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# Datasheet for the decision of 23 May 2006

**Case Number:** T 0600/05 - 3.3.04

**Application Number:** 97927282.0

**Publication Number:** 0942741

**IPC:** A61K 38/16

**Language of the proceedings:** EN

**Title of invention:**
Lectin compositions and uses thereof

**Patentee:**
Alizyme Therapeutics Limited

**Opponent:**
Phylogix, Inc.

**Headword:**
Lectin compositions/ALIZYME

**Relevant legal provisions:**
EPC Art. 54, 83, 111(1), 114(2)
RPBA Art. 10a(1)

**Keyword:**
"Main request: sufficiency of disclosure (yes)"
"Novelty (yes)"
"Remittal (yes)"
"Admissibility of late filed documents (no)"

**Decisions cited:**
G 0005/83

**Catchword:**
-

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**Case Number:** T 0600/05 - 3.3.04

# D E C I S I O N
**of the Technical Board of Appeal 3.3.04**
**of 23 May 2006**

**Appellant:** (Patent Proprietor)
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**Decision under appeal:**
**Decision of the Opposition Division of the European Patent Office posted 17 March 2005 revoking European patent No. 0942741 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chair:** U. Kinkeldey
**Members:** R. Gramaglia
G. Weiss

## Summary of Facts and Submissions

I. European Patent No. 0 942 741 (application No. 97 927 282.0, published as WO-A-97/49420) was granted with 16 claims. The patent relates to lectins compositions and uses thereof.

II. Notice of opposition was filed by the opponent requesting the revocation of the European patent on the grounds of Article 100(a), (b) and (c) EPC. The opposition division revoked the patent on the grounds that the main and auxiliary claim requests then on file did not fulfil the requirements of Articles 54 and 83 EPC. The issues of, inter alia, inventive step and priority rights were not dealt with (see paragraph XII of the decision under appeal).

III. The patentee (appellant) filed an appeal against the decision of the opposition division.

IV. With a letter dated 23 March 2006, the appellant submitted amended sets of claims in the form of a main request and 1st to 6th auxiliary requests.

Independent claims 1 and 9 of the main request read as follows:

"1. Use of a lectin in the manufacture of a medicament for the reduction and/or treatment of damage to mucosal cells and/or tissues, wherein the damage is caused by radiotherapy, a chemotherapeutic agent or a combination thereof, wherein the lectin causes proliferation of said mucosal cells and/or tissues."

"9. A pharmaceutical composition comprising a lectin and a cytoprotectant selected from a radiosensitiser, a chemoprotectant, a growth factor or combinations thereof wherein the lectin causes proliferation of mucosal cells and/or tissues."

Claims 2 to 8 and 10 to 13 related to specific embodiments of the use according to claim 1 or the pharmaceutical composition according to claim 9, respectively.

V. The following documents are cited in the present decision:

O7 Pusztai A., European Journal of Clinical Nutrition, Vol. 47, pages 691-699 (1993);

O8 Pusztai A., Archivos Latinoamericanos de Nutricion, Vol. 44, No. 4 (Suppl.), pages 10S-15S (1994);

O25 Wimer B.M., Mol. Biother., Vol. 2, pages 74-90 (June 1990);

O35 Richter M. et al., The Lancet, Vol. 2, page 894 (21 October 1967);

O36 Morelli D. et al., Cancer Research, Vol. 56, pages 2082-2085 (May 1996);

O40 Bardocz S. et al., Gut, Vol. 37, page 353-360 (1995);

O58 Declaration of Dr M.J. Chrispeels dated 23 December 2004;

O67B Declaration of Dr J.G. Moore dated 18 May 2006 with Exhibits 1 to 12;

O68 Pusztai A. et al., J. Sci. Fd. Agric., Vol. 28, pages 620-623 (1977);

O69 US-A-4,889,842;

O70 Sonis S.T. et al., Cancer Research, Vol. 54, pages 1135-1138 (1994);

O71 Keelan M., Digestion, Vol. 53, pages 101-107 (1992);

O72 Declaration of Prof. K. Pritchard-Jones dated 4 April 2006.

