. Because Patent Owner substantively challenges the proposed construction of the term "nucleic acid-lipid particle" and relies on its narrower definition of the term in its arguments addressing the grounds asserted, we address the construction of that term, but find that we need not construe any other terms addressed by Petitioner for the purpose of reaching our institution decision. We do note, however, that Petitioner provides the same definition for "cationic lipid" as the express definition set forth in the specification of the '435 patent, namely, "any of a number of lipid species that carry a net positive charge at a selected pH, such as physiological pH (e.g., pH of about 7.0)." *Compare* Pet. 24, *with* Ex. 1001, 12:59–61.

nucleic acid-lipid particle

Petitioner proposes that "nucleic acid-lipid particle" means "a composition of lipids and a nucleic acid for delivering a nucleic acid to a target site of interest." Pet. 24 (citing Ex. 1001, 11:14–17; Ex. 1007 ¶ 87). Patent Owner contends that Petitioner's proposed construction is unreasonably broad, and that the specification's use of "nucleic acid-lipid particle" refers to "particles specifically formulated for systemic (*in vivo*) administration and having the nucleic acid component encapsulated within the lipid." Prelim. Resp. 16.[7]

On this record and at this stage of the proceeding, we find that neither Petitioner's nor Patent Owner's proposed constructions of "nucleic acid-lipid particle" are appropriate. Petitioner's proposed construction is a general restatement of the composition recited in claim 1 and a use thereof as described in the '435 patent. *See* Ex. 1001, 11:14–17, 89:55–63. Also, Patent Owner's proposed construction is inconsistent with claim 1 because it limits the term "nucleic acid-lipid particle" as used in claim 1 to the definition of a *stable* nucleic acid-lipid particle or SNALP. Prelim. Resp. 16–17 (citing Ex. 1001, 11:31–42 (defining SNALP), 5:62–6:2, 6:25–30, 2:38–47, 13:38–49). Because claim 1 is drawn to the broader term "nucleic acid-lipid particle," it should not be limited to the definition of SNALP. *Compare* Ex. 1001, 11:14–22 (describing "lipid particle" used to deliver an active or therapeutic agent such as a nucleic acid), *with* Ex. 1001, 11:23–46

[7] We note in the companion request for *inter partes* review, Patent Owner defined the same term "nucleic acid-lipid particle" somewhat differently as "non-lamellar particles formulated to fully encapsulate the nucleic acid component and to be stable in serum following systemic (*in vivo*) administration." *See* IPR2018-00739, Prelim Resp. 4.

(describing SNALP" as a lipid particle that fully encapsulates the nucleic acid with the lipid).

We also find on this record that "nucleic acid-lipid particle" is not limited to *in vivo* use. The specification of the '435 patent states that

> The 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).
>
> . . . The lipid particles and compositions of the present invention may be used for a variety of purposes, including the delivery of associated or encapsulated therapeutic agents to cells, both in vitro and in vivo.

Ex. 1001, 6:31–34. Example 2 in the '435 patent also describes in vitro use of nucleic acid-lipid particles. *See id*. at 69:6–70:52 (stating 1:57 SNALP are Potent Inhibitors of Cell Growth In Vitro). Because the specification of the '435 patent describes both in vitro and in vivo use of nucleic acid-lipid particles, we also find nucleic acid-lipid particle is not limited to in vivo use as Patent Owner contends.

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

comprises a nucleic acid and lipids, in which the nucleic acid may be encapsulated in the lipid portion of the particle." *See* Ex. 1001, 11:14–22.

We determine that we need not expressly construe any other terms for purposes of determining whether to institute an *inter partes* review in this case. *See Vivid Techs.*, 200 F.3d at 803

C. Principles of Law

To show anticipation, each and every claim element, arranged as in the claim, must be found in a single prior art reference either explicitly or inherently. *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008); *see Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999) (quoting *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997)). The prior art need not, however, use the same words as recited in the claims in order to find anticipation. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). To the contrary, it is permissible to take into account not only the literal teachings of the prior art reference, but also the inferences the skilled artisan would be reasonably expected to draw from the reference. *Eli Lilly v. Los Angeles Biomedical Res. Inst.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017); *In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

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

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Id.*

(citing *Titanium Metals*, 778 F.2d at 782). "It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art." *Titanium Metals*, 778 F.2d at 782.

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious to the person of ordinary skill in the art at the time of the invention. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). "If a person of ordinary skill in the art can implement a predictable variation [of the claimed subject matter from what is taught and suggested in the prior art], § 103 likely bars its patentability." *Id*. at 417. The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of obviousness. *Graham v. John Deere Co*., 383 U.S. 1, 17–18 (1966). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.*

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

D. Obviousness over '196 PCT and '189 Publication

Petitioner asserts that claims 1–20 of the '435 patent are unpatentable as obvious over the '196 PCT and the '189 Publication. Pet. 32–48. Patent

Owner advances several arguments in response to Petitioner's assertions. Prelim. Resp. 22–33.

1. '196 PCT (Ex. 1002)

The invention of the '196 PCT is described as "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. 1002 ¶ 2. More particularly, the invention of the '196 PCT is described as "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 SNALPs 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 id*. ¶¶ 86–107. Concerning the preferred makeup of the 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. 1002 ¶ 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. For the bilayer stabilizing component such as a conjugated lipid, the '196 patent 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. '189 Publication (Ex. 1003)

The '189 Publication describes "nucleic acid-lipid particles comprising siRNA molecules that silence [Apolipoprotein B "ApoB"] expression and methods of using such nucleic acid-lipid particles to silence ApoB expression." Ex. 1003, Abst., ¶ 0007. In describing these nucleic acid-lipid particles, the '189 Publication states that they may comprise a 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 SNALPs). The '189 Publication describes embodiments wherein the siRNA is fully encapsulated in the nucleic acid-lipid particle. *Id*. ¶ 14.

3. Analysis

a. Obviousness – claim 1

Petitioner provides a detailed analysis of how each claim limitation of claim 1 is met by the disclosure of the '196 PCT. *See* Pet. 32–40.[8] Petitioner concludes that:

> While the '196 PCT does not disclose the exact same range of lipid components from claim 1 of the '435 patent explicitly, it discloses encompassing and overlapping ranges that establish a *prima facie* case of obviousness and the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶ 106.
>
> The '189 publication is substantively similar to the '196 PCT and also discloses SNALPs comprising overlapping ranges of the lipid components similar to those discussed below for the '196 PCT. In addition, the '189 publication discloses testing relating to the admitted prior art 2:40 formulation.

Pet. 32–33.

Petitioner also argues that Patent Owner cannot rely on any unexpected results for the claimed ranges for the components of the nucleic acid-lipid particle because the testing as described in the '435 patent "dealt

[8] Petitioner also details how each additional limitation of claims 2–20 that depend either directly or indirectly on claim 1 is met by the disclosure of the '196 PCT. *See* Pet. 40–48. At this stage of the proceeding, Patent Owner has not addressed the dependent claims individually for any of the asserted grounds. *See* Prelim. Resp. 23–45.

with only a few lipid species and proportions [that are] not co-extensive with the claim scope." Pet. 34–38. Specifically, Petitioner asserts the following.

> *In vitro* testing (Example 2) showed that Sample 10 (claimed formulation) apparently performed worse than Sample 16 (admitted prior art). Ex. 1001, Fig. 1; Janoff Decl. ¶¶ 81–82. In *vivo* testing (Example 3), Group 14 (claimed formulation) apparently performed worse than Group 7 (admitted 2:40 prior art). Ex. 1001, Figure 2; Janoff Decl. ¶¶ 83–84.
>
> . . . the *in vivo* testing in Example 3 shows that even minor variations in lipid percentages (and potentially changes to Lipid to drug ratios) appeared to impact efficacy. Janoff Decl. ¶ 106. Specifically, Sample 2 and Sample 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 (and potentially changes to Lipid to drug ratios) lead to apparently different transfection efficiencies. *Id.*, Fig. 2; Janoff Decl. ¶ 112. A POSITA would expect that similar minor variations in lipid proportions within the claimed range might lead to similar variations in transfection efficiency. *Id.*; Ex. 1006, 740 (parenthetical omitted).

