The opinion in support of the decision being entered today was not written
for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte FRANCIS J. MARTIN and SAMUEL ZALIPSKY

Appeal No. 2004-2202
Application No. 10/016,324

ON BRIEF

Before SCHEINER, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 29-59, all of the claims remaining. Claim 29 is representative and reads as follows:

29. A method of administering a therapeutic agent, comprising, administering via inhalation liposomes formed of vesicle-forming lipids and having a coating of hydrophilic polymer chains on the liposome outer surface, said liposomes having an entrapped therapeutic agent.

The examiner relies on the following references:

DeFrees et al. (DeFrees)	5,604,207	Feb. 18, 1997
Chestnut et al. (Chestnut)	5,800,815	Sep. 01, 1998
Marshall et al. (Marshall)	5,939,401	Aug. 17, 1999

Mihalko et al. (Mihalko) WO 86/06959 Dec. 04, 1986

Klibanov et al. (Klibanov) "Long-circulating Liposomes : Development and Perspectives," Journal of Liposome Research, Vol. 2, No. 3 pp. 321-324 (1992)

Gao et al . (Gao) "A Novel Cationic Liposome Reagent For efficient Transfection of Mammalian Cells," Biochemical and Biophysical Research Communications," Vol. 179, No. 1 pp. 280-285 (1991)

Claims 29-31, 33-37, and 39-45 stand rejected under 35 U.S.C. § 102(e) as anticipated by Marshall.

Claims 29, 30, 34-37, 39-41, 44-49, and 55 stand rejected under 35 U.S.C. § 103 as obvious in view of Mihalko and Klibanov.

Claims 29-31, 33-37, and 39-45 stand rejected under 35 U.S.C. § 103 as obvious in view of Marshall, either alone or combined with Mihalko.

Claims 31-33 stand rejected under 35 U.S.C. § 103 as obvious in view of Marshall, either alone or combined with Mihalko, and further in view of Gao.

Claims 49-57 stand rejected under 35 U.S.C. § 103 as obvious in view of Mihalko, Klibanov, Chestnut, DeFrees, and "applicant's statements of prior art."

We reverse all of the rejections.[1]

Background

The specification discloses "a fusogenic liposome composition for fusion with a target membrane," such as the plasma membrane of a cell. Page 9. "The composition includes liposomes . . . composed of vesicle-forming lipids. . . . The liposome has an

[1] None of the rejections set out in the Examiner's Answer includes claims 38, 58, or 59, even though the examiner has stated that all of claims 29-59 have been rejected. See, e.g., the Office action mailed March 27, 2003. The status of claims 38, 58, and 59 is therefore unclear. Since we are reversing all of the rejections on appeal, however, it makes no difference whether claims 38, 58, and 59 were inadvertently omitted from one or more of the rejections.

outer surface coating of hydrophilic polymer chains, . . . which are preferably densely packed to form a brushlike coating effective to shield liposome surface components." Pages 9-10 (reference numerals omitted).

> In addition to their role in "solubilizing" the hydrophobic chains, and shielding them from interactions with other bilayer membranes, the hydrophilic chains also preferably have a surface density sufficient to create a molecular barrier effective to substantially prevent interaction of serum proteins with the liposome surface. As such, the hydrophilic chain coating is effective to extend the circulation time of liposomes in the bloodstream for periods up to several hours to several days.
>
> In the latter embodiment, the hydrophilic chains are preferably present in the outer lipid layer of the liposomes in an amount corresponding to between about 1-20 mole percent of the liposome surface lipids.

Page 11.

"Suitable hydrophilic polymers for use in the conjugates, where the polymers are also intended to extend liposome-circulation time, include polyvinylpyrrolidone, . . . polyethyleneglycol, and polyaspartamide. In a preferred embodiment, the hydrophilic polymer is polyethyleneglycol." Page 16

"Finally, the liposome is prepared to contain one or more therapeutic or diagnostic[ ] agents which are to be delivered to the target cell site. . . . The agent may be entrapped in the inner aqueous compartment of the liposome or in the lipid bilayer, depending on the nature of the agent." Page 13.

Discussion

Claim 29, the broadest claim on appeal, is directed to a method of administering a therapeutic agent by inhalation, where the therapeutic agent is entrapped in liposomes "formed of vesicle-forming lipids and having a coating of hydrophilic polymer

chains on the liposome outer surface." The examiner rejected the claims as anticipated by and obvious over the prior art.

