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D E C I S I O N
of 19 November 1998

Case Number: T 0051/95 - 3.3.4

Application Number: 86105365.0

Publication Number: 0211148

IPC: C12N 15/20

Language of the proceedings: EN

Title of invention:
Mature human leukocyte interferons, process for their bacterial production, intermediates therefor and compositions containing them

Patentee:
F. Hoffmann-La Roche AG, et al

Opponent:
Boehringer Ingelheim GmbH
Amgen Inc

Headword:
Mature leukocyte interferons/HOFFMANN-LA-ROCHE

Relevant legal provisions:
EPC Art. 114(1), 112(1), 87, 88, 54, 56
EPC R. 88

Keyword:
"Inventive step - yes"

Decisions cited:
G 0003/89, G 0003/93, G 0009/91, T 0081/87

Catchword:
-

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Case Number: T 0051/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 19 November 1998

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 4 January 1995 concerning maintenance of European patent No. 0 211 148 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
W. Moser

Summary of Facts and Submissions

I. European patent No. 0 211 148 with the title "Mature human leukozyte interferons, process for their bacterial production, intermediates therefor and compositions containing them" was granted with 46 claims, on the basis of European application No. 86 105 365.0 with the four priority dates of 1 July 1980, 8 September 1980, 10 November 1980 and 21 April 1981. The publication of the grant of a patent took place on 26 August 1992.

Granted claim 1 read as follows:

"1. A mature human bacterially produced leukocyte interferon characterized in that it consists of 165-166 amino acids and contains Cys-Asp-Leu or Cys-Asn-Leu in positions 1, 2 and 3 and such mature leukocyte interferon with at the N-terminus an additional methionine residue."

Dependent claims 2 to 5 specified the sequence of the claimed leukocyte interferons (LeIF) at defined positions in the molecule. Dependent claims 6 to 13 related to interferons characterized by specific amino-acid sequences. Dependent claims 14 and 15 further defined the claimed interferons by the method of their production. The groups of claims 16 to 20, 21 to 23, 24 to 30, 31 to 33, 37 to 39, 41 to 43 were addressed respectively to DNAs, expression vectors, plasmids and bacterial hosts carrying/expressing the claimed interferons DNAs/proteins and uses thereof; claims 34 to 36 and 40 related to pharmaceutical preparations and the use of the claimed interferons for treatment. Claims 44 to 46 were addressed to processes for preparing the interferons, bacteria and expression vectors producing them.

II. Two notices of opposition were filed requesting the revocation of the patent in suit under Article 100(a) EPC (lack of novelty and inventive step). Appellant II (Opponent 02) also submitted at a later stage arguments alleging insufficiency of disclosure (Article 100(b)).

III. The Opposition Division maintained the patent in suit in amended form on the basis of the auxiliary claim request filed at oral proceedings which was identical to the granted set of claims but for the deletion of claim 5 and the subsequent renumbering of claims 6 to 46. They declined to accept into the proceedings the submissions pursuant to Article 83 EPC by Appellant II, as they had been submitted after the expiry of the opposition period.

IV. Both Appellants I and II (Opponents 01 and 02) filed an appeal, paid the appeal fee and submitted written statements setting out the grounds of their appeals.

V. The Respondent (Patentee) submitted his answer to the grounds of appeal.

VI. A communication was sent according to Article 11(2) of the Rules of Procedure of the Boards of Appeal, setting out the Board's provisional, non-binding opinion.

VII. The Board's communication was answered by the Respondent.

VIII. Oral proceedings took place on 19 November 1998. Appellant II did not take part in the proceedings (cf. letter dated 9 November 1998). The Respondent submitted a new main request (claims 1 to 40) and one auxiliary request as sole claim requests to be considered by the Board.

The main request differed from the granted claims in that:

- variants: 165-Cys-Asn-Leu; 166-Cys-Asn-Leu, Val 114 and 167-Cys-Asn-Leu, Val 115 were deleted from claims 1 to 3 respectively and,

- claims 5, 11, 12, 18, 29, 30 were deleted and,

- the amino acid sequence of leukocyte interferon B (LeIF B) was attributed to leukocyte interferon C (LeIF C) and the amino acid sequence of LeIF C was attributed to LeIF B.

IX. The following documents on file were considered by the Board:

(1): EP-A-0 032 134

(2): Mantei, N. et al., Gene, vol. 10, 1980, pages 1 to 10,

(4): Nagata, S. et al., Nature, vol. 284, 27 March 1980, pages 316 to 320,

(5): Goeddel, D. et al., Nature, vol. 281, 1979, pages 544 to 548,

(7): DE-A-2 947 134

(9): Streuli, M. et al., Science, vol. 209, 19 September 1980, pages 1343 to 1347,

(10): Nagata, S. et al., Nature, vol. 287, 2 October 1980, pages 401 to 408,

(11): Goeddel, D. et al., Nature, vol. 287, 2 October 1980, pages 411 to 416,

(14): Talmadge, K. et al., Proc.Natl.Acad.Sci. USA vol. 77, No. 7, July 1980, pages 3988 to 3992,

(18): Rubinstein, M., Biochim.Biophys.Acta, vol. 695, 1982, pages 5 to 16.

(19): Allen, G. and K. Fantes, Nature, vol. 287, 2 October 1980, pages 408 to 411,

(20): Petska, S., Scientific American, vol. 249, 1983, pages 37 to 43,

(22): Rubinstein, M. et al., Arch.Biochem.Biophy., vol. 210, No. 1, 1981, pages 307 to 318.

X. The submissions in writing and during oral proceedings by Appellant I can be summarized as follows:

The generic claims to human leukocyte interferons defined by the amino acid sequence Cys-Asn-Leu at the NH2-terminal end (amongst other features) merely enjoyed the third or later priority dates because this amino-acid sequence was disclosed for the first time in the third priority document. For the same reason, the subject-matter of claim 9 which related to the specific mature LeIF-H defined by its sequence only enjoyed the third priority date.

Documents (2) and (4) were the closest prior art to the claims enjoying the first or second priority date. They disclosed the entire cDNA and amino-acid sequence of human leukocyte pre-interferon and its expression from a fused construct in E.coli. The sequence of the mature protein was highlighted in Figure 3 of document (2). In document (4) (passages bridging pages 309 and 310), the presence of the signal sequence was pointed out as the most likely reason for the observed low level of bioactivity. It was also stated therein that an

increase in said activity could be achieved by appropriate means, which would necessarily have suggested to the skilled person to express only the part of the cDNA encoding the mature protein.

The problem to be solved was thus to provide further mature interferons and processes for preparing them. Document (5) provided a generally applicable method for manipulating a cloned DNA sequence for direct expression in bacteria. Applying this method to the cDNAs comprising the sequences encoding human mature LeIFs involved no more than routine efforts. The combination of the above documents was thus detrimental to inventive step.

Document (11) published between the second and third priority dates represented the closest prior art to the claims to LeIF-H and to the generic Cys-Asn-Leu LeIFs. It disclosed the expression of mature LeIF-A in E.coli and also that LeIFs existed as a family. A method to construct an expression vector capable of expressing a mature LeIF DNA sequence in E.coli was given in Figure 4. Thus, the skilled person only had to follow the teachings of this document to isolate the claimed generic Cys-Asn-Leu interferons. Furthermore, differences in sequences at the NH2-terminal end would not have been considered unexpected since it was already known from document (2) (page 7) that as many as 9 differences in sequence existed in the first 35 amino acids of LeIF-A and lymphoblastoid interferon. Inventive step was thus lacking from all claims/parts thereof directed to Cys-Asn-Leu interferons. The same was true of claim 9 relating to LeIF-H defined by its entire sequence as it did not exhibit any surprising properties.

XI. The submissions in writing by Appellant II with regard to inventive step were essentially the same as those of Appellant I.

Appellant II also argued that by refusing to consider his submissions under Article 100(b) EPC, the Opposition Division had violated the requirements of Article 114(1) EPC that the EPO shall examine the facts of its own motion.

The requirements of Article 83 EPC were not fulfilled because:

- claim 1 comprised a near infinity of LeIF molecules whereas the patent specification provided no guidance on how to isolate those of them with interferon activity and,

- no teachings were given on how to separate the Met- and des-Met- forms of the LeIF polypeptide.

Furthermore, Appellant II submitted that document (7) anticipated the subject-matter of claim 1, and that the teachings of document (1) (enjoying priority rights from 3 April 1980) as well as those of documents (2) and (4) were detrimental to the novelty of the claim to LeIF-D.

XII. The Respondent argued as follows:

The first priority document of the patent in suit disclosed the essential steps for the production of mature human LeIF-A and -B and the existence of at

least six further LeIF DNAs characterized by their restriction maps. It was, thus, fully enabling with regard to making any and all of the claimed interferons. All claims enjoyed the first priority date.

- Document (7) did not disclose a LeIF with the same molecular weight as the now claimed interferons. The other documents cited against novelty either disclosed protein sequences deduced from cDNA sequences or LeIFs with a different amino-acid sequence from those claimed. None could have any bearings on novelty.

- Document (4), which had been published before the first priority date, represented the closest prior art to all claims. It disclosed the expression in E.coli of pre-LeIF from a DNA construct wherein pre-LeIF cDNA was fused to the E.coli beta-lactamase gene. Starting from this prior art, the problem to be solved was to express LeIF in mature form in E.coli. As shown by document (14), the skilled person expected E.coli to be able to cleave off the signal sequence present at the NH2 terminal end of a protein. Thus it would not have been considered necessary to shorten the DNA sequence encoding pre-LeIF DNA to the DNA encoding the mature sequence before insertion into an expression vector. Furthermore, document (5) which allegedly disclosed a general method to tailor DNA sequences for the direct expression of mature proteins in E.coli also disclosed that mature human growth hormone (HGH) expressed in this manner was susceptible to proteolytic degradation. It gave no evidence that E.coli produced mature HGH had biological activity. There was thus no reason to combine the teaching

of documents (2) and (4) with that of document (5) to obtain the claimed LeIFs, and no expectation that mature biologically active LeIF could be obtained.

Finally, it ought to be taken into account that in the course of the proceedings the Appellants had proposed two alternative strategies for obtaining the LeIF interferons which the Respondent had been able to prove unworkable. The claimed invention could therefore not have been obvious.

Document (11) was not a document which jeopardized the inventive step of any of the claimed embodiments, quite irrespective of their priority dates, because it did not go beyond the content of the first priority application and it had been published by the inventors themselves. The opinion which the Enlarged Board of Appeal gave on analogous priority issues in the case G 3/93 (OJ EPO 1993, 018), could not be followed because the factual situation underlying that opinion was different.

Nonetheless, inventive step could be acknowledged even if the claims to LeIF-H and to the LeIFs generically defined by the three amino-acids Cys-Asn-Leu were considered to derive their priority from the third or a later priority document and if document (11) was taken as closest prior art. Indeed all LeIFs known at the third priority date (documents (2), (9), (19)) had Cys-Asp-Leu at the NH2 terminal end. This sequence identity at the NH2-terminal end would have been taken as evidence that this portion of the molecule was conserved and, thus, the presence of Asn in position 2 would not have been expected.

- Article 100(b) EPC had not been mentioned as a ground for opposition within the opposition term. The arguments relative thereto should not be allowed into the proceedings.

XIII. The Appellants requested that the decision under appeal be set aside and that the European patent No. 0 211 148 be revoked.

The Respondent requested that the decision under appeal be set aside and the patent be maintained on the basis of the following documents:

(a) claims 1 to 40 submitted during the oral proceedings as main request, or

(b) claims 1 to 38 submitted during oral proceedings as auxiliary request I.

The Respondent further requested to refer the following question to the Enlarged Board of Appeal: "Is the principle of the opinion G 3/93 also applicable if the intervening publication corresponds with regard to the disclosure to the priority document and if the intervening publication is derived from the inventor?"

Reasons for the Decision

1. The appeal is admissible.

Articles 114(1) and 100(b) EPC

2. Appellant II objected against the fact that the arguments with regard to Article 100(b) EPC which he submitted one month before the oral proceedings before the Opposition Division had been disregarded for being submitted late. In his view, they ought to have been taken into consideration, although Article 100(b) EPC had not been cited as a ground for opposition in the notice of opposition, in application of Article 114(1) EPC which required that the EPO shall examine the facts of its own motion.

3. In principle, an Opposition Division shall examine only such grounds for opposition which have been properly submitted and substantiated in accordance with Article 99(1) in conjunction with Rule 55(c) EPC (cf. Decision of the Enlarged Board of Appeal G 9/91 (OJ EPO 1993, 408), point 6 of the reasons). Exceptionally, the Opposition Division may in application of Article 114(1) EPC consider other grounds for opposition which, prima facie, in whole or in part would seem to prejudice the maintenance of the European patent (cf. G 9/91, point 16 of the reasons). On the other hand, the possibility of disregarding facts and evidence in support of fresh grounds not submitted in due time under Article 114(2) EPC must also be kept in mind (cf. G 9/91, point 16 of the reasons).

4. In the present case, the Opposition Division was obviously of the opinion that, prima facie, the ground for opposition pursuant to Article 100(b) EPC did not prejudice the maintenance of the patent in suit. Consequently, it refrained from examining that ground. In the Board's judgment, it was within the discretionary power of the Opposition Division to make such a decision. Thus, by refusing to consider the submissions of Appellant II under Article 100(b) EPC, the Opposition Division did not contravene the requirements of Article 114(1) EPC.

5. It is not in conformity with the purpose of the appeal procedure *inter partes* to consider grounds for opposition on which the decision of the Opposition Division has not been based (cf. G 9/91, point 18 of the reasons). It is therefore justified to apply Article 114(1) EPC generally in a more restrictive manner in such procedure than in opposition procedure (cf. G 9/91, point 18 of the reasons). In particular fresh grounds for opposition may only be introduced at the appeal stage if the patentee agrees that a fresh ground for opposition may be considered (cf. G 9/91, point 18 of the reasons).

6. In the present case, given the facts that:

(i) the ground for opposition pursuant to Article 100(b) EPC was not properly submitted and substantiated in accordance with Article 99(1) in conjunction with Rule 55(c) EPC, and

(ii) Article 114(1) EPC is to be applied in a more restrictive manner in the appeal procedure inter partes than in opposition procedure (cf. point 5, above), and

(iii) the submissions of Appellant II under Article 100(b) EPC are, in the Board's judgment, not of prima facie relevance, and

(iv) the Respondent already argued in opposition proceedings before the first instance that the argumentation pursuant to Article 100(b) EPC should be considered inadmissible (letter dated 25 November 1994),

the issue of whether or not the patent in suit and the invention to which it relates meet the requirement of Article 83 EPC will not be examined.

Main request

Articles 123(2)(3) EPC

7. All of the interferons, DNA/plasmid/bacterial hosts encoding/expressing them and processes which are claimed have been disclosed in the application as filed. The requirements of Article 123(2)EPC are fulfilled.

8. Claims 1 to 3 of the main request comprise a smaller number of alternative interferons than claims 1 to 3 as granted. Granted claims 5, 11, 12, 18, 29 and 30 have been deleted. None of these amendments results in an extension in the protection conferred by the granted claims. The requirements of Article 123(2) EPC are fulfilled.

9. The sequence of LeIFB (claim 5) corresponds to the sequence of LeIFC claimed in claim 7 of the granted claim request. The sequence of LeIFC (claim 6) corresponds to the sequence of LeIFB claimed in claim 6

of the granted claim request. The Respondent argued that the sequences of LeIFB and LeIFC had mistakenly been exchanged in the granted claims, and that therefore, a correction was allowable under Rule 88 EPC.

10. In accordance with the case law of the EPO (cf. G 3/89, OJ EPO 1993, 117), the correction of obvious errors is only allowable if it can objectively be derived from the description, claims and drawings of the European patent application as filed, and if it is immediately evident that nothing else would have been intended than what is offered as the correction.

11. The application as filed discloses the protein sequences of LeIFB and LeIFC in Figure 4. They are identical to the sequences of LeIFB and LeIFC in claims 5 and 6 of the main request. Furthermore, the DNA sequences encoding LeIFB and LeIFC are given in Figure 3. They are such that the LeIFB DNA can only encode the protein sequence shown in Figure 4 as that of LeIFB and that the LeIFC DNA can only encode the protein sequence shown in Figure 4 as that of the LeIFC interferon. Accordingly, it is immediately obvious that no other sequence could have been intended for LeIFB than that disclosed in the application as filed and claimed in claim 5 of the main request and that no other sequence could have been intended for LeIFC than that disclosed in the application as filed and claimed in claim 6 of the main request. The correction under Rule 88 EPC is allowable.

12. The same two molecules are claimed in claims 5 and 6 of the main request as in claims 6 and 7 of the granted set of claims (albeit under a different denomination). The protection conferred is not extended.

13. The requirements of Article 123(3) EPC are fulfilled.

Priority: Articles 87 and 88 EPC

14. The claimed generic molecules can be regrouped in two clusters, depending on the amino-acid sequence at their NH2-terminal end being either Cys-Asp-Leu or Cys-Asn-Leu. The specific LeIF-B to D and LeIF-F molecules (claims 5 to 8) belong to the first cluster whereas LeIF-H (claim 9) belongs to the second one.

15. The first and second priority documents disclose the first cluster of molecules as well as methods of general applicability for the isolation of cDNAs encoding LeIFs and for their insertion into an expression vector in such a manner that the DNA sequence encoding mature LeIF is expressed in unfused form. By applying these methods, it is in principle possible to obtain any LeIF, quite irrespective of its amino-acid sequence.

16. The second cluster of LeIFs and LeIF-H are described for the first time in the third priority document. The specific amino acid sequence Cys-Asn-Leu at the NH2-terminal end is the feature which distinguishes these LeIFs from all other known interferons. It is thus an essential characterising feature of the cluster, which could have been derived neither explicitly nor implicitly from the teachings of the first two priority documents.

17. The dependent claims cover subject-matter disclosed in the same priority documents as the independent claims/parts thereof they depend upon.

18. Accordingly, in line with established case law (cf. e.g. T 81/87, OJ EPO 1990, 250), claim 9 and claims 1 to 4, insofar as they relate to Cys-Asn-Leu LeIFs (and dependent claims thereof) are not entitled to the first

or the second priority date, but only to the third or later priority dates depending on which of these priority documents discloses the specific sequences (including Cys-Asn-Leu) characterising them.

Article 54 EPC

19. Document (7) was argued to be detrimental to the novelty of claim 1 relating to LeIF-166-Cys-Asp-Leu belonging to the first cluster, provided that its teachings were corrected with those of the post-published document (18). Documents (2) and (4) were argued to be detrimental to the novelty of the claim to LeIF-D also belonging to the first cluster of interferon molecules.

20. Document (7) discloses the molecule IFN-γ2 isolated from natural sources and characterized by a molecular weight of 17500 daltons (determined, according to document (22), with cytochrome C and chymotrypsinogen A as molecular weight standards), and by the fact that it is composed of 152 amino-acids. In document (18), the molecular weight of IFN-γ2 was experimentally determined as being 19500 daltons (using a different set of molecular weight markers from that of document (7)) and the number of amino-acids in the molecule was experimentally found to be 164.

21. The molecular weight of LeIF-D can be approximately calculated as 19500 daltons and the molecule comprises 166 amino acids.

22. There is no evidence on file as to which molecular weight markers will provide the experimentally determined molecular weight closest to the approximately calculated one. Furthermore, it is not readily apparent why the number of amino acids experimentally determined in document (18) should be

more accurate than the number of amino-acids experimentally determined in document (7). In the Board's judgment, the available data do not provide an unambiguous characterization of IFN-γ2. In addition, the experimentally determined number of amino-acids is different in both documents from the claimed number of amino-acids (165 or 166). Accordingly, the Board does not consider document (7) as detrimental to novelty.

23. Document (2) discloses cDNAs encoding leukocyte pre-interferons and the protein sequences deduced therefrom. Document (4) discloses the expression in E.coli of the pre-LeIF of document (2) from a fused construct. As for document (1), the part of this document which enjoys the priority of 3 April 1980 corresponds to Documents (2) and (4). None of these documents discloses the DNA encoding the mature form of LeIF or the LeIF mature protein. Accordingly, they cannot be detrimental to novelty.

24. No other documents on file disclose subject-matter which could destroy novelty. The requirements of Article 54 EPC are fulfilled.

Inventive step

Claims enjoying the first or second priority date

25. The closest prior art is represented by document (4) published on 27 March 1980. This describes an experiment aimed at expressing in E.coli a DNA construct comprising part of the E.coli beta-lactamase gene and, attached to it, a DNA fragment comprising the pre-leukocyte interferon coding sequence. The protein expressed from this hybrid construct is shown to have LeIF biological activity. Its molecular weight does not correspond to that expected for the fused protein. It is rather consistent with that of a polypeptide, the

translation of which was initiated at the physiological initiation site of the pre-LeIF sequence. The authors discuss the possibilities that the observed biological activity is due to pre-LeIF and that the low level of synthesis observed might be caused by the rare occurrence of the internal translational event. They suggest that this problem could be alleviated by modifying the structure of the hybrid plasmid.

26. Starting from the closest prior art, the objective technical problem to be solved is the production of mature members of the LeIF family in E.coli.

27. The solution provided is to clone the cDNAs encoding the pre-LeIFs, to shorten their sequences to those sequences encoding the mature LeIFs and to insert the DNA fragments thus obtained into a vector for direct expression in E.coli.

28. The Board is satisfied that mature LeIFs have been obtained as disclosed in the patent in suit.

29. Appellant I argued that document (4) itself suggested to insert the DNA sequences encoding the mature LeIFs into an expression vector. In the Board's judgment, however, no such suggestion is made. The authors of document (4) discuss appropriate modifications of the hybrid plasmid, they had constructed, in connection with eliminating the problem associated with internal translation initiation. This problem is not connected with making mature LeIFs rather than pre-LeIFs.

30. Failing to find any suggestion in document (4) on how to produce mature LeIFs in E.coli, the skilled person may have turned to the general state of the art for guidance. The evidence on file shows that in the mid-80s, the art of expressing in E.coli eukaryotic

proteins in their natural, biologically active forms was very much in its infancy. In fact, the only document published before the first or second priority date which is cited in this context is document (5). According to its authors, the then conventional expression methods utilised either chemically synthesized DNA or cDNA exclusively, the cDNA approach being used to express fusion proteins (passage bridging column 1 and 2, page 544). Document (5) discloses a method for the expression of mature human growth hormone in E.coli which involves shortening the cDNA to the DNA fragment consisting of the "mature coding sequence" and inserting this fragment into an expression vector. The presence of human growth hormone in the bacterial extracts is shown by radioimmunoassay. The biological activity of the protein is not tested. Evidence is presented for some proteolytic degradation taking place.

31. It is possible that the skilled person may have thought of combining the teaching of document (4) (cloning of LeIF cDNAs) with the teaching of document (5) (insertion of the "mature coding sequence" in the expression vector), to produce mature LeIFs in E.coli. Yet, in the Board's judgment, this combination would not have been regarded as having a reasonable expectation of success, as document (5) appears to have been the only state of the art pointing in this direction and did not provide such conclusive results neither with regard to the possibility of producing the mature protein in stable form, nor with regard to its properties.

32. Document (14) published between the first and second priority date advises that bacteria are capable of cleaving eukaryotic signals (page 3991). If anything, it teaches away from the present invention, as it precludes the necessity of using DNA sequences encoding

the mature protein to produce said protein in a foreign host. There are no other documents on file, the combination of which with document (4) would be detrimental to inventive step.

33. Accordingly, inventive step is acknowledged in respect of the subject-matter of the claims enjoying the first or second priority date.

Claim 9 and claims to LeIF characterized by the sequence Cys-Asn-Leu at the NH2-terminal end

34. Claim 9 enjoys the third priority date. Claims relating to generic Cys-Asn-Leu LeIFs similarly enjoy the third or a later priority date depending on which of these priority documents disclose the specific features (including Cys-Asn-Leu) characterising them (see points 14 to 16 above).

35. The closest prior art is represented by document (11) published on 2 October 1980. This document discloses the direct expression in E.coli of mature leukocyte interferon LeIF-A characterized by the sequence Cys-Asp-Leu at the NH2-terminal end . It teaches that there exists a family of LeIFs (page 411). The method used to obtain the expression of mature LeIF-A is said to be generally applicable (page 415).

36. Starting from this prior art, the objective technical problem to be solved can be defined as the provision of another member of the LeIF family. The formulation of this problem is not in itself inventive since the existence of the LeIF family was known.

37. The solution is the claimed LeIFs characterized in particular by the sequence Cys-Asn-Leu at the NH2-terminal end.

38. The state of the art at the third priority date discloses four other interferons in addition to LeIF-A: LeIF-I (document (2)), LE-IFα2 (document(9)), IFαA and IFαB from Namalva cells (document (19)). The five interferons have the following amino-acid sequence at the NH2 terminal end: Cys-Asp-Leu-Pro- (Glu or Gln) - Thr-His-Ser-Leu- (Asp or Gly) -... In the Board's judgment, these data would be interpreted by the skilled person as meaning that the NH2-terminal end is relatively well conserved (80%) and that the amino-acids in positions 5 and 10 are the ones which can vary without altering the biological properties of the molecule. Otherwise stated, starting from the available prior art, the skilled person would not have expected that a member of the interferons family could differ from the other members of the family in position 2. This unexpected result justifies recognition of inventive step for the subject-matter of the claims enjoying the third priority date.

39. Post-published document (20) shows that LeIF-H is the only interferon out of eleven members of the IFN family to carry Cys-Asn-Leu at the NH2-terminal end. Thus, this last feature remained unexpected even after the filing date of the patent in suit. Accordingly, all claims to LeIFs characterized by the sequence Cys-Asn-Leu are considered inventive irrespective of their priority date being the third or a later priority date.

40. The requirements of Article 56 EPC are fulfilled by the subject-matter of all claims.

Question to the Enlarged Board of Appeal

41. This question (cf. point XIII, above) was submitted by the Respondent in the context of determining whether document (11) is a prior art document to be taken into account when assessing the inventive step of the

subject-matter of the claims enjoying the third or a later priority date. In the course of the proceedings, it was established that the subject-matter of these claims involves an inventive step, even if document (11) is considered the closest prior art (cf. points 34 to 39, above). The question, thus, need not be addressed. No decision within the meaning of Article 112(1)(a) EPC is required. Consequently, the Respondent's request is refused (Article 112(1)(a), last sentence EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of claims 1 to 40 submitted during oral proceedings as main request, and the description, pages 3, 5, 6, 17, 18, 20 submitted during oral proceedings and pages 4, 7 to 16, 19 as granted, and drawings, Figure 4 submitted during oral proceedings and Figures 1 to 3, 5 to 9 as granted.

3. The request to refer a question to the Enlarged Board of Appeal is refused.

The Registry: The Chairman:

A. Townend L. Galligani