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D E C I S I O N
of 28 October 2003

Case Number: T 0093/03 - 3.3.4

Application Number: 95924715.6

Publication Number: 0768889

IPC: A61K 38/19

Language of the proceedings: EN

Title of invention:
Cancer therapy using lymphotoxin

Applicant:
GENENTECH, INC.

Opponent:
-

Headword:
Lymphotoxin/GENENTECH

Relevant legal provisions:
EPC Art. 123(2), 84, 54, 56

Keyword:
"Added matter - new main request - (no)"
"Clarity - new main request - (yes)"
"Novelty - new main request - (yes)"
"Inventive activity - new main request - (yes)"

Decisions cited:
T 0245/93, G 0002/88

Catchword:
-

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Case Number: T 0093/03 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 28 October 2003

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 7 October 2002 refusing European application No. 95924715.6 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: R. E. Gramaglia
Members: A. L. L. Marie
R. A. M. Moufang

Summary of Facts and Submissions

I. European patent application No. 95 924 715.6, resulting from international patent application PCT/US 95/08085 published as WO 96/01121, and having the title "Cancer therapy using lymphotoxin", was refused by decision of the examining division dated 7 October 2002 pursuant to Article 97(1) EPC.

II. The examining division based its decision on the fact that claim 18 of the main request contravened the requirements of Article 52(4) EPC, whereas the subject-matter of claims 1, 5, 6, 10 and 13, all relating to the use of lymphotoxin (LT) in conjunction with chemotherapeutic compounds did not meet the requirements of Article 54 EPC. The subject-matter of the claims of a first auxiliary request was also considered by the examining division not to fulfil the requirements of Article 54 EPC. The examining division also indicated that an inventive step (Article 56 EPC) could not be acknowledged for the subject-matter of the claims of the main request.

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

(2) K. Matsunaga and H. Mashiba, Cancer Letters, 1983, Vol. 20, pages 21 to 28

(3) H. Mashiba et al., Immunobiology, 1987, Vol. 175 (1-2), page 98

(4) S. Pichyangkul and A. Khan, Proceedings of the Society for Experimental Biology and Medicine, 1986, Vol. 183, pages 231 to 236

(7) N.J. Buckley et al., Journal of Biological Response Modifiers, 1989, Vol. 8, No. 3, pages 287 to 296.

IV. Although no reason was given by the examining division for explaining why claim 18 of the main request was considered as contravening the requirements of Article 52(4) EPC, it can be derived from the section 1(a) of the minutes of the oral proceedings that said claim was considered to be directed to a method of treatment of the human/animal body by therapy. The arguments put forward in view of Articles 54 and 56 EPC against the main and the first auxiliary requests can be summarized as follows:

Article 54 EPC:

- documents (2) to (4) showed that the use of LT in conjunction with chemotherapeutic agents, such as adriamycin (doxorubicin), resulted in an increase of the cytotoxic effect on various cancerous cells.

- although it was not known at the priority date of the present application that the combined use of LT and chemotherapeutic agents sensitised the cancerous cells while protecting at the same time the non-cancerous cells, the use as claimed was not distinguishable from the medical use as already described in the prior art and these newly discovered effects were inseparably tied to the

known use. Reference was made to decision T 254/93 (OJ EPO 1998, 285).

Article 56 EPC:

– the technical problem as defined in the application (page 3, lines 31 to 37) was to investigate the therapeutic effects of LT and anti-cancer therapies. In view of the teachings of anyone of documents (2) to (4) on the combined use of LT and chemotherapeutic agents, the solution proposed in the application was obvious, since TNF-α, which had similar biological effects as LT, was known from document (7) to sensitise cancerous cells and protect non-cancerous ones.

V. The applicant lodged an appeal against the decision of the examining division and filed with its statement of grounds of appeal a new main request containing 17 claims, claims 1, 7, 10 , 12, 13 and 15 of which read:

"1. Use of lymphotoxin for the preparation of a medicament for treating a mammal having cancer, wherein the medicament is administered to the mammal in conjunction with chemotherapy, sensitises the mammal's cancerous cells to chemotherapy and protects the mammal's non-cancerous cells from chemotherapy."