1. Anticipation

The examiner rejected claims 29-31, 33-37, and 39-45 as anticipated by Marshall. The examiner characterizes Marshall as "disclos[ing] liposome formulations containing a cationic amphiphile, DOPE and PEG (5000)-DMPE for the administration of therapeutic molecules by inhalation . . . (note the abstract, col. 34, line 27 et seq., column 54, line 31 et. Seq.)." Examiner's Answer, page 3.

Appellants argue that Marshall does not anticipate the instant claims because it "fails to show at least three of the following presently claimed elements: (1) a liposome; (2) a liposome having a coating of hydrophilic polymer chains; and (3) a liposome having an entrapped therapeutic agent." Appeal Brief, page 3. Appellants argue that Marshall does not teach the claimed composition because, among other things, it "describe[s] preparing a dispersion of a cationic amphiphile; contacting the dispersion with a biologically active molecule to form a complex [not a liposome] between said amphiphile and said molecule." Id., page 4.

The examiner bears the burden of showing that a claimed invention is anticipated by the prior art. See In re Wilder, 429 F.2d 447, 450, 166 USPQ 545, 548 (CCPA 1970) ("[I]n an ex parte proceeding to obtain a patent . . . the Patent Office has the initial burden of coming forward with some sort of evidence tending to disprove novelty."). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In this case, although Marshall's disclosure is not without ambiguity, we agree with Appellants that the reference has not been shown to anticipate the claims. Marshall teaches cationic amphiphiles comprising a lipophilic group (preferably a steroid, see column 22, lines 12-15) attached to a cationic group. Marshall teaches that "co-lipids that are useful . . . for mixing with one or more cationic amphiphiles include dioleoylphosphatidylethanolamine ('DOPE')". Column 32, lines 28-30. Marshall also teaches that polyethylene glycol 5000-dimyristoylphosphatidyl ethanolamine ($PEG_{(5000)}$-DMPE) "is believed to stabilize the therapeutric [sic] compositions by preventing further aggrregation [sic] of formed amphiphile/DNA complexes." Column 53, lines 46-49. Thus, Marshall appears to teach a composition comprising vesicle-forming lipids (e.g., DOPE), hydrophilic polymer chains (e.g., $PEG_{(5000)}$), and a therapeutic agent (e.g., DNA).

However, we agree with Appellants that Marshall does not anticipate because it does not teach liposomes having the therapeutic agent entrapped within them. Marshall teaches that the

> [p]harmaceutical compositions of the invention facilitate entry of biologically active molecules into tissues and organs. . . . The amphiphilic nature of the compounds of the invention enables them to associate with the lipids of cell membranes, other cell surface molecules, and tissue surfaces, and to fuse or to attach thereto. One type of structure that can be formed by amphiphiles is the liposome, a vesicle formed into a more or less spherical bilayer. . . . However, unlike the case for many classes of amphiphiles or other lipid-like molecules that have been proposed for use in therapeutic compositions, the cationic amphiphiles of the invention need not form highly organized vesicles in order to be effective, and in fact can assume (with the biologically active molecules to which they bind) a wide variety of loosely organized structures.

Column 33, lines 25-47.

This passage is evidence that the compositions disclosed by Marshall do not contain a therapeutic agent entrapped in lipid vesicles. Further evidence that Marshall's therapeutic DNA is not contained within liposomes is provided by the working examples: in each case, the cationic amphiphile is mixed with lipid(s) and solvent, the solvent is evaporated to form a thin film, and the film is then hydrated with an aqueous medium. Only then is the DNA added to allow formation of a "complex". See Example 1 (columns 44-45):

> [S]permidine cholesterol carbamate (amphiphile No. 35) and the neutral lipid [DOPE] were each dissolved in chloroform as stock preparations. Following combination of the solutions, a thin film was produced by removing chloroform from the mixture by evaporation. . . .
>
> To produce a dispersed suspension, the lipid film was then hydrated with sterile deionized water (1 ml) for 10 minutes, and then vortexed for 1 minute. . . . The resulting suspension was then diluted with 4 ml of water. . . .
>
> The following procedure was used to test a 1:1 molar mixture of the cationic amphiphile spermidine cholesterol carbamate in combination with DOPE. A 165 µl aliquot of spermidine cholesterol carbamate (670 µ M) containing also the colipid (at 670 µ M) was pipetted into 8 separate wells [and serially diluted to yield 64 solutions]. . . .
>
> Independently, DNA solutions (165 µl, 960 µM) were pipetted into 8 wells [and serially diluted to yield 64 solutions]. . . .
>
> The 64 test solutions(cationic amphiphile:neutral lipid) were then combined with the 64 DNA solutions to give separate mixtures in 64 wells. . . . The solutions of DNA and amphiphile were allowed to stand for 15 to 30 minutes in order to allow complex formation.

