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Datasheet for the decision of 1 August 2006

Case Number: T 0923/03 - 3.3.02

Application Number: 99963103.9

Publication Number: 1140022

IPC: A61K 9/127

Language of the proceedings: EN

Title of invention:
Method of administering a compound to multi-drug resistant cells

Applicants
HADASIT MEDICAL RESEARCH SERVICES & ALZA CORPORATION

Opponent:
-

Headword:
Treatment of multi-drug resistant cancer/HADASIT & ALZA

Relevant legal provisions:
EPC Art. 123(2), 83, 111(1)

Keyword:
"Sufficiency of disclosure: main request (no), lack of disclosure which cannot be overcome with the common general knowledge in the field; auxiliary request (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0923/03 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 1 August 2006

Appellants:
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 8 April 2003 refusing European application No. 99963103.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
J. Willems

Summary of Facts and Submissions

I. European patent application No. 99 963 103.9 based on international patent application WO 00/35422 was filed with 14 claims. Claim 1 read as follows:

"1. A composition for administration of a therapeutic compound to a multi-drug resistant cell, comprising a carrier molecule at least one folate ligand attached to the carrier molecule; and a therapeutic compound associated with the carrier,
wherein said composition is effective to achieve accumulation of the therapeutic compound in the cell in an amount sufficient to be cytotoxic."

II. The following documents cited during the proceedings are relevant for the present decision:

(1) A. T. Horowitz, D. Goren, A. Gabizon, 11th Symposium 1997, "Chemistry and Biology of Pteridines and Folates", Berchtesgarden, Blackwell Wissentschaftsverlag, Berlin, pages 353-356

(3) R. J. Lee, P. S. Low, Biochimica et Biophysica Acta, vol. 1233, pages 134-144, 1995

(7) S. Zalipsky, et al, Bioconjugate Chem., 4, pages 296-299, 1993

(9) A. Gabizon, M. Chemla, D. Tzemach, A. T. Horowitz, D. Goren, Journal of Drug Targetting, vol. 3, pages 391-398, 1996

(11) R. J. Lee, P. S. Low, The Journal of Biological Chemistry, vol. 269, No 5, pages 3198-3204, 1994

III. The appeal lies from a decision of the examining division refusing the patent application under Article 97(1) EPC pursuant to the requirements of Articles 123(2), 84 and 54 EPC on the basis of the set of claims filed with the letter of 18 November 2002.

Claim 1 of the set of claims serving as the basis for the first-instance decision read as follows:

"1. A composition for use in treating multi-drug resistance, comprising a carrier molecule, at least one folate ligand attached to the carrier molecule, and a therapeutic compound associated with the carrier, said composition when administered to a subject suffering from multi-drug resistance being capable of achieving accumulation of the therapeutic agent in multi-drug resistant cells in an amount sufficient to be cytotoxic."

Claim 3 read as follows:

"3. The composition according to claim 1, wherein the carrier is a protein or peptide."

IV. The examining division considered that the subject-matter claimed in the set of claims filed with the letter of 18 November 2002 did not comply with the requirements of Article 123(2) EPC, since not every peptide appearing in claim 3 was necessarily a macromolecule, which was a feature originally disclosed as compulsory.

The examining division also considered that the subject-matter claimed in claim 1 lacked novelty since the claimed products were already known for use in a therapeutic method.

Finally, the examining division further considered that the claim's wording did not meet the requirements of Article 84 EPC, since it related to an attempt to define the invention by a result-to-be-achieved.

V. The appellant (applicants) lodged an appeal against said decision and supported it with arguments. Moreover, it filed with its notice of appeal a set of claims as main request.

VI. A communication from the board dated 25 January 2006 conveyed the board's preliminary opinion in respect of the requirements of Articles 123(2) and 83 EPC.

VII. The appellant filed with its response of 4 April 2006 a new main request.

Claim 1 of the main request read as follows:

"1. The use of a composition comprising:
a liposome carrier having a surface coating of hydrophilic polymer chains and at least one folate ligand covalently attached to a distal end of the polymer end; and a chemotherapeutic drug entrapped in the liposome carrier, in the manufacture of a medicament for the treatment of multi-drug resistant cancer."

VIII. A communication by the board was sent as an annex to the invitation for oral proceedings.

IX. The appellant filed by fax on 30 June 2006 an auxiliary request.

X. A brief communication from the board was sent by fax on 20 July 2006 in which the board's preliminary opinion concerning Article 123(2) EPC for the set of claims of the auxiliary request was expressed.

XI. The appellant filed by fax on 27 July 2006 an amended auxiliary request.

Claim 1 of the amended auxiliary request (only one single claim) reads as follows:

"1. The use of a composition consisting of:
a liposome carrier composed of hydrogenated soybean phosphatidylcholine (HSPC), cholesterol and distearoyl phosphatidyl ethanolamine-polyethylene glycol-folate (DSPE-PEG-folate) and doxorubicin entrapped in the liposome carrier, wherein the doxorubicin to phospholipid ratio is between 110-150 µg/µmol in the manufacture of a medicament for the treatment of multi-drug resistant cancer."

XII. Oral proceedings took place on 1 August 2006.

During the oral proceedings the appellant filed an amended main request.

Claim 1 of the amended main request filed during the oral proceedings differs from claim 1 of the main

request filed with the letter of 4 April 2006 in that the expression "polymer end" has been replaced by "polymer chains".

XIII. The arguments submitted by the appellant may be summarised as follows:

The amended main request filed during the oral proceedings should be considered as admissible since the amendment introduced merely related to the avoidance of a linguistic tautology, namely "attached to a **distal end** of the **polymer end**". The basis for the amendment was to be found in the claims as originally filed (originally filed claim 4).

The auxiliary request filed with the letter of 27 July 2006 had been filed as a clear and direct response to the board's communication of 20 July 2006. This request merely differed from the previously filed auxiliary request in that the component cholesterol had been included in claim 1 and in that claim 2 of the previous request had been deleted. The basis for claim 1 of the auxiliary request was to be found in example 5 and page 7 of the application as originally filed.

As regards the requirements of sufficiency of disclosure the appellant's arguments may be summarised as follows:

The invention relates to the use of folate-mediated or folate-targeted liposomes with entrapped drugs for treating multi-drug resistant cancer. The loaded folate-targeted liposomes address the cancer cells with over-expressed folate receptors. Liposomes having in

their outer surface a hydrophilic polymer, and also those further modified as folate-targeted liposomes, were known to be suitable for targeting cancer cells (documents (1) and (3)). It was, however, not known that when folate-targeted liposome approaches the folate receptors of the cell, it is internalised into the cell by endocytosis. Moreover, it was also not known that the material which goes inside the cell, i.e. the drug associated with the lipid material, is not removed by the efflux mechanism related to P-glycoprotein. This efflux mechanism is associated with multi-drug resistance in cancer cells because it pumps out the drug from the cell. Only when the drug enters the cell entrapped in the liposome it is successfully released bypassing the P-glycoprotein efflux mechanism. The appellant also stated that the second medical use claims of the main request and auxiliary request were very specifically directed to the treatment of multi-drug resistant cancer.

The appellant pointed to example 5 as the illustration of a liposome according to the invention. However, it acknowledged that the application as filed did not contain any data concerning the ratio of the lipid components forming the liposomes. Furthermore, it also stated that since the invention underlying the application was mechanistically broad it could happen that if one did not get the appropriate ratio then one would not get the invention right. However, the appellant also submitted that document (9), cited in example 5, taught how to improve liposome longevity and stability by introducing PEG-derivatised lipids and that the specific ratios of the different lipids were not relevant for defining the invention which concerned

the fact that folate-targeted liposomes with entrapped drug were used for treating multi-drug resistant cancer.

