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Datasheet for the decision of 16 November 2010 and 20 December 2010

Case Number: T 1872/06 - 3.3.07

Application Number: 94913349.9

Publication Number: 0692972

IPC: A61K 7/00

Language of the proceedings: EN

Title of invention:
Method for delivering beneficial compositions to hair follicles

Applicant:
AntiCancer, Inc.

Headword:
-

Relevant legal provisions:
EPC R. 80
EPC Art. 123(3), 54, 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Rule 80 EPC - (no; main request)"
"Article 123(3) EPC - (yes; auxiliary request)"
"Article 54 EPC - (yes; auxiliary request)"
"Article 56 EPC - (yes, auxiliary request)"

Decisions cited:
-

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1872/06 - 3.3.07

D E C I S I O N
of the Technical Board of Appeal 3.3.07
of 16 November 2010 and
Correction Decision
of the Technical Board of Appeal 3.3.07
of 20 December 2010

Appellant: (Patent Proprietor)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 10 October 2006 revoking European patent No. 0692972 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: S. Perryman
Members: B. ter Laan
F. Rousseau

Summary of Facts and Submissions

1. The appeal by the patent proprietor lies against the decision by the opposition division, posted on 10 October 2006, revoking European patent No. 0 692 972 (application no. 94 913 394.0).

II. The patent was granted on the basis of fourteen claims, independent claim 1 reading:

"1. Use of a composition that comprises liposomes that have a cosmetically active ingredient incorporated therein, said composition being free of said cosmetically active ingredient in an unencapsulated form,
for delivery of said cosmetically active ingredient selectively to the hair follicles of a subject by applying said composition to the skin of said subject containing hair follicles to which said active ingredient is to be delivered, wherein said liposomes deliver said active ingredient selectively and directly into hair follicle cells by transfer into the follicle and do not deliver the active ingredient to the cells surrounding the hair follicles that are not hair follicle cells or to the systemic circulatory system."

Independent claim 12 read:
"12. Use of liposomes that have a medicament incorporated therein, in the manufacture of a medicament composition comprising said liposomes, where said composition is free of unencapsulated medicament, said composition being for use in a method for selectively delivering said medicament to hair follicles of a subject, which method comprises

applying said composition the skin of said subject containing hair follicles to which said medicament is to be delivered

wherein said liposomes deliver said medicament selectively and directly into hair follicle cells by transfer into the follicle and do not deliver the medicament to the cells surrounding the hair follicles that are not hair follicle cells or to the systemic circulatory system."

III. A notice of opposition against the patent was filed on 5 September 2002, in which the revocation of the patent in its entirety was requested on the grounds of Article 100(a) EPC (lack of novelty as well as lack of an inventive step) and Article 100(b) (lack of disclosure). The opposition was supported by

D1 Li L. et al., in Vitro Cellular and Developmental Biology, 28A, pages 679 to 681 (1992)
D2 Lieb L. et al., The Journal of Investigative Dermatology, 99(1), pages 108 to 113 (1992)
D3 DE-A-4 113 346
D4 W0-A-92/00057
D5 FR-A-2 648 132
D6 Pharmazie in unserer Zeit, 11(4), pages 97 to 108 (1982).

IV. By letter of 12 June 2003 the opposition was withdrawn, but the opposition division continued the proceedings of its own motion according to Rule 60(2) EPC 1973. The decision under appeal was based on a main and one auxiliary request, claim 1 of the main request differing from the one as granted in the addition of the word "topically" between "... applying said

composition" and "to the skin..."; in the auxiliary request "topically in vivo" was added. Both claims 12 of said requests were amended in the same way.

V. The opposition division held that

(a) The main request fulfilled the requirements of Article 83 EPC since there was sufficient guidance on how to implement the invention.

(b) Novelty was accepted for both the main as well as the auxiliary request since D1 did not refer to a cosmetic active and described only in vitro use of the composition. D3 to D5 did not disclose exclusive delivery to the hair follicle and the compositions of D2 were not free of non-entrapped active material.

(c) However, the claimed use was not inventive since D1, which was considered to be the closest prior art document, described that liposomes in an in vitro system delivered active agents selectively to the hair follicle. With that knowledge, the skilled person would introduce any active substance, e.g. those disclosed in D3 to D5, that could be incorporated into liposomes. The introduction of the terms "topical" or "topically in vivo" could not change that view.

VI. On 14 December 2006 the patent proprietors (appellants) lodged an appeal against the above decision. The prescribed fee was paid on the same day. The statement setting out the grounds of appeal was filed on 16 February 2007, together with a main and an auxiliary

request, as well as a declaration by Prof. Sheldon Penman. In response to a communication by the Board in preparation of the oral proceedings, the appellants filed further arguments by letters dated 6 and 18 October 2010, together with a new main and two auxiliary requests and the curriculum vitae of Prof. Dr. Robert M. Hoffman, an expert who was to be present to assist on technical questions at the oral proceedings.

VII. Oral proceedings before the Board were held on 16 November 2010, during which the appellants filed a new main request and one auxiliary request, replacing all other previous requests. Claim 1 of both the main and auxiliary request as actually submitted at the oral proceedings, read:

"1. Use of a liposome composition in the manufacture of a medicament wherein the liposome composition comprises liposomes in which a therapeutic compound is encapsulated and wherein said composition is free of unencapsulated therapeutic compound;

said medicament being for use in a method for selectively delivering said therapeutic compound to hair follicles of a mammal, which method comprises applying said composition topically *in vivo* to the skin of said mammal containing hair follicles to which said therapeutic compound is to be delivered

wherein said liposomes deliver said therapeutic compound selectively and directly into hair follicle cells by transfer into the follicle and do not deliver the therapeutic compound to the cells surrounding the hair follicles that are not hair follicle cells or to the systemic circulatory system."

The main request also contains new dependent claims 2 to 12 as well as claims 13 and 14 which are modified versions of claims 13 and 14 as granted and read:

"13. Use according to claim 1 wherein said therapeutic compound comprises an antisense nucleic acid molecule or an expression system therefor that hybridizes to an androgen receptor gene so as to inhibit androgen receptor expression, or is an antiandrogen."

"14. Use according to claim 1 wherein the liposomes are comprised of phosphatidylcholine (PC), phosphatidylethanolamine (PE) and cholesterol, or wherein the liposomes are formed from egg phosphatidylcholine (EPC) or from dipalmitoyl phosphatidylcholine (OPPC) or mixtures thereof.

Claim 1 of the auxiliary request read:

"1. Use of a liposome composition which comprises liposomes in which a therapeutic compound is encapsulated and wherein said composition is free of unencapsulated therapeutic compound

in a method for selectively delivering said therapeutic compound to hair follicles of a mammal, by applying said composition topically *in vivo* to the skin of said mammal containing hair follicles to which said therapeutic compound is to be delivered

wherein said liposomes deliver said therapeutic compound selectively and directly into hair follicle cells by transfer into the follicle and do not deliver the therapeutic compound to the cells surrounding the

hair follicles that are not hair follicle cells or to the systemic circulatory system."

The auxiliary request further contains claims 2 and 3 which are identical to claims 13 and 14 of the main request.

VIII. A corrected version of claim 1 of the allowed auxiliary request was submitted by the appellants with letter of 23 November 2010, undoing various deletions compared to the claim 12 as granted which had appeared in the text of claim 1 of the auxiliary as filed at the oral proceedings, so that claim 1 read:

"1. Use of a liposome composition in the manufacture of a medicament

wherein the liposome composition comprises liposomes in which a therapeutic compound is encapsulated and wherein said composition is free of unencapsulated therapeutic compound;

said medicament being for use in a method for selectively delivering said therapeutic compound to hair follicles of a mammal, by applying said composition topically *in vivo* to the skin of said mammal containing hair follicles to which said therapeutic compound is to be delivered

wherein said liposomes deliver said therapeutic compound selectively and directly into hair follicle cells by transfer into the follicle and do not deliver the therapeutic compound to the cells surrounding the hair follicles that are not hair follicle cells or to the systemic circulatory system."

IX. The appellants' arguments can be summarised as follows:

(a) The problem solved by the patent in suit was to deliver medicaments selectively, i.e. specifically and only to the hair follicle. To that end, the active substance needed to be entrapped in liposomes, in order to prevent the active substance from ending up in undesired places by e.g. entering the systemic circulatory system. That was especially important when medicaments were involved that might have undesirable effects on other body parts than hair follicles. But even if the medicaments were harmless, it was necessary to know where they went when applied to the body.

(b) D1 addressed the problem of how to get active substances actually into the hair follicle and it described a model for that. The model involved a piece of skin mounted on a sponge immersed in a medium containing the entrapped active substance and from which the unentrapped active substance had been removed. The same model was used in the patent in suit for the same purpose. That model however did not entail topical application and D1 did not teach that the effect of topical application was improved when the unentrapped material was separated.

In D1 a portion of skin below the dermis was immersed, and the experiment provided no guidance as to whether an *in vivo* application to the surface of the skin would achieve the same effect.

There were a number of possibilities to administer medical substances, such as by injection or orally. In D6 several methods were described, but topical application was not mentioned. It was therefore not obvious to apply the composition topically.

(c) D5 did not disclose the application of medical substances and it did not describe any entrapment step such as sonication, so that it was doubtful if the word "encapsulation" used in D5 involved the entrapment as required by the present claims. Anyway, no removal of unencapsulated material was described, so that there existed the possibility that the active substance would go outside the hair follicles. Also, in D5 it had not been recognized that material entrapped in liposomes would specifically get to the hair follicles and be released there. Therefore, also a combination with D5 did not lead to the claimed subject-matter.

X. The appellants (patent proprietors) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or the auxiliary request submitted during the oral proceedings on 16 November 2010.

XI. At the end of the oral proceedings the debate was declared closed and the decision announced.

XII. By fax dated 23 November 2010, a revised version of the auxiliary request was filed containing changes bringing the independent claim back to the form substantially as granted, see point VIII above.

Reasons for the Decision

1. The appeal is admissible.

Main request

Amendments

2. According to Rule 80 EPC, any amendments to a granted patent should be occasioned by a ground for opposition. Therefore, an opposition is not an opportunity to add (further) dependent claims to the claims as granted if those are not intended or suitable to remove objections raised under any of the opposition grounds. Even though the opposition has been withdrawn, the subject of the current appeal is still a granted patent which cannot be treated as if it were still in the application stage. Therefore, Rule 80 EPC applies.

2.1 The main request contains 14 claims. Claims 1, 13 and 14 are amended versions of claims 12, 13 and 14 as granted. Claims 2 to 12 are dependent claims that have no counterpart in the granted claims but derive their basis from the patent specification. Those added dependent claims do not serve to avoid objections under any of the opposition grounds, nor have the appellants argued that they did. Therefore, the main request is not allowable in accordance with Rule 80 EPC.

Auxiliary request

Amendments

3. In the auxiliary request all newly added dependent claims of the main request have been deleted so that the objections under Rule 80 EPC have been overcome.

4. On consideration of the appellants' submissions of 23 November 2010, the Board agrees that the claim 1 it believed it was considering at the oral proceedings on 16 November 2010 is correctly reflected in the claim 1 submitted by the appellants on 23 November 2010, and not in the claim 1 of the auxiliary request actually attached to the minutes of the oral proceedings. The Board thus hereby decides to correct the minutes of the oral proceedings of 16 November 2010, in that the claim 1 of the auxiliary request is to read as submitted on 23 November 2010 and set out in point VIII above.

5. The amended claims do not differ from the ones as granted in a way that would contravene Article 123(2) EPC. In particular, the addition of "topically *in vivo*" finds its basis in original claims 30 and 45 as well as several passages in the original description (page 5, lines 16 to 19; page 7, lines 8 to 18; page 9, lines 6 to 18; page 36, lines 13 to 18; page 36, lines 26 to 33 and the whole of point 4, beginning on page 61). Whether the claims as granted comply with Article 123(2) EPC has not been a point of consideration by the Board as the objection had not been raised by the opponents. Therefore, the requirements of Article 123(2) EPC are considered to be met.

6. Claim 1 corresponds substantially to claim 12 as granted, but limited to the pharmaceutical composition being applied "topically *in vivo* to the skin of said

mammal", together with some minor tidying up of the language. The requirements of Article 123(3) EPC are thus met.

7. The opposition division had decided that the claims complied with Articles 83 and 54 EPC and the Board sees no reason to take a different point of view on the more restricted claims before it.

Inventive step

8. The patent in suit concerns *inter alia* a method for delivering therapeutic compounds to hair follicles. Such a method is known from D1, which the opposition division considered to be the closest prior art document.

9. D1 is a scientific article that mentions the need of finding a way in particular to treat alopecia in humans (page 679, left column, first paragraph). To that end, a model is described for establishing optimal liposomal compositions as well as conditions for optimal delivery of the liposomal content into target cells.

9.1 According to the model of D1, a three-dimensional histoculture is used for following fine details of product-delivering liposome interactions with hair-follicles at the cellular level. The model involves putting pieces of mouse skin on a collagen-gel sponge (D1, page 679, paragraph bridging the columns), as also described in the patent in suit, paragraphs [0038] to [0079]. Liposomes containing a dye are prepared and then separated from the non-entrapped dye (D1, right column, first full paragraph). The skin histocultures

are then incubated with the liposomes, but as to the incubation method D1 is silent. Instead, it refers to a previous article, two authors of which are the present inventors. Prof. Hoffmann, also one of the co-authors of that previous article, who was present at the oral proceedings, declared that the liposomes were added to the medium in which the sponge was immersed, which is in accordance with the detailed description of the assay in the patent in suit, in particular paragraph [0073]. Therefore, the Board can accept that in the model according to D1, the liposomes are also added to the medium so that D1 does not disclose topical application of the liposomes to the skin, even in an *in vitro* system.

9.2 As D1 only concerns an *in vitro* model, the problem to be solved in the present case has to be seen as to provide an *in vivo* method to deliver medicaments specifically to hair follicles.

10. From the *in vivo* examples in the patent in suit, paragraphs [0225] to [0236], it can be seen that that problem has been effectively solved. In particular, liposome entrapped calcein and melanin were delivered to the hair follicles and shafts, whereas non-entrapped calcein and melanin did not enter or only hardly entered the hair shafts or follicles (paragraphs [0230], [0232] and [0234]). Also, no detectable calcein had entered the blood circulation (paragraph [0236], showing that the delivery of calcein was indeed specific.

11. Therefore, the question remains to be answered whether or not the claimed solution to the problem as above

defined, i.e. to provide an *in vivo* method to deliver medicaments specifically to hair follicles, can be derived in an obvious manner from the cited prior art.

11.1 As D1 describes an in vitro model in which only a portion of the skin below the dermis is in contact with the liposomes and as D1 is silent about the incubation method, it contains no pointer to topical application *in vivo*.

Various methods of in vivo application of medicaments entrapped in liposomes are described in D6. In point 2.3, page 105, apart from intravenous injection, also intramuscular, subcutaneous, intraperitoneal and oral administration are mentioned. Nothing is said about the possibility of topical application. Therefore, topical application would not be a method of choice for the skilled person desiring to apply the teaching of D1 to an *in vivo* situation.

11.2 D5 describes pigmentogenic compounds for the skin and hair characterised by a specific formula (claim 1). In examples 5 and 6 the "encapsulation" of such compounds is disclosed by a method that is referred to as known by itself. The compositions of examples 5 and 6 are applied topically (D5, examples 8 and 9, respectively). In example 5 an "ultradisperseur" and "ultrasons" are mentioned. In that light, there is no reason to assume that the active pigmentogenic compounds of D5 are not entrapped in the sense of the patent in suit. However, D5 concerns a cosmetic composition rather than one for administering medicaments. Therefore, it is not evident that the skilled person, looking for a method to administer medicaments, would even consider D5.

Moreover, there is no mention in D5 of any separation of the non-entrapped compounds, nor is there any indication that that might lead to the undesired presence of the active substance outside the hair follicles. In fact, D5 does not only concern colouring of the hair, but also of the skin so that selective delivery is not a point of consideration.

11.3 In view of the above and since the other cited documents are more remote, the Board comes to the conclusion that the subject-matter of claim 1 of the auxiliary request, as well as that of claims 2, 3 depending on claim 1, cannot be derived in an obvious manner from the prior art, so that the requirements of Article 56 EPC are fulfilled.

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the claims of the auxiliary request submitted at the oral proceedings on 16 November 2010 with claim 1 corrected as submitted on 23 November 2010 and a description yet to be adapted thereto.

Registrar Chairman

S. Fabiani S. Perryman