BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

A		B	X	C	

File Number: T 500/91 - 3.3.2

Application No.: 81 300 050.2

Publication No.: 0 032 134

Title of invention: DNA sequences, recombinant DNA molecules and processes for producing human interferon-alpha like polypeptides

Classification: C12N 15/00

D E C I S I O N
of 21 October 1992

Proprietor of the patent: Biogen N.V.

Opponent:
01) F. Hoffmann-La-Roche & Co.
02) The Upjohn Company
03) Boehringer Ingelheim Zentrale GmbH
04) Bender & Co Ges mbH
05) Cetus Corporation/Triton Biosciences Inc.
06) Hoechst Aktiengesellschaft, Frankfurt
07) Boehringer Mannheim GmbH
09) Boehringer Ingelheim Pharma Ges mbH

Headword: Alpha-interferon II/BIOGEN

EPC Art. 56, 112(1)

Keyword: "Inventive step (yes) - No realistic expectation of success - Activities to be expected from the notional person skilled in the art"
"Assessment of evidence not a question of law"

Case Number : T 500/91 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 21 October 1992

Appellant 01 : (Opponent 03)
Boehringer Ingelheim Zentrale GmbH
W-6507 Ingelheim am Rhein (DE)

Representative :
Kinzebach, Werner, Dr.
Patentanwälte
Reitstötter, Kinzebach und Partner
Sternwartstrasse 4
Postfach 86 06 49
W-8000 München 86 (DE)

Appellant 02 : (Opponent 04)
Bender & Co Ges mbH
Dr. Boehringer-Gasse 5-11
Postfach 103
A-1121 Vienna (AT)

Representative :
Kinzebach, Werner, Dr.
Patentanwälte
Reitstötter, Kinzebach und Partner
Sternwartstrasse 4
Postfach 86 06 49
W-8000 München 86 (DE)

Appellant 03 : (Opponent 07)
Boehringer Mannheim GmbH
Sandhofer Strasse 116
Postfach 31 01 20
W-6800 Mannheim 31 (DE)

Representative :
Huber, Bernhard, Dipl.-Chem.
Patentanwälte
H. Weickmann, Dr. K. Fincke
F.A. Weickmann, B. Hunber
Dr. H. Liska, Dr. J. Prechtel
Kopernikusstrasse 9
Postfach 86 08 20
W-8000 München 86 (DE)

Appellant 04 :
(Opponent 09)

Boehringer Ingelheim Pharma Ges mbH
Dr. Boehringer-Gasse 5-11
A-1121 Vienna (AT)

Representative :

Kinzebach, Werner, Dr.
Patentanwälte
Reitstötter, Kinzebach und Partner
Sternwartstrasse 4
Postfach 86 06 49
W-8000 München 86 (DE)

Respondent :
(Proprietor of the patent)

Biogen N.V.
15 Pietermaai
Willemstad
Curacao, Netherlands Antilles

Representative :

Ritter, Stephen David
Mathys & Squire
10 Fleet Street
London EC4Y 1AY (GB)

Vossius & Partners
Patentanwälte
Siebertstraße 4
W - 8000 München 86

Other party :
(Opponent 01)

F. Hoffmann-La Roche & Co.
Aktiengesellschaft
Grenzacherstrasse 124
CH-4002 Basel (CH)

Representative :

Lederer, Franz, Dr.
Lederer, Keller & Riederer
Patentanwälte
Lucile-Grahn-Strasse 22
W-8000 München 80 (DE)

Other party :
(Opponent 02)

The Upjohn Company
301 Henrietta Street
Kalamazoo, Michigan (US)

Representative :

Perry, Robert Edward
Gill, Jennings & Every
53-64 Chancery Lane
London WC2A 1HN (GB)

Other party :
(Opponent 05)

Cetus Corporation / Triton Biosciences, Inc.
A Division of Shell Oil Company
1400 Fifty-Third Street / 1501 Harbor Bay Parkway
Emmeryville / Alameda
California 94608 / California 94501 (US)

Representative :

Werner, Hans-Karsten, Dr.
Deichmannhaus am Hauptbahnhof
W-5000 Köln 1 (DE)

.../...

Other party :
(Opponent 06)

Hoechst Aktiengesellschaft, Frankfurt
Ressortgruppe Patente, Marken und Lizenzen
W-6230 Frankfurt am Main 80 (DE)

Representative :

Decision under appeal :

Interlocutory decision of the Opposition Division of the European Patent Office dated 12 November 1990, posted on 4 April 1991 concerning **maintenance of European patent No.** 0 032 134 in amended form.

Composition of the Board :

Chairman : P.A.M. Lançon
Members : D. Holzner }
R.K. Spangenberg } Co-Rapporteurs
E.M.C. Holtz
J-C. Saisset

Summary of Facts and Submissions

I. European patent No. 32 134 was granted on 15 August 1984 in response to European patent application No. 81 300 050.2, claiming priority from three earlier applications dated 8 January 1980, 3 April 1980 and 2 October 1980. By a decision notified on 10 June 1987 the Opposition Division revoked the patent in response to eight oppositions and one Notice of Intervention.

