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D E C I S I O N
of 25 September 2002

Case Number: T 0450/98 - 3.3.4

Application Number: 88907884.6

Publication Number: 0375724

IPC: CO7K 1/107

Language of the proceedings: EN

Title of invention:
Biologically active bactericidal/permeability-increasing protein fragments

Patentee:
NEW YORK UNIVERSITY

Opponent:
Incyte Pharmaceuticals, Inc.

Headword:
BPI fragments/NEW YORK UNIVERSITY

Relevant legal provisions:
EPC Art. 54, 56, 87, 113, 116, 123(2)

Keyword:
"Added subject-matter - (no)"
"Right to priority - (yes)"
"Novel and inventive - (yes)"

Decisions cited:
T 0288/92, T 0823/96, G 0004/93

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0450/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 25 September 2002

Appellant I: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 18 February 1998 concerning maintenance of European patent No. 0 375 724 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: A. L. L. Marie
V. Di Cerbo

Summary of facts and submissions

I. The patentee (appellant I) lodged an appeal against the interlocutory decision of the opposition division to maintain European Patent No. 0 375 724, claiming priority from US 084,335 (11 August 1987) and US 228,035 (5 August 1988), in an amended form on the basis of a set of 14 claims, claim 1 of which read:

> "1. A polypeptide fragment of the NH_2 terminal domain of bactericidal/permeability increasing protein (BPI) having less than one half the molecular weight of BPI, wherein the polypeptide fragment retains the biological activity of BPI.",

and differed from claim 1 as granted which read:

> "1. A polypeptide having less than one half the molecular weight of bactericidal/permeability increasing protein (BPI) and derived from the NH_2-terminal domain of said protein, wherein the polypeptide retains the biological activity of BPI.",

and had been considered by the opposition division as contravening the requirements of Articles 100(c)/123(2) EPC, since the expression "...derived from..." had no basis in the application as filed, claims 1 and 15 of which, for instance, read:

"1. A purified, isolated polypeptide fragment having the properties of bactericidal/permeability-increasing holoprotein, said polypeptide fragment having a substantially lower molecular weight and substantially fewer amino acids than said holoprotein.",

"15. A purified, isolated protein comprising the amino acid sequence from amino acid residue 1 to about amino acid residue 200 as set out in Figure 5.".

II. The opponent (appellant II) also lodged an appeal with his letter of 8 April 1998, but failed to submit any statement of the grounds of appeal within the time limit defined by Article 108 EPC. The Board sent on 3 August 1998 a communication pursuant to Article 108 and Rule 65(1) EPC warning him that the appeal could be rejected as inadmissible. The opponent did not react to it.

III. The following documents are mentioned in this decision:

(2) J. Weiss et al., Clinical Research, 1986, Vol. 34(2), page 537A,

(4) C.E. Ooi et al, Jornal of Biological Chemistry, 5 November 1987, Vol. 262(31), pages 14891 to 14894,

(5) P. Gray et al., Clinical Research, 1988, Vol. 36(3), page 620A,

(6) EP-0 272 489,

(10) P. Elsbach and J.Weiss, Bacteria-Host Cell Interaction, 1988, pages 47 to 60.

IV. In order to persuade the Board that claim 1 as granted did meet the requirements of Articles 100(c)/123(2) EPC, appellant I argued in its written submissions that the application had to be read in the light of the common general knowledge of the skilled person, for which derivatization of protein and/or nucleotidic sequences was at the priority date of the patent in suit a routine matter. Furthermore, the application pointed at a derivatization of the 25 kD fragments obtained by making reference to the differences between the human and rabbit BPI amino acid sequences and to the nucleotidic sequences obtained by hybridization under stringent conditions, since said conditions nevertheless allowed some degree of mismatch between the retrieved sequence and the probe. It was further argued that the reasons given by the opposition division to allow the auxiliary request in relation to the requirements of Articles 54, 56, 83 and 87 EPC equally applied to the claims as granted, ie the present main request.

V. Appellant I requested that the decision under appeal be set aside and a patent granted on the basis of the claims as granted or, as an auxiliary request, that "*the patent be maintained with a set of claims and description adapted to the maintained claims, in a manner acceptable to the Board of appeal and the appellant/patentee, with the drawings as granted.*". Oral proceedings were requested, if the Board did not agree with the main request.

