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D E C I S I O N
of 5 September 2000

Case Number: T 0767/95 - 3.3.4

Application Number: 85301752.3

Publication Number: 0165654

IPC: C07K 13/00

Language of the proceedings: EN

Title of invention:
Purified interleukin 1

Patentee:
IMMUNEX CORPORATION

Opponent:
New England Medical Center Hospitals, Inc.

Headword:
Interleukin 1/IMMUNEX CORPORATION

Relevant legal provisions:
EPC Art. 54, 56, 88

Keyword:
"Main request "novelty of a purified product: yes"
"Inventive step of the purification process and the purified product: yes"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0767/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 5 September 2000

Appellant: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 6 July 1995 rejecting the opposition filed against European patent No. 0 165 654 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
C. Holtz

Summary of Facts and Submissions

I. The appeal lies against the decision of the opposition division rejecting the opposition against European patent No. 0 165 654 (application No. 85301752.3) filed on 13 March 1985 and claiming priorities from US 622201 of 19 June 1984 (P1), US 635006 of 27 July 1984 (P2), US 674555 of 26 November 1984 (P3), US 676533 of 30 November 1984 (P4) and US 687646 of 31 December 1984 (P5). The patent had been granted on the basis of 12 claims for all the Contracting States. It relates to purified interleukin-1, now known as interleukin-1ß (IL-1ß). Claims 1 and 2 as granted for the non-AT Contracting States read as follows:

"1. A protein composition consisting essentially of human interleukin-1 having

a. a molecular weight of about 17,500 daltons as determined by SDS-PAGE;

b. a pI of about 5.9-6.3 when solubilised in a buffer comprising 2% (w/v) SDS and 2% (v/v) 2-mercapto-ethanol prior to electrophoresis; and

c. an amino acid sequence comprising the series Ser-Leu-Val-Met-Ser-Gly-Pro-Tyr-Glu-Leu-Lys-Ala-Leu-His-Leu-Gln-Gly-Gln-Asp-Met-Glu-Gln-Gln-Val-Val-Phe near the N-terminal portion of the protein, wherein said protein composition is detected as a single band by SDS-PAGE and silver staining, and is sufficiently homogeneous to have the above noted amino acid sequence determined by Edman degradation."

"2. A process for preparing a purified human interleukin-1 composition as defined in claim 1 from a crude solution of human interleukin-1, comprising the steps of

a. exposing the crude solution of human interleukin-1 to a red triazinyl dye-ligand bound to a support matrix;

b. washing unbound components of the crude solution from the support matrix; and

c. eluting a purified human interleukin-1 from the dye-ligand with a salt gradient.

Dependent claims 3 to 5 related to specific embodiments of the process of claim 2, while claims 6 to 12 related to medical uses of the interleukin-1 composition of claim 1. The claims for the Contracting State AT were drafted as corresponding process claims.

II. The following documents are referred to in the present decision:

(1) Dinarello C.A. et al., Proc. Natl. Acad. Sci. USA, Vol. 74, pages 4624-4627 (1977);

(2) Rosenwasser L.J. et al., J. Exp. Med., Vol. 150, pages 709-714 (1979);

(3) Dinarello C.A. et al., Reviews on Infectious Diseases, Vol. 6, pages 51-95 (January-February 1984);

(4) EP-A-0 161 901;

(5) Welte K. et al., J. Exp. Med., Vol. 156, pages 454-464 (1982);

(6) Mosley B. et al., Proc. Natl. Acad. Sci. USA, Vol. 84, pages 4572-4576 (1987);

(8) Sterling J., Genetic Engineering News, Vol. 5, pages 1 and 21 (1985);

(9) Auron P.E. et al., Proc. Natl. Acad. Sci. USA, Vol. 81, pages 7907-7911 (1984);

(12) Dinarello C.A., Fever, edited by J.M. Lipton, Raven Press, New York, pages 1-9 (1980).

III. The appellant submitted essentially the following arguments:

Right to priority

- Owing to the presence of a partial amino acid sequence in claim 1, the claimed subject-matter could only base its priority on priority document (P3) filed 26 November 1984. The respondent had indeed no sequenceable IL-1ß before that date. It was only after the amino acid sequence of IL-1ß had become available to a scientist of the respondent upon peer reviewing the manuscript underlying document (9) submitted by Dr Auron for publication in July 1984, that accurate amino acid information was filed with the priority document (P3) of 26 November 1984. This was supported by the respondent's filing in late 1984 of an application claiming the DNA encoding IL-1ß comprising the same 6 errors as in Dr Auron's manuscript.

- Priority document (P1) did not report any amino acid sequence but only an amino acid composition in Table I. This Table I, however, had been corrected after the respondent's scientist had access to the amino acid sequence reported in the manuscript underlying document (9) (a comparison of Table I of both priority documents (P1) and (P4) shows more His and Arg in (P1)).

- During the Fourth International Lymphokine Workshop held on 17 to 21 October 1984 at Schloß Elmau in Klais/Oberbayern (FRG), Dr Auron, the co-author of document (9), presented his work on the cloning of IL-1ß and briefly displayed the amino acid sequence thereof. However, a representative of the respondent misstated that Dr Auron had cloned the wrong gene.

Novelty

- The claimed interleukin-1 lacked novelty (Article 54(3) EPC) over document (4), which disclosed human IL-1ß and a method to obtain it in pure form.

- The claimed interleukin-1 and the leukocytic pyrogen (LP) disclosed by document (1) were the same protein subsequently termed IL-1ß. Document (1) disclosed highly purified LP as shown by a single peak of radioactivity at pI = 7.0-7.1 in the IEF SDS-PAGE of Fig. 5. Homogeneity of this "labelled LP" preparation was further confirmed by subjecting this peak to RP-HPLC chromatography.

- The differences in molecular weight (mw) (15 kd of document (1) compared with 17.5 kd of claim 1) were not significant because mw measurements could be expected to vary by 4-5 kd.

- Document (1) reported for the LP material a pI of 7.0-7.1, which was the accepted pI for mature IL-1ß (see document (6)). This was a proof that the LP material was pure IL-1ß.

- The value for the pI of 5.9-6.3 recited in claim 1.b was an aberration due to contamination or a different procedure which could not serve to distinguish over the prior art.

- As for the partial amino acid sequence stated in claim 1 of the patent in suit, providing the partial amino acid sequence of a known protein did not render the protein novel since it was an intrinsic feature thereof. The opposition division accepted that "the statement of a partial amino acid sequence in claim 1 of the patent in suit was a distinguishing feature over the non sequenceable protein referred to in document (1)". However, the claimed protein was no more purified than the protein disclosed in document (1). In fact, the information about the partial amino acid sequence stated in claim 1 of the patent and the correct amino acid composition of Table 1 had become available to the respondent from peer reviewing the manuscript underlying document (9)(see under the heading "right to priority" supra). All these facts together with the above mentioned discrepancy in the pI value showed that the claimed protein could not be any more pure than that disclosed by document (1).

- Subsequent work (see documents (2) and (3)) confirmed that the authors of document (1) had obtained pure IL-1ß. Therefore, claim 1 was also not novel in respect of documents (2) and (3), respectively.

Inventive step

- Since no claim of the patent is suit was entitled to a priority date earlier than that of priority document (P3) (26 November 1984), the oral disclosure at the meeting reported in document (8) (see page 21, r-h column), namely the Fourth International Lymphokine Workshop held on 17 to 21 October 1984 at Schloß Elmau in Klais/Oberbayern (FRG)), the content of which was given in document (9), was citable as prior art. This conference made available a cloning strategy for obtaining pure IL-1ß in an obvious fashion.

- Assuming that the partial amino acid sequence in claim 1 of the patent in suit were a distinguishing feature over the LP protein referred to in document (1), obtaining pure IL-1ß was an obvious desideratum

- The purified protein had no unexpected advantageous properties over the protein of document (1).

- Further, the procedure disclosed in document (5) involved dye ligands for separating interleukin-2 from contaminants. It would have been obvious for the skilled person to further purify the protein of document (1) by adopting this technique in order to arrive at the process of claim 2 and the interleukin-1 of claim 1.

VI. The submissions by the respondent can be summarized as follows:

Right to priority

- Claim 1 of the patent in suit validly claimed priority from the second priority document (P2) filed on 27 July 1984 (see paragraph I supra), since it disclosed the N-terminal amino acid sequence stated therein. The appellant's assertions with regard to the Fourth International Lymphokine Workshop and the peer review by a scientist of the respondent of the manuscript underlying document (9) were strongly denied.

Novelty

- Documents (1) to (3) did not disclose a single protein in a form sufficiently pure to allow amino acid sequencing. The semipurified nature of this preparation was admitted by the author of document (1) in documents (12), (3) and (10).

- Document (4) did not disclose a purified mature IL-1ß protein as stated in claim 1 of the patent in suit but only related to the inactive precursor of interleukin-1ß.

Inventive step

- Even by assuming that the content of Document (9) had been made available to the public at Schloß Elmau in October 1984, this was anyway after 27 July 1984, ie the date of filing of priority document (P2), on which the priority of the claimed subject-matter was validly based.

- The problem to be solved was to provide sufficient homogeneous IL-1ß for various therapeutic purposes. The patent solved this problem for the first time.

- The skilled person would not have been motivated to use the method for purifying IL-2 of document (5) to purify IL-1ß to homogeneity because this document taught that IL-2 and IL-1 had very different properties.

VII. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 165 654 be revoked.

The respondent (patentee) requested as main request that the appeal be dismissed; or as first and second auxiliary requests, that the decision under appeal be set aside and the patent be maintained on the basis of the claims of the "First Auxiliary request" or the claims of the "Second Auxiliary request", both filed with the letter dated 11 January 2000.

Reasons for the Decision

1. The appeal is admissible

Main request
Right to priority

2. The respondent maintains that the claimed subject-matter can only base its priority on document (P3) filed 26 November 1984 because the respondent had no sequenceable IL-1ß before that date. However, the board observes that the sequence stated in claim 1 of the patent in suit Ser-Leu-Val-Met-Ser-Gly-Pro-Tyr-Glu-Leu-Lys-Ala-Leu-His-Leu-Gln-Gly-Gln-Asp-Met-Glu-Gln-Gln-Val-Val-Phe is to be found on page 10 of priority document (P2) filed on 27 July 1984, upon which the priority of the claimed subject-matter is thus validly based. As a consequence, the Fourth International Lymphokine Workshop held on 17 to 21 October 1984 at Schloß Elmau in Klais/Oberbayern (FRG)), the content of which the appellant maintains to be given in document (9), is not citable as prior art.

Novelty over documents (1) to (3)

3. It has to be established whether or not the LP preparation of documents (1) or (2), or the IL-1 as it is named in document (3) exhibit features (a) to (c) stated in claim 1 of the patent in suit.

4. As for feature (a), ie the molecular weight, the board cannot accept the appellant's proposition that the difference in mw (15 kd of document (1) compared with 17.5 kd of claim 1) is not significant. While it is true that Fig. 1, track B of document (1) shows a protein with a possible mw of 15,000 d after gel filtration, the mw of the LP preparation in Fig. 1, track D has shifted to a mw less than that of the cytochrome C standard (mw = 12,382

d) following immunoadsorbtion (compare tracks B, C and D of Fig. 1, taking into account that the mw's increase rightwards). Thus, a correct comparison is not 15 kd of document (1) compared with 17.5 kd of claim 1 but rather < 12,382 with 17,500. Therefore, the conclusion cannot be drawn that document (1) discloses a protein having a mw of 17,5 kd as stated in claim 1 of the patent in suit.

5. As regards feature (b), namely a pI of about 5.9-6.3 when solubilised in a buffer comprising 2% (w/v) SDS and 2% (v/v) 2-mercaptoethanol prior to electrophoresis, it has to be noted that document (1) relates to a "pool I" which contains all the pyrogen activity and which gives upon IEF three proteins having pI = 4.7, 5.6 and 7.0 (see page 4626, l-h column). Moreover, the pI value depends on the particular conditions used for performing the IEF SDS-PAGE. A higher SDS concentration renders the protein more acidic (more negative groups). In view of this, a comparison between the pI's of the LP material referred to in document (1) with the claimed one is not possible. Therefore, the appellant's proposition that the pI of 5.9-6.3 recited in claim 1.b is an aberration due to contamination or a different procedure, fails.

6. Feature (c) of claim 1 states a partial amino acid sequence, the requirements that IL-1ß be detected as a single band by SDS-PAGE and silver staining, and be sufficiently homogeneous to have the above noted amino acid sequence determined by Edman degradation. The appellant maintains that Fig. 5 of document (1) discloses homogeneous highly purified IL-1ß because it represents an IEF SDS-PAGE showing a single peak of radioactivity at pI = 7.0-7.1, which in turn yields a single peak when

subjected to RP-HPLC chromatography (see page 4626, r-h column of document (1): "Further evidence that labelled LP was homogeneous was confirmed ...under high pressure gradient of CH_3CN/10mM KH_2PO_4...a single peak of radioactivity was observed"). However, the board notes that the major peak in Fig. 5 has a distinct shoulder indicative of more protein species. Furthermore, it is possible to deduce from Fig. 2 on page 5 of document (12), a review of studies on "Endogenous Pyrogens" originating from the same author, that the result of subjecting this single peak from IEF SDS-PAGE to RP-HPLC chromatography step is a peak with a great many shoulders. Therefore, both Fig. 5 of document (1) and Fig. 2 of document (12) suggest a mixture of proteins for the LP material. The semipurified nature of the LP preparation is indeed confirmed by the following statements to be found in the scientific literature : "It was clear that the homogeneous band of the pyrogen consisted of at least three proteins" (document (1), page 4626, l-h column); "one cannot rule out the presence of interfering substances" (document (12), page 6); "However, there is **no** analysis of the amino acid sequence of IL-1 that would provide definitive proof of the homogeneity of IL-1 preparations" (document (3), page 55, r-h column; emphasis added). There was thus a blockage preventing the skilled person from sequencing the LP material of documents (1) or (2), or the IL-1 of document (3). Regardless of whether it arose from the semipurified nature of these preparations or from the process yielding only traces of the protein, this blockage prevented the teaching of documents (1), (2) or (3) from making available to the public a protein having technical feature (c) of claim 1.

7. In conclusion, since there is no evidence before the board that the LP material of documents (1) or (2) or the IL-1 of document (3) exhibit features (a) and (c) of claim 1 of the patent in suit, these documents do not affect the novelty thereof.

8. The appellant submits that the claimed protein is no more purified than the protein disclosed in document (1). In support of his proposition, arguments are provided inter alia about a peer review of the manuscript underlying document (9) by a respondent's scientist. In the board's judgement, however, it is the appellant who carries the burden of proof regarding facts barring patentability. Since the appellant failed to provide any corroborating evidence, these unsubstantiated allegations must be disregarded and the patent proprietor has to be given the benefit of doubt.

Novelty over document (4)

9. Document (4) is a European patent application enjoying a first priority date earlier than that of (P2) (see point 2 supra) and is thus prior art according to Article 54(3) EPC. It does not disclose a purified mature IL-1ß protein as stated in claim 1 of the patent in suit but merely relates to the inactive precursor of interleukin-1ß having a mw of 30 kd (page 7, line 3). Potential signal sequence cleavage sites are given between Ala^{8} and Ser^{9} and between Lys^{210} and Met^{211} (page 8, lines 18, 22 and 23). However, even assuming that document (4) enables the skilled person to cut the precursor protein at these sites, no mature IL-1ß as stated in claim 1 of the patent in suit would be obtained

because these cutting sites have turned out to be wrong.

10. In view of the above findings, the novelty of the subject-matter of claim 1 has to be accepted. Since claims 2 to 12 all rely on the novel IL-1ß of claim 1, they have equally to be considered novel.

Inventive step

11. The board views document (1) as representing the closest prior art (documents (2) and (3) disclose essentially the same subject-matter as document (1)). However, the "LP" material of document (1) was not pure. The patent in suit addresses the problem of providing homogenous IL-1ß for inter alia clinical investigations and a process for its preparation. The board accepts that the patent solves the above problem. It has thus to be established whether or not homogenous IL-1ß and the process for its preparation follow in an obvious fashion from the prior art.

12. The appellant argues (see page 7 of the notice of appeal, 5th paragraph, case (3)) that "a purified protein can be patentable over a crude preparation thereof if no method was known for purifying the impure protein" and that "pure IL-1ß was an obvious desideratum, satisfied once a suitable purification technique became available" (ibidem, paragraph 4). The board agrees. As, on the evidence, the provision of homogenous IL-1ß for inter alia clinical investigations was only possible by solving the problem of developing a suitable purification technique, an inventive step can here be acknowledged for the provision of homogenous IL-1ß if the purification technique stated in claim 2 of the patent in suit does

not follow in an obvious way from the prior art. Thus, contrary to the appellant's view, the purified protein need not exhibit unexpected advantageous properties over the protein of document (1) to be inventive, should the process for its preparation not be obvious.

13. The appellant maintains in essence that the skilled person would adopt the procedure disclosed in document (5) involving chromatography on dye ligands (procion red agarose) for separating interleukin-2 from contaminants in order to further purify the LP material of document (1). There was a high expectation of success in obtaining homogenous IL-1ß by applying this technique since IL-2 and IL-1ß were known to have the same size and pI and were expected to be contaminated by the same proteins (lymphokines) given their biological activity and origin.

However, according to document (5), "The binding of IL-2 to these dyes is likely a result of the electrostatic or hydrophobic interactions" (page 460, last paragraph) and "Lymphokines...such as IL-1, á-interferon, ß-interferon,... have different capabilities of forming hydrophobic interactions. We have exploited these properties to separate IL-2 from other lymphokines..." (top of page 461). These passages demonstrate that IL-2 and IL-1ß behave **differently** vis-à-vis chromatography on a dye ligand. Therefore, the skilled person reading document (5) would not have been motivated to adopt this technique for separating IL-1ß from contaminants. Consequently, the process of claim 2 and the homogeneous IL-ß of claim 1 fulfil the requirements of Article 56 EPC. Since claims 3 to 12 all rely on the inventive homogeneous IL-1ß of claim 1 or inventive process of claim 2, their inventive step has equally to be accepted.

14. The board is satisfied that the claims of the main request meet the requirements of the EPC. No need arises to consider the "First Auxiliary request" or the "Second Auxiliary request".

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

U. Bultmann U. M. Kinkeldey