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THOMAS | HORSTEMEYER, LLP
3200 WINDY HILL ROAD, SE
SUITE 1600E
ATLANTA, GA 30339

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte TATSIANA LOBOVKINA, GUNILLA B. JACOBSON, RICHARD N. ZARE, EVGENIOS NEOFYTOU, RAMIN E. BEYGUI, and MARIE RUSSO

Appeal 2017-006689
Application 13/799,883
Technology Center 1600

Before ULRIKE W. JENKS, ELIZABETH A. LAVIER, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellants[1] submit this appeal under 35 U.S.C. § 134 involving claims to a composition comprising a nanoparticle that includes a siRNA-cationic lipid conjugate. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM-IN-PART.

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[1] Appellants identify the Real Party in Interest as The Board of Trustees of the Leland Stanford Junior University. App. Br. 3.

STATEMENT OF THE CASE

According to the Specification, "small interfering RNAs (siRNAs) hold promise as nucleic-acid based therapeutics" but "effective and well-controlled *in vivo* delivery remains challenging." Spec. 1. For example, "unmodified siRNA molecules are not taken up efficiently by most cells owing to their size (~13,000 Mw) and anionic nature, and therefore may not result in effective gene silencing *in vivo*." *Id.* The Specification, however, explains that lipid-based nanoparticles engineered for slow and controlled release of functional siRNA may lead to more effective therapies. *Id.*

The Specification describes a composition that may include "a nanoparticle including a siRNA-cationic lipid conjugate, wherein the siRNA-cationic lipid conjugate is disposed within the nanoparticle." *Id.* at 2. As the Specification explains, the nanoparticle may further include a core comprising a solid lipid or a "liquid lipid (*i.e.*, oil, which remains liquid at room temperature and body temperature, for example, vegetable oil or a lipid extracted from human adipose tissue)." *Id.*

Claims 1, 2, 10, and 12–15 are on appeal. Claims 1 and 2 are illustrative and are reproduced below:

1. A composition comprising:

> a nanoparticle including a siRNA-cationic lipid conjugate, wherein the siRNA-cation lipid conjugate is disposed within the nanoparticle, and
>
> wherein a nanoparticle core includes a liquid lipid, wherein the liquid lipid is a lipid extracted from human adipose tissue.

2. A composition comprising:

a nanoparticle including a siRNA-cationic lipid conjugate, wherein the nanoparticle has a lipid monolayer enclosing a nanoparticle core, wherein the siRNA-cationic lipid conjugate is disposed within the nanoparticle core, wherein the lipid monolayer is selected from the group consisting of: lecithin, phosphatidylcholines, phosphatidic acid, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, cardiolipins, lipidpolyethyleneglycol conjugates, and a combination thereof,

wherein the nanoparticle core includes a liquid lipid, and

wherein the liquid lipid is a lipid extracted from adipose tissue.

App. Br. 21 (Claims App'x).

The claims stand rejected as obvious under 35 U.S.C. § 103 over Hope[2] and Mumper,[3] as evidenced by Dayton.[4] *See* Ans. 2–4; Final Act. (Final Rejection dated Aug. 5, 2016) 2–4.

DISCUSSION

Claim 1

The Examiner rejected claim 1 as obvious over Hope, Mumper, and Dayton. According to the Examiner, Hope teaches "nucleic acid-lipid particles that provide efficient encapsulation of nucleic acids, and efficient

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[2] Hope et al., US 2011/0256175 A1, published Oct. 20, 2011.
[3] Mumper et al., US 2011/0195030 A1, published Aug. 11, 2011.
[4] Seymour Dayton et al., *Composition of lipids in human serum and adipose tissue during prolonged feeding of a diet high in unsaturated fat*, 7 J. OF LIPID Research 103–111 (1966).

delivery of the encapsulated nucleic acids to cells in vivo." Ans. 2 (citing Hope, Abstract). The Examiner finds that Hope teaches formation of lipid vesicles, formed at least partly from cationic lipids, and that "siRNA was added to the vesicles with mixing and incubation to allow encapsulation of the siRNA." *Id.* (citing Hope ¶ 328).

