UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Moderna Therapeutics, Inc.

Petitioner

v.

Protiva Biotherapeutics, Inc.

Patent Owner

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U.S. Patent No. 9,404,127

Issued: August 2, 2016

Named Inventor: Ed Yaworski, Lloyd B. Jeffs, Lorne R. Palmer

Title: Non-Liposomal Systems for Nucleic Acid Delivery

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,404,127

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LIST OF EXHIBITS RELIED UPON IN THE PETITION

Exhibit No.	Reference
1001	U.S. Patent No. 9,404,127 ("'127 patent")
1002	U.S. Patent No. 8,058,069 ("'069 patent")
1003	PCT Application No. PCT/CA2008/002285, Publication No. WO 2009/082817A1 ("'817 PCT")
1004	U.S. Patent No. 7,514,099 ("'099 patent")
1005	Koltover et al., *An Inverted Hexagonal Phase of Cationic Liposome-DNA Complexes Related to DNA Release and Delivery*, 281 SCIENCE 78–81 (1998) ("Koltover")
1006	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")
1007	Declaration of Dr. Andrew S. Janoff
1008	Hui et al., *The Role of Helper Lipids in Cationic Liposome-Medicated Gene Transfer*, 71 BIOPHYSICAL JOURNAL 590–99 (1996) ("Hui 1996")
1009	Semple et al., *Rational Design of Cationic lipids for siRNA Delivery*, 28 NATURE BIOTECHNOLOGY 172–78 (2010) ("Semple 2010")
1010	Heyes et al., *Cationic Lipid Saturation Influences Intracellular Delivery of Encapsulated Nucleic Acids*, 104 JOURNAL OF CONTROLLED RELEASE 277–87 (2005) ("Heyes 2005")
1011	U.S. Patent No. 7,981,027 ("'027 patent")
1012	U.S. Patent No. 7,799,565 ("'565 patent")
1013	U.S. Patent No. 7,838,658 ("'658 patent")
1014	File History Excerpt For U.S. Patent Application No. 13/807,288
1015	File History Excerpt For '069 Patent
1016	U.S. Provisional Patent Application No. 61/045,228
1017	U.S. Patent No. 5,885,613 ("'613 Patent")
1018	U.S. Patent Publication No. 20040142025
1019	U.S. Patent Publication No. 20070042031
1020	U.S. Patent Publication No. 20060083780
1021	Andrew Janoff Curriculum Vitae
1022	File History for '127 Patent

In accordance with 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42.100 *et seq*., Moderna Therapeutics, Inc. ("Moderna" or "Petitioner") respectfully requests that the Board institute *inter partes* review and cancel claims 1–22 of U.S. Patent No. 9,404,127 ("'127 patent," Ex. 1001).

I. INTRODUCTION

The '127 patent is directed to a composition of nucleic acid-lipid particles (*e.g.*, particles that can be used to deliver therapeutic nucleic acid payloads to a patient) that have a non-bilayer three-dimensional structure. *See* Ex. 1001, cl. 1 (claiming a "non-lamellar morphology").

The '127 patent is just one of many unrelated patents, some of which date back to the early 2000s, owned by Protiva Biotherapeutics, Inc. ("Patent Owner") that disclose substantially the same nucleic acid-lipid particles with only trivial or inconsequential differences in claim scope. By obtaining overlapping claims in these unrelated patent families, Patent Owner has improperly extended its patent protection by years. Patent Owner is now using these patent families, including the '127 patent, to improperly block the public and industry participants from using basic combinations of nucleic acid-lipid particle components explicitly described long before the '127 priority date.

Claims 1-22 of the '127 patent recite a composition of nucleic acid-lipid particles, wherein each particle comprises a nucleic acid and various lipid

components (*i.e.*, a cationic lipid, a non-cationic lipid and a conjugated lipid). The prior art, including the '069 patent (Ex. 1002), the '817 PCT (Ex. 1003) or the '099 patent (Ex. 1004),[1] shows that the claimed composition was available well before the priority date of the '127 patent. The sole alleged point of novelty is the added claim limitation that "at least about 95% of the particles … have a non-lamellar morphology" (*i.e.*, a non-bilayer structure). Ex. 1001, cl. 1. According to the '127 patent itself, this is an inherent property of the prior art compositions. It is well established that claiming an inherent property of a prior art composition, even if previously unknown, is insufficient, as a matter of law, to confer patentability. *See In re Best*, 562 F.2d 1252, 1254 (C.C.P.A. 1977).

Moreover, even when a prior art composition is the same as that of the claimed composition, but the function is not explicitly disclosed by the prior art, the claim is nonetheless obvious under 35 U.S.C § 103. One skilled in the art would appreciate that it would have been obvious that the transfection efficacy of the complexes disclosed in the '069 patent and the '817 PCT could have been related to the three-dimensional structure of the complexes disclosed therein and it

[1] Exhibit 1002 is U.S. Patent No. 8,058,069 (the "'069 patent"), Exhibit 1003 is PCT Application No. PCT/CA2008/002285, Publication No. WO 2009/082817A1 ("'817 PCT"), Exhibit 1004 is U.S. Patent No. 7,514,099 (the "'099 patent").

would have been obvious to characterize those structures to determine whether the compositions were comprised entirely (for instance, greater than 95%) of complexes displaying non-lamellar morphology. It also would have been obvious for the ’099 patent composition nucleic acid-lipid particles to be comprised entirely (*i.e.*, greater than 95% of the particles) of particles with non-lamellar morphology given the stated intentions therein to transition to such a structure. Thus, in the alternative, each of the ’069 patent, the ’817 PCT or the ’099 patent renders the challenged claims obvious.

In addition, the prior art references Koltover (Ex. 1005) and/or Ewert (Ex. 1006) teach that there was a recognized potential benefit to using nucleic acid-lipid particles comprised entirely of particles with non-lamellar morphology. One skilled in the art would have been motivated to combine these disclosures with the ’817 PCT or the ’099 patent as described herein.

II. MANDATORY NOTICES

A. NOTICE OF REAL PARTY-IN-INTEREST (37 C.F.R. § 42.8(b)(1))

The real party-in-interest is Moderna Therapeutics, Inc.

B. NOTICE OF RELATED MATTERS (37 C.F.R. § 42.8(b)(2))

There are no pending Related Matters as defined in 37 C.F.R. § 42.88(b)(2).

C. DESIGNATION OF LEAD AND BACK-UP COUNSEL (37 C.F.R. § 42.8(b)(3))

Lead Counsel: Michael Fleming (Reg. No. 67,933). Email:

mfleming@irell.com.

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D. SERVICE INFORMATION (37 C.F.R. § 42.8(b)(4))

Petitioner consents to electronic service at ModernaIPR@irell.com.

E. PAYMENT OF FEES (37 C.F.R. § 42.103)

The Office is authorized to charge required fees to Deposit Account No. 09-0946.

F. CERTIFICATION OF GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Petitioner certifies that the '127 patent is eligible for *inter partes* review and that Petitioner is neither barred nor estopped from requesting a review of the challenged claims on the grounds identified herein.

III. CHALLENGE AND RELIEF REQUESTED

Petitioner respectfully requests *inter partes* review and cancellation of all claims of the '127 patent based on the grounds detailed below in Section IX.

A. GROUND 1: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '069 PATENT

B. GROUND 2: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '817 PCT

C. GROUND 3: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '099 PATENT OR OBVIOUS IN VIEW OF '099 PATENT IN LIGHT OF KOLTOVER AND/OR EWERT

D. GROUND 4: CLAIMS 1-22 ARE OBVIOUS IN VIEW OF THE '817 PCT IN LIGHT OF KOLTOVER, AND/OR EWERT

IV. PRIORITY DATE

The '127 patent claims priority to U.S. Provisional Application No. 61/360,480, filed on June 30, 2010. *See* Ex. 1001, cover page. For purposes of this paper only, Petitioner assumes (without conceding) that the '127 patent is entitled to this date.

V. PERSONS HAVING ORDINARY SKILL IN THE ART

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. *See* Ex. 1007, Declaration of Dr. Andrew S. Janoff ("Janoff Decl."), ¶¶30-33. This level of skill is representative of the inventors on the '127 patent and authors/inventors of prior art cited herein. *Id.*

VI. BACKGROUND

A. LIPID CARRIER PARTICLES FOR NUCLEIC ACID PAYLOADS

The Janoff Declaration, paragraphs 60-68, details the basic formulation of nucleic acid-lipid particles and mechanism by which the nucleic acid payload is delivered. Gene therapy—addressing disease at the level of the genetic cause, typically with nucleic acids—is an area of intensive medical research. Therapeutic nucleic acids can be used for both gene delivery (*e.g.*, mRNA) and gene silencing (*e.g.*, small interfering RNA ("siRNA")). *Id.*, ¶61.

Long before the '127 patent, it was known that systems comprised of combinations of different types of lipids with nucleic acids could result in lipid-nucleic acid particles, an accepted delivery strategy for nucleic acid therapeutics. *Id.*, ¶¶61-62; *see also* Ex. 1002 ('069 patent), cl. 1; Ex. 1003 ('817 PCT), [0001]; Ex. 1004 ('099 patent), 2:11-16; Ex. 1005 (Koltover), 78; Ex. 1006 (Ewert), 33–34. The '127 patent refers to a version of these lipid carrier particles as "stable nucleic acid-lipid particles" or "SNALPs." Ex. 1001, 15:64-65. These particles are also referred to as "cationic lipid-nucleic acid particles" or "cationic LNPs." *See* Janoff Decl. ¶72.

1. COMPONENTS OF LIPID CARRIER PARTICLES

The components of lipid-nucleic acid particles, *e.g.*, SNALPs, were well-known prior to the '127 patent. Janoff Decl. ¶¶60-61. Cationic lipids are useful in such particles because cationic lipids can interact with the negative charge on

nucleic acids facilitating formation of lipid-nucleic acid complexes. *Id.* ¶62. Effective delivery of the nucleic acid payload in such complexes is thought to require fusion between the complex and a cell membrane. *Id.*; *see also* Ex. 1008 (Hui 1996), 598. It is believed that cationic lipids interact with negative charges on cell membranes which promotes the fusion event necessary for the effective delivery of the nucleic acid. Janoff Decl. ¶62; *see also,* Ex. 1009 (Semple 2010), 172-175; Ex. 1010 (Heyes 2005), 277 ("[C]ationic and fusogenic[2] lipids … enable the cellular uptake and endosomal release of the particle's contents."). Alternatively fusion can be promoted by constructing nucleic acid cationic lipid complexes to transition from the common lamellar phase to non-lamellar phases at pH values internal to cell.

