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D E C I S I O N
of 13 May 2004

Case Number: T 1074/00 - 3.3.4

Application Number: 87905074.8

Publication Number: 0314705

IPC: C07K 14/00

Language of the proceedings: EN

Title of invention:
A novel family of primate hematopoietic growth factors

Patentee:
GENETICS INSTITUTE, INC.

Opponents:
DSM Gist Holding B.V.
Monsanto Company

Headword:
Hematopoietic growth factors/GENETICS INSTITUTE

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 87

Keyword:
"Sufficiency of disclosure - (yes)"
"Clarity - (yes)"
"Priority right - from second priority application - (yes)"
"Novelty - (yes)"
"Inventive step - (yes)"

Decisions cited:
G 0002/88, G 0002/98, G 0001/03, T 0301/87, T 0128/92, T 0923/92, T 0412/93, T 0207/94, T 0239/95, T 0728/98, T 0822/98, T 0120/00, T 1084/00

Catchword:
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Case Number: T 1074/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 13 May 2004

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 6 September 2000 concerning maintenance of European patent No. 0314705 in amended form.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 0 314 705, claiming priority from US patent applications No. 885 060 of 14 July 1986 (**P1**), No. 893 764 of 6 August 1986 (**P2**), No. 916 335 of 7 October 1986 (**P3**) and No. 21 865 of 4 March 1987 (**P4**), was granted, for the Contracting States BE, CH, DE, FR, GB, IT, LI, LU, NL and SE, on the basis of 21 claims, claims 1, 2 and 3 of which read:

"1. A DNA sequence that encodes a polypeptide comprising one or more of the mature peptide sequences as shown in Table I or Table II wherein amino acid 27 is Serine and which possesses at least one of the biological properties of primate IL-3, said biological properties being selected from the group consisting of:

(a) the ability to support the growth and differentiation of primate progenitor cells committed to erythroid, lymphoid and myeloid lineages;

(b) the ability to stimulate granulocytic colonies and erythroid bursts in a standard human bone marrow assay;

(c) the ability to sustain the growth of primate pluripotent precursor cells; and

(d) the ability to stimulate primate chronic myelogenous leukemia (CML) cell proliferation in the CML assay.

2. A DNA sequence capable of hybridizing under relaxed or stringent conditions, or which would be capable of hybridizing under said conditions but for the degeneracy of the genetic code, to a DNA sequence selected from the group consisting of:

(a) the DNA sequence of Table I;

(b) the DNA sequence of Table II, wherein the codon for amino acid 27 is TCC;

(c) the XhoI insert in pXM (ATCC 67154); and

(d) the BamHI or BglII genomic insert in bacteriophage lambda M13 cloning vector mp9 (ATCC 40246);

said DNA encoding a polypeptide having at least one biological property of primate IL-3, selected from the group consisting of:

(i) the ability to support the growth and differentiation of primate progenitor cells committed to erythroid, lymphoid and myeloid lineages;

(ii) the ability to stimulate granulocytic colonies and erythroid bursts in a standard human bone marrow assay;

(iii) the ability to sustain the growth of primate pluripotent precursor cells; and

(iv) the ability to stimulate primate chronic myelogenous leukemia (CML) cell proliferation in the CML assay.

3. The DNA sequence of claim 1 or 2 wherein the DNA comprises a cDNA."

Claims 4 to 21 were directed to further embodiments of the DNA sequences of claims 1 or 2 and to recombinant vectors, host cells, polypeptides, methods for production, therapeutic compositions or uses related to the claimed DNA sequences or the corresponding polypeptides.

The patent contains a specific set of claims for the Contracting State AT, which, while mainly consisting of method claims, in essence corresponds to the above-mentioned set of claims for the other Contracting States.

II. Notices of opposition were filed by opponent 1 and opponent 2. Revocation of the patent was requested on the grounds that the requirements of Article 100(a), (b) and (c) EPC were not fulfilled, because of lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC), insufficiency of disclosure (Article 83 EPC) and added subject-matter (Article 123(2) EPC).