Because the Examiner finds that "Hope does not disclose lipids extracted from human adipose tissue, as recited in claim 1," the Examiner turns to Mumper and Dayton. Ans. 2–3. According to the Examiner, "Mumper discloses nanoparticle compositions comprising liquid oil cores," and further teaches that such liquid oils comprise triglycerides, including linoleic triglycerides. *Id.* at 2 (citing Mumper, Abstract, ¶ 15). The Examiner finds that Mumper describes advantages of such liquid oil cores including lower toxicity because they are bio-derived and biocompatible. *Id.* at 3 (citing Mumper ¶ 53). Citing Dayton, the Examiner finds that "triglyceride lipids are present in adipose tissue of humans and that adipose tissue comprises linoleic acid." *Id.* at 3 (citation omitted); Dayton 103, 107 (disclosing, *inter alia*, a "progressive rise in linoleic acid content of adipose tissue, at the expense of all other major fatty acids with the possible exception of stearic").

The Examiner concludes the subject matter of claim 1 would have been obvious over the cited references. More specifically, the Examiner reasons that it would have been obvious "to have formulated Hope's composition with triglycerides" and that the skilled artisan would have been "motivated because lipid-based delivery systems having cores comprised of bio-derived liquid lipids have the advantage of a lower toxicity" as taught by

Mumper. Ans. 3 ("Mumper's lipids . . . are not structurally distinct from lipids that can be isolated from human adipose tissue, as evidenced by Dayton.").

Appellants raise essentially three arguments. First, Appellants contend Hope "teaches away from the use of cationic lipids, and one skilled in the art would be dissuaded from conjugating siRNA with cationic lipids." App. Br. 10–12, 15. Second, Appellants contend that the cited art does not teach "a 'siRNA-cationic lipid conjugate' disposed in a nanoparticle core in Appellant's claim 1." *Id.* at 13–15. According to Appellants, in claim 1 "[t]here is a lipid that is bound to the siRNA which in turn is encapsulated by a lipid mixture" and "one skilled in the art would clearly not read an siRNA-lipid conjugate disposed within a nanoparticle core as siRNA associated with a nanoparticle core [in Hope] as the Office says." *Id.* at 13.[5] And third, Appellants contend Mumper and Dayton do not disclose a nanoparticle core having a liquid lipid from adipose tissue as claimed. App. Br. 16–17 (arguing Dayton is "directed towards fatty acids and NOT

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[5] *See also* App. Br. 14 (arguing that in Hope "[l]ipid-only mixtures are formed which encapsulate[] nucleic acids to form nucleic acid-lipid particles"), 15 ("The siRNA encapsulated by lipids in Hope is NOT equivalent to the siRNA-lipid conjugate that is disposed within a nanoparticle . . . [because the siRNA] of Hope is NOT conjugated to a lipid, it is merely encapsulated by it.") and ("[T]he siRNA-lipid conjugate of Appellant's claims is not bound to the vesicle surface . . . ."); Reply Br. 2–4 ("Hope merely teaches nucleic-lipid particles comprised of siRNA encapsulated by lipids, which are missing the feature of siRNA-cationic lipid conjugates disposed within nanoparticles as claimed by Appellants.").

triglycerides," and that neither Mumper nor Dayton provides a motivation to use adipose tissue as the source of the liquid lipid).

The preponderance of the evidence on this record supports the Examiner's conclusion that claim 1 would have been obvious over Hope, Mumper, and Dayton. Hope's "invention provides cationic lipids and lipid particles comprising these lipids, which are advantageous for the in vivo delivery of nucleic acids, as well as nucleic acid-lipid particle compositions suitable for in vivo therapeutic use." Hope ¶ 4; Ans. 4. Hope further expressly teaches that "[t]herapeutic nucleic acids include, e.g., small interfering RNA (siRNA)." Hope ¶ 6; *see*, *e.g.*, *id.* ¶¶ 49–50, 57–60, 325–328. Hope teaches encapsulation of siRNA agents in lipid particles, yet Hope's teachings are also broader. Ans. 5, 9. For example, as noted by the Examiner, Hope teaches that portions of the siRNA molecule may also attached to a surface of the lipid particles; and Hope teaches that siRNA molecules may be partially or fully encapsulated within the particle. *Id.*; *see*, *e.g.*, Hope ¶¶ 49–50, 137, 219–220.[6] To the extent Hope, thus, suggests that siRNA molecules may be associated with or attached to cationic lipids

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[6] Indeed, Hope teaches that "[t]he lipid particles and compositions of the present invention may be used for a variety of purposes, including the delivery of associated or encapsulated therapeutic agents to cells," signaling that the agent being "associated" with the lipid particle is broader than the agent simply being fully encompassed by the particle, consistent with the Examiner's interpretation. Hope ¶ 59; Ans. 5; *see also* Hope ¶ 130 (disclosing that the "active agent is associated with the lipid particle" and then disclosing that the agent may, for example, be encapsulated within the lipid particle, be present within lipid layers of the particle, or be "bound to the exterior or interior lipid surface of a lipid particle").

forming the particle, such as at the particle's interior surface, we conclude that claim 1's limitation reciting "the siRNA-cation lipid conjugate is disposed within the nanoparticle" is met.

