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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*.

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

I. INTRODUCTION

Moderna Therapeutics, Inc. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–22 of U.S. Patent 9,404,127 B2 (the "'127 patent"). Paper 2 ("Pet."). Protiva Biotherapeutics, Inc. ("Patent Owner")[1] filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp.").

We have authority under 35 U.S.C. § 314(a) to determine whether to institute an *inter partes* review. To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). For the reasons set forth below, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the '127 patent. Therefore, we institute an *inter partes* review for claims 1–22 of the '127 patent.

A. Related Proceedings

Patent Owner identifies the following related matters:

Moderna Therapeutics, Inc. v. Protiva Biotherapeutics, Inc., IPR2018-00739 regarding U.S. Patent No. 9,364,435; and European Patent Office Opposition proceedings regarding EP 2 279 254. Paper 12, 2.

[1] According to Patent Owner, Protiva Biotherapeutics, Inc. ("Protiva") existed as a wholly-owned subsidiary of Arbutus Biopharma Corporation and was amalgamated into Arbutus Biopharma Corporation in January 2018. Paper 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*.

B. The ’127 Patent (Ex. 1001)

The ’127 patent relates to “stable nucleic acid-lipid particles (SNALP) that have a non-lamellar structure and that comprise a nucleic acid.” Ex. 1001, Abstract. 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. 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 and enhanced silencing ability when used to deliver an interfering nucleic acid, such as an siRNA molecule.

Id. at 3:2–10.

The ’127 patent identifies several specific SNALP formulations that encapsulate siRNA as the nucleic acid, such as the 2:30 formulation, the 1:57 formulation, and the 1:62 formulation.[2] *See, e.g.*, *id*. at 105:30–53. For example, the ’127 patent describes the “2:30” formulation as 2% PEG-C-DMA, 30% DLinDMA, 20% DSPC, and 48% cholesterol. *Id*. at 105:45–47. According to the ’127 patent, data for the “2:30 formulation prepared by the

[2] Patent Owner states that this nomenclature (e.g., 2:30, 2:40, etc.) “refers only to the ratio of conjugated lipid to cationic lipid in a composition, but does not identify other constituents, particular lipid species, or physical characteristics of a composition.” Prelim. Resp. 11, n.5.

Direct Dilution Method" shows that "the vast majority of particles in the 2:30 SNALP formulation are non-lamellar (1386 of 1400)." *Id.* at 109:11–15. The '127 patent 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. 20070042031,[3] the disclosure of which is herein incorporated by reference in its entirety for all purposes." *Id.* at 104:32–37.

C. Illustrative Claim

Petitioner challenges claims 1–22 of the '127 patent. Claim 1 is 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.

Claim 1 is the only independent claim, and claims 2–22 are directly or indirectly dependent on claim 1. *Id*. at 149:38–150:65.

D. The Asserted Grounds of Unpatentability

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

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

Reference[s]	Basis	Claims challenged
U.S. Patent No. 8,058,069[4]	§§ 102/103	1–22
WO 2009/082817[5]	§§ 102/103	1–22
U.S. Patent No. 7,514,099,[6] and Koltover[7] and/or Ewert[8]	§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 also relies on the Declaration of Dr. Andrew S. Janoff, Ph.D. ("Janoff Declaration" or "Decl."). Ex. 1007.

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.*,

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[4] Yaworski et al., US 8,058,069 B2, issued Nov. 15, 2011 ("'069 patent"). Ex. 1002. The '069 patent is owned by Patent Owner. Prelim. Resp. 5.
[5] Maclachlan et al., WO 2009/082817 A1, published July 9, 2009 ("'817 PCT"). Ex. 1003.
[6] Chen et al., US 7,514,099 B2, issued April 7, 2009 ("'099 patent"). Ex. 1004.
[7] Ilya Koltover et al., *An Inverted Hexagonal Phase of Cationic Liposome-DNA Complexes Related to DNA Release and Delivery*, Science 281, 78–81 (1998) ("Koltover"). Ex. 1005.
[8] Kai K. Ewert et al., *Cationic lipid-DNA complexes for non-viral gene therapy: relating supramolecular structures to cellular pathways*, Expert Opin. Biol. Ther. 5(1), 33–53 (2005) ("Ewert"). Ex. 1006.

biophysics, microbiology, biochemistry) or an equivalent combination of education and experience." Pet. 5 (citing Ex. 1007 ¶¶ 30–33). Petitioner further states that "[t]his level of skill is representative of the inventors on the '127 patent and authors/inventors of prior art cited herein." *Id.*

Patent Owner contends that "Petitioner's proposed level of ordinary skill is improper at least to the extent that Petitioner equates the level of ordinary skill with knowledge possessed by the inventors themselves." Prelim. Resp. 3, n1.

On this record and at this stage of the proceeding, we find that a person of ordinary skill in the art would have specific experience with lipid particle formation and use in the context of delivering therapeutic payloads, and would have a Ph.D., an M.D., or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience. At this stage of the proceeding, we need not decide whether Petitioner's proposed level of ordinary skill is representative of the inventors identified on the '127 patent. We also find on this record that Dr. Janoff is one of at least ordinary skill under this standard.

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

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light

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

Petitioner provides a proposed construction of several claim terms, including the term "nucleic acid-lipid particle." Pet. 15–16. According to Patent Owner, "[t]he terms identified in the petition do not require construction in order to reach a decision denying institution," and "[t]he constructions proposed in the petition . . . should be rejected as being unreasonably broad and largely detached from the '127 patent specification." Prelim. Resp. 3. Because Patent Owner substantively challenges the proposed construction of the term "nucleic acid-lipid particle," we address that term, but find that we need not construe any other terms addressed by Petitioner for the purpose of reaching our decision.

nucleic acid-lipid particle

Petitioner proposes that "nucleic acid-lipid particle" means "a composition of lipids and a nucleic acid for delivering a nucleic acid to a target site of interest." Pet. 15. Patent Owner contends that Petitioner's proposed construction is unreasonably broad, and that the specification's use of "nucleic acid-lipid particle" refers to "non-lamellar particles formulated to

fully encapsulate the nucleic acid component and to be stable in serum following systemic (*in vivo*) administration." Prelim. Resp. 4.

On this record and at this stage of the proceeding, we find that neither Petitioner's nor Patent Owner's proposed constructions of "nucleic acid-lipid particle" are appropriate. Petitioner's proposed construction is a general restatement of the composition recited in claim 1 and a use thereof as set forth in the '127 patent. Patent Owner's proposed construction is not consistent with claim 1. If a nucleic acid-lipid particle is construed as a non-lamellar particle, that construction would be inconsistent with the final "wherein" clause that recites the percentage of nucleic acid-lipid particles having a non-lamellar morphology.

Our preliminary construction of "nucleic acid-lipid particle," at this stage of the proceeding and for purposes of this decision, is derived from the express definition of "lipid particle," as set forth in the '127 patent, that describes use of such a lipid particle to deliver nucleic acid as an active or therapeutic agent. At this stage of the proceeding, we define "nucleic acid-lipid particle" as "a particle that comprises a nucleic acid and lipids, in which the nucleic acid may be encapsulated in the lipid portion of the particle." *See* Ex. 1001, 15:52–63.

We determine, for purposes of determining whether to institute an *inter partes* review in this case, we need not expressly construe any undisputed terms. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only those terms which are in controversy need to be construed and only to the extent necessary to resolve the controversy).

C. Principles of Law

"'To anticipate a claim, a prior art reference must discloses every limitation of the claimed invention, either explicitly or inherently.'" *Atlas*

Powder Co. v. Ireco, Inc., 190 F.3d 1342, 1346 (Fed. Cir. 1999) (quoting *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997)). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Id*. at 1347.

Anticipation requires a finding that the claim at issue "reads on" a prior art reference. *Id.* at 1346 (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).

"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, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Id*. (citing *Titanium Metals*, 778 F.2d at 782).

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

D. Anticipation by or obviousness in view of the '069 patent

Petitioner asserts that claims 1–22 of the '127 patent are unpatentable as anticipated by or obvious in view of the '069 patent. Pet. 24–42. Patent

Owner advances several arguments in response to Petitioner's assertions. Prelim. Resp. 5–23.

1. '069 patent (Ex. 1002)

The '069 patent describes "stable nucleic acid-lipid particles (SNALP) comprising a nucleic acid (such as one or more interfering RNA)." Ex. 1002, Abstract. The '069 patent 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 further states, for example, that "[t]he 2:30 SNALP formulation used in this study is lipid composition 2:30:20:48 as described in molar percentages of PEG-C-DMA, DLinDMA, DSPC, and cholesterol." *Id*. at 73:13–15. The '069 patent also 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.

2. Analysis

Anticipation – claim 1

Petitioner's anticipation challenge is based on the contention 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.

Petitioner identifies formulations in the '069 patent, such as the 2:30 and 1:57 formulations, that it contends explicitly describe all of the elements of claim 1, other than the final "wherein" clause ("wherein at least about 95% of the particles in the plurality of particles have a non-lamellar morphology").[9] Pet. 26–28. Regarding the final "wherein" clause of claim 1, Petitioner asserts that "[t]he '069 patent inherently anticipates [that element] because it is a property that the '127 patent asserts invariably results from formulations disclosed therein." *Id.* at 28. Petitioner further states 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). Petitioner further asserts that "both the particle composition and the formation processes disclosed in the '127 patent are the same as the ones

[9] 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.

disclosed in the ’069 patent,” and that “[t]he ’127 patent itself identifies these variables as resulting in the claimed property.” Pet. 29; *see also* Pet. 10–14.

On this record and at this stage of the proceeding, we are persuaded that Petitioner has established a reasonable likelihood that it would prevail in showing that claim 1 of the ’127 patent is anticipated by the ’069 patent. The recited components of the claimed composition read on formulations described in the ’069 patent. Ranges (in mol %) of components of formulations in the ’069 patent are the same as or lie within ranges of components of compositions in the ’127 patent. *Compare* (for example) Ex. 1002, 3:36–45 *with* Ex. 1001, 29:45–56 and 3:10–19. Furthermore, both the ’069 patent and the ’127 patent state that the direct dilution process or method is “described in detail” in the ’031 patent publication (which is expressly incorporated therein). *Compare* Ex. 1002, 59:12–16, *with* Ex. 1001, 93:14–18 and 104:32–37. The ’127 patent also 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.” Ex. 1001, 92:15–21 (*Compare with* Ex. 1002, 57:50–55). Accordingly, on this record and at this stage of the proceeding, we find that Petitioner has sufficiently shown that the non-lamellar morphology recited in the final “wherein” clause of claim 1 is an inherent property of one or more formulations disclosed in the ’069 patent. *See Atlas Powder*, 190 F.3d at 1346–47.

Patent Owner’s Arguments (A–C)

As an initial matter, Patent Owner contends that “Ground 1 is not presented with the requisite degree of particularity as it states alternate theories of challenge and lacks clarity as to the particular references on

which the alternate obviousness theory rests." Prelim. Resp. 5. We do not find this persuasive because this challenge is based on the '069 patent and we find that Petitioner has provided sufficient information to establish a reasonable likelihood of prevailing in showing the unpatentability of claim 1.

Argument A

Patent Owner contends that Petitioner fails to demonstrate inherent disclosure of the final "wherein" clause of claim 1. Prelim. Resp. 6–8. That contention is premised on several arguments. First, Patent Owner argues that there is no presumption of inherency that Petitioner bears the burden of proving unpatentability, and that Petitioner is attempting to shift the burden to Patent Owner to prove no inherency. *Id*. at 7, 10–11.

Patent Owner's arguments "fail[] to appreciate that there is a significant difference between a petitioner's burden to establish a 'reasonable likelihood of success' at institution, and actually proving invalidity by a preponderance of the evidence at trial." *Trivascular*, 812 F.3d at 1068. Clearly the burden of persuasion in an *inter partes* review is on Petitioner to prove unpatentability (e.g., anticipation of claim 1 by the '069 patent) by a preponderance of the evidence, and that burden never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). However, the analysis at the institution stage is "very different" and "made under a qualitatively different standard" than the standard applicable in reaching the Final Written Decision. *See Trivascular*, 812 F.3d at 1068. On this record and at this stage of the proceeding, we find that the institution standard has been met by Petitioner, at least with respect to anticipation of claim 1 by the '069 patent.

Second, Patent Owner contends that Petitioner's assertion regarding similarities in disclosure as between the '069 patent and the '127 patent is unexplained and unfounded, and leaves Patent Owner and the Board with the task of evaluating the cited disclosures. Prelim. Resp. 7–8, 10–11. We are not persuaded because a comparison of the disclosures of the '069 patent and the '127 patent specifically cited by Petitioner and its declarant, *see* Pet. 29, is not unduly burdensome on the Board, and would not be unduly burdensome on Patent Owner given that the '069 patent and the '127 patent are "commonly owned" by Patent Owner and have overlapping named inventors. *See* Prelim. Resp. 5; Ex. 1001, 1; Ex. 1002, 1.

Third, Patent Owner argues that Petitioner's assertion that the compositions and production methods in the '127 patent are the "same" as those disclosed in the '069 patent is wrong, and that "the cited materials actually underscore the erroneous nature of Petitioner's assumption that all formulations would include the same physical properties (*e.g.*, non-lamellar morphology) when the disclosures unambiguously report different physical properties for the various formulations (*i.e.*, the disclosures prove the opposite of inherently 'the same')." Prelim. Resp. 8. We are not persuaded on this record at least because Petitioner specifically states 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 (emphasis added)), and Petitioner cites to several formulations in the respective patents that are identical or substantially identical. *See* Petition 25–28. It is sufficient to show anticipation that claim 1 covers any of the compositions disclosed in the '069 patent. *See Titanium Metals*, 778 F.2d at 782.

Argument B

Patent Owner argues that "[t]he petition materials lack any cogent analysis supporting its inherency theory and improperly attempt to shift the burden to [Patent Owner]." Prelim. Resp. 9–11 (emphasis omitted). Patent Owner's position is premised on the contention that a comparison of the disclosures in the '127 patent with disclosures in the '069 patent is an insufficient analysis or explanation of Petitioner's anticipation challenge. *Id.* However, Patent Owner does not identify what further analysis or explanation is necessary, and we find that the analysis provided by Petitioner is sufficient to institute *inter partes* review with respect to the anticipation challenge based on the '069 patent.

Argument C

Comparison of formulations

Patent Owner argues that "[t]he particle compositions and the formulation processes in the '069 patent are NOT 'the same' as those disclosed in the '127 patent." Prelim. Resp. 11–20 (emphasis omitted). Patent Owner supports this argument with multiple contentions.

Patent Owner contends that various formulations, such as the 1:57, 2:40, 2:30, and 1:62 formulations, are not the same in both the '069 patent and the '127 patent. Prelim. Resp. 11–15. In making that contention, Patent Owner points to differences such as mean particle size, polydispersity, nucleic acid encapsulation, lipid-to-drug ratio, and use of a different non-cationic lipid. *Id.* Patent Owner further objects to the assertion that one non-cationic lipid (DSPC), used in formulations 1:57 and 2:40 of the '127 patent, could be substituted in lieu of another non-cationic lipid (DPPC), arguing that "an anticipation theory cannot be supported by mixing and matching different embodiments." Prelim. Resp. 13.

We do not find Patent Owner's arguments persuasive, particularly in light of the breadth of claim 1.[10] The components of claim 1 include a plurality of nucleic acid-lipid particles, wherein each comprises (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, 149:29–35. The compositions compared by Petitioner include those components. Furthermore, claim 1 does not include limitations directed to mean particle size, polydispersity, nucleic acid encapsulation, or lipid-to-drug ratio, or even a particular non-cationic lipid. Moreover, even if the anticipation analysis was based on the substitution of one non-cationic lipid for another non-cationic lipid, that would not necessarily defeat an anticipation challenge because both DSPC and DPPC are listed as examples of non-cationic lipids in the '069 patent. Ex. 1002, 50:6–13; *see Kennametal, Inc. v. Ingersoll Cutting Tool Co*., 780 F.3d 1376, 1382 (Fed. Cir. 2015).

Testimony of Dr. Janoff

Patent Owner also contests Petitioner's assertion that the particle size, polydispersity, and encapsulation efficiency of formulations disclosed in the '069 patent '"indicate particles having a non-lamellar structure.'" Prelim. Resp. 15 (citing Pet. 31–32). According to Patent Owner, this assertion is

[10] We also note, for example, that the comparisons made by Patent Owner between formulations in the '069 patent and the '127 patent refer to formulations in the '127 patent that are "Prepared by Stepwise Dilution Method (SDM)" rather than the direct dilution method. Prelim. Resp. 12–15 (Table 4).

based solely on the deficient testimony of Dr. Janoff, which should be disregarded. Prelim. Resp. 15–17.

First, Patent Owner contends that Dr. Janoff's statement that non-bilayer structures *may* be present is insufficient to prove inherent disclosure. *Id*. at 16. Second, Patent Owner contends that Petitioner's argument fails to address the relevant claim language because Dr. Janoff's statement refers to *a* non-bilayer structure rather than to "at least about 95% of the particles in the plurality of particles have a non-lamellar morphology." *Id*. Finally, Patent Owner contends that Dr. Janoff's testimony is contradicted by disclosures in the '127 patent. *Id.* at 16–17.

