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# D E C I S I O N
# of 14 July 2000

**Case Number:** T 1147/98 - 3.3.4

**Application Number:** 85304848.6

**Publication Number:** 0169016

**IPC:** C07K 14/00

**Language of the proceedings:** EN

**Title of invention:**
Polypeptide cartilage-inducing factors found in bone

**Patentee:**
CELTRIX PHARMACEUTICALS, INC.

**Opponents:**
Novartis AG Patent and Trademark Dept.
OSI Pharmaceuticals, Inc.

**Headword:**
Cartilage-inducing factor/CELTRIX PHARMACEUTICALS INC.

**Relevant legal provisions:**
EPC Art. 84, 123(2)(3), 54, 56, 87(1)

**Keyword:**
"Main request : Entitlement to priority (yes), Novelty (yes)"
"Inventive step (yes)"

**Decisions cited:**
T 0184/91, G 0011/91

**Catchword:**
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**Case Number:** T 1147/98 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 14 July 2000**

**Appellant:** (Proprietor of the patent)
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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 8 October 1998 revoking European patent No. 0 169 016 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey
**Members:** R. E. Gramaglia
W. Moser

## Summary of Facts and Submissions

I. The appeal is against the decision of the opposition division revoking European patent No. 0 169 016 (application No. 85 304 848.6) filed on 8 July 1985 and claiming priority from US 630938 of 16 July 1984 (P). The patent relates to a cartilage inducing factor (CIF-B, now known as TGF-ß2) found in bone and had been granted on the basis of 9 claims for the non-AT Contracting States and 8 claims for AT. Claims 1 and 4 as granted for the designated Contracting States, except AT, read as follows:

"1. A process for isolating a polypeptide cartilage-inducing factor from bone, which factor:

(a) is found in mammalian bone;

(b) is a co-factor for inducing cartilage formation;

(c) has activity in the TGF-ß assay; and

(d) is a dimer having an approximate molecular weight of 26,000 daltons as determined by SDS-PAGE;

the process comprising:

(i) treating demineralized bone with a chaotropic extractant that solubilizes nonfibrous proteins;

(ii) subjecting the extract from step (i) to gel filtration to recover a fraction containing proteins of molecular weight 10,000-40,000 daltons;

(iii) adsorbing the fraction from step (ii) onto a carboxymethyl cellulose cation exchanger at approximately pH 4.5-5.5 under denaturing conditions;

(iv) eluting the adsorbed fraction from the cation exchanger with a sodium chloride gradient;

(v) subjecting the portion of the eluate of (iv) that elutes at approximately 150 to 250 mM sodium chloride to RP-HPLC or a nondenaturing gel electrophoresis; and

(vi) recovering said factor from the RP-HPLC or nondenaturing gel electrophoresis.

4. A polypeptide cartilage-inducing factor, which factor:

(a) is found in mammalian bone;

(b) is a co-factor for inducing cartilage formation;

(c) has activity in the TGF-ß assay;

(d) is a dimer having an approximate molecular weight of 26,000 daltons as determined by SDS-PAGE;

(e) is isolatable by a process according to claim 1 or claim 2; and

(f) does not have the N-terminal sequence

Ala-Leu-Asp-Thr-Asn-Tyr-Cys-Phe-Ser(Ser)Thr-Glu-

Lys-Asn-Cys-Cys-Val-Arg-Gln-Leu-Tyr-Ile-Asp-Phe-
Arg-Lys-Asp-Leu-Gly-Trp- "

II. The reasons given for the refusal was that the subject-matter of the amended claims of all requests then on file did not comply with the requirements of Articles 84 and 123(2) EPC. In view of this negative finding, the decision under appeal did not relate to the issues of entitlement to priority, novelty and inventive step of the claimed subject-matter. A third auxiliary request was rejected under Article 114(2) EPC because the opposition division considered this request to be against the principle of procedural expediency and fairness to the other parties.

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

(R1) Seyedin S.M. et al., Proc. Natl. Acad. Sci. USA, Vol. 82, pages 2267 to 2271 (April 1985);

(R2) EP-A-0 128 849 (published 12 December 1984);

(R10) Seyedin S.M. et al., J. Cell Biology, Vol. 97, pages 1950 to 1953 (December 1993);

(R11) US-A-4 434 094 (published 28 February 1984);

(R12) Holley R.W. et al., Cell Biology International Reports, Vol. 7, pages 525 to 526 (July 1983);

(R13) Holley R.W. et al., Proc. Natl. Acad. Sci. USA, Vol. 77, pages 5989 to 5992 (October 1980);

(R16) Tucker R.F. et al., Science, Vol. 226, pages 705

to 707 (November 1994);

(R17) Holley R.W. et al., Growth factors in biology and medicine, Pitman, London (Ciba Foundation Symposium 116), pages 241 to 252 (January 1985) and

(R25) McPherson J.M. et al., Biochemistry, Vol. 28, pages 3342 to 3347 (1989).

IV. On appeal, the appellant (patentee) filed claims 1 to 4 of a main request and claims 1 to 4 of a first, second and third auxiliary request and requested that the decision under appeal be set aside and that the patent be maintained on the basis of either of these claim requests. Claims 1 to 4 of the main request for all designated Contracting States, except AT, wherein the amendments over the corresponding granted claims are shown in bold, read as follows:

"1. A **homogenous chondrogenic/osteogenic protein**, which **protein**:

(a) is found in mammalian bone;

(b) **promotes** cartilage formation;

(c) has activity in the **in vitro chondrogenic** assay;

(d) is a dimer having an approximate molecular weight of 26,000 daltons as determined by SDS-PAGE;

(e) **is not TGF-ß1; and**

(f) is isolatable by a process consisting of the steps

of:

(i) treating demineralized bone with a chaotropic extractant that solubilizes nonfibrous proteins;

(ii) subjecting the extract from step (i) to gel filtration to recover **chondrogenically active** fraction containing proteins of molecular weight 10,000-40,000 daltons;

(iii) adsorbing the **chondrogenically active fraction** from step (ii) onto a carboxymethyl cellulose cation exchanger at approximately pH 4.5-5.5 under denaturing conditions;

(iv) eluting the **chondrogenically active** fraction from the cation exchanger with a **10 to 400 mM** sodium chloride gradient;

(v) subjecting to RP-HPLC or nondenaturing gel electrophoresis the **chondrogenically active** portion of the eluate of (iv) **that elutes after the bulk proteins, which portion yields only two peaks of chondrogenic activity in RP-HPLC**, and

(vi) recovering said **protein** from the second of said two peaks on RP-HPLC or recovering the corresponding protein from the nondenaturing gel electrophoresis.

2. A protein according to claim 1 wherein the bone of (a) is bovine bone.

3. An implant composition for inducing chondrogenesis/ osteogenesis which contains the protein of claim 1.

4. Use of the protein of claim 1 in the manufacture of an implant composition for inducing chondrogenesis/ osteogenesis."

Claims 1 to 4 of the main request for the Contracting State AT were formulated as corresponding process or use claims.

V. As regards the main request, the arguments submitted by the appellant were essentially as follows:

*Article 84 EPC*

- All passages decided by the opposition division as lacking clarity had been replaced by a wording which fully met the requirements of Article 84 EPC.

*Article 123(2) and (3) EPC*

- All the amendments satisfied the requirements of Article 123(2) and (3) EPC.

*Entitlement to priority (Article 87(1) EPC)*

- All the claims were entitled to priority because they found a basis in the priority document (P).

*Novelty and inventive step*

- None of the cited prior art documents disclosed or

rendered obvious the claimed homogeneous chondrogenic/osteogenic protein.

VI. Respondents I and II (opponents O1 and O2) withdrew their oppositions with letters dated 1 and 5 November 1999, respectively.

## Reasons for the Decision

1. The appeal is admissible.

*Main request*

*Article 123(2) and (3) EPC*

*Claims 1 to 4 for all designated Contracting States, except AT*

2. Claim 1 is based on claims 1 and 4 as granted with a series of amendments therein. The wording "a homogeneous chondrogenic/osteogenic protein" instead of a "co-factor for inducing cartilage formation" (claim 4 as granted) finds a basis in the application as filed on page 17, lines 15 to 16 ("Chondrogenically/osteogenically effective amounts of the protein..") and on page 1, lines 26 to 29 ("homogeneity"). Feature (b) of claim 1 "promotes cartilage formation" instead of "a co-factor for inducing cartilage formation" is to be found on page 17, line 13 ("for inducing cartilage growth") of the application as filed. Feature (c) of claim 1 "in vitro chondrogenic assay" instead of "TGF-assay" is to be found on page 10, line 23 ("chondrogenic activity") of the application as filed. The wording "chondrogenically active fraction" in steps (ii), (iii)

and (iv) of claim 1 finds a basis in the application as filed on page 10, lines 24 to 27. The wording in step (iv) of claim 1 "a 10 to 400 mM sodium chloride gradient" finds a basis in the application as filed on page 9, lines 23 to 24. The wording in step (v) of claim 1 "that elutes after the bulk proteins, which portion yields only two peaks of chondrogenic activity in RP-HPLC" relates to the portion of the eluate from the preceding step which is subjected to RP-HPLC. It finds a basis in the application as filed on page 9, lines 25 to 29, on page 10, lines 1 to 10 and in Figures 2 and 3. Re-worded step (vi) of claim 1 relates to the specific protein to be recovered, namely protein "CIF-B" from the second of the two peaks on RP-HPLC. It finds a basis in the application as filed on page 15, lines 3 to 4. In claims 2, 3, and 4, the term "factor" has been replaced by "protein". This is to be found on page 15, line 6 ("both proteins") of the application as filed. Furthermore, the claims are narrower than the granted claims since they are limited to one single homogeneous protein corresponding to peak B of Figure 3, while the granted claims were not so limited. In conclusion, the claims of the main request do not infringe Article 123(2) and (3) EPC.

*Claims 1 to 4 for the Contracting State AT*

3. Claims 1 to 4 of the main request for the Contracting State AT comprising the same allowable amendments referred to in paragraph 2 above also do not infringe Article 123(2) and (3) EPC.

*Article 84 EPC (Clarity)*

*Claims 1 to 4 for all designated Contracting States, except AT*

4. Claim 1 states that the protein is homogeneous, should not be TGF-ß1 (another name for "CIF A" having the N-terminal amino acid sequence stated in granted claim 4(f)) and should inter alia be obtained through steps (v) and (vi), which indicate without ambiguity which portion of the eluate from the preceding step has to be subjected to RP-HPLC (step (v)) and which specific protein must be recovered ("CIF B")(step (vi)). For these reasons, the board is satisfied that claim 1 and claims 2 to 4, comprising a reference to claim 1, are clear.

*Claims 1 to 4 for the Contracting State AT*

5. Claim 1 of the main request for the Contracting State AT includes the same technical features referred to above found by the board to be clear to the skilled person. Therefore, claim 1 and claims 2 to 4, comprising a reference to claim 1, are also clear.

*Extent of scrutiny*

6. In the decision under appeal, the opposition division does not comment on the issues of the entitlement to priority of the claimed subject-matter and the novelty/inventive step thereof. Since the application underlying the patent in suit has already been object of appeal proceedings (T 0184/91 of 11 June 1993, not published in the OJ EPO) and subsequent referral to the Enlarged Board of Appeal (G 011/91, OJ EPO 1993, 125), the board, for the sake of procedural expediency exerts its power of discretion under Article 114(1) EPC for also deciding whether or not the claims at issue fulfil the requirements of novelty/inventive step.

*Entitlement to priority (Article 87(1) EPC)*

*Claims 1 to 4 for all designated Contracting States, except AT*

7. It has been argued before the opposition division that the claims lacked novelty and/or inventive step in view of one or more of documents (R1), (R2), (R16) and (R17) published between the filing date of priority document (P) and that of the application. It has thus to be decided whether the above documents are prior art or not depending upon whether the claimed subject-matter is or is not entitled to the priority date of (P).

8. The combination of all the features stated in claim 1 has been disclosed in the priority document (P), exception made for the "product-by-process" feature of step (ii) which relates to the molecular weight range of the fraction being subjected to carboxymethyl cellulose chromatography (CMC) of step (iii). In claim 1 under consideration, the range is defined as 10,000-40,000 daltons while in the priority document (P), it is 10,000-30,000 daltons. On page 9, lines 19 to 29 of the latter, the fraction being subjected to CMC ("fraction F2") is labelled as the "LMW 10,000-30,000 daltons", while the same "fraction F2" is named "LMW 10,000-40,000 daltons" in the application as filed (page 9, lines 10 to 13). In spite of this discrepancy, in the board's view, there is no reason for assuming that the skilled person would not arrive at the same "CIF-B" protein which is claimed, by following the purification protocol disclosed in the priority document (P). This is because both documents state that it is "fraction F2 of Figure 1 with the greatest activity" that has to be selected for CMC. Fraction F2 corresponds to fraction numbers ~98 to ~108 (see abscissa of Figure 1 of both documents), and thus this fraction has of necessity to contain proteins in the same range of molecular weight, regardless of its different labelling as "LMW 10,000-30,000 daltons" or "LMW 10,000-40,000 daltons" in the two documents. Therefore, the board is satisfied that what is disclosed in the priority document (P) is the same invention as that described in the application as filed and thus claim 1 at issue and hence claims 2 to 4, because they comprise a reference to claim 1, are entitled to the priority date of document (P). As a consequence, documents (R1), (R2), (R16) and (R17) are not prior art.

*Claims 1 to 4 for the Contracting State AT*

9. The conclusion arrived at under paragraph 8 supra also applies to claims 1 to 4 for the Contracting State AT since the fact that the range in claim 1 step (ii) is defined as 10,000-40,000 daltons while in the priority document (P), it is 10,000-30,000 daltons, is immaterial to the issue of Article 87(1) EPC (see paragraph 9 supra).

*Novelty*

*Claims 1 to 4 for all designated Contracting States, except AT*

10. It has been argued before the opposition division that the claims lacked novelty in view of documents (R12) and (R13), relating to growth inhibitors capable of arresting the growth of various cells, isolated from the culture medium of BSC-1 (African green monkey kidney epithelial) cells by concentration, gel filtration and HPLC. However, later document (R25) taken as an expert opinion shows that the growth inhibitory activity from these BSC-1 cells is actually a mixture of 90% TGF-ß2 (CIF-B) and 10% TGF-ß1 (CIF-A) (see page 3446, r-h column, second full paragraph). Documents (R12) and (R13) do not disclose and thus do not make available to the public homogeneous CIF-B as required by claim 1 at issue. For these reasons, the board is satisfied that the subject-matter of claim 1 is novel. Since claims 2 to 4 all rely on the novel protein of claim 1, there is no need to consider their novelty separately from that of claim 1.

*Claims 1 to 4 for the Contracting State AT*

11. Claims 1 to 4 for the Contracting State AT also rely on the homogeneous chondrogenic/osteogenic CIF-B protein, found to be novel (see paragraph 10 supra). Therefore, they are also novel.

*Inventive step*

*Claims 1 to 4 for all designated Contracting States, except AT*

12. Once the respective amino acid sequences have been compared after the priority date of the patent in suit, the claimed CIF-B protein has turned out, it is true, to be related to, but different from, the growth inhibitor disclosed by documents (R12) and (R13). While these documents are relevant for the novelty issue (see point 7 supra), they are not when deciding on the issue of inventive step, because the information that CIF-B was related to growth inhibitor had not been available to the skilled person at the priority date of the patent in suit. In the absence of that information, there was no reason for a skilled person, looking for a factor involved in the generation of bone tissue and cartilage, to turn to documents (12) and (13), which relate to growth inhibitors capable of arresting the growth of various cells, which growth inhibitors have been isolated from the culture medium of African green monkey kidney epithelial cells (BSC-1 cells). Rather, in the board's judgement, document (R11) represents the closest prior art (with document (R10) essentially disclosing the same subject-matter as document (R11)). Document (R11) relates to osteogenic factor partially purified from demineralized bone. The disclosure of document (R11), however, does not lead to a homogeneous

protein capable of inducing bone tissue and cartilage growth, namely a protein susceptible of various therapeutic applications because the "partially purified osteogenic factor" disclosed therein is not pure. The board is satisfied that the patent in suit solves the problem of providing such homogeneous chondrogenic/ osteogenic protein. It has thus to be established whether or not the claimed protein follows in an obvious way from the prior art. In the board's view, document (R11) does not suggest that it is possible to isolate the claimed homogeneous chondrogenic/osteogenic protein from the partially purified osteogenic factor extracted from demineralized bone disclosed therein, much less teaches a purification process that would yield that protein. Consequently, the subject-matter of claim 1 fulfils the requirements of Article 56 EPC. Since claims 2 to 4 all rely on the inventive homogeneous chondrogenic/osteogenic protein of claim 1, there is no need to consider their inventive step separately from that of claim 1.

*Claims 1 to 4 for the Contracting State AT*

13. Since the processes of claims 1 to 3 and the use of claim 4 for the Contracting State AT rely on the homogeneous chondrogenic/osteogenic CIF-B protein found to be inventive (see paragraph 12 supra), they also involve an inventive step.

*Conclusions*

14. The board is thus satisfied that the claims of the main request for all designated Contracting States meet the requirements of the Convention. No need arises to

consider the auxiliary requests.

15. Having regard to the restriction of the scope of the claims of the main request compared to that of granted ones, the necessary adaptation of the description should be left to the competent opposition division.

## 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 maintain the patent on the basis of claims 1 to 4 of the main request for all designated Contracting States, except AT, as filed on 17 February 1999 and claims 1 to 4 of the main request for the Contracting State AT as filed on 20 July 2000, and a description to be adapted thereto.

The Registrar: The Chairwoman:

U. Bultmann U. M. Kinkeldey