By its decision T 301/87 of 16 February 1989, published in OJ EPO 1990, 335, the Technical Board of Appeal 3.3.2 remitted the case to the Opposition Division for further prosecution on the basis of amended claims, having stated that the subject-matter of these claims satisfied the requirements of Articles 83/100(b), 84 and 54 EPC. In respect of Article 56 EPC, an inventive step was acknowledged insofar as document (16), the "Nagata-publication" was concerned. The only remaining issue was that of inventive step insofar as it had not yet been examined by the first instance (see T 301/87, item 8 of the reasons).

II. By a decision delivered orally on 12 November 1990, with written reasons posted on 4 April 1991, the Opposition Division maintained the patent in amended form on the basis of the claims remitted by the decision T 301/87 and a description adapted thereto.

III. Notices of appeal were filed by Opponents III, IV, VII and IX and the corresponding fees paid in due time.

IV. Claims 1 and 2, the allowability of which was contested in the present appeal proceedings, read as follows:

1. A recombinant DNA molecule for use in cloning a DNA sequence in bacteria, yeasts or animal cells, said recombinant DNA molecule comprising a DNA sequence selected from:

(a) the DNA inserts of Z-pBR322(Pst)/HcIF-4c, Z-pBR322(Pst)/HcIF-2h, Z-pBR322(Pst)/HcIF-SN35, Z-pBR322(Pst)/HcIF-SN42 and Z-pKT287(Pst)/HcIF-2h-AH6, said DNA inserts being the DNA inserts of the recombinant DNA molecules carried by the microorganisms identified by accession numbers DSM1699-1703, respectively.

(b) DNA sequences which hybridize to any of the foregoing DNA inserts and which code for a polypeptide of the IFN-α type, and

(c) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences and inserts defined in (a) and (b) and which code for a polypeptide of the IFN-α type.

2. A recombinant DNA molecule according to Claim 1, wherein said DNA sequence (b) which hybridizes to said DNA insert (a) is selected from:

(d) the DNA inserts of Z-pBR322(Pst)/HcIF-II-206 and Z-pBR322(Pst)/HcIF-SN35-AHL6, said DNA inserts being the DNA inserts of the recombinant DNA molecules carried by the microorganisms identified by accession numbers ATCC 31633-31634, respectively,

(e) DNA sequences which hybridize to any of the foregoing DNA inserts and which code for a polypeptide of the IFN-α type, and

(f) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences and inserts defined in (d) and (e) and which code for a polypeptide of the IFN-α type.

The Opposition Division, after consideration of more than 200 documents, among which

(4) Cavalieri et al., **Proc. Natl. Acad. Sci. USA 74**, 1977, pages 3287 to 3291

(9) Rubinstein et al., **Proc. Natl. Acad. Sci. USA 76**, 1979, pages 640 to 644

(14) **Research Disclosure, No. 18309**, July 1979, pages 361 and 362

(15) Taniguchi et al., **Proc. Japan. Acad. 55**, Ser.B., 1979, pages 464 to 469

(16) Nagata et al., **Nature, 284**, 27 March 1980, pages 316 to 320

(108) Zoon et al., Abstract No. 32, referring to an oral disclosure at the Conference on Regulatory Functions of Interferons, New York 1979.

(109) Szostak et al., **Nature, 265**, 1977, pages 61 to 63

(110) Wallace et al., **Nucleic Acid Research, 6(11)**, 1979, pages 3542 to 3557

(111) Noyes et al., **Proc. Natl. Acad. Sci. USA, 76(4)**, 1979
pages 1770 to 1774

(112) Szostak et al., **Methods in Enzymology, 68,** 1979, pages 419 to 429

remained relevant to the present appeal proceedings, held that in respect of the subject-matter enjoying the first priority date, the closest state of the art was illustrated by document (14), which document described some hypothetical routes for obtaining inter alia alpha-interferon from recombinant DNA. However, the Opponents, who had the burden of proof, had been unable to demonstrate that these hypothetical possibilities could be put into practice, at the relevant date, without inventive effort and without undue experimentation. In particular, the method disclosed in document (15) was not applicable to the production of **alpha**-interferon. Moreover, this document did not even disclose the successful preparation of beta-interferon from plasmids containing DNA-sequences coding for this protein.

The possibility of selecting clones containing the desired DNA-sequences coding for alpha-interferon, starting from the so-called "Zoon sequence" of the N-terminal amino acids of alpha-interferon, was held by the Opposition Division not to have been, at the relevant date, a method of proven practical value, in particular having regard to the high degree of degeneracy of the DNA coding for the said amino acid sequence. Thus, in the absence of a reasonable expectation of success, a person skilled in the art would not have tried it.

Regarding the subject-matter of the disputed patent which only enjoyed the other priority dates, the relevant state of the art was unchanged, taking into account that, according to the decision T 301/87, document (16) did not form part of the relevant state of the art.

V. Oral proceedings took place on 21 October 1992. Of the other opponents who were duly summoned, only Opponent I was represented. During the appeal proceedings, the Appellants I, II, and IV (Opponents III, IV and IX) additionally relied upon

(232) Morser et al., J. gen. Virol. 44 1979, pages 231 to 234.