Non-cationic "helper" lipids, *e.g.*, phospholipids and/or cholesterols, can be combined with the cationic lipid to influence the ability of the particles to fuse with the cell membrane. Janoff Decl. ¶62; *see also* Ex. 1010 (Heyes 2005), 277.

In addition, it was well known in the art that a "conjugated lipid" (*e.g.*, a polyethylene glycol ("PEG") lipid) could be added to increase *in vivo* stability by "provid[ing] a neutral, hydrophilic coating to the particle's exterior." Janoff Decl.

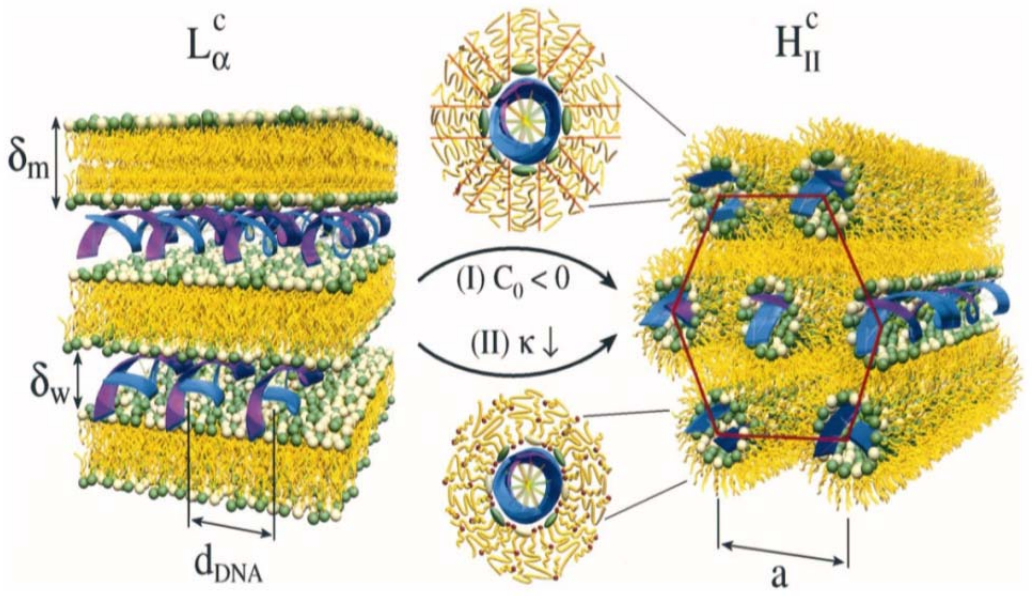
[2] In the art, "[t]he term 'fusogenic' refers to the ability of a lipid particle … to fuse with the membranes of a cell" thereby delivering its payload. Ex. 1001, 17:48-51.

¶62; *see also* Ex. 1010 (Heyes 2005), 277; *see also* Ex. 1006 (Ewert), 44.

2. STRUCTURE OF CATIONIC LIPID CARRIER PARTICLES

Lipid-nucleic acid particles can assume different three-dimensional structures. Particles comprised of a lipid bilayer are said to be "lamellar." Janoff Decl. ¶63. Particles in which the lipids are arranged in a non-bilayer morphology are said to be "non-lamellar." *Id.*

The ability of lipids to form lamellar and non-lamellar structures has been known in the field for decades. *Id.* In the late 1990s, researchers determined specifically that cationic lipid-nucleic acid complexes could assemble into different structures, including lamellar and non-lamellar (*e.g.*, "inverse hexagonal") architectures. *Id.* ¶64; *see also* Ex. 1005 (Koltover), 78, Fig. 1 (lamellar and inverse hexagonal phases shown):



Researchers pursued lipid-nucleic acid complexes that exhibited an inverted

hexagonal structure *in vitro* because such complexes were known to readily fuse with cell membranes allowing effective transfection. Janoff Decl. ¶65; Ex. 1004 ('099 patent), 5:53-54, 5:57-60; *see also* Ex. 1010 (Heyes 2005), 277 ("Lipidic systems are most fusogenic when arranged in the reversed hexagonal phase ….''). Indeed, the cationic lipid used in the non-bilayer geometries disclosed in the '127 patent, DLin-DMA, was specifically known to have a propensity for promoting a non-lamellar structure. Ex. 1010 (Heyes 2005), 282.

Nucleic acid-lipid complexes assembled into the inverted hexagonal morphology were known to be effective transfection systems well before the '127 patent. Janoff Decl. ¶66. For example, as early as 1998, complexes comprised of a cationic lipid, the helper lipid DOPE and DNA were known to assemble into the inverted hexagonal geometry and fuse with model membranes. Ex. 1005 (Koltover), 78 ("[Cationic lipid]-DNA complexes containing DOPE … empirically known to transfect exhibit the [hexagonal geometry].''); *see also* Ex. 1006 (Ewert), 37 (transfection compositions of cationic lipid, helper lipid DOPC and DNA assemble into the inverse hexagonal geometry).

Lipid-nucleic acid complexes can reconfigure from a lamellar to a non-lamellar geometry based upon variables such as the molecular geometries and proportions of the lipids selected and pH. Janoff Decl. ¶67; *see also* Ex. 1004 ('099 patent), 6:10-15; Ex. 1005 (Koltover), 78; Ex. 1010 (Heyes 2005), 285. As

an example, nucleic acid-lipid complexes can exhibit a lamellar geometry at a pH 7.4 and rearrange to a non-lamellar geometry at a pH of 5.5. Ex. 1004 ('099 patent), 33:36-54; Janoff Decl. ¶67.

It was known well before the priority date of the '127 patent that lipid complexes might exist in a lamellar morphology, purely non-lamellar morphology, or as a combination of lamellar and non-lamellar morphologies. Janoff Decl. ¶68; *see also* Ex. 1006 (Ewert), 42 (mixed morphologies and strictly non-lamellar morphology in cationic lipid-DNA complexes); Ex. 1005 (Koltover), Fig. 2 (complexes transition from lamellar, to a mix of morphologies, to exclusively non-lamellar morphology depending on the concentration of helper lipid). Indeed, prior art formulations in both Koltover and Ewert were designed to exhibit only non-lamellar morphologies. Janoff Decl. ¶68.

B. THE '127 PATENT DISCLOSURE

1. THE '127 PATENT: REPRESENTATIVE CLAIM

The '127 patent contains one independent claims and twenty-one dependent claims. Claim 1 is representative of the claims and reads:

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.

2. THE '127 PATENT: PRIOR ADMISSIONS

The '127 patent acknowledges that the following was known to a POSITA before to its priority date (*see* Janoff Decl. ¶69):

- Nucleic acid-lipid particles comprising a nucleic acid, cationic lipid, non-cationic lipid, and a conjugated lipid that inhibits aggregation of particles. *See* Ex. 1001, 15:64-16:12 (SNALP component combinations known in the art).
- The methods of making the nucleic acid-lipid particles disclosed in the '127 patent. *See id.*, 92:14-21 (list of known methods), 104:14-31 (Stepwise Dilution Method known), 104:32-44 (Direct Dilution Method known).
- The methods of judging the three-dimensional structure of the nucleic acid-lipid particles. *See id.*, 9:29-37 (cryo-TEM known in the art).

The sole remaining limitation in claim 1 of the '127 patent on which to base patentability is "wherein at least about 95% of the particles in the plurality of

particles have a non-lamellar morphology." *Id.*, cl. 1; Janoff Decl. ¶70. As shown below, however, this property is both inherent in prior disclosures and expressly disclosed in the prior art.

3. THE '127 PATENT: INTRINSIC EVIDENCE SHOWS THAT THE PATENT WAS GRANTED BASED SOLELY ON AN INHERENT CLAIM LIMITATION

The '127 patent discloses that the claimed non-lamellar nucleic acid-lipid particles result from (1) "the lipid composition of [the] formulation" and (2) "the formation process used." Ex. 1001, 2:64-3:10 ("controlling the lipid composition of a SNALP formulation as well as the formation process used to prepare the SNALP formulation ... [to achieve] a novel non-lamellar (*i.e.*, non-bilayer) morphology."); Janoff Decl. ¶74. The '127 patent specification acknowledges, however, that both the lipid compositions and formation process used to generate particles with the non-lamellar morphology were known in the art.

a) THE '127 PATENT FINDS THAT KNOWN LIPID COMPOSITIONS RESULT IN 95% OF THE PARTICLES HAVING A NON-LAMELLAR MORPHOLOGY

The '127 patent describes an experiment in which nucleic acid-lipid particles (specifically SNALPs) were created and then analyzed using cryo-Transmission Electron Microscopy ("cryo-TEM"). Ex. 1001, 104:1-110:29 (Examples 1-2). The nucleic acid-lipid particles tested included the following components: a PEG-conjugate (PEG-cDMA), a cationic lipid (DLin-DMA), and non-cationic lipids

(DSPC and cholesterol). *Id.*, 105:31-52. All of these components were known and had been combined to form nucleic acid-lipid particles long-before the '127 patent. *See id.*, 15:64-16:12 (SNALP component combinations known in the art); Janoff Decl. ¶71.

The '127 patent discloses the following lipid composition ratios (PEG-cDMA:DLin-DMA:DSPC:Chol): 2/30/20/48 ("2:30"); 2/40/10/48 ("2:40"); 1.4/57.1/7.1/34.3 ("1:57"); and, 1.5/62/0/37 ("1:62"). Ex. 1001, 105:31-52. While these ratios are not included as claim limitations, these exact lipid composition ratios are disclosed in the prior art. Janoff Decl. ¶72 ('069 patent and '817 PCT discussed below).

b) THE '127 PATENT FINDS THAT KNOWN METHODS OF CREATION RESULT IN 95% OF THE PARTICLES HAVING A NON-LAMELLAR MORPHOLOGY

The '127 patent discloses creating the cationic LNPs using either "a Stepwise Dilution Method or a Direct Dilution Method," both of which were admittedly known in the art.[3] Ex. 1001, 104:9-14; Janoff Decl. ¶72. The '127 patent specifically refers to the Direct Dilution process described in U.S. Patent Publication No. 20070042031. Ex. 1001, 104:32-60.

