UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Moderna Therapeutics, Inc.

Petitioner

v.

Protiva Biotherapeutics, Inc.

Patent Owner

U.S. Patent No. 9,364,435

Issued: June 14, 2016

Named Inventor: Edward Yaworski, Kieu Lam, Lloyd Jeffs, Lorne Palmer, Ian MacLachlan

Title: Lipid Formulations for Nucleic Acid Delivery

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,364,435

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TABLE OF AUTHORITIES

List of Evidence and Exhibits Relied Upon in the Petition

Exhibit No.	Reference
1001	U.S. Patent No. 9,364,435
1002	International Publication No. WO 2005/007196
1003	U.S. Publication No. US2006/0134189
1004	U.S. Publication No. US2006/0240554
1005	Lin, Alison J. et al., *Three-Dimensional Imaging of Lipid Gene-Carriers: Membrane Charge Density Controls Universal Transfection Behavior in Lamellar Cationic Liposome-DNA Complexes*, 84 BIOPHYSICAL JOURNAL, 3307–16 (2003) ("Lin")
1006	Ahmad, Ayesha et al., *New multivalent cationic lipids reveal bell curve for transfection efficiency versus membrane charge density: lipid-DNA complexes for gene delivery*, 7 J GENE MED 739–48 (2005) ("Ahmad")
1007	Declaration of Dr. Andrew S. Janoff
1008	Gao, Xiang et al., *Nonviral Gene Delivery: What We Know and What Is Next*, 9 AAPS JOURNAL Article 9, pp. E92-E104 (2007) ("Gao")
1009	Bennett, Michael J. et al., *Cholesterol Enhances Cationic Liposome-Mediated DNA Transfection of Human Respiratory Epithelial Cells*, 15 Bioscience Reports, pp. 47-53 (1995) ("Bennett")
1010	Heyes, James et al., *Cationic lipid saturation influences intracellular delivery of encapsulated nucleic acids*, 107 JOURNAL OF CONTROLLED RELEASE 276–87 (2005) ("Heyes")
1011	U.S. Patent No. 5,753,613
1012	U.S. Patent No. 7,939,505
1013	U.S. Publication No. US2007/0042031
1014	U.S. Publication No. US2006/0008910
1015	Excerpts from '069 Patent File History
1016	'435 Patent File History
1017	U.S. Patent No. 5,264,618
1018	Curriculum Vitae of Dr. Andrew S. Janoff

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 1–20 of U.S. Patent 9,364,435 ("'435 patent," Ex. 1001).

I. INTRODUCTION

The '435 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) comprising three lipid components (*i.e.*, cationic lipid, non-cationic lipid and conjugated lipid), each of which fall within a claimed proportion with regard to the total lipid in the particles. *See, e.g.*, Ex. 1001, claim 1.

The '435 patent is just one of many unrelated patents owned by Protiva Biotherapeutics, Inc. ("Patent Owner"), some of which date back to the early 2000s, that disclose substantially the same nucleic acid-lipid particles with only 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 '435 patent, to improperly block the public and industry participants from using basic combinations of nucleic acid-lipid particle components explicitly described long before the '435 priority date.

The Patent Owner's own prior art disclosures in PCT Application No.

PCT/CA2004/001051, Publication No. WO2005007196 A2 ("'196 PCT") (Ex. 1002) and U.S. Patent Publication No US2006/0134189 ("'189 publication") (Ex. 1003), and other prior art, including U.S. Patent Publication No. 2006/0240554 ("'554 publication") (Ex. 1004), show that the claimed composition of lipid components was available well before the priority date of the '435 patent. These references disclose overlapping and encompassing ranges for each of the three lipid components, and, in the case of the '554 publication, specific examples of nucleic acid-lipid particles meeting the claim limitations.

Moreover, the disclosure of overlapping ranges for the three lipid components establishes a *prima facie* case of obviousness under 35 U.S.C § 103. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("[E]ven a slight overlap in range establishes a *prima facie* case of obviousness.").[1] One skilled in the art would appreciate that generating lipid complexes with lipid components in the ranges claimed would have been simple matter of using prior art production

[1] The overlapping ranges establish a *prima facie* showing of obviousness. As detailed herein, the overlapping ranges, content of the cited art, knowledge of a POSITA and testing data also demonstrate invalidity by the preponderance of the evidence. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364 (Fed. Cir. 2016) (petitioner's burden of showing invalidity by preponderance of the evidence).

methods to combine appropriate proportions of prior art lipid components. *Id.* at 1330 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."). Thus, each of the references renders the challenged claims obvious.

During prosecution of the parent of the '435 patent, U.S. Patent No. 8,058,069 ("'069 patent"), which contains claims to similar nucleic acid-lipid particles with similar components in narrower ranges, the Patent Owner overcame cited prior art disclosing overlapping ranges based upon alleged unexpected test results attributable to a cationic lipid proportion greater than 50%. This testing, however, shows that data points falling within the broader ranges claimed in the '435 patent actually perform worse than the admitted prior art formulations—*i.e.*, there are no unexpected advantages. It is well-settled that "unexpected results" must be demonstrated for the entire claimed range to support patentability. *In re Clemens*, 622 F.2d 1029, 1035 (C.C.P.A. 1980) ("In order to establish unexpected results for a claimed invention, objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.").

In addition, the prior art references Lin (Ex. 1005) and/or Ahmad (Ex. 1006) teach that there was a recognized potential benefit to using a cationic lipid proportion over 50%. One skilled in the art would have been motivated to combine these disclosures with the '196 PCT and/or '189 publication as described herein further rendering the claims obvious.

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.

Backup Counsel: C. Maclain Wells (Reg. No. 48,991). Email: mwells@irell.com. Alan Heinrich (*pro hac vice* TBD). Email: aheinrich@irell.com.

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

Please address all correspondence to the lead and backup counsel above. Petitioner agrees 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 ’435 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 ’435 patent based on the grounds detailed below in Section IX.

A. GROUND 1: CLAIMS 1-20 ARE OBVIOUS IN VIEW OF PATENT OWNER’S PRIOR DISCLOSURES IN THE ’196 PCT AND ’189 PUBLICATION

B. GROUND 2: CLAIMS 1-20 ARE OBVIOUS IN VIEW OF PATENT OWNER’S PRIOR DISCLOSURES IN LIGHT OF LIN AND/OR AHMAD

C. GROUND 3: CLAIMS 1-20 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE ’554 PUBLICATION

IV. PRIORITY DATE

The ’435 patent claims priority to provisional application No. 61/045,228, filed on April 15, 2008. Ex. 1001, cover page. For purposes of this paper only, Petitioner assumes (without conceding) that the ’435 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 nucleic acid payloads, and would have a Ph.D., an M.D. or a similar advanced degree in an allied field (*e.g.*, biophysics, microbiology, biochemistry) or an equivalent combination of education and experience. *See* Ex. 1007, Declaration of Dr. Andrew S. Janoff ("Janoff Decl."), ¶¶31-32. This level of skill is representative of the inventors on the '435 patent and authors/inventors of prior art cited herein. *Id.*

VI. BACKGROUND

A. LIPID CARRIER PARTICLES FOR NUCLEIC ACID PAYLOADS

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.*, ¶60; *see also* Ex. 1008 (Gao), E92; Ex. 1005 (Lin), 3307.

Long before the '435 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.*, ¶60; *see also* Ex. 1008 (Gao), E95. The '435 patent refers to such nucleic acid-lipid carrier particles as "stable nucleic acid-lipid particles" or "SNALPs." Ex. 1001, 5:62-6:2.

B. THE '435 PATENT CLAIMS ARE DIRECTED TO KNOWN LIPID COMPONENTS

The '435 patent discloses three lipid components: a "cationic lipid," a "non-cationic lipid," and a "conjugated lipid." *See, e.g., id.*, claim 1. These lipid components were known to be basic building blocks of nucleic acid-lipid particles long before the ’435 patent. Janoff Decl. ¶61; *see also* Ex. 1006 (Ahmad), 740, 746 (“[cationic lipids] for transfection typically consist of a mixture of cationic and neutral (helper) lipid” and “strategies for optimization … could involve introducing PEG-lipids … to block … unspecific interactions”);[2] Ex. 1008 (Gao), E95 (cationic lipid carrier particles “are often formulated with a noncharged phospholipid or cholesterol as a helper lipid … PEG-lipid conjugates have been incorporated … to minimize interaction with blood components ….”).

Cationic lipids are used because they interact with the negative charge on nucleic acid payload facilitating formation of complexes. Janoff Decl. ¶62; *see also* Ex. 1008 (Gao), E95. Effective delivery of the nucleic acid (called the “transfection efficiency”) is thought to require fusion between the lipid complex and a cell membrane.[3] Janoff Decl. ¶62; *see also* Ex. 1009 (Bennett), 48; Ex. 1008 (Gao), E95. The positive charge on cationic lipids can interact with negative charges on cell membranes. Janoff Decl. ¶62. This is believed to promote, in some cases, the fusion event necessary for the effective delivery of the nucleic acid. *Id.*; *see also* Ex. 1006 (Ahmad), 745 (“[A]n overall positive [cationic lipid]-

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[2] A PEG-lipid is an example of a conjugated lipid.

[3] 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, 13:20-21.

DNA charge is required to promote initial electrostatic interactions with cell membranes.”).

Non-cationic “helper” lipids, *e.g.*, certain phospholipids and/or cholesterols, can be combined with the cationic lipid to influence the ability of the particles to transfect cells. Janoff Decl. ¶63; *see also* Ex. 1008 (Gao), E95 (cationic lipids “are often formulated with a noncharged phospholipid or cholesterol as a helper lipid to form liposomes.”); Ex. 1009 (Bennett), 47 (helper lipids used).

In addition, a conjugated lipid, *e.g.*, a PEG-lipid, can be added to increase *in vivo* circulation time by providing a neutral, hydrophilic coating to the particle’s exterior. Janoff Decl. ¶64; *see also* Ex. 1008 (Gao), E97 (“PEG-lipid conjugates have been incorporated into the lipoplexes to minimize the nonspecific interaction of lipoplexes with blood components.”); Ex. 1010 (Heyes), 277 (“PEG-lipids both stabilize the particle during the formulation process and shield the cationic bi-layer, preventing rapid systemic clearance.”).

C. THE OPTIMAL LIPID COMPONENT PROPORTIONS IN A NUCLEIC ACID-LIPID PARTICLE VARIES

“The structure of lipoplexes is influenced by multiple factors, including the charge ratio, the concentration of individual lipids and DNA, the structure of the cationic lipid and the helper lipid, [and] the physical aggregation state of the lipids ([*e.g.*,] multilamellar or unilamellar liposomes, or micelles) ….” Ex. 1008 (Gao), E95. Transfection efficacy is complex because “[a] large number of parameters

[are] involved." Ex. 1006 (Ahmad), 740. It was well-known that different transfection mechanisms "may be facilitated by alterations in liposome formulation …." Ex. 1009 (Bennet), 48. The claims of the ’435 patent are not limited to a specific combination of lipids and encompass broad ranges of lipids that have dramatically varying structures likely resulting in drastically different activities. Janoff Decl. ¶66. Effective proportions of lipid components for one set of lipid species may not be effective for an alternative lipid species. *Id.*

For example, it was well-established at the time of the ’435 patent that "[t]he chemical structure of the cationic lipid has a major impact on the transfection efficiency." Ex. 1008 (Gao), E95; Janoff Decl. ¶67. Indeed references incorporated into the ’435 patent acknowledge that "alternative cationic lipids" to the one tested would have "different [transfection] efficiencies." *See* Ex. 1011 (U.S. Patent No. 5,753,613 ("’613 patent")), 1:26-28 ("… alternative cationic lipids [] work in essentially the same manner but with different efficiencies."); Ex. 1001, 12:65-13:5 (incorporating ’613 patent). Cationic lipid variables impacting transfection efficiency include "the chemical structure of the cationic lipid [and] … the charge ratio between the cationic lipid and the DNA …." Ex. 1008 (Gao), E95. These variables could impact the proportion of cationic lipid that is most effective for a given lipid component combination. Janoff Decl. ¶68.

