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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 IPR2018-00680
Patent 9,404,127 B2

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

SMITH, *Administrative Patent Judge*.

FINAL WRITTEN DECISION AND RELATED ORDERS

Determining That Claims 1–22 Have Been Shown To Be Anticipated
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Denying-in-part and Dismissing-in-part Patent Owner's Motion to Strike
37 C.F.R. § 42.64

I. INTRODUCTION

Moderna Therapeutics, Inc. ("Petitioner")[1] filed a Petition to institute an *inter partes* review of claims 1–22 ("challenged claims") of U.S. Patent No. 9,404,127 B2 ("'127 patent"). Paper 2 ("Pet."). Protiva Biotherapeutics, Inc. ("Patent Owner")[2] filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp.").

On September 12, 2018, we entered our Decision on Institution (Paper 13, "Inst. Dec." or "Institution Decision") instituting *inter partes* review of all challenged claims under all asserted grounds. Inst. Dec. 28. Patent Owner filed a Response (Paper 22, "PO Resp."), Petitioner filed a Reply (Paper 26, "Reply"), and Patent Owner filed a Sur-reply (Paper 31, "Sur-reply").

Patent Owner also filed a Motion to Strike (Paper 30), Petitioner filed an Opposition to the Motion to Strike (Paper 40), and Patent Owner filed a Reply to Petitioner's Opposition to the Motion to Strike (Paper 44). At the request of both parties, we held an oral hearing on June 6, 2019, and the transcript of that hearing has been entered into the record. Paper 45 ("Tr.").

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[1] Petitioner states that the name of its parent has been changed to Moderna, Inc., and that Moderna, Inc.'s intellectual property matters are now conducted under the name of ModernaTX, Inc., which is a fully-owned subsidiary of Moderna, Inc. Paper 41, 2.

[2] Patent Owner states that it existed as a wholly-owned subsidiary of Arbutus Biopharma Corporation and was amalgamated into Arbutus Biopharma Corporation in January 2018. Paper 12, 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*.

We have jurisdiction under 35 U.S.C. § 6(b). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a). Having reviewed the arguments of the parties and the supporting evidence, we find that Petitioner has demonstrated by a preponderance of the evidence that all challenged claims of the ’127 patent are unpatentable. Our factual findings supporting anticipation of the challenged claims are set forth herein.

A. Related Matters

Petitioner identifies the following related matters:

IPR2018-00739 regarding U.S. Patent No. 9,364,435 B2,[3] and IPR2019-00554 regarding U.S. Patent No. 8,058,069 B2.[4] Paper 41, 2.

Patent Owner identifies the following additional related matter:

European Patent Office Opposition proceedings regarding EP 2 279 254. Paper 12, 2.

B. The ’127 Patent (Ex. 1001)

The ’127 patent was filed on March 9, 2015, and claims priority to provisional application No. 61/360,480, filed June 30, 2010. Ex. 1001, 1 (22), (60). The ’127 patent issued August 2, 2016, and names Ed Yaworski, Lloyd B. Jeffs, and Lorne R. Palmer as co-inventors. *Id.* at 1 (45) (72).

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[3] Yaworski, et al., U.S. Patent No. 9,364,435 B2, issued June 14, 2016 (“’435 patent”). Ex. 3001. The oral hearing in IPR2018-00739 was consolidated with the oral hearing in the present case. *See* Paper 45.

[4] Yaworski et al., U.S. Patent No. 8,058,069 B2, issued Nov. 15, 2011 (“’069 patent”). Ex. 1002.

The ’127 patent states that “the present invention provides stable nucleic acid-lipid particles (SNALP) that have a non-lamellar[5] structure and that comprise 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, 1 (Abstract). According to the ’127 patent, “[t]he present invention addresses . . . needs” such as “for novel and more efficient methods and compositions for introducing nucleic acids such as siRNA into cells,” and “for methods of downregulating the expression of genes of interest to treat or prevent diseases and disorders such as cancer and atherosclerosis.” *Id.* at 2:54–60.

The ’127 patent states that “[t]he present invention is based, in part, upon the surprising discovery that by controlling the lipid composition of a SNALP formulation as well as the formation process used to prepare the SNALP formulation, a novel non-lamellar lipid nanoparticle (i.e., SNALP) can be produced.” *Id.* at 2:64–3:1, 8:51–55. The ’127 patent further states that

> it has surprisingly been found that lipid particles that comprise 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 10 mol % of a lipid conjugate, and that are made using the Direct Dilution Method as described herein have a novel non-lamellar (i.e., non-bilayer) morphology.

Id. at 3:2–10; *see also id*. at 8:55–62.

The ’127 patent identifies several SNALP formulations, such as formulations that are “generally referred to herein” as the “1:57” formulation

[5] The ’127 patent states that “non-lamellar” means non-bilayer —“a non-lamellar morphology, i.e., a non-bilayer structure.” Ex. 1001, 3:7–8, 24–25.

and the "1:62" formulation.[6] *See, e.g.*, *id*. at 5:61–6:32, 105:30–53. The ’127 patent describes an example for characterizing SNALP structure in which "SNALP formulations of varying compositions were prepared using either a Stepwise Dilution Method or a Direct Dilution Method." *Id.* at 104:1–107:30; *see also id*. at 104:9–11. Process parameters used for the Stepwise Dilution Method and the Direct Dilution Method are listed in Table 1 of the ’127 patent. *Id.* at 104:44–60.

The ’127 patent further describes the characterization of SNALP structure using Cryo-Transmission Electron Microscopy ("Cryo-TEM"). *Id.* at 107:32–110:29. SNALP formulations prepared by the Direct Dilution Method and analyzed by Cryo-TEM include compositions identified as "1:57" and "1:62." *Id.* at 109:1–10 (Table 7). According to Cryo-TEM data reported in the ’127 patent, the "vast majority" of the particles in formulations prepared by the Direct Dilution Method were non-lamellar, including the 1:57 and 1:62 formulations. *Id.* at 108:65–110:30.

The ’127 patent states that "[t]he lipid particles of the present invention . . . can be formed by any method known in the art including, but not limited to, a continuous mixing method, a direct dilution process, and an in-line dilution process." *Id.* at 92:15–21. The ’127 patent also states that "[t]he Direct Dilution Method ("DDM") . . . as well as the apparatuses for carrying out the DDM are described in detail in U.S. Patent Publication No.

[6] Patent Owner states that "the first number refers to the approximate molar percentage of the conjugated lipid, and the second number refers to the approximate molar percentage of the cationic lipid." PO Resp. 17 (citing Ex. 2009 ¶ 47; Ex. 2028, 152:10–14; Ex. 1002, 3:36–56).

20070042031,[7] the disclosure of which is herein incorporated by reference in its entirety for all purposes." *Id.* at 104:32–37.

C. Illustrative Claims

Independent claim 1 is representative and reproduced below:

> **1**. A composition comprising:
> a plurality of nucleic acid-lipid particles, wherein each particle in the plurality of particles comprises:
> (a) a nucleic acid;
> (b) a cationic lipid;
> (c) a non-cationic lipid; and
> (d) a conjugated lipid that inhibits aggregation of particles,
> wherein at least about 95% of the particles in the plurality of particles have a non-lamellar morphology.

Ex. 1001, 149:29–37.

Claims 2–19 are directly or indirectly dependent on claim 1. *Id*. at 149:38–150:57. Claims 20–22 read as follows:

> **20.** A pharmaceutical composition comprising a composition of claim **1** and a pharmaceutically acceptable carrier.
>
> **21.** A method for introducing a therapeutic agent into a cell, the method comprising:
> contacting the cell with a composition of claim **l**.
>
> **22.** A method for the in vivo delivery of a therapeutic agent, the method comprising:
> administering to a mammal a composition of claim **1.**

Id. at 150:58–65.

D. Instituted Grounds

We instituted an *inter partes* review on all of Petitioner's requested grounds, as more specifically shown below. Inst. Dec. 28.

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[7] MacLachlan et al., US 2007/0042031 A1, published Feb. 22, 2007 ("'031 patent publication"). Ex. 1019.

Reference[s]	**Basis**	**Claims challenged**
’069 patent	§§ 102/103	1–22
WO 2009/082817[8]	§§ 102/103	1–22
U.S. Patent No. 7,514,099,[9] and Koltover[10] and/or Ewert[11]	§102 (’099 patent) or §103 (’099 patent alone or in light of Koltover and/or Ewert)	1–22
’817 PCT in view of Koltover and/or Ewert	§103	1–22

Petitioner relies on two Declarations of Dr. Andrew S. Janoff, Ph.D., dated February 21, 2018 (Ex. 1007), and dated March 22, 2019 (Ex. 1025), to support its Petition and Reply, respectively.

Patent Owner relies on the Declaration of David H. Thompson, Ph.D. (Ex. 2009) and the Declaration of James Heyes, Ph.D. (Ex. 2030) to support its Response and Sur-reply.

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[8] MacLachlan et al., WO 2009/082817 A1, published July 9, 2009 (“’817 PCT”). Ex. 1003.

[9] Chen et al., U.S. Patent No. 7,514,099 B2, issued April 7, 2009 (“’099 patent”). Ex. 1004.

[10] Ilya Koltover et al., *An Inverted Hexagonal Phase of Cationic Liposome-DNA Complexes Related to DNA Release and Delivery*, 281 SCIENCE 78–81 (1998) (“Koltover”). Ex. 1005.

[11] Kai K. Ewert et al., *Cationic lipid-DNA complexes for non-viral gene therapy: relating supramolecular structures to cellular pathways*, 5(1) EXPERT OPIN. BIOL. THER. 33–53 (2005) (“Ewert”). Ex. 1006.

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 ¶¶ 30–33). We applied that description for purposes of our Institution Decision. Inst. Dec. 5–6.

Patent Owner objects to Petitioner's proffered definition for two reasons. PO Resp. 11–12 (citing Ex. 2009 ¶¶ 17–21). First, Patent Owner objects to Petitioner's statement that "[t]his level of skill [proffered by Petitioner] is representative of the inventors on the '127 patent." *Id.* (citing Pet. 5). According to Patent Owner, "equating the level of skill of the artisan with the level of skill of the artisans of the '127 patent is indicative of impermissible hindsight." *Id.* at 11 (citing Ex. 1007 ¶ 32; Ex. 2028, 44:8–12). Patent Owner further states that "[t]he inventors of the '127 patent . . . are artisans of exceptional skill" and "the petition has improperly assumed a much higher level of skill than that of a person having ordinary skill in the art." *Id.* at 11–12 (citing Ex. 2009 ¶¶ 19–20).

As an initial matter, we did not rely on Petitioner's statement that the proposed level of skill "is representative of the inventors on the '127 patent" in our Institution Decision, and we do not rely on it for purposes of this Decision. *See* Inst. Dec. 6. We do not view Petitioner's statement that its proffered level of skill is "representative of the inventors on the '127 patent" as part of Petitioner's proposed level of ordinary skill in the art.

Second, Patent Owner objects to Petitioner's definition of a person of ordinary skill because it is "ultimately indeterminable." PO Resp. 12. Patent Owner bases this contention on its characterization of Dr. Janoff's testimony during cross-examination. *Id.* Patent Owner states that Dr. Janoff "repeatedly indicat[ed] that Petitioner's own definition is 'too vague' to understand." *Id.* (citing Ex. 2028, 33:6–14, 34:7–35:25, 36:1–37:5). Although Dr. Janoff may not have been as responsive to some questions during his deposition as may have been appropriate (*see id.* at 2–7), what Dr. Janoff said in the cited portions of his testimony was that the *questions* from Patent Owner's counsel were "too vague." *See* Ex. 2028, 33:6–14, 34:7–35:25, 36:1–37:5. The cited portions of Dr. Janoff's testimony indicate that, rather than specifically asking about Petitioner's proposed definition of a person having ordinary skill in the art, Dr. Janoff was asked questions about his work experience. *Id.*; *see, e.g., id.* at 33:7–8, 35:7–8 ("Do you have specific experience working with lipid particles?" "Do you have any experience with any therapeutic payload?").

Although Patent Owner cites to Dr. Thompson's testimony in support of its objections to Petitioner's definition, it does not expressly proffer its own definition of a person of ordinary skill in the art. PO Resp. 11–12 (citing Ex. 2009 ¶¶ 17–21). However, Patent Owner's expert, Dr. Thompson, does indicate that, for purposes of his review, he has assumed a person of ordinary skill in the art "would be generally familiar with lipid particle formation and use in the context of delivering therapeutic payloads and would have a Ph.D., an M.D., or similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience." Ex. 2009 ¶ 21. This definition differs from Petitioner's only in the use of "be generally familiar with," rather than “having specific experience with,” lipid particle formation, but neither party explains, nor can we discern, an appreciable distinction in the definitions based on that difference. For example, general familiarity may be the result of specific experience, and may actually encompass specific experience. In any event, we discern no appreciable difference in the respective definitions of a person having ordinary skill in the art.

Accordingly, we find on the record as a whole that a person of ordinary skill in the art would have specific experience with, and/or be generally familiar with, lipid particle formation and use in the context of delivering therapeutic payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g*., biophysics, microbiology, biochemistry) or an equivalent combination of education and experience. We also find on this record that both Dr. Janoff and Dr. Thompson are ones of at least ordinary skill in the art under this standard. *See* Ex. 1007 ¶¶ 9–23; Ex. 1021 (*curriculum vitae* of Dr. Janoff); Ex. 2009 ¶¶ 2–6; Ex. 2010 (*curriculum vitae* of Dr. Thompson).

We further note that prior art may also demonstrate 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

For petitions filed before November 13, 2018,[12] 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. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Limitations, however, may not be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993).