[3] The challenged claims are not limited to any production process. *See, e.g.*, Ex. 1001, cl. 1.

The resulting nucleic acid-lipid particles were analyzed by cryo-TEM and the number of non-lamellar particles were compared to the "particles possessing bilayer structures, including those with multiple compartments, LUVs [large, unilamellar vesicles] and MLVs [mutlilamellar vesicles]." *Id.*, 107:60-66. According to the '127 patent, "the 2:30, the 2:40, the 1:57 and the 1:62" formulations prepared using the Direct Dilution method contained at least 95% particles with a non-lamellar structure. *Id.*, Fig.12. Using the Stepwise Dilution method, the '127 patent asserts that the 1:57 and the 1:62 formulations contained at least 95% particles with a non-lamellar structure. *Id.*, Fig.7.

Thus, the '127 patent acknowledges that both the lipid composition and formulation process resulting in the claimed non-lamellar particles were known in the art. Janoff Decl. ¶74; Ex. 1001, 2:64-3:10.

4. PROSECUTION HISTORY

During the prosecution of the parent of the application leading to the '127 patent, U.S. App. No. 13/807,288, the examiner cited Patent Owner's earlier, unrelated '565 patent ("MacLachlan *et al*.") (Ex. 1012 discussed below) as prior art. In response, Patent Owner relied on the allegedly novel non-lamellar morphology to differentiate the prior art, arguing that "MacLachlan *et al.* does not teach a plurality of nucleic-acid-lipid particles wherein at least about 95% of the particles have a non-lamellar morphology." Ex. 1014, 12/11/2014, Resp. at 8;

Janoff Decl. ¶69.

VII. CLAIM CONSTRUCTION

Petitioner bases the instant petition upon the broadest reasonable interpretation of the claim language. Petitioner's position regarding the scope of the claims under their broadest reasonable interpretation is not to be taken as stating any position regarding the appropriate scope to be given the claims in a court or other adjudicative body under the different claim interpretation standards which apply in such proceedings.

A. CLAIM 1: "NUCLEIC ACID-LIPID PARTICLE"

Under the BRI standard, the term "nucleic acid-lipid particle" in independent claim 1 means "a composition of lipids and a nucleic acid for delivering a nucleic acid to a target site of interest." *See* Ex. 1001, 15:52-63. This construction is based upon the disclosures provided in the '127 patent. Janoff Decl. ¶75.

B. CLAIM 1: "AT LEAST ABOUT 95%"

It is unclear from the '127 patent specification what "at least about 95%" encompasses. The specification is silent on the meaning of this term. Janoff Decl. ¶76. While not admitting that this claim term is sufficiently definite, for the purposes of this Petition, under the BRI standard, Petitioner submits that this term would include, at least, the range from 95%-100% of the particles in the plurality of particles. *See id.* (under BRI standard, claim term would encompass something more than the expressed range).

C. CLAIM 1: "NON-LAMELLAR MORPHOLOGY"

Under the BRI standard, the term "non-lamellar morphology" in independent claim 1 means "a non-bilayer structure." Ex. 1001, 17:52-59, 107:60-108:3. This construction is based upon the definition provided in the '127 patent. Janoff Decl. ¶77.

D. CLAIMS 10-18: "COMPRISES FROM ABOUT [X]%"

It is unclear from the '127 patent specification what "comprises from about [x] %" encompasses. The specification is silent on the meaning of the term. *Id.* ¶78. During prosecution of Patent Owner's '069 patent, which has similar claims and limitations, the examiner stated that in the context of similar claims "'comprising about' could embrace an amount ± 10, 20, 30 mol % of a lipid component." Ex. 1015, 5/12/11, Rejection at 2. While not admitting that this claim term is sufficiently definite, for the purposes of this Petition, under the BRI standard, Petitioner submits that this term would include something more than the specifically expressed ranges. Janoff Decl. ¶78 (under BRI standard, claim term would encompass something more than the expressed range).

VIII. PRIOR ART

A. PATENT OWNER'S '069 PATENT AND '817 PCT

The '127 patent family is but one of many patent families with substantially overlapping disclosures that Patent Owner filed in a transparent effort to improperly extend its patent protections. Because these unrelated patent families,

with differing inventors, do not claim priority to one another, the earlier disclosures are prior art to the '127 patent. Janoff Decl. ¶79; Ex. 1002 ('069 patent); Ex. 1003 ('817 PCT).

1. PATENT OWNER'S DISCLOSURES LEADING TO THE '069 PATENT AND '817 PCT

Patent Owner filed the provisional applications leading to unrelated U.S. Patent No. 7,982,027 (the "'027 patent") in 2003—seven years before the application leading to the '127 patent. Ex. 1011. The '027 patent discloses the exact same lipid components (*i.e.*, cationic, non-cationic, conjugated lipids) tested in the '127 patent. *Id.*, cl. 1; Janoff Decl. ¶80.

A year later, Patent Owner filed provisional applications leading to unrelated U.S. Patent No. 7,799,565 (the "'565 patent")—six years before the priority date for the '127 patent. Ex. 1012. The '565 patent discloses using the same lipids (*i.e.*, PEG-cDMA, DLin-DMA, DSPC, and Cholesterol), and also discloses the exact 2:30 formulation of those components (*id.*, 52:54-53:17) as well as a siRNA payload for targeting ApoB (*id.*, 23:59). This is the same siRNA target and 2:30 formulation tested in the '127 patent that the '127 patent asserts demonstrates a non-lamellar structure in at least about 95% of the particles. Janoff Decl. ¶81.

In 2005, Patent Owner filed provisional applications leading to unrelated U.S. Patent No. 7,838,658 (the "'658 patent")—five years before the priority date for the '127 patent. Ex. 1013. The '658 patent discloses not only the same lipids,

but also discloses the 2:30 and 2:40 formulations of those lipids (*id.*, 50:60-51:27). The '658 patent also discloses using "a direct dilution process" for production. *Id.*, 33:21-25. A direct dilution process is one of the production processes used in the '127 patent. Janoff Decl. ¶82.

2. PATENT OWNER DISCLOSURES IN THE '069 PATENT AND '817 PCT ARE PRIOR ART

a) '069 PATENT IS PRIOR ART

In 2008, Patent Owner filed provisional application number 61/045,228 ("'228 provisional" (Ex. 1016)) leading to the unrelated '069 patent—two years before the priority date for the '127 patent. Ex. 1002. The '069 patent inventors are Ian MacLachlan, Edward Yaworski, Kieu Lam, Lloyd Jeffs, and Lorne Palmer, a different inventive entity from the '127 patent inventive entity. Also, the '127 patent and the '069 patent do not claim priority to one another. *See* Exs. 1001, 1002. The '069 patent is therefore prior art to the '127 patent under 35 U.S.C. § 102(e)(2) (pre-AIA). Janoff Decl. ¶83. The '069 patent published on May 27, 2010 before the earliest priority date of the '127 patent and is thus also prior art under 35 U.S.C. § 102(a) (pre-AIA). *Id.*

The '069 patent is titled "Lipid Formulations for Nucleic Acid Delivery" and discloses "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, cover page.

The SNALPs are cationic LNPs comprising "one or more active agents or therapeutics agents [*e.g.*, siRNA] … [a] cationic lipid … [a] non-cationic lipid … [and a] conjugated lipid …." *Id.*, 3:11-20; Janoff Decl. ¶84. The '069 patent discloses not only the same lipid components, but also the 2:30, 2:40, 1:57 and 1:62 formulation of those components. Ex. 1002, 73:13-39, Tables 4-7.[4] The same lipid to siRNA ratios as found in the '127 patent are disclosed in the '069 patent. *Id.*, Tables 4-7. In addition, the siRNA targeting ApoB disclosed is exactly the same as used in the '127 patent. *Id.*, 70:55-67, Table 3. The '069 patent also references the exact same Direct Dilution preparation method described in U.S. Patent Publication No. 20070042031 (also cited for the same purpose in the '127 patent). *Id.*, 59:12-16. The '069 patent characterizes the resulting particles. *See, e.g.*, *id.*, Tables 2, 4, and 6. The particle size, polydispersity and encapsulation efficiency indicate particles having a non-lamellar structure. Janoff Decl. ¶¶ 86, 107. This reference is cited as prior art in Ground 1 below.

In addition, the '069 patent incorporates by reference "in its entirety for all

[4] The '069 patent tested cationic lipids using the phospholipid DPPC rather than DSPC with the 2:40 and 1:57 formulations. Ex. 1002, 73:13-39. The '069 patent, however, discloses that DSPC can be used in lieu of DPPC. *Id.*, 50:6-31; Janoff Decl. ¶85.

purposes" U.S. Patent No. 5,885,613 (the "'613 patent" (Ex. 1017)). Ex. 1002, 11:56-65. The '613 patent is directed at "a fusogenic liposome comprising a lipid capable of adopting a non-lamellar phase, yet capable of assuming a bilayer structure in the presence of a bilayer stabilizing component." Ex. 1017, Abstract. The '613 patent discloses lipid complexes with strictly (*e.g.*, greater than 95%) non-lamellar structures (*see, e.g.*, Fig. 1, N=0) and further discloses that inducing a non-lamellar structure was well within the abilities of one of skill in the art: "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.*, 7:63-8:4; Janoff Decl. ¶87.

b) THE '817 PCT IS PRIOR ART

In 2008, Patent Owner filed the '817 PCT. Ex. 1003. The '817 PCT inventors are Ian MacLachlan and Adam Judge, a different inventive entity from both the '127 patent and '069 inventive entities. *See* Exs. 1001-1003. The '817 PCT was filed by different inventors on an international application filed under the Patent Cooperation Treaty designating the United States and was published as document WO 2009/082817 A1 on July 9, 2009 in the English language before the earliest possible priority date of the '127 patent. Ex. 1003. The '817 PCT is therefore prior art to the '127 patent under 35 U.S.C. § 102(e)(1) (pre-AIA). Janoff Decl. ¶88. The '817 PCT is also prior art to the '127 patent under 35 U.S.C.

§ 102(a) (pre-AIA). *Id.* The ’817 PCT claims priority to and “incorporate[s] by reference in [its] … entirety for all purposes” the ’228 provisional discussed above which is also the priority document of the ’069 patent. Ex. 1003, [0001]. The ’228 provisional in turn incorporates by reference the ’613 patent. Ex. 1016, [0078].

The ’817 PCT is titled “Silencing of Polo-like Kinase Expression Using Interfering RNA” and discloses “serum-stable nucleic acid-lipid particles … comprising an interfering RNA molecule … a cationic lipid, and a non-cationic lipid, which can further comprise a conjugated lipid that inhibits aggregation of particles.” Ex. 1003, [0010]. The ’817 PCT contains data which augments both the testing done in the ’228 provisional and the disclosures related to the testing done in the ’069 patent. Janoff Decl. ¶90. This reference is cited as prior art in Grounds 2 and 4 below.

By filing the ’069 patent and ’817 PCT, two full years or more before the priority date of the ’127 patent, the Patent Owner had disclosed nucleic acid-lipid particles with the same lipid components, the same lipids, the same nucleic acid payload, and the same Direct Dilution production method used to produce the particles exhibiting a non-lamellar morphology disclosed in the ’127 patent. The ’127 patent specifically asserts that these compositions created via the Direct Dilution process result in nucleic acid-lipid particles with the claimed non-lamellar morphology. Ex. 1001, 2:64-3:1; Janoff Decl. ¶¶83-90.

B. THE '099 PATENT IS PRIOR ART

U.S. Patent 7,514,099 (the "'099 patent") was patented on April 7, 2009. Ex. 1004. The '099 patent is therefore prior art to the '127 patent under 35 U.S.C. § 102(b). Janoff Decl. ¶91.

The '099 patent is titled "Lipid Nanoparticle Based Compositions and Methods for the Delivery of Biologically Active Molecules." Ex. 1004. The '099 patent discloses "novel cationic lipids, transfection agents, microparticles, nanoparticles, and short interfering nucleic acid (siNA) molecules." *Id.*, Abstract. The cationic LNPs disclosed are comprised of, for example, "(a) a cationic lipid … (b) a neutral lipid; (c) a polyethyleneglycol conjugate …; and (d) a short interfering nucleic acid (siNA) molecule that mediates RNA interference (RNAi) against apolipoprotein RNA (e.g., apo AI, apo A-IV, apo B, apo C-III, and/or apo E RNA) …." *Id.*, 28:36-48. Of note, these are the same components and payload described in the '127 patent. Janoff Decl. ¶91.

In addition, the '099 patent discloses that the compositions are arranged in a non-lamellar structure at pH 5.5 or below. Ex. 1004, 33:41-46 (particles "can transition from a stable lamellar structure adopted in circulation (i.e., in plasma or serum) at physiologic pH (about pH 7.4) to a less stable and more efficient delivery composition having an inverted hexagonal structure at pH 5.5-6.5, which is the pH found in the early endosome."). A POSITA wishing to deliver such non-lamellar

compositions would have had no difficulty formulating them in suitable pharmaceutical carrier at pH 5.0. Janoff Decl. ¶92. The '099 patent thus discloses nucleic acid-lipid particles comprised of the same components arranged in the same geometry claimed in the '127 patent, including having a non-lamellar structure. *Id*. This reference is cited as prior art in Ground 3 below.

C. KOLTOVER IS PRIOR ART

Koltover et al. ("Koltover") is an publication titled "An Inverted Hexagonal Phase of Cationic Liposome-DNA Complexes Related to DNA Release and Delivery." Ex. 1005. It was published in *Science* on July 3, 1998, in Volume 281, at pages 78–81. *See id.* Koltover is therefore prior art to the '127 patent under 35 U.S.C. § 102(b). Janoff Decl. ¶93.

Using video microscopy, Koltover studied the interaction of cationic lipid:helper lipid complexes determined by small angle x-ray scattering to be assembled exclusively in non-lamellar morphology with G-vesicles, a model for the cell membranes. Ex. 1005, 78–79. It was shown that these complexes, but not complexes comprised of the same lipids in different proportions that exhibited purely lamellar morphology, fused readily with the G vesicle membranes. *Id*. This early research established the fusogenic properties of cationic lipid complexes organized into non-lamellar structures. Koltover concluded that cationic lipid complexes organized in this geometry were "significantly more efficient in

transfecting mammalian cells … compared to [compositions organized into] the lamellar [] structure." *Id.*, 78; Janoff Decl. ¶94.

D. EWERT IS PRIOR ART

Ewert et al. ("Ewert") is a publication titled "Cationic lipid-DNA complexes for non-viral gene therapy: relating supramolecular structures to cellular pathways." Ex. 1006. It was published in *Expert Opin Biol Ther*. in 2005, in Volume 5(1), at pages 33–53. *See id.* Ewert is therefore prior art to the '127 patent under 35 U.S.C. § 102(b). Janoff Decl. ¶95.

Ewert discloses that complexes comprised of a cationic lipid (*e.g.*, DOTAP) and a helper lipid (*e.g.*, DOPE) can exist in either a purely lamellar organization, organizations in which lamellar architectures and non-lamellar architectures coexist, or in purely hexagonal organizations. Ex. 1006, 42. Ewert then discloses a schematic diagram representing how purely hexagonal organizations of lipids would transfect cells. *Id.*, 43. Ewert also teaches that the incorporation of PEG-lipids into such structures would make them a viable option for nucleic acid delivery. *Id.*, 44. The transfective hexagonal structure that Ewert discloses is identical to Figure 21 of the '127 patent. *Id.*, 42, Fig. 3; Janoff Decl. ¶96.

IX. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE '127 PATENT IS UNPATENTABLE

A. GROUND 1: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '069 PATENT

Claims 1-22 of the '127 patent are anticipated under 35 U.S.C. § 102(e)(2)

(pre-AIA) and § 102(a) (pre-AIA) by or obvious under 35 U.S.C. § 103 in view of the ’069 patent. Where citations are provided for the ’069 patent in the following sections, corresponding disclosures for the ’228 provisional (Ex. 1016) are provided in parenthesis.

The 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. *See* Ex. 1001, cl. 1; Janoff Decl. ¶103. Patent Owner, however, 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. The ’069 patent formulations include the same components, the same lipids, in the same ratios, with the same payload, made by the same formulation processes as found in the ’127 patent. Ex. 1002, 59:12-16, 70:55-67, 73:13-39, Tables 3-7; Janoff Decl. ¶104. Moreover, the ’127 patent specifically asserts that lipid complexes created with these lipids in these ratios using this formulation process results in particles with the claimed non-lamellar morphology. Ex. 1001, 2:64-3:1.

Even if Patent Owner was unaware of the resulting non-lamellar morphology at the time of the ’069 patent, the law is clear that “the 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.” *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d

1342, 1347 (Fed. Cir. 1999); *see also In re Crish*, 393 F.3d 1253, 1258 (Fed. Cir. 2004) ("A long line of cases confirms that one cannot establish novelty by claiming a known material by its properties.").

Moreover, it would have been obvious to a POSITA to characterize the particles resulting from the processes in the '069 patent, which would have revealed the greater than 95% non-lamellar structure therein, thereby rendering the claims obvious. Janoff Decl. ¶105.

1. THE COMPONENTS IN CLAIM 1 ARE DISCLOSED IN THE '069 PATENT

a) CLAIM ELEMENT 1[A]: A COMPOSITION COMPRISING: A PLURALITY OF NUCLEIC ACID-LIPID PARTICLES, WHEREIN EACH PARTICLE IN THE PLURALITY OF PARTICLES COMPRISES:

The '069 patent teaches "a lipid particle (e.g., SNALP) composition comprising a plurality of lipid particles." Ex. 1002, 23:15-17 ([0010]). The particles in turn comprise various lipid components and a nucleic acid payload. *Id.*, 11:13-26 ([0074]). As one example, in the 1:62 formulation, "the SNALP 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 … ; (c) a non-cationic lipid … ; and (d) a conjugated lipid that inhibits aggregation of particles." *Id.*, 24: 13-23, 3:36-45 ([0021]). Other examples include the 2:30, 2:40 and 1:57 formulations. *Id.*, 3:46-56, 68:13-25, 73:13-39, Tables 2, 4-6

([0022, 0231, 0237, 0242]); Janoff Decl. ¶98.

b) CLAIM ELEMENT 1[B]: A NUCLEIC ACID

The '069 patent teaches "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)." Ex.1002, 3:21-26 ([0010]). As one example, "FIG. 5 illustrates data demonstrating the activity of 1:62 SNALP containing ApoB siRNA following intravenous administration in mice." *Id.*, 4:29-31 ([0035]). The '069 patent also discloses using the ApoB siRNA with the 2:30, 2:40 and 1:57 formulations. *Id.*, Tables 4, 5-6 ([0022, 0231, 0237, 0242]); Janoff Decl. ¶99.

c) CLAIM ELEMENT 1[C]: A CATIONIC LIPID

The '069 patent teaches "one or more cationic lipids comprising from about 50 mol % to about 85 mol % of the total lipid present in the particle." Ex. 1002, 3:12-15 ([0010]). As one example, in Table 6, Group 3, the cationic lipid is identified as DLin-DMA. *Id.*, Table 6 ([0247]). The '069 patent also discloses using DLin-DMA with the 2:30, 2:40 and 1:57 formulations. *Id.*, Tables 4, 5-6 ([0022, 0231, 0237, 0242]); Janoff Decl. ¶100.

d) CLAIM ELEMENT 1[D]: A NON-CATIONIC LIPID

The '069 patent teaches "one or more non-cationic lipids comprising from about 13 mol % to about 49.5 mol % of the total lipid present in the particle." Ex. 1002, 3:14-16 ([0010]). As one example, in Table 6, Group 3, the non-cationic

lipid is identified as cholesterol. *Id.*, Table 6 ([0247]). The '069 patent also discloses using the non-cationic lipids DSPC:Cholesterol with the 2:30 formulation and DPPC:Cholesterol with 2:40 and 1:57 formulations. *Id.*, Tables 4, 5-6 ([0022, 0231, 0237, 0242]); Janoff Decl. ¶101.

e) CLAIM ELEMENT 1[E]: A CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES

The '069 patent teaches "one or more conjugated lipids that inhibit aggregation of particles comprising from about 0.5 mol % to about 2 mol % of the total lipid present in the particle." Ex. 1002, 3:16-19 ([0010]). As one example, in Table 6, Group 3, the conjugated lipid is identified as PEG (2000)-C-DMA. *Id.*, Table 6 ([0247]). The '069 patent also discloses using PEG (2000)-C-DMA with the 2:30, 2:40 and 1:57 formulations. *Id.*, Tables 4, 5-6 ([0022, 0231, 0237, 0242]); Janoff Decl. ¶102.

f) CLAIM ELEMENT 1[F]: WHEREIN AT LEAST ABOUT 95% OF THE PARTICLES IN THE PLURALITY OF PARTICLES HAVE A NON-LAMELLAR MORPHOLOGY

The '069 patent inherently anticipates the last element of claim 1, because it is a property that the '127 patent asserts invariably results from formulations disclosed therein. A prior art reference "may anticipate when the claim limitations not expressly found in that reference are nonetheless inherent in it." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). Inherency can be demonstrated when an "application itself instructs that [the claimed limitation] is

not an additional requirement imposed by the claims on the [invention], but rather a property necessarily present in the [invention]." *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009); *see also Alcon Research Ltd. v. Apotex Inc.,* 687 F.3d 1362, 1369 (Fed. Cir. 2013) (claim limitation "stabilizing conjunctival mast cells" is an inherent property when the patent itself "defines mast cell stabilization as a property that is necessarily present at those concentrations."). While 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." Ex. 1001, 2:64-3:10; Janoff Decl. ¶103. As in *Kubin* and *Alcon*, here both the particle composition and the formation processes disclosed in the '127 patent are the same as the ones disclosed in the '069 patent. Janoff Decl. ¶¶103-104; *see also* Ex. 1001, 104:9-14, 104:32-105:7, 105:31-52, 107:60-66, Tables 3-4, Figs. 7, 12; Ex. 1002, 59:12-16 ([0176], [0184]), 70:55-67 ([0236]), 73:13-39 ([0242]), Tables 3-7 ([Tables 3-7]). The '127 patent itself identifies these variables as resulting in the claimed property. Ex. 1001, 2:64-3:1.

Moreover, a property that is "natural result flowing from the combination of certain ingredients listed in" the prior art is inherently anticipated by it. *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007); *see also Ex Parte*

Hacker, No. 2012-003449, 2014 WL 2536376, at *4–5 (P.T.A.B. May 5, 2014) (claim for an "improved" weed control inherently anticipated because the patentee applied the chemical compound in the exact same ratio as the prior art); *King Pharm., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275–76 (Fed. Cir. 2010) (a claim for an increased bioavailability of the drug inherently anticipated by a prior art that disclosed the "identical" method of production). As in *Ex Parte Hacker*, the compositions in the '127 patent are the same as disclosed in the '069 patent and the natural properties of those compositions are therefore inherent.

It is well-established that inclusion of an inherent property of a prior art composition, such as in claim 1 of the '127 patent, does not make the subject matter patentable. *In re Crish*, 393 F.3d at 1258 ("[T]he identification and characterization of a prior art material" does not satisfy the novelty requirement.); *see also Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (A claim "directed to … the same use," which are the "results of known processes directed to the same purpose are not patentable because such results are inherent."); *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1369 (Fed. Cir. 2006) ("[T]he recognition of a new property of the prior art process" is not patentable.). For example, a patent claiming sprouts "rich in glucosinolates," a previously unappreciated cancer-fighting property, was inherently anticipated for doing "nothing more than recogniz[ing] properties inherent in certain prior art

sprouts." *In re Cruciferous Sprout Litig.*, 301 F.3d at 1350–51.

The '127 patent aspires to find "more efficient methods and compositions for introducing nucleic acids such as siRNA into cells," a statement copied verbatim from the '069 patent. *Compare* Ex. 1001, 1:51-52, 2:54-56, *with* Ex. 1002, 1:52-53 ([0003]), 2:55-57 ([0009]). To illustrate support for the added limitation in the '127 patent regarding the non-lamellar structure, the '127 patent relies on the same compositions, made with the same formation processes as found in the prior art '069 patent. The '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. Ex. 1001, 104:9-14, 104:61-63, 105:31-52, Table 3, Figs. 7, 10. According to the '127 patent, the three-dimensional structure of the cationic LNPs observed in these tests is a natural result flowing from the combination of these lipid ingredients. 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 comprising small interfering RNA ("siRNA") directed at silencing ApoB (a protein that in humans is encoded by the apoB gene) created using the same Direct Dilution Method. *Id.*, 104:61-105:7, Tables 3-4; Ex. 1002, 57:50-55 ([0176]), 73:13-39 ([0242]), Tables 4-6 ([0022, 0231, 0237, 0242]); Janoff Decl. ¶104. In addition, the '069 patent characterizes the resulting particles. *See, e.g.*, Ex. 1002, Tables 2, 4, and 6. The

particle size, polydispersity and encapsulation efficiency indicate particles having a non-lamellar structure. Janoff Decl. ¶¶ 86, 107.

Patent Owner has improperly extended its patent monopoly by disclosing cationic LNPs in the ’069 patent, and then trying to claim those exact same compositions, reciting an inherent property of those compositions, in the ’127 patent. As in *Omeprazole*, the prior disclosure of the composition of the claimed cationic LNPs anticipates the ’127 patent’s attempt to claim such particles and the natural properties related thereto.

In the alternative, this limitation would have been obvious in light of the disclosures in the ’069 patent and the knowledge of a POSITA. Janoff Decl. ¶106. One 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. *Id.* Indeed, the ’613 patent (incorporated by reference in the ’069 patent) discloses that lipid complexes are capable of forming different three-dimensional structures and that these three-dimensional structures are related to transfection efficacy. *See* Ex. 1017, 7:14-54. The ’613 patent further discloses combinations of lipids can “promote HII [non-lamellar] phase formation.” *Id.* The ’613 patent further discloses particle populations that are entirely non-lamellar (Fig. 1, N=0) 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.*, 7:63-8:4; Janoff Decl. ¶106.

In addition, a POSITA would have appreciated that the particle characterization in the '069 patent (*e.g., id.*, Tables 2, 4, and 6 (particle "size" and "encapsulation"), are indicative of particles having a non-lamellar structure. Janoff Decl. ¶¶86, 107. It 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.*, ¶108.

2. CLAIM 2: THE COMPOSITION OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS AN INTERFERING RNA

The '069 patent teaches a "nucleic acid-lipid particle … wherein the nucleic acid comprises a small interfering RNA (siRNA)," a type of interfering RNA used for gene silencing. Ex. 1002, cl. 2 ([cl. 2]); Janoff Decl. ¶109.

3. CLAIM 3: THE COMPOSITION OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS MRNA

The '069 patent teaches a "nucleic acid" which includes "a polymer containing at least two deoxyribonucleotides or ribonucleotides …. RNA may be in the form of siRNA, asymmetrical interfering RNA (aiRNA), microRNA (miRNA), mRNA, tRNA, rRNA, tRNA, viral RNA (vRNA), and combinations thereof." Ex. 1002, 10:16-26 ([0070]); Janoff Decl. ¶110.

4. CLAIM 4: THE COMPOSITION OF CLAIM 1, WHEREIN THE NON-CATIONIC LIPID IS A MIXTURE OF A PHOSPHOLIPID AND CHOLESTEROL OR A CHOLESTEROL DERIVATIVE

The '069 patent teaches "a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof." Ex. 1002, cl. 1(c) ([0143]); Janoff Decl. ¶111.

5. CLAIM 5: THE COMPOSITION OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES IS A POLYETHYLENE GLYCOL (PEG)-LIPID CONJUGATE

The '069 patent teaches a "nucleic acid-lipid particle … wherein the conjugated lipid that inhibits aggregation of particles comprises a polyethyleneglycol (PEG)-lipid conjugate." Ex. 1002, cl. 10 ([0150]); Janoff Decl. ¶112.

6. CLAIM 6: THE 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

The '069 patent teaches 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." Ex. 1002, cl. 11 ([0151]). Because the claimed group includes PEG-DAG and PEG-DAA, which are in the prior art, the claim limitation is disclosed. Janoff Decl. ¶113.

7. CLAIM 7: THE COMPOSITION OF CLAIM 6, WHEREIN THE PEG-DAA CONJUGATE IS A MEMBER SELECTED FROM THE GROUP CONSISTING OF A PEG-DIDECYLOXYPROPYL (C10) CONJUGATE, A PEG-DILAURYLOXYPROPYL (C12) CONJUGATE, A PEG-DIMYRISTYLOXYPROPYL (C14) CONJUGATE, A PEG-DIPALMITYLOXYPROPYL (C16) CONJUGATE, A PEG-DISTEARYLOXYPROPYL (C18) CONJUGATE, AND A MIXTURE THEREOF

The '069 patent teaches "[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." Ex. 1002, 21:56-60 ([0159]). Because the claimed group includes (C12) conjugate, a PEG-dimyristyloxypropyl (C14) conjugate, a PEG-dipalmityloxypropyl (C16) conjugate, a PEG-distearyloxypropyl (C18) conjugate, which are in the prior art, the claim limitation is disclosed. Janoff Decl. ¶114.

8. CLAIM 8: THE COMPOSITION OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS FULLY ENCAPSULATED IN THE PARTICLES

The '069 patent teaches a "nucleic acid-lipid particle … wherein the nucleic acid is fully encapsulated in the nucleic acid-lipid particle." Ex. 1002, cl. 17 ([0010]); Janoff Decl. ¶115.

9. CLAIM 9: THE COMPOSITION OF CLAIM 1, WHEREIN THE NON-LAMELLAR MORPHOLOGY OF THE PARTICLES COMPRISES AN INVERSE HEXAGONAL (HII) OR CUBIC PHASE STRUCTURE

The '069 patent inherently anticipates the added limitation of claim 9 of the '127 patent, 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 above regarding claim element 1[f] and is therefore inherent. *See* Ex. 1001, 9:21-24, Fig. 21; Janoff Decl. ¶116.

10. CLAIM 10: THE 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

The ’069 patent teaches “[i]n some embodiments, the cationic lipid may comprise … from about 50 mol % to about 60 mol % of the total lipid present in the particle.” Ex. 1002, 18:40-46 ([0014]). This overlaps with the claimed range. In addition, the ’069 reference incorporates by reference U.S. Patent Publication No. 20040142025 “in its entirety for all purposes.”[5] *Id.*, 58:18-21 ([0176]). U.S. Patent Publication No. 20040142025 discloses a “molar composition is about 20:45:10:25 DSPC:Chol:PEG-DSG:DODMA,” in which the cationic lipid concentration is 25%. Ex. 1018, [0052], [0098]. The ’069 reference also incorporates by reference U.S. Patent Publication No. 20070042031 “in its entirety for all purposes.” Ex. 1002, 59:12-16 ([0176]). U.S. Patent Publication No. 20070042031 discloses a cationic lipid with the composition “2 mol % PEG-C-

[5] “Material not explicitly contained in the single, prior art document may still be considered for purposes of anticipation if that material is incorporated by reference into the document.” *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

DMA, 30% DlinDMA, 20 mol % DSPC and 48 mol % Chol," in which the cationic lipid concentration is 30%. Ex. 1019, [0088]. The '069 reference also incorporates by reference U.S. Patent Publication No. 20060083780 "in [its] entirety for all purposes." Ex. 1002, 12:57-64 ([0084]). U.S. Patent Publication No. 20060083780 discloses that "[t]he cationic lipid of Formula I or Formula II typically comprises from about 2% to about 60%, from about 5% to about 50%, from about 10% to about 45%, from about 20% to about 40%, or about 30% of the total lipid present in said particle." Ex. 1020, [0051]. The overlapping and encompassing ranges (*e.g.*, "about 5% to about 50%") and the examples within the claimed range disclose the claimed range with sufficient specificity to anticipate.[6] Janoff Decl. ¶117.

11. CLAIM 11: THE 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

The '069 patent teaches "[i]n some embodiments, the cationic lipid may comprise … from about 50 mol % to about 60 mol % of the total lipid present in the particle." Ex. 1002, 18:40-46 ([0014]). This overlaps with the claimed range.

[6] Overlapping ranges that are disclosed with "sufficient specificity" constitute an anticipation under the statute. *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012).

In addition, the disclosures discussed above in U.S. Patent Publication Nos. 20040142025, 20070042031, 20060083780 for claim 10 include examples within the claimed range and the disclosed range of "about 5% to about 50%" encompasses and discloses the claimed range. Exs. 1018-1020 (cited above). These disclosures together provide the claimed range with sufficient specificity to anticipate. Janoff Decl. ¶118.

12. CLAIM 12: THE 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

The disclosures discussed above in U.S. Patent Publication Nos. 20040142025, 20070042031, 20060083780 for claim 10 include examples within the claimed range and the disclosed range of about 20% to about 40% expressly discloses the claimed range. Janoff Decl. ¶119; Exs. 1018-1020 (cited above).

13. CLAIM 13: THE 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

The '069 patent teaches "[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 % … of the total lipid present in the particle." Ex. 1002, 19:39-50 ([0146-0149]); Janoff Decl. ¶120.

14. CLAIM 14: THE 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

The '069 patent teaches "[i]n some embodiments, the non-cationic lipid (e.g., one or more phospholipids and/or cholesterol) may comprise …from about 20 mol % to about 55 mol % … of the total lipid present in the particle." Ex. 1002, 19:39-50 ([0146-0149]); Janoff Decl. ¶121.

15. CLAIM 15: THE 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

The '069 patent teaches "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." Ex. 1002, 19:54-62 ([0146-0149]). While it is unclear what "about 50%" encompasses, a POSITA would understand that it encompasses 49.5%. Janoff Decl. ¶122. The disclosed range of "about 20% to about 49.5%" therefore encompasses and discloses the claimed range and does so with sufficient specificity to anticipate. *Id.* In addition, the '069 patent discloses the 1:57 formulation with a non-cationic lipid component of 41.4%, anticipating the claimed range. *See, e.g.*, Ex. 1002, Table 4; Janoff Decl. ¶122.

16. CLAIM 16: THE 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

The '069 patent teaches "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." Ex. 1002, 22:30-42 ([0173]). This discloses an overlapping range. Janoff Decl. ¶123. The '069 patent also discloses a number of actual particles formulated in the claimed range. Ex. 1002, Tables 2, 4, 6-7 (*e.g.*, 1:57 formulation). Janoff Decl. ¶123.

The '069 patent also incorporates by reference U.S. Patent Application 20060083780 "in its entirety for all purposes." Ex. 1002, 12:57-64. U.S. Patent Publication No. 20060083780 discloses "[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." Ex. 1020, [0051]; Janoff Decl. ¶124. When combined with the "about 0.5 mol % to about 2 mol %" range in the body of the '069 patent, the entire range of 0.5%-20% is disclosed with sufficient specificity to anticipate. *Id.*

17. CLAIM 17: THE 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

See claim 16. In addition, the "about 1% to about 20%" disclosed range encompasses and discloses the claimed range with sufficient specificity to anticipate. Janoff Decl. ¶125.

18. CLAIM 18: THE 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

See claim 16. In addition, the "about 1.5% to about 18%" range is specifically disclosed. Janoff Decl. ¶126.

19. CLAIM 19: THE COMPOSITION OF CLAIM 1, WHEREIN GREATER THAN 95% OF THE PARTICLES HAVE A NON-LAMELLAR MORPHOLOGY

The '069 patent inherently anticipates the added limitation of claim 19 of the '127 patent, because it claims a property that is a natural result of the formulations disclosed in the '069 patent that is inherent as addressed above regarding claim element 1[f]. Janoff Decl. ¶127.

20. CLAIM 20: A PHARMACEUTICAL COMPOSITION COMPRISING A COMPOSITION OF CLAIM 1 AND A PHARMACEUTICALLY ACCEPTABLE CARRIER

The '069 patent teaches "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." Ex. 1002, 63:18-22 ([0198]); Janoff Decl. ¶128.

21. CLAIM 21: A METHOD FOR INTRODUCING A THERAPEUTIC AGENT INTO A CELL, THE METHOD COMPRISING: CONTACTING THE CELL WITH A COMPOSITION OF CLAIM 1

The '069 patent teaches "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)." Ex. 1002, 3:60-64 ([0024]); Janoff Decl. ¶129.

22. CLAIM 22: A METHOD FOR THE IN VIVO DELIVERY OF A THERAPEUTIC AGENT, THE METHOD COMPRISING: ADMINISTERING TO A MAMMAL A COMPOSITION OF CLAIM 1

The '069 patent teaches "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)." Ex. 1002, 3:65-4:2 ([0024]); Janoff Decl. ¶130.

B. GROUND 2: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '817 PCT

Claims 1-22 of the '127 patent are anticipated under 35 U.S.C. § 102(a) and § 102(e)(1) (pre-AIA) by or obvious under 35 U.S.C. § 103 in view of the '817 PCT. Ex. 1003; Janoff Decl. ¶131. The '817 PCT claims priority to and

"incorporate[s] by reference in [its] entirety for all purposes" the '228 provisional (Ex. 1016). Ex. 1003, [0001]. Through the publication of the '817 PCT, the disclosures in the provisional application also qualify as prior art under 35 U.S.C. § 102(a) and § 102(e)(1) (pre-AIA) as of July 9, 2009 under 37 C.F.R. § 1.14(a)(1)(vi) (allowing public access to unpublished pending applications that are incorporated by reference in an international publication of an international application); *see also* PCT Rule 17.2(c) ("priority documents" available for public inspection as of the date of international publication).[7] Janoff Decl. ¶131.

The challenged claims are invalid for at least the reasons stated above in Ground 1 (citations to the '228 provisional are provided above in parenthesis (*e.g.*, ([0001]))). The disclosures in the '817 PCT are not cumulative of the bases presented in Ground 1 for several reasons. First, in addition to the citations to the '228 provisional presented above in Ground 1, the '817 PCT contains the additional disclosures rendering claims 1-22 invalid as detailed below. Second, 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.

[7] As is shown on the cover of Ex. 1016, the '228 provisional was provided to the International Bureau of WIPO on February 11, 2009. The '817 PCT identifies the '228 provisional on its face and was published on July 9, 2009. Ex. 1003.

1. CLAIMS 1-9, 13-15 AND 19-22

For the reasons stated above in Ground 1, claims 1-9, 13-15 and 19-22, the '817 PCT anticipates these claims of the '127 patent. Janoff Decl. ¶132.

2. ADDITIONAL BASES FOR CLAIMS 10-12

The '817 PCT teaches "[t]he cationic lipid may comprise from about 2 mol % to about 60 mol %, about 5 mol % to about 45 mol %, about 5 mol % to about 15 mol %, about 20 mol % to about 50 mol %, about 30 mol % to about 50 mol %, about 40 mol % to about 50 mol %, or about 40 mol % of the total lipid present in the particle." Ex. 1003, [0025]. This encompasses the 10 mol% to about 50 mol% and 20 mol% to about 40 mol% ranges with sufficient specificity to anticipate. Janoff Decl. ¶133. The about 20 mol% to about 50 mol% range is specifically disclosed. *Id.*

3. ADDITIONAL BASES FOR CLAIMS 16-18

The '817 PCT teaches "[t]he conjugated lipid that prevents aggregation of particles may be from 0 mol % to about 20 mol %, about 0.5 mol % to about 20 mol %, about 1 mol % to about 15 mol %, about 4 mol % to about 10 mol %, or about 2 mol % of the total lipid present in the particle." Ex. 1003, [0027]. This encompasses the about 1 mol% to about 20 mol%, about 1.5 mol% to about 18 mol% ranges with sufficient specificity to anticipate. Janoff Decl. ¶134. The about 0.5 mol % to about 20 mol % range is specifically disclosed. *Id.*

C. GROUND 3: CLAIMS 1-22 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '099 PATENT ALONE OR IN VIEW OF KOLTOVER AND/OR EWERT

Claims 1-22 of the '127 patent are anticipated under 35 U.S.C. § 102(b) or obvious under 35 U.S.C. § 103 in view of the '099 patent alone or further in view of Koltover and/or Ewert. Janoff Decl. ¶135.