For example, hundreds of cationic lipids, both univalent and multivalent, were known at the time of the '435 patent, some with differing charges. Ex. 1008 (Gao), E95 ("[H]undreds of new cationic lipids have been developed … [that] differ by the number of charges in their hydrophilic head group and by the detailed structure of their hydrophobic moiety."). The charge density on the surface of a nucleic acid-lipid particle, at a fixed cationic lipid proportion, can be modulated by introducing cationic lipids with different charges. Janoff Decl. ¶69. This would have been expected to impact the ability of the resulting particle to promote fusion events with target cell membranes. *Id.*; *see also* Ex. 1006 (Ahmad), 740. Indeed, both Ahmad and Lin identified charge density as an important determinate of transfection efficacy in the systems studied. Ex. 1006 (Ahmad), 744, Ex. 1005 (Lin), 3312; Janoff Decl. ¶69.

It was also well-known at the time of the '435 patent that certain lipid component combinations favor having a 50% or greater proportion of cationic lipid. Janoff Decl. ¶70. First, early researchers often chose a 50% proportion of cationic lipid as a default in evaluating particle transfection efficiency. *See, e.g.*, Ex. 1009 (Bennett), 49 (50% cationic lipid); Ex. 1012 (U.S. Patent No. 7,939,505), 44:61-65 (cationic lipid of "about 0.5% to about 70% (mol %) of the total amount of lipid"), 96:40-67 (Example 32 and Table 12) (formulations with 50% cationic lipid), 99:34-101:45 (Examples 34-35 and Tables 15-18) (same). Second, Researchers determined that, in some cases, increasing the cationic lipid proportion above 50% increased transfection efficiency. Ex. 1006 (Ahmad), 744, Ex. 1005 (Lin), 3312.

As with cationic lipids, at the time of the ’435 patent, the number of species of non-cationic lipids that could be employed was large, and differences among such lipids had been reported to impact the structure of the resulting nucleic acid-lipid particles. Janoff Decl. ¶71; Ex. 1008 (Gao), E95 (transfection efficiency varies with “the structure and proportion of the helper lipid in the complexes”). For instance, in the blood, the non-cationic lipid cholesterol seemed to stabilize certain formulations, “while formulations containing DOPE [another non-cationic lipid] tend[ed] to fall apart more easily.” Ex. 1008 (Gao), E96; Janoff Decl. ¶71. In addition, variations in the proportions of non-cationic lipids in certain formulations were reported to impact their ability to deliver nucleic acid payloads. Ex. 1009 (Bennett), 51.

The selection of conjugated lipid was also known to potentially impact the particle’s chemistry and efficacy. Janoff Decl. ¶72; Ex. 1002 (’196 PCT), [0094] (“By controlling the composition and concentration of the bilayer stabilizing component, one can control … the rate at which the liposome becomes fusogenic.”).

A POSITA at the time of the ’435 patent would have known that varying specific lipid species as well as the lipid proportions could change the performance of the nucleic acid-lipid particle. Janoff Decl. ¶73. The range of lipids falling under the scope of the claims of the ’435 patent is immense and a POSITA would have had no way of knowing if lipid combination at any given proportion would have resulted in formulations of superior therapeutic index to other formulations. *Id.*; *see also* Ex. 1006 (Ahmad), 740 (“[I]n comparative studies, typically only one or two data points per lipid are evaluated, allowing the ideal lipid composition (the ratio of neutral to cationic lipid) or cationic lipid/DNA ratio to be overlooked.”).

D. THE INTRINSIC RECORD SHOWS THAT THE ’435 PATENT WAS GRANTED ON ALLEGED UNEXPECTED RESULTS THAT ARE NOT APPLICABLE TO THE CLAIMED RANGES

The ’435 patent is entitled “Lipid Formulations For Nucleic Acid Delivery” and lists Edward Yaworski, Kieu Lam, Lloyd Jeffs, Lorne Palmer, and Ian MacLachlan as inventors. Ex. 1001. The ’435 patent is premised on an alleged “surprising discovery” that prior art lipid components in certain proportions perform better than expected *in vitro* and *in vivo*. *Id.*, 5:55-62 (lipids “comprising from about 50 mol% to about 85 mol% of a cationic lipid, from about 13 mol% to about 49.5 mol% of a non-cationic lipid, and from about 0.5 mol% to about 2 mol% of a lipid conjugate provide advantages ….”). According to the ’435 patent, using the claimed lipid proportions result in “increased activity of the encapsulated nucleic acid … and improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index ….” *Id.*, 5:62-6:2; Janoff Decl. ¶74.

1. THE ’435 PATENT: REPRESENTATIVE CLAIM

The ’435 patent contains one independent claim and nineteen dependent claims. Claim 1 is representative of the claims and reads:

1. A nucleic acid-lipid particle comprising:

    (a) a nucleic acid;

    (b) a cationic lipid comprising from 50 mol% to 85 mol% of the total lipid present in the particle;

    (c) a non-cationic lipid comprising from 13 mol% to 49.5 mol% of the total lipid present in the particle; and

    (d) a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol% to 2 mol% of the total lipid present in the particle.

2. THE ’435 PATENT: PRIOR ART ADMISSIONS

The ’435 patent acknowledges that the following was known to a POSITA before its priority date (*see* Janoff Decl. ¶75):

- 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, 11:34-36 (“SNALP and SPLP typically contain a cationic lipid, a non-cationic lipid, and a lipid conjugate (*e.g.,* a PEG-lipid conjugate).”).
- Preparation of such nucleic acid-lipid particles. *See id.*, 11:54-58

("Nucleic acid-lipid particles and their method of preparation are disclosed in, e.g., U.S. Patent Publication Nos. 20040142025 and 20070042031, the disclosures of which are herein incorporated by reference in their entirety for all purposes.").

- In addition, the prior art cited in the '435 patent discloses nucleic acid-lipid particles with the listed component lipids having overlapping ranges: a cationic lipid range of "about 2% to about 70%," a non-cationic lipid range of "about 5% to about 90%," a cholesterol range of "about 20% to about 55%," and a PEG-lipid conjugate range of "about 0.5% to about 20%." *See, e.g.*, Ex. 1013 (U.S. Publication No. US2007/0042031 ("'031 publication")), [0033].

Thus, nucleic acid-lipid particles with (1) the claimed nucleic acid payload and (2) the same lipid components in overlapping ranges were admittedly known in the art. Janoff Decl. ¶75. The sole basis for alleged novelty of the '435 patent claims is that a nucleic acid-lipid particle comprising component lipids in the claimed proportions achieves unexpected efficacy. *Id*.

3. '435 PATENT: THE PROSECUTION HISTORY CONFIRMS PATENT OWNER'S RELIANCE ON UNEXPECTED RESULTS

During the prosecution of the application leading to the '069 patent (parent of the '435 patent), the examiner cited Patent Owner's earlier, unrelated US2006/0008910 publication ("'910 publication") (Ex. 1014) as prior art disclosing nucleic acid-lipid particles with the claimed components and overlapping ranges. *See, e.g.*, Ex. 1015, 7/30/2010 Rejection at 3–5. The applicant put forth the following chart illustrating the overlap:

Lipid Component	Claim 1 as Amended	US 2006/0008910*
Cationic Lipid	50-65 mol %	"2-60, 5-50, 10-45, 20-40, 30 mol%"
Phospholipid	4-10 mol %	"5-90 mol%"
Cholesterol	30-40 mol %	"20-55 mol %"
Conjugated Lipid	0.5-2 mol %	"1-20 mol %"

Id., 8/11/2011 Amendment at 7–9.

In response, the Patent Owner argued that the claimed ranges in the '069 patent lead to "***new and unexpected results***" and cited to test results regarding the "1:57 SNALP" in the specification. *Id.,* 1/31/2011 Amendment at 11. Patent Owner argued that "[a]pplicants have found that SNALP formulations having <u>increased</u> amounts of cationic lipid, *e.g.,* one or more cationic lipids comprising from about 50 mol% to about 65 mol% of the total lipid present in the particle, provide ***unexpectedly superior advantages*** when used for the *in vitro* or *in vivo* delivery of an active agent …." *Id.* Patent Owner relied on Examples 3-4 from the specification arguing that these examples demonstrated that the 1:57 SNALP formulation was "more efficacious as compared to a nucleic acid-lipid particle previously described ('2:30 SNALP') … [and] more effective at silencing the expression of a target gene as compared to nucleic acid-lipid particles previously described ('2:40 SNALP')." *Id.*

Patent Owner further argued that the "claimed narrower ranges are <u>not</u> disclosed with 'sufficient specificity' [in the '910 publication] to constitute an anticipation …." *Id.,* 8/11/2011 Amendment at 7–9. Thereafter, the examiner allowed the claims.

The claims of the '435 patent are substantially similar to the claims in the '069 patent and were allowed subject only to a non-statutory double patenting rejection vis-à-vis the '069 patent claims. Ex. 1016 ('435 patent file history) (1/27/16 terminal disclaimer). The identified lipid components are the same, but the phospholipid and/or cholesterol are referred to as a single "non-cationic lipid" component. *See* Ex. 1001, claim 1. The ranges for the '435 patent also vary slightly, but similarly overlap. *Id.* Based upon the intrinsic record, it is clear that the examiner allowed the claims of the '435 patent based upon the Patent Owner's prior arguments regarding alleged unexpected results resulting from a cationic lipid percentage above 50%. Janoff Decl. ¶¶76-79.

4. '435 PATENT: THE INTRINSIC RECORD SHOWS THAT THE CERTAIN EXAMPLES OF FORMULATIONS COVERED BY THE CLAIMS PERFORM WORSE THAN THE PRIOR ART

The '435 patent includes *in vitro* (Example 2) and *in vivo* (Examples 3-4) testing of various nucleic acid-lipid formulations for comparison to the admitted prior art (*i.e.,* the 2:30 and 2:40 formulations). Ex. 1001, 69:6-74:4. Patent Owner argued during prosecution of the '069 patent that these test results established unexpected advantages. Certain examples of formulations that fall within the '435 patent claims, however, appear to perform worse than examples of the admitted prior art formulations.

a) EXAMPLE 2 SHOWS THAT CERTAIN *IN VITRO* EXAMPLES OF CLAIMED FORMULATIONS PERFORMED WORSE THAN THE ADMITTED PRIOR ART

Example 2 is the *in vitro* test in the '435 patent. *Id.*, 69:6-70:52. It involved a siRNA payload targeting the Eg5 gene with various lipid components in various proportions. *Id.,* Table 2 (combined and annotated below):

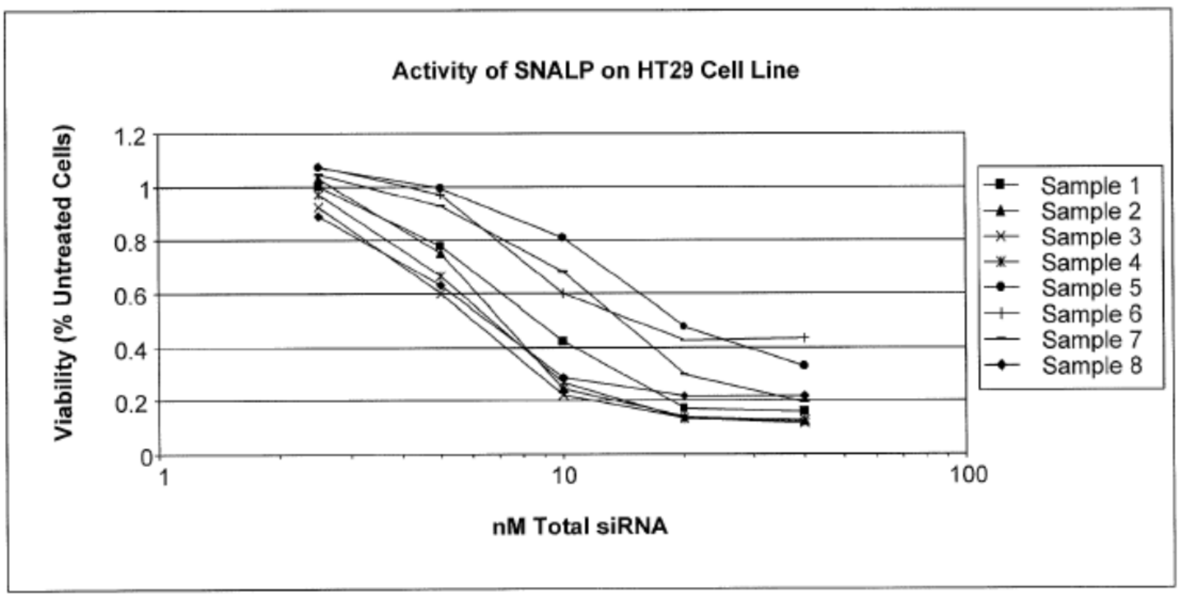
TABLE 2

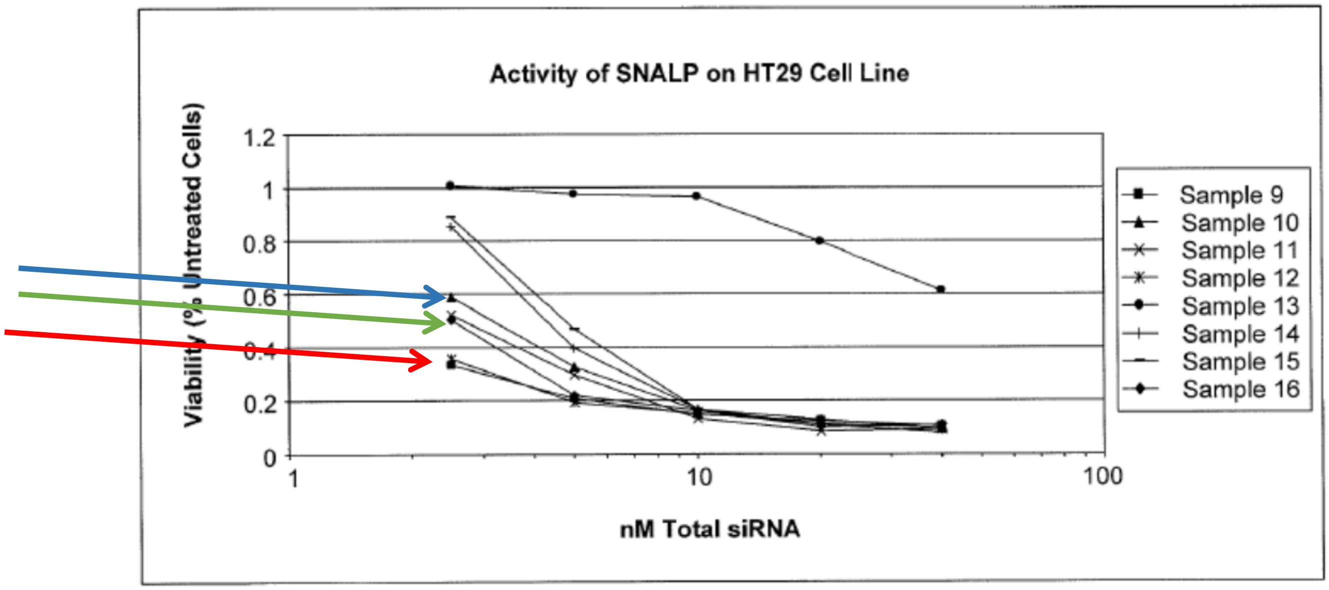
Characteristics of the SNALP formulations used in this study.

Sample No.	Formulation Composition, Mole % PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol	Lipid/Drug Ratio	Finished Product Characterization: Size (nm)	Polydispersity	% Encapsulation
1	2 | 40 | 10 | 48	12.4	57	0.07	90
2	1.8 | 36.4 | 18.2 | 43.6	14.0	72	0.12	89
3	1.4 | 27.0 | 6.8 | 64.9	16.5	70	0.12	92
4	1.3 | 25.3 | 12.7 | 60.8	18.1	76	0.07	93
5	3.9 | 39.2 | 9.8 | 47.1	13.5	53	0.27	86
6	3.6 | 35.7 | 17.9 | 42.9	15.1	58	0.18	87
7	2.7 | 26.7 | 6.7 | 64.0	17.6	56	0.17	92
8	2.5 | 25.0 | 12.5 | 60.0	19.2	61	0.13	92
9	1.4 | 57.1 | 7.1 | 34.3	17.8	84	0.10	88
10	1.3 | 53.3 | 13.3 | 32.0	19.5	83	0.10	89
11	1.1 | 42.6 | 5.3 | 51.1	22.0	80	0.10	93
12	1.0 | 40.4 | 10.1 | 48.5	23.6	78	0.11	88
13	2.8 | 56.3 | 7.0 | 33.8	19.0	62	0.14	80
14	2.6 | 52.6 | 13.2 | 31.6	20.6	66	0.14	82
15	2.1 | 42.1 | 5.3 | 50.5	23.1	71	0.16	91
16	2 | 40 | 10 | 48	24.7	67	0.14	92

Of the tested lipid formulations, only Sample 9 (1:57 SNALP) and Sample 10 fall within the lipid ranges in claim 1 of the '435 patent. *Id.*, claim 1; Janoff Decl. ¶81. Other than these samples, the '435 patent did not test any combinations covered by the claims for comparison to the admitted prior art. *Id.*

Samples 1 and 16 in Table 2 above reflect the 2:40 formualtion that is admitted prior art. Janoff Decl. ¶82. Sample 12 above is similar to the 2:40 SNALP, but with slight variations in the lipid proportions. The results of the testing from Example 2 are shown in Figures 1(a)-(b) (reproduced below):





As can be seen from the figures, (1) Sample 10 (claimed formulation indicated by blue arrow) appears to have performed worse than each of Sample 16 (admitted prior art 2:40 SNALP indicated by green arrow), Sample 12 (a 2:40-type SNALP with 40.4% cationic lipid indicated at red arrow), and Sample 9 (1:57 SNALP also indicated at red arrow); (2) Sample 9 (1:57 SNALP) appears to be no more effective at gene silencing than Sample 12 (a 2:40-type SNALP), which it overlaps at every data point; (3) Sample 9 (1:57 SNALP) appears to outperform Sample 16 (2:40 SNALP) only at extremely low total siRNA amounts. Janoff Decl. ¶82. Therefore, there is no clear advantage of using the claimed formulations, nor is there data that the entire claimed range of particles is superior to particles with less than 50% cationic lipid. *Id.*

b) EXAMPLES 3-4 SHOW THAT EXAMPLES OF PARTICLES WITH LIPID COMPONENTS IN THE CLAIMED RANGES WERE NO MORE EFFECTIVE THAN EXAMPLES OF FORMULATIONS WITH LESS THAN 50% CATIONIC LIPID

Examples 3-4 of the ’435 patent compare various SNALP formulations to formulations with lipid components outside of the claimed ranges *in vivo*. Ex. 1001, 70:54-74:4. Example 3 involved testing the silencing activity of an siRNA payload targeting the Apo B gene with various lipid components in various proportions. *Id.*, 70:54-72:59; Table 4 (below):

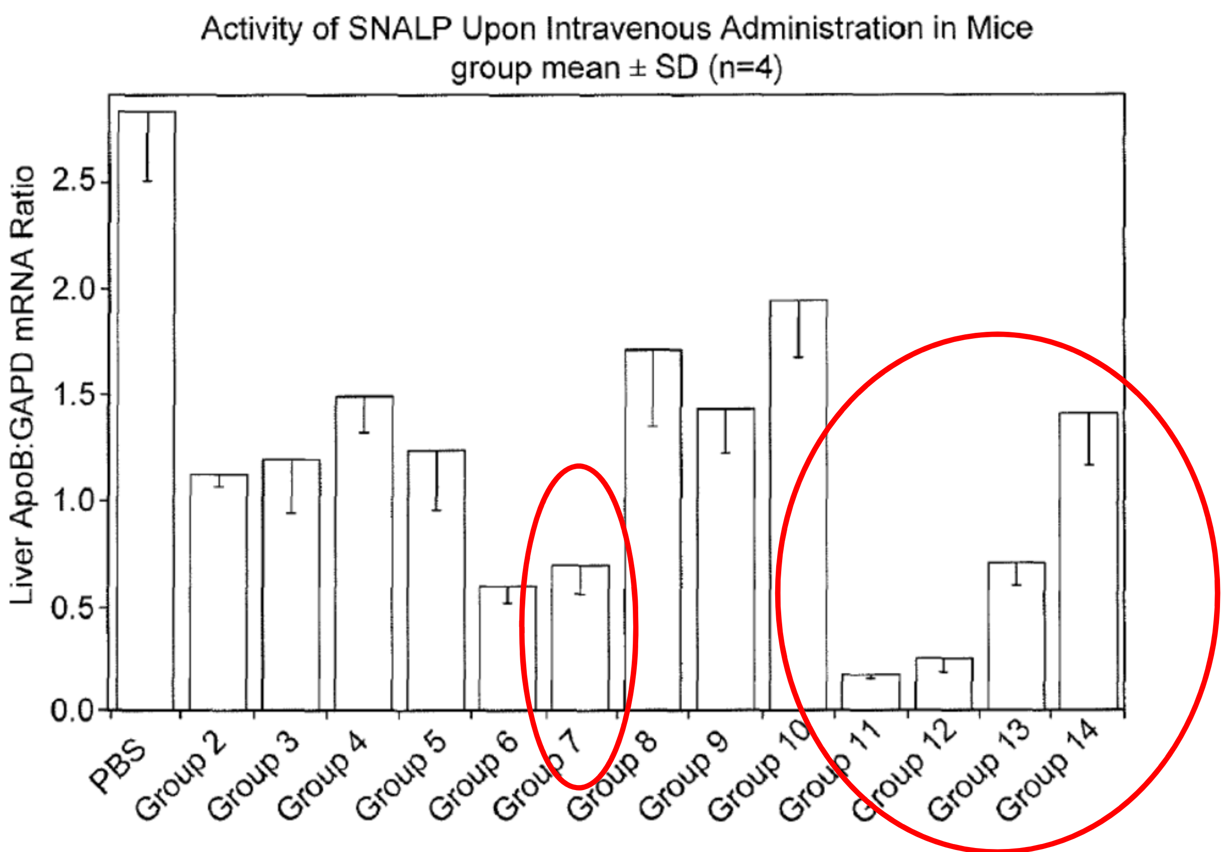
TABLE 4

Characteristics of the SNALP formulations used in this study.

Group	Formulation Composition Lipid Name & Mole %	Lipid/Drug Ratio	Finished Product Characterization Size (nm)	Polydispersity	% Encapsulation
2	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 2 | 40 | 10 | 48	12.4	59	0.15	93
3	PEG(2000)-C-DMA | DLinDMA | Cholesterol 2.2 | 44.4 | 53.3	10.7	55	0.17	91
4	PEG(2000)-C-DMA | DLinDMA | DOPC | Cholesterol 2 | 40 | 10 | 48	12.5	59	0.16	92
5	PEG(2000)-C-DMA | DLinDMA | DMPC | Cholesterol 2 | 40 | 10 | 48	12.2	56	0.11	92
6	PEG(2000)-C-DMA | DLinDMA | DPPE | Cholesterol 1.8 | 36.4 | 18.2 | 43.6	13.8	66	0.16	93
7	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholestanol 2 | 40 | 10 | 48	12.4	56	0.12	92
8	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.4 | 27.0 | 6.8 | 64.9	16.5	60	0.10	93
9	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.3 | 25.3 | 12.7 | 60.8	18.1	74	0.13	92
10	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 2.5 | 25.0 | 12.5 | 60.0	19.2	60	0.13	93
11	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.4 | 57.1 | 7.4 | 34.3	17.8	79	0.09	94
12	PEG(2000)-C-DMA | DLinDMA | DPPC | Cholesterol 1.0 | 40.4 | 10.1 | 48.5	23.6	72	0.11	93
13	PEG(2000)-C-DMA | DLinDMA | DPPC 2 | 70 | 28	8.7	73	0.09	87
14	PEG(2000)-C-DMA | DLinDMA | DPPC 1.6 | 54.7 | 43.8	11.3	65	0.11	87

Again, of the tested lipid combinations, only Sample 11 (1:57 SNALP) and Samples 13-14 (all circled in red) fall within the lipid ranges claimed in the ’435 patent. *Id.*; Janoff Decl. ¶83. Samples 2, 4-5 and 7 reflect the 2:40 SNALP proportions (Samples 4-5 employ different lipid species from Samples 2 and 7).