Petitioner provides a proposed construction of several claim terms, including the term "nucleic acid-lipid particle." Pet. 15–16. We provided a preliminary construction of "nucleic acid-lipid particle" in the Institution Decision. Inst. Dec. 8. Petitioner states that "Petitioner and its expert submit that the construction by the Board is appropriate and agree with it." Reply 3 (citing Ex. 1025 ¶ 13).

Patent Owner argues that "the Board's [] construction adopted in the Institution Decision is [] unreasonably broad in view of the specification."

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[12] The Petition was filed February 21, 2018. Paper 5. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42).

PO Resp. 13 (citing Ex. 2009 ¶¶ 38–41; Ex. 2028, 119:5–22).[13] Rather than providing its own alternative construction, Patent Owner states that "the petition can be rejected no matter what construction is applied." *Id.* (citing Ex. 2009 ¶ 42).

We address the term "nucleic acid-lipid particle" because Patent Owner disputes the construction of that term as set forth in our Institution Decision.

nucleic acid-lipid particle

Our construction of "nucleic acid-lipid particle" is the broadest reasonable construction in light of the Specification of the '127 patent. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs.,* 136 S. Ct. at 2142. The '127 patent states that "[i]n preferred embodiments, the lipid particle of the invention is a nucleic acid-lipid particle, which is typically formed from a cationic lipid, a non-cationic lipid, and optionally a conjugated lipid," followed by the statement that "[i]n other preferred embodiments, the active agent or therapeutic agent, such as a nucleic acid, may be encapsulated in the lipid portion of the particle." Ex. 1001, 15:55–63. The '127 patent also states that "[i]n certain embodiments, lipid particles of the present invention are associated with a nucleic acid, resulting in a nucleic acid-lipid particle (e.g. SNALP)." *Id.* at 33:52–54.

Accordingly, we construe "nucleic acid-lipid particle" as "a particle that comprises a nucleic acid and lipids, in which the nucleic acid may be

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[13] Patent Owner contends that Dr. Janoff "confirmed" that our construction is unreasonably broad. PO Resp. 13 (citing Ex. 2028, 119:5–22). However, Dr. Janoff's cited testimony refers to a lipid particle or particle, and also states that "it's my recollection that the [B]oard also weighed in on what a particle is, and we could look there." Ex. 2028, 119:5–22.

encapsulated in the lipid portion of the particle." *See* Ex. 1001, 15:52–63. This is the same construction we applied for purposes of the Institution Decision. Inst. Dec. 8.

Dr. Thompson states that a nucleic acid-lipid particle "expressly includes a nucleic acid." Ex. 2009 ¶ 39. Our construction also includes a "nucleic acid" which "may be encapsulated in the lipid portion of the particle." *See* Ex.1001, 15:61–62. Moreover, the '127 patent states that the active or therapeutic agent (e.g. nucleic acid) is "fully encapsulated within the lipid portion of the lipid particles" in "certain embodiments" (i.e. but not all embodiments). *Id.* at 3:26–28.

We determine that we need not expressly construe any undisputed terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'") (*quoting Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

C. Principles of Law

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Anticipation requires a finding that the claim at issue "reads on" a prior art reference. *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999) (citing *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781 (Fed. Cir. 1985)). "[I]f . . . [a] disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether it also covers subject matter not in the prior art." *Id.* "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 (citation omitted).

Inherent anticipation requires "merely that the disclosure [of the prior art] is sufficient to show that the natural result flowing from the operation as taught [in the prior art] would result in' the claimed product." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343–44 (Fed. Cir. 2005) (citing cases). Moreover, "[b]ecause inherency places subject matter in the public domain as well as an express disclosure, the inherent disclosure of the entire claimed subject matter anticipates as well as inherent disclosure of a single feature of the claimed subject matter." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003).

"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*, 778 F.2d at 780, 782). "[T]he discovery of a previously unappreciated property of a prior art composition . . . does not render the old composition patentably new to the discoverer." *Id*. (citing *Titanium Metals*, 778 F.2d at 782).

The Federal Circuit has also held that "[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Bristol–Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (citing cases).

A finding of anticipation "does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Schering Corp.*, 339 F.3d at 1380. Whether a prior art reference anticipates is assessed from the perspective of one skilled in the art. *See Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003).

D. Anticipation by the ’069 patent

Petitioner asserts that claims 1–22 of the ’127 patent are unpatentable as anticipated by the ’069 patent[14] under pre-AIA 35 U.S.C. § 102(e)(2).[15] Pet. 18, 24–42. Patent Owner advances several arguments in response to Petitioner’s anticipation assertions. PO Resp. 14–33; Sur-reply 2–14, 20.

1. ’069 patent (Ex. 1002)

The ’069 patent was filed on April 15, 2009, and claims priority to provisional application No. 61/045,228, filed April 15, 2008. Ex. 1002, 1 (22), (60). The ’069 patent issued November 15, 2011, and lists the same three co-inventors named on the ’127 patent, as well as Kieu Lam and Ian MacLachlan.[16] *Id.* at (45), (75). The ’069 patent is a parent of the ’435

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[14] Petitioner also asserts, in the alternative, that claims 1–22 are obvious over the ’069 patent. Pet. 24. However, as discussed *infra*, we do not reach that obviousness challenge.

[15] Petitioner also contends that the ’069 patent is prior art under pre-AIA 35 U.S.C. § 102(a). Pet. 18. Patent Owner challenges that contention by asserting that the ’069 patent fails to qualify as prior art under pre-AIA 35 U.S.C. § 102(a). PO Resp. 33–36. Patent Owner does not dispute that the ’069 patent is prior art under pre-AIA 35 U.S.C. § 102(e)(2), but contends that its prior art status under only that statute prohibits its use in an obviousness analysis based on common ownership of the ’069 patent and ’127 patent. *Id.* (citing 35 U.S.C. § 103(c)). Because we decide this case on anticipation alone, we need not resolve the issue of whether the ’069 patent is prior art under pre-AIA 35 U.S.C. § 102(a).

[16] The ’127 patent was filed during the pendency of the ’069 patent but did not claim priority to the ’069 patent. *See* Ex. 1001, 1; Ex. 1002, 1.

patent (through a series of continuations) and is commonly owned (with the ’127 patent) by Patent Owner. PO Resp. 33–34 (citing Ex. 1001; Ex. 1002).

The ’069 patent states that “the present invention provides 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. 1002, 1 (Abstract). The ’069 patent also states that “[t]he present invention addresses . . . needs” such as “for novel and more efficient methods and compositions for introducing nucleic acids such as siRNA into cells,” and “for methods of downregulating the expression of genes of interest to treat or prevent diseases and disorders such as cancer and atherosclerosis.” *Id.* at 2:55–61.

The ’069 patent further states that

> [i]n certain embodiments, the nucleic acid-lipid particle (e.g., SNALP) comprises: (a) a nucleic acid (e.g., an interfering RNA); (b) a cationic lipid comprising from about 50 mol % to about 85 mol % of the total lipid present in the particle; (c) a non-cationic lipid comprising from about 13 mol % to about 49.5 mol % of the total lipid present in the particle; and (d) a conjugated lipid that inhibits aggregation of particles comprising from about 0.5 mol % to about 2 mol % of the total lipid present in the particle.

Id. at 3:27–35.

The ’069 patent also discloses particle formulations, including formulations that are “generally referred to herein as” the “1:57” formulation and the “1:62” formulation. *Id.* at 3:36–56. The ’069 patent states that “[t]he present invention also provides pharmaceutical compositions comprising a lipid particle described herein (e.g., SNALP) and a pharmaceutically acceptable carrier.” *Id.* at 3:57–59. Although the ’069 patent describes the characterization of certain properties of prepared

SNALP formulations, it does not describe a characterization of the lamellar or non-lamellar morphology of the particles. *See, e.g.*, 67:62–80:45.

The ’069 patent states that “[t]he lipid particles of the present invention, e.g., SNALP . . . can be formed by any method known in the art including, but not limited to, a continuous mixing method or a direct dilution process.” *Id.* at 57:50–55. Regarding the direct dilution process, the ’069 patent states that “[t]hese processes and the apparatuses for carrying out these direct dilution processes are described in detail in [the ’031 patent publication], the disclosure of which is herein incorporated by reference in its entirety for all purposes.” *Id.* at 59:12–16.

In addition to the incorporation of the ’031 patent publication, the ’069 patent also incorporates by reference U.S. Patent No. 5,885,613 (Ex. 1017, “’613 patent”), U.S. Patent Publication No. 20040142025 (Ex. 1018, “’025 patent publication”), and U.S. Patent Publication No. 20060083780 (Ex. 1020, “’780 patent publication”). *Id.* at 11:62–64, 51:58–61, 58:18–21, 47:59–64. With respect to the ’613 patent and the ’025 patent publication, the ’069 patent states that “the disclosure of which is herein incorporated by reference in its entirety for all purposes.” *Id.* at 11:62–64, 58:18–21. With respect to the ’780 patent publication, the ’069 patent states “the disclosures of which are each herein incorporated by reference in their entirety for all purposes.” *Id.* at 47:59–64.

The disclosure of the ’069 patent thus includes the disclosures of the ’031 patent publication, the ’613 patent, the ’025 patent publication, and the ’780 patent publication. *See Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000); s*ee also Harari v. Lee*, 656 F.3d 1331, 1335 (Fed. Cir. 2011) (holding that the statement in the specification that "[t]he disclosures of the two applications are hereby incorporate[d] by reference . . . incorporates the entire disclosure of the two applications").

Both the claimed and unclaimed disclosures of the '069 patent are presumed to be enabled, and Patent Owner does not argue otherwise. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). Dr. Janoff testified that the '069 patent is enabled: "a person of ordinary skill would have no difficulty reproducibly making the particles described in [the] '069 [patent]." Ex. 2028, 192:2–6 (cited at Reply 7). Thus, the disclosure of the '069 patent is enabled, "such that a person of ordinary skill in the field of the invention can practice the subject matter based on the ['069 patent], without undue experimentation." *See Sanofi-Synthelobo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008).

The disclosures of the '069 patent are further discussed below.

2. Analysis

Introduction

The challenged claims of the '127 patent recite a composition comprising a plurality of nucleic acid-lipid particles, "wherein at least about 95% [or greater than 95% (claim 19)] of the particles in the plurality of particles have a non-lamellar morphology." Ex. 1001, 149:29–150:65. That morphology limitation recites a physical property of the particles. PO Resp. 24–25. No method steps or process limitations for preparing the claimed compositions are recited in the challenged claims of the '127 patent.[17] *See* Pet. 13 n.3; Reply 4; Ex. 1001, 149:29–150:65.

[17] Although claims 21 and 22 are method claims, both recite the composition of claim 1, and neither recite any method steps or process limitations for preparing the composition of claim 1. *See* Ex. 1001, 150:58–65.

Each of the particles in the claimed plurality of particles is described as comprising (a) a nucleic acid, (b) a cationic lipid, (c) a non-cationic lipid, and (d) a conjugated lipid that inhibits aggregation of particles. Ex. 1001, 149:29–150:65. Those components (a) – (d) recite a formulation for the particles. The challenged claims thus recite a composition comprising a plurality of particles (a recited formulation) having a morphological property. *Id.* According to the ’127 patent, that property was discovered in particle formulations (with the recited components) “that are made using the Direct Dilution Method as described herein,” and specifically the Direct Dilution Method “described in detail in [the ’031 patent publication].” Ex. 1001, 8:50–61, 93:14–18.

The principal contested issue in this case is whether the morphological property recited in claim 1 is inherent in a prior art disclosure (the ’069 patent) that discloses the same formulations as claimed, and further discloses that the method of making the formulations (the direct dilution process) is also “described in detail in [the ’031 patent publication].”

Anticipation – Claim 1

Petitioner argues that the limitations of claim 1 are expressly or inherently disclosed in the ’069 patent, and supports that argument with the testimony of Dr. Janoff. Pet. 24–32; Ex. 1007 ¶¶ 97–105. We address each claim limitation in turn.

A composition comprising: a plurality of nucleic acid-lipid particles, wherein each particle in the plurality of particles comprises:

Petitioner cites to the disclosure in the ’069 patent of “a lipid particle (e.g., SNALP) composition comprising a plurality of lipid particles.” Pet. 26

(citing Ex. 1002, 23:15–17; Ex. 1007 ¶ 98).[18] Petitioner further asserts that lipid particles comprise various lipid components and a nucleic acid payload. *Id.* (citing Ex. 1002, 11:13–26). Petitioner cites to the 1:62 formulation disclosed in the ’069 patent as an example. Pet. 26 (citing Ex. 1002, 3:36–45).

We find that the ’069 patent discloses a “nucleic acid-lipid particle” as that term has been construed. *See, e.g.*, Ex. 1002, 11:4–12; 27:36–40.

(a) a nucleic acid

Petitioner cites to the disclosure in the ’069 patent that “the present invention provides serum-stable nucleic acid-lipid particles (SNALP) comprising a nucleic acid (e.g., one or more interfering RNA molecules such as siRNA, aiRNA, and/or miRNA).” Pet. 27 (citing Ex. 1002, 3:21–26; Ex. 1007 ¶ 99). As an example, Petitioner refers to Figure 5 of the ’069 patent as illustrating data “demonstrating the activity of 1:62 SNALP containing ApoB siRNA following intravenous administration in mice.” *Id.* (citing Ex. 1002, 4:29–31).

(b) a cationic lipid

Petitioner cites to the disclosure in the ’069 patent of “one or more cationic lipids comprising from about 50 mol % to about 85 mol % of the total lipid present in the particle.” Pet. 27 (citing Ex. 1002, 3:12–15; Ex. 1007 ¶ 100). Petitioner also cites to one disclosed example in which the cationic lipid is identified as DLin-DMA. *Id.* (citing Ex. 1002, Table 6).

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[18] Petitioner provides citations to the ’069 patent and corresponding citations (in parentheses) to U.S. Provisional Application No. 61/045,228, filed April 15, 2008 (“’228 provisional”). Ex. 1016. The ’228 provisional is incorporated by reference into the ’069 patent. Ex. 1002, 1:7–10.

(c) a non-cationic lipid

Petitioner cites to the disclosure in the ’069 patent of “one or more non-cationic lipids comprising from about 13 mol % to about 49.5 mol % of the total lipid present in the particle.” Pet. 27 (citing Ex. 1002, 3:14–16; Ex. 1007 ¶ 101). Petitioner cites to one disclosed example in which the non-cationic lipid is cholesterol. *Id.* at 27–28 (citing Ex. 1002, Table 6). Petitioner also cites to the disclosure of the non-cationic lipids DSPC:Cholesterol with the 2:30 formulation and DPPC:Cholesterol with the 2:40 and 1:57 formulations. *Id.* at 28 (citing Ex. 1002, Tables 4, 5, 6).

(d) a conjugated lipid that inhibits aggregation of particles

Petitioner cites to the disclosure in the ’069 patent of “one or more conjugated lipids that inhibit aggregation of particles comprising from about 0.5 mol % to about 2 mol % of the total lipids present in the particle.” Pet. 28 (citing Ex. 1002, 3:16–19; Ex. 1007 ¶ 102). Petitioner also cites to a disclosed example of PEG (2000)-C-DMA as the conjugated lipid, which the ’069 patent also discloses using with the 2:30, 2:40, and 1:57 formulations. *Id.* (citing Ex. 1002, Tables 4, 5, 6).

Patent Owner does not substantively address the disclosure by the ’069 patent of the claimed formulation limitations, but rather argues that the Petition does not identify a specific formulation in the ’069 patent. PO Resp. 16. Patent Owner further argues that “[s]pecificity in this regard is critically important. As both experts agree, a POSITA would expect that differences in lipid composition of a formulation to affect the physical properties of resulting lipid particles.” *Id.* at 16–17 (citing Ex. 2009 ¶¶ 46–48, 51, 53; Ex. 2028, 182:12–20, 191:6–192:2). Patent Owner also argues that “the petition’s broad reference to ‘2:30, 2:40, 1:57, and 1:62 formulations’ is misleading and provides little information,” and that “[s]uch terminology only identifies classes of formulations, and not any specific formulation." *Id.* at 17 (citing Ex. 2009 ¶¶ 46, 47, 50, 54).

Petitioner responds that "[t]he '069 [patent] and '127 patent[] define these terms [2:30, 2:40, 1:57, and 1:62] as including the same component percentages for all four lipid components with only insubstantial differences in rounding." Reply 14 (citing Ex. 1001, 105:31–65, Table 3; Ex. 1002, 72:61–73:44); *see also* Pet. 29–31. Petitioner further responds that Dr. Thompson "admitted that the particles actually tested in the '069 [patent] and '127 patent[] had only inconsequential differences in formulation." *Id.* at 14–16 (citing Ex. 1023, 158:20–159:4; Ex. 1024, 318:21–319:5, 326:7–19). Petitioner specifically cites to Dr. Thompson's testimony when asked whether he would expect a change in the three-dimensional structure of the resulting particles if there were a minor difference in the formulations, such as a change in the DLin-DMA (cationic lipid) from 62.0% to 61.5%: "I would not expect a change . . . that kind of emphasizes my point that the composition is just one of the parameters. It's—it's in this—this is a great example of where the process becomes spotlighted."[19] Ex. 1024, 326:7–19 (cited at Reply 15).

Based on the full trial record, we find that the '069 patent discloses the above referenced formulation limitations of claim 1, and credit the testimony of Dr. Janoff in support of that finding. *See* Ex. 1007 ¶¶ 98–102. We credit Dr. Janoff's testimony because it is supported by objective factual evidence of record, such as factual corroboration by the '069 patent.

[19] The percentage of cationic lipid of the 1:62 formulation studied in the '127 patent is described as 62 mol %, whereas it is described as 61.5 mol % in the 1:62 formulation studied in the '069 patent. *See* Ex. 1001, 105:55–65 (Table 3); Ex. 1002, 74:16–36 (Table 6, Group 3).

Specifically, we find that the ’069 patent expressly discloses:

1. A composition comprising:
a plurality of nucleic acid-lipid particles, wherein each particle in the plurality of particles comprises:
(a) a nucleic acid;
(b) a cationic lipid;
(c) a non-cationic lipid; and
(d) a conjugated lipid that inhibits aggregation of particles.

See Ex. 1001, 149:29–35; Pet. 11, 26 (citing Ex. 1002, 3:36–45, 23:15–17).

Patent Owner’s arguments regarding the lack of specificity of the formulations are unavailing. PO Resp. 16–17. Petitioner relies on several specific formulations in the ’069 patent, including the 1:62 formulation. Pet. 26–27 (citing Ex. 1002, 3:36–45). Notably, citations to the 1:62 and 1:57 formulations in the ’069 patent state that “[t]his preferred embodiment of nucleic acid-lipid particle is generally referred to herein as the ‘1:62’ [or ‘1:57’] formulation.” Ex. 1002, 3:43–45, 54–56. Moreover, Petitioner specifically points out the disclosure of the claimed formulation limitations set forth in the ’069 patent by column and line numbers. *See* Pet. 24–42.

As reflected in the evidence of record discussed above, we are not persuaded by Patent Owner’s argument that the Petition fails to specifically identify formulations, or that the reference to formulations by their stated identifier (e.g., 1:62) is misleading or provides little information. Accordingly, based on the trial record as a whole, we find that the formulation limitations recited in claim 1, prior to the recited morphological property limitation, recite a particle formulation that is expressly disclosed in Patent Owner’s ’069 patent.

wherein at least about 95% of the particles in the plurality of particles have a non-lamellar morphology

Petitioner argues that "[t]he only limitation from claim 1 of the '127 patent not disclosed explicitly in the '069 patent is 95% of the claimed particles having a non-lamellar morphology," but that "Patent Owner . . . uses several of the formulations disclosed in the '069 patent to illustrate in the later '127 patent a greater than 95% non-lamellar morphology among such particles." Pet. 25 (citing Ex. 1001, 149:29–37 (claim 1); Ex. 1007 ¶ 103). Regarding the morphology limitation of claim 1, Petitioner asserts that "[t]he '069 patent inherently anticipates [that morphology limitation] because it is a property that the '127 patent asserts invariably results from formulations disclosed therein." *Id.* at 28.

Petitioner further argues that "[w]hile the '069 patent does not explicitly mention the proportion of particles with a non-lamellar morphology, according to the '127 patent this is an inherent natural property resulting from (1) the 'lipid composition of a SNALP formulation' and (2) 'the formation process used to prepare the SNALP formulation.'" Pet. 29 (citing Ex. 1001, 2:64–3:10; Ex. 1007 ¶ 103). Petitioner further asserts that "both the particle composition and the formation processes disclosed in the '127 patent are the same as the ones disclosed in the '069 patent," and that "[t]he '127 patent itself identifies these variables as resulting in the claimed property." Pet. 29 (citing Ex. 1001, 2:64–3:10, 104:9–14, 104:32–105:7, 105:31–52, 107:60–66, Tables 3–4, Figs. 7, 12; Ex. 1002, 59:12–16, 70:55–67, 73:13–39, Tables 3-7; Ex. 1007 ¶¶ 103–104). Petitioner cites to the testimony of Dr. Janoff that, from disclosures of the '127 patent and the '069 patent, "a POSITA would appreciate that the '069 patent disclosed the lipid composition of a SNALP formulation tested in the '127 patent and the formation process used to prepare the SNALP formulation." Ex. 1007 ¶ 104 (cited at Pet. 29).

Petitioner further argues that the '127 patent has the same goal of finding "more efficient methods and compositions for introducing nucleic acids such as siRNA into cells" as stated verbatim in the '069 patent. Pet. 31 (*comparing* Ex. 1001, 1:51–52, 2:54–56, *with* Ex. 1002, 1:52–53, 2:55–57). Petitioner also argues that, to illustrate support for the morphology limitation in the '127 patent, "the '127 patent relies on the same compositions, made with the same formation processes as found in the prior art '069 patent," and specifically that "[t]he '127 patent relies on the 2:30, 2:40, 1:57, and 1:62 formulations with an ApoB siRNA payload created using the Direct Dilution Method." Pet. 31 (citing Ex. 1001, 104:9–14, 61–63, 105:31–52, Table 3, Figs. 7, 10). Petitioner further argues that "the '069 patent discloses the exact same cationic lipid components in the same 2:30, 2:40, 1:57, and 1:62 formulations with the same lipid to drug ratios, and the same nucleic acid payload [siRNA directed at silencing ApoB] created using the same Direct Dilution Method." *Id.* (citing Ex. 1001, 104:61–105:7, Tables 3–4; Ex. 1002, 57:50–55, 73:13–39, Tables 4–6; Ex. 1007 ¶ 104). Petitioner also refers to the characterization of the generated particles in the '069 patent, and the testimony of Dr. Janoff that "[a] POSITA would have appreciated that the particle characterization in the '069 patent (e.g., [] Tables 2, 4, and 6 (particle 'size' and 'encapsulation') is indicative of particles having a non-lamellar structure." *Id.* at 32–33 (citing Ex. 1002, Tables 2, 4, and 6; Ex. 1007 ¶ 86).

Therefore, as supported by Petitioner's arguments and evidence, we find that the morphology limitation of claim 1 is the "natural result" of following the disclosure of the ’069 patent, which corresponds to the disclosure of the ’127 patent. Pet. 29–32.

Patent Owner’s Arguments

Patent Owner responds with several arguments that focus on the asserted inherency of the morphology limitation of claim 1. PO Resp. 14–33. According to Patent Owner, “Petitioner, at a minimum, fails to show that ‘at least about 95% of the particles in the plurality of particles have non-lamellar morphology’ as claimed is inherently disclosed . . . in view of the cited art.” *Id.* at 14.

No Presumption of Inherency

Patent Owner argues that there is no presumption of inherency, and that Petitioner improperly “attempt[s] to shift the burden to Patent Owner to prove no inherency based on mere assertions of similarity with the prior art.” *Id.* at 14–15. Patent Owner further argues that “Petitioner has not provided any evidence in this case demonstrating that the particles of the ’069 patent inherently have the morphology required by the challenged claims,” pointing to the lack of experimental testing by Petitioner. *Id.* at 15; Sur-reply 2.

Patent Owner also contends that “Petitioner’s argument presumes that identified compositions in the ’069 patent . . . would have the same physical characteristics as similar formulations in the ’127 patent,” but “both experts agree, [that] the formation process used to generate particle compositions affects physical properties of resulting particles—and altering the process would be expected to alter the physical properties.” PO Resp. 24 (citing Pet. 31; Ex. 1002, 73:13–39, Tables 2–7; Ex. 2009 ¶¶ 46, 53, 65, 66; Ex. 2028, 191:2–192:2). Patent Owner cites to Tables 2, 5, and 7 of the ’069 patent and Tables 4 and 5 of the ’127 patent as support for the contention that experimental data shows that “physical properties such as mean particle size, polydispersity, encapsulation and lipid-to-drug ratio . . . [of] particles of the ’069 patent are not the same as the particles of the ’127 patent, made by the exact same process.” *Id.* at 24–28; *see id.* at 28 (citing Ex. 2009 ¶¶ 66–84). Based on that assertion, Patent Owner states that “there is no reason to presume that cited formulations from the ’069 patent would necessarily have the same morphology, which is also a physical property, as formulations disclosed by the ’127 patent.” *Id.* at 28 (citing Ex. 2009 ¶ 83).

Petitioner responds that “actual reduction to practice is not required to anticipate,” citing *Schering*, 339 F.3d at 1380. Reply 9. Petitioner also argues and that “[e]ven if the actual particles tested in the ’069 patent were at issue, Patent Owner’s expert testified repeatedly that he would expect the particles produced in the ’435 patent (a continuation of the ’069 patent with the same disclosures and detailing exactly the same prior art experiments) to have >95% a non-lamellar morphology.” Reply 9–10 (citing Ex. 1023, 161:9–162:8). Thus, according to Petitioner, “[t]his same assessment would necessarily apply to the particles disclosed in the parent ’069 patent.” *Id.* at 10.

Patent Owner states in its Sur-reply that Dr. Thompson did not admit that the particles tested in the ’069 patent met the claimed morphology limitation, and that “Dr. Thompson was discussing his expectation about uniform lipid composition.” Sur-reply 10.

We are not persuaded by Patent Owner’s arguments. Petitioner does not rely on a presumption of inherency, nor do we. *See, e.g.*, Pet. 28–32. We also made clear in the Institution Decision that the burden of persuasion is on Petitioner and never shifts to Patent Owner. Inst. Dec. 13.

Patent Owner argues that Petitioner does not demonstrate that particles actually generated based on the ’069 patent inherently possess the claimed morphological property. *See* PO Resp. 15 (referring to lack of experimental testing by Petitioner); *id.* at 24–28 (comparing properties of the prepared particles); *id.* at 23 (arguing that Petitioner failed to show that cited formulations were generated by a direct dilution process). However, we agree with Petitioner that there is no requirement that Petitioner show that particles actually generated, based on the ’069 patent, possess the claimed inherent property because “anticipation does not require actual performance of suggestions in a disclosure.” *See Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005) (citing cases). Moreover, Petitioner repeatedly refers to the *disclosure* of the ’069 patent. *See, e.g.*, Pet. 12, 17–20, 25–32; s*ee also SmithKline Beecham*, 403 F.3d at 1343–44 (inherent anticipation shown by “the disclosure [of the prior art]”).