VI. On 18 May 2006, the respondent submitted Declaration O67B and documents O68 to O71.

VII. Oral proceedings were held on 23 May 2006.

VIII. The submissions by the appellant (patentee), insofar as they are relevant to the present decision, can be summarized as follows:

*Sufficiency of disclosure* (*Article 83 EPC)*

– The term "lectin" in present claims 1 and 9 had now been defined as being "a lectin which causes proliferation of mucosal cells and/or tissues", so

that the skilled person was taught how to carry out the invention.

– The patent provided extensive teaching to the skilled person which would enable him to select lectins other than phytohaemagglutinin (PHA) of the kidney bean (Phaseolus vulgaris) to carry out the invention.

– It would be clear to a skilled person that the lectin looked for would need to bind to a cell and then trigger the cellular activities which lead to the biological effect (see declaration O58, paragraph 6)

*Novelty (Article 54 EPC)*
*Documents O25 and O35*

– It was well established in the art that leukopenia and damage to mucosal tissues represented separate clinical indications which had different treatments.

– Document O25 or O35 merely taught that lectins had a beneficial effect on leukopenia caused by chemotherapy.

– 6-Mercaptopurine, especially if administered subcutaneously did not cause mucositis.

– The skilled person could have reasonably concluded that the total weight loss of 25-30% referred to in document O25 or O35 could be ascribed to different factors such as leukopenia or myelosuppression.

– The technical effect relied upon in the patent in suit was not the total weight loss of the animal but the restoration of the dry weights of organs of the gastrointestinal tract.

– Therefore, the skilled person could not unambiguously derive from document O25 or O35 that the reduction of weight loss upon concomitant administration of PHA was due to the healing of mucositis.

*Documents O7 and O8*

– There was no discussion in these documents of treating gut damages caused by radiotherapy or chemotherapy.

IX. The submissions by the respondent (opponent), insofar as they are relevant to the present decision, can be summarized as follows:

*Sufficiency of disclosure* (*Article 83 EPC)*

– The patent provided no guidance to the skilled person as to how to select lectins other than the PHA of the kidney bean (Phaseolus vulgaris).

– Different types of animal cells had different complex glycans (i.e., different from typical asparagine-bound sugars) on their surface and lectins bound to them in a very specific manner. The gut mucosa exhibited such glycoproteins to which PHA bound.

– However, binding of a lectin to an animal cell was a necessary but not sufficient condition to get a biological response, since the binding had to trigger the intracellular activities that lead to said biological effect.

– There was no similar information from the scientific literature that other lectins behaved as PHA because they could not bind to gut mucosal cells and/or trigger the same intracellular event that lead to the biological effect of PHA.

*Novelty (Article 54 EPC)*
*Documents O25 and O35*

– Although document O25 addressed two different problems caused by cancer therapy, namely weight loss due to mucosal tissue damage and leukopenia, it taught that PHA had protective effect against the damage to gut mucosae from radiation and chemotherapy.

– Document O36 taught that mucositis was the main side effect of chemotherapy and that weight loss reflected intestinal damage. The skilled person reading document O25 or O35 in the light of document O36 would thus conclude that the reduction of weight loss in animals treated with PHA was the result of reduction or treatment of the mucosal tissue damage by the chemotherapeutic drug 6-mercaptopurine.

*Documents O7 and O8*

– Specifying "radiotherapy or chemotherapy" as causes of the gut damage did not confer novelty on the second medical use of claim 1 insofar as it was already known from these documents to treat the damage to gut tissues with lectins.

X. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request or of the 1st to 6th auxiliary requests filed with letter dated 23 March 2006.

The respondent (opponent) requested that the appeal be dismissed.

## Reasons for the Decision

*Late filed documents*

1. In accordance with Article 114 EPC in conjunction with Article 10a(1) RPBA the criteria for the admission of new subject matter (here: late filed documents) take account of the right of the other parties to a fair procedure and is aimed at the more pragmatic and reliable conduct of proceedings. Emphasis is placed on timely filing and, although late filing is not entirely excluded by fixing strict time limits, it is discouraged by the growing probability of non-admittance as the proceedings draw to a close. Thus, new issues raised late in the proceedings and which need further extensive consideration may be disregarded

without even examining them in detail. In other words, there would be no requirement to consider whether or not these documents are "relevant" if they cannot be dealt with in the time available.

2. The board considers declaration O67B comprising Exhibits 1 to 12 in annex and documents O68 to O71 to be late-filed, these documents having been submitted on 18 May 2006, i.e., five days before the oral proceedings. As a consequence, the time remaining up to the oral proceedings before the board and even during those proceedings was insufficient for the board and the appellant to consider the implications created by the new documents.

3. Therefore, the board, in its discretion under Article 114(2) EPC in conjunction with Article 10a(1) RPBA to disregard facts or evidence which are not submitted in due time by the parties concerned, does not admit these late-filed documents into the proceedings.

*Main Request*
*Sufficiency of disclosure* (*Article 83 EPC)*

4. The respondent maintains that the subject-matter of claims 1 and 9 is not sufficiently disclosed because the patent in suit fails to teach how to select biologically active lectins other than the exemplified PHA.

5. The board first notes that claims 1 and 9 require that the lectin be one which "causes proliferation of said mucosal cells and/or tissues". Therefore, lectins which

do not exhibit the above property do not fall under the terms of the claims, so that the objection at issue is one to be strictly dealt with under Article 83 EPC only. The relevant question is thus whether lectins having the required biological activity can be arrived at without undue burden.

6. Lectins and their properties are described in paragraph [0033] of the patent in suit. Furthermore, the skilled person would understand that a prerequisite for a lectin to be physiologically active in the gut is that the lectin looked for should first bind to cells of the gut (see document O7, page 692, l-h column, third paragraph: "Binding to membrane glycans of epithelial cells of the small intestine is a necessary prerequisite for a lectin to be physiologically active in the gut"). The skilled person is thus guided to perform the binding test as illustrated e.g. in Table 1 on page 692 of document O7, showing the screening of a panel of lectins to establish their binding properties to cells of the small intestine.

7. The skilled person was also aware of the fact that the binding of a lectin to an epithelial/tissue cell of the gut was a necessary but not sufficient condition in order to induce a biological response, since the lectin looked for had also to exhibit proliferative effects on these cells and/or tissues as set out in paragraph [0014] of the patent in suit (see the expression "positive growth factors").

8. Whether or not a given lectin, once bound to a epithelial/tissue cell of the gut possessed the property of triggering the intracellular activities

leading to mitosis could easily be tested and measured by observing the weight increase of the gut tissues (see document O40, page 357, Fig. 4 and page 358, l-h column: "The strong binding of PHA to the brush border membrane of the small intestine resulted in a polyamine dependent, hyperplastic and hypertrophic growth of the tissue"). Table 1 and the legend thereof on page 692 of document O7 also illustrate the weight increase of the small intestine of rats fed with diets containing various lectins. In fact it has not been disputed by the respondent that the observed weight increase of the gut tissues during the test mostly reflects the effects of the lectin on the rapidly dividing mucosal (epithelial) cells. This view finds support on page 692, r-h column of document O7, according to which SBA (a lectin other than PHA) turns out to satisfy both requirements of binding to a cell of the gut and inducing proliferation.

9. The board accepts that it may take some time and effort to carry out the above tests but whether or not this amounts to undue burden in a way so as to violate the requirements of Article 83 EPC has to be judged in each case on the basis of the technical circumstances. In the present case the board is convinced that the skilled person will not face undue time and effort to test the known lectins for their ability as claimed.

*Novelty (Article 54 EPC)*

10. No objections under this Article have been raised against the pharmaceutical composition of independent claim 9 and the board also sees no reasons to question the novelty of this claim.

11. The novelty of claim 1 and dependent claims 2 to 8 has however been disputed. Claim 1 is in the form of a second/further medical use of a lectin for making a medicament for reducing and/or treating damage to mucosal cells and/or tissues caused by radiotherapy and/or chemotherapy. The relevant issue is whether or not this use relates to a **novel** medical use in the sense of decision G 5/83 (OJ EPO 1985, 64).

*Documents O25/O35*

12. The relevant passage in document O25 is to be found on page 83, r-h column, penultimate paragraph, citing document O35, according to which "PHA is capable of neutralizing the debilitating effects of mercaptopurine. Animals protected with concomitant injections of Difco PHA-M lost no weight and experienced no leukopenia, whereas all unprotected rabbits lost 20% to 30% weight and experienced a drop in leukocytes from mean levels of 7,000/$mm^3$ to 2,000/$mm^3$."

13. The respondent argues that the skilled person reading the above passage in document O25 or O35 in the light of document O36, teaching that weight loss during treatment with chemotherapeutic drugs was an accepted parameter for evaluating mucositis, the main side effect of these drugs (see page 2084, r-h column, last paragraph: "Since the presence of gastrointestinal mucositis adversely affects the uptake of nutrients substances, change in body weight can provide an objective measurement of intestinal damage") would conclude that the reduction of weight loss in animals treated with PHA was the result of reduction or

treatment of the mucosal tissue damage caused by the chemotherapeutic drug 6-mercaptopurine. Hence, document O25 or O35 anticipated the medical use of present claim 1.

14. However, the following facts should be noted. Firstly, treatment with any chemotherapeutic medicament has its own spectrum of adverse side effects. In the case of 6-mercaptopurine referred to in documents O25/O35, there is no evidence before the board that this immunosuppressant/chemotherapeutic drug, especially if administered subcutaneously (with no substantial exposure of the gut to the drug; see document O35: "were injected daily subcutaneously with 6-M.P."), causes mucositis. According to Declaration O72 (see paragraph 7) provided by the appellant, mucositis is rather uncommon in the treatment with 6-mercaptopurine.

15. Secondly, while it may be true that weight loss during treatment with a chemotherapeutic drug correlated with the extent of mucositis (see point 13 supra) in the case of doxorubicin, methotrexate, 5-fluorouracil, bleomycin, cytarabine and actinomycin D (see document O36, page 2082, l-h column, lines 4-7), this conclusion could not be extended to the administration of 6-mercaptopurine dealt with in documents O25/O35. The skilled person could thus have reasonably concluded that the total weight loss of 20-30% referred to in document O25 or O35 could be ascribed to different factors such as leukopenia, lack of food intake, dehydration, myelosuppression or cachexia. This leaves doubts about a disclosure by documents O25/O35 of a clear and unambiguous link between 6-mercaptopurine treatment and weight loss.

16. Finally, the technical effect relied upon in the patent in suit is not only the total weight loss of the animal but, more importantly, the restoration of the dry weights of organs of the gastrointestinal tract (see Table 12 and paragraph [0099] of the patent: "the lectin was able to protect the small intestine from damage by 5-FU and the dry weights were similar to that of the control"). This is in line with the fact already pointed out under point 8 supra, that the observed weight increase of the gut tissues during the test mostly reflects the healing effects of the lectin on the rapidly dividing mucosal (epithelial) cells.

17. In view of the foregoing, the board concludes that the skilled person could not directly and unambiguously derive from document O25 or O35, even when (in favour of the respondent's position) read in the light of the disclosure of document O36 (a questionable approach for evaluating the novelty) that the reduction of weight loss upon concomitant administration of PHA was due to the healing of mucositis.

*Documents O7 and O8*

18. These documents relate to the in vivo effects of dietary lectins on the body. It is stated on page 692, r-h column, last paragraph of document O7 and on page 11-S, r-h column, lines 1-4 of document O8 that lectins can be used "to stimulate growth in intestinal hypoplasia caused by parenteral feeding, gut resection and other gut lesions". However, there is no disclosure in these documents of treating damage to mucosal cells and/or tissues caused by radiotherapy and/or

chemotherapy, which is a pathological situation different from e.g. a bacteria-induced gut lesion.

19. In summary, treating the specific side effect of chemotherapy/radiotherapy stated in claim 1 (protection of mucosal cells/tissues) is a novel medical use different from treating e.g., bone marrow suppression or leukopenia. Treating mucositis also translates into treating a distinct pathology (and hence a distinct sub-cohort of patients), since mucositis may occur without e.g., bone marrow suppression or leukopenia caused by radiotherapy and/or chemotherapy, as shown by declaration O72, illustrating the possible side effects induced by various cancer treatment protocols.

*Remittal*

20. Since the patent was revoked on the grounds of lack of novelty and insufficiency of disclosure, and no examination of the remaining grounds for opposition has yet taken place, the board exercises its discretionary power under Article 111(1) EPC to remit the case to the first instance for further prosecution.

## Order

## For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution on the basis of claims 1 to 13 of the main request submitted with letter of 23 March 2006.

The Registrar: Chair:

P. Cremona U. M. Kinkeldey