Pet. 35–36.

By the same token, Petitioner asserts, the testing of only one cationic lipid, DLinDMA, in the '435 patent when the claimed range of species of cationic lipids is much more extensive does not support the conclusion that other cationic lipids within the claim will behave in the same manner as the one tested. *Id.* at 37. Petitioner asserts that "[t]o the contrary, Example 5 in the '435 patent shows variation of the cationic lipid impacts efficacy." *Id.* (citing Ex. 1001, Table 6 (Samples 2 % 6 (DLin-DMA) vs. Sample 4 (DODMA)); *see also* Pet. 38 (citing acknowledgement that alternative cationic lipids that work in essentially the same manner may have different efficiencies).

On this record and at this stage of the proceeding, we are persuaded that Petitioner has established a reasonable likelihood that it would prevail in showing that claim 1 of the '435 patent would have been obvious over either the '196 PCT or the '189 Publication. Petitioner has shown that each of the '196 PCT and the '189 Publication disclose nucleic acid-lipid particles that comprise a nucleic acid, and the lipid components—a cationic lipid, a non-cationic lipid, and a conjugated lipid—in mol percentage ranges that overlap with the claimed ranges. *See* Pet. 32–48; *see* Ex. 1007 ¶¶ 106–118; *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("A *prima facie* case of obviousness typically exists when the ranges of the claimed composition overlap the ranges disclosed in the prior art") (citations omitted).

Specifically with regard to the claimed range for the cationic lipid component, which Patent Owner asserts was contrary to the conventional wisdom concerning "the community's aversion to the toxicity and poor *in vivo* efficacy associated with formulations with a high level of cationic lipid," *see* Prelim. Resp. 1, Dr. Janoff testifies as follows.

> The '196 PCT teaches "[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle … [i]n other preferred embodiments, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle." *Id.*, [0088]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.* In addition, the '196 PCT incorporates by reference the '618 patent, which discloses nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol, as well as various other formulations containing over 50% cationic lipid. Ex. 1017, 34:54-35:23. Given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious. In addition, 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. 1007 ¶ 110. On the record before us, we credit Dr. Janoff's testimony and agree that given the disclosure of overlapping ranges for the compositions in each of the '196 PCT and the '189 Publication as compared to the claimed ranges, one of skill in the art would determine the optimum combination of percentages for the lipid components of the claimed composition. *See Peterson*, 315 F.3d at 1330 ("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 percentage ranges is the optimum combination of percentages.").

Although the rubric for determining whether a particular composition in the prior art with overlapping ranges to a claimed composition renders it obvious involves application of a *prima facie* case of obviousness that may be rebutted by an applicant/patent owner, we are mindful that Petitioner continuously bears the burden of persuasion in an *inter partes* proceeding to establish the unpatentability of the challenged claims. *See In re Magnum Oil Tools Internat'l, Ltd.*, 829 F.3d 1364, 1375–77 (Fed. Cir. 2016); *Dynamic Drinkware v. National Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). We find, however, that the disclosure in the prior art of the overlapping ranges to the claimed invention shows a reasonable likelihood that Petitioner will prevail in establishing that at least claim 1 of the '435 patent would have been obvious to one of skill in the art.

b. Patent Owner's Arguments

In order to address Patent Owner's arguments concerning the deficiencies in the Petition, Patent Owner's view of the claimed invention of the '435 patent is instructive. Patent Owner describes the claimed invention

of the ’435 patent as solving the problems created by the “community’s aversion to the toxicity and poor *in vivo* efficacy associated with the formulations with a high level of cationic lipid,” and the trend “to incorporate higher than the claimed levels of conjugated lipids to stabilize the particle so that the therapeutic payload could reach the target cells.” Prelim. Resp. 1–2. The Patent Owner states that

> The inventors solved these problems by requiring cationic lipids at “50 mol % to 85 mol %,” non-cationic lipids at “13 mol % to 49.5 mol %,” and conjugated lipids at “0.5 mol % to 2 mol %.” This specific combination, it turns out, is surprisingly effective, stable following systemic (*in vivo*) administration, and does not elicit the feared toxic effects associated with formulations having a high level of cationic lipid.

Prelim. Resp. 2. With this background in mind, we address each of Patent Owner’s arguments concerning the Petition.

As an initial matter, Patent Owner contends that the grounds of challenge are not presented with the requisite degree of particularity because “[a]ll three grounds include various alternate legal theories and/or different permutations and combinations of the ‘cited references.’” Prelim. Resp. 19. Specifically, Patent Owner asserts that Ground 1 provides no meaningful discussion of the ’189 Publication that is part of the obviousness challenge for the ground. We do not find this persuasive because Petitioner bases its challenge in ground 1 on the asserted facts that each of the ’196 PCT and the ’189 Publication discloses overlapping ranges of the lipid components of the claimed nucleic acid-lipid particle. *See* Pet. 32–33. We find that Petitioner has provided sufficient information by specific citation to the two references as well as a discussion by Dr. Janoff concerning these teachings. *Id*. at 32–48. Thus, we conclude on this record that Petitioner has presented sufficient

evidence to establish a reasonable likelihood of prevailing in showing the unpatentability of claim 1.

Specifically, Patent Owner asserts the following arguments that we address in turn. First, Patent Owner asserts that Petitioner fails to address the claims as a whole. Second, Patent Owner asserts that Petitioner inappropriately relies on the teachings of *In re Peterson* to shift the burden from Petitioner to Patent Owner, a shifting that may not be done in an *inter partes* context, and thus fatally fails to address any motivation to combine or a reasonable expectation of success. Third, Patent Owner asserts that Petitioner mischaracterizes the unexpected results detailed in the '435 patent.

(i) Invention as a Whole

Patent Owner asserts that Petitioner addresses separately each claim limitation of the challenged claims rather than "addressing the claimed invention as a whole." We are not persuaded by this argument. Claim 1 is a composition claim with various ranges for the lipid components of the claimed nucleic acid-lipid particle. Citing to disclosures in the two asserted references that each present overlapping ranges for the same components for a nucleic acid-lipid particle is sufficient to establish a reasonable likelihood of prevailing on showing that claim 1 would have been obvious to one of skill in the art in light of these disclosures. *See* Pet. 32–48; *In re Peterson*, 315 F.3d at 1330; *In re Wertheim*, 541 F.2d 257 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990). It is not apparent to us what else Petitioner must address to show a likelihood of success on showing the obviousness of claim 1.

Part of Patent Owner's argument concerning addressing the invention as a whole is that Petitioner ignored more pertinent disclosure in the '196 PCT disclosing a more limited range, (from about 5% to about 15% of the total lipid in the particle) for systemic delivery. As discussed above, however, with regard to the construction of the claim term "nucleic acid-lipid particle," claim 1 is not limited to systemic delivery. *See supra* Section II.B.

(ii) *Application of In re Peterson, Motivation to Combine, and Reasonable Expectation of Success*

Patent Owner asserts that the burden shifting of *In re Peterson* is inapplicable in this *inter partes* context. We agree with Patent Owner that the ultimate burden of proving unpatentability always remains with Petitioner throughout an *inter partes* review, but the disclosure in the prior art of the overlapping ranges to the claimed invention shows a reasonable likelihood that Petitioner will prevail in establishing that at least claim 1 of the '435 patent would have been obvious to one of skill in the art. *See supra* Section II.D.3.a.

Patent Owner asserts, however, that this case is more akin to that of *Genetics Institute v. Novartis Vaccines*, which Patent Owner asserts states that "*Peterson* does not apply to broad prior art ranges that would encompass a 'very large number of possible distinct compositions,'" and that there must be "identification of some reason that would have prompted a researcher to modify the prior art compounds in a particular manner to arrive at the claimed compounds." Prelim. Resp. 4, 26 (citing *Genetics Institute*, 655 F.3d 1291, 1306 (Fed. Cir. 2011). We do not agree, however, that the factual scenario of *Genetics* is more applicable to the case before us.

Genetics involved a comparison of claimed truncated Factor VIII proteins that differed between the two patents claiming such truncated proteins by "size of the permitted amino acid deletions, the location of the permitted amino acid deletions, and the degree of allowable amino acid substitutions." 655 F.3d at 1303. The Federal Circuit concluded that because of these structural differences between the claimed truncated proteins, "the district court correctly required as part of the *prima facie* obviousness inquiry the identification of some reason that would have prompted a researcher to modify the prior art compounds in a particular manner to arrive at the claimed compounds." *Id*. at 1304, 1307 (stating about 68,000 protein variants are encompassed by the claims of the patent at issue).

Here claim 1 involves a composition with particular components in ranges of mol percent of the total amount of lipid content. Such ranges for the various components are akin to the ranges of the components of the compound at issue in *Peterson*. *See Peterson*, 315 F.3d at 1329. We agree with Petitioner on this record 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." *Id*. at 1330; Pet. 34 ("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") (citing Ex. 1007 ¶ 110).

Patent Owner argues that one of skill in the art would not be motivated to use higher percentages of cationic lipid with a reasonable expectation of success because the prior art teaches that "formulations with a high level of cationic lipid were toxic and poorly tolerated *in vivo* and had little to no *in vivo* transfection efficiency." Prelim. Resp. 7; *see id*. at 7–11.

The cited references, however, appear to refer to these problems when the overall charge of a liposome complex is positive, not in reference to the amount of cationic lipid that is used in such a complex. *Id*. 7–11 (*see* cited references). Although disclosing overlapping ranges for the lipid components with claim 1 of the ’435 patent, including the cationic lipid, the ’196 PCT recognized that compositions with an overall neutral charge are preferred. Ex. 1002 ¶ 15. Therefore, we are not persuaded by Patent Owner’s argument, on the current record, that one of skill in the art would not be motivated to optimize the nucleic acid-lipid particle to the claimed ranges with a reasonable expectation of success because higher percentages of cationic lipid content was discouraged in the prior art.

(iii) *Unexpected Results*

Petitioner asserts that because of the numeric range for the cationic lipid in claim 1 and the range of cationic lipids as defined by the ’435 patent that may be used in claim 1, there are no unexpected results provided by Patent Owner in the ’435 patent across the claimed numeric range or type of cationic lipid of claim 1. *See Pet.* 34–38.[9] For instance, Petitioner asserts that Example 2 of the ’435 patent shows that certain *in vitro* examples of claimed formulations performed worse than the prior art formulations, Examples 3 and 4 of the ’435 patent show that examples of particles with lipid components in the claimed ranges were no more effective than examples of formulations with less than 50% cationic lipid, and the testing in the ’435 patent shows that even slight variations of the lipid component

[9] Petitioner asserts that the “sole basis for alleged novelty of the ’435 patent claims is that a nucleic acid-lipid particle comprising component lipids in the claimed proportions achieves unexpected efficacy.” Pet. 14.

proportions or the species of lipid components impact efficacy. *See* Pet. 16–23.

Patent Owner counters that "the claimed formulations are well-tolerated and possess favorable *in vivo* transfection efficiency at far lower dosages than prior art formulations." Prelim. Resp. 30. Patent Owner also states that the "Petitioner similarly overlooks that the claimed formulations are well-tolerated following systemic delivery." *Id*. at 32. As we have stated in our claim construction of the term "nucleic acid-lipid particle," the claim 1 is not limited to *in vivo* administration.[10] In any event, such a fact intensive inquiry concerning unexpected results is best vetted during trial on a full record.

E. Obviousness over the '196 PCT, the '189 Publication, Lin, and Ahmed

Petitioner asserts that claims 1–20 of the '435 patent are unpatentable as obvious in view of the '196 PCT, the '189 Publication, Lin, and Ahmed. Pet. 48–51. Patent Owner advances several arguments in response to Petitioner's assertions. Prelim. Resp. 33–37.

1. Lin (Ex. 1005)

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. 1005, Abst. 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.

[10] We recognize that the method claims 16–20 do require *in vivo* delivery. *See* Ex. 1001, 92:8–22.

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_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.

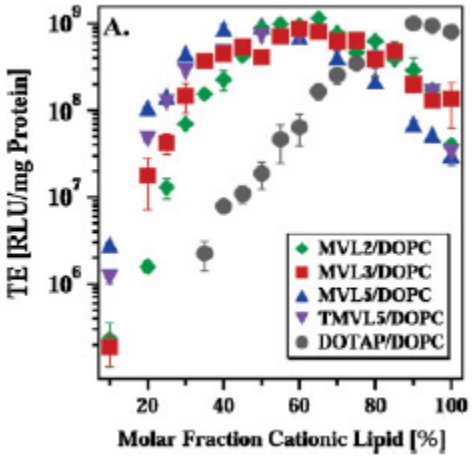
2. Ahmad (Ex. 1006)

Ahmad also studied transfection efficiencies with differing membrane charge densities of CL-DNA complexes finding a universal, bell-shaped curve. Ex. 1006, 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 in 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. *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 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." *Id*. at 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. *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 against 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.

3. Analysis

a. Obviousness – claim 1

Petitioner states that to the extent that the disclosures in the '196 PCT and the '189 Publication[11] 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. 48–49 (citing Ex. 1007 ¶¶ 138–139; Ex. 1005, Fig. 3(a); Ex. 1006, 739–40, Fig. 3(a)). Petitioner asserts that one of skill in the art would have been motivated to

[11] Patent Owner asserts that it is unable to tell to what "Patent Owner's prior disclosures" in the ground refers. Prelim. Resp. 33. We believe that is clear from the context of Ground 2 that "Patent Owner's prior disclosures" refers to the '196 PCT and the '189 Publication. *See* Pet. 48.

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. 50–51 (citing Ex. 1007 ¶ 141).

Patent Owner asserts that Petitioner picks and chooses, and thus, mischaracterizes the teachings of the Lin and Ahmad references. Prelim. Resp. 34–35. Specifically, Patent Owner states that Petitioner ignores the statement in Ahmad that "minimizing the amount of cationic lipid is desirable to reduce cost as well as potential toxic effects of the cationic lipid." *Id*. (citing Ex. 1006, 745). Patent Owner also takes issue with the Petitioner's assertion that one of skill in the art would be motivated to combine the teachings of Lin and Ahmad with the '196 PCT and the '189 Publication. *See* Prelim. Resp. 35–37. Patent Owner complains that Petitioner does not provide a sufficient explanation as to how one of skill in the art in viewing the teachings of the references would combine the teachings to arrive at the claimed invention with a reasonable expectation of success, especially considering the statement in Ahmad concerning minimizing the amount of cationic lipid. *Id*.