Moreover, the appellant asserted that the structure of the liposome was not critical for the intended use and argued that there was a variety of folate-targeted liposomes used in the prior art to treat cancer. Furthermore, the invention related to the disclosure that the drug was not ejected by the P-glycoprotein efflux mechanism of the multi-drug resistant cancer cell. This was achieved by the fact that the drug "*was targeted*" in a way that it was not ejected. The invention did not relate to the explanation of a mechanism but to a new indication since the prior art documents (1) and (3) related to the treatment of cancer cells susceptible to doxorubicin, whereas multi-drug resistant cancer specifically concerned cancer cells capable of ejecting the drug by a P-glycoprotein efflux mechanism. There were two different types of cancer which did not overlap.

The appellant also stressed that the doxorubicin resistant cancer cells were different from multi-drug resistant cancer cells, which had to be resistant not only to doxorubicin but also to other drugs. It also argued that previous to the invention a medical doctor would have treated multi-drug resistant cancer with antisense oligonucleotides to target P-glycoprotein specifically.

The appellant further stressed that the disclosure of the invention was sufficiently illustrated by examples 5 and 9. Although it was correct that the application as filed did not give the exact percentage for the

lipid components, the reference to document (9) in example 5 provided the skilled person with the information he needed for obtaining a liposome.

The appellant also argued that in the absence of anything to the contrary the skilled person would have thought that the folate-targeted liposome used in example 9 would be that of example 5. Moreover, the declaration of Mr Gabizon dated 26 July 2006, filed with the letter of 27 July 2006, pointed out that this was indeed the case.

Example 9 concerned an *in vivo* adoptive tumour growth assay using M109R-HiFR cells. The results displayed in fig. 15 showed the evolution in mean footpad thickness (which correlates with tumour growth) in respect to the days after tumour injection. The comparison in the regression after 20 days between control, doxil, free doxorubicin and folate targeted liposome with doxorubicin entrapped allowed one to arrive at the conclusion that the folate-targeted liposomes were internalised in the cells by endocytosis and that in that case the drug was not ejected by the P-glycoprotein efflux mechanism.

Furthermore, the appellant explained that the M09R-HiFR cells employed in example 9 were a subline of M09 cells selected for multi-drug resistance and cited page 6, lines 7-8. It also explained that the amount of folate receptor expressed on the surface of cancer cells did not correlate with multi-drug resistance.

XIV. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis

of the set of claims of the main request, filed during the oral proceedings, or alternatively, on the basis of the auxiliary request, filed with letter dated 27 July 2006.

Reasons for the Decision

1. *Admissibility*

1.1 The appeal is admissible.

1.2 The amended main request filed during the oral proceedings is admissible since the only difference to the previous main request (filed with the letter of 4 April 2006 as a response to the board's communication dated 25 January 2006) relies upon the correction of a tautological wording. Moreover, the basis for the correction could be immediately identified in the wording of the original claims (see claim 4).

The amended auxiliary request filed with the letter of 27 July 2006 is admissible since the only difference to the previous auxiliary request (filed with the letter of 30 June 2006 as a response to the board's communication sent as an annex to the summons for oral proceedings) relies upon the introduction of the component cholesterol in claim 1 and the deletion of previous claim 2, as a clear and direct response to the board's objections raised in the board's communication dated 20 July 2006.

2. *Articles 123(2) and 84 EPC*

2.1 Both sets of claims, the main request and the auxiliary request meet the requirements of Article 123(2) EPC. The basis for claim 1 of the main request can be found on page 7, lines 14-19, and on page 3, first, second and third paragraphs, of the application as originally filed.

The basis for claim 1 of the auxiliary request can be found in example 5 of the application as originally filed.

2.2 The examining division's findings in respect of Article 123(2) EPC no longer apply since the objected-to claim 3 has been deleted.

2.3 The examining division's findings in respect of Article 84 EPC no longer apply since the contested expression has been replaced in both sets of claims by specific definitions.

3. *Article 83 EPC*

3.1 Article 83 EPC requires an invention to be disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. When considering whether the requirements of sufficiency of disclosure are met the contents of the whole patent, i.e. claims and description, have to be investigated in the light of the general knowledge of the skilled person in the technical field involved. If the description contains working examples, they should illustrate specific way(s) of performing the invention.

As for the amount of technical detail needed for a sufficient disclosure, this is a matter which depends on an assessment of the facts of each particular case, such as the character of the technical field, the corresponding general technical knowledge, and the actual technical detail disclosed.

3.2 The appellant has stressed that the invention relates to the treatment of multi-drug resistant cancer by using folate-targeted liposomes with entrapped drugs. Moreover, it has argued on the one hand that the folate-targeted liposomes were those known in the prior art (it mentioned specifically documents (1) and (3)) and on the other that the liposome structure was not crucial for the intended use. From the appellant's argumentation it can be assumed that the gist of the invention relies upon the alleged ability of the folate-targeted liposomes with entrapped drug to be internalised by endocytosis into the cancer cells, and then on their ability to release the drug inside the cell, bypassing the P-glycoprotein efflux mechanism, which especially acts in the multi-drug resistant cancer cells.

3.3 Hence, the question to be answered is not whether or not the skilled person is able to prepare a folate-targeted liposome loaded with a chemotherapeutic drug at all, but whether the application as filed discloses the alleged invention in a way that the skilled person is able to reproduce it. For this purpose it is necessary to know which folate-targeted liposomes loaded with a chemotherapeutic drug are capable of effectively treating multi-drug resistant cancer and how to produce or have access to them.

Therefore the contents of the description of the application in suit have to be investigated.

3.4 The board agrees with the appellant that only example 5 can be considered when investigating whether a realisation mode illustrating the invention has been disclosed, since example 3 (referred to on page 11, line 11, as a method for preparing the liposome formulations tested according to Table 2) is incomplete and contains misleading information. The reasons lie in the fact that example 3 refers to document (7) as disclosing the preparation of liposomes. However, document (7) discloses neither the actual preparation of liposomes nor the introduction of a folate ligand. Moreover, document (7) discloses a functionalised DSPE-PGE derivative (namely a DSPE-PGE conjugate bearing a hydrazine group) which is different from that of figure 1 of the application in suit, which is referred to in example 1, line 33. Finally, example 3 does not relate to liposomes loaded with a chemotherapeutic drug.

Furthermore, a closer look at example 5 on page 27 of the application in suit shows that it relates to "Preparation of Doxorubicin Liposomes and *In vitro* Binding". However, only the following information can be read under the heading on page 27: "Liposome preparation": "Preparation of liposomes was carried out as described by Gabizon (J. Drug Targeting, 3, 391-398, (1996) (*i.e. document (9)*), and were composed of hydrogenated soybean phosphatidylcholine (HSPC, Avanti Polar Lipids, Birmingham LA, USA), cholesterol (Sigma), DSPE-PEG-Folate. The doxorubicin to phospholipid ratio was between 110-150 µg/µmol."

An inspection of document (9) shows that it does not disclose any folate-targeted liposomes. Document (9) concerns the study of liposome longevity and stability in circulation and the effects on the *in vivo* delivery to tumours and therapeutic efficacy of encapsulated anthracyclines (*inter alia* doxorubicin). The only liposomes disclosed in document (9) having a surface coating of hydrophilic polymer chains are polyethylene glycol (PEG) coated liposomes containing a specific PEG-derivatised lipid component, namely distearoyl-phosphatidylethanolamine derivatised with PEG (DSPE-PEG), without further ligand. Apart from this fact, although document (9) discloses a general preparation method for liposomes under the heading "Materials and Methods", it also explicitly teaches the use of cholesterol as compulsory component, since it "is needed to ensure stable encapsulation of the drug" (page 392, left column, second paragraph). Additionally, document (9) further refers to other documents in respect of the method suitable for encapsulating doxorubicin.

3.5 Therefore, the application in suit does not disclose, as would be necessary in the present case, a complete preparation example but only contains an example of a liposome formulation where the components are listed (HSPC, cholesterol, DSPE-PEG-Folate, Doxorubicin) and which includes a reference to a liposome preparation method which should be employed by analogy.

In this context it should be borne in mind that the appellant has acknowledged that the ratio of the lipid components is not disclosed in the application in suit

and that it may play a role in the reproduction of the invention.

3.6 As already mentioned in point 3.1 above the amount of technical detail needed for a sufficient disclosure depends *inter alia* on the character of the technical field.

In general terms, the amount of technical detail to be specifically disclosed in the application may be concise and brief in order to spare the reader the well-known details of a generally known technique.

Therefore, the skilled person's knowledge about folate-targeted liposomes with entrapped chemotherapeutic drugs able to target cancer cells at the priority date of the invention needs to be assessed. More particularly, the contents of documents (1) and (3), cited by the appellant in support of its argumentation, have to be investigated.

3.7 It belongs to the general knowledge of the skilled person in the field that prior to folate-targeted liposomes, liposome formulations with prolonged circulation times, in particular liposomes coated with polyethyleneglycol(PEG)-derivatised lipids and loaded with chemotherapeutic drugs were developed for achieving prolonged circulation times in order to be able to deliver *in vivo* the chemotherapeutic drugs to tumour cells (see document (9), introduction). To these sterically stabilised liposomes (stealth liposomes) belongs the known commercial product Doxil^{R} (N-carbonyl-methoxypolyethyleneglycol(mPEG)-DSPE/HSPC/Cholesterol,

entrapped Doxorubucin) which has been used in the application in suit for comparative purposes.

3.8 Documents (1), (3) and (11) (cited in document (1) as document (13)) relate to scientific publications in the field of folate-targeted liposomes to be loaded with chemotherapeutic drugs. These documents can be considered to represent the general technical knowledge of the skilled person at the priority date of the application in suit.

Therefore it can be concluded that further-functionalised **PEG** stabilised liposomes (introduction of a folate ligand able to interfere with the cell membrane-associated folate receptors) were generally known.

However, folate-targeted liposomes loaded with a chemotherapeutic drug and bearing other hydrophilic polymer chains than PEG cannot be considered to belong to the general knowledge of the skilled person since they are not disclosed in the prior art documents cited by the appellant (in particular documents (1) and (3)), or in document (11) (cited in document (1) as document (13)). Moreover, as already mentioned, the liposome preparation method disclosed in document (9), which has been cited in example 5 of the application in suit as suitable preparation process by analogy, also employs a **PEG**-DSPE modified lipid.

3.9 Additionally, further investigation of the contents of documents (1), (3) and (11) shows that the constitution of the folate-targeted liposomes of these documents is very specific. These documents do not disclose or refer

to the provision of generically defined folate-targeted liposomes.

Document (1) discloses liposomes of FA-PEG-DSPE/HSPC/ Cholesterol/DSPE-PEG at a molar ratio of 2:94:70:4 with encapsulated doxorubicin. Apart from the statement that folate is covalently coupled to PEG-DSPE, document (1) is silent about the exact nature and/or the preparation of the FA-PEG-DSPE construct employed. According to document (1)'s findings based on *in vitro* tests the liposomes were not internalised by the cancer cells employed in the tests.