The'099 patent describes particles designed to achieve a lamellar to non-lamellar reorganization at a prescribed pH. While the '099 patent is silent on the percentage of particles undergoing such a reorganization, given the description in the specification, a POSITA would appreciate that it was intended that particles designed in such a fashion would undergo a complete reorganization. Janoff Decl. ¶141.

Moreover, given the descriptions in the '099 patent, a POSITA would have had reason to believe that the nucleic acid-lipid particles created with the disclosed components using the '099 patent formulation processes would result in particles with the claimed non-lamellar morphology at the described pH, thereby rending the claims obvious. *Id.* In addition, other prior art, *e.g.*, Koltover and/or Ewert, establish obviousness by describing the existence of lipid in purely non-lamellar organizations.

1. CLAIM ELEMENT 1[A]: A COMPOSITION COMPRISING: A PLURALITY OF NUCLEIC ACID-LIPID PARTICLES, WHEREIN EACH PARTICLE IN THE PLURALITY OF PARTICLES COMPRISES:

The ’099 patent teaches “novel cationic lipids … and formulations thereof with biologically active molecules.” Ex. 1004, 7:3-5. As one example, “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, PEP-cholesterol, or PEG-DMB conjugate.” *Id.*, 21:66-22:6; Janoff Decl. ¶136.

2. CLAIM ELEMENT 1[B]: A NUCLEIC ACID

The ’099 patent teaches “compositions … with biologically active molecules” including “nucleic acids.” Ex. 1004, 6:42-55, 7:3-17. As one example, “the invention features a composition comprising a biologically active molecule (e.g., a polynucleotide such as a siNA, antisense, aptamer, decoy, ribozyme, 2-5A, triplex forming oligonucleotide, [or] other nucleic acid molecule …).” *Id.*, 21:66-22:6; Janoff Decl. ¶137.

3. CLAIM ELEMENT 1[C]: A CATIONIC LIPID

The ’099 patent teaches “[c]ationic lipids that are useful in the present invention can be any of a number of lipid species which carry a net positive charge at a selected pH, such as physiological pH.” Ex. 1004, 113:48-50; Janoff Decl. ¶138.

4. CLAIM ELEMENT 1[D]: A NON-CATIONIC LIPID

The '099 patent teaches "[t]he noncationic lipids used in the present invention can be any of a variety of neutral uncharged, zwitterionic or anionic lipids capable of producing a stable complex." Ex. 1004, 114:3-5; Janoff Decl. ¶139.

5. CLAIM ELEMENT 1[E]: A CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES

The '099 patent teaches "[i]n addition to cationic and neutral lipids, the formulated molecular compositions of the present invention comprise a polyethyleneglycol (PEG) conjugate." Ex. 1004, 114:57-59; Janoff Decl. ¶140.

6. CLAIM ELEMENT 1[F]: WHEREIN AT LEAST ABOUT 95% OF THE PARTICLES IN THE PLURALITY OF PARTICLES HAVE A NON-LAMELLAR MORPHOLOGY

The '099 patent discloses a "… formulated molecular composition [that] undergoes a structural change to adopt an inverted hexagonal structure at about pH 5.5-6.5." Ex. 1004, 33:38-46; *see also* 5:42-52; Fig. 7; Janoff Decl. ¶141. The '099 patent describes this transition as "a rapid pH-dependent phase transition." Ex. 1004, 33:48. The '099 patent teaches "the inverted hexagonal structure transfects mammalian cells more efficiently than the lamellar structure." *Id.*, 5:52-54. Because the disclosed cationic LNPs 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. Janoff Decl.

¶142.

Moreover, 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. Janoff Decl. ¶143. In Example 8 (Ex. 1004, 140:49-141:19), the ’099 patent presents data relating to an experiment wherein certain formulations were exposed to a range of pH values. Referring to this data, the ’099 patent discloses that the formulations underwent “….a phase transition.” *Id.* A POSITA would understand that a single “phase transition” was reported, meaning that all of the lipid participated in this transition. It would have been obvious in view of the stated goals of the ’099 patent to design the system consistent with these descriptions. Janoff Decl. ¶143.

Moreover, a POSITA would understand lipid complexes can achieve populations of complexes that have strictly non-lamellar structures. *Id.* ¶144; *see* Koltover (Ex. 1005) and Ewert (Ex. 1006). The disclosed formulations in the ’099 patent were intended to transition to a non-lamellar structure at the disclosed pH. Janoff Decl. ¶143. A POSITA would have found it obvious to manipulate variables such as the pH in the ’099 patent to drive the transition to completion. *Id.*; *see also* Ex. 1017 (’613 patent), 7:63-8:4 (“[I]t 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 ….").

7. CLAIM 2: THE COMPOSITION OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS AN INTERFERING RNA

The '099 patent teaches "formulations for the delivery of chemically modified synthetic short interfering nucleic acid (siNA) molecules that modulate target gene expression or activity in cells, tissues, such as in a subject or organism, by RNA interference (RNAi)." Ex. 1004, 7:22-28; Janoff Decl. ¶145.

8. CLAIM 3: THE COMPOSITION OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS MRNA

The '099 patent discloses "the invention relates to compounds, compositions and methods for delivering nucleic acids, polynucleotides, and oligonucleotides … to cells by facilitating transport across cellular membranes in, for example, epithelial tissues and endothelial tissues." Ex. 1004, 1:46-52. A POSITA would understand nucleic acids to include mRNA. Janoff Decl. ¶146.

9. CLAIM 4: THE COMPOSITION OF CLAIM 1, WHEREIN THE NON-CATIONIC LIPID IS A MIXTURE OF A PHOSPHOLIPID AND CHOLESTEROL OR A CHOLESTEROL DERIVATIVE

The '099 patent teaches "[e]xamples of noncationic lipids useful in the present invention include phospholipid-related materials …. Noncationic lipids or sterols such as cholesterol may be present." Ex. 1004, 114:7-22; Janoff Decl. ¶147.

10. CLAIM 5: THE COMPOSITION OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES IS A POLYETHYLENE GLYCOL (PEG)-LIPID CONJUGATE

The '099 patent teaches "a composition comprising a biologically active molecule … , a cationic lipid, a neutral lipid, and a polyethyleneglycol conjugate, such as a PEG-diacylglycerol, PEG-diacylglycamide, PEG-cholesterol, or PEG-DMB conjugate." Ex. 1004, 21:66-22:6; Janoff Decl. ¶148.

11. CLAIM 6: THE 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

The '099 patent teaches "[s]uitable polyethyleneglycol-diacylglycerol or polyethyleneglycol-diacylglycamide (PEG-DAG) conjugates include those comprising a dialkylglycerol or dialkylglycamide group having alkyl chain length independently comprising from about C4 to about C40 saturated or unsaturated carbon atoms." Ex. 1004, 23:9-14. As one example, "the invention features a composition comprising … a polyethyleneglycol conjugate, such as a PEG-diacylglycerol, PEG-diacylglycamide, PEG-cholesterol, or PEG-DMB conjugate." *Id.*, 21:66-22:6. In another example, "the formulated molecular composition[]" may "comprise a diacylglycerol-polyethyleneglycol conjugate, i.e., a DAG-PEG conjugate." *Id.*, 114:57-61; Janoff Decl. ¶149.

12. CLAIM 7: THE COMPOSITION OF CLAIM 6, WHEREIN THE PEG-DAA CONJUGATE IS A MEMBER SELECTED FROM THE GROUP CONSISTING OF A PEG-DIDECYLOXYPROPYL (C10) CONJUGATE, A PEG-DILAURYLOXYPROPYL (C12) CONJUGATE, A PEG-DIMYRISTYLOXYPROPYL (C14) CONJUGATE, A PEG-DIPALMITYLOXYPROPYL (C16) CONJUGATE, A PEG-DISTEARYLOXYPROPYL (C18) CONJUGATE, AND A MIXTURE THEREOF

The ’099 patent teaches “the PEG conjugate can be selected from PEG-dilaurylglycerol (C12), PEG-dimyristylglycerol (C14), PEG-dipalmitoylglycerol (C16), PEG-disterylglycerol (CI8), PEG-dilaurylglycamide (C12), PEG-dimyristylglycamide (C14), PEG-dipalmitoylglycamide (C16), and PEG-disterylglycamide (CI8), PEG-cholesterol (1-[8’-(Cholest-5-en-3β-oxy)carboxamido-3’,6’-dioxaoctanyl]carbamoyl-ω-methyl-poly (ethyleneglycol), and PEG-DMB (3,4-Ditetradecoxylbenzyl-ω-methyl-poly(ethyleneglycol)ether).” Ex. 1004, 23:14-25. As one example, “Rl and R2 are each independently a C2 to C30 alkyl group.” *Id.*, 23:15-25; Janoff Decl. ¶150.

13. CLAIM 8: THE COMPOSITION OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS FULLY ENCAPSULATED IN THE PARTICLES

The ’099 patent teaches “[t]he use of cationic lipids for cellular delivery of biologically active molecules has several advantages. The encapsulation of anionic compounds using cationic lipids is essentially quantitative due to electrostatic interaction.” Ex. 1004, 4:64-67. The ’099 patent further teaches “the present invention provides a serum-stable formulated molecular composition … in which

the biologically active molecule is encapsulated in a lipid bilayer and is protected from degradation." *Id.*, 33:4-12. A POSITA would understand that the nucleic acid could be fully encapsulated in the non-bilayer structure as well. Janoff Decl. ¶151. This is disclosed for example in Ewert. *Id.*; Ex. 1006 (Ewert), 36.

14. CLAIM 9: THE COMPOSITION OF CLAIM 1, WHEREIN THE NON-LAMELLAR MORPHOLOGY OF THE PARTICLES COMPRISES AN INVERSE HEXAGONAL (HII) OR CUBIC PHASE STRUCTURE

See claim 1[f].

15. CLAIM 10: THE 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

The '099 patent teaches "[i]n one embodiment, the cationic lipid component … of a composition of invention comprises from about 2% to about 60%, from about 5% to about 45%, from about 5% to about 15%, or from about 40% to about 50% of the total lipid present in the formulation." Ex. 1004, 29:54-59; *see id.*, 81:30-33. The about 2% to about 60% range discloses the claimed range with sufficient specificity to anticipate claim 10. Janoff Decl. ¶153. In addition, the '099 patent discloses specific formulations containing cationic lipid within the claimed range. Ex. 1004, Table IV (*e.g.*, Formulation L051); Janoff Decl. ¶153.

16. CLAIM 11: THE 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

See claim 10. The about 2% to about 60% range discloses the claimed range

with sufficient specificity to anticipate claim 11. Janoff Decl. ¶154. In addition, the '099 patent discloses specific formulations containing cationic lipid within the claimed range. Ex. 1004, Table IV (*e.g.*, Formulation L051); Janoff Decl. ¶154.

17. CLAIM 12: THE 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

See claim 10. The about 5% to about 45% range discloses the claimed range with sufficient specificity to anticipate claim 12. Janoff Decl. ¶155. In addition, the '099 patent discloses specific formulations containing cationic lipid within the claimed range. Ex. 1004, Table IV (*e.g.*, Formulation L053); Janoff Decl. ¶155.

18. CLAIM 13: THE 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

The '099 patent teaches "[t]he neutral lipid component can comprise from about 5% to about 90%, from about 20% to about 85% of the total lipid present in the formulation." Ex. 1004, 81:33-35. As an example, "[i]n one embodiment, the neutral lipid component of a composition of the invention comprises from about 5% to about 90%, or from about 20% to about 85% of the total lipid present in the formulation." *Id.*, 29:60-63. The about 20% to about 85% range discloses the claimed range with sufficient specificity to anticipate claim 13. Janoff Decl. ¶156. In addition, '099 patent discloses specific formulations containing non-cationic lipid within the claimed range. Ex. 1004, Table IV (*e.g.*, Formulation L051);

Janoff Decl. ¶156.

19. CLAIM 14: THE 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

See claim 13 ("about 20% to about 55%" disclosed). In addition, the '099 patent discloses specific formulations containing cationic lipid within the claimed range. Ex. 1004, Table IV (*e.g.*, Formulation L051); Janoff Decl. ¶157.

20. CLAIM 15: THE 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

See claim 13. The about 20% to about 55% range discloses the claimed range with sufficient specificity to anticipate claim 15. Janoff Decl. ¶158. In addition, the '099 patent discloses specific formulations containing cationic lipid within the claimed range. Ex. 1004, Table IV (*e.g.*, Formulation L051); Janoff Decl. ¶158.

21. CLAIM 16: THE 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

The '099 patent teaches "[t]he PEG-DAG conjugate can comprise from about 1% to about 20%, or from about 4% to about 15% of the total lipid present in the formulation." Ex. 1004, 82:35-37; *see also* 30:5-12 ("… a PEG conjugate … comprising about 0 to about 10% of the total lipid present in the formulation");

Janoff Decl. ¶159. While it is unclear what "about 0.5% mol %" encompasses, a POSITA would understand that "about 0.5%" is disclosed by "about 1 %." Ex. 1001, cl. 16. In addition, the '099 patent discloses specific formulations containing conjugated lipid within the claimed range. Ex. 1004, Table IV (*e.g.*, Formulation L051); Janoff Decl. ¶159.

22. CLAIM 17: THE 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

See claim 16. The about 1% to about 20% range discloses the claimed range with sufficient specificity to anticipate claim 17. Janoff Decl. ¶160. In addition, the '099 patent discloses specific formulations containing conjugated lipid within the claimed range. Ex. 1004, Table IV (*e.g.*, Formulation L051); Janoff Decl. ¶160.

23. CLAIM 18: THE 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

See claim 16. The about 1% to about 20% range discloses the claimed range with sufficient specificity to anticipate claim 18. Janoff Decl. ¶161. In addition, the '099 patent discloses specific formulations containing conjugated lipid within the claimed range. Ex. 1004, Table IV (*e.g.*, Formulation L051); Janoff Decl. ¶161.

24. CLAIM 19: THE COMPOSITION OF CLAIM 1, WHEREIN GREATER THAN 95% OF THE PARTICLES HAVE A NON-LAMELLAR MORPHOLOGY

See claim 1[f].

25. CLAIM 20: A PHARMACEUTICAL COMPOSITION COMPRISING A COMPOSITION OF CLAIM 1 AND A PHARMACEUTICALLY ACCEPTABLE CARRIER

The '099 patent teaches "the invention featur[ing] a composition comprising a formulated molecular composition of the invention, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising formulated molecular compositions of the invention, targeting one or more genes in a pharmaceutically acceptable carrier or diluent." Ex. 1004, 77:50-56. As an example, "[i]n one embodiment, formulated molecular compositions of the invention are administered to a subject by systemic administration in a pharmaceutically acceptable composition or formulation." *Id.*, 130:65-131:1; Janoff Decl. ¶163.

26. CLAIM 21: A METHOD FOR INTRODUCING A THERAPEUTIC AGENT INTO A CELL, THE METHOD COMPRISING: CONTACTING THE CELL WITH A COMPOSITION OF CLAIM 1.

The '099 patent teaches "the invention relates to novel cationic lipids, microparticles, nanoparticles and transfection agents that effectively transfect or deliver biologically active molecules … to relevant cells and/or tissues, such as in a subject or organism." Ex. 1004, 1:24-37. As an example, "[i]n one embodiment, the invention features a method for delivering or administering a biologically

active molecule to a cell or cells in a subject or organism ….” *Id.*, 38:33-39; Janoff Decl. ¶164.

27. CLAIM 22: A METHOD FOR THE IN VIVO DELIVERY OF A THERAPEUTIC AGENT, THE METHOD COMPRISING: ADMINISTERING TO A MAMMAL A COMPOSITION OF CLAIM 1

The ’099 patent teaches “[i]n one embodiment, the siNA component of a formulated siNA composition of the invention is chemically modified so as not to stimulate an interferon response in a mammalian cell, subject, or organism.” Ex. 1004, 26:21-24; Janoff Decl. ¶165.

28. MOTIVATION TO COMBINE ’099 PATENT WITH KOLTOVER AND/OR EWERT

A POSITA would have been motivated to combine the teachings of the ’099 patent with Koltover and/or Ewert. Janoff Decl. ¶¶166-168.

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. *Id.* Given the success of generating non-lamellar particles at a pH of 5.5-6.5 in the ’099 patent, a POSITA would have appreciated a reasonable expectation of doing so. Moreover, Koltover is cited on the face of the ’099 patent and the ’099 patent discusses the use of lipid complexes in describing the state of the art. *Id.*; Ex. 1004, 4:45-5:4. Further, POSITA would have recognized that a homogenous 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. Janoff Decl. ¶166.

A POSITA would also have found it obvious to use the insights in Ewert with the ’099 patent in addition to, or in lieu of, Koltover. *Id.* ¶167. Ewert cites to the Koltover paper. Ex. 1006, 51. Furthermore, Ewert addresses the non-lamellar structures in cationic nucleic acid-lipid complexes, the same type of lipid complexes that are the subject of the ’099 patent. *Id.*, 33. Further, 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. Janoff Decl. ¶167; *see also* Ex. 1017, 7:63-8:4 (“[I]t 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 ….”). Given the success of generating non-lamellar particles at a pH of 5.5-6.5 in the ’099 patent, a POSITA would have appreciated a reasonable expectation of success

in generating a greater than 95% non-lamellar structure.[8] Janoff Decl. ¶ 167.

D. GROUND 4: CLAIMS 1-22 ARE OBVIOUS IN VIEW OF THE '817 PCT IN LIGHT OF THE '099 PATENT, KOLTOVER, HEYES AND/OR EWERT

As discussed above, the '817 PCT (and the '228 provisional incorporated therein and as detailed in Ground 1) qualifies as prior are under 35 U.S.C. § 102(a) and § 102(e)(1) (pre-AIA). As discussed above, Koltover, and Ewert qualify as prior art under 35 U.S.C. § 102(b). As discussed above in Ground 2, the only element of the claim not expressly disclosed in the '817 PCT is claim element 1[f] (and related dependent claims 9 and 21). To the extent that claim element 1[f] 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), this element would be obvious in view of the '817 PCT in light of Koltover and/or Ewert.

A POSITA would have been motivated to combine the '817 PCT with Koltover and/or Ewert. Janoff Decl. ¶¶169-173. The '817 PCT expressly states "examples of additional lipid-based carrier systems suitable for use in the present invention" include "lipoplexes," "cationic lipid-based compositions," and "cationic

[8] The above discussion is based upon the level of skill in the art articulated in Section V. A lower level of skill in the art, however, would not alter the outcome in this proceeding. Janoff Decl. ¶168.

liposomes," these include the lipid species used type in the carrier complexes described in Koltover and Ewert. Ex. 1003, [0324].

A POSITA would have looked to existing disclosures in Koltover and Ewert to establish the possibility of producing completely non-lamellar structures as a means of increasing transfection efficacy. Janoff Decl. ¶171. A POSITA would have, in light of Koltover and Ewert, been motivated to identify the impact of certain variables (such as specific lipids used, lipid ratios, processes) on the biophysical characteristics of the formulations disclosed in the '817 PCT. A POSITA would have found it obvious to try manipulating these to achieve only non-lamellar particles. *See* Ex. 1017, 7:63-8:4 ("[L]ipids known to those of skill in the art to adopt a nonlamellar phase ….can…be used"); 7:63-8:4 ("[I]t 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 …."). Moreover, according to the '127 patent, at least 95% of the SNALPs resulting from the component ratios and formulation processes described in the '817 PCT have non-lamellar structure. Confirming the existence of such structures would have been a simple matter of examining the SNALPs with a

known technique such as cryo-TEM.[9] Janoff Decl. ¶172.

Dated: February 21, 2018

Respectfully submitted,

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[9] The above discussion is based upon the level of skill in the art articulated in Section V. A lower level of skill in the art, however, would not alter the outcome in this proceeding. Janoff Decl. ¶173.

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24(d), I certify that the present paper contains 13,236 words as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, table of exhibits, mandatory notices, certificate of service, or this certificate of word count.

Dated: February 21, 2018

/s/ Michael R. Fleming

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. sections 42.6 and 42.105, that a complete copy of the Petition for Inter Partes Review of U.S. Patent No. 9,044,127 and Exhibits 1001 through 1022 are being served via Express Mail upon the patent prosecution counsel of record for the Patent Owner on the 21st day of February 2017, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board:

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