The same procedure was followed in the example (Example 6) cited by the examiner. See column 53:

> Following generally the procedures described in Example 1, a thin film (evaporated from chloroform) is produced . . . . The amphiphile-containing film is rehydrated in water-for-injection with gentle vortexing. . . .

> Without being limited as to theory, $PEG_{(5000)}$-DMPE is believed to stabilize the therapeutic [sic] compositions by preventing further aggrregation [sic] of formed amphiphile/DNA complexes. . . .
>
> pCF1-CFTR plasmid . . . is provided in water-for-injection. . . . Complexing of the plasmid and amphiphile is then allowed to proceed by gentle contacting of the two solutions for a period of 10 minutes.

Thus, Marshall does not provide any examples in which the therapeutic DNA is included in the aqueous medium used to rehydrate the lipid-containing film (thus forming liposomes, if any liposomes indeed form), nor does Marshall characterize any of the disclosed compositions as comprising liposomes with entrapped DNA. Both the methods disclosed by Marshall and Marshall's characterization of the resulting product support Appellants' position that the DNA in the compositions is associated with the surface of the cationic amphiphile/colipid structures (as a "complex") rather than being entrapped in structures that would be classified as liposomes.

Since Marshall does not disclose all of the limitations of the claims, it does not anticipate. The rejection under 35 U.S.C. § 102(e) is reversed.

2. Obviousness

The examiner rejected claim 29, among others, as obvious in view of Marshall, alone or combined with Mihalko. The examiner argues that it would have been obvious to administer the composition disclosed by Marshall via inhalation, because Marshall suggests that route of administration (column 34, lines 20-30) and because Mihalko "shows that this route [is] a successful mode of administration of liposomes." Examiner's Answer, page 6.

We will reverse this rejection. Marshall, as we have just discussed, does not disclose compositions comprising a therapeutic agent entrapped within liposomes.

Thus, even assuming the references would have suggested administering Marshall's composition by inhalation, the method made obvious by the prior art would not be the method of claim 29.

Mihalko discloses a method of administering a liposome-entrapped drug by inhalation. See page 4, lines 21-26 ("[A] method for moderating the initial (short-term) and extended (long-term) drug-level effects of a drug administered by inhalation. The drug is provided in a form in which it is predomi[n]antly entrapped in the liposomes of a liposome suspension."). However, the examiner has pointed to nothing in Mihalko that would have suggested the claim limitation requiring a "coating of hydrophilic polymer chains on the liposome outer surface," nor anything that would have suggested combining one of the components of Marshall's composition (e.g., $PEG_{(5000)}$-DMPE) with Mihalko's liposomes. Thus, the examiner has not shown that Marshall supports a prima facie case of obviousness, either alone or combined with Mihalko.

The examiner also rejected claim 29, among others, as obvious in view of Mihalko and Klibanov. The examiner correctly noted that Mihalko teaches compositions containing liposome-encapsulated drugs but does not teach "coating of the liposomal surface with a hydrophilic polymer." Examiner's Answer, page 5. The examiner relied on Klibanov for suggesting this limitation. See id.: "Klibanov teaches that when the liposomal surface is coated with a hydrophilic layer of oligosaccharides, glycoproteins, polysaccharides and synthetic polymers such as PEG, the liposomes avoid the RES [reticuloendothelial system] and circulate in the blood for longer periods."

The examiner concluded that to "coat the liposomes of [Mihalko] with a hydrophilic polymer would have been obvious to one of ordinary skill in the art because

such a coating would enable the liposomes to circulate longer and reach the target tissue as taught by Klibanov." Id.