We are not persuaded by these arguments on the current record. Patent Owner focuses on two sentences in the Petition and one paragraph in Dr. Janoff's Declaration. Prelim. Resp. 15–17. The cited paragraph of Dr. Janoff's Declaration states that disclosures in the '069 patent of high encapsulation efficiencies and small mean diameters "would be known to a POSITA to be inconsistent with bilayer vesicles," and that the encapsulation efficiencies reported "would have indicated to a POSITA that a non-bilayer structure may be present." Decl. ¶ 107. Patent Owner does not persuasively explain why the alleged failure of that declaration paragraph 107 to conclusively "prove" inherent disclosure or specifically address the final "wherein" clause of claim 1 should cause us to decline institution, given the "reasonable likelihood" standard at this stage of the proceeding. Moreover, whether paragraph 107 of the Janoff Declaration is inconsistent with the '127 patent, and the significance of any such inconsistency, may be explored during trial.

Direct Dilution Method

Patent Owner contests Petitioner's assertion that the same formulation process (direct dilution method) is used in the '069 patent and the '127 patent. Prelim. Resp. 17–19. First, Patent Owner contends that direct dilution refers to a general blending technique, and that "merely asserting that two references employ a 'direct dilution method' does not establish they employ *the same* dilution method—or 'the same' formation process as asserted in the petition." *Id.* at 17–18. Second, Patent Owner contends that a meaningful review of the '127 patent and '069 patent "reveals there is no reasonable basis to conclude that 'the exact same' formation processes were utilized." *Id.* at 18. Finally, Patent Owner contends that "the cited disclosure of the '127 patent identifies different parameters not identified in either the '069 patent or [the '031 patent publication]." *Id.* at 19.

We are not persuaded by these arguments on the current record. As discussed above, both the '069 patent and the '127 patent state that the direct dilution process or method is "described in detail" in the '031 patent publication. The '127 patent also states that the lipid particles of the invention "can be formed by any method known in the art." Ex. 1001, 92:14–21. Furthermore, the contention that the '127 patent identifies certain process parameters that are not expressly identified or disclosed in the '069 patent or the '031 patent publication, does not persuasively explain why or how that shows that the disclosure of the '069 patent does not anticipate claim 1.

Accordingly, on this record, we determine that Petitioner has demonstrated a reasonable likelihood that it would prevail in its assertion that claim 1 of the '127 patent is anticipated by the '069 patent.

Anticipation – dependent claims

Petitioner identifies disclosures in the ’069 patent, or patent publications incorporated therein, that it contends correspond to the limitations of dependent claims 2–8, 10–18, and 20–22. Pet. 33–42. In addition, for the claimed ranges, Petitioner points to prior art disclosures that overlap the claimed range. *See id*.

Petitioner argues that the ’069 patent inherently anticipates the additional limitations of claims 9 and 19. Pet. 35–36, 41. However, because Petitioner offers only a single conclusory sentence as to claim 9 (reciting that the non-lamellar morphology comprises “an inverse hexagonal (H_{II}) or cubic phase structure”), we do not find on this record that a sufficient showing has been made of inherent anticipation of claim 9 by the ’069 patent. Claim 19 recites “wherein greater than 95% of the particles have a non-lamellar morphology,” and Petitioner relies on its inherency position as advanced in connection with claim 1. Pet. 41. Our view of claim 19 at this stage of the proceeding is the same as set forth above regarding claim 1.

Patent Owner does not advance any arguments specific to dependent claims 2–22, focusing instead on the Petitioner’s inherency contention regarding the final “wherein” clause of claim 1. *See* Prelim. Resp. 5–20. As trial proceeds, possible issues to develop regarding the dependent claims may include (1) whether Petitioner’s reliance on incorporation by reference is appropriate, and (2) whether the prior art ranges anticipate the claimed ranges.

Obviousness

Petitioner advances an alternative position that the final “wherein” clause of claim 1 “would have been obvious in light of the disclosures in the ’069 patent and the knowledge of a POSITA,” and that “[o]ne skilled in the

art would appreciate that the transfection efficacy of the complexes disclosed in the '069 patent could have been related to the three-dimensional structure of the complexes disclosed therein." Pet. 32.

Petitioner points to the '613 patent[11] as disclosing "that lipid complexes are capable of forming different three-dimensional structures and that these three-dimensional structures are related to transfection efficacy," and that "combinations of lipids can 'promote HII [non-lamellar] phase formation.'" Pet. 32. According to Petitioner, the '613 patent further discloses "particle populations that are entirely non-lamellar" and "states that 'it will be readily apparent to those of skill in the art that other lipids can be induced to adopt a non-lamellar phase by various non-physiological changes including, for example, changes in pH or ion concentration.'" *Id.* at 32–33. Petitioner further contends that "a POSITA would have appreciated that the particle characterization in the '069 patent . . . [is] indicative of particles having a non-lamellar structure," and that "[i]t would have been obvious to a POSITA given these disclosures to directly characterize the three dimensional structure of the particles resulting from the processes in the '069 patent, which would have revealed the greater than 95% non-lamellar structure therein." *Id.* at 33.

Patent Owner advances several arguments in response to Petitioner's alternative obviousness position. Prelim. Resp. 20–23. First, Patent Owner contends that "35 U.S.C. § 103(c) disqualifies the '069 patent from use in an obviousness challenge." Prelim. Resp. 20. Patent Owner asserts that the

[11] Holland et al., US 5,885,613, issued March 23, 1999 ("'613 patent"). Ex. 1017. The '613 patent is incorporated into the '069 patent. Ex. 1002, 11:63–64.

’127 patent and the ’069 patent were commonly owned by Protiva or under common obligation to assign, that 35 U.S.C. § 103(c) disqualifies the ’069 patent for use in the obviousness challenge because it is prior art under 35 U.S.C. § 102(e)(2) (pre-AIA), and that the petition erroneously asserts that the ’069 patent published on May 27, 2010, and is available as prior art under 35 U.S.C. § 102(a). *Id.* at 20–21, n.8.

On this record, we are not persuaded by that argument. The face of the ’069 patent identifies US 2010/0130588 A1, published May 27, 2010, as a “prior publication” of US Patent Application Serial No. 12/424,367, that issued as the ’069 patent. Ex. 1002, 1. Moreover, that publication date precedes the earliest priority date of the ’127 patent, such that the published application qualifies as prior art under 35 U.S.C. § 102(a) (pre-AIA). *See* Pet. 18. Thus, the ’069 patent does not appear to be prior art “only under” 35 U.S.C. § 102(e). *See* 35 U.S.C. § 103(c)(1).

Second, Patent Owner asserts that Petitioner’s “obviousness theory also requires unsubstantiated inherency,” that “Petitioner asserts that it would have been obvious for one to conduct testing to investigate its inherent anticipation allegations,” and that Petitioner improperly conflates inherency and obviousness. Prelim. Resp. 21–23, n.9. We are not convinced on this record that Petitioner’s “alternative” obviousness position is based on inherency given its stated reliance on “disclosures in the ’069 patent and the knowledge of a POSITA.” Pet. 32.

Finally, Patent Owner asserts that Petitioner’s “alleged obviousness discussion underscores the deficiencies in the inherent anticipation case,” arguing that the Petition “asserts it would have been obvious to characterize the structure of compositions from ‘processes in the ’069 patent,’” but that Petitioner did not submit any such extrinsic evidence with its Petition.

Prelim. Resp. 23. We recognize that the burden of proving unpatentability remains with Petitioner and, in this regard, it may be appropriate for Petitioner to submit such extrinsic evidence during trial.

E. Anticipation by or obviousness in view of the '817 PCT

Petitioner asserts that claims 1–22 of the '127 patent are unpatentable as anticipated by or obvious in view of the '817 PCT. Pet. 42–44. According to Petitioner, "[t]he challenged claims are invalid for at least the reasons stated above in Ground 1" (referencing citations to the '228 provisional which is also incorporated into the '817 PCT). *Id.* at 43. However, Petitioner also states that "[t]he disclosures of the '817 PCT are not cumulative of the bases presented in Ground 1" because (1) the '817 PCT contains additional disclosures regarding dependent claims 10–12 and 16–18, and (2) "the '817 PCT qualifies as prior art under both 35 U.S.C. § 102(a) and § 102(e)(1) (pre-AIA) and has an earlier publication date." *Id.* at 43–44.

Patent Owner argues that "Ground 2 is not presented with the requisite degree of particularity," and that "the petition fails to explain sufficiently how each element of the challenged claims can allegedly be found in the ['817 PCT]." Prelim. Resp. 24. In addition, Patent Owner argues that "[t]he alternate obviousness theory in Ground 2 is additionally defective as wholly lacking any obviousness inquiry specific to the cited '817 PCT." *Id.* at 25.