Turning to claim 1's limitation requiring "a nanoparticle core includes a liquid lipid . . . [that] is a lipid extracted from human adipose tissue," we agree with the Examiner that this limitation is satisfied by the teachings of Mumper and Dayton. At the outset, we agree with the Examiner on this record that the source of the liquid lipid (i.e., from human adipose tissue) does not *structurally* distinguish over the prior art — to the extent the art teaches or suggests use of a liquid lipid found in human adipose tissue, even where the art is silent about the lipid's source. Ans. 3. Here, as the Examiner notes, Mumper teaches bio-derived and biocompatible triglycerides (e.g., linoleic triglyceride) as suitable liquid lipids for a nanoparticle's liquid core, and Dayton evidences that fatty acids and such triglycerides are found in human adipose tissue. Mumper ¶¶ 15, 53; Dayton 103.[7]

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[7] Dayton reported marked increases in the concentrations of esterified forms of linoleic acid in sera — "most marked in triglyceride." Dayton 103, 107. Although Dayton further discusses fatty acids (linoleic acid) measured in adipose tissue, triglycerides (a glycerol backbone with three esterified fatty acid groups) comprise a primary form of energy storage in deposited human fat. *See* Dayton 108 n.2 ("There is evidence that adipose tissue contains at least two pools [storage droplet and cytoplasmic] of triglyceride . . . ."). On balance, the record indicates that human adipose tissue comprises triglycerides, including triglycerides derived from linoleic acid (linoleic triglycerides). In the face of this evidence, Appellants argue that triglycerides and fatty acids are not the same thing (App. Br. 16), but

Appellants' argument that Hope teaches away from, or would discourage, the use of cationic lipids with siRNA is unpersuasive. Quite the opposite, Hope repeatedly teaches that cationic lipids not only may, but *should*, be used. *See*, *e.g.*, Hope ¶ 57 ("The present invention is based, in part, upon the identification of novel cationic lipids that provide superior results when used in lipid particles for the in vivo delivery of a therapeutic agent."); Ans. 5–7. In support of the teaching away argument, Appellants identify cationic lipids in Hope that showed little or no activity, or that resulted in significant toxicity. App. Br. 11–12 (citing, e.g., certain lipids in Tables 5 and 6). But, as the Examiner points out, the cationic lipids identified by Appellants as raising safety or efficacy concerns (DOTAP.Cl, DLinTap.Cl, DLin-K-TMA) are not the only cationic lipids described in Hope. Ans. 8–9 (citing DLinDMA, DLinAP, DODAP, and other cationic lipids described in Hope); Hope ¶ 120 (listing various cationic lipids), ¶ 362 (Table 5 ("cationic lipids and the results of these experiments are shown in Table 5"), ¶ 367 (describing DLin-K-DMA as "the new benchmark lipid"). And, importantly, claim 1 is not limited to use of any particular cationic lipid. *Compare* claim 1, *with* claim 15 (reciting the cationic lipid is selected from DOTAP, DC-Cholesterol, DODAP, and certain other lipids).

Appellants' argument that Hope teaches away from modifying the siRNA construct is also unpersuasive. App. Br. 15. Appellants contend "the association of cationic lipid with siRNA [by ionic association] to form a siRNA-cationic lipid conjugate as taught and claimed by the appellants

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Appellants provide no persuasive rebuttal evidence that such triglycerides are missing in adipose tissue.

(which is then encapsulated)" is not taught in Hope and would not be expected to be efficiently encapsulated in a lipid vesicle. *Id.* Appellants' contention presumes claim 1 is limited to a particular method described in the Appellants' Specification for making the nanoparticles that include the siRNA-cationic lipid conjugates. Spec. Fig. 1 (schematic showing an exemplary preparation technique). It is not. *See* Ans. 11–12 (also explaining that "claims reciting siRNA-cationic lipid conjugates having a more positive or neutral surface charge are not currently pending"). We are unpersuaded claim 1 requires the conjugate *first* be formed by an association of the positively-charged cationic lipids and a negatively-charged portion of the siRNA molecules, and *then* separately be encapsulated by a lipid nanoparticle as suggested by Appellants. Claim 1 is to a composition, not a method of manufacture, and the manner in which the composition is made is not specifically limiting here. As explained above, we conclude that Hope's disclosure of associating cationic lipids with siRNA molecules satisfies the siRNA-cationic lipid conjugates recited in claim 1 — even if they might be formed by techniques in Hope that differ from those exemplified in Appellants' disclosure.