"7. Use of lymphotoxin for the preparation of a medicament for treating a mammal having cancer, wherein the medicament is administered to the mammal in conjunction with radiation therapy, sensitises the mammal's cancerous cells to

radiation therapy and protects the mammal's non-cancerous cells from radiation therapy."

"10. Use of lymphotoxin for the preparation of a medicament for reducing chemotherapy induced bone marrow damage in a mammal having cancer, wherein the medicament is administered to the mammal in conjunction with chemotherapy."

"12. Use of lymphotoxin for the preparation of a medicament for reducing radiation therapy induced bone marrow damage in a mammal having cancer, wherein the medicament is administered to the mammal in conjunction with radiation therapy."

"13. Use of lymphotoxin for the preparation of a medicament for reducing chemotherapy induced alopecia in a mammal having cancer, wherein the medicament is administered to the mammal in conjunction with chemotherapy."

"15. Use of lymphotoxin for the preparation of a medicament for reducing radiation therapy induced alopecia in a mammal having cancer, wherein the medicament is administered to the mammal in conjunction with radiation therapy."

Dependent claims 2 to 6, 8, 9, 11, 14, 16 and 17 defined further embodiments of the uses claimed in the above mentioned claims.

VI. Oral proceedings were held on 28 October 2003.

VII. The arguments put forward by the appellant in writing and during the oral proceedings can be summarized as follows:

Article 54 EPC:

- whereas documents (2) to (4) disclosed that LT increased the cytotoxicity of the chemotherapeutic agents, they were silent on the protecting effect on the non-cancerous cells and even showed that LT, used alone or in combination with chemotherapeutic agents, was toxic to non-cancerous cells and hence taught away from the claimed medical uses.

- sensitisation of the cancerous cells and protection of the non-cancerous ones were two different technical effects affecting different populations of cells and not tied to each other.

- therefore, the conclusions reached in decision T 254/93 (cf *supra* section IV) did not apply to the present case, since the final effect (combination of protection of the non-cancerous cells and sensitisation of the cancerous cells) was not apparent using the known composition for the known purpose and was not disclosed or suggested in any of the prior art using LT.

- the relevant legal basis for the present case was decision G 2/88 (OJ EPO 1990, 93) which indicated that a technical effect (in the present case, the protective effect of LT on non-cancerous cells), which had not been previously made available to

the public, justified the acknowledgement of novelty.

- none of documents (2) to (4) disclosed a medicament, since supernatants were used, which were supposed to contain LT. However, LT was neither purified nor quantified in these supernatants. The nature and amount of the contaminants were also not determined. On the contrary, the application provided the skilled practitioner, for the first time, with a medicament and, hence, defined a group of patients susceptible to be treated with said medicament.

- claims 10 and 12 were also novel because they indicated applications (reducing bone marrow damage and alopecia) which were neither disclosed nor suggested in the prior art.

- claims 7 to 9, 12, 15 to 17, relating to radiation therapy were novel, because none of the cited documents referred to this aspect.

Article 56 EPC:

- there was no motivation from prior art for the skilled person to conduct experiments to further study the effect of LT, in particular, experiments which could lead him/her to discover the protecting effect of LT. Documents (2) and (4), indeed, taught away from the solution disclosed in the present application, since they showed that a combined use of LT and chemotherapeutical agents

resulted in an increase of the cytotoxicity not only on cancerous, but also on non-cancerous cells.

- a combination of anyone of documents (2) to (4) with document (7), concerned with TNF-α, was also not possible, since LT and TNF-α were two structurally and functionally different proteins.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims 1 to 17 of the main request submitted with the statement of grounds of appeal dated 17 February 2003.

Reasons for the decision

Article 84 and 123(2) EPC

1. The subject-matter of the claims of the new main request can be derived from the application as filed, in particular from the subject-matter of claims 1 to 26, so that the requirements of Article 123(2) EPC are met. The Board has no objection against the claims of the new main request under Article 84 EPC.

Article 54 EPC

2. The examining division cited documents (2) to (4) against the novelty of the subject-matter of the claims of the then main and first auxiliary requests. The new main request is identical to the main request considered by the examining division, apart from the deletion of claims 18 (*ex vivo* method of treatment) and

claims 19 and 20 (referring to an article of manufacture) and the amendment of "radiotherapy" to "radiation therapy" in claim 7. Therefore, the objection raised by the examining division in view of documents (2) to (4) also applies to the subject-matter of the claims of the new main request and the Board needs to decide whether the claims of the new main request lack novelty in view of documents (2) to (4).

3. The purpose of document (2) is to study the cytotoxic effect of LT on mouse L-929 fibroblasts, Sarcoma 180 and Ehrlich ascites tumor cells. It uses, as a LT preparation, the supernatant of human peripheral blood lymphocytes stimulated with PHA-P, which has been passed through a 0.22 µm filter or the supernatant of a "home-made" LT-producing human lymphoid cell line (page 22). Document (2) concludes that the cytotoxic activity of LT against L-929, Sarcoma 180 and Ehrlich tumor cells is increased, when combined to other chemotherapeutic agents (page 27).

4. Document (3) is an abstract published by the authors of document (2) and dealing with the antitumor effect of LT on the growth of MethA tumors. LT is obtained from the supernatant of the cultured human lymphoid cell line AL1E, which is dialysed using a Millipore ultrafiltration system. It shows that LT, alone or in combination with antitumor drugs, inhibits the tumor growth.

5. Document (4) is also concerned with a study of the cytotoxic effect of LT on various cell lines, such as HeLa (human carcinoma of cervix), Me-180 (human carcinoma of cervix) and L-929 (mouse transformed

fibroblast) in conjunction with other antitumor drugs. LT is produced by culturing PHA-P stimulated-lymphocytes, the supernatant of which is purified by chromatography on Blue Agarose and Con-A Sepharose, it is further characterized as being deprived of TNF and interferon γ (page 234, right column) and it has a specific activity of $5x10^4$ units (page 232, left column). Since the LT preparation is defined on page 234 (right column) as being "*partially* purified", this specific activity is hence indicative of a state of "*partial purification*" of the LT preparation. The conclusion reached in document (4) is that the antitumor drugs used (adriamycin, cisplatin and bleomycin) greatly potentiate the cytotoxicity of LT against the transformed mouse fibroblast and the two human carcinoma of the cervix (page 234, left column).

6. The Board firstly observes that none of the LT preparations disclosed in documents (2) to (4) has a purity level which is expected from a medicament. Indeed, the use of a 0.22 µm filter (document (2)) or of an ultrafiltration system (document (3)) does not result in some kind of purification, apart from discarding cell debris from the supernatant. The LT preparation of document (4) is said to be "*partially purified*" and has a specific activity of $5x10^4$ units. However, the specific activity of a pure LT preparation has not been determined. In the absence of this information the mention of the specific activity of the LT preparation is meaningless, since it does not allow an estimation of the degree of (im)purity of this LT preparation. Therefore, the LT preparations of documents (2) to (4) are no medical preparations, but impure fractions, wherein the presence of LT is merely

suspected, and, in the Board's view, this would have prevented the skilled person from seriously contemplating putting the claimed medical uses into practice.

7. Furthermore, the fact that documents (2) to (4) show additive *in vitro/in vivo* antitumor cytotoxicity does not mean that this effect will automatically be translated by a skilled person into clinical application. This is because, while it may be promising that a molecule achieves an *in vitro/in vivo* increase in cytotoxicity when combined with cytotoxic chemotherapeutic agents, the therapeutic index, ie the relationship between the desired and undesired effects of therapy may in reality be unchanged or made worse in an *in vivo* environment owing to a possible increase in normal cell lethality (cf document (7), page 294, end of first full paragraph, considered as an expert opinion). The Board notes that none of documents (2) to (4) provides an answer to the above question of whether or not the combination of LT with a cytotoxic chemotherapeutic agent does not damage normal cells to an unacceptable extent precluding clinical application. Indeed, the results of Table 1 (page 27) in document (2) concerning the survival of mice with Ehrlich ascites tumor do not provide this answer, because they lack statistical relevance, due to the small number of mice tested, and also because the treatment with LT obtained from peripheral blood lymphocytes (P-LT) alone or in combination with 0.6 µg actinomycin is inefficient and does not result in an increased mice survival. On the contrary, the present application, for instance in the Examples, demonstrates that LT protects rats from the adverse effects of chemotherapy and thus opens the door

to the clinical application of a combination of LT with a cytotoxic chemotherapeutic agent.

8. In view of the foregoing, the Board considers that none of the documents (2) to (4) discloses the use of LT for the preparation of a medicament for treating of mammals having cancer in conjunction with other antitumor drugs. Therefore, the subject-matter of claims 1 to 6, 10, 11, 13, 14, 16 and 17 fulfils the requirements of Article 54 EPC, as far as the combined use of LT and chemotherapy is concerned. Since none of documents (2) to (4) describes the use of LT in conjunction with radiation therapy, the subject-matter of claims 7 to 9, 12, 15 to 17 also meets the requirements of Article 54 EPC.

Article 56 EPC

9. Anyone of documents (2) to (4) can, in the Board's view, be considered as the closest prior art, since all these documents have a similar teaching concerning the combined use of a supernatant of lymphocytes cells or cells of a lymphoid cell line assumed to contain LT with other chemotherapeutic agents (cf *supra*, points 3 to 5) in order to provide a composition for the treatment of cancers. Documents (2) to (4) are preliminary "bench scale" experiments on the cytotoxic properties of LT and use LT preparations, which are either grossly impure (documents (2) and (3)), or partially purified (document (4)), whereby the degree of (im)purity of these LT preparations can be neither precisely assessed nor even roughly estimated in any of these documents.

10. In this context, the technical problem which can be defined from any of documents (2) to (4) is the provision of a suitable composition to treat cancer.

11. The solution disclosed in the claims of the main request is the provision of a combination therapy based on LT and chemotherapeutic agents or radiation therapy. The Board is satisfied in view of the results shown in the examples of the present application that this problem has been solved.

12. The question to be answered in view of the assessment of inventive step is whether this solution can be deduced in an obvious manner from anyone of documents (2) to (4) considered alone or in combination with the common general knowledge of the skilled person or other prior art documents.

13. First of all, because of the impurity of the LT preparations used in documents (2) to (4), the Board considers it rather speculative and "adventurous" for the skilled person to blindly rely upon the experimental results reported in these documents and to ascribe them to LT, in particular, since the nature and the amount of the contaminants present in these preparations, as well as their interaction with LT and the cancerous target cells, are neither known, nor determined nor even addressed to in documents (2) to (4).

14. Further, the prior art does not provide any answer to the fundamental question of whether the combination of LT with chemotherapeutic agents or radiation therapy would not damage normal cells to an unacceptable extent

precluding any clinical application of this new route (cf *supra*, section 7). Rather, document (2) (pages 23 and 24) and document (4) (page 232, right column, second full paragraph), which show that LT alone or in combination with chemotherapeutic agents is cytotoxic to L929 cells would, in the Board's view, make the skilled person, known to adopt a conservative attitude, feel insecure as to whether LT could also be cytotoxic to normal, non-cancerous cells. It should be noted that, although the L929 cells used in documents (2) and (4) are mouse transformed fibroblasts which share common features with cancerous cells, there is nevertheless no evidence on file that said cells, which derive from normal cells, are to be equated to cancerous cells and have lost all the features of normal cells.

15. Furthermore, the combination of anyone of documents (2) to (4) with document (7), showing that TNF-α at the same time sensitises the cancerous cells and protects the non-cancerous ones, as suggested by the examining division, is in the Board's view not feasible, since LT and TNF-α are two structurally and functionally distinct molecules, so that the results obtained with one of them cannot be automatically transposed to the other one. If anything, document (7) (page 295, last paragraph) shows that "*...the marked enhancement of systemic toxicity...warrants extreme caution...*" and thus rather suggests to the skilled person that combining LT with a chemotherapeutic agent might be deleterious also to normal cells.

16. Therefore, the Board is convinced that the subject-matter of the claims of the new main request cannot be derived in an obvious manner from anyone of documents

(2) to (4), considered alone or in combination with any other cited prior art document or the common general knowledge and thus fulfils the requirements of Article 56 EPC.

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 with the order to grant a patent on the basis of the following documents:

   - claims 1 to 17 of the main request filed with letter of 17 February 2003

   - description of the application as filed

   - drawing sheets 1/12 to 12/12 as filed.

The Registrar: The Chairman:

P. Cremona R. Gramaglia