Document (3) discloses folate-targeted liposomes prepared by incorporating 0.1% of a folate-PEG-DSPE construct into the lipid bilayer, the liposomes are loaded with doxorubicin. Basically, two liposome compositions are disclosed in document (3): (a) folate-PEG liposomes composed of **DSPC/cholesterol/folate-PEG-DSPE** (56:40:0.1) and (b) folate-PEG liposomes with 4% PEG (MW 2000) coating composed of DSPC/Cholesterol/PEG2000-DSPE/folate-PEG-DSPE (56:40:4:0.1) (page 136, left column). Document (3) also discloses the synthesis and specific structure of the folate-PEG-DSPE construct employed (page 135). Document (3) reports internalisation by endocytosis of the folate-PEG-liposomal DOX (doxorubicin) by the cancer cells (KB and HeLa cells) used in the tests and further release of the drug following endocytosis (page 138, end of left column and right column).

Document (11) discloses folate-targeted liposomes in which the folate ligand is "attach(ed) to the distal end of a few lipid-conjugated **PEG** molecules of the

liposome surface" (page 3198, right column, third paragraph). The synthetic pathway for preparing the liposomes of document (11) is illustrated in figure 1 on page 3199 and goes through a very specific "liposome-maleiimide" intermediate. Document (11) employs KB cells for the delivery tests and reports that "following binding, cell-associated folate-PEG liposomes were internalized by folate-receptor-mediated endocytosis at 37°C but not at 4°C. These folate-targeted liposomes show potential for delivering large quantities of low molecular weight compounds non-destructively into folate-receptor bearing cells" (summary). However, document (11) does not specifically disclose folate-targeted liposomes with an entrapped chemotherapeutic drug.

3.10 In conclusion, the skilled person trying to reproduce the invention underlying the application in suit faces a lack of disclosure concerning the loaded liposomes to be used, which he can only try to overcome by making use of his common general technical knowledge.

However, even when considering the scientific documents (1), (3) and (11) as reflecting the common general knowledge at the priority date of the application in suit, the skilled person still faces a lack of knowledge when trying to reproduce the invention as defined in the main request, since for the purpose of Article 83 EPC he cannot make use of his inventive skills.

Contrary to this, and in view of the existence of document (3) and the liposome composition (a) disclosed therein (i.e. **DSPC/cholesterol/folate-PEG-DSPE** with

entrapped doxorubicin), the skilled person would be in a position to reproduce the invention as defined in the auxiliary request and appearing in examples 5 and 9.

Indeed, it can be accepted that it is plausible that the folate-targeted liposome employed in the tests disclosed in example 9 is that mentioned in example 5, since example 5 is the only example of the application in suit relating to a doxorubicin loaded folate-targeted liposome. Moreover, the *in vivo* adoptive tumour growth assay where M109R-HiFR are used can in principle be accepted as support for the effect on multi-drug resistant cells, since it has been specified in the description that the M109R-HiFR cells are a subline of M109 cells (murine lung carcinoma cells) selected for multi-drug resistance (page 6, lines 7-8).

3.11 The appellant's allegation that the liposome structure is not crucial for achieving the intended use is seriously called into question by the cited prior art knowledge which sets high standards, only achieved by very specific liposome formulations, for effectively attaining *in vivo* the cancer cells without releasing beforehand a highly toxic drug such as doxorubicin.

3.12 Therefore, in view of the above, the board comes to the conclusion that there is insufficient disclosure in the application in suit to allow the skilled person to reproduce the invention claimed in claim 1 of the main request, whereas he would be in a position to reproduce the invention claimed in the auxiliary request in the light of his common general knowledge in the field, without making use of his inventive skills.

4. *Remittal to the department of first instance*

4.1 The set of claims on which the first-instance decision was based related to very broadly defined product claims whereas the set of claims of the auxiliary request filed with the letter of 27 July 2006 relates exclusively to a second medical use claim in Swiss-type form, with specifically defined subject-matter.

Therefore, the board decides to make use of its discretionary power under Article 111(1) EPC to remit the case to the first-instance department in order not to deprive the applicant of two instances for dealing with the main issues concerning novelty and inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance for further prosecution on the basis of the auxiliary request, filed with letter dated 27 July 2006.

The Registrar The Chairman

D. Sauter U. Oswald