Appellants' argument that Hope does not teach "a 'siRNA-cationic lipid conjugate' disposed in a nanoparticle core in Appellant's claim 1" is also unavailing. App. Br. 13–15; Reply Br. 2–4. As an initial matter, claim 1 (unlike independent claims 2 and 15) does not specify that the conjugate is "disposed within a nanoparticle core" as argued by Appellants. Claim 1 merely recites that the "conjugate is disposed within the nanoparticle." We consider the claim language in light of the Specification, which discloses

that the "the composition includes a nanoparticle that includes a siRNA-cationic lipid conjugate *disposed within* the nanoparticle *or inside* of the nanoparticle." Spec. 9 (emphasis added). Based on the Specification, we therefore conclude the phrase "disposed within the nanoparticle" is broad, and does not require the conjugate be fully encapsulated or "inside" the nanoparticle. Insofar as Appellants' argument seeks to distinguish Hope as not describing a conjugate that itself is wholly encapsulated by the lipid particle or that is inside the nanoparticle's core, Appellants' argument does not account for the broadest reasonable interpretation of claim 1.

Finally, as explained above, we agree with the Examiner that Mumper and Dayton teach or suggest "a nanoparticle core [that] includes a liquid lipid . . . [that] is a lipid extracted from human adipose tissue." Appellants' attorney argument to the contrary is unpersuasive on this record. *See supra* p. 7 and note 7; *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (confirming that sufficient factual evidence, not attorney argument, is required to rebut a prima facie case of obviousness); *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974) (same).

For the above reasons, we find that the preponderance of the evidence on this record supports the Examiner's conclusion that claim 1 would have been obvious over Hope, Mumper, and Dayton. The Examiner's rejection of claim 1 is, thus, affirmed.

Claims 2 and 15

Claims 2 and 15 differ from claim 1 in at least the following respects: *first*, claims 2 and 15 both require a "nanoparticle [that] has a lipid monolayer enclosing a nanoparticle core" and *second*, both claims require

"the siRNA-cationic lipid conjugate is disposed within the nanoparticle core." App. Br. 21–22 (Claims App'x). Based on the plain meaning of the claims in light of the Specification, those limitations impart features that structurally distinguish claims 2 and 15 from claim 1. Importantly, a lipid monolayer must *enclose* and therein define a distinct feature of the nanoparticle — its core. Moreover, the siRNA-cationic lipid conjugate is within the enclosed core. We are unpersuaded on this record that an siRNA molecule that is merely "associated with" a lipid forming the nanoparticle (e.g., a nucleic acid attached to a surface of the nanoparticle), such as described in Hope, would meet the limitations of claims 2 and 15. Here, unlike claim 1, we conclude claims 2 and 15 expressly require the conjugate be within the nanoparticle's core — the conjugate itself must be inside the nanoparticle consistent with Appellants' arguments.[8] App. Br. 12–14, 17–18; Reply Br. 2–4.

Beyond the Examiner's findings relative to claim 1, for claims 2 and 15 the Examiner states that "Hope discloses single-layered liposomes." Ans. 3. But the Examiner's assertions do not address in a sufficiently clear and persuasive manner the specific claim requirements of claims 2 and 15, and how those claims differ from claim 1 as discussed above. Accordingly, on the present record, we reverse the Examiner's rejection of claims 2 and 15 as

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[8] Claims 2 and 15 do not read on simply having a portion of the nucleic acid be inside the nanoparticle where the another portion of the recited conjugate (the cationic lipid) is part of the lipid layer or surface enclosing a "core" as seemingly suggested by the Examiner. Ans. 5. In other words, we do not agree that a portion of the lipid layer forming the nanoparticle both encloses the nanoparticle's core and is within the core.

obvious over Hope, Mumper, and Dayton. Claims 10 and 12–14 depend from claim 2 and, therefore, we similarly reverse the rejection of those dependent claims. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious . . . .").

SUMMARY

We affirm the rejection of claim 1, but reverse the rejection of claims 2, 10, and 12–15.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART