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D E C I S I O N
of 24 January 2003

Case Number: T 0091/99 - 3.3.2

Application Number: 85904186.5

Publication Number: 0191824

IPC: A61K 9/60

Language of the proceedings: EN

Title of invention:
Encapsulation of antineoplastic agents in liposomes

Patentee:
THE LIPOSOME COMPANY, INC.

Opponent:
NeXstar Pharmaceuticals Inc.
Alza Corporation

Headword:
Liposomes/THE LIPOSOME COMPANY INC.

Relevant legal provisions:
EPC Art. 84, 87, 123(2), 83, 56, 104(1), 116(1) R. 57a

Keyword:
"Inventive step - no: obvious alternative"
"Apportionment of costs - no"

Decisions cited:
-

Catchword:
-

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Case Number: T 0091/99 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 24 January 2003

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 11 November 1998 revoking European patent No. 0 191 824 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo

Summary of Facts and Submissions

I. European Patent No. 0 191 824 based on international application No. W O86/01 102, and claiming priority from US 638 809 of 8 August 1984 and US 749 161 of 21 June 1985, was granted on the basis of 21 claims.

Independent claims 1, 2, 4, 15 and 16 as granted read as follows:

"1. A method for loading liposomes with a relatively lipophilic ionizable antineoplastic agent so that it will partition into the liposome membranes with a trapping efficiency of 95% and higher for preparing a pharmaceutical preparation comprising the steps of:
(a) preparing a liposome preparation wherein the liposomes have a concentration gradient of one or more charged species across their membranes, said concentration gradient being capable of generating a transmembrane potential having an orientation which will cause the ionizable agent to be loaded into the liposomes; and
(b) admixing the ionizable antineoplastic agent with the liposome preparation.

2. A method for loading liposomes with a relatively lipophilic ionizable antineoplastic agent so that it will partition into the liposome membranes with a trapping efficiency of 95% and higher, for preparing a pharmaceutical preparation comprising the steps of:
(a) preparing a liposome preparation;
(b) dehydrating the liposome preparation;
(c) storing the dehydrated preparation;
(d) rehydrating the dehydrated preparation; and
(e) admixing the ionizable agent with the rehydrated preparation;
wherein either the liposomes in the liposome

preparation have a concentration gradient of one or more charged species across their membranes, said concentration gradient being capable of generating a transmembrane potential having an orientation which will load the ionizable antineoplastic agent into the liposomes, or wherein for rehydrating and admixing steps (d) and (e), the liposomes are surrounded with an external medium which will produce a concentration gradient of one or more charged species across the membranes of the liposomes, said concentration gradient being capable of generating a transmembrane potential having an orientation which will load the ionizable antineoplastic agent into the liposomes.

4. A method for reducing the rate of release of a relatively lipophilic ionizable antineoplastic agent so that it will partition into the liposome membranes from liposomes stored in an external medium, comprising generating a transmembrane potential across the liposome membranes which has an orientation such that if the agent is positively charged, the internal potential of the liposomes is negative relative to the potential of the external medium, and if the agent is negatively charged, the internal potential of the liposomes is positive relative to the potential of the external medium, excluding the methods according to Article 52(4) EPC.

15. A pharmaceutical preparation comprising a relatively lipophilic ionizable antineoplastic agent so that it will partition into the liposome membranes encapsulated in a liposome which has been loaded into liposomes obtainable by the method of any one of claims 1 to 14 wherein the liposome comprises a transmembrane potential across the liposome membranes which has an orientation such that if the agent is positively charged in its ionized form the internal potential of

the liposomes is negative relative to the potential of the external medium, and if the agent is negatively charged in its ionized form, the internal potential of the liposomes is positive relative to the potential of the external medium.

16. A pharmaceutical preparation comprising a relatively lipophilic ionizable agent so that it will partition into the liposome membranes encapsulated in a liposome stored in an external medium so that the rate of release of the antineoplastic agent is reduced according to any one of claims 4 to 14."

II. Oppositions were filed against the granted patent by respondent 1 (opponent 01) and respondent 2 (opponent 02). The patent was opposed under Article 100(a) for lack of novelty and inventive step, under Article 100(b) for insufficiency of disclosure of the invention and under Article 100(c) EPC because the content of the opposed patent extended beyond the content of the application as originally filed.

The following documents were cited *inter alia* during the proceedings before the Opposition Division and the Board of Appeal:

(4) Biochimica et Biophysica Acta, 455 (1976), 269-271

(11) Biochimica et Biophysica Acta, 812 (1985), 66-76 (published 16 January 1985)

(P1) Priority document US 638809 of 8 August 1984.

III. By its decision pronounced on 8 October 1998, the Opposition Division revoked the patent under Article 102(1) EPC.

During the oral proceedings, the patentee filed one main and three auxiliary requests. The set of claims of the third auxiliary request corresponds to the set of claims as granted limited to "adriamycin" as "relatively lipophilic ionizable antineoplastic agent" and to a pH-gradient as concentration gradient, and stipulating that loading takes place in the absence of an ionophore.

Accordingly, claim 1 of this set of claims reads:

"1. A method for loading liposomes with **adriamycin** so that it will partition into the liposome membranes with a trapping efficiency of 95% and higher for preparing a pharmaceutical preparation comprising the steps of:
(a) preparing a liposome preparation wherein the liposomes have a concentration gradient of one or more charged species across their membranes, said concentration gradient being capable of generating a transmembrane potential having an orientation which will cause the ionizable agent to be loaded into the liposomes **wherein the concentration gradient is a pH-gradient** and
(b) admixing the ionizable antineoplastic agent with the liposome preparation, **wherein said loading takes place in the absence of an ionophore**."

Original claims 4, 7, 8 and 19 were deleted and the remaining claims adapted accordingly.

The Opposition Division held that the contested patent was not entitled to the first claimed priority date. In its view, the content of the first priority (P1) failed to disclose the features of the subject-matter of the patent in suit relating to the loading of the liposomes with a trapping efficiency of 95% or higher and to the absence of protective sugars. Moreover the first priority document dealt with a method of active

loading of the liposomes involving a transmembrane potential linked to a dehydration/rehydration process, whereas in the attacked patent no dehydration/rehydration process is involved.

Accordingly, it considered document (11) as belonging to the state of the art which could be opposed to the patent in suit, even though it was published after the date of filing of the first priority document.

The Opposition Division was of the opinion that process claim 1 of the main request was not novel over the disclosure of document (11), that product claim 12 of the first auxiliary request was not novel over this document and that process claim 1 of the second auxiliary request was not inventive over document (11) in combination with document (4).

As regards the last most restricted request, ie auxiliary request 3, the Opposition Division was also of the opinion that the subject-matter of process claim 1 could be derived in an obvious way from the disclosure in document (11) in combination with document (4) as, in its view, the limitation of the subject-matter of the process of the second auxiliary request to adriamycin did not bring any inventive matter to the claimed process.

The Opposition Division considered that the problem to be solved over document (11), which related to liposome loading experiments using a transmembrane potential generated using a Na+/K+ gradient, was to provide for an alternative method for actively loading adriamycin into liposomes in the absence of an ionophore so that a trapping efficiency of at least 95% could be obtained.

In the light of the teaching in documents (11) and (4) that the accumulation of ionizable agent into cells can be similarly achieved with a pH gradient, the Opposition Division considered that the replacement of a Na+/K+ gradient by a pH gradient was an obvious alternative, the more so since it was clear from document (4), which dealt with a pH gradient, that this type of gradient works in the absence of ionophores.

As to the argument that a trapping efficiency of more than 95% would be obtained by the combination of chemical pH gradient plus the selection of a particular lipophilic ionizable antineoplastic agent, the Opposition Division considered that this might be indeed the case, but only in association with other factors such as the lipid composition and the lipid/drug ratio, which greatly influenced the trapping efficiency. Since these features were not in the claims, the feature relating to efficiency could not be taken into account for the assessment of inventive step.

Finally, the Opposition Division considered that the mere indication in document (4) that the slow loading of the drug used in this document was probably caused by its high hydrophilicity was not sufficient to constitute a technical prejudice against the loading in liposomes of other hydrophilic drugs such as adriamycin with pH gradients.

IV. The appellant (patentee) lodged an appeal against the said decision.

V. The appellant filed as its main request the set of claims of the third auxiliary request presented during the proceedings before the Opposition Division.

Concerning the validity of the first priority document,

it simply stated in a single sentence that the subject-matter of this set of claims was to be found in the first priority document.

It nevertheless considered document (11) as representing the closest state of the art. It mainly argued that nothing in the available prior art provided the skilled person with any indication or incentive to conclude that, by using a pH-gradient transmembrane potential as opposed to a potential generated by a Na+/K+ gradient, the antineoplastic drug adriamycin could be loaded into the liposomal membrane with a trapping efficiency of 95% or higher even in the absence of an ionophore.

VI. Respondent 2 (opponent 02) submitted that, as the appellant did not file a reasoned statement of grounds for appeal in connection with the issue of entitlement to priority, this aspect should not be dealt with anymore in the appeal procedure.

It considered that the restriction of claim 1 to adriamycin was, contrary to the requirement of Rule 57a EPC, not occasioned by the grounds of opposition since the closest prior art document (ie document (11)) dealt precisely with adriamycin.

It also considered that claim 1 was moreover not clear since the feature "a trapping efficiency of 95%" contradicted the results of the example relating to adriamycin, which infringed the requirements of Article 84 EPC.

It contested the introduction of the term "in the absence of an ionophore" in claim 1 under Article 123(2) EPC because, in its opinion, there was no general disclosure or discussion of the feature of loading liposomes in the absence of an ionophore.

Concerning Article 83 EPC, respondent 1 referred back to submissions it made during the opposition proceedings.

As to inventive step, it mainly repeated the arguments of the decision of the Opposition Division.

Respondent 1 (opponent 01) did not intervene in the appeal proceedings.

VII. The parties were summoned to the oral proceedings on 6 December 2002 by the Board's communication of 22 April 2002.

VIII. In a letter dated 4 December 2002, the appellant informed the Board that it did not intend to attend the oral proceedings. It further mentioned that it would rely on the written submissions of the parties.

IX. By a communication dated 4 December 2002, the Board informed the parties that the oral proceedings had been cancelled.

X. In its letter dated 5 December 2002, respondent 1 requested the award of costs against the appellant since, in its opinion, as a result of the late notification to the European Patent Office by the appellant of its intention not to attend the oral proceedings, the respondent had wasted time and money.

XI. The appellant requested that the decision of the Opposition Division be set aside and that the patent be maintained on the basis of the set of claims filed with its letter dated 22 March 1999, corresponding to the set of claims of the third auxiliary request presented before the Opposition Division.

Respondent 2 (opponent 02) requested that the appeal be dismissed and that the costs be apportioned.

Reasons for the Decision

1. The appeal is admissible.

2. *Priority*

The right to priority is governed by Article 87 EPC which requires that the first application for the **"same invention"** be filed in a State party to the Paris Convention during a period of 12 months immediately preceding the filing of a European patent application.

Two applications relate to **"the same invention"** within the meaning of Article 87 EPC when they both contain **"the same subject-matter"**. This follows from Article 87(4) EPC, which uses the latter expression. The invention or subject-matter of a previous application is to be considered the same as that of a subsequent application if the disclosure of both applications is the same.

This not only requires that the solution to a given problem is the same, but also that the problem itself is the same in both applications.

Applying these criteria, the question of whether the appellant was correct in claiming the priority of 8 August 1984 should be answered, ie whether the subject-matter/invention of the contested patent, whose priority is claimed, is the same as that of the earlier US application.

The Board considers that the Opposition Division's decision with respect to the assessment of the validity of the first priority document holds good and concludes therefore that document (11) belongs to the prior art which can be opposed to the contested patent as (P1) does not relate to the same invention as the contested patent (see above under III and Opposition Division's decision, point 2, pages 3 to 8).

In that respect, the Board also observes that the grounds of appeal do not provide any reason why the Opposition Division's findings in connection with the issue of entitlement to priority would not hold good, or why the first priority date should be valid. The Board also notes that the appellant itself considers in its submissions that document (11) represents the closest prior art document.

3. *Rule 57a EPC*

The Board notes that the subject-matter of claim 1 claiming the loading of adriamycin constitutes a very important limitation of the scope of the claims as granted which, *a priori*, must be considered as occasioned by the novelty and inventive step objections of the grounds for opposition and appeal. The Board therefore does not agree with respondent 1's view that this set of claims cannot be allowed under Rule 57a EPC merely because this limitation, in its opinion, does not provide for an inventive step over document (11) since this document also mentions the drug adriamycin.

Accordingly, the Board judges that this set of claims fulfils the requirements of Rule 57a EPC.

4. *Article 84 EPC*

It is indeed correct that Example 1B of the description of the contested patent describes liposomes containing adriamycin with either 98% or 72% trapping efficiency whereas the claims requires a trapping efficiency of 95%.

This however merely implies that the liposomes with 72% trapping efficiency do not fall within the scope of the claims, which does not put into question the clarity of the claim.

The question raised by respondent 2 in that respect, ie whether the method now claimed is therefore applicable across the scope of the claims, relates in fact rather to the issue of the sufficiency of disclosure of the invention and not to the question of whether it is possible to determine if an embodiment falls within the scope of the claims or not as required by Article 84 EPC.

5. *Article 123(2) EPC*

The Board does not agree with respondent 2's view that the feature "in the absence of an ionophore" introduced in claim 1 is an unallowable generalisation of a feature which is only disclosed in a specific example. It is in fact clear from the passage on page 8, third paragraph of the description of the application as originally filed that, beside the specific examples, ionophores are disclosed in general terms as **optional** permeability enhancing agents which may or may not have to be added.

Accordingly, the Board concludes that the introduction of this feature is in agreement with the requirements of Article 123(2) EPC.

6. *Article 83 EPC*

As apparent from the minutes of the oral proceedings (see 2.1), objections under Article 83 EPC were not raised during the oral proceedings. The decision of the Opposition Division does not deal with this ground for opposition either. In its letter filed during the appeal proceedings, however, respondent 2 mentions this ground of opposition referring back to its written submissions made before the Opposition Division.

Having regard to its conclusions with respect to the assessment of inventive step, the Board sees however no reason to discuss this point further.

7. *Inventive step*

The Board agrees with the Opposition Division that document (11) represents the closest state of the art and that the problem to be solved over this document is to provide for an alternative method for actively loading adriamycin into liposomes in the absence of an ionophore so that a trapping efficiency of at least 95% can be obtained.

The Board further considers that the Opposition Division's decision with respect to the assessment of inventive step holds good.

The written submissions of the appellant relating to inventive step do not contain any new matter not properly dealt with in the Opposition Division's. decision.

The Board therefore concludes that, contrary to the requirements of Article 56 EPC, the subject-matter of claim 1 of the sole set of claims under consideration lacks inventive step (see above under III above, and the Opposition Division's decision, pages 12 to 16, points 6.2 and 7.2).

Accordingly, there is no need to discuss the remaining claims.

8. *Request for apportionment of costs*

In the present case respondent 2 submitted that as a result of the extremely late notification to the EPO by the appellant of its intention not to attend the oral proceedings respondent 1 had wasted time and money and in particular that the representatives were already in transit from London to Munich and that, by the time the appellant's letter had been faxed, someone coming from the USA was already in transit from California to Munich.

Article 104(1) EPC provides that each party to the proceedings shall as a rule bear its own costs. To deviate from this principle requires special circumstances, such as improper behaviour, which make it equitable to award costs against one of the parties.

According to Article 116(1) EPC it is a genuine right of any party to request oral proceedings if it considers them to be necessary. Moreover, the Board observes that there is nothing in the European Patent Convention which prevents a party from withdrawing a request for oral proceedings at any stage of the procedure. Therefore, the fact that an appellant

withdrew its request for oral proceedings is not culpable conduct as such and cannot be a factor in assessing the reasons of equity under Article 104(1) EPC.

However, the fact that the appellant filed the notice not to attend the oral proceedings only two working days before the date set for oral proceedings could be a negligent or wilful conduct which has to be considered under Article 104(1) EPC.

The Board held that there was an equitable obligation on every party summoned to oral proceedings to inform the EPO and the other party as soon as it knew for certain that it would not be attending oral proceedings, despite these having be requested. Consequently, in cases where a party delayed its decision not to attend the oral proceedings or the communication of this decision to the Board, an apportionment of costs in favour the other party could be justified insofar as the costs were directly caused by the fact that the notice had not been filed in appropriate time before the oral proceedings.

However, in the present case, the Board would not have been in a position to decide about the case any earlier so that the cancellation of the oral proceedings could not have been decided in advance. As a result, the late cancellation of the oral proceedings did not result from the appellant’s allegedly late filed notice not to attend the oral proceedings, but from the Board's opinion about the need to hear the respondent, which was reached only at that stage. Additionally, there are no facts on file that the appellant unduly delayed its notice not to attend the oral proceedings. Under these specific circumstances, the Board considers that there is no culpable conduct on the part of the appellant which could provide for an apportionment of costs under

Article 104(1) EPC. In addition, the decision of the appellant to rely on its written arguments rendered, in fact, the procedure more simple and economic, as it resulted in saving for respondent 2 at least the time and money associated with its presence at the European Patent Office on the day of the oral proceedings.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The respondent 2's request for apportionment of costs is dismissed.

The Registrar: The Chairman:

A. Townend U. Oswald