VI. The Appellants' submissions can be summarised as follows:

The appeals only contested the inventive step of the subject-matter of Claim 1(a), insofar as the DNA insert of Z-pBR322(Pst)/HcIF-4c was concerned, Claim 1(b) and Claim 2(e). Three lines of argument were developed:

(a) The above-defined subject-matter of Claim 1(a) was a DNA-fragment of 320 base-pairs only and was, therefore, unsuitable for coding for alpha-interferon (IFN-α). Thus it did not solve the technical problem with which the disputed patent was concerned and, consequently, could not be regarded as inventive.

Further, the subject-matter of Claims 1(b) as well as 2(e) comprised any DNA coding for IFN-α, since all DNAs which coded for IFN-α necessarily hybridized to the inserts of Claim 1(a).

In the disputed patent the subject-matter of Claims 1(b) and 2(e) was only described as a desideratum. In fact it was claimed everything being similar to the deposited inserts. Thus the subject-matter of these claims does not establish an inventive technical teaching.

(b) Document (14) did not comprise a multitude of possibilities for carrying out the different steps of preparing interferon by genetic engineering methodology, since this multitude could be reduced to a few standard routes. This view was confirmed by document (15), the author of which, in principle, had chosen the same approach as had been used in the patent in suit, i.e. (±)-hybridization. Document (14) suggested that interferons could be produced by adaptation of conventional methods of genetic engineering, and the method successfully adopted according to the patent in suit was one of them. Missing details in document (14) could be found in the references cited therein or were a matter of routine experimentation. Since, according to document (15), a procedure quite similar to that followed in the disputed patent had already been successful in the case of a mRNA fraction (termed "interferon RNA" in document (15)), which was used as the template for cDNA synthesis, the person skilled in the art would have tried analogous conventional procedures with a view to isolate mRNA producing IFN-α. Suitable sources of mRNA capable of producing IFN-α, i.e. mRNA-mixtures in which this mRNA was present in sufficient concentration, were available before the priority date of the patent in suit, e.g. by inducing the corresponding cells with Sendai virus, a procedure which had also been used in the test report submitted by Opponent III on 28 November 1986.

Although cycloheximide, the substance applied for superinduction in document (15), was not capable of inducing IFN-α production in leukocytes, and, therefore, superinduction in the narrow meaning of this technical term was not applicable to leukocytes, there were other known effective ways of obtaining

increased IFN-α titers, e.g. priming of leukocytes with IFN-α and 24 hours' treatment of Namalva cells with sodium butyrate.

The fact that Table I in document (4) showed that it was very likely that a mRNA-mixture obtained from the cell culture described there would contain IFN-α producing mRNA in a concentration much lower than that of mRNA producing IFN-ß was explained by the assumption that the method for inducing the cells used in document (4) was less effective than the induction by Sendai virus which was also known before the priority date of the disputed patent and had been used in the above test report as well as in the patent in suit. Further, the experimental data in the patent specification confirmed that sufficient amounts of the desired mRNA were formed by induction with Sendai virus.

Therefore it was readily possible, by applying the methods known from documents (14) and (15) and routine experimentation, to arrive at subject-matter falling within the terms of Claim 1(b) or 2(e), and no inventive step was present.

(c) It was already acknowledged in document (16) that the inventor would have tried another approach to solving the present technical problem, if sequence information on the structure of IFN-α had been known. Since it was no longer in dispute that in fact a partial amino acid sequence, the "Zoon-sequence", was available to the public before the first priority date of the patent in suit, it already followed from the statements in the patent itself that it was possible to obtain, without inventive activity, a DNA-molecule having the features set out in Claims

1(b) and 2(e), which both comprise all possible DNA-molecules encoding for IFN-α. The Appellants emphasised that, in this respect, they relied upon the Inventor's own expert opinion, derivable from the patent specification, which was further confirmed by documents (109) to (112) and Prof. Gassen's experiments submitted with the letter dated 12 October 1990. In particular, they pointed out during the oral proceedings, that "mixed probes" of synthetic oligonucleotides generally contained the "correct" sequence in very low concentration and were known to be used, provided that the mRNA searched for or, respectively, the cDNA obtained from it, is sufficiently highly populated in a gene bank. This requirement was met in the case of mRNA producing leukocyte interferon because document (232) taught how such mRNA could be obtained and partially purified.

It was not necessary that a "mixed probe" of synthetic oligonucleotides contained the fully correct base sequence, since a positive result would also be obtained if one or even more "mismatches" occur. It was only under very stringent hybridization conditions, normally only applied for analytical purposes, that already one mismatch prevented hybridization. A person skilled in the art would, however, have chosen such hybridization conditions which gave a sufficiently low number of "positive" results, thereby admitting that a limited number of them were "false positive", i.e. hybridization occurred with DNA-sequences not coding for IFN-α. Since it was possible to eliminate these false-positive results by a simple test, the necessary adaptation of hybridization conditions was no more than a matter of routine experimentation. It would

also not have exceeded the area of routine experimentation to make more than one attempt to reduce, according to the well-established "wobble-rules" referred to e.g. in document (112), the complexity of the synthetic oligonucleotide mixture if the first attempt had failed, since, as a consequence of the reduction strategy, no DNA-sequence of sufficient similarity to the correct one was present in the probe. In any case, a certain amount of "trial and error" was common in the field of genetic engineering.