III. By interlocutory decision pursuant to Article 102(3) and 106(3) EPC, the opposition division found that, in view of the amendments made by the proprietor during the opposition proceedings, the patent met the requirements of the EPC. The amendments consisted in the deletion of the term "relaxed or" in claim 2 of both sets of claims and in changes on pages 3 and 9 of the description.

IV. Notices of appeal were filed by appellant I (opponent 1) and appellant II (opponent 2); however, only appellant II filed a statement of grounds of appeal.

V. Oral proceedings were held on 13 May 2004 in the presence of appellant II and the respondent. In a letter of 29 April 2004, appellant I had expressed its intention not to attend these oral proceedings.

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

(1) R. Palacios, Journal of Immunology, 1984, Vol. 132, pages 1833 to 1836

(3) T. Yokota et al., Proceedings of National Academy of Science USA, 1984, Vol. 81, pages 1070 to 1074

(4) M.C. Fung et al., Nature, 1984, Vol. 307, pages 233 to 237

(8) A. Ythier et al., Proceedings of National Academy of Science USA, 1985, Vol. 82, pages 7020 to 7024

(18) D.R. Cohen et al., Nucleic Acids Research, 1986, Vol. 14, No. 9, pages 3641 to 3658

(34) EP-A1-0 275 598

(40) L.C.J. Dorssers et al., Journal of Biological Chemistry, 1991, Vol. 266, pages 21310 to 21317

(47) P.O. Olins et al., Journal of Biological Chemistry, 1995, Vol. 270, pages 23754-23760

(62) "Molecular Cloning", T. Maniatis et al., ed. 1982, Cold Spring Harbor Laboratory, pages 382 to 389

(65) Expert opinion of Prof. H. G. Gassen dated 13 March 2000

VII. The arguments submitted in writing or during the oral proceedings by appellant II are as follows:

Article 84 EPC

There was no clear limit between relaxed and stringent hybridisation conditions, so that the subject-matter encompassed by amended claim 2 had been rendered unclear through the deletion of "*relaxed or*". The functional features mentioned in this claim, which were *per se* unclear, did not make the position any clearer.

Article 83 EPC

The subject-matter of the claims covered an uncountable number of sequences and there were serious doubts as to whether the invention could be reproduced over the whole area claimed without undue burden or inventive skill, particularly since the claimed subject-matter was characterized by unclear structural and functional features and was not defined by reference to an activity but to an "*ability*". No criteria were given in the patent in suit for assessing the result of the functional assays for IL-3. Contrary to the situation defined in decision T 128/92 of 30 November 1994, there was no structural similarity between all the variants covered by the present claims, and no testable, narrowly defined activity linking them together. Furthermore, no guidance was given in the patent in suit for modifying the sequences of Tables I or II in order to obtain active variants and, as shown in Table II of document (47), large differences were noted in the activity of the variants listed, of which the active variants represented no more than 19.1%.

Articles 87 and 54 EPC

In none of the priority documents P1 to P3 had the invention, as far as it concerned the sequence coding for human interleukin 3 (IL-3), been in the possession of the inventor. The sequence depicted in Table II of the second priority document P2 was a putative sequence constructed from information derived from the gibbon sequence of Table I and there was no evidence that it encoded human IL-3. This sequence was not a cDNA sequence according to the definition given in decision T 412/93 of 21 November 1994. Furthermore, the concept of "*the same invention*" could not function with a putative sequence. The patent in suit could only validly claim priority from the fourth priority document P4. However, document (34), which had a priority date anterior to P4, was novelty-destroying for the subject-matter of claim 2 within the meaning of Article 54(3) EPC, since it disclosed a cDNA encoding human IL-3 with the amino acid proline at position 27.

Article 56 EPC

Document (18), disclosing the expression of the rat IL-3 gene, was the closest prior art, in view of which the technical problem to be solved was the provision of a sequence encoding primate/human IL-3. The solution defined by the subject-matter of the claims was derivable in an obvious manner from document (18) considered in conjunction with documents (1) or (8), identifying activated T cells as a source for human IL-3. Document (18) further taught that high sequence homology was to be found between the rat and mouse IL-3 genes in the 3' non-translated region of the gene and,

if reference was made to failures to isolate other mammalian IL-3 genes using the mouse counterpart as a probe, this was in a section dedicated to the prior art. In document (34) the use of a probe derived from the 3'-untranslated part of the mouse gene led to successful identification of the human IL-3 coding sequence. Alternatively, documents (3) or (4), which also disclosed the cloning of murine IL-3 cDNA, could also be considered as the closest prior art, and led to the same conclusion as document (18).