We agree with Patent Owner that Petitioner does not adequately address teachings in Lin and Ahmad and may not support its position that one of skill in the art would increase the mole fraction of cationic lipid in a nucleic acid-lipid particle to arrive at the invention of claim 1. We provided above an extensive quotation from Lin that is instructive on this point. Lin explains the complicated nature of maximizing transfection efficiencies that

includes the nanostructure of the CL-DNA, the valence of the cationic lipid, and the amount of neutral lipid. *See* Ex. 1005, 3314–15 (stating "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 from cationic lipid and anionic charge from DNA, and the variation in σ_M is achieved simply by varying the amount of neutral lipid) (further stating "[i]n 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"). Also, the focus of studies in Lin and Ahmad appears to be on changing the membrane charge density by changing the amount of neutral lipids in the CL-DNA complexes, while maintaining a constant lipid/DNA charge ratio of 2.8 using the same amount of DNA for each particle and varying the valence of the cationic lipid to maintain the charge.

Lin and Ahmad's recognition of the complicated nature of what affects transfection efficiencies of the CL-DNA complexes does not appear to support the broad statement that a person of ordinary skill in the art would have read Lin and Ahmad to teach that 50–85% mol percentage of cationic lipid may increase transfection efficacy. *See* Pet. 48–50; Ex. 1007 ¶¶ 138–139. We do recognize that Ahmad is concerned with the toxicity of cationic lipids, but Ahmad noted 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." Ex. 1006, 746. Because claim 1 is not limited to *in vivo* use of the claimed nucleic acid-lipid particle, the statement in Ahmad to which Patent Owner directs us concerning minimizing the amount of cationic lipid to avoid cost and

toxicity, is not necessarily persuasive that Ahmad does not encourage increased amounts of cationic lipid in certain circumstances. For instance, as we quoted above, Ahmad reports that maximum transfection efficiency was achieved from between 65 and 90 mol % of different cationic lipids in the CL-DNA complex. *Id*. at 743. We find that the sufficiency of this ground is best vetted during trial on a full record.

F. Anticipation by or obviousness over '554 Publication

Petitioner asserts that claims 1–20 of the '435 patent are unpatentable as anticipated by or obvious over the '554 Publication. Pet. 51–64. Patent Owner advances several arguments in response to Petitioner's assertions. Prelim. Resp. 37–45.

Petitioner sets forth where in the '554 Publication the claim limitations are met. Pet. 51–64. Petitioner states that "[w]hile the '554 publication does not disclose exactly the same ranges of lipid components from claim 1 of the '435 patent explicitly, it discloses encompassing and overlapping ranges and specific examples falling within the claimed ranges with sufficient specificity to anticipate. *Id*. at 51 (citing Ex. 1007 ¶ 143).

Dr. Janoff testifies concerning a specific example, formulation L054, that falls within the claimed ranges of at least claim 1 that:

> The '554 publication also includes various specific formulations, including formulation L054, which contains 50% cationic lipid (DMOBA), 48% non-cationic lipid (CHol/DSPC), and 2% conjugate lipid (PEG-n-DMG). Ex. 1004, Table 4. This formulation was tested, for example, with siRNA for reducing HBsAg levels. *See id.*, Fig. 16. The disclosed nucleic acid-lipid particles meet all of the limitations in claim 1 of the '435 patent.

We credit Dr. Janoff's testimony on this record and for purposes of this decision on institution, Petitioner has established a reasonable likelihood

of success in establishing anticipation by or obviousness over the '554 Publication of claim 1. *See Titanium Metals*, 778 F.2d at 782; *KSR*, 550 U.S. at 406.

Patent Owner relies on its narrow definition of nucleic acid-lipid particle as requiring systemic or *in vivo* administration asserting that "the petition fails to address which, if any, of the cited embodiments provide a nucleic acid-lipid particle specifically formulated for systemic (*in vivo*) administration." Prelim. Resp. 40–41. We are not persuaded by this argument as we have stated that on this record, we do not find "nucleic acid-lipid particle" to be so limited. *See supra* Section I.C. Patent Owner also raises similar arguments concerning the application of *In re Peterson*, which we address with regard to the first ground. *See supra* II.D.3.b.(ii). The same analysis applies here.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least claim 1 of the '435 patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on all grounds as set forth in the Petition.

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 commencing on the entry date of this decision.

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