VII. In a letter received by the EPO on 14 October 1992, Appellants II, III and IV requested

- permission to provide for a neutral expert opinion if the Board did not feel inclined to accept that the test reports dated 12 October 1990 and 28 November 1986, drawn up by Prof. Gassen on behalf of the Appellants, demonstrated an obvious route for obtaining a DNA-molecule according to Claims 1 to 3, in particular Claim 1(b) and 2(e), and,

  if the Board found, in accordance with the decision under appeal, that a person skilled in the art would not have used the route via the "Zoon-sequence" outlined by the Appellants and referred to in the decision under appeal,

- that the question be referred to the Enlarged Board of Appeal whether or not it would be admissible, in assessing inventive step, to disregard the opinion of the inventor himself and his closest co-workers and to base the decision on a different opinion.

VIII. The Respondent submitted that the Appellants' first line of argument amounted to no more than an attempt to raise again the question of clarity already finally settled by the preceding decision T 301/87. He also contested that document (14) contained an enabling disclosure of a route to isolating a DNA-molecule coding for IFN-α or even a molecule being capable of hybridizing with such a DNA-molecule and therefore having the same function as the DNA-insert of Z-pBR322(Pst)/HcIF-4c. Therefore, he argued, the patent could not be used to demonstrate that any of the great number of possibilities encompassed by document (14) would have led to the desired result with a reasonable expectation of success. Regarding document (15), the situation in the case of IFN-ß was different because a mRNA-mixture containing a considerably higher concentration of the desired mRNA producing IFN-ß was available through "superinduction", which was not possible in the case of IFN-α. Thus, Taniguchi's successful isolation of a clone, the recombinant DNA of which contains the sequence for the ß-interferon mRNA, was no incentive to try the same route in the case of IFN-α, because the possibility of success was too uncertain.

This situation was in no way changed by the disclosure of the amino acid sequence called "Zoon-sequence" in these proceedings, since it was never shown in the literature at the relevant date that the "mixed probe"-approach, the only possible one in the case of a highly degenerate DNA-sequence such as the one coding for the above "Zoon-sequence", gave reliable results. This approach was at best mentioned in the documents (109) to (112) as a theoretical possibility. In fact, no one had reported probing a cDNA bank with mixtures of short oligonucleotides before November 1981. Therefore, starting from the knowledge relevant at the priority date of the

disputed patent, there was no reasonable expectation of success.

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

The Respondent requested that the appeals be dismissed.

At the end of the oral proceedings the decision of the Board to dismiss the appeals was announced.

Reasons for the Decision

1. The appeals are admissible.

2. The only issue which falls to be decided in these appeal proceedings is that of inventive step, in particular in respect of the subject-matter of Claims 1(a), 1(b) and 2(e).

2.1 At the first priority date, human IFN-α was available from human cells grown in tissue culture or from human leukocytes collected from blood donors, (see e.g. document (9)). This document illustrates the closest state of the art. As stated in the description of the disputed patent, these sources were not adequate to provide sufficient quantities of human IFN-α. Therefore, the technical problem which the patent sets out to solve was to provide an additional procedure being capable of producing human IFN-α in quantities sufficient to meet the demand for IFN-α for extended clinical studies and for potential therapeutical applications.

The patent proposes to solve this problem by the methods of recombinant DNA-expression claimed in Claims 15 and 21,

for which Claims 1 and 2 provide the necessary tools, i.e. DNA-probes required for selecting, from natural sources, a DNA coding for IFN-α (Claim 1(a)) and DNA-sequences which code for polypeptides having the desired IFN-α activity.

Having regard to the examples contained in the patent specification, the Board is satisfied that the above technical problem has thereby been effectively solved. The Appellants' submission that the first DNA insert mentioned in Claim 1(a), Z-pBR322(Pst)/HcIF-4c, is itself too small for coding for a polypeptide having IFN-α activity does not contradict the above finding since this DNA insert is a tool not only suitable but, at the priority date, even necessary to isolate, from natural sources, DNA molecules required for producing the desired polypeptides in a reliable and repeatable manner. It therefore makes an essential contribution to the solution of the present technical problem.

2.2 It is true that at the priority date of the disputed patent, only a limited number of persons were skilled in recombinant DNA-technology and that probably all of them were advanced senior scientists with skills above the average level in the broader art of biochemistry. As this Board said in decision T 60/89, OJ EPO 1992, 268, the notional person skilled in the art of genetic engineering would not be defined as a Nobel Prize laureate, but rather a graduate scientist or a team of scientists of that level of skill, working in laboratories which were developing genetic engineering techniques, in contrast to developing the science of molecular genetics, at the time in question (in that particular case around 1978).

In other words, in accordance with the established jurisprudence of the Boards of Appeal, the notional skilled person who may be represented by a team of

appropriate specialists (T 141/87 of 29 September 1989, not published in the OJ EPO and T 60/89 mentioned above), is oriented towards practicalities, (see T 5/81, OJ EPO 1982, 249), and the development of the art normally expected by him does not include solving technical problems by performing scientific research in areas not yet explored.

2.3 On the basis of the above closest state of the art, the activities which can be expected to be performed by the notional person skilled in the art and the technical problem which has been solved by the patent in suit, it has now to be decided whether or not the state of the art, at the relevant priority dates, would have led that notional person skilled in the art to the subject-matter covered by the present claims. The Appellants' objections in this respect were limited to the subject-matter of Claims 1(a), 1(b) and 2(e). The Board is satisfied that, if the subject-matter of these claims involves an inventive step, essentially the same considerations would also apply to the subject-matter of all other claims.

2.3.1 One of the Appellants' first submissions was that the subject-matter of Claims 1(b) and 2(e) must necessarily cover naturally occurring DNA coding for human IFN-α and that at least this DNA molecule was a mere "desideratum" and, for this reason alone, unpatentable.

A "desideratum" may correspond to the desire of a particular effect or of a particular product. As such, it amounts to the expression of a technical problem which can or cannot be solved by the patent in question. However, there is no provision in the EPC pursuant to which "desiderata" are excluded from patentability, provided that means to fulfil them are disclosed in a manner sufficiently clear and complete to be carried out by a

person skilled in the art and that such means were not made available to the public pursuant to Article 54(1) EPC or were not obvious to a person skilled in the art pursuant to Article 56 EPC. In contrast to the situation underlying the decision T 877/90 - 3.3.2 of 28 July 1992, the present Claims 1(b) and 2(e) are not directed to a known substance in purer form, but to novel DNA-sequences, as has been decided in T 301/87.

In Claims 1(b) and 2(e) the number of DNA-sequences is limited by functional technical features. In the Board's judgment, at the priority date, it was only possible with the deposited inserts of Claims 1(a) and 2(d) to find, without undue experimentation, DNA-sequences out of the great number of leukocyte-DNAs fulfilling these functional requirements.

In other words, the Board is unable to accept the Appellants' allegation that a person skilled in the art, at the relevant date, would have been able to isolate the desired DNA from any source containing it, albeit possibly in very low concentration, e.g. from cDNA-mixtures obtained from mRNA-mixtures isolated from induced Namalva-cells or leukocytes, solely by applying common general knowledge. It follows from point 5 of the Reasons for the Decision T 301/87 that the Board has already denied that a person skilled in the art was able to isolate the desired DNA from "Lawn's gene bank", by application of the common general knowledge, see in particular point 5.5. In the Board's judgment, in the absence of any additional evidence, the reasons given there in respect of "Lawn's gene bank" are equally applicable to any other DNA-mixture of similar complexity which may have existed or could have been prepared at the priority date of the patent in suit. Thus the Board is satisfied that inventive step in the present case cannot be disputed solely because the above

"desideratum" could be fulfilled on the basis of common general knowledge.

2.3.2 Insofar as the Appellants intended, with their reference to a "desideratum", to raise again the issue that Claims 1(b) and 2(c) comprised subject-matter not described in sufficient detail in the patent specification, their arguments cannot be considered here, since this issue has already been finally decided in T 301/87.

2.3.3 The Appellants' second line of argument was based upon documents (14), (15) and (232), in combination with the common general knowledge. Document (14) is an anonymous disclosure in "Research Disclosure" of July 1979 and describes some hypothetical routes for obtaining interferon in general from recombinant DNA. Document (15), called Taniguchi I in the earlier proceedings, relates to the production of IFN-ß.

Referring to document (14), the Appellants pointed out that this disclosure must not be considered in isolation. Experimental instructions, which in the Respondent's view were missing, could be found in the references cited therein.

However, in the Board's judgment, it is rather doubtful whether document (14) concerns, even implicitly, the production of recombinant human leukocyte interferon (IFN-α), and not only that of fibroblast interferon (IFN-ß), since literature relevant to leukocyte IFN, such as documents (4), (9) and (232), is not cited. Thus, in respect of the possibility of inducing IFN mRNA, reference No. 27 of document (14) relates to "Cavalieri et al, 1977, PNAS 74, 4415", which, however, is not identical with

document (4), "Cavalieri et al, 1977, PNAS 74, 3287", as alleged by the Appellants.

The state of the art relating to induction of corresponding cells for IFN production must be regarded in a differentiated manner: Induction of human fibroblasts is described in document (4) and in reference 27 of document (14), induction of the Namalva line of human lymphoblastoid cells is described in documents (4) and (232), and induction of human leukocytes is described in document (9) and the patent in suit (see page 8, line 6 to 8, referring to the Cantell procedure).