VI. According to the above mentioned notice of appeal dated 8 April 1998, the opponent/appellant II requested that the decision under appeal be set aside and the patent be revoked in its entirety.

Reasons for the Decision

Procedural matters

1. The appeal of appellant I is admissible under Article 108 and Rule 64 EPC.

2. Appellant II has not submitted any ground for appeal within the time limit set out in Article 108 EPC, even after having been summoned by the EPO (communication of 3 August 1998). This appeal is, therefore, pursuant to Article 108 and Rule 65(1) EPC inadmissible. Appellant II nevertheless remains a party as of right to the appeal procedure under Article 107 EPC.

3. The consequence of the inadmissibility of the opponent's appeal is that the sole admissible appeal presently on file is from the patentee and thus the conclusions mentioned in Decision G 4/93 (EPO OJ 1994, 875) apply, ie neither the Board nor the non-appealing opponent as a party as of right under Article 107 EPC may challenge the maintenance of the patent as amended in accordance with the interlocutory decision.

Main Request

Article 123(2) EPC

4. Article 123(2) EPC requires that a European patent

application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed and prohibits, according to the established case law of the Boards of appeal, for instance decision T 288/92 (18 November 1993), the introduction of any technical information which a skilled person would not have objectively, directly and unambiguously derived from the disclosure of the application as filed, said disclosure being explicit or implicit, whereby the term "implicit disclosure" relates solely to matter which is not explicitly mentioned, but is a clear and unambiguous consequence of what is explicitly mentioned (see also decision T 823/96 of 28 January 1997).

5. The formulation of claim 1 as maintained by the opposition division results in the exclusion from the scope of claim 1 as granted (ie the present main request) of the **derivatives** of the claimed BPI fragments, for which the application as filed, according to the opposition division, does not offer any basis (Article 123(2) EPC). The incriminated expression "...derived from..." is related in claim 1 of the main request to BPI polypeptides. Therefore, the derivatives in question are peptidic ones. The skilled person at the priority date of the patent in suit was aware of the existence of methods for the chemical or enzymatic modification of the side chain of the amino acids of a given polypeptide and for the preparation of polypeptide by chemical synthesis or using recombinant DNA technology, ie methods allowing the skilled person to modify at will the amino acid sequence of a given polypeptide or its post-translational state. Thus, the derivatives in question are BPI polypeptides modified in their amino acid sequence and/or amino acid side

chains.

6. The Board has not found in the application as filed an explicit disclosure of such derivatives.

7. The question to be answered in view of the case law mentioned above (cf supra point 4) is thus whether the skilled person using his common general knowledge would consider that the application as filed implicitly contains a basis for such "derivatives".

8. An application is not generated by a *de novo* process and is not normally the result of a "spontaneous generation"-process, but is, on the contrary, embedded in a technical context which cannot be left unconsidered, when evaluating for the purpose of Article 123(2) EPC which subject-matter is embraced. In other words, an application has to be read in the light of the common general knowledge of the skilled person of the given technical field.

9. In several places in the application as filed the attention of the skilled reader is drawn to the possibility of structural variations of the BPI polypeptide in relation with its preparation using methods of recombinant DNA technology (page 5, lines 8-13; page 5, line 31 to page 6, line 1; page 7, line 34 to page 8, line 7; page 12, lines 9-28; Example 5, claims 8-11). It is, for instance, contemplated on page 7, lines 29-33 to use BPI from mammalian species other than human. In this context hybridization with a nucleotide probe is mentioned. However, this method, even carried out under stringent conditions, may lead to the isolation of nucleotidic sequences having some mismatches with the probe sequence, which might result

in the appearance in the peptidic sequence of amino acids different from those found in a "reference" BPI polypeptide.

10. The application as filed further indicates on page 2, lines 8-14 that the human and rabbit BPI differ from each other by their molecular weight. This could be due to a difference either in the amino acid sequences or in the degree of glycosylation. If the difference in the molecular weights is explained by a difference in the glycosylation patterns, a post-translational modification of the side chains of some amino acids, then the attention of the skilled person is drawn to the possibility of differential derivatization of the side-chain of some amino acids of BPI without affecting its activity. On the other hand, if the former explanation is correct, then it is suggested that modification of the amino acid sequence may not destroy the activity of BPI. Therefore, in the Board's opinion, the mention in the application as filed of the differences in the molecular weight of human and rabbit BPI leads the skilled person to assume that BPI activity is at least to some extent independent from the amino acid sequence and/or the post-translational modification of the amino acid side-chains, this assumption consequently leading to the idea of derivatization.