VIII. The arguments submitted by the respondent in writing or during the oral proceedings can be summarized as follows:

Article 84 EPC

Claim 2 as maintained by the opposition division was not open to consideration under this article, since the term "*stringent conditions*" had not resulted from an amendment, but was already in claim 2 as granted. This term was furthermore well known to the skilled person, as shown in document (62), and was used in decisions T 412/93, T 239/95 of 6 March 2001 and T 120/00 of 18 February 2003.

Article 83 EPC

Following the conclusions in decisions T 128/92 and T 207/94 of 8 April 1997, the number of sequences falling within the scope defined by the claims was irrelevant, since the patent in suit, by providing the sequences of Tables I and II, enabled the skilled

person to prepare these sequences and variants thereof using well-known methods.

Articles 87 and 54 EPC

The subject-matter of the claims maintained by the opposition division was entitled to the priority of the second priority document (P2), in which the same invention as in the application as filed and the patent in suit was disclosed in an enabling manner. As a consequence, document (34) was not novelty-destroying under Article 54(3) EPC.

Article 56 EPC

The subject-matter of the claims was not derivable in an obvious manner from document (18), which reported on failures to isolate the gene encoding mammalian IL-3 using the mouse gene as a probe and on the surprisingly low homology between the IL-3 coding sequences of mouse and rat. Furthermore, there was no known source for the provision of human IL-3 mRNA at the priority date.

IX. The appellants requested that the decision under appeal be set aside and the patent revoked.

X. The respondent requested that the appeal by appellant I be rejected as inadmissible and that the appeal by appellant II be dismissed.

Reasons for the decision

Admissibility of the appeals

1. The appeal by appellant II, who filed the notice of appeal and the statement of grounds of appeal and paid the appeal fee in due time, is admissible pursuant to Articles 106 to 108 EPC and Rule 64 EPC.

2. Appellant I filed no written statement setting out the grounds of appeal. Therefore, its appeal does not comply with the requirements of Article 108 EPC, third sentence, and has to be rejected as inadmissible pursuant to Rule 65(1) EPC.

Article 84 EPC

3. When amendments are made to a patent during opposition, Article 102(3) requires them to be examined to ascertain whether the EPC, including Article 84 EPC, is contravened as a result. However, Article 102(3) EPC does not allow objections to be based upon Article 84 EPC if they do not arise out of the amendments made (see T 301/87, OJ EPO 1990, 335, point 3.8).

4. Claim 2 as granted included the technical feature that the DNA sequence is capable of "hybridizing under relaxed or stringent conditions" to a certain DNA sequence. By deleting the terms "relaxed or" during the opposition procedure, the respondent has limited the technical feature so that it now merely refers to stringent conditions. The respondent argues that, since the term "stringent conditions" was left unchanged, no lack of clarity can have arisen out of the amendment

itself and that therefore no objection under Article 84 EPC needs to be examined.

5. However, the Board is not convinced by this argument for the following reason: When **both** relaxed and stringent conditions were referred to in the claim, the clarity of the definition of the subject-matter for which protection was sought could not be affected by the question whether the skilled person was able to draw a borderline between relaxed and stringent conditions. However, due to the amendment made by the respondent, this question has become relevant since a DNA sequence capable of hybridizing only under relaxed conditions, but not under stringent conditions would now fall outside the subject-matter defined by the amended claim.

6. The requirement of clarity under Article 84 EPC serves the purpose of ensuring legal certainty. The public should be able to determine which subject-matter is covered by a particular claim and which is not (see e.g. T 728/98, OJ EPO 2001, 319, point 3.1; G 2/88, OJ EPO 1990, 93, point 2.5). However, it would be unrealistic to assume that language, even technical language, can always be so precise that no room for interpretation is left at all. The question to be asked in the context of Article 84 EPC is therefore not whether the claim is clear in absolute terms, but whether it is sufficiently clear, having regard to the particular nature of the subject-matter. This view is supported by decision G 1/03 (OJ EPO 2004, 413, point 3) which states with respect to the clarity requirement that a balance has to be struck between the interest of the applicant in obtaining adequate protection and the interest of the

public in determining the scope of protection with reasonable effort. In this context the Board also notes the following statement made in the decision T 412/93 (point 60): "Frequently where something has to be measured there will be a grey area where measurement error may make it difficult to determine whether a particular product falls within a claim or not. This does not justify an objection under Article 84 EPC."

7. In the present case, the subject-matter of claim 2 is defined *inter alia* by its capability of "hybridizing under stringent conditions" with one of four specific DNA sequences. In relation to this feature, the description (page 9, lines 25-26), refers to document (62), a standard textbook in the field of genetic engineering. In addition, the description (page 9, lines 27-29) provides the following information: "An example of one such stringent hybridization condition is hybridization at 4XSSC at 65° C, followed by a washing in 0.1XSSC at 65° C for an hour. Alternatively an exemplary stringent hybridization condition is in 50% formamide, 4XSSC at 42° C."

8. Appellant II maintained that the term "*stringent conditions*" was not clear for the skilled person since the reference document (62) did not give an unambiguous definition of the term "stringent". Different sets of stringent conditions existed and there was no guidance as to which conditions had to be chosen. The particular experimental conditions and the degree of hybridization were not reflected in the claims. No precise boundary between stringent and relaxed hybridization conditions could be drawn. Appellant II relied on document (65),

an expert opinion by Prof. Dr. Gassen, to support its argumentation on this point.

9. The Board is not convinced by the arguments of appellant II. The term "hybridization under stringent conditions" is well-known in the art of genetic engineering (see decision T 1084/00 of 11 April 2003, point 9.2) and has been used in the patent practice for numerous years as a quasi-structural feature for defining DNA claims, frequently - as in the present claim 2 - in combination with a functional feature relating to the biological activity of the polypeptide encoded by the claimed DNA sequence (see e.g. decision T 412/93, Annex II, claim 1). In decision T 923/92 of 8 November 1995, point 35.4, it was explained that "under stringent conditions only long sequences with nearly perfect complementary matching will secure anneal". Other decisions have used the term "hybridization under stringent conditions" or made reference to it, apparently without feeling the need to define it further (see e.g. T 822/98 of 11 October 2001, point 8; T 120/00 of 18 February 2003, point 8).

10. The Board accepts that different experimental protocols may be applied for assessing hybridization under stringent conditions. Various physical or chemical parameters of the hybridization process may be modified. Formamide, for instance, can be present or absent from the hybridization medium. The existence of different protocols is acknowledged in the description since it gives at page 9, lines 27-29 two alternative examples of stringent hybridization conditions. However, this does not necessarily mean that these protocols, if different in respect of the reagents used and the steps

involved, will lead to different results as far as the detected nucleotide sequence is concerned.

11. Moreover it has to be taken into account that the present claim 2 defines its subject-matter not only by the capability of hybridizing under stringent conditions, but also by a further functional feature, namely that the polypeptide encoded by the claimed DNA sequence has at least one of four specific biological properties. Uncertainty about the protection conferred by claim 2 could thus be caused by the existence of different experimental protocols only if there were DNA sequences which fulfilled this further functional requirement **and** which, when subjected to different experimental conditions, led to ambiguous results. However, no concrete evidence in this respect has been submitted by appellant II.

12. As a consequence, the Board considers that the term "capable of hybridizing under stringent conditions" contained in amended claim 2 is sufficiently clear for the purposes of Article 84, having regard to the particular nature of the subject-matter. Thus, claim 2 has not been rendered unclear by the deletion of the term "*relaxed or*" during opposition proceedings.

Article 83 EPC

13. Claim 1 is directed to a DNA sequence which encodes a polypeptide comprising one or more of the mature peptide sequences as shown in Table I or Table II and which exhibits at least one of the four listed biological properties. The subject-matter of claim 2 is also a DNA sequence, which is characterized by the same

functional features as in claim 1. However the structural feature is defined by reference to hybridization under stringent conditions to the nucleotide sequences of Tables I and II.

14. Appellant II has objected that claims 1 and 2, because of the characterization of their subject-matter by inaccurate structural and functional parameters, comprise an uncountable number of sequences without any physical relation to each other or a testable narrowly defined activity.

15. First of all, by providing the sequences of Tables I and II, the patent in suit enables the skilled person to prepare the claimed DNA sequences using methods and materials which were already part of the common general knowledge of the skilled person, even at the first priority date of the patent in suit, such as the site-directed mutagenesis or the cleavage with various restriction endonucleases to introduce substitutions or deletions in the nucleotide sequences of Tables I and II. These methods are also mentioned in the patent in suit from page 8 (line 39) to page 9 (line 22) and in Example III. In the Board's opinion, there would hence be no technical difficulty for the skilled person to prepare all the sequences encompassed by claims 1 and 2.

16. Furthermore, due to the well-known relationship between the 3-dimensional structure of a polypeptide and its biological function and the negative influence of the extent of substitution or deletion of amino acids on the structure and biological activity of a given polypeptide, the skilled person would expect the variants produced, which according to claims 1 and 2

have to be active, to have a structure close to that of the parental sequence. Confirmation thereof is found in Table II of post-published document (40), cited as an expert opinion, in which the deletion of a stretch of up to 10 amino acids from the sequence of human IL-3 generally results in a drastic decrease of the biological activity of several orders of magnitude. This reduces the number of possible active variants embraced by claims 1 and 2 and gives them a structural link.

17. The functional features mentioned under items (a) to (d) in claim 1 and under items (i) to (iv) in claim 2 can be determined using the assays defined in Example VI of the patent in suit. GM-CSF appears to be the only growth factor liable to interfere with the identification of IL-3; the other growth factors, which act primarily on monopotent progenitors, are easily distinguishable from IL-3 which supports proliferation of multipotent progenitors. As far as GM-CSF is concerned, it follows from the patent in suit (page 17, lines 21 to 22) that anti-human GM-CSF antibodies can be used to avoid this interference in the CML assay and Example VI (page 17, lines 29 to 41) shows that a distinction between IL-3 and GM-CSF can be made on the basis of the qualitative differences seen in human bone marrow assays. Furthermore, the question of the interference of other growth factors, which could cast doubt on the true nature of the growth factor obtained, is only of importance when IL-3 is obtained by extraction from a natural source in which other growth factors might be present, ie for natural IL-3. This question is pointless for IL-3 variants produced by recombinant DNA technology or chemical synthesis,

because in this case, unless the expression has been made in a host also expressing other growth factors, the only growth factor present is IL-3.

18. The formulation used for defining these functional features ("*ability to...*"), which has been objected to by appellant II, is, in the Board's view, not ambiguous, since a substance which has the "*ability to*" is a substance active in the assay under consideration, of which it modifies the outcome.

19. Therefore, as in decision T 128/92, point 9, in spite of the considerable number of theoretically possible variant sequences, there is still likely to be a structural similarity between all the variants covered by claims 1 and 2 as well as a testable narrowly defined activity.

20. The argument of the appellant II that the invention cannot be reproduced by the skilled person, since the patent in suit gives no guidance in establishing in advance which alterations of the nucleotide sequence would give rise to active IL-3 variants, is not tenable, because there is, in the Board's view, no necessity for such guidance. Indeed, even if appellant II's estimate, based on the results disclosed in Table 2 of document (47), of the number of active variants obtained using routine methods to introduce deletions or substitutions of amino acids into the parental IL-3 sequence is taken into consideration, then at least 19.1% of the variants are active (appellant II's letter of 10 January 2002, page 4). This estimate has been contested by the respondent, who considered that 80% of the variants are active. Nevertheless, even if appellant II's estimate

is taken into consideration, the value of 19.1% of active variants represents for a biological process a rather high percentage of successful modifications obtained using well-known routine methods and it renders unnecessary the design of new experimental conditions to fulfil the task of establishing in advance which alterations lead to active primate or human IL-3 variants. Furthermore, even if the skilled person is not *stricto sensu* provided by the patent in suit with precise guidance on how to prepare an active IL-3 variant, his basic knowledge of the structure-function relationship in proteins (cf *supra* point 16), will have given him an empirical basis for estimating beforehand the impact of a given structural modification on the activity of the resulting variant; this gives him sufficient guidance for modifications leading to active variants.

21. In view of the above, the Board considers that the requirements of Article 83 EPC are met by the subject-matter of claims 1 and 2.

Article 87 EPC

22. Pursuant to Article 87(1) EPC a European patent application enjoys the right of priority from a first patent application in respect of the same invention. Decision G 2/98 (OJ EPO 2001, 413) indicates that the term "*the same invention*" should be given a narrow interpretation. Furthermore, in accordance with the established case law (Case Law of the Boards of Appeal of the European Patent Office, 4th edition, 2001, pages 242 and 243), the priority document must disclose

the invention claimed in the subsequent application in such a way that a skilled person can carry it out.

23. Appellant II has argued that none of the first three priority applications P1, P2 and P3 contains an enabling disclosure for a cDNA sequence coding for human IL-3 and that therefore the amended claims of the patent in suit, as far as they are directed to or encompass this subject-matter, cannot validly claim the benefit from any of these priority applications.

24. The first priority application (P1) deals with human IL-3 and DNA sequences encoding it only in its example VI. This example is mainly theoretical and contains several suggestions as to how one might use the gibbon IL-3 coding sequence of Table I as a probe in order to obtain DNA sequences coding for human IL-3. However, P1 does not specifically disclose any such sequence and in particular does not contain any table corresponding to Table II of the patent. The Board therefore concludes that the claims of the patent in suit, as far as they define their subject-matter by reference to the DNA sequence of Table II, do not benefit from the priority of P1.

25. The second priority application (P2) discloses in Table II the same sequence as the corresponding Table of the patent in suit. This sequence is said to have been obtained by screening a human genomic library using the nucleotide sequence encoding gibbon IL-3 as a probe and, assuming a high sequence homology between gibbon and human, by splicing together the exons of the human genomic sequence, which were identified by comparison with the gibbon nucleotide and amino acid

sequences of Table I. P2 then states (page 7, lines 12 to 15, page 10, lines 7 to 10) that this human sequence codes for a putative polypeptide of approximately 152 amino acids, which is a member of the family of IL-3-like primate proteins.

26. According to Example IV of P2, the "putative cDNA sequence for a human IL-3-like polypeptide as indicated in Table II" may be obtained in three ways: Firstly, the sequence may be chemically synthesized according to well known procedures. Secondly, it may be obtained by the successive steps of excising the human genomic sequence as a Bgl II fragment from the deposited bacteriophage lambda CSF-16, cloning this sequence in a plasmid expression vector by standard techniques, amplifying it in bacteria, transfecting the expression vector containing the gene into a mammalian cell, where the human gene is transcribed and the RNA correctly spliced, obtaining mRNA from these cells, synthesizing cDNA from the mRNA by standard procedures and isolating the human cDNA. The third method involves the isolation of mRNA from peripheral blood lymphocytes as a human tissue source, conversion of the mRNA to cDNA, cloning of the cDNA and identification of the relevant cDNA clone by using the gibbon cDNA sequence of Table I as a probe.

27. The Board considers that the use of the term "putative" in the above context would not make the skilled reader of P2 believe that the information given was pure speculation without technical content. Rather, he would interpret this wording as a sign of scientific caution and as an indication that the authors of the description of P2 were not yet absolutely certain

whether the sequence of Table II was indeed the fully correct cDNA for human IL-3. However, unless the skilled reader has clear and objective reasons for discarding a particular piece of information as mere speculation, the question as to whether a technical disclosure is enabling or not does not depend on the degree of certainty of its author at the point of time when making the disclosure. The decisive question in the framework of Articles 83 and 87(1) EPC is whether the invention is sufficiently disclosed to enable the skilled person to carry out the invention.

28. The text passages of P2 summarised above inform the skilled reader about three different ways of obtaining the cDNA sequence of Table II. The appellant II has not convincingly shown that, contrary to this disclosure, the skilled person was prevented from following any of these ways. No experimental data has been submitted according to which the skilled person would be unable to obtain the sequence without undue burden. The Board furthermore notes that the appellant II has not contested that the DNA sequence given in Table II of P2 is indeed the correct cDNA sequence for human IL-3. Under these circumstances, the appellant II cannot be considered to have discharged its onus of proof for the allegation that the above disclosure of P2 was not enabling.

29. Appellant II has drawn attention to the decision T 412/93 where a claim to a cDNA sequence was considered not to comply with the requirements of Article 83 EPC and argued that a similar conclusion should be reached in the present case with respect to the priority of the subject-matter of claim 3 which is

explicitly directed, *inter alia*, to a cDNA for human IL-3. Appellant II also referred to point 19 of the decision in which the term cDNA was said to refer to "the product obtained by *in vitro* synthesis of a double-stranded DNA sequence by enzymatic 'reverse transcription' of mRNA".

30. The present case cannot be compared to the factual situation underlying the decision T 412/93. As follows from the detailed reasons given in points 21 to 29 of that decision, the patent description considered did not disclose the sequence of the claimed cDNA and there was ample evidence before the Board demonstrating that the skilled person would be confronted with many difficulties when setting out to obtain the cDNA. This is in clear contrast to a situation such as the present one where the cDNA for human IL-3 is specifically disclosed in Table II of P2 and where information is given about three ways for obtaining this sequence, two of them containing the above-mentioned step of synthesizing cDNA from isolated mRNA.

31. The Board concludes that the second priority application (P2) contains an enabling disclosure for a cDNA sequence coding for human IL-3. The amended claims of the patent in suit, as far as they are directed to or encompass this subject-matter, can therefore validly claim the priority right of P2. Thus the relevant date for the determination of the prior art pursuant to Article 54 EPC in this respect is the filing date of the second priority document, ie 6 August 1986.

Article 54 EPC

32. As a consequence of the above conclusion (cf point 31), document (34), the first priority of which, ie 16 December 1986, is posterior to the second priority of the patent in suit, is not novelty-destroying for the subject-matter of the present claims, which, therefore, meets the requirements of Article 54 EPC.

Article 56 EPC

33. The Board agrees with appellant II and the respondent in considering document (18) as the closest prior art. Document (18) discloses the cloning and the expression in COS-1 cells of the rat IL-3 gene, which has been isolated by screening a rat genomic library with a 467 bp long fragment of murine IL-3 cDNA (page 3645). This screening results in the isolation of a 5.8 kb fragment encompassing the rat IL-3 gene (page 3646) composed of five exons interrupted by four introns (page 3647). The growth factor activity of rat IL-3 is tested in the bone marrow cell assay (page 3654). Fields of application of the discovered rat IL-3 are indicated on page 3655 of document (18) as being arthritis and graft rejection.

34. The indication that fields of application for IL-3 were arthritis and graft rejection suggests an application in human medicine, so that the technical problem to be solved in view of document (18) can be defined as the provision of a nucleotide sequence coding for primate IL-3, in particular for human IL-3.

35. In view of the detailed information contained in the patent in suit on the preparation of the nucleotide sequences and the corresponding amino acid sequences of Tables I and II and the variants thereof, the Board is satisfied that the above stated technical problem has been solved. The question to be answered for the assessment of inventive step is whether this solution can be deduced in an obvious manner from document (18) considered alone or in combination with other prior art document(s) or the common general knowledge of the skilled person.

36. In document (18) the rat IL-3 gene is compared with its mouse counterpart. The low amino acid homology at the amino acid (54%) and nucleotide levels (76%) between rat and mouse IL-3 is considered in relation to the poor cross reactivity between the two, suggesting that rat IL-3, together with its receptor, has evolved significantly away from the murine IL-3/receptor system (pages 3654 and 3655, heading "*Discussion*"). The sentence (page 3654) indicating that the homology of the mouse and rat IL-3 coding sequences is only 76% is introduced by the term "*surprisingly*". This shows that the authors of document (18), due to the fact that mouse and rat are two closely related species, would have expected a higher homology. The absence of precise information in document (18) on the homology of the rat or mouse IL-3 coding sequences (or their corresponding amino acid sequences) with mammalian or human ones is not surprising, since the authors of document (18) state on page 3641 that "*little is known about IL-3 species in other mammals*". Furthermore, it is indicated on pages 3641 and 3642 of document (18) that it is not established whether an exactly analogous lymphokine to

murine IL-3 exists in man and that Southern hybridization analysis of mammalian DNAs, using a murine IL-3 cDNA probe, fails to detect homologous sequences in most mammalian species, even under conditions of relatively low stringency. Of course, this statement, as pointed out by appellant II, only concerns the results obtained in documents which constitute the prior art of document (18). However, it has not been invalidated by the teaching of document (18), which only concerns the rat, ie a species phylogenically closely related to the mouse. The teaching of document (18) for the skilled person at the second priority date of the patent in suit, as far as it concerns mammalian IL-3, can thus be summarized in three pieces of information:

(a) there is no evidence of the existence of a human counterpart to murine IL-3,

(b) Southern hybridization experiments fail to detect sequences homologous to mouse IL-3 in other mammals,

(c) the homology of the rat and mouse IL-3 coding sequences is surprisingly low, despite the phylogenic relation between these two species.

37. The Board is of the opinion that the skilled person who, according to the established case law of the boards of appeal, is considered to be cautious, to have a conservative attitude and not to enter unpredictable areas or take incalculable risks would not have been prompted by the teaching of document (18) to use the mouse or rat IL-3 coding sequences as a probe for detecting a primate or human IL-3 gene. He would have expected the homology between the nucleotide or amino acid sequences of mouse or rat and primate or human

IL-3 (if correctly assuming that IL-3 exists at all in these latter species) to be even lower than that between mouse and rat because these species are less closely related.

38. Appellant II argued that the skilled person would have used the 3' or 5' untranslated regions of the mouse or rat IL-3 coding sequences, since high nucleotide homology was said in document (18) to be found in these regions (pages 3647 and 3650; Figure 3), and that confirmation of the feasibility of this method could be found in post-published document (34), in which a human cDNA clone was isolated using a complete murine IL-3 cDNA containing both the coding and the untranslated 3' downstream portion. However, this procedure was not a routine method at the time of the second priority date of the patent in suit, as shown by the fact that the authors of document (34) use the term "*unexpectedly*" in conjunction with this method (page 2, lines 45 to 46) and indicate on page 6 (lines 8 and 9) that they "*...are unaware of any prior art disclosure of the use of 3' untranslated sequence homology to retrieve an alternate species gene*". Therefore, this method at the time of the second priority of the patent in suit was not at the disposition of the skilled person, who would have been obliged to *invent* it in order to arrive at the subject-matter of the present claims.

39. The teaching of document (18) remains the same and does not prompt the skilled person to use said murine sequences as a probe if documents (3) or (4), which also disclose the isolation of a nucleotide sequence coding for murine IL-3, are considered as an alternative closest prior art.

40. The question as to whether documents (1) and (8) provided the skilled person at the time of the second priority of the patent in suit with a source for human IL-3 mRNA is pointless, since in the Board's view the skilled person would not even have come to this point: he would have considered the attempt to isolate a primate/human IL-3 encoding sequence using murine IL-3 cDNA as a probe as an uncertain undertaking with an unpredictable outcome, on which he would not have embarked.

41. Therefore, the Board considers that the subject-matter of the present claims cannot be deduced in an obvious manner from document (18) or alternatively from documents (3) or (4), considered alone or in combination with other prior art documents such as documents (1) or (8), and that it hence fulfils the requirements of Article 56 EPC.

Order

For these reasons, it is decided that:

1. The appeal by appellant I is rejected as inadmissible.

2. The appeal by appellant II is dismissed.

The Registrar: The Chairman:

P. Cremona R. Moufang