Appellants argue that

> it is clear from the teaching of Klibanov et al. that the purpose of providing a coating of hydrophilic polymer chains on a liposome is to extend the blood circulation lifetime of the liposomes. That is, the hydrophilic polymer shields the liposomes from recognition and uptake by the reticuloendothelial system (RES) (page 324, lines 19-22). However, the liposomes of Mihalko et al. are administered by inhalation to the lung (page 4, lines 16-19 and 24-27). . . .
>
> . . . [T]he liposomes of Mihalko et al. are administered by inhalation to the lung. The drug is released from the liposomes into the pulmonary region of the respiratory tract by efflux from the liposome (page 25, lines 9-13) and only the drug enters the blood for circulation (page 25, lines 17-22). As the purpose of the liposome with a hydrophilic polymer coating is to protect the liposome from the RES for longer circulation, one would not be motivated to modify the liposomes of Mihalko et al. as the liposomes do not circulate.

Appeal Brief, page 7.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. " In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). "[T]o establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000).

We agree with Appellants that the examiner has not adequately explained what would have led those skilled in the art to combine the references, since Mihalko is directed to administration of liposomes by inhalation and Klibanov is directed to

lengthening the time of liposome circulation in the bloodstream. The skilled artisan would have been aware that liposomes function by fusing with the membranes of a target cell, thereby delivering the contents of the liposome to the cytoplasm of the cell and adding the lipophilic component of the liposome to the lipid bilayer of the membrane. See, e.g., Marshall, column 33, lines 33-41 ("One type of structure that can be formed by amphiphiles is the liposome, a vesicle formed into a more or less spherical bilayer, that is stable in biological fluids and can entrap biological molecules targeted for intracellular delivery. By fusing with cell membranes, such liposomal compositions permit biologically active molecules carried therewith to gain access to the interior of a cell through one or more cell processes including endocytosis and pinocytosis.").

Those skilled in the art would also have recognized that breathing is not simply a process of air being breathed in and taken up directly by red blood cells. Rather, oxygen must diffuse across the "blood-gas barrier" before it can be taken up by red blood cells. The same would be expected for any other agent administered by inhalation – it would have to traverse the various cell membranes that make up the blood-gas barrier in order to enter the circulatory system.

Thus, those skilled in the art would expect that the liposomes administered by inhalation by Mihalko would deliver the entrapped therapeutic agent by fusing with the membranes of the cells lining the lung, and therefore, that only the entrapped drug would be taken up by the cell and passed through to the systemic circulation. Mihalko provides evidence that those skilled in the art would have expected the lipid bilayer of the liposome to remain associated with the lipid bilayer of the lung cells. See page 31,

lines 7-13: "Lipid soluble drugs, which are contained predominantly in the lipid bilayer region of liposomes, gradually become associated with endogenous lung lipids . . ., and in this form, the drugs can traverse the blood-gas barrier to enter the pulmonary circulation."

Therefore, those skilled in the art would have expected that, when a liposome-encapsulated drug is administered by inhalation, any drug that enters the bloodstream would be in the form of free drug, as opposed to liposome-encapsulated drug. For this reason, we agree with Appellants that those skilled in the art would not have been motivated to combine Klibanov's polymer-coating of liposomes with Mihalko's method of administering liposomes by inhalation in order to gain the advantage of long circulation times taught by Klibanov. Those skilled in the art would have expected that the composition of the liposomes would have no effect on the length of systemic circulation because the liposomes themselves would not be expected to enter the bloodstream.

We therefore agree with Appellants that Mihalko and Klibanov do not support a prima facie case of obviousness. The rejection based on those references is reversed.

The examiner also rejected dependent claims 31-33 as obvious in view of Marshall, alone or combined with Mihalko, and further combined with Gao, and rejected dependent claims 49-57 as obvious in view of Mihalko, Klibanov, two secondary references, and "applicant's statements of prior art." Our analysis with respect to the rejections of claim 29 apply to these rejections as well, since the additional references do not make up for the deficiencies (discussed above) of Marshall, Mihalko, and Klibanov.

Other Issues

Appellants filed an Information Disclosure Statement on January 25, 2005. Upon return of this application, the examiner should treat the IDS as appropriate under 37 CFR § 1.97.

Summary

The examiner has not shown that the claimed invention is anticipated or rendered obvious by the cited references. The rejections under 35 U.S.C. §§ 102(e) and 103 are reversed.

REVERSED

Toni R. Scheiner	)
Administrative Patent Judge	)
	)
	)
	) BOARD OF PATENT
Eric Grimes	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
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