On this record and at this stage of the proceeding, Petitioner does not appear to have made a sufficient showing of anticipation or obviousness of claim 1 (and thus any of claims 2–22) based on the '817 PCT. In pointing to "additional bases" for unpatentability of claims 10–12 and 16–18, Petitioner

fails to sufficiently explain where each element of claim 1 (on which those dependent claims depend) is found in the ’817 PCT. *See* 37 C.F.R. § 42.104(b)(4). Rather, Petitioner requires the Board to review and match up the citations to the ’228 provisional, as provided in the challenge based on the ’069 patent, to the elements of claim 1 (and other claims). In addition, Petitioner apparently expects the Board to extrapolate Petitioner’s “reasons stated” in connection with the challenge based on the ’069 patent to the challenge based on the ’817 PCT. *See* Pet. 42–43. Moreover, Petitioner provides no analysis of its purported challenge under 35 U.S.C. § 103.

F. Anticipation by or obviousness in view of the ’099 patent alone or obvious in view of the ’099 in light of Koltover and/or Ewert

Petitioner asserts that claims 1–22 of the ’127 patent are unpatentable as anticipated by or obvious in view of the ’099 patent alone, or in view of the ’099 patent in light of Koltover and/or Ewert. Pet. 45–59. Patent Owner advances several arguments in response to Petitioner’s assertions. Prelim. Resp. 26–34.

1. ’099 patent (Ex. 1004)

The ’099 patent discloses “novel cationic lipids . . . and formulations thereof with biologically active molecules.” Ex. 1004, 7:3–5. The ’099 patent states that “the invention features a composition comprising a biologically active molecule (e.g., a polynucleotide such as a siNA, . . . [or] other nucleic acid molecule . . .), a cationic lipid, a neutral lipid, and a polyethyleneglycol conjugate, such as a PEG-diacylglycerol, PEG-diacylglycamide, PEG-cholesterol, or PEG-DMB conjugate.” *Id*. at 21:66–22:6.

2. Analysis

Anticipation

Petitioner provides citations to disclosures in the ’099 patent that purportedly teach the various components of claim 1. Pet. 45–47. Regarding the final “wherein” clause of claim 1 (“wherein at least about 95% of the particles in the plurality of particles have a non-lamellar morphology”), Petitioner states that “the ’099 patent is silent on the percentage of particles undergoing such a reorganization.” Pet. 45. However, rather than advancing an inherency position, Petitioner refers to the disclosures in the ’099 patent of a “formulated molecular composition [that] undergoes a structural change to adopt an inverted hexagonal structure at about pH 5.5-6.5,” and that “the inverted hexagonal structure transfects mammalian cells more efficiently than the lamellar structure.” *Id.* at 47 (citing Ex. 1004, 5:52–54 and 33:38–46). Based on those disclosures, Petitioner concludes that “[b]ecause the disclosed cationic [lipid nanoparticles] were designed to transition at a pH 5.5-6.5, a POSITA would understand that all the particles of that population were designed to rapidly transition to a non-lamellar phase at such a pH.” *Id.* at 47–48. Petitioner cites to the Janoff Declaration that essentially restates the position set forth in the Petition followed by the statement that “[f]rom these disclosures, a POSITA would appreciate that the claim limitation is expressly disclosed.” Decl. ¶ 142.

On this record, we are not persuaded that Petitioner has sufficiently shown that claim 1, and thus any of dependent claims 2–22, are anticipated by the ’099 patent. Petitioner states that “the ’099 patent is silent on the percentage of particles undergoing such a reorganization,” but then cites to the Janoff Declaration’s statement that “a POSITA would appreciate that the

claim limitation is expressly disclosed." *See* Pet. 45, 47–48; Decl. ¶ 142. Moreover, Petitioner relies on disclosures in the '099 patent that appear to describe process parameters (e.g., pH 5.5–6.5) in which particles may undergo "a rapid pH-dependent phase transition." Pet. 47 (citing Ex. 1004, 33:48). But the challenged claims are directed to a "composition" and we are not persuaded that each and every element of the claimed composition is expressly or inherently disclosed in the '099 patent.

