Trials@uspto.gov
571-272-7822

Paper No. 8
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

ARBUTUS BIOPHARMA CORPORATION,
Patent Owner.

Case IPR2019-00554
Patent 8,058,069 B2

Before CHRISTOPHER G. PAULRAJ, JACQUELINE T. HARLOW and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

HARLOW, *Administrative Patent Judge*.

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

I. INTRODUCTION

Petitioner, Moderna Therapeutics, Inc., filed a Petition (Paper 1, "Pet."), requesting *inter partes* review of claims 1–22 of U.S. Patent No. 8,058,069 B2 (Ex. 1001, "the '069 patent"). Patent Owner, Arbutus Biopharma Corporation, timely filed a Preliminary Response (Paper 7, "Prelim. Resp.").

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." For the reasons stated below, we determine that there is a reasonable likelihood that Petitioner would prevail with respect to at least one challenged claim. We hereby institute *inter partes* review of the challenged claims on all the grounds of unpatentability asserted in the Petition.

A. Related Matters

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.

[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.

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, (63).

B. The '069 Patent

The '069 patent relates to "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. 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 stable nucleic acid-lipid particles (SNALP) that advantageously impart increased activity of the encapsulated nucleic acid (e.g., an interfering 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, 5:61–6:3. 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 68:39–44. 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).

C. 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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