Id. The results of testing are shown in Figure 2 (annotated below):



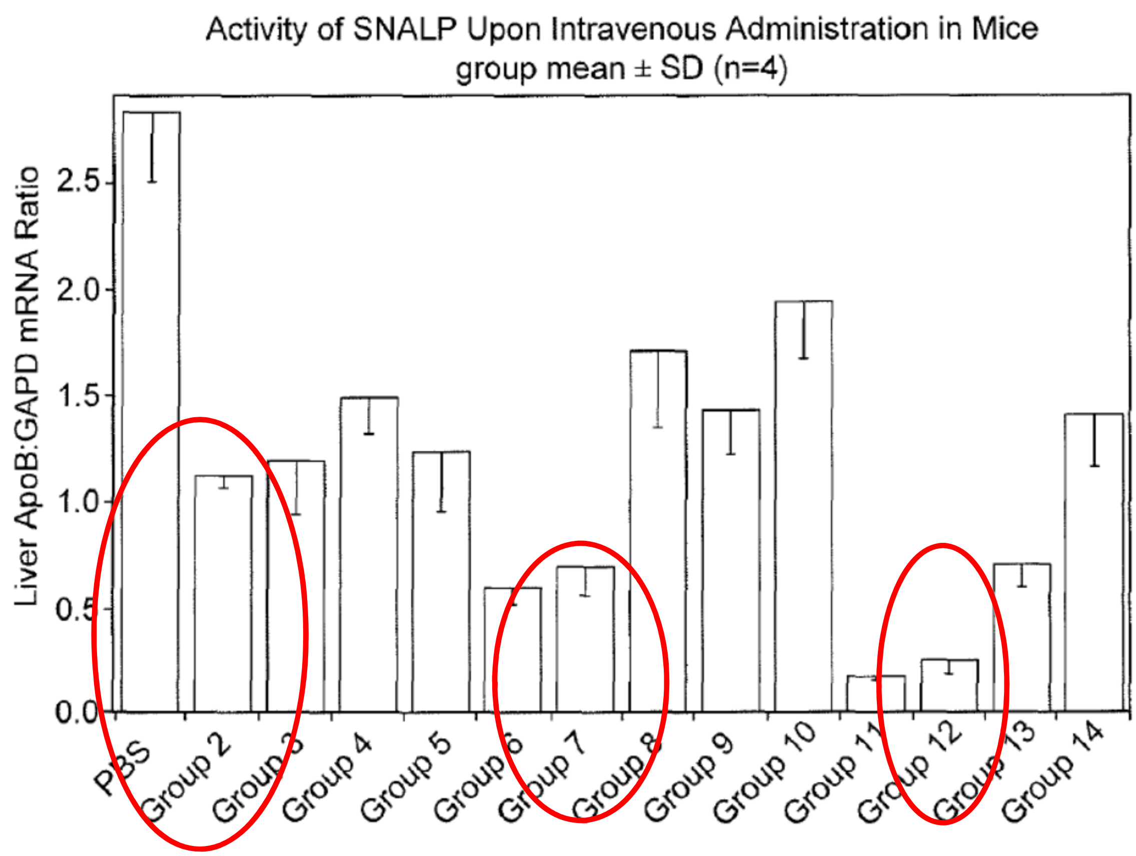
As can be seen from Figure 2, the 1:57 SNALP (Group 11) is likely not statistically significantly more efficacious than Group 12, which is comprised of only 40.4% cationic lipid (*see* Table 4 above). Janoff Decl. ¶84. On the other hand, Group 12 appears to be more efficacious than Groups 2 and 7 (both examples of the admitted prior art 2:40 SNALP formulation) even though it varies only slightly from this formulation, comprising of 1 mol% rather than 2 mol% PEG-2000-C-DMA. *Id.* Group 14 (also in the claimed range) appears to have performed worse than Group 7, and perhaps Group 2 as well. *Id.*

Example 4 compares the silencing activity of the 1:57 SNALP formation with the 2:30 SNALP formulation. Both SNALPs were formulated with a siRNA payload targeting the Apo B gene. Ex. 1001, 72:60-74:4; Table 5. At most, this example established that the 1:57 SNALP comprised of the specific species of lipid components and nucleic acid to lipid ratio disclosed, dosed as disclosed, outperformed the 2:30 SNALP comprised of the lipid species disclosed and dosed as disclosed. Janoff Decl. ¶85.

In conclusion, the identified testing demonstrates that certain examples of formulations that fall within the ’435 patent claims perform worse than examples of the admitted prior art formulations. Janoff Decl. ¶86.

5. THE ’435 PATENT: THE TESTING SHOWS THAT EVEN SLIGHT VARIATIONS OF THE LIPID COMPONENT PROPORTIONS AND/OR THE SPECIES OF LIPID COMPONENTS IMPACT EFFICACY

The *in vivo* testing in Example 3 shows that minor variations in lipid percentages (and potentially differences in lipid to drug ratios) may appreciably impact efficacy. Janoff Decl. ¶84. Specifically, Groups 2, 7 and 12 from Table 4 contain the same lipid components. Ex. 1001, Table 4. Groups 2 and 7 are comprised of exactly the same ratios (*i.e.*, 2/40/10/48). *Id.* Group 12 is comprised of the ratio 1/40.4/10.1/48.5. *Id.* According to Figure 2, Group 12 is comparable to the alleged advantages of using Group 11 (1:57 SNALP), but apparently superior to Groups 2 and 7 (prior art 2:40 SNALP). Janoff Decl. ¶84.



Several other examples illustrate that transfection efficiency may be influenced by varying the species of lipid components. *Id.*, ¶86. For instance, comparing Groups 2 and 6 to Group 4 in Example 5, in which DLinDMA was replaced with DODMA without changing the ratios of the components used (Ex. 1001, Table 6), Group 4 apparently exhibited inferior results. Example 5 also shows by comparing Groups 2 and 6 (PEG(2000)-c-DMA) to Group 5 (PEG(5000)-c-DMA), that variation of the conjugated lipid apparently impacts efficacy. Janoff Decl. ¶86.

VII. CLAIM CONSTRUCTION

Petitioner bases the instant petition upon the broadest reasonable interpretation ("BRI") of the claim language. Petitioner's position regarding the scope of the claims under the BRI standard 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 which apply different claim interpretation standards.

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, 11:14-17. This construction is based upon the disclosures provided in the '435 patent. Janoff Decl. ¶87.

B. CLAIM 1: "CATIONIC LIPID"

Under the BRI standard, the term "cationic lipid" in independent Claim 1 means "any of a number of lipid species that carry a net positive charge at a selected pH, such as physiological pH (e.g., pH of about 7.0)." *See* Ex. 1001, 12:59-61. This construction is based upon the disclosures provided in the '435 patent. Janoff Decl. ¶88.

VIII. PRIOR ART

A. PATENT OWNER'S PRIOR DISCLOSURES ARE PRIOR ART UNDER 35 U.S.C. § 102(b)

The '435 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, these earlier disclosures are prior art to the '435 patent. *Id.*, ¶89; Ex. 1002 ('196 PCT); Ex. 1003 ('189 publication); Ex. 1014 ('910 publication (cited in '069 patent file history)).

One example of such a prior, unrelated disclosure is the '196 PCT. Ex. 1002. Patent Owner filed the provisional applications leading to the '196 PCT in 2003—five years before the priority date of the '435 patent. *Id.* The '196 PCT inventors are Ian MacLachlan, Ellen Ambegia, and James Heyes, a different inventive entity from the '435 patent. *Id.* The '196 PCT was published on Jan. 27, 2005. *Id.* The '196 PCT and the '435 patent do not claim priority to one another. The '196 PCT is therefore prior art to the '435 patent under 35 U.S.C. § 102(b) (pre-AIA). Janoff Decl. ¶90.

The '196 PCT is titled "Lipid Encapsulated Interfering RNA" and discloses "a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." Ex. 1002, [0002]. The disclosed SNALPs comprise "a cationic lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles and a siRNA." *Id.*, [0011]. The non-cationic lipids may include a phospholipid and cholesterol. *Id.*, [0089]; Janoff Decl. ¶91. The '196 PCT thus discloses the same lipid components as claimed in the '435 patent. Janoff Decl. ¶91.

The ’196 PCT also discloses overlapping ranges of these components. According to the ’196 PCT, “[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle … [i]n other preferred embodiments, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle.” Ex. 1002, [0088]. “The non-cationic lipid typically comprises from about 5% to about 90% of the total lipid present … [and] [t]he nucleic acid-lipid particles … may further comprise cholesterol … from about 20% to about 45% of the total lipid present ….” *Id.*, [0091]. “[T]he SNALP further comprises a bilayer stabilizing component (BSC). …. [T]he BSC is a conjugated lipid that inhibits aggregation of the SNALPs … present from about 0.5% to about 25% of the total lipid ….” *Id.*, [0092-0093]. Janoff Decl. ¶92-93.

The ’196 PCT specifically discloses that “[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied ….” Ex. 1002, [0088]; Janoff Decl. ¶94. In addition, the ’196 PCT incorporates by reference U.S. Patent No. 5,264,618 (the “’618 patent”). Ex. 1002, [0087], [0146]. The ’618 patent in turn discloses a nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol, as well as various other formulations with over 50% cationic lipid. Ex. 1017, 34:54-35:23.

Another example of Patent Owner’s prior, unrelated disclosures is the ’189 publication. Ex. 1003. Patent Owner filed the provisional applications leading to the ’189 publication in 2004-2005—three years before the priority date of the ’435 patent. *Id*. The ’189 publication inventors are Ian MacLachlan, Lloyd Jeffs, Adam Judge, Amy Lee, Lorne Palmer, and Vandana Sood, a different inventive entity from the ’435 patent. *Id.* The ’189 publication was published on June 22, 2006. *Id.* The ’189 publication and the ’435 patent do not claim priority to one another. The ’189 publication is therefore also prior art to the ’435 patent under 35 U.S.C. § 102(b) (pre-AIA). Janoff Decl. ¶95.

The ’189 publication discloses SNALPs comprising overlapping ranges of lipid components similar to those discussed above for the ’196 PCT. Ex. 1003, [0009-0012], [0014], [0148-0181]. In addition, the ’189 publication discloses testing relating to the 2:40 formulation that the Patent Owner identified as a prior art formulation. *Id.*, [0350-0391]; Janoff Decl. ¶96.

B. THE ’554 PUBLICATION IS PRIOR ART UNDER 35 U.S.C. § 102(b)

The ’554 publication was published as US 2006/0240554 A1 on October 26, 2006. Ex. 1004. The ’554 publication is therefore prior art to the ’435 patent under 35 U.S.C. § 102(b) (pre-AIA). Janoff Decl. ¶97.

The ’554 publication is titled “Lipid Nanoparticle Based Compositions and Methods for the Delivery of Biologically Active Molecules.” Ex. 1004. The ’554 publication 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-diacylglycerol (PEG-DAG) conjugate …; and (d) a short interfering nucleic acid (siNA) molecule …." *Id.*, [0103]. These are the same components and payload described in the '435 patent. Janoff Decl. ¶98.

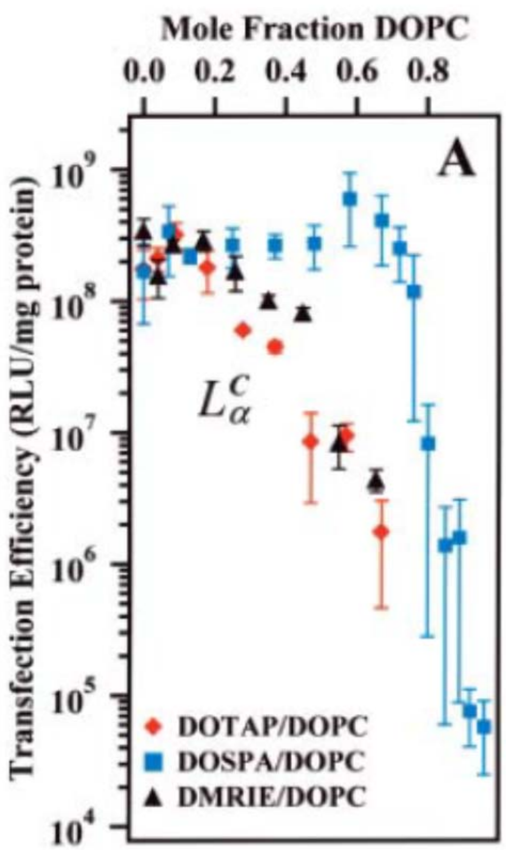
The '554 publication discloses various ranges for the lipid components that overlap or encompass the ranges disclosed in the '435 patent, including the cationic lipid (*e.g.,* about 2% to about 60%), the neutral, non-cationic lipid (about 5% to about 90%), and the PEG conjugate (about 1% to about 20%). The '554 publication also includes various specific formulations, including formulation L054, which contains 50% cationic lipid (DMOBA), 48% non-catioinc lipid (Chol/DSPC), and 2% conjugate lipid (PEG-n-DMG). Ex. 1004, Table 4. This formulation was tested, for example, with siRNA for reducing HBsAg levels. *See id.*, Fig. 16. The disclosed nucleic acid-lipid particles meet all of the limitations in Claim 1 of the '435 patent.

C. LIN IS PRIOR ART UNDER 35 U.S.C. § 102(b)

Lin et al. ("Lin") is a publication titled "Three-Dimensional Imaging of Lipid Gene-Carriers: Membrane Charge Density Controls Universal Transfection Behavior in Lamellar Cationic Liposome-DNA Complexes." Ex. 1005. It was published in *Biophysical Journal* in May 2003, in Volume 84, at pages 3307–16.

See id. Lin is therefore prior art to the '435 patent under 35 U.S.C. § 102(b). Janoff Decl. ¶100.

Lin studied the impact of cationic lipid mole fraction on the transfection efficiency of lipid particles with a DNA payload in *ex vivo* experiments. Ex. 1005, 3307. Using the cationic lipids DOTAP, DMRIE and DOSPA and the helper lipid DOPC, Lin determined that transfection efficiency increased as the cationic lipid mole fraction increased. *Id.*, 3309. In Figure 4(a), Lin shows the transfection efficiency as a function of the mole fraction of neutral lipid (DOPC). The mol% of cationic lipid (*e.g.*, DOTAP, DOSPA, DMRIE) is derived by deducting the mole fraction of neutral lipid from 1 and multiplying by 100. As can be seen from the figure, for each formulation the transfection efficiency increased with the mol% of cationic lipid incorporated. Janoff Decl. ¶101. Starting at about 35 mol%, transfection efficiency increased monotonically with increasing mol% for DOTAP formulations. For DMRIE formulations, over the same range, there was a



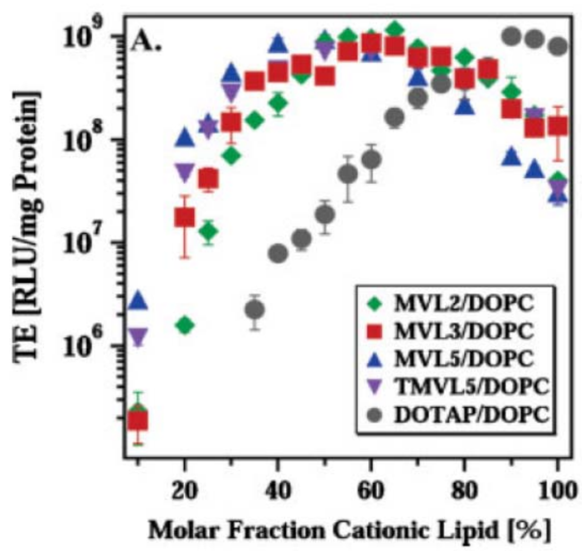
steep increase in transfection efficiency from about 45-55 mol%. For formulations comprised of the multivalent lipid DOSPA, transfection efficiency seemed to be biphasic—it increased monotonically up to about 35 mol% and then seemed to saturate. *Id.*, ¶102.

A POSITA would understand the testing of Lin to suggest that the mol% of cationic lipid in nucleic acid-lipid particles can impact transfection efficiency, and that for certain cationic lipids transfection efficiency might continue to improve at a mol% above 50 percent. *Id.* A POSITA would further understand that precisely how the mol% of cationic lipid might impact transfection efficiency depends on both the cationic lipid species and neutral lipid species chosen. *Id.*

D. AHMAD IS PRIOR ART UNDER 35 U.S.C. § 102(b)

Ahmad et al. ("Ahmad") is a publication titled "New multivalent cationic lipids reveal bell curve for transfection efficiency versus membrane charge density: lipid–DNA complexes for gene delivery." Ex. 1006. It was published in *The Journal of Gene Medicine* on January 31, 2005, in Volume 7, at pages 739–48. *See id.* Ahmad is therefore prior art to the '435 patent under 35 U.S.C. § 102(b). Janoff Decl. ¶103.

Ahmad studied the impact of membrane charge density on the transfection efficiency of cationic liposome-DNA complexes comprised of cationic and neutral helper lipids. Ex. 1006, 739. Ahmad contemplated adding cholesterol and PEG-lipids to these lipid complexes. *Id.*, 744 ("[C]holesterol, which leads to lamellar complexes, is increasingly used as a neutral lipid for *in vivo* applications."), 746 ("strategies for optimization … could involve introducing … PEG–lipids … to block the unspecific electrostatic interactions …."). Thus all three lipid components from the '435 patent were disclosed. Janoff Decl. ¶104.



Ahmad found that a variety of cationic lipids increased the transfection efficiency in the DOPC formulations he studied as shown on Figure 3(a). In Ahmad, cationic lipids with multiple charges were observed to provide higher transfection efficiencies. Ex. 1005, 740 ("Numerous lipids with varied chemical and physical properties have been synthesized to improve the transfection efficiencies …. These include multivalent lipids, which have been described as superior to their monovalent counterparts."). More specifically, Ahmad determined that for the multivalent cationic lipids he studied, a maximum transfection efficiency occurred at around 50 mol%. Yet for the monovalent lipid DOTAP, transfection efficiency increased monotonically from a cationic lipid percentage of about 35 mol% to a cationic percentage of about 90 mol%. *Id.*, 744. Ahmad reported that the optimal transfection efficiency for MLV 5 (a multivalent cationic lipid) was at 55 mol% when incorporated into DOPC formulations, whereas the maximal TE for DOTAP, incorporated into DOPC formulations was at 90 mol%. *Id.*, 743; Janoff Decl. ¶105.

A POSITA would understand the testing of Ahmad to suggest that the mol% of cationic lipid in nucleic acid-lipid particles can impact transfection efficiency, and that for certain cationic lipids transfection efficiency might continue to improve at a mol% above 50 percent. Janoff Decl. ¶105.

IX. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE ’435 PATENT IS UNPATENTABLE

A. GROUND 1: CLAIMS 1-20 ARE OBVIOUS IN VIEW OF PATENT OWNER’S PRIOR DISCLOSURES IN THE ’196 PCT AND ’189 PUBLICATION

Claims 1-20 of the ’435 patent are obvious under 35 U.S.C. § 103 in view of the ’196 PCT. While the ’196 PCT does not disclose the exact same range of lipid components from claim 1 of the ’435 patent explicitly, it discloses encompassing and overlapping ranges that establish a *prima facie* case of obviousness and the testing in the ‘435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶106.

The ’189 publication is substantively similar to the ’196 PCT and also discloses SNALPs comprising overlapping ranges of the lipid components similar to those discussed below for the ’196 PCT. Ex. 1003, [0009-0012], [0014], [0148-

0181]; Janoff Decl. ¶107. In addition, the ’189 publication discloses testing relating to the admitted prior art 2:40 formulation. Ex. 1003 [0350]-[0391]; Janoff Decl. ¶107.

1. THE COMPONENTS IN CLAIM 1 ARE DISCLOSED IN THE ’196 PCT

a) CLAIM ELEMENT 1(A): A NUCLEIC ACID-LIPID PARTICLE COMPRISING:

The ’196 PCT teaches “compositions and methods for silencing gene expression by delivering nucleic acid-lipid particles comprising a siRNA molecule to a cell.” Ex. 1002, (Abstract); Janoff Decl. ¶108.

b) CLAIM ELEMENT 1(B): A NUCLEIC ACID

The ’196 PCT patent teaches “the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery.” Ex. 1002, [0002]. siRNA is a nucleic acid. Janoff Decl. ¶109.

c) CLAIM ELEMENT 1(C): A CATIONIC LIPID COMPRISING FROM 50 MOL% TO 85 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The ’196 PCT teaches “[t]he cationic lipid typically comprises from about 2% to about 60% of the total lipid present in said particle … [i]n other preferred embodiments, the cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle.” Ex. 1002, [0088]. The ’196 PCT discloses that “[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied ….” *Id.* In addition, the ’196 PCT incorporates by reference the ’618 patent, which discloses nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol, as well as various other formulations containing over 50% cationic lipid. Ex. 1017, 34:54-35:23. “[E]ven a slight overlap in range establishes a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious. Janoff Decl. ¶110. In addition, determining the optimal proportion of cationic lipid for a given lipid combination would be a simple matter of varying the proportion using prior art methodologies. *Id.*

The testing in the ’435 patent is insufficient to rebut this *prima facie* showing. “[U]nexpected results” must exist with regard to the prior art for the entire claimed range. *In re Clemens*, 622 F.2d at 1035. Here, the claim limitation includes <u>two</u> ranges: (1) a numeric range for the cationic lipid proportion, and (2) a range of cationic lipids as that claim term is defined in the ’435 patent. It is well-known that “[t]he structure of lipoplexes is influenced by multiple factors, including the charge ratio, the concentration of individual lipids and DNA, the structure of the cationic lipid and the helper lipid, [and] the physical aggregation state of the lipids ….” Ex. 1008 (Gao), E95; *see also* Ex. 1006 (Ahmad), 740 (for “CL-DNA complexes … [a] large number of parameters involved”); Ex. 1009 (Bennett), 48 (“transfection pathway may be facilitated by alterations in liposome formulation"). The testing in question, however, dealt with only a few lipid species and proportions, not co-extensive with the claim scope.

As a preliminary matter, the Patent Owner only asserted unexpected results occurred vis-à-vis the 2:30 and 2:40 formulations. The prior art, however, is not so limited. Janoff Decl. ¶111. For example, the Patent Owner ignores Group 12 in Figure 2 of the '435 patent that has a cationic lipid percentage of 40.4% and is clearly in the prior art given the admitted 2:40 formulation. In addition, as discussed above in Sections VI-VII, numerous other prior art formulations contain cationic lipid percentages over 50%. *See, e.g.*, Exs. 1005-1006, 1009, 1012, 1014. Patent Owner thus failed to address the entire scope of the prior art in asserting unexpected results. Janoff Decl. ¶111.

Regarding the numeric range, during prosecution of the parent '069 patent, the patentee argued that testing in Examples 2-4 rebutted the *prima facie* case *vis a vis* the overlapping ranges in the '910 publication. Ex. 1015, 1/31/2011 Amendment at 8–10. The same assertions do not hold true for the broader ranges in the '435 patent. *In vitro* testing (Example 2) showed that Sample 10 (claimed formulation) apparently performed worse than Sample 16 (admitted prior art). Ex. 1001, Figure 1; Janoff Decl. ¶¶81-82. In *vivo testing* (Example 3), Group 14 (claimed formulation) apparently performed worse than Group 7 (admitted 2:40 prior art). Ex. 1001, Figure 2; Janoff Decl. ¶¶83-84. In short, there are no unexpected results across the claimed numeric range of cationic lipid for the ’435 patent.

Given the disclosures in the ’435 patent, a POSITA would not expect all alternative data points falling within the recited numeric range to perform similarly. *See In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (“If an applicant demonstrates that an embodiment has an unexpected result and provides an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with [the] scope of the claims.”). As discussed above, the *in vivo* testing in Example 3 shows that even minor variations in lipid percentages (and potentially changes to Lipid to drug ratios) appeared to impact efficacy. Janoff Decl. ¶106. Specifically, Sample 2 and Sample 12 from Table 4 contain the exact same lipid species in the respective ratios 2/40/10/48 and 1/40.4/10.1/48.5. Ex. 1001, Table 4. According to Figure 2, these slight variations in lipid proportions (and potentially changes to Lipid to drug ratios) lead to apparently different transfection efficiencies. *Id.*, Fig. 2; Janoff Decl. ¶112. A POSITA would expect that similar minor variations in lipid proportions within the claimed range might lead to similar variations in transfection efficiency. *Id.*; Ex. 1006 (Ahmad), 740 (“[I]n comparative studies, typically only one or two data points per lipid are evaluated, allowing the ideal lipid composition (the ratio of neutral to cationic lipid) or cationic lipid/DNA ratio to be overlooked.”).

Regarding the range of species of cationic lipids, the ’435 patent defines “cationic lipid” as “any of a number of lipid species that carry a net positive charge at a selected pH, such as physiological pH (e.g., pH of about 7.0).” Ex. 1001, 12:59-61. The ’435 patent includes almost three dozen examples of cationic lipids. *Id.*, 47:44-50:3. At the time of the ’435 patent, hundreds of additional lipids that are cationic at physiological pH were known in the art. Janoff Decl. ¶113; Ex. 1008 (Gao), E95 (“[H]undreds of new cationic lipids have been developed ….”). In addition, because claim 1 of the ’435 patent does not contain any limitation to a specific pH, the additional lipids that are cationic at a certain pH would also meet the definition of the term.

The testing in the ’435 patent compares only one cationic lipid, DLinDMA, to the admitted prior art formulations to illustrate alleged unexpected results. Ex. 1001, Tables 2, 4, 5; Ex. 1015, 1/31/2011 Amendment at 8–10; Janoff Decl. ¶114. There is no support for “the conclusion that other embodiments falling within the claim will behave in the same manner” as DLinDMA. *See In re Kao*, 639 F.3d at 1068. To the contrary, Example 5 in the ’435 patent shows variation of the cationic lipid impacts efficacy. Ex. 1001, Table 6 (Samples 2 & 6 (DLin-DMA) vs. Sample 4 (DODMA)). A POSITA would understand these results to suggest that a preferred proportion for one cationic lipid (*e.g.*, DLinDMA) does not necessarily apply to all other cationic lipids (*e.g.*, DODMA). Janoff Decl. ¶114.

In addition, it was well-known in the art that "[t]he chemical structure of the cationic lipid [had] a major impact on the transfection efficiency." Ex. 1008 (Gao), E95; Janoff Decl. ¶115. Indeed the '613 patent incorporated by reference in the '435 patent acknowledges that "alternative cationic lipids" to the one tested would have "different [transfection] efficiencies." *See* Ex. 1011, 1:26-28 ("[A]lternative cationic lipids that work in essentially the same manner but with different efficiencies."); Janoff Decl. ¶115. A POSITA would have no reason to believe that the alleged unexpected advantages of a 50-85% proportion of DLinDMA would be applicable to all cationic lipids. Janoff Decl. ¶115.

d) CLAIM ELEMENT 1(D): A NON-CATIONIC LIPID COMPRISING FROM 13 MOL% TO 49.5 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The '196 PCT teaches that "[t]he non-cationic lipid typically comprises … preferably from about 20% to about 85% of the total lipid present in said particle." Ex. 1002, [0091]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.*, [0088]. In addition, the '196 PCT incorporates by reference the '618 patent, which discloses a nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol. Ex. 1017, 34:54-35:23. Given the breadth of the claimed range, these disclosures are sufficiently specific to disclose the claimed range. Janoff Decl. ¶116.

Moreover, "even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of an encompassing range, this limitation is *prima facie* obvious and, as discussed above, and the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶116.

e) CLAIM ELEMENT 1(E): A CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISING FROM 0.5 MOL% TO 2 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE.

The '196 PCT teaches that "[t]he SNALP further comprises a bilayer stabilizing component (BSC). …. [T]he BSC is a conjugated lipid that inhibits aggregation of the SNALPs … present from about 0.5% to about 25% of the total lipid …." Ex. 1002, [0092-0093]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.,* [0088]. "By controlling the composition and concentration of the bilayer stabilizing component, one can control … the rate at which the liposome becomes fusogenic" impacting the transfection efficiency. *Id.,* [0094]. Given the breadth of the claimed range for the conjugated lipid, these disclosures are sufficiently specific to disclose the claimed range. Janoff Decl. ¶117.

This limitation would have been obvious in view of the '196 PCT in light of the knowledge of a POSITA. A POSITA would have been aware that conjugated lipids stabilize carrier particles by inhibiting fusogenicity. *Id.*, ¶118. It would have been obvious for a POSITA to try to increase fusogenicity, and hence potentially transfection efficiency, by choosing a proportion of conjugated lipid in the 0.5%-2% range. *Id.*

Moreover, "even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶118.

2. CLAIM 2: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID COMPRISES AN INTERFERING RNA, MRNA, AN ANTI-SENSE OLIGONUCLEOTIDE, A RIBOZYME, A PLASMID, AN IMMUNOSTIMULATORY OLIGONUCLEOTIDE, OR MIXTURES THEREOF

The '196 PCT patent teaches "the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery." Ex. 1002, [0002]. siRNA is an interfering RNA, one of the alternatives put forth in the claim. Janoff Decl. ¶119.

3. CLAIM 3: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN THE INTERFERING RNA COMPRISES A SMALL INTERFERING RNA (SIRNA), AN ASYMMETRICAL INTERFERING RNA (AIRNA), A MICRORNA (MIRNA), OR MIXTURES THEREOF

The ’196 PCT patent teaches “the present invention is directed to using a small interfering RNA (siRNA) encapsulated in a serum-stable lipid particle having a small diameter suitable for systemic delivery.” Ex. 1002, [0002]; Janoff Decl. ¶120.

4. CLAIM 4: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CATIONIC LIPID COMPRISES FROM 50 MOL% TO 65 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(c). Given the breadth of the claimed range, the disclosures above are sufficiently specific to disclose the claimed range. Janoff Decl. ¶121. For example, not only does the disclosed broader range substantially overlap with the claimed range, a preferred embodiment in the reference recites a narrower range that also partially overlaps. *Id.*

Moreover, “even a slight overlap in range establishes a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious. Janoff Decl. ¶121.

5. CLAIM 5: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NON-CATIONIC LIPID COMPRISES A MIXTURE OF A PHOSPHOLIPID AND CHOLESTEROL OR A DERIVATIVE THEREOF

The ’196 PCT teaches that the non-cationic lipids may include a phospholipid and cholesterol. Ex. 1002, [0089]. "The non-cationic lipid typically comprises … preferably from about 20% to about 85% of the total lipid present in said particle …. If present … preferably the cholesterol comprises from about 20% to about 45% of the total lipid." *Id.*, [0091]; Janoff Decl. ¶122.

6. CLAIM 6: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 5, WHEREIN THE PHOSPHOLIPID COMPRISES DIPALMITOYLPHOSPHATIDYLCHOLINE (DPPC), DISTEAROYLPHOSPHATIDYLCHOLINE (DSPC), OR A MIXTURE THEREOF

The '196 PCT patent teaches that "[e]xamples of noncationic lipids useful in the present invention include: phospholipid-related materials, such as … DSPC … DPPC …." Ex. 1002, [0089]. The '196 PCT patent also teaches using more than one phospholipid (*i.e.,* a mixture). *Id.,* [0128]; Janoff Decl. ¶123.

7. CLAIM 7: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 5, WHEREIN THE PHOSPHOLIPID COMPRISES FROM 3 MOL% TO 15 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The '196 PCT teaches that "[t]he non-cationic lipid typically comprises … preferably from about 20% to about 85% of the total lipid present in said particle." Ex. 1002, [0091]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.*, [0088]. In addition, the '196 PCT incorporates by reference the '618 patent, which discloses nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol. Ex. 1017, 34:54-35:23.

Not only does the disclosed range encompass the claimed range, when combined with a cationic lipid proportion of 60%, the available range for cholesterol is 20-40% and the range for the other non-cationic lipid (*e.g.,* a phospholipid) is decreased to 0%-20%. Janoff Decl. ¶124. Given the breadth of the claimed range for the phospholipid, these disclosures are sufficiently specific to disclose the claimed range. *Id*.

Moreover, "even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶124.

8. CLAIM 8: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 5, WHEREIN THE CHOLESTEROL OR DERIVATIVE THEREOF COMPRISES FROM 30 MOL% TO 40 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The '196 PCT teaches that "If present … preferably the cholesterol comprises from about 20% to about 45% of the total lipid …." Ex. 1002, [0091]. The '196 PCT discloses that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *Id.*, [0088]. In addition, the '196 PCT incorporates by reference the '618 patent, which discloses nucleic acid-lipoplex with 56% cationic lipid, 14% phospholipid and 30% cholesterol. Ex. 1017, 34:54-35:23. Given the breadth of the claimed range for cholesterol, these disclosures are sufficiently specific to disclose the claimed range.

Janoff Decl. ¶125.

Moreover, "even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, and the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶125.

9. CLAIM 9: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISES A POLYETHYLENEGLYCOL (PEG)-LIPID CONJUGATE

The '196 PCT patent teaches that "[b]ilayer stabilizing components include, but are not limited to, conjugated lipids that inhibit aggregation of the SNALPs, polyamide oligomers (*e.g.*, ATTA-lipid derivatives), peptides, proteins, detergents, lipid-derivatives, PEG-lipid derivatives …." Ex. 1002, [0052], *see also* [0013]; Janoff Decl. ¶126.

10. CLAIM 10: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 9, WHEREIN THE PEG-LIPID CONJUGATE COMPRISES A PEG-DIACYLGLYCEROL (PEG-DAG) CONJUGATE, A PEG-DIALKYLOXYPROPYL (PEG-DAA) CONJUGATE, OR A MIXTURE THEREOF

The '196 PCT patent teaches that "[t]he PEG-lipid conjugate may be one or more of a PEG-dialkyloxypropyl (DAA), a PEG-diacylglycerol (DAG), … and combinations thereof." Ex. 1002, [0013]; Janoff Decl. ¶127.

11. CLAIM 11: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 10, WHEREIN THE PEG-DAA CONJUGATE COMPRISES A PEG-DIMYRISTYLOXYPROPYL (PEG-DMA) CONJUGATE, A PEG-DISTEARYLOXYPROPYL (PEG-DSA) CONJUGATE, OR A MIXTURE THEREOF

The '196 PCT patent teaches "three exemplary PEG-dialkyloxypropyl derivatives suitable for use in the present invention, *i.e.*, … PEG-C-DMA … PEG-A-DMA … and … PEG-S-DMA." Ex. 1002, [0031]. The '196 PCT patent teaches "[o]ther PEG DAAs suitable for use in the present invention can be synthesized using similar protocols. For instance, PEG-A-DSA and PEG-C-DSA can be synthesized …." *Id.*, [0242]; Janoff Decl. ¶128.

12. CLAIM 12: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISES FROM 1 MOL% TO 2 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(e). For the reasons stated above, the '196 PCT discloses this range with sufficient specificity to disclose this limitation. Janoff Decl. ¶129. In the alternative, this range is *prima facie* obvious given the overlapping range in the '196 PCT. *Id.*

13. CLAIM 13: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS FULLY ENCAPSULATED IN THE NUCLEIC ACID-LIPID PARTICLE

The '196 PCT patent teaches "[i]n some embodiments, the siRNA molecule is fully encapsulated within the lipid bilayer of the nucleic acid-lipid particle such that the nucleic acid in the nucleic acid-lipid particle is resistant in aqueous solution to degradation by a nuclease." Ex. 1002, [0011]; Janoff Decl. ¶130.

14. CLAIM 14: A PHARMACEUTICAL COMPOSITION COMPRISING A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1 AND A PHARMACEUTICALLY ACCEPTABLE CARRIER

The '196 PCT patent teaches "[t]he invention also provides for pharmaceutically acceptable compositions comprising a nucleic acid-lipid particle." Ex. 1002, [0019]; Janoff Decl. ¶131.

15. CLAIM 15: A METHOD FOR INTRODUCING A NUCLEIC ACID INTO A CELL, THE METHOD COMPRISING: CONTACTING THE CELL WITH A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1

See Claim 1. The '196 PCT patent teaches "the present invention provides for a method of introducing a siRNA molecule into a cell by contacting a cell with a nucleic acid-lipid particle …." Ex. 1002, [0017]; Janoff Decl. ¶132.

16. CLAIM 16: A METHOD FOR THE IN VIVO DELIVERY OF A NUCLEIC ACID, THE METHOD COMPRISING: ADMINISTERING TO A MAMMALIAN SUBJECT A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1

See Claim 1. The '196 PCT patent teaches "the present invention provides a method of treating a disease or disorder in a mammalian subject. A therapeutically effective amount of a nucleic acid-lipid particle comprising a cationic lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles, and siRNA is administered to the mammalian subject …." Ex. 1002, [0021]; Janoff Decl. ¶133.

17. CLAIM 17: A METHOD FOR TREATING A DISEASE OR DISORDER IN A MAMMALIAN SUBJECT IN NEED THEREOF, THE METHOD COMPRISING: ADMINISTERING TO THE MAMMALIAN SUBJECT A THERAPEUTICALLY EFFECTIVE AMOUNT OF A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1

See Claim 1. The '196 PCT patent teaches "the present invention provides a method of treating a disease or disorder in a mammalian subject. A therapeutically effective amount of a nucleic acid-lipid particle comprising a cationic lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles, and siRNA is administered to the mammalian subject …." Ex. 1002, [0021]; Janoff Decl. ¶134.

18. CLAIM 18: THE METHOD OF CLAIM 17, WHEREIN THE DISEASE OR DISORDER IS A VIRAL INFECTION

The '196 PCT patent teaches "[i]n some embodiments, the disease is a viral disease such as, for example, hepatitis (*e.g.*, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Hepatitis G, or a combination thereof)." Ex. 1002, [0021]; Janoff Decl. ¶135.

19. CLAIM 19: THE METHOD OF CLAIM 17, WHEREIN THE DISEASE OR DISORDER IS A LIVER DISEASE OR DISORDER

The '196 PCT patent teaches "[i]n some embodiment, the disease or disorder is a liver disease or disorder, such as, for example, dyslipidemia." Ex. 1002, [0021]; Janoff Decl. ¶136.

20. CLAIM 20: THE METHOD OF CLAIM 17, WHEREIN THE DISEASE OR DISORDER IS CANCER

The ’196 PCT patent teaches “the present invention provides a method of treating a disease or disorder in a mammalian subject. A therapeutically effective amount of a nucleic acid-lipid particle comprising a cationic lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles, and siRNA is administered to the mammalian subject (*e.g.*, a rodent such as a mouse, a primate such as a human or a monkey) with the disease or disorder. In some embodiments, the disease or disorder is associated with expression and/or overexpression of a gene and expression or overexpression of the gene is silenced by the siRNA.” Ex. 1002, [0021]. A POSITA would be aware that genetic changes that lead to cancer development are associated with aberrant gene expression including overexpression of genes. Janoff Decl. ¶137. Thus, the disclosure in the ’196 PCT of the use of siRNA to address gene overexpression discloses or renders obvious the use of siRNA in the context of cancer treatment. *Id.*

B. GROUND 2: CLAIMS 1-20 ARE OBVIOUS IN VIEW OF THE PATENT OWNER’S PRIOR DISCLOSURES IN LIGHT OF LIN AND/OR AHMAD

Claims 1-20 of the ’435 patent are obvious under 35 U.S.C. § 103 in view of the Patent Owner’s prior disclosures in the ’196 PCT and ’189 publication, in light of Lin and/or Ahmad. Claims 2-3 and 5-20 are disclosed by the Patent Owner’s prior disclosures as discussed in Ground 1 above. To the extent that those disclosures alone are determined not to disclose a proportion of cationic lipid in the

50%-85% range (claim 1) and/or the 50%-65% range (claim 4), a POSITA would have understood from Lin and/or Ahmad that such proportions of cationic lipid may increase transfection efficacy and would have been motivated to combine those disclosures with the system disclosed in the ’196 PCT and ’189 publication. Janoff Decl. ¶138.

1. CLAIM ELEMENT 1(C): A CATIONIC LIPID COMPRISING FROM 50 MOL% TO 85 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

To the extent that the Patent Owner’s prior disclosures are determined not to disclose the claimed range for cationic lipids, this limitation would have been obvious in light of Lin and/or Ahmad. As discussed in Section VIII above, a POSITA would understand the testing of Lin to suggest that the cationic lipid mol% of nucleic acid-lipid particles can impact transfection efficiency and that for certain lipid components a mol% greater than 50% may increase the transfection efficiency of the carrier particles. Janoff Decl. ¶139; Ex. 1005 (Lin), Fig. 3(a). A POSITA would understand the testing of Ahmad to support the proposition that for certain formulations, cationic lipids can increase transfection efficiency when they are incorporated above 50 mol%. Janoff Decl. ¶139; *see also* Ex. 1006 (Ahmad), 739–40; Fig. 3(a). In these formulations, transfection efficiency was also reported to decrease above a certain mol% cationic lipid (*e.g.*, around 70%). Ex. 1006 (Ahmad), 739–40; Fig. 3(a). It would have been obvious for a POSITA to combine the disclosed ranges in, *e.g.*, the '196 PCT with the teaching of Lin and/or Ahmad to increase the cationic lipid to the 50%-85% range in order to potentially increase the transfection efficiency. Janoff Decl. ¶139.

2. CLAIM 4: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CATIONIC LIPID COMPRISES FROM 50 MOL% TO 65 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(c). For the reasons stated above, this range is obvious in view of the '196 PCT when combined with Lin and/or Ahmad. Janoff Decl. ¶140.

3. MOTIVATION TO COMBINE '196 PCT WITH LIN AND/OR AHMAD

A POSITA would have been motivated to combine the teachings of the Patent Owner's prior disclosures with Lin and/or Ahmad. *Id.*, ¶141. First, the Lin and Ahmad systems tested helper lipids and cationic lipids to create carrier particles for nucleic acids, *i.e.*, "nucleic acid-lipid particles," the same general carrier particles described in the Patent Owner's prior disclosures. Second, the Patent Owner's disclosures specifically state that "[d]epending on the intended use of the nucleic acid-lipid particles, the proportions of the components are varied …." *See, e.g.*, Ex. 1002, [0088]. A POSITA would have been aware that the lipid proportions used could impact transfection efficiency. Janoff Decl. ¶141. A POSITA would have looked to the prior art, including Lin and Ahmad, in order to determine the appropriate proportions of, *e.g.*, cationic lipid. *Id.* Third, given the success of generating nucleic acid-lipid particles with a cationic lipid proportion greater than 50% as described in the Patent Owner's prior disclosures, a POSITA would have appreciated a reasonable expectation of doing so. *Id.* Given that Ahmad builds on the work described in Lin (Ex. 1006 (Ahmad), 743), a POSITA would have been motivated to combine the references. Janoff Decl. ¶141.

In short, a POSITA would have found it obvious to use the insights of Lin regarding increasing the cationic mol% of nucleic acid-lipid particles to increase transfection efficiency and the Patent Owner's prior disclosures regarding nucleic acid-lipid particles with a cationic lipid proportion greater than 50%. *Id.* ¶142.

C. GROUND 3: CLAIMS 1-20 ARE ANTICIPATED BY OR OBVIOUS IN VIEW OF THE '554 PUBLICATION

Claims 1-20 of the '435 patent are anticipated under 35 U.S.C. § 102(b) (pre-AIA) or obvious under 35 U.S.C. §103 in view of the '554 publication. While the '554 publication does not disclose exactly the same ranges of lipid components from claim 1 of the '435 patent explicitly, it discloses encompassing and overlapping ranges and specific examples falling within the claimed ranges with sufficient specificity to anticipate. Janoff Decl. ¶143. Moreover, the disclosed ranges establish a *prima facie* case of obviousness and the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. *Id.*

1. THE COMPONENTS IN CLAIM 1 ARE DISCLOSED IN THE ’554 PUBLICATION

a) CLAIM ELEMENT 1(A): A NUCLEIC ACID-LIPID PARTICLE COMPRISING:

The ’554 publication teaches “novel cationic lipids … and formulations thereof with biologically active molecules.” Ex. 1004, [0019]. 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.*, [0082]. One example of such particles with siRNA for reducing HBsAg levels using the L054 formulation are described in Figure 16. *Id.*, [0395] (“FIG. 16 shows a non-limiting example of in vitro efficacy of siNA nanoparticles in reducing HBsAg levels in HepG2 cells … treated with formulated active siNA L053 and L054 nanoparticles ….”); Janoff Decl. ¶144.

b) CLAIM ELEMENT 1(B): A NUCLEIC ACID

The ’554 publication teaches “compositions … with biologically active molecules” including “nucleic acids.” Ex. 1004, [0018-0019]. 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.*, [0082]. One example is siRNA for reducing HBsAg levels as described in Figure 16. *Id.*,

[0395]; Janoff Decl. ¶145.

c) CLAIM ELEMENT 1(C): A CATIONIC LIPID COMPRISING FROM 50 MOL% TO 85 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The ’554 publication 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, [0454]. “[T]he cationic lipid component … comprises from about 2% to about 60% … or from about 40% to about 50% of the total lipid ….” *Id.*, [0116]. For example, the L054 formulation tested in Figure 16 contains 50% cationic lipid (DMOBA). *Id.*, Table 4; Janoff Decl. ¶146.

The ’554 publication also teaches 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.” Ex. 1004, [0137]. The cationic lipid is the active component in such the pH-dependent nucleic acid-lipid particles: “[s]uitable cationic lipid include those cationic lipids which carry a net positive charge at a selected pH ….” *Id.*, [0083]. A POSITA would understand that increasing the mol% of a cationic lipid with pH sensitivity in these particles might increase transfection efficiency since this event is fusion related and thought to occur as a result of the described phase shift. Janoff Decl. ¶147.

Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. *Id.*, ¶148. For example, not only does the disclosed range overlap with the claimed range, a specific example falls within the claimed range. In addition, a POSITA would be compelled to choose cationic lipid proportions at the top end of the recited range to increase the efficiency of the described phase shift. *Id.* ¶149.

Moreover, "even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of overlapping ranges, this limitation is *prima facie* obvious. Janoff Decl. ¶149. As discussed above, the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. *Id.*

d) CLAIM ELEMENT 1(D): A NON-CATIONIC LIPID COMPRISING FROM 13 MOL% TO 49.5 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The '554 publication 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, [0455]. Neutral lipids are defined as "any lipophilic compound having non-cationic change (e.g., anionic or neutral charge)." *Id.*, [0315]. "[T]he neutral lipid component … comprise[s] … from about 20% to about 85% of the total lipid present in the formulation." *Id.*,

[0313]. For example, the L054 formulation tested in Figure 16 contains 48% non-cationic lipid (cholesterol and DSPC). *Id.*, Table 4; Janoff Decl. ¶113. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Janoff Decl. ¶150.

Moreover, "even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶150.

e) CLAIM ELEMENT 1(E): A CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISING FROM 0.5 MOL% TO 2 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The '554 publication teaches "[i]n addition to cationic and neutral lipids, the formulated molecular compositions of the present invention comprise a polyethyleneglycol (PEG) conjugate." Ex. 1004, [0457]. "[T]he PEG conjugate … comprises from about 1% to about 20% … of the total lipid present …." *Id.*, [0118]. The '554 publication further teaches "[i]t is often desirable to include other components that act in a manner similar to the DAG-PEG conjugates and that serve to prevent particle aggregation …." *Id.*, [0504]. For example, the L054 formulation tested in Figure 16 contains 2% conjugate lipid (PEG-n-DMG). *Id.*, Table 4; Janoff Decl. ¶114. Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Janoff Decl. ¶151.

This limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. A POSITA would have been aware that conjugated lipids stabilize carrier particles by inhibiting fusogenicity. *Id.*, ¶152. It would have been obvious for a POSITA to try to increase the fusogenicity, and hence potentially the transfection efficiency, by choosing a proportion of conjugated lipid in the 0.5%-2% range. *Id.* Moreover, "even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of encompassing ranges, this limitation is *prima facie* obvious and, as discussed above, the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶152.

2. CLAIM 2: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID COMPRISES AN INTERFERING RNA, MRNA, AN ANTI-SENSE OLIGONUCLEOTIDE, A RIBOZYME, A PLASMID, AN IMMUNOSTIMULATORY OLIGONUCLEOTIDE, OR MIXTURES THEREOF

The '554 publication 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, [0020]. One example is siRNA for reducing HBsAg levels as described in Figure 16. *Id.*, [0395]; Janoff Decl. ¶153.

3. CLAIM 3: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 2, WHEREIN THE INTERFERING RNA COMPRISES A SMALL INTERFERING RNA (SIRNA), AN ASYMMETRICAL INTERFERING RNA (AIRNA), A MICRORNA (MIRNA), OR MIXTURES THEREOF

The ’554 publication 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, [0020]. The ’554 publication further teaches “the invention features novel … formulations that effectively transfect or deliver small nucleic acid molecules, such as short interfering nucleic acid (siNA) … [and] micro-RNA (miRNA) … to relevant cells and/or tissues ….” *Id.*, [0019]. One example is siRNA for reducing HBsAg levels as described in Figure 16. *Id.*, [0395]; Janoff Decl. ¶154.

4. CLAIM 4: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CATIONIC LIPID COMPRISES FROM 50 MOL% TO 65 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1. Given the claimed range, the disclosures are sufficiently specific to anticipate the claimed range. Janoff Decl. ¶118. Moreover, “even a slight overlap in range establishes a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of an overlapping range, this limitation is *prima facie* obvious and, as discussed above, the testing in the ‘435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶155.

5. CLAIM 5: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NON-CATIONIC LIPID COMPRISES A MIXTURE OF A PHOSPHOLIPID AND CHOLESTEROL OR A DERIVATIVE THEREOF

The '554 publication 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, [0455]. "Examples of noncationic lipids useful in the present invention include phospholipid-related materials …." *Id.* "[S]uitable neutral lipids include … cholesterol, as well as other neutral lipids described herein below, and/or a mixture thereof." *Id.*, [0085]. For example, the L054 formulation tested in Figure 16 contains 48% non-cationic lipid (cholesterol and DSPC). *Id.*, Table 4; Janoff Decl. ¶156.

6. CLAIM 6: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 5, WHEREIN THE PHOSPHOLIPID COMPRISES DIPALMITOYLPHOSPHATIDYLCHOLINE (DPPC), DISTEAROYLPHOSPHATIDYLCHOLINE (DSPC), OR A MIXTURE THEREOF

The '554 publication teaches "suitable neutral lipids include … DSPC … DPPC … and/or a mixture thereof." Ex. 1004, [0085]; Janoff Decl. ¶157.

7. CLAIM 7: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 5, WHEREIN THE PHOSPHOLIPID COMPRISES FROM 3 MOL% TO 15 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The '554 publication 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, [0455]. "[T]he neutral lipid component … comprises … from about 20% to about 85% of the total lipid present in the formulation … the cholesterol component … comprises … from about 20% to about 45% of the total lipid present ….” *Id.*, [0117-0119]. When cholesterol is present, the range for a phospholipid is 0-40%. Janoff Decl. ¶158. Not only does the disclosed range encompass the claimed range, when combined with a cationic lipid proportion in the 60% range and cholesterol in the 20-40% range, the range for the phospholipid is decreased to 0%-20%. *Id.* Given the breadth of the claimed range for the phospholipid, these disclosures are sufficiently specific to anticipate the claimed range. *Id.*

Moreover, "even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of a non-cationic lipid range "from about 20% to about 85%," including cholesterol "from about 20% to about 45%," an overlapping range of 0%-40% is disclosed. Janoff Decl. ¶159. This limitation is *prima facie* obvious and, as discussed above, the testing in the '435 patent does not support alleged unexpected results for the claimed ranges. *Id.*

8. CLAIM 8: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 5, WHEREIN THE CHOLESTEROL OR DERIVATIVE THEREOF COMPRISES FROM 30 MOL% TO 40 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

The '554 publication teaches "the cholesterol component … comprises … from about 20% to about 45% of the total lipid present." Ex. 1004, 29:60-30:4. In addition, the ’554 publication also includes various specific formulations which include cholesterol at a 30% proportion. *Id.*, Table 4 (*e.g.*, L106). Given the breadth of the claimed range, these disclosures are sufficiently specific to anticipate the claimed range. Janoff Decl. ¶160.

Moreover, “even a slight overlap in range establishes a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d at 1329. Given the explicit disclosure of an encompassing range, this limitation is *prima facie* obvious and, as discussed above, the testing in the ‘435 patent does not support alleged unexpected results for the claimed ranges. Janoff Decl. ¶160.

9. CLAIM 9: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISES A POLYETHYLENEGLYCOL (PEG)-LIPID CONJUGATE

The ’554 publication teaches “[i]n addition to cationic and neutral lipids, the formulated molecular compositions of the present invention comprise a polyethyleneglycol (PEG) conjugate.” Ex. 1004, [0457]. For example, the L054 formulation tested in Figure 16 contains 2% conjugate lipid (PEG-n-DMG). *Id.*, Table 4; Janoff Decl. ¶161.

10. CLAIM 10: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 9, WHEREIN THE PEG-LIPID CONJUGATE COMPRISES A PEG-DIACYLGLYCEROL (PEG-DAG) CONJUGATE, A PEG-DIALKYLOXYPROPYL (PEG-DAA) CONJUGATE, OR A MIXTURE THEREOF

The ’554 publication teaches “[s]uitable polyethyleneglycol-diacylglycerol or polyethyleneglycol-diacylglycamide (PEG-DAG) conjugates …." Ex. 1004, [0086]. Because one of the listed species of PEG-lipid conjugates is disclosed, this element is anticipated. Janoff Decl. ¶162.

11. CLAIM 11: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 10, WHEREIN THE PEG-DAA CONJUGATE COMPRISES A PEG-DIMYRISTYLOXYPROPYL (PEG-DMA) CONJUGATE, A PEG-DISTEARYLOXYPROPYL (PEG-DSA) CONJUGATE, OR A MIXTURE THEREOF

This limitation would have been obvious in view of the '554 publication in light of the knowledge of a POSITA. Janoff Decl., ¶163. A POSITA would have been aware that PEG-dialkyloxypropyl (PEG-DAA) conjugates could be used in lieu of PEG-diacylglycerol (PEG-DAG) conjugates and that PEG-dialkyloxypropyl (PEG-DAA) conjugates can comprises a PEG-dimyristyloxypropyl (PEG-DMA) conjugate, a PEG-distearyloxypropyl (PEG-DSA) conjugate, or a mixture thereof. *Id*. Indeed, the Patent Owner's prior disclosures from years before the '435 patent priority date address using PEG-DAA conjugates (*e.g.*, PEG-DMA or PEG-DSA) in lieu of PEG-DAG conjugates. *See, e.g.*, Ex. 1014 ('910 publication), [0016].

12. CLAIM 12: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE CONJUGATED LIPID THAT INHIBITS AGGREGATION OF PARTICLES COMPRISES FROM 1 MOL% TO 2 MOL% OF THE TOTAL LIPID PRESENT IN THE PARTICLE

See Claim 1(e). For the reasons stated above, the '554 publication discloses this range with sufficient specificity to anticipate. Janoff Decl. ¶164. In the alternative, this range is *prima facie* obvious given the overlapping range in the

’554 publication. *Id.*

13. CLAIM 13: THE NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1, WHEREIN THE NUCLEIC ACID IS FULLY ENCAPSULATED IN THE NUCLEIC ACID-LIPID PARTICLE

The ’554 publication teaches “[t]he encapsulation of anionic compounds using cationic lipids is essentially quantitative due to electrostatic interaction.” Ex. 1004, [0011]. A POSITA would understand that full encapsulation requires only an excess of cationic lipid with regard to the nucleic acid for electrostatic interaction. Janoff Decl. ¶165.

14. CLAIM 14: A PHARMACEUTICAL COMPOSITION COMPRISING A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1 AND A PHARMACEUTICALLY ACCEPTABLE CARRIER

The ’554 publication teaches “[t]he pharmaceutical carrier is generally added following formulated siNA composition formation. Thus, after the formulated siNA composition is formed, the formulated siNA composition can be diluted into pharmaceutically acceptable carriers such as normal saline.” Ex. 1004, [0502]; Janoff Decl. ¶166.

15. CLAIM 15: A METHOD FOR INTRODUCING A NUCLEIC ACID INTO A CELL, THE METHOD COMPRISING: CONTACTING THE CELL WITH A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1

See Claim 1. The ’554 publication teaches “[t]he invention relates to … methods for delivering nucleic acids … to cells by facilitating transport across cellular membranes ….” Ex. 1004, [0003]. A POSITA would understand this to include contacting the cell with the carrier particle. Janoff Decl. ¶167.

16. CLAIM 16: A METHOD FOR THE IN VIVO DELIVERY OF A NUCLEIC ACID, THE METHOD COMPRISING: ADMINISTERING TO A MAMMALIAN SUBJECT A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1

See Claim 1. The '554 publication teaches "'[s]ubject' also refers to an organism to which the nucleic acid molecules of the invention can be administered. A subject can be a mammal or mammalian cells, including a human or human cells." Ex. 1004, [0369]; Janoff Decl. ¶168.

17. CLAIM 17: A METHOD FOR TREATING A DISEASE OR DISORDER IN A MAMMALIAN SUBJECT IN NEED THEREOF, THE METHOD COMPRISING: ADMINISTERING TO THE MAMMALIAN SUBJECT A THERAPEUTICALLY EFFECTIVE AMOUNT OF A NUCLEIC ACID-LIPID PARTICLE OF CLAIM 1

See Claims 1 & 16. The '554 publication teaches "the invention features a method for treating or preventing a disease, disorder, trait or condition related to gene expression in a subject or organism comprising contacting the subject or organism with a formulated molecular composition of the invention under conditions suitable to modulate the expression of the target gene in the subject or organism." Ex. 1004, [0274]; Janoff Decl. ¶169.

18. CLAIM 18: THE METHOD OF CLAIM 17, WHEREIN THE DISEASE OR DISORDER IS A VIRAL INFECTION

The '554 publication teaches "[i]n one embodiment, the degree of reduced immunostimulatory response is selected for optimized RNAi activity. For example, retaining a certain degree of immunostimulation can be preferred to treat viral infection …." Ex. 1004, [0310]; Janoff Decl. ¶170.

19. CLAIM 19: THE METHOD OF CLAIM 17, WHEREIN THE DISEASE OR DISORDER IS A LIVER DISEASE OR DISORDER

The ’554 publication teaches “the invention features compositions and methods that independently or in combination modulate the expression of target genes encoding proteins, such as proteins associated with the maintenance and/or development of a disease, trait, or condition, such as a liver disease, trait, or condition.” Ex. 1004, [0021]; Janoff Decl. ¶171.

20. CLAIM 20: THE METHOD OF CLAIM 17, WHEREIN THE DISEASE OR DISORDER IS CANCER

The ’554 publication teaches “the invention features a method for treating or preventing cancer in a subject or organism comprising contacting the subject or organism with a formulated molecular composition of the invention ….” Ex. 1004, [0275]; Janoff Decl. ¶172.

Dated: March 5, 2018

Respectfully submitted,

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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 13,594 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: March 5, 2018

/s/ Susan M. Langworthy
Susan M. Langworthy

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. 9,364,435 and Exhibits 1001 through 1018 are being served upon the patent prosecution counsel of record for the Patent Owner via Express Mail at the address listed below on the 5 day of March, 2018, 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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/s/ Susan M. Langworthy
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