11. Therefore, the Board considers that the application as filed does implicitly disclose the derivatization of the BPI polypeptide (ie the modification of the amino acid side chains and/or of the amino acid sequence), which is, as required by T 823/96 (cf supra point 4), a clear and unambiguous consequence of what is explicitly mentioned and thus offers a basis for the expression

"...derived from..." in claim 1 of the main request (ie as granted), which hence does not contravene the requirements of Article 123(2) EPC.

Article 87 EPC

12. As far as the use of recombinant DNA technology methods is concerned, the first priority document differs only in its wording from the application as filed, in particular, the following parts, which are mentioned by reference to the application as filed in which they appear for the first time:

. page 5, lines 8-13,

. page 5, line 31 to page 6, line 1,
. page 12, lines 9-28,

. Example 5,

. claims 8-12

are missing in said first priority document. Nevertheless, since the first priority document refers on page 7, lines 9-19 (corresponding to page 7, line 34 to page 8, line 7 of the application as filed) to the preparation of the claimed BPI polypeptide fragments by methods of recombinant DNA technology and the other parts of the application as filed can also be found in the first priority document, the Board is satisfied that the application as filed, considered as a whole, relates to the same subject-matter as the priority document. Although the sentence on page 4, lines 16-18 of the patent in suit cannot be found in the application as filed, the disclosures of both the

patent in suit and the application as filed are identical, since said sentence only summarizes the teaching disclosed on page 5, lines 8-9, page 7, lines 24-39 and page 8, lines 43-45 of the patent in suit which respectively corresponds to the disclosure of the application as filed on page 6, lines 13-14, page 12, lines 9-28 and page 15, lines 18-22. Therefore, the patent in suit, as does the application as filed, relates to the same subject-matter as the first priority document, from which they enjoy the priority right. The relevant date for the definition of the state of the art according to Article 54(2) EPC is hence 11 August 1987.

Article 54 EPC

13. The consequence of the acknowledgement of the priority right is that documents (4), (5) and (10) are post-published and cannot be taken into consideration, whereas document (6) could only be considered for novelty under Article 54(3) EPC.

14. Document (2) describes human and rabbit BPI fragments having less than one half the molecular weight of BPI (eg 23-25, 15 and 10 kD) and obtained by treatment with elastase, ie a cleavage treatment different from that described in the patent in suit. However, nothing indicates that they originate from the NH_2-terminal part of the molecule as required by claim 1 of the main request. Furthermore, they appear to be active only when associated.

15. Document (6) describes polypeptidic antimicrobial agents derived from human polymorphnuclear leucocytes with molecular weights of 54, 29, 18, 13, 3.5 kD and

24823 daltons. The nucleotidic and amino acid sequences of the latter species is given in Fig. 20 and tremendously differs from the sequences mentioned in Fig. 5 and Table 2 of the patent in suit. According to the last Figure of document (6) none of the polypeptides described, except for the 54 kD species (ie the intact BPI which is not the subject-matter of the claims of the main request), have a NH_2-terminal sequence identical or similar to that described in the patent in suit.

16. Neither document (2) nor document (6) are thus novelty-destroying for the claims of the main request.

Article 56 EPC

17. The closest prior art is document (2), which describes (cf supra, point 14) BPI fragments obtained by elastase digestion that remain active when associated. The technical problem to be solved in view of document (2) could be defined as the provision of alternative biologically active BPI fragments. However, nothing in document (2), considered alone or in combination with the other documents presently on file, suggests the solution of claim 1 of the main request, ie fragments having their origin in the NH_2-terminal part of the BPI molecule. Furthermore, nothing in said documents indicates that such fragments could still be active in a dissociated state. Therefore, the claims of the main request fulfil the requirements of Article 56 EPC.

Articles 113 and 116 EPC

18. Appellant I has requested for oral proceedings in case the Board would not allow his main request. Since on

the basis of the above given reasons the claims as granted are allowable, this decision is given without oral proceedings.

Order

For these reasons it is decided that:

1. The appeal filed by appellant II is inadmissible.

2. The decision under appeal is set aside.

3. The patent is maintained as granted.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey