UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BRAYDON CHARLES GUILD, FRANK DEROSA, and MICHAEL HEARTLEIN

Appeal 2016-008388
Application 13/800,501
Technology Center 1600

Before RICHARD J. SMITH, RACHEL H. TOWNSEND, and DAVID COTTA, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of delivery of messenger RNA for *in vivo* production of protein, which have been rejected as anticipated and/or obvious.[1] We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

STATEMENT OF THE CASE

Individuals suffering from diseases that result from protein and/or enzyme deficiencies "may have underlying genetic defects that lead to the

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[1] Appellant is the Applicant Shire Human Genetic Therapies, Inc., which according to the Appeal Brief, is the real party in interest. (Appeal Br. 2.)

compromised expression of a protein or enzyme, including, for example, the non-synthesis of the protein, the reduced synthesis of the protein, or synthesis of a protein lacking or having diminished biological activity." (Spec. ¶ 8.) "Novel therapies that increase the level or production of an affected protein or enzyme in target cells, such as hepatocytes, or that modulate the expression of nucleic acids encoding the affected protein or enzyme could provide a treatment or even a cure for metabolic disorders." (Spec. ¶ 6.) The claims at issue concern methods of intracellular delivery of nucleic acids that can be translated into a gene product of interest following successful delivery to target tissue. (Spec. ¶ 7.)

Claims 1, 3, 4, 7, 10–14, 16, 18–28, and 30–38 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method of delivery of messenger RNA (mRNA) for *in vivo* production of protein, comprising
>
> administering systemically to a subject in need of delivery a composition comprising an mRNA encoding a protein, encapsulated within a liposome such that the administering of the composition results in the prolonged stable expression of the protein encoded by the mRNA in the liver;
>
> wherein the protein encoded by the mRNA is an enzyme, a hormone, a receptor or an antibody; and
>
> wherein the liposome comprises one or more cationic lipids, one or more non-cationic lipids, one or more cholesterol-based lipids and one or more PEG-modified lipids and has a size less than about 100 nm.

(Appeal Br. 32.)

The following grounds of rejection by the Examiner are before us on review:

Claims 1, 3, 4, 7, 14, 22, 31–34, and 37 under 35 U.S.C. § 102(b) as anticipated by MacLachlan.[2]

Claims 1, 3, 4, 7, 10-12, 14, 16, 18–28, and 30–38 under 35 U.S.C. § 103(a) as unpatentable over MacLachlan, Ye[3] and Okumura.[4]

Claims 1, 3, 4, 7, 10-14, 16, 18–28, and 30–38 under 35 U.S.C. § 103(a) as unpatentable over MacLachlan, Ye, Okumura, and Kariko.[5]

DISCUSSION

Anticipation

According to the Examiner, MacLachlan teaches a method of delivering protein-encoding messenger RNA (mRNA) encapsulated within liposomes of the type recited in claim 1 via intravenous administration. (Final Action 3.) The Examiner recognizes that "the preferred embodiment in MacLachlan [] is using SNALPs[6] to deliver siRNA[7] to silence genes of

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[2] MacLachlan et al., US 2006/0008910 Al, published Jan. 12, 2006
[3] Ye et al. "Prolonged Metabolic Correction in Adult Ornithine Transcarbamylase-deficient Mice with Adenoviral Vectors," 271 *J. Biol. Chem.*, 3639–3646 (1996).
[4] Okumura et al., "Bax mRNA therapy using cationic liposomes for human malignant melanoma," 10 *J. Gene Med.*, 910–917 (2008).
[5] Kariko et al., "Incorporation of Pseudouridine into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability," 16 (10) *Mol. Ther.* 1833–1840 (2008).
[6] SNALP is the acronym for "stabilized nucleic acid-lipid particles." (MacLachlan ¶¶ 10, 57.)
[7] siRNA is the acronym used in MacLachlan for "small-interfering RNA." (MacLachlan ¶ 77.) MacLachlan defines "interfering RNA," also called

interest." (Ans. 6.) But the Examiner contends that MacLachlan also teaches protein-encoding mRNA delivery with SNALP for protein expression in vivo because (a) it indicates SNALPs "are suitable for the delivery of nucleic acids ([0057]; [0084])," (b) it "define[s] that the term 'nucleic acid' is used interchangeably with gene, cDNA, mRNA, and an interfering RNA ([0073])," and (c)

> in [0142] and [0148] MacLachlan et al. specifically teach gene **(and not** siRNA) delivery as follows:
>
> > "Anti-angiogenic genes are able to inhibit neovascularization. These genes are particularly useful to treat cancers in which angiogenesis play a role in the pathological development of the disease". [0142]
> >
> > "Tumor suppressor genes are genes that are able to inhibit the growth of a cell, particularly tumor cells. Thus, **delivery of these genes** to tumor cells is useful in the treatment of cancer." [0148]
>
> [And as] clearly taught by MacLachlan et al. and as commonly known in the prior art, inhibition of neovascularization and of tumor cell growth requires the activity of the antiangiogenic and tumor suppressor polypeptides/proteins, not their silencing. Thus, MacLachlan et al. teach using SNALPs for the in vivo delivery of genes encoding therapeutic polypeptides/proteins.

(Ans. 6–8; *see also* Final Action 3, 7.) The Examiner thus concludes that "MacLachlan et al. is an anticipatory reference with respect to using SNALP technology to deliver mRNA for protein/enzyme production *in vivo*." (Ans. 8 (emphasis omitted).)

RNAi, as "double-stranded RNA that results in the degradation of specific mRNAs and can be used to interfere with translation from a desired mRNA target transcript." (*Id.*) MacLachlan further explains the siRNA is short RNAi that is "about 15-30 nucleotides in length." (*Id.*)

We disagree with the Examiner's factual finding that MacLachlan discloses encapsulating protein encoding mRNA in liposomes or systemically administering such liposomes for in vivo delivery of genes encoding therapeutic proteins.

As Appellant points out (Appeal Br. 7–10; Reply Br. 3–8), MacLachlan's disclosure regarding the use of SNALP technology is solely directed to delivery of interfering RNA, notwithstanding that it broadly defines (a) the term "nucleic acid" to be interchangeably used with cDNA, mRNA encoded by a gene, and an interfering RNA molecule (MacLachlan ¶ 73), and (b) the term "gene" as referring "to a nucleic acid (e.g., DNA or RNA) sequence that comprises partial length or entire length coding sequences necessary for the production of a polypeptide or precursor. . . "(*id.* ¶ 75).

In the "Field of the Invention," MacLachlan states that "[t]he present invention relates to" therapeutic delivery of encapsulated nucleic acid "to provide efficient RNA interference." (*Id.* ¶ 2.) MacLachlan then explains that RNAi is a "sequence specific mechanism triggered by double stranded RNA(dsRNA) that induces degradation of complementary target single stranded mRNA and 'silencing' of the corresponding translated sequences." (*Id.* ¶ 3.) In MacLachlan's "Brief Summary of the Invention" it is stated:

> The present invention comprises novel, stable nucleic acid-lipid particles (SNALP) encapsulating one or more interfering RNA molecules, methods of making the SNALPs and methods of deliver[in]g and/or administering the SNALPs.

(*Id.* ¶ 12.) In the "Detailed Description of the Invention," MacLachlan states:

> The present invention demonstrates the unexpected success of *encapsulating short interfering RNA* (siRNA) molecules in

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