As clarified during the oral proceedings, cycloheximide, while stimulating the production of IFN-ß mRNA in high concentration if used for the superinduction of fibroblasts, does not stimulate the production of IFN-α mRNA in Namalva cells or leukocytes. As Table 1 of document (4) shows, the obtainable concentrations of mRNAs differ very much from each other, depending upon the type of starting cells and the respective method of induction. In the Board's judgment, the Appellants' explanation of these differences, namely that the induction of Namalva cells by Newcastle disease virus used in document (4) was less effective than induction by Sendai virus, suggesting that Newcastle disease virus was an inferior means for induction, is not convincing, because precisely Newcastle disease virus is also used for induction of human leukocytes for interferon production according to the later document (9).

In addition, the Appellants referred to other possibilities of inducing the production of IFN-α, i.e. the priming of leukocytes with IFN-α as well as 24 hours' treatment of Namalva cells with sodium butyrate, the latter described by Wellcome GB in connection with the

conventional production of IFN (Wellferon^{R}), without, however, submitting relevant documents. Therefore, in the Board's judgment, it cannot be established at which date the Wellcome procedure became available to the public and whether it would have been applicable to leukocytes with expectation of better success compared to document (9) and the Cantell procedure referred to in the disputed patent.

The Appellants' reference to the test report submitted by Opponent III on 28 November 1986 is also not convincing, since a cell line derived from the Burkitt lymphoma was used there as a starting material to give the so-called "Interferon-RNA Namalva". Document (232) starts from human lymphoblastoid cells of the Namalva line which are grown in suspension culture and induced with Sendai virus. Details of this procedure cannot be taken from document (232) as the reader is referred to "as will be published elsewhere" (see page 231, last paragraph, first sentence).

Considering the above, particularly the fact that document (4) demonstrates that the amount of mRNA produced from induced Namalva cells is much lower than that produced from superinduced fibroblasts (see page 3288, Table 1), and that the amount of IFN-alpha mRNA should be even lower than the amount of "Namalva-IFN mRNA" because Namalva interferon is a mixture of two types of interferon, leukocyte and fibroblast interferon (see page 3289, last sentence), the Board is satisfied that the skilled person, at the relevant date, knew that leukocytes can be induced for interferon production with Newcastle disease virus (document (9), page 640) or with Sendai virus (Cantell procedure), but would have expected the IFN-α mRNA to be formed in considerably lower quantity than IFN-ß mRNA from superinduced fibroblasts.

This means that a person skilled in the art was well aware of a significant difference in abundance of the starting materials for IFN-production, mRNA from superinduced fibroblasts for IFN-ß on one hand, and mRNA from induced leukocytes for IFN-α on the other hand. The results communicated in document (15) in relation to interferon-beta were thus not an incentive to try the procedure reported there in an attempt aimed at the production of IFN-α. Therefore, in the Board's judgment, a skilled person could not reasonably expect that a procedure, similar to that published in document (15), would, by analogy, be a successful way to obtaining IFN-α by genetic engineering.

The tests performed by the Appellants do not demonstrate more than the patent itself does, namely that, contrary to what could be inferred from the literature available at the relevant date, it was nevertheless possible to succeed in preparing a DNA-probe, useful in a procedure for the production of recombinant IFN-α, starting from induced leukocytes. They cannot prove, however, that the person skilled in the art would have expected this success before the priority date of the patent in suit.

Thus, on the basis of the available evidence and the proper definition of the activities which can be expected from the notional "person skilled in the art" in the present situation (see paragraph 2.2 above), the Board is satisfied that there was no straightforward possibility of producing recombinant IFN-α on the basis of the disclosure of documents (14), (15) and (232).

2.3.4 Regarding the Appellants' third line of argument (see paragraph VII(c) above), there is no dispute among the parties that the most important prerequisite for obtaining a clone containing the desired HuIFN-α cDNA by another

method than trial and error with little expectation of success was the existence of a suitable screening method (see the patent specification, page 12, line 64 to page 13, line 8). In this paragraph the possibility of hybridization with a synthetic probe was mentioned, referring to document (111), as one of several possibilities. Thus, this paragraph does not support the Appellants' submission that the inventor himself has admitted that he would have used this possibility, had a partial amino acid sequence of HuIFN-α been known.

In addition and contrary to the Appellants' submission the state of the art at the relevant date (Zoon sequence in connection with documents (109) to (112)) does not describe in detail searching for a particular gene by means of degenerated oligonucleotide probes (mixed probes).

In document (109) a unique 15-mer was synthesised according to the known partial sequence of a mRNA, but not starting from an amino acid sequence of a polypeptide. Considerations of the genetic code and its degeneracy were not involved here at all.

Document (111) shows that a chemically synthesised unique 12-mer (deduced from the unique amino acid sequence -Trp-Met-Glu-Glu- of gastrin; see page 1773 right-hand column) does hybridize to a specific RNA. Thus, it does not suggest applying mixed oligonucleotide probes either.

While document (112) in the introduction points out that oligonucleotides are potentially useful as hybridization probes, the authors of document (112) themselves nevertheless applied unique probes only for their hybridization experiments. Their concluding remarks read as follows:

"The complexity of mammalian DNA requires a 15- to 16-nucleotide-long sequence to be unique, and probably an 18- to 20-nucleotide sequence is more desirable to avoid unwanted hybridization with related sequences."

In the the Board's judgment this statement does not invite a skilled person to consider mixed oligonucleotides as hybridization probes for the purpose of the patent in suit.

Thus, documents (109), (111) and (112) only relate to the use of a "unique" probe, consisting of only one oligonucleotide, tuned to quite specific, known nucleotide sequences or amino acid sequences.

It is further true that the authors of document (110) state: "We propose to use a chemically synthesized mixture of oligonucleotides whose sequences represent all possible codon combinations predicted from a particular peptide sequence within a protein. One of this mixture must be complementary to a region of DNA coding for the protein. Stringent hybridization criteria would then be used to select the single correct sequence from the mixture" (see page 3544, lines 10-17).

However, they themselves did not use any mixed probe, but a unique 17-mer, derived from a known nucleotide sequence (see page 3547, lines 4-7). Moreover, they conclude as follows:

"It was the main purpose of this study to examine the effects of such mismatches for a defined naturally occurring DNA in order to establish conditions under which the formation of mismatched duplexes could be eliminated. Such conditions are necessary in order to use the

specificity of oligonucleotide hybridization as a probe for defined DNA sequences" (see page 3554 under "Discussion").

Thus, document (110) does not promise success to a skilled person faced with the technical problem set out in the patent in suit.

No other conclusion can be drawn from the Appellants' submission during oral proceedings, where they pointed out that the success of hybridization depends upon the complementarity of the probe, the length of the probe, the number of the G≡C base pairs, the possible secondary structure, the self-complementarity, the kinetics of nucleation, the choice of solvents and additives, ionic strength, hybridization temperature, the elution steps, the filter material, the extent of radioactive labelling, the secondary structure of the DNA aimed at, the quality of DNA-preparation etc, and further stated that the experimental conditions of a probe hybridization have to be determined empirically.

In respect of the tests performed by Prof. Gassen on behalf of the Appellants in 1990 the situation is similar to that in respect of the tests performed in 1986 in respect of documents (14) and (15), i.e. they cannot help to answer the question whether or not the notional person skilled in the art would have expected, at the priority date of the disputed patent, the result which had been proved later to be in fact obtainable.

On the contrary, it follows from Prof. Gassen's explanations of these tests and the considerations which were applied in order to select the appropriate mixture of synthetic oligonucleotide molecules, in particular from the fact that he admitted that the possibility of

unsuccessful selections could not be ruled out, that these tests have rather the character of scientific research to be performed by an inventor (as defined in point 2.2 above) than of routine adaptation of a known method to a specific technical problem, an activity which can be expected from the notional "person skilled in the art". This view is strongly confirmed by the fact that all documents cited in relation to the use of synthetic oligonucleotide probes used well defined "unique" oligonucleotide sequences. "Mixed probes", which had to be used in the case of the highly degenerate "Zoon-sequence", were at best mentioned as a further potential, not yet explored possibility. Having further regard to the fact that there is no evidence before the Board that, at the priority date, it was common to use hybridization conditions which tolerated a certain degree of "mismatches" but nevertheless gave a sufficiently low number of false positive results, the Board concludes that the notional person skilled in the art was in no different situation with or without knowing the "Zoon sequence".

No other conclusion can be drawn from the Appellants' reference to the content of document (16) (Nagata I; see page 316, right-hand column, paragraph 4) because the authors of this publication do not fit the definition in point 2.2 above of the notional "person skilled in the art" addressed in Article 56 EPC. Therefore, their opinion as to what they would have done had they known the "Zoon-sequence" does not answer the different question what the notional "person skilled in the art" would have done in the same situation.

2.4 The Board therefore concludes that, having regard to the fact that the area of genetic engineering here under consideration was relatively new at the relevant date, having further regard to the uncertainty at that date

about facts influencing the success of the attempted recombinant-DNA techniques, and to the absence of a well-established general level of knowledge in this particular technical area, the present successful technical application of recombinant-DNA techniques, according to Claims 1 and 2 under consideration, involves an inventive step.

3. In respect of the procedural requests made by the Appellants the Board concludes as follows:

3.1 The Board has taken due account of Prof. Gassen's explanations during the oral proceedings and finds no contradiction with the considerations upon which the Board's decision was based. Thus, there was no need to appoint a further technical expert.

3.2 The request that a question be referred to the Enlarged Board of Appeal rests on the assumption that there is a general obligation to accept all offered evidence. However, in accordance with the principle of free assessment of evidence to which the organs of the European Patent Office adhere, these organs are entitled to assess the evidence offered by the parties in any way they see fit, including finding it irrelevant or unimportant, and without having to say so explicitly in their decisions.

As matters of assessment of evidence by way of the mentioned principle cannot give rise to any question of law, the Board finds that Article 112 EPC does not apply. Consequently, it is not possible to refer the question suggested by the Appellants to the Enlarged Board of Appeal.

Order

For these reasons, it is decided that:

The appeals are dismissed.

The Registrar | The Chairman

P. Martorana | P.A.M. Lançon

In der Anlage erhalten Sie

☐ eine Kopie des Berichtigungsbeschlusses

☐ ein neues Vorblatt (Form 3030)

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zur Entscheidung _____

Please find enclosed

☐ a copy of the decision correcting errors in

☐ a new covering page (Form 3030) for

☒ a revised copy of the cover pages to the decision T 500/91 - 332 (Addition of Vossius & Partners as representative of Respondent).

Veuillez trouver en annexe

☐ une copie de la décision rectifiant des erreurs dans

☐ une nouvelle page de garde (Form 3030) pour

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la décision _____

BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS
BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE
CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

A		B	X	C	

File Number: T 500/91 - 3.3.2

Application No.: 81 300 050.2

Publication No.: 0 032 134

Title of invention: DNA sequences, recombinant DNA molecules and processes for producing human interferon-alpha like polypeptides

Classification: C12N 15/00

D E C I S I O N
of 21 October 1992

Proprietor of the patent: Biogen N.V.

Opponent:
01) F. Hoffmann-La-Roche & Co.
02) The Upjohn Company
03) Boehringer Ingelheim Zentrale GmbH
04) Bender & Co Ges mbH
05) Cetus Corporation/Triton Biosciences Inc.
06) Hoechst Aktiengesellschaft, Frankfurt
07) Boehringer Mannheim GmbH
09) Boehringer Ingelheim Pharma Ges mbH

Headword: Alpha-interferon II/BIOGEN

EPC Art. 56, 112(1)

Keyword: "Inventive step (yes) - No realistic expectation of success - Activities to be expected from the notional person skilled in the art"
"Assessment of evidence not a question of law"

Case Number : T 500/91 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 21 October 1992

Appellant 01 : (Opponent 03)
Boehringer Ingelheim Zentrale GmbH
W-6507 Ingelheim am Rhein (DE)

Representative :
Kinzebach, Werner, Dr.
Patentanwälte
Reitstötter, Kinzebach und Partner
Sternwartstrasse 4
Postfach 86 06 49
W-8000 München 86 (DE)

Appellant 02 : (Opponent 04)
Bender & Co Ges mbH
Dr. Boehringer-Gasse 5-11
Postfach 103
A-1121 Vienna (AT)

Representative :
Kinzebach, Werner, Dr.
Patentanwälte
Reitstötter, Kinzebach und Partner
Sternwartstrasse 4
Postfach 86 06 49
W-8000 München 86 (DE)

Appellant 03 : (Opponent 07)
Boehringer Mannheim GmbH
Sandhofer Strasse 116
Postfach 31 01 20
W-6800 Mannheim 31 (DE)

Representative :
Huber, Bernhard, Dipl.-Chem.
Patentanwälte
H. Weickmann, Dr. K. Fincke
F.A. Weickmann, B. Hunber
Dr. H. Liska, Dr. J. Prechtel
Kopernikusstrasse 9
Postfach 86 08 20
W-8000 München 86 (DE)

.../...

Appellant 04 :
(Opponent 09)

Boehringer Ingelheim Pharma Ges mbH
Dr. Boehringer-Gasse 5-11
A-1121 Vienna (AT)

Representative :

Kinzebach, Werner, Dr.
Patentanwälte
Reitstötter, Kinzebach und Partner
Sternwartstrasse 4
Postfach 86 06 49
W-8000 München 86 (DE)

Respondent :
(Proprietor of the patent)

Biogen N.V.
15 Pietermaai
Willemstad
Curacao, Netherlands Antilles

Representative :

Ritter, Stephen David
Mathys & Squire
10 Fleet Street
London EC4Y 1AY (GB)

Vossius & Partners
Patentanwälte
Siebertstraße 4
W - 8000 München 86

Other party :
(Opponent 01)

F. Hoffmann-La Roche & Co.
Aktiengesellschaft
Grenzacherstrasse 124
CH-4002 Basel (CH)

Representative :

Lederer, Franz, Dr.
Lederer, Keller & Riederer
Patentanwälte
Lucile-Grahn-Strasse 22
W-8000 München 80 (DE)

Other party :
(Opponent 02)

The Upjohn Company
301 Henrietta Street
Kalamazoo, Michigan (US)

Representative :

Perry, Robert Edward
Gill, Jennings & Every
53-64 Chancery Lane
London WC2A 1HN (GB)

Other party :
(Opponent 05)

Cetus Corporation / Triton Biosciences, Inc.
A Division of Shell Oil Company
1400 Fifty-Third Street / 1501 Harbor Bay Parkway
Emmeryville / Alameda
California 94608 / California 94501 (US)

Representative :

Werner, Hans-Karsten, Dr.
Deichmannhaus am Hauptbahnhof
W-5000 Köln 1 (DE)

.../...

Other party :
(Opponent 06)

Hoechst Aktiengesellschaft, Frankfurt
Ressortgruppe Patente, Marken und Lizenzen
W-6230 Frankfurt am Main 80 (DE)

Representative :

Decision under appeal :

Interlocutory decision of the Opposition Division of the European Patent Office dated 12 November 1990, posted on 4 April 1991 concerning maintenance of **European patent No.** 0 032 134 in amended form.

Composition of the Board :

Chairman : P.A.M. Lançon
Members : D. Holzner)
R.K. Spangenberg) Co-Rapporteurs
E.M.C. Holtz
J-C. Saisset