Obviousness

Petitioner's obviousness challenge based on the '099 patent alone is based on the assertion that "even if the '099 patent did not disclose at least 95% of the particles having a non-lamellar morphology post-transition, a POSITA would appreciate that it was intended that all the lipid exist in a non-lamellar phase post-transition." Pet. 48. That statement is followed by several statements regarding what "a POSITA would understand" and what "would have been obvious." *See id.* Such conclusory statements are not sufficient to support an obviousness challenge. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Moreover, even if "[t]he disclosed formulations in the '099 patent were intended to transition to a non-lamellar structure at the disclosed pH" as Petitioner contends (Pet. 48), Petitioner never explains whether a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. *See In re Stepan Co.*, 868 F.3d 1342, 1345–46 (Fed. Cir. 2017) ("An obviousness determination requires finding both 'that a skilled artisan would have been motivated to combine the teachings of the prior art . . . and that the skilled artisan would have had a reasonable expectation of success in doing so.'") (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016)).

Petitioner also advances an obviousness challenge based on the '099 patent in view of Koltover and/or Ewert. Pet. 57–59. Regarding Koltover, Petitioner argues that a POSITA "would have found it obvious to use the insights of Koltover regarding the fusogenicity of non-lamellar lipid morphologies and the disclosures of the '099 patent regarding pH sensitive cationic lipid complexes to create pharmaceutical formulations comprised entirely of non-lamellar structures," and "would have appreciated a reasonable expectation of doing so." *Id*. at 57. Petitioner further argues that a POSITA "would have recognized that a homogeneous non-lamellar population of particles as described in Koltover could be obtained using the system in the '099 patent by optimizing known variables (e.g., pH), using known production methods, to yield predictable results." *Id*. at 57–58.

Regarding Ewert, Petitioner states that a POSITA "would have recognized that a homogenous non-lamellar population of complexes as described in Ewert could be obtained using the system in the '099 patent at a pH 5.5 or lower, using known production methods, to yield predictable results," and "would have appreciated a reasonable expectation of success in generating a greater than 95% non-lamellar structure." *Id.* at 58–59.

As with the obviousness challenge based on the '099 patent alone, the obviousness challenge based on the '099 patent in view of Koltover and/or Ewert consists of conclusory statements that we do not view as sufficient to support an obviousness challenge. *See KSR*, 550 U.S. at 418. Accordingly, on this record, Petitioner has not sufficiently shown that claim 1, and thus any of dependent claims 2–22, would have been obvious in view of the '099 patent alone, or the '099 patent in view of Koltover and/or Ewert.

Patent Owner's Preliminary Response

We have also reviewed Patent Owner's response to Petitioner's challenge based on the '099 patent. *See* Prelim. Resp. 26–34. On this record, it appears that Patent Owner's analysis of the '099 patent may have merit, particularly as it relates to the "(1) a serum-stable lamellar particle form which, following uptake and processing by cells, purportedly transitions to (2) the destabilized, more non-lamellar form that disintegrates to release the nucleic acid payload." Prelim. Resp. 27 (citing Ex. 1004, 33:40–54).

G. Obviousness in view of the '817 PCT in light of Koltover and/or Ewert

Petitioner asserts that claims 1–22 are unpatentable as obvious in view of the '817 PCT in light of Koltover and/or Ewert. Pet. 59–61. In particular, Petitioner argues that the final "wherein" clause of claim 1 would have been obvious in view of the '817 PCT in light of Koltover and/or Ewert to the extent that that element "is determined not to be inherent in the formulations disclosed in the '228 provisional and incorporated in the '817 PCT by reference or obvious in view of the '817 PCT (and the '613 patent incorporated therein by reference)." *Id.* at 59.

Patent Owner argues that "[i]t is unclear precisely what is being asserted," that "Ground 4 is not presented with the requisite degree of particularity," and that "Ground 4 can additionally be denied for lacking any meaningful obviousness analysis or motivation to combine." Prelim. Resp. 35–38.

On this record and at this stage of the proceeding, Petitioner does not make a sufficient showing of obviousness of claim 1 (and thus any of claims 2–22) based on the '817 PCT in light of Koltover and/or Ewert. Petitioner's obviousness challenge consist of a series of statements that are conclusory in

nature and fail to establish a coherent basis for Petitioner's purported obviousness challenge. *See KSR*, 550 U.S. at 418. Moreover, Petitioner's challenge appears to be a back-up or supplement to its challenge based on the '817 patent alone, and only with respect to whether the final "wherein" clause of claim 1 is inherent. *See* Pet. 59. Yet this obviousness challenge concludes by stating that "[c]onfirming the existence of [non-lamellar structures in the '817 patent] would have been a simple matter of examining the SNALPs with a known technique such as cryo-TEM." *Id.* at 60–61. Petitioner does not explain how this conclusory statement relates to this apparent supplement to its challenge based on the '817 patent alone.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim of the '127 patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

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

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

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