

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 49

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte LINGNA LI and VALERYI LISHKO

Appeal No. 2003-1020
Application No. 08/859,051¹

HEARD: October 9, 2003

Before WINTERS, LORIN and SCHEINER, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 116-127, all of the claims remaining in the application.

Claims 116 and 122 are representative:

116. A method for treating androgenic alopecia in a subject which method comprises
applying to the skin of said subject, wherein said skin contains hair follicles, a formulation of liposomes, which liposomes have incorporated therein at least one active ingredient selected from the group consisting of
(a) an antisense nucleic acid molecule;
(b) an expression system therefor that hybridizes to an androgen receptor gene so as to inhibit androgen receptor expression; and
(c) an antiandrogen and
wherein said formulation is free of active ingredient not encapsulated in said liposomes and

¹ Application for patent filed May 20, 1997. According to appellants, this application is a divisional of application serial no. 08/486,520, filed June 7, 1995, now U.S. Patent 5,753,263, and a continuation-in-part of application serial no. 08/181,471, filed January 13, 1994, now U.S. Patent 5,641,508.

wherein said formulation delivers said active ingredient directly and selectively specifically to the cells of the hair follicle and to the hair shaft itself and does not deliver said active ingredient generally to the dermis or circulation.

122. A formulation of liposomes containing at least one active ingredient that is effective in treating androgenic alopecia selected from the group consisting of
(a) an antisense nucleic acid molecule;
(b) an expression system therefor that hybridizes to an androgen receptor gene so as to inhibit androgen receptor expression; and
(c) an antiandrogen and
said active ingredient encapsulated in said liposomes and said formulation free of unencapsulated active ingredient.

The references relied on by the examiner are:

Bonte et al. (Bonte)	5,384,126	Jan. 24, 1995
Roy et al. (Roy)	5,556,956	Sep. 17, 1996
Rössling et al. (Rössling)	5,723,146	Mar. 3, 1998

Mezei et al. (Mezei), "Liposomes - A Selective Drug Delivery System for the Topical Route of Administration, Life Science, Vol. 26, pp. 1473-1477 (1980)

Juliano et al. (Juliano), "Liposomes as a Drug Delivery System for Antisense Oligonucleotides," Antisense Research and Development, Vol. 2, pp. 165-176 (1992)

du Plessis et al. (du Plessis), "Topical Delivery of Liposomally Encapsulated Gamma-Interferon," Antiviral Research, Vol. 18, pp. 259-265 (1992)

Claims 116-127 stand rejected under 35 U.S.C. § 103 as unpatentable over Bonte, Rössling, du Plessis and Mezei; the claims also stand rejected as unpatentable over Bonte, Rössling, du Plessis, Mezei, Roy and Juliano.

We reverse both of these rejections.

DISCUSSION

The examiner has rejected claims 116-127 as obvious over the combined teachings of Bonte, Rössling, du Plessis and Mezei, and also over the combined teachings of Bonte, Rössling, du Plessis, Mezei, Roy and Juliano. As the examiner's proposed combination of Bonte, Rössling, du Plessis and Mezei is central to both rejections, we will discuss the two rejections together; as Roy and Juliano are directed

to limitations not required by any of the claims, we need not discuss those references further.

Bonte describes a method of promoting hair growth by topical application of labdane derivatives or plant extracts containing labdanes. According to the reference, “activity, which remains weak for certain of these compounds, may be very considerably potentialized by their incorporation in . . . liposomes” (column 2, lines 37-42). The examiner does not assert that the labdanes are antiandrogens, but does note that Bonte mentions a “generic ‘alpha-reductase inhibitor’ . . . deemed to include [the] instant inhibitor” (Answer, page 4). In this regard, we note Bonte’s disclosure from column 6, line 59 to column 7, line 8:

According to a variant embodiment, a cosmetic or pharmaceutical, particularly dermatological composition . . . comprises in addition [to labdane] at least one other active substance, . . . selected from xanthines, vitamins, particularly vitamin B’s, tyrosine or its derivatives, . . . quinine or its derivatives, rubefaciants . . . , a supernatant of culture of fibroblasts of papillae, . . . keratin hydrolysates, oligo-elements such as zinc, selenium, copper, 5- α -reductase inhibitors such as: progesterone, cyproterone acetate, Minoxidil, azaleic acid and its derivatives . . . said active substance possibly being incorporated at least in part in [] hydrated lipidic lamellar phases, notably liposomes.

Rössling describes a method of topically treating androgen-dependent alopecia with liposome-encapsulated active agents, including anti-androgenic 5- α -reductase inhibitors. According to Rössling (column 1, lines 41-58):

[A] therapeutically sufficient and uniform rate of penetration of antiandrogenic active ingredients through the skin [] is achieved if the ingredients are encapsulated in liposomes. Thus, it is possible to provide topically applicable preparations, which show their action basically on the peripheral androgen receptors in the area of application. As a result, systemic side effects are avoided or minimized. Since the active ingredient is concentrated in the liposomes, it is possible to use small amounts of the active ingredient and still achieve a high active ingredient amount concentration at the site of action . . . it is believed that much higher concentrations of antiandrogen can be achieved in the corium and connective tissue of the skin using the pharmaceutical preparations . . .

Mezei describes the relative activities of two different preparations of triamcinolone: 0.1% triamcinolone in “ointment dosage form,” and a liposomal preparation of 0.1% triamcinolone free of unencapsulated triamcinolone. According to Mezei, “liposomal encapsulation favorably altered [triamcinolone] deposition; the greatest changes occurred in the target tissue, and at the sites where toxic actions are localized.” “[P]ercutaneous absorption was greatly reduced, while at the same time, the concentration of the drug was significantly increased at the site (i.e., epidermis and dermis), where its activity is desired” (page 1474). Thus, “the presently accepted therapeutic concentration can be achieved by a four-fold reduction in the dose . . . [which] would lead to . . . an additional decrease in unwanted systemic effects” (pages 1475-1476).

du Plessis teaches that “the deposition of [a topically administered liposome-encapsulated] drug into the living epidermis and/or dermis cannot be predicted by determination of the amount of drug in the total skin” as “[t]he amounts in the deeper skin strata were also in the order of increasing number of follicles/hair in the skin species, suggesting that the transfollicular route is an important pathway for liposomal topical therapeutics” (Abstract, page 259). That is, “liposomal drug transport into strata below and beyond the stratum corneum may occur via a follicular route” (page 263).²

According to the examiner, “[i]t is unclear from . . . Bonte and Rössling whether the unencapsulated active agent was removed,” but “[o]ne skilled in the art would be motivated to remove the [un]encapsulated material if it is detrimental since [] Mezei teaches that [un]encapsulated material can be removed by chromatography” and “[o]ne

² The stratum corneum is the outer layer of the epidermis, consisting of several layers of flat keratinized non-nucleated cells. Stedman’s Medical Dictionary, Illustrated, 24th Edition, Williams & Wilkins, Baltimore/London, page 1347 (1982).

skilled in the art would reasonably expect the topically applied liposomal composition of Bonte and R[ö]ssling would enter the hair follicles from the teachings of [du] Plessis” (Answer, page 5).

Nevertheless, the examiner does not identify anything in Rössling or Bonte (or du Plessis) that would indicate that there is any disadvantage associated with liposomal preparations containing some unencapsulated agent. Indeed, Bonte specifically teaches that “it is not necessary that the whole of the active principle be incorporated or encapsulated in order to obtain the desired effect” (Bonte, column 7, lines 40-44). Mezei, like Bonte and Rössling, demonstrates that encapsulating an active agent in liposomes results in higher local potency and fewer systemic effects, but does not comment on the effect, if any, of removing all unencapsulated active agent from the liposomal preparation. In any case, claims 116-121, at least, require selective deposition “to the cells of the hair follicle and to the hair shaft itself” rather than “the dermis or the circulation,” but Mezei noted substantial deposition of liposomally-encapsulated triamcinolone in the dermis and epidermis. Finally, we cannot agree with the examiner’s interpretation of du Plessis - there is nothing in the reference to indicate that liposome-encapsulated active agent preferentially enters the hair follicles; rather, du Plessis seems to indicate that the “follicular route” or “follicular pathway” is an effective conduit for “drug transport into strata below and beyond the stratum corneum,” i.e., transport into dermal layers below the skin’s surface (page 263).

Clearly, the examiner has established that individual parts of the claimed invention were known in the prior art. However, as explained in In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (citations omitted):

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art

references and the then-accepted wisdom in the field. [] Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one “to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher.” []

Most if not all inventions arise from a combination of old elements However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. [] Rather, to 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.

“It is impermissible to use the claimed invention as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is rendered obvious.” In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992), citing In re Gorman, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). The examiner may establish a case of prima facie obviousness based on a combination of references “only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.” Id., 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

The fact that the prior art could have been modified in a manner consistent with appellants’ claims would not have made the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). On this record, the examiner has not identified a reason or suggestion, stemming from the prior art, to combine the references in the manner claimed. Accordingly, we reverse the rejections of claims 116-127 under 35

U.S.C. § 103.³

OTHER ISSUES

Upon return of this case to the examining group, we would recommend that appellants and the examiner review claims 116 and 122 for clarity. It appears that appellants' argument that "the claim[s] as [presently] worded [do] not make sense" is well founded.

REVERSED

Sherman D. Winters)
Administrative Patent Judge)
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) BOARD OF PATENT
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Hubert C. Lorin) APPEALS AND
Administrative Patent Judge)
) INTERFERENCES
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Toni R. Scheiner)
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³ Having found that the examiner has not established a prima facie case of obviousness for the claims on appeal, we find it unnecessary to comment on the declarations executed June 28, 2000 and May 13, 2002.

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