Patent Owner’s comparison of properties to show that inherency cannot be presumed is also unpersuasive. Patent Owner argues that the experimental data shows that “physical properties such as mean particle size, polydispersity, encapsulation and lipid-to-drug ratios . . . [of] particles of the ’069 patent are not the same as the particles of the ’127 patent, *made by the exact same process*.” PO Resp. 24–28; *see id.* at 28 (emphasis added). But the assertion that the respective particles are made by the exact same process is inconsistent with Patent Owner’s statement that “none of cited Tables 2, . . . 5 or 7 [of the ’069 patent], or corresponding discussions in the specification, identify the listed formulations as having been made by a direct dilution process.” PO Resp. 22. That is, Patent Owner compares Tables of formulations in the ’069 patent, that it asserts are not identified as being made by a direct dilution process, to Table 5 of the ’127 patent that indicates the Direct Dilution Method was utilized. *See* PO Resp. 25–27; *see also* Ex. 1001, 107:1–16 (Table 5) (“Characterization of Formulations

Prepared By Direct Dilution Method (DDM)”). Thus, Patent Owner’s argument regarding a comparison of particles *made by the exact same process* is contradicted by its own arguments.

Patent Owner’s argument challenging Petitioner’s characterization of Dr. Thompson’s testimony is also unpersuasive. Petitioner cites the following testimony of Dr. Thompson in support of the argument that particles disclosed in the parent ’069 patent would be expected to have 95% non-lamellar forms:

> Q. Right. I’m actually talking about the ’435 patent here?
>
> A. Yeah, yeah. I am too. I am too.
>
> Q. So in the ’435 patent you’re expecting these to have 95 percent nonlamellar forms?
>
> A. I’m expecting that based on how these particles are produced for these experiments, that that is their — that’s their state.

Ex. 1023, 161:25–162:8. (cited at Reply 9–10).

Patent Owner’s reply that “Dr. Thompson was discussing his expectation about uniform lipid composition” (Sur-reply 10) is attorney argument and not supported by any statement of Dr. Thompson. Relying on Dr. Thompson’s actual testimony, we are persuaded by Petitioner’s argument regarding the non-lamellar morphology of the tested particles in the ’069 patent, based on Petitioner’s uncontested contention that the ’435 patent is a continuation of the ’069 patent with the same disclosures and detailing exactly the same prior art experiments. Reply 9.

Lack of Specificity

Patent Owner argues that Petitioner fails to identify in the ’069 patent a specific formulation generated by a specific formulation process. PO Resp. 16–20 (citing Ex. 2009 ¶¶ 44, 45, 70); Sur-reply 2–3, 5. Patent Owner cites to testimony by Dr. Thompson and Dr. Janoff for the proposition that differences in lipid composition of a formulation, and different formulation processes and parameters, would affect the physical properties of the resulting formulations. PO Resp. 16–17 (citing Ex. 2009 ¶¶ 46–48, 51, 53; Ex. 2028, 182:12–20, 191:6–192:2). Patent Owner also argues that "[a] POSITA would also understand that there are many parameters that may be varied as to the formulation composition, as well as a myriad of parameters that can be varied in the process used to formulate the particles." *Id.* at 17 (citing Ex. 2009 ¶¶ 46, 51, 53; Ex. 2028, 191:14–21).

Patent Owner's arguments regarding a lack of a specific formulation process focus on Petitioner's reference to the direct dilution process or method. *Id.* at 18–19. Patent Owner argues that referring to "direct dilution process" does not identify any specific process, "but refers to classes of processes that may encompass innumerable process parameters." *Id.* at 18 (citing Ex. 2009 ¶ 51). Patent Owner refers to Dr. Janoff's testimony that "[t]here are varieties of methods that practitioners call direct dilution method,"[20] and argues that "Dr. Janoff [] conceded there is no such thing as 'the Direct Dilution Method.'" *Id.* (citing Ex. 2028, 164:11–12, 165:10–22).

Patent Owner further argues that the Petition "never identif[ies] any specific direct dilution method with any specific parameters." *Id.* at 18 (citing Pet. 31). Patent Owner acknowledges Petitioner's citation to the '031 patent publication, but refers to Dr. Thompson's testimony and the '031 patent publication as support for the contention that the '031 patent

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[20] The remainder of the quoted response reads "and that direct dilution method that's used here is a method that's incorporated by reference someplace. We would know what it is if we looked at this patent." Ex. 2028, 164:12–15.

publication does not provide "only a single direct dilution process," but rather "shows different examples of apparatuses that may be used, separate processes and variety of different parameters." *Id.* at 18–19 (citing Ex. 2009 ¶ 52; Ex. 2028, 181:4–14; Ex. 1002, 58:57–59:1; Ex. 1007 ¶ 86; Ex. 1019 ¶ 38, FIGS. 3A–3B). As to the possible different parameters that might result in different particles, Patent Owner refers to "flow rate," "mixing parameters," "temperature," and "the speed of the direct dilution mixing." *Id.* at 19 (citing Ex. 2028, 165:18–22; 191:14–17). Thus, Patent Owner argues that broadly referring to formulations, such as the 1:57 formulation and the 1:62 formulation, and a direct dilution method, "at best, only differentially identifies classes of formulations and classes of formation processes," thereby lacking sufficient specificity. *Id.* at 19 (citing Ex. 2009 ¶ 54).

Patent Owner also contends that we suggested in the Institution Decision "that the claimed nucleic acid-lipid particles can be formed using any method known in the art," but that, according to Dr. Thompson, that is a "misreading" of the '127 patent specification.[21] PO Resp. 11 (citing Inst. Dec. 12; Ex. 2009 ¶ 35.). According to Patent Owner, "data presented in the '127 patent makes clear that not every process results in a composition in which at least about 95% of the particles have a non-lamellar morphology." *Id.* (citing Ex. 2009 ¶¶ 31–35; Ex. 1001, FIG. 7).

[21] The statement we quoted from the '127 patent was "[t]he lipid particles of the present invention . . . can be formed by any method known in the art including, but not limited to, a continuous mixing method, a direct dilution process." Inst. Dec. 12; Ex. 1001, 92:15–21. We do not agree that quoting from the '127 patent constitutes a "misreading" thereof.

Petitioner responds that “Patent Owner improperly relies on unclaimed process parameters” in an effort to differentiate the prior art. Reply 4. Petitioner argues that “[w]hile the ’127 patent specification discloses specific production parameters used in the testing (Table 1), there is no discussion in the specification of how such parameters relate to the claimed particle morphology or what range of parameters might be acceptable.” *Id.* at 4–5 (citing Ex. 1025 ¶ 15). Petitioner further argues that “[t]o the contrary, the ’127 patent states unequivocally that ‘[t]he lipid particles of the present invention . . . can be formed by <u>any method known in the art</u>,’” and that “[a] POSITA would not ignore this express disclosure.” *Id.* at 5 (citing Ex. 1001, 92:15–21 (emphasis by Petitioner); Ex. 2028, 186:13–19). Petitioner interprets this statement from the ’127 patent as a simple acknowledgement “that a POSITA would be able to make the claimed particles with methodologies known in the art.” *Id.* at 6.

Petitioner further argues that the same production methods are disclosed in both the ’127 patent and the ’069 patent, and that “Patent Owner’s expert further confirmed that for a given formulation and production method, [particle morphology] is inherent.” Reply 6–7 (citing Ex. 2009 ¶ 23; Ex. 1024, 356:7–15; *see id.* at 356:13–15 (“If it’s the same process parameters and the same formulation, I would expect the same outcome for a robust process.”).

Petitioner further argues that the ’127 patent identifies the ’031 patent publication for the direct dilution method, and that the ’031 patent publication is incorporated into the ’069 patent. *Id.* at 7 (citing Ex. 1001, 104:13–32; Ex. 1002, 11:37–48). Petitioner cites Dr. Janoff’s testimony that a person of ordinary skill “would have no difficulty reproducibly making the particles described in [the] ’069 [patent] and ’127 [patent].” *Id.* (citing Ex. 2028, 191:2–6).

Patent Owner argues in its Sur-reply that “specific production parameters are not established merely by identifying the method as ‘Direct Dilution.’” Sur-reply 4 (citing Ex. 2009 ¶¶ 50–64). Patent Owner also argues that “Petitioner makes no attempt to rebut the fact that ‘Direct Dilution’ is not a single method and that production parameters are critical.” *Id.* Patent Owner further argues that “the assertion that the claimed particles can be made by any method [] ignores the uncontroverted evidence that this is simply not the case.” *Id.* at 6 (citing Ex. 2009 ¶¶ 31–35; Ex. 1001, FIG. 7; Ex. 2028, 191:6–192:2).

Patent Owner’s arguments regarding the alleged lack of specificity by Petitioner of the cited formulations are addressed above. Patent Owner also argues that Petitioner’s reference to the direct dilution method lacks specificity, and that the ’031 patent publication shows different apparatuses, separate processes, and a variety of different parameters. PO Resp. 18–19.

As an initial matter, we agree with Petitioner that Patent Owner’s arguments are an attempt to rely on unclaimed process parameters in an effort to differentiate the prior art. *See* Reply 4. It is well settled that anticipation of a claim cannot be avoided by arguing process limitations that are not recited in the claim. *See Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938); *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1366–67 (Fed. Cir. 2009) (citing cases); *Verdegaal Bros.,* 814 F.2d at 632. Here, neither composition claim 1, nor any of the other challenged claims, recite or even suggest process limitations or parameters for preparing the recited composition. Pet. 13 n.3; Reply 4; Ex. 1001, 149:29–150:65. Patent Owner’s arguments regarding whether the direct dilution method is the “same,” or encompasses more than a single method, and the variety of parameters described in the ’031 patent publication, thus fail at the outset.

Patent Owner’s arguments that the term “direct dilution process” refers to “classes of processes that may encompasses innumerable process parameters,” and that the ’031 patent publication shows separate processes (not a single direct dilution process) and a variety of different parameters, are also unavailing. The pertinent inquiry is how the ’127 patent and ’069 patent describe the direct dilution process, because those descriptions are sufficient for a person of ordinary skill in the art to make the claimed compositions. *See* Ex. 2028, 191:2–6 (“a person of ordinary skill would have no difficulty reproducibly making the particles described in [the] ’069 [patent] and ’127 [patent].”); *see also* 35 U.S.C § 112(a). Moreover, Petitioner has argued throughout that the disclosure that is sufficient to practice the direct dilution method in the ’127 patent is the same disclosure in the ’069 patent. *See* Pet. 28–32; Reply 6–8.

The only disclosure of the Direct Dilution Method in the ’127 patent that results in the claimed morphological property is “described in detail” in the ’031 patent publication, which is also incorporated by reference. *See* Ex. 1001, 93:14–18, 104:32–37. Even the relevant direct dilution parameters listed in Table 1 of the ’127 patent, that were used to prepare formulations for testing, fall within the disclosure of the ’031 patent publication. Ex. 1024, 295:4–17; Ex. 1025 ¶ 17. That disclosure of the ’031 patent publication in the ’127 patent is thus sufficient for a person skilled in the art to make and use the claimed compositions, having the claimed morphological property, without undue experimentation. *See* 35 U.S.C § 112(a); *see also Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365

(Fed. Cir. 1997) (citing cases). Moreover, we also agree with Petitioner that the unequivocal statement in the ’127 patent that “[t]he lipid particles of the present invention . . . can be formed by any method known in the art” may be understood as meaning “that a POSITA would be able to make the claimed particles with methodologies known in the art.” *See* Reply 6.

The disclosure of the ’031 patent publication is the same in both the ’069 patent and the ’127 patent. *See* Ex. 1001, 104:32–37; Ex. 1002, 59:12–16. The disclosure that is sufficient to practice the direct dilution method in the ’127 patent is the same disclosure in the ’069 patent. *Id.* The disclosure of the ’069 patent is thus also sufficient to produce the claimed compositions, including compositions possessing the claimed morphological property. Stated another way, and as Petitioner has argued, both the ’127 patent and the ’069 patent teach those of ordinary skill in the art how to make the claimed compositions, having the claimed morphological property, using the direct dilution process as described in detail in the ’031 patent publication. *See* Pet. 28–32; Reply 6–8.

No Identified Formulations Produced by the same Direct Dilution Method

Patent Owner argues that, contrary to Petitioner’s assumption or implication, none of the 2:30, 2:40, 1:57, and 1:62 formulations are described in the ’069 patent as “having been generated using the direct dilution process.” PO Resp. 20–23; *see id* at 21. Thus, according to Patent Owner, the Petition “fails to establish that the specific cited formulations . . . were generated by a direct dilution process as forth in the ’031 [patent] publication, or any specific direct dilution method.” *Id.* at 23 (citing Ex. 2009 ¶ 64).

Petitioner responds that “actual reduction to practice is not required to anticipate,” citing *Schering Corp.*, 339 F.3d at 1380. Reply 8. We agree and find Patent Owner's argument unpersuasive because there is no requirement for a finding of anticipation that the '069 patent disclose that any of the formulations disclosed therein were actually prepared by the direct dilution process. *See Novo Nordisk*, 424 F.3d at 1355. Accordingly, this Decision is not based on whether the cited formulations are described in the '069 patent as "having been generated using the direct dilution process" (i.e. actually reduced to practice using the direct dilution method).

Experimental Evidence Submitted by Patent Owner

Patent Owner submitted the Heyes Declaration for the purpose of showing "experimental evidence demonstrating that lipid particles generated using a dilution process produced lamellar particles." PO Resp. 31. Patent Owner describes that experimental evidence as involving the preparation of two 2:30 nucleic acid-lipid formulations having the lipid composition described at column 73, lines 13–38, of the '069 patent. *Id.* at 32. Patent Owner states that column 73, lines 13–38, "is the only citation to the '069 patent in the petition materials identifying a specific formulation with any corresponding indication (*i.e.*, 'by syringe press') of the process by which particles were generated." *Id.* at n.8; Sur-reply 11. Patent Owner further states that "Dr. Heyes used a direct dilution process consistent with FIG. 3A of the '031 [patent] publication and the parameters therein, further modified to utilize[] a syringe press to drive the mixing of fluids in the experimental apparatus." PO Resp. 32. Patent Owner states that "a POSITA would not assume that 'a syringe press' recited at 73:13–39 of the '069 patent" indicates any particular process, and that the '031 patent publication does not discuss a syringe press. *Id.* at n.9 (citing Ex. 2009 ¶¶ 60–63).

According to Patent Owner, a report from NanoImaging Service, Inc. indicates that "neither 2:30 formulation meets the at least 95% non-lamellar morphology required by the challenged claims of the ’127 patent.” PO Resp. 32 (citing Ex. 2030 ¶¶ 20–23, Appendix A). Thus, according to Patent Owner, “[t]he study performed by Dr. Heyes further demonstrates that the formulations of the ’069 patent, even when made by a direct dilution method, do not necessarily and inevitably result in nucleic acid-lipid particles having the at least 95% non-lamellar morphology as recited in the challenged claims of the ’127 patent.” *Id.* at 33.

Petitioner responds that “Patent Owner relies on ‘testing’ to allege that every formulation and production method embodiment disclosed in the ’031 [patent] publication does not result in the claimed non-lamellar morphology.” Reply 10 (citing PO Resp. 31–32). Petitioner argues, however, that “there is no requirement that every embodiment result in non-lamellar morphologies” because, to anticipate by inherency, “a prior art reference need only describe ‘at least one embodiment that necessarily featured or resulted in the subject matter.’” *Id.* at 11 (citing *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1321 (Fed. Cir. 2004)).

Petitioner also argues that the two tests run by Patent Owner’s “longtime employee” Dr. Heyes are fundamentally flawed. *Id.* at 11–12. Petitioner argues that Dr. Heyes admitted that the parameters for the tests were chosen in large part by Patent Owner’s counsel, including the use of manual syringes and the selection of the 2:30 formulation.[22] Reply 11 (citing Ex. 1026, 77:22–78:6; 53:19–54:2). As an example, Petitioner states that “counsel for Patent Owner instructed Dr. Heyes to use two syringes to

[22] Patent Owner’s counsel argued at the Oral Hearing that the testing “was designed by counsel . . . Petitioner’s counsel was the one that designed this experiment . . . by virtue of . . . what was being asserted [in the Petition] as being providing the inherency.” Tr. 102:8–15.

manually inject the starting materials for mixing . . . despite the fact that such a method leads to flow rate variations . . . and an automatic syringe press is typically used in the field." *Id.* at 11–12 (citing Ex. 1026, 74:25–75:7, 83:7–14 ("[t]he syringe press is manual, so by virtue of that there are going to be some fluctuations."), 80:10–15). Petitioner also states that "Dr. Heyes also targeted a low flow rate that is known to potentially result in inconsistent mixing and estimated the flow rate by counting to five as he depressed the two syringe plungers." *Id.* at 12 (citing Ex. 1026, 82:21–83:6, 86:7–87:2). Petitioner further asserts that Dr. Heyes "specifically acknowledged that these [flow rate] parameters may have induced variation in the particles." *Id.* (citing Ex. 1026, 98:2–11; PO Resp. 2; Ex. 2028, 64:5–12; Ex. 1024, 359:13–360:22, 33:4–24).

Petitioner also cites to Dr. Janoff's testimony as support for the contention that a POSITA would not consider the tests conducted by Dr. Heyes "to be consistent with the disclosures in the '031 [patent] publication and the '069 patent." *Id.* at 12 (citing Ex. 1025 ¶ 19).

Petitioner further argues that the procedures and results of the testing by Dr. Heyes demonstrates that the data is unreliable. *Id.* at 13. First, Petitioner cites to the testimony of Dr. Heyes as support for the contentions that "he has not conducted such tests before . . . , [and] was unfamiliar with . . . the production methods in the '069 patent." *Id.* (citing Ex. 1026, 139:4–14, 11:15–25, 20:18–21:4).[23]

[23] Dr. Heyes specifically testified that he did not know how the SNALPs described at column 73, lines 13–39, of the '069 patent were formulated. Ex. 1026, 20:18–25 ("I would need to go away and review the '069 patent to —in detail to say how exactly they were formulated.").

Second, Petitioner cites to Dr. Janoff's testimony as support for the assertion that "the testing lacked protocols necessary to ensure reliability and reproducibility, including, *e.g.*, testing the particles produced, stability testing, and running the experiments in duplicate." *Id.* (citing Ex. 1025 ¶ 20). Petitioner also cites to the testimony of Dr. Heyes as support for the assertions that "Dr. Heyes did not test the lipid compositions of the formed particles to ensure that they represented the 2:30 formulation . . . He stored the samples for 7 days without doing any stability studies . . . [and he] further testified that he does not know if the test results are even reproducible." *Id.* (citing Ex. 1026, 72:12–73:12, 69:5–22, 67:12–23).

Petitioner further cites to the testimony of Dr. Heyes as support for the assertions that "the cryo-TEM procedures used in his 'tests' were different from those used in the '127 patent . . . cryo-TEM results for his tests indicate that there were 'very few particles' in each sample (41 and 110 compared with stated minimum of 250 particles)," and that "large amounts of the particles (22.7% and 12.2%) could not be evaluated as lamellar or non-lamellar." *Id.* (citing Ex. 1026, 144:19–145:3, 129:2–130:22; Ex. 2030, 13 [sic, 23]).

Patent Owner states in reply that "Dr. Heyes made particles according to the only specific process parameters and composition cited in the Petition [] and used parameters consistent with the direct dilution methodology disclosed in the '031 [patent] publication. [] That is, Patent Owner tried to follow the vague instructions in the Petition." Sur-reply 12 (citing Ex. 1002, 73:13–39; Ex. 1019; Resp. 32). Patent Owner also argues that "Petitioner quibbles that Dr. Heyes' data is unreliable . . . [but] Petitioner never articulates what procedure it believes Dr. Heyes should have followed." *Id.* at 13–14.

The testing performed by Dr. Heyes, and Patent Owner's arguments regarding such testing, are unpersuasive. We note at the outset that test results as to one formulation (2:30) and the purported use of a direct dilution method do not refute inherent anticipation. As Petitioner argues, the '069 patent need only describe "<u>at least one embodiment</u> that necessarily featured or resulted in the subject matter." Reply 11 (quoting *Toro*, 355 F.3d 1321); *see also Titanium Metals*, 778 F.2d at 782. If the law were otherwise, the public would be excluded from practicing the prior art. *See Atlas Powder*, 190 F.3d at 1346.

We also find that the probative value of the testing is diminished by the involvement of Patent Owner's counsel, as well as the selection of Dr. Heyes, an interested party, to do the testing. There is no evidence that Patent Owner's counsel [or Petitioner's counsel] is a person skilled in the art, to which the '069 patent is directed. *See* 35 U.S.C. § 112(a); *see also* Reply 12 (citing Ex. 1025 ¶ 19). Moreover, the testing was conducted by Dr. Heyes, an employee of Patent Owner, or a predecessor or successor of Patent Owner, since receiving his Ph.D. in 2001, rather than a disinterested third party. *See* Ex. 2030 ¶¶ 2–5.

We are also persuaded by Petitioner's arguments that call into question the reliability of the testing conducted by Dr. Heyes. Reply 13. We are persuaded by the testimony of Dr. Heyes reflecting an apparent lack of experience involving characterization of lamellar versus non-lamellar morphology of SNALP particles. Pet. 13; Ex. 1026, 139:4–21 ("I don't recall running an experiment where I counted lamellar versus nonlamellar, myself . . . [o]r had anybody else do it for me."). We are also persuaded by Dr. Janoff's testimony that Patent Owner's testing lacked protocols necessary to ensure reliability and reproducibility because of Dr. Janoff's experience with liposomes and lipid-delivery systems, including lipids having a non-lamellar morphology. *See* Reply 13–14 (Ex. 1025 ¶ 20); *see also* Ex. 1007 ¶¶ 10–23.

Petitioner specifically points to the lack of testing to ensure the particles represented the 2:30 formulation, storage of the samples for 7 days without stability studies, and the lack of knowledge by Dr. Heyes of whether the tests were reproducible. Pet. 13. We are also persuaded that the cryo-TEM analysis of the particles further confirms the unreliability of the testing by Dr. Heyes. *Id.* at 13–14 (citing Ex. 1025 ¶ 21). Patent Owner characterizes Petitioner's arguments regarding the reliability of the testing by Dr. Heyes as quibbling ("Petitioner quibbles that Dr. Heyes' testing is unreliable"), but that characterization does not persuade us that Petitioner's reliability arguments and evidence are unfounded or incorrect. *See* Sur-reply 13–14.

Analysis of Morphology Limitation

The named inventors on the '127 patent, which include all the named inventors on the '069 patent, assert that they made the "surprising discovery that by controlling *the lipid composition of a SNALP formulation* as well as *the formation process used to prepare the SNALP formulation*, a novel non-lamellar lipid nanoparticle (i.e., SNALP) can be produced." Ex. 1001, 8:51–55 (emphases added). Examples of "the lipid composition of a SNALP formulation" include formulations referred to as the 1:62 and 1:57 formulations, which are described in the '127 patent as "exemplary formulations of the present invention." *Id.* at 10:6–8. The formation process is described as "the Direct Dilution Method as described herein," which is "described in detail in [the '031 Patent Publication], the disclosure of which is herein incorporated by reference in its entirety for all purposes." *Id.* at

8:60–61, 104:32–37. Such statements in the ’127 patent may be used as evidence to establish inherent anticipation. *See In re Cruciferous Sprout Litigation*, 301 F.3d 1343, 1345, 1349–1351 (relying on statements in the patents-in-suit to show inherency); *see also Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1345 (Fed. Cir. 2018) (“[i]t is well established that [] reliance on extrinsic evidence is proper in an inherency analysis . . . [and] need not antedate the critical date of the patent at issue.”) (citations omitted).

Petitioner relies on statements in the ’127 patent, such as those referenced above, as evidence establishing the inherency of the claimed morphological limitation. *See* Pet. 25, 28–32. Petitioner points to formulations disclosed in the ’069 patent that are taught in the ’127 patent as having the claimed morphological property when they are prepared by the direct dilution process described in the ’031 patent publication. *See id.* at 24–32.

The identical nature of disclosed formulations is exemplified by the 1:62 formulation (Pet. 26) in both the ’069 patent and the ’127 patent,[24] as shown below:

[24] A similar comparison of formulations can be made with respect to the 1:57 formulation. *Compare* Ex. 1002, 24:13–25 *with* Ex. 1001, 6:18–32.

’069 Patent (1:62 formulation)	**’127 Patent (1:62 formulation)**
the nucleic acid-lipid particle (e.g., SNALP) comprises: (a) an siRNA; (b) a cationic lipid comprising from about 56.5 mol % to about 66.5 mol % of the total lipid present in the particle; (c) cholesterol or a derivative thereof comprising from about 31.5 mol % to about 42.5 mol % of the total lipid present in the particle; and (d) a PEG-lipid conjugate comprising from about 1 mol % to about 2 mol % of the total lipid present in the particle. Ex. 1002, 3:36–43.	a plurality of nucleic acid-lipid particles, wherein each particle in the plurality of particles comprises: (a) one or more unmodified and/or modified interfering RNA (e.g., *siRNA*, aiRNA, miRNA) that silence target gene expression; (b) a cationic lipid comprising from about 56.5 mol % to about 66.5 mol % of the total lipid present in the particle; (c) a non-cationic lipid comprising from about 31.5 mol % to about 42.5 mol % of the total lipid present in the particle; and (d) a conjugated lipid that inhibits aggregation of particles comprising from about 1 mol % to about 2 mol % of the total lipid present in the particle, *wherein at least about 95% of the particles in the plurality of particles have a nonlamellar morphology*. Ex. 1001, 5:61–6:7 (emphases added).

The ’069 patent also states that “the present invention provides a lipid particle (e.g, SNALP) *composition comprising a plurality of lipid particles*.” Ex. 1002, 23:15–17 (emphasis added).

The ’069 patent describes siRNA as silencing target gene expression (*id.* at 17:9–12), and “cholesterol or a derivative thereof” as a preferred embodiment of a non-cationic lipid (*id.* at 19:10–15). The ’127 patent describes a preferred embodiment of the 1:62 formulation wherein the non-cationic lipid is cholesterol. Ex. 1001, 6:8–11. Thus, in the comparison shown above, the ranges of the respective lipids in the 1:62 formulation of the ’069 patent are identical to the ranges of the respective lipids in the 1:62 formulation of the ’127 patent.

As also taught by the ’127 patent, the claimed morphological property results from using the Direct Dilution Method to prepare particle formulations. *Id.* at 8:50–62. For example, the ’127 patent uses the 1:62 formulation comprising ApoB siRNA as the nucleic acid, 1.5 mol % PEG2000-C-DMA (conjugated lipid), 62 mol % DLinDMA (cationic lipid), and 37 mol % Cholesterol (non-cationic lipid), prepared by the Direct Dilution Method of the ’031 patent publication, to show that 707 particles out of 709 resulting particles (99.7%) had a non-lamellar morphology. *Id.* at 104:32–37, 61–63, 105:51–65 (Table 3); 109:29–35; *see also* Pet. 31. But the ’069 patent discloses the 1:62 formulation comprising ApoB siRNA as the nucleic acid, 1.5 mol % PEG(2000)-C-DMA (conjugated lipid), 61.5 mol % DLinDMA (cationic lipid), and 36.9 mol % Cholesterol (non-cationic lipid),[25] and also teaches the preparation of that formulation, as well as others, by the direct dilution process or method of the ’031 patent publication. Ex. 1002, 74:16–36 (Table 6, Group 3); 57:50–55; 59:12–16; *see also* Pet. 31.

As shown by Petitioner, the direct dilution method is also described in the same way in both the ’127 patent and the ’069 patent. *See* Pet. 29, 31; *see also* Ex. 1001, 104:32–37 (“[t]he Direct Dilution Method (“DDM”) . . .

[25] As acknowledged by Dr. Thompson, and addressed above, minor percentage differences in formulations would not be expected to change the morphological structure of the resulting particles. Ex. 1024, 326:7–19 (cited at Reply 15).

as well as the apparatuses for carrying out the DDM are described in detail in [the ’031 patent publication], the disclosure of which is herein incorporated by reference in its entirety for all purposes.”); Ex. 1002, 59:12–16 (“[t]hese processes and the apparatuses for carrying out these direct dilution processes are described in detail in [the ’031 patent publication], the disclosure of which is herein incorporated by reference in its entirety for all purposes.”).

Petitioner also correctly asserts that “the discovery of a previously unappreciated property of a prior art composition . . . does not render the old composition patentably new to the discoverer.” Pet. 25–26 (citing *Atlas Powder*, 190 F.3d at 1347); *see also Titanium Metals*, 778 F.2d at 782 (“it is immaterial, on the issue of [the] novelty [of claims to an alloy that recited a property of the alloy], what inherent properties the alloys have or whether these applicants discovered certain inherent properties”).

Petitioner has persuasively shown that one or more formulations disclosed in the ’069 patent, such as the 1:62 formulation cited by Petitioner and reproduced above, are the same or essentially the same as formulations disclosed in ’127 patent, and that the direct dilution process or method disclosed in both the ’069 patent and the ’127 patent is “described in detail” in the ’031 patent publication. *Compare* Ex. 1002, 59:12–16, *with* Ex. 1001, 104:32–37, 93:14–18. Moreover, the ’127 patent teaches that making its disclosed formulations with the process described in the ’031 patent results in particles wherein at least about 95% [or greater than 95%] of the particles in the plurality of particles have a non-lamellar morphology. Ex. 1001, 8:51–62, 104:32–37, 109:11–110:21. That is, according to the ’127 patent, making formulations disclosed therein with the process described in the ’031 patent publication would naturally result in a composition having the claimed morphological property. *See SmithKline Beecham*, 403 F.3d at 1343–44.

We thus find that, prior to the filing of the ’127 patent, a person skilled in the art following the disclosure of the ’069 patent, could readily make a composition as recited in claim 1 having the inherent morphological property recited in claim 1. Stated another way, claim 1 as written “would allow [Patent Owner] to exclude the public from practicing the prior art.” *See Atlas Powder*, 190 F.3d at 1346.

Patent Owner’s arguments do not persuade us otherwise. As discussed above, Patent Owner’s arguments focus on actual reduction to practice and unclaimed (and undisclosed) process limitations to distinguish the prior art. As further discussed above, the testing done by Dr. Heyes and submitted by Patent Owner has little or no probative value on the issue of whether the disclosure of the ’069 patent anticipates the ’127 patent.

Conclusion – Anticipation of Claim 1

We find that Petitioner has shown by a preponderance of the evidence that the morphology limitation recited in claim 1 is an inherent property or natural result of making one or more formulations disclosed in the ’069 patent by the direct dilution process of the ’031 patent publication, which is also disclosed in the ’069 patent. We credit the testimony of Dr. Janoff for this finding because his testimony is based on objective factual evidence, such as factual corroboration by the identity of the formulations and process to make the claimed particles as described in the ’069 patent and the ’127 patent.

Accordingly, having persuasively established that the formulation limitations of claim 1 are expressly disclosed by the ’069 patent, and that the morphological property limitation is inherently disclosed by the ’069 patent, we find, based on the trial record as a whole, that Petitioner has shown by a preponderance of the evidence that claim 1 is anticipated by the ’069 patent.

Anticipation – Claims 2–22

Petitioner identifies disclosures in the ’069 patent, including patent publications incorporated therein, that it argues disclose the limitations of claims 2–22. Pet. 33–42 (citing Ex. 1007 ¶¶ 109–130). Patent Owner generally argues the patentability of claims 2–22 “by virtue of their dependency from claim 1—which the petition fails to demonstrate as unpatentable.” PO Resp. 38 (citing Ex. 2009 ¶¶ 91–92). Patent Owner also generally argues that the challenges to claims 2–22 are not presented with the requisite degree of particularity. PO Resp. 39 (citing 35 U.S.C. § 312(a)(3); 37 C.F.R. § 42.104(b); Prelim. Resp. 5); Sur-reply 20. Patent Owner asserts that, for a vast majority of the claims, it is unclear what specific challenge is being advanced (i.e. anticipation or obviousness). *Id.*

As set forth above, we find claim 1 to be anticipated by the ’069 patent. *See* II.D.2 *supra*. Moreover, as to Petitioner’s challenge based on the ’069 patent, Petitioner makes clear that its obviousness arguments are an “alternative” to its inherency arguments regarding the morphology limitation, and Petitioner specifically argues inherent anticipation as to dependent claims 9 and 19. Pet. 32, 35, 41.

Patent Owner also advances specific arguments regarding certain claims, and those are addressed below in connection with the respective claim.

Claim 2

Claim 2 recites “[t]he composition of claim **1**, wherein the nucleic acid is an interfering RNA.” Ex. 1001, 149:38–39. Petitioner cites the disclosure of the ’069 patent of a “nucleic acid-lipid particle . . . wherein the nucleic acid comprises a small interfering RNA (siRNA).” Pet. 33 (citing Ex. 1002, 91:36–37 (claim 2); Ex. 1007 ¶ 109). Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 2 is anticipated by the disclosure of the ’069 patent.

Claim 3

Claim 3 recites “[t]he composition of claim **1**, wherein the nucleic acid is mRNA.” Ex. 1001, 149:40–41. Petitioner cites the disclosure of the ’069 patent that the term “nucleic acid” refers to “a polymer containing at least two deoxyribonucleotides or ribonucleotides . . . RNA may be in the form of . . . mRNA.” Pet. 33 (citing Ex. 1002, 10:16–26; Ex. 1007 ¶ 110).

Patent Owner responds that “[a] POSITA would understand that mRNA is typically larger than siRNA, and the size of the payload would be expected to affect the physical properties of a particle.” PO Resp. 39–40 (citing Ex. 2009 ¶¶ 93–94). But the inquiry here is what is taught by the disclosure of the ’069 patent, which expressly teaches that the nucleic acid can be mRNA. Also, Patent Owner’s arguments are not persuasive of what a POSITA would understand when the patent at issue, the ’127 patent, also expressly states that the term “nucleic acid” refers to “a polymer containing at least two deoxyribonucleotides or ribonucleotides . . . RNA may be in the form of . . . mRNA.” Ex. 1001, 14:62–15:6. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 3 is anticipated by the disclosure of the ’069 patent.

Claim 4

Claim 4 recites “[t]he composition of claim **1**, wherein the non-cationic lipid is a mixture of a phospholipid and cholesterol or a cholesterol derivative.” Ex. 1001, 149:42–44. Petitioner cites the disclosure of the ’069 patent of “a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof." Pet. 34 (citing Ex. 1002, 91:28–33 (claim 1 (c)); Ex. 1007 ¶ 111). Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 4 is anticipated by the disclosure of the ’069 patent.

Claim 5

Claim 5 recites "[t]he composition of claim **1**, wherein the conjugated lipid that inhibits aggregation of the particles is a polyethyleneglycol (PEG)-lipid conjugate." Ex. 1001, 149:45–47. Petitioner cites the disclosure of the ’069 patent (claim 10) of a "nucleic acid-lipid particle . . . wherein the conjugated lipid that inhibits aggregation of particles comprises a polyethyleneglycol (PEG)-lipid conjugate." Pet. 34 (citing Ex. 1002, 91:56–58 (claim 10); Ex. 1007 ¶ 112). Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 5 is anticipated by the disclosure of the ’069 patent.

Claims 6 and 7

Claim 6 recites "[t]he composition of claim **5,** wherein the PEG-lipid conjugate is selected from the group consisting of a PEG-diacylglycerol (PEG-DAG) conjugate, a PEG dialkyloxypropyl (PEG-DAA) conjugate, a PEG-phospholipid conjugate, a PEG-ceramide (PEG-Cer) conjugate, and a mixture thereof." Ex. 1001, 149:48–52. Petitioner cites to the disclosure in claim 11 of the ’069 patent, which depends on claim 10, of a "nucleic acid-lipid particle . . . wherein the PEG-lipid conjugate comprises a PEG-diacylglycerol (PEG-DAG) conjugate, a PEG-dialkyloxypropyl (PEG-DAA) conjugate, or a mixture thereof." Pet. 34 (citing Ex. 1002, 91:59–62 (claim 11)). Petitioner further asserts that, because the group recited in claim 6 includes PEG-DAG and PEG-DAA, the claim limitation is disclosed by the ’069 patent. *Id.* (citing Ex. 1007 ¶ 113).

Claim 7 recites "[t]he composition of claim **6,** wherein the PEG-DAA conjugate is a member selected from the group consisting of a PEG-didecyloxypropyl (C_{10}) conjugate, a PEG-dilauryloxypropyl (C_{12}) conjugate, a PEG-dimyristyloxypropyl (C_{14}) conjugate, a PEG-dipalmityloxypropyl (C_{16}) conjugate, a PEG-distearyloxypropyl (C_{18}) conjugate, and a mixture thereof." *Id.* at 149:53–59. Petitioner cites to the disclosure in the '069 patent that "[t]he PEG-DAA conjugate may be PEG-dilauryloxypropyl (C12), a PEG-dimyristyloxypropyl (C14), a PEG-dipalmityloxypropyl (C16), a PEG-distearyloxypropyl (C18), or mixtures thereof." Pet. 35 (citing Ex. 1002, 21:56–60). Petitioner further asserts that, because the group recited in claim 7 includes [PEG-dilauryloxypropyl] (C12) conjugate, a PEG-dimyristyloxypropyl (C14) conjugate, a PEG-dipalmityloxypropyl (C16) conjugate, a PEG-distearyloxypropyl (C18) conjugate, the claim limitation is disclosed by the '069 patent. *Id*. (citing Ex. 1007 ¶ 114).

Patent Owner argues as to claims 6 and 7 that "[t]here is no explanation as to how the cited disclosure relates to the different arguments made in the context of claim 1," and that "[t]here is no explanation of what is being modified or how the modified formulation would inherently meet the limitations required by the claim." PO Resp. 40 (citing Ex. 2009 ¶¶ 95–98]. We are not persuaded because Patent Owner's arguments appear to be directed to obviousness, whereas the anticipation inquiry relates to the disclosure of the '069 patent relative to whether each of the limitations of claims 1 and 5–7 are taught. It is clear that Petitioner is arguing that each of the limitations of claim 6, as dependent on claims 1 and 5, and claim 7, as dependent on claims 1, 5, and 6, are expressly disclosed in the '069 patent. *See, e.g.*, Ex. 1002, claims 1, 10, 11; 21:56–60. Therefore, we find that

Petitioner has shown by a preponderance of the evidence that claims 6 and 7 are anticipated by the disclosure of the ’069 patent.

Claim 8

Claim 8 recites “[t]he composition of claim **1**, wherein the nucleic acid is fully encapsulated in the particles.” Ex. 1001, 149:60–61. Petitioner cites the disclosure of the ’069 patent of a “nucleic acid-lipid particle . . . wherein the nucleic acid is fully encapsulated in the nucleic acid-lipid particle.” Pet. 35 (citing Ex. 1002, 92:42–44 (claim 17); Ex. 1007 ¶ 115). Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 8 is anticipated by the disclosure of the ’069 patent.

Claim 9

Claim 9 recites “[t]he composition of claim **1**, wherein the non-lamellar morphology of the particles comprises an inverse hexagonal (H_{II}) or cubic phase structure.” Ex. 1001, 149:62–64. Petitioner asserts that this additional limitation is inherently anticipated “because the ’127 patent claims a property, the ‘inverse hexagonal (H_{II}) or cubic phase structure,’ that is a natural result of the formulations disclosed in the ’069 patent as addressed” in connection with the morphological property limitation of claim 1. Pet. 35–36 (citing Ex. 1001, 9:21–24, Fig. 21; Ex. 1007 ¶ 116). Figure 21 of the ’127 patent, cited by Petitioner, is descried as illustrating “an inverse Hexagonal (H_{II}) or Cubic Phase structure of the non-lamellar stable nucleic acid-lipid particles prepared by the Direct Dilution Method.” Ex. 1001, 8:44–46.

Patent Owner argues that “the Board already determined [that Petitioner’s anticipation challenge to claim 9] is insufficient to establish anticipation.” PO Resp. 40 (citing Inst. Dec. 19). Not so. The Institution Decision included all claims and all grounds, and no claim was "determined" to be patentable or unpatentable in the Institution Decision. Patent Owner further argues that "one conclusory comment is insufficient to establish anticipation for [] claim 9." *Id.*

Petitioner responds that various non-lamellar 3-dismensional structures were well-known in the art, and that the '613 patent (incorporated into the '069 patent) "identifies different 3-dimensional structures for nucleic acid-lipid particles, including the inverse hexagonal phase . . . and cubic phases." Reply 21 (citing Ex. 1010, 273 [sic, 277]; Ex. 1017, 7:14–36; 19:1–12; Ex. 1007 ¶ 34 [sic, ¶ 64]).

We find on the trial record as a whole that the claimed inverse hexagonal (H_{II}) or cubic phase structure, recited in claim 9, is a property of the inherent non-lamellar morphology recited in claim 1. *See* Pet. 8 (discussing and illustrating inverted hexagonal structure of non-lamellar particles). We also find that the structures recited in claim 9 are disclosed in the '069 patent through incorporation of the '613 patent. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 9 is anticipated by the disclosure of the '069 patent.

Range Claims

Claims 10–18 are directly dependent on claim 1. Each of those claims recite percentage ranges for one of the lipid components (cationic lipid, non-cationic lipid, and conjugated lipid) recited in claim 1. As discussed below, the '069 patent discloses, including by incorporation by reference, (a) a percentage point within the claimed range, thereby anticipating that range, *see Titanium Metals*, 778 F.2d at 781, and/or (b) its own range that "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." *See Ineos USA LLC v. Berry*

Plastics Corp., 783 F.3d 865, 869 (Fed. Cir. 2015) (finding anticipation of claimed range of 0.05–0.5% by weight lubricant by prior art disclosing 0.1%–1% by weight lubricant).[26] Anticipation has also been found when the prior art range "does not exactly correspond to [the] claimed range," but the prior art "range entirely encompasses, and does not significantly deviate from, [the] claimed ranges." *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005) (finding that prior art range of 0.01–20% by weight fatty acid ester encompassed and did not significantly deviate from a claimed range of from about 0.025–5% by weight of a fatty acid ester).

Claims 10 and 11

Claim 10 recites "[t]he composition of claim **1**, wherein the cationic lipid comprises from about 10 mol % to about 50 mol % of the total lipid present in the particle." Ex. 1001, 149:65–67. Claim 11 recites "[t]he composition of claim **1**, wherein the cationic lipid comprises from about 20 mol % to about 50 mol % of the total lipid present in the particle." *Id.* at 150:29–31.

Petitioner cites to several disclosures in the '069 patent, through incorporation by reference, that disclose cationic lipid amounts of 25% (the '025 patent publication), 30% (the '031 patent publication), and "about 10% to about 45%, from about 20% to about 40%, or about 30% of the total lipid present in said particle" (the '780 patent publication). Pet. 36–38 (citing Ex. 1018 ¶¶ 52, 98; Ex. 1019 ¶ 88; Ex. 1020 ¶ 51; Ex. 1007 ¶¶ 117, 118).

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[26] *Ineos USA* also addresses the role that criticality may play in evaluating a claimed range. *Ineos USA*, 783 F.3d at 871. Patent Owner has not advanced any evidence or argument that the claimed ranges are critical. *See generally* P.O. Resp. and Sur-reply.

The disclosures of 25% and 30% recite specific points that lie within the ranges recited in claims 10 and 11. *See Titanium Metals*, 778 F.2d at 781. The prior art ranges of about 10% to about 45% and from about 20% to about 40% also describe the claimed ranges with sufficient specificity to anticipate. *See* Ex. 1007 ¶¶ 117, 118; *see also Ineos USA*, 783 F.3d at 869.

Patent Owner argues that Petitioner relies on "a patchwork of disclosures" and, "[r]ather than identifying a single embodiment with the recited claim features, Petitioner picks and chooses amongst different disclosures from different references." PO Resp. 41. We disagree. The '069 patent is the anticipatory reference, and its disclosure includes the disclosures of the '025 patent publication, the '031 patent publication, and '780 patent publication. *See Advanced Display Sys.*, 212 F.3d at 1282. Petitioner's citations discussed above are simply multiple specific points or ranges within the '069 patent disclosure, *all* of which disclose a point or range that anticipates the claimed ranges. Furthermore, the 2:40 formulation disclosed in the '069 patent includes about 40 mol % cationic lipid (DLinDMA), which lies within the claimed ranges. *See* Ex. 1002, 72:24–54, Table 4 (Groups 2–7); Pet. 26, 29.

Patent Owner further argues that "it is also unclear how the disclosure of overlapping and encompassing ranges relates to Petitioner's theory that the '069 patent inherently anticipates claim 1 of the '127 patent." PO Resp. 42 (citing Ex. 2009 ¶¶ 100, 101). As explained in the Petition and set forth above, the claimed formulation components and their ranges are expressly disclosed in the '069 patent, including the above cited references disclosing various amounts of the claimed cationic lipid, and the morphological limitation is an inherent property of the expressly discloses formulations. Moreover, the '025 patent publication, the '031 patent publication, and '780 patent publication are cited in the ’069 patent in connection with nucleic acid-lipid particles. *See* Ex. 1002, 11:44–46; 47:29–60. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claims 10 and 11 are anticipated by the disclosure of the ’069 patent.

Claim 12

Claim 12 recites “[t]he composition of claim **1**, wherein the cationic lipid comprises from about 20 mol % to about 40 mol % of the total lipid present in the particle.” Ex. 1001, 150:32–34. Petitioner refers to the disclosures cited in connection with claim 10 as including examples of points within the claimed range, and that the disclosed range of about 20% to about 40% expressly discloses the claimed range. Pet. 38 (citing Ex. 1007 ¶ 119; Ex. 1018; Ex. 1019; Ex. 1020). As discussed above in connection with claim 10, those disclosures include specific percentages of 25%, 30%, and “from about 20% to about 40%, or about 30% of the total lipid present in said particle.” All of those disclosures anticipate the claimed range of “about 20 mol % to about 40 mol % of the total lipid present in the particle” for the reasons discussed in connection with claim 10. *See Ineos USA*, 783 F.3d at 869; *see also Titanium Metals*, 778 F.2d at 781. Moreover, the prior art range of from about 20% to about 40% is the same as, and encompasses, the claimed range. *See Perricone*, 432 F.3d at 1377.

Patent Owner argues that Petitioner refers to specific formulations in discussing claim 1, “but pivots to disclosures of the ’025, ’031, and ’780 publications in discussing claim 12.” PO Resp. 42–43 (citing Pet. 38; Ex. 2009 ¶ 102). We are not persuaded, at least because the anticipation challenge is based on the disclosure of the ’069 patent, which includes the disclosures of the ’025 patent publication, the ’031 patent publication, and the ’780 patent publication, which are cited in the ’069 patent in connection with the nucleic acid-lipid particles. *See* Ex. 1002, 11:44–46, 47:29–60. Furthermore, a 2:40 formulation disclosed in the ’069 patent includes about 36.4 mol % cationic lipid (DLinDMA), which lies within the claimed range. *See* Ex. 1002, 72:24–54, Table 4 (Group 6); Pet. 26, 29. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 12 is anticipated by the disclosure of the ’069 patent.

Claims 13–14

Claim 13 recites “[t]he composition of claim **1**, wherein the non-cationic lipid comprises from about 10 mol % to about 60 mol % of the total lipid present in the particle.” Ex. 1001, 150:35–37. Claim 14 recites “[t]he composition of claim **1**, wherein the non-cationic lipid comprises from about 20 mol % to about 55 mol % of the total lipid present in the particle.” *Id.* at 150:38–40.

Petitioner cites to the disclosures in the ’069 patent that “[i]n some embodiments, the non-cationic lipid (e.g., one or more phospholipids and/or cholesterol) may comprise from about 10 mol % to about 60 mol % . . . [or] about 20 mol % to about 55 mol % . . . of the total lipid present in the particle.” Pet. 38–39 (citing Ex. 1002, 19:39–50; Ex. 1007 ¶¶ 120, 121). That disclosure exactly encompasses the claimed ranges. *See* Ex. 1007 ¶¶ 120, 121; *see also Perricone*, 432 F.3d at 1377. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claims 13 and 14 are anticipated by the disclosure of the ’069 patent.

Claim 15

Claim 15 recites “[t]he composition of claim **1**, wherein the non-cationic lipid comprises from about 25 mol % to about 50 mol % of the total lipid present in the particle.” Ex. 1002, 150:41–43. Petitioner cites to the disclosure in the ’069 patent that “the non-cationic lipid (e.g., one or more phospholipids and/or cholesterol) may comprise . . . from about 20 mol % to about 49.5 mol % . . . of the total lipid present in the particle." Pet. 39 (citing Ex. 1002, 19:54–62). Petitioner asserts that "about 50%" as claimed encompasses 49.5%, and would be so understood by a POSITA, relying on the testimony of Dr. Janoff. *Id.* (citing Ex. 1007 ¶ 122). Petitioner thus asserts that the prior art range of from about 20 mol % to about 49.5 mol % "encompasses and discloses the claimed range and does so with sufficient specificity to anticipate." *Id.* (citing Ex. 1007 ¶ 122); *see Perricone*, 432 F.3d at 1377; *Ineos USA*, 783 F.3d at 869.

Patent Owner argues that Petitioner refers to a "1:57 formulation" and Tables in the '069 patent, but that it is unclear precisely which formulation is being relied upon. PO Resp. 43 (citing Pet. 39–40; Ex. 2009 ¶ 103). That argument is unavailing, however, because that citation by Petitioner is not necessary to establish anticipation given Petitioner's other evidence discussed above. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 15 is anticipated by the disclosure of the '069 patent.

Claim 16

Claim 16 recites "[t]he composition of claim **1**, wherein the conjugated lipid that inhibits aggregation of the particles comprises from about 0.5 mol % to about 20 mol % of the total lipid present in the particle." Ex. 1001, 150:44–47. Petitioner cites to the disclosure of the '069 patent that "the conjugated lipid that inhibits aggregation of particles (e.g., PEG-lipid conjugate) may comprise . . . from about 0.5 mol % to about 2 mol % . . . of the total lipid present in the particle." Pet. 40 (citing Ex. 1002, 22:30–42).

Petitioner also cites to the ’780 patent publication, that is incorporated into the ’069 patent, for the disclosure that “[t]he PEG-lipid conjugate typically comprises from about 1% to about 20%, from about 1.5% to about 18%, from about 4% to about 15%, from about 5% to about 12%, or about 2% of the total lipid present in said particle.” *Id.* (citing Ex. 1020 ¶ 51; Ex. 1007 ¶ 124). Petitioner argues that the disclosure of the ’069 patent thus discloses the claimed range of 0.5%–20% with sufficient specificity to anticipate. *Id.* (citing Ex. 1007 ¶ 124); *see also Ineos USA*, 783 F.3d at 869. We also find that “about 2%” falls within the claimed range. *See Titanium Metals*, 778 F.2d at 781.

Patent Owner argues that Petitioner refers to a “1:57 formulation” and Tables in the ’069 patent, but that it is unclear precisely which formulation is being relied upon. PO Resp. 43 (citing Pet. 39–40; Ex. 2009 ¶ 103). That argument is unavailing, however, because that citation by Petitioner is not necessary to establish anticipation given Petitioner’s other evidence discussed above. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 16 is anticipated by the disclosure of the ’069 patent.

Claim 17

Claim 17 recites “[t]he composition of claim **1**, wherein the conjugated lipid that inhibits aggregation of the particles comprises from about 2 mol % to about 20 mol % of the total lipid present in the particle.” Ex. 1001, 150:48–51. Petitioner refers back to its discussion of claim 16, and specifically that the disclosure of about “1% to about 20%” in the ’780 patent publication encompasses the claimed range. Pet. 41 (citing Ex. 1007 ¶ 125). Petitioner cites to Dr. Janoff’s testimony that “[f]rom these disclosures, a POSITA would appreciate that the claim limitation is disclosed with sufficient specificity to anticipate." Ex. 1007 ¶ 125. We find that the prior art range entirely encompasses, and does not significantly deviate from, the claimed range. *See Perricone*, 432 F.3d at 1377; *see also Ineos USA*, 783 F.3d at 869. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 17 is anticipated by the disclosure of the ’069 patent.

Claim 18

Claim 18 recites "[t]he composition of claim **1**, wherein the conjugated lipid that inhibits aggregation of the particles comprises from about 1.5 mol % to about 18 mol % of the total lipid present in the particle." Ex. 1001, 150:52–55. Petitioner refers back to its discussion of claim 16, and specifically that the disclosure of "about 1.5% to about 18%" is specifically disclosed in the ’780 patent publication. Pet. 41 (citing Ex. 1007 ¶ 126). Petitioner cites to Dr. Janoff's testimony that the claimed range is specifically disclosed and "a POSITA would appreciate that the claim limitation is expressly disclosed." *Id.* (citing Ex. 1007 ¶ 126). We find that the prior art range encompasses the claimed range, and describes the claimed range with sufficient specificity to anticipate. *See Perricone*, 432 F.3d at 1377; *Ineos USA*, 783 F.3d at 869. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 18 is anticipated by the disclosure of the ’069 patent.

Claim 19

Claim 19 recites "[t]he composition of claim 1, wherein greater than 95% of the particles have a non-lamellar morphology." Ex. 1001, 150:56–57. Petitioner asserts that the ’069 patent inherently anticipates the limitation of claim 19 because it claims a property that is the natural result of the formulations disclosed in the ’069 patent, as discussed above in connection with morphology limitation of claim 1. Pet. 41 (citing Ex. 1007 ¶ 127). That is, "to the extent that the '069 patent discloses particle populations 'where at least about 95%' are non-lamellar, the same reasoning would apply" to claim 19. Reply 20.

Patent Owner asserts that claim 19 recites language not found in the morphology limitation of claim 1, and is wholly unaddressed in the Petition. PO Resp. 40. Patent Owner further argues that "one conclusory comment [in the Petition] is insufficient to establish anticipation for [] claim 9." *Id.*

We are persuaded by Petitioner. In describing the "surprising discovery that by controlling the lipid composition of a SNALP formulation as well as the formation process . . . a novel non-lamellar lipid nanoparticle (i.e., SNALP) can be produced," the '127 patent states that "wherein at least about 95% of the particles in the plurality of particles have a non-lamellar morphology. In preferred embodiments, greater than 95%." Ex. 1001, 8:51–9:9; *see also id*. at 2:64–3:22. The '127 patent also teaches that formulations, such as the 1:57 and 1:62 formulations, prepared by the Direct Dilution Method (describe in detail in the '031 patent publication), result in greater than 95% of the particles having a non-lamellar morphology. *See, e.g.,* 109:22–37. Thus, for the same reasons that the claim limitation "at least about 95%" of the particles have a non-lamellar morphology is an inherent property, as describe above in connection with claim 1, the limitation "greater than 95%" of the particles have a non-lamellar morphology is also an inherent property. *See* Section II.D.2 *supra*. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claim 19 is anticipated by the disclosure of the '069 patent.

Claims 20–22

The recitations of claims 20–22 are set forth above. *See* Section I.C. *supra*. As to claim 20, Petitioner cites to the disclosure in the '069 patent that "when administered intravenously, the lipid particle formulations are formulated with a suitable pharmaceutical carrier. Many pharmaceutically acceptable carriers may be employed in the compositions and methods of the present invention." Pet. 41–42 (citing Ex. 1002, 63:18–22; Ex. 1007 ¶ 128).

As to claim 21, Petitioner cites to the disclosure in the '069 patent that "the present invention provides methods for introducing an active agent or therapeutic agent (e.g., nucleic acid) into a cell, the method comprising contacting the cell with a lipid particle described herein such as a nucleic acid-lipid particle (e.g., SNALP)." *Id.* at 42 (citing Ex. 1002, 3:60–64; Ex. 1007 ¶ 129).

As to claim 22, Petitioner cites to the disclosure in the '069 patent that "the present invention provides methods for the in vivo delivery of an active agent or therapeutic agent (e.g., nucleic acid), the method comprising administering to a mammalian subject a lipid particle described herein such as a nucleic acid-lipid particle (e.g., SNALP)." *Id.* (citing Ex. 1002, 3:65–4:2; Ex. 1007 ¶ 130).

Patent Owner states that Petitioner's arguments regarding claims 20–22 fail for the same reasons as Petitioner's analysis of claim 1, and the additional citations to the '069 patent do not remedy the deficiencies discussed by Patent Owner as to claim 1. PO Resp. 43 (citing Ex. 2009 ¶ 104). This argument by Patent Owner fails because we find Petitioner's analysis of claim 1 persuasive. Therefore, we find that Petitioner has shown by a preponderance of the evidence that claims 20–22 are anticipated by the disclosure of the '069 patent.

Conclusion – Anticipation of Claims 2–22

Accordingly, based on the trial record as a whole and the reasons set forth above, we find that the ’069 patent discloses the limitations of claims 2–22, and that Petitioner has shown by a preponderance of the evidence that claims 2–22 are anticipated. Our reasons include the reasons set forth above regarding claim 1 and all other claims from which any of claims 2–22 directly or indirectly depend. We credit the testimony of Dr. Janoff as support for these findings because his testimony is supported by objective factual evidence of record, such as factual corroboration by the ’069 patent.

Objections and Other Arguments

Patent Owner filed a Notice of Objection to Evidence in response to Petitioner’s Reply. Paper 28. However, those objections were not subsequently preserved with a motion to exclude, and thus no relief can be granted concerning those objections. 37 C.F.R. § 42.64(c) (“A motion to exclude evidence must be filed to preserve any objection.”). Patent Owner’s Notice of Objection to Evidence is overruled.

Patent Owner also filed a Notice of Objection to Petitioner’s Demonstrative Exhibits. Paper 43. Patent Owner’s objections are presented as general categories of objections with identification of Petitioner’s slides that it contends fall within those broad categories. *Id.* at 1. However, it is not the Board’s duty to sort through multiple slides in an effort to discern what particular information is subject to Patent Owner’s general objection. Nevertheless, we overrule Patent Owner’s objections to Petitioner’s demonstrative exhibits (slides), at least because demonstrative exhibits are not evidence, and we rely on evidence in the trial record in reaching our Decision. *See* Office Patent Trial Practice Guide, August 2018 Update, 21, 83 Fed. Reg. 39,989 (Aug. 13, 2018) ("Demonstrative exhibits used at the final hearing are aids to oral argument and not evidence").

Arguments Regarding Experts

Petitioner and Patent Owner assert that the testimony of the other party's expert, Dr. Thompson and Dr. Janoff, respectively, should be accorded limited or no weight. *See* Reply 2–3; PO Resp. 2–3.

Petitioner's Arguments

Petitioner argues that Dr. Thompson "is not qualified to offer [] opinions" that the prior art does not disclose formulations resulting in the claimed non-lamellar structure, and that the physical properties of the particles described as tested in the '069 patent are different from those tested in the '127 patent. Reply 2 (citing Ex. 2009 ¶¶ 12–30). According to Petitioner, Dr. Thompson "does not appear to have any significant experience with lipid particle formation and use in the context of delivering therapeutic payloads." *Id.* at 2–3 (citing Ex. 1023, 21:9–25, 46:3–10, 49:11–17, 74:20–75:13). Petitioner also argues that Dr. Thompson "did not even completely review references . . . cited in his declarations." *Id.* at 3 (citing Ex. 1024, 388:9–13, 389:17–22, 397:24–398:11).

Our Decision does not rest on an evaluation of Dr. Thompson's qualifications. For example, Patent Owner's argument regarding differences in physical properties of tested particles in the '069 patent and the '127 patent is unpersuasive for the reasons set forth above, which are not based on the qualifications of Dr. Thompson. Accordingly, we find no reason on this record to address the qualifications of Dr. Thompson.

Patent Owner's Arguments

Patent Owner argues that Dr. Janoff's Declaration (Ex. 1007) should be accorded "no weight." PO Resp. 2. Patent Owner argues that, according to Dr. Janoff's testimony, his declaration is "based on the petition," and thus constitutes attorney argument. *Id.* at 3–4 (citing Ex. 1007 ¶¶ 27, 5–7; Ex. 2028, 93:10–11; 91:18–92:20, 92:21–93:11, 26:12–27:5). Patent Owner argues further about the conduct of Dr. Janoff and Petitioner's counsel during cross-examination, contending that it was "disruptive and prejudicial," and that "[s]uch conduct is particularly prejudicial in the context of the present proceeding, as Patent Owner has repeatedly raised issues as to the lack of clarity in the petition." *Id.* at 4–7 (citing multiple excerpts from Ex. 2028).

Petitioner responds that Dr. Janoff testified "that he was aware of the Petition when executing his declaration," and also "testified unequivocally that the opinions in his declaration represent <u>his</u> opinions in the matter." Reply 24 (citing Ex. 2028, 89:4–92:20, 26:12–18). Petitioner further responds that "[t]he transcript illustrates that counsel for Patent Owner repeatedly asked questions devoid of any context and without reference to either Dr. Janoff's declaration or the '127 patent," but that "Dr. Janoff, nonetheless, provided answers to the extent possible." *Id.* at 24–25 (citing multiple excerpts from Ex. 2028).

We decline to exercise the extraordinary remedy of according "no weight" to Dr. Janoff's testimony based on the contention that Dr. Janoff's testimony is attorney argument because it is based on the Petition. PO Resp. 2–7. Similarly, although Dr. Janoff may not have been as responsive to some questions during his deposition as may have been appropriate, we decline to accord "no weight" to his entire testimony (*see id.*), particularly given that some questions appear to have been vague, or lacking context or proper foundation. *See, e.g.*, Ex. 2028, 35:7–8, 29:19–20, 56:24–57:17; *see also* Reply 24–25.

In making the argument that "Dr. Janoff's declaration merely adopts the attorney arguments set forth in the petition," Patent Owner omits the remainder of the cited quotes from Dr. Janoff's declaration. *See* PO Resp. 3. All of those quotes actually state that Dr. Janoff's opinions are based on the Petition "and other documents and materials identified in this declaration" (Ex. 1007 ¶ 27) or "and the exhibits cited in the Petition as well as other documents" (*id.* ¶¶ 5–7).

We are also unpersuaded by Patent Owner's argument of a "lack of clarity in the petition." PO Resp. 6. The anticipation challenge based on the '069 patent is fundamentally the argument that one of Patent Owner's patents (the '127 patent) is anticipated by an earlier one of Patent Owner's patents (the '069 patent). *See, e.g.*, Pet. 24–42.

Conclusion of Anticipation

Accordingly, based on the trial record as a whole and for the reasons set forth herein, we find that Petitioner has shown by a preponderance of the evidence that claims 1–22 are anticipated by the '069 patent.

E. Other Grounds

Having found that all of the challenged claims are anticipated, we decline to address Petitioner's other challenges. Specifically, we decline to address the parties arguments directed to obviousness over the '069 patent or any arguments directed to any challenge other than anticipation of the challenged claims by the '069 patent. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding that a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *see also Beloit Corp. v. Valmet Oy*, 742 F.2d 1421, 1423 (Fed. Cir. 1984) (holding that once a dispositive issue is decided, there is no need to decide other potentially dispositive issues); *see also SZ DJI Tech. Co., LTD. v. Drone-Control, LLC*, Case IPR2018-00207, slip op. at 30–33 (Paper 44) (PTAB June 11, 2019) (discussing basis for declining consideration of other grounds when all challenged claims are shown to be unpatentable); *cf. In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (not reaching other grounds of unpatentability after affirming the anticipation ground).

F. Motion to Strike

Patent Owner filed a Motion to Strike Petitioner's Reply in its entirety or, alternatively, to strike sections thereof as addressed by Patent Owner in its motion. Paper 30, 1. For the reasons set forth below, we deny or dismiss Patent Owner's motion to strike.

Patent Owner argues that the Reply improperly attempts to introduce an entirely different reference—U.S. Publication 2010/0130588—to cure the alleged defect that the '069 patent is not prior art under 35 U.S.C. § 102(a). Paper 30, 1–2; Paper 44, 4–5. As mentioned above, we do not rely on the purported status of the '069 patent as prior art under 35 U.S.C § 102(a). *See* Section II.D. *supra*. Therefore, for these reasons, we dismiss the motion to strike on this basis as moot.

Patent Owner argues that Petitioner expands its inherency theory to "any method known in the art," and particularly that "Petitioner now asserts for the first time [in the Reply] that the particles claimed in the '127 patent may 'be formed by <u>any method known in the art</u>.'" Paper 30, 2–3 (citing Reply 5); *see also* Paper 44, 4. Petitioner responds that this argument was raised in the Petition and cited in our Institution Decision. Paper 40, 7 (citing Pet. 11; Inst. Dec. 18).

We agree with Petitioner that the argument that "the particles claimed in the '127 patent may be formed by any method known in the art" was not raised for the first time in the Reply. The Petition cites to that statement in the ’127 patent as an admission in the ’127 patent. Pet. 11 (citing Ex. 1001, 92:14–21). Patent Owner also addresses that statement in its response. PO Resp. 11. Therefore, for these reasons, we deny the motion to strike on this basis.

Patent Owner argues that “Petitioner argues for the first time in the Reply that the ’069 patent ‘confirms the goal of achieving non-lamellar morphology, stating that in a preferred embodiment the nucleic acid is ‘encapsulated within the lipid portion of the lipid particle.’” Paper 30, 3–4 (citing Reply 9 (quoting Ex. 1002, 3:3–7)); Paper 44, 4. We view Petitioner’s argument to be directed to its obviousness challenge, and do not rely on it for purposes of this Decision.[27] Therefore, for these reasons, we dismiss the motion to strike on this basis as moot.

Patent Owner argues that “Petitioner contends for the first time in reply . . . that inherency is proven if any one embodiment encompassed by the ’069 patent meets the claimed morphology.” Paper 30, 4; Paper 44, 3–4. Petitioner responds that “this is simply a statement of the controlling legal standard.” Paper 40, 5–6. We agree. *See* Inst. Dec. 9 (citing *Titanium Metals*, 778 F.2d at 782). Therefore, for these reasons, we deny the motion to strike on this basis.

Patent Owner argues that Petitioner’s Reply introduces a new “routine optimization” theory for obviousness, and entirely new mappings of claim limitations for Ground 4. Paper 30, 4–6. Because these arguments relate to

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[27] To be clear, Petitioner properly relies on claim 17 of the ’069 patent for the disclosure of a “nucleic acid-lipid particle . . . wherein the nucleic acid is fully encapsulated in the nucleic acid-lipid particle” to show anticipation of claim 8. Pet. 35 (citing Ex. 1002, 92:42–44 (claim 17); Ex. 1007 ¶ 115).

obviousness, which is not addressed in this Decision, we dismiss these arguments as moot.

III. CONCLUSION

For the reasons given above, we are persuaded that the arguments and evidence presented by Petitioner establish by a preponderance of the evidence that claims 1–22 of the ’127 patent are unpatentable. Accordingly, we determine that:

Claims 1–22 are unpatentable as anticipated by the ’069 patent under 35 U.S.C. § 102(e)(2).

For the reasons given above, we also overrule Patent Owner’s objections to evidence and objections to Petitioner’s demonstratives, and we deny-in-part and dismiss-in-part Patent Owner’s Motion to Strike.

IV. ORDER

Accordingly, it is

ORDERED that Petitioner has proved by a preponderance of the evidence that claims 1–22 of U.S. Patent No. 9,404,127 B2 are unpatentable;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 328(b), upon expiration of the time for appeal of this Decision, or the termination of any such appeal, a certificate shall issue canceling claims 1–22 of U.S. Patent No. 9,404,127 B2;

FURTHER ORDERED that Patent Owner’s Notice of Objection to Evidence and Notice of Objection to Petitioner’s Demonstrative Exhibits are overruled.

FURTHER ORDERED that Patent Owner’s Motion to Strike is denied as to certain arguments and dismissed as to other arguments; and

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

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