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Paper 40
Entered: July 23, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

ARBUTUS BIOPHARMA CORPORATION,
Patent Owner.

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IPR2019-00554
Patent 8,058,069 B2

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Before TINA E. HULSE, CHRISTOPHER G. PAULRAJ, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

PAULRAJ, *Administrative Patent Judge*.

# JUDGMENT
Final Written Decision - *35 U.S.C. § 318(a)*
Determining No Challenged Claims Unpatentable
Denying Patent Owner's Motion to Strike
Denying Patent Owner's Motion to Exclude

# I. INTRODUCTION

## *A. Background and Summary*

This is a Final Written Decision entered pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

On January 9, 2019, Moderna Therapeutics, Inc., ("Petitioner") filed a Petition requesting institution of an *inter partes* review of claims 1–22 of U.S. Patent No. 8,058,069 B2 ("the '069 patent," Ex. 1001). Paper 1 ("Pet."). Arbutus Biopharma Co. ("Patent Owner") timely filed a Preliminary Response (Paper 7, "Prelim. Resp."). In our Institution Decision, we determined that there was a reasonable likelihood that Petitioner would prevail with respect to at least one challenged claim and, accordingly, instituted an *inter partes* review pursuant to 35 U.S.C. § 314 based on all grounds presented in the Petition. Paper 8 ("Inst. Dec."). Following institution, Patent Owner filed its post-institution Patent Owner Response (Paper 15, "PO Resp."), Petitioner filed its Reply to Patent Owner's Response (Paper 21, "Pet. Reply"), and Patent Owner filed its Sur-Reply (Paper 30, "Sur-Reply"). No motion to amend was filed in this proceeding. An oral hearing was held on April 22, 2020, and a transcript of that hearing has been entered into the record. Paper 39 ("Tr.").

For the reasons set forth below, having considered all the evidence and arguments set forth by the parties, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–22 of the '069 patent are unpatentable under 35 U.S.C. § 103. We also deny Patent Owner's Motion to Strike Petitioner's Reply (Paper 28) and Patent Owner's Motion to Exclude certain evidence (Paper 31).

*B. Related Proceedings*

Petitioner filed petitions seeking *inter partes* review of two additional patents held by Patent Owner in IPR2018-00680, challenging U.S. Patent No. 9,404,127 B2, and IPR2018-00739 ("the '739 IPR"), challenging U.S. Patent No. 9,364,435 B2 ("the '435 patent).[1] Pet. 4; Paper 4, 2–3. The Board instituted review in each proceeding on September 11, 2018. *See* IPR2018-00680 (Paper 13); IPR2018-00739 (Paper 15). The '435 patent at issue in the '739 IPR is a continuation of the '069 patent challenged here. Ex. 1002, code (63).

*C. The '069 Patent (Ex. 1001)*

The '069 patent relates to lipid formulations for nucleic acid delivery and, in particular, "stable nucleic acid-lipid particles (SNALP) comprising a nucleic acid (such as one or more interfering RNA), methods of making the SNALP, and methods of delivering and/or administering the SNALP." Ex. 1001, Abstract. These nucleic-acid lipid particles may be used to deliver nucleic acids to cells for therapeutic techniques such as RNA interference (RNAi). *Id.* at 1:28–40. The '069 patent states that

> [t]he present invention is based, in part, upon the surprising discovery that lipid particles 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 when used for the in vitro or in vivo delivery of an active agent, such as a therapeutic nucleic acid (e.g., an interfering RNA).

*Id.* at 5:44–51. The '069 patent further states that

> the present invention provides [SNALPs] that advantageously impart increased activity of the encapsulated nucleic acid (e.g., an interfering

[1] Patent Owner explains that Protiva Biotherapeutics, Inc., identified as the patent owner in IPR2018-00680 and IPR2018-00739, previously "existed as a wholly-owned subsidiary of Arbutus Biopharma Corporation," and was "amalgamated into Arbutus Biopharma Corporation in January 2018." Paper 4, 2.

> RNA such as siRNA) and improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index as compared to nucleic acid-lipid particle compositions previously described. Additionally, the SNALP of the invention are stable in circulation, e.g., resistant to degradation by nucleases in serum and are substantially non-toxic to mammals such as humans.

*Id.* at 5:51–61.

The '069 patent identifies specific SNALP formulations that encapsulate siRNA as the nucleic acid, such as the "1:57 SNALP" and the "1:62 SNALP," and states that "the Examples herein illustrate that the improved lipid particle formulations of the invention are highly effective in downregulating the mRNA and/or protein levels of target genes." Ex. 1001, 6:6–15. In characterizing the 1:57 SNALP and 1:62 SNALP formulations, the '069 patent explains that these are "target formulations, and [] the amount of lipid (both cationic and non-cationic) present and the amount of lipid conjugate present in the formulation may vary." *Id.* at 68:35–39. In this regard, the '069 patent explains that the 1:57 SNALP formulation usually includes 57 mol % ± 5 mol % cationic lipid and 1.5 mol % ± 0.5 mol % lipid conjugate, with non-cationic lipid making up the balance of the formulation. *Id.* at 68:39–43. Similarly, the 1:62 SNALP formulation typically includes 62 mol % ± 5 mol % cationic lipid and 1.5 mol % ± 0.5 mol % lipid conjugate, with non-cationic lipid making up the remainder. *Id.* at 68:44–48.

The '069 patent describes several studies comparing the efficacy of siRNA encapsulated in different SNALP formulations. For example, in a study examining siRNA SNALP formulations directed at silencing Eg5, a kinesin-related protein critical for mitosis in mammalian cells (Ex. 1001, 68:55–62), the '069 patent reports that the 1:57 SNALP formulation "was among the most potent inhibitors of tumor cell growth at all siRNA concentrations tested" (*id.* at 70:19–22). Similarly,

in a test of SNALP formulations targeting apolipoprotein B ("ApoB"), a protein associated with hypercholesterolemia (*id.* at 70:55–59), the '069 patent explains that the 1:57 SNALP formulation "was the most potent at reducing ApoB expression in vivo" (*id.* at 72:21–23). The '069 patent also reports experimental results indicating that the ApoB 1:57 SNALP formulation "was more than 10 times as efficacious as the 2:30 SNALP [a prior art SNALP composition] in mediating ApoB gene silencing in mouse liver at a 10-fold lower dose" (*id.* at 73:64–67), and that the "1:57 and 1:62 SNALP formulations had comparable ApoB silencing activity in vivo" (*id.* at 74:51–53).

*D. Challenged Claims*

Petitioner challenges claims 1–22 of the '069 patent. Claim 1, the sole independent claim of the '069 patent, is illustrative, and is reproduced below:

> 1. A nucleic acid-lipid particle comprising:
>
> (a) a nucleic acid;
>
> (b) a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the particle;
>
> (c) a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from 4 mol % to 10 mol % of the total lipid present in the particle and the cholesterol or derivative thereof comprises from 30 mol % to 40 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.

Ex. 1001, 91:23–35.

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