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Aktenzeichen / File Number / Numéro du dossier

T 0223 / 92 -332

In der Anlage erhalten Sie	Please find enclosed	Veuillez trouver en annexe
☐ eine Kopie des Berichtigungsbeschlusses	☒ a copy of the decision correcting errors	☐ une copie de la décision rectifiant des erreurs
☐ ein korrigiertes Vorblatt (Form 3030)	☐ a corrected covering page (Form 3030)	☐ une page de garde (Form 3030) corrigée
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Anmeldung Nr. / Patent Nr.:	Application No. / Patent No.:	Demande n° / Brevet n°:
_____	82305521.5	_____
(soweit nicht aus der Anlage ersichtlich)	(if not apparent from enclosure)	(si le n° n'apparaît pas sur l'annexe)

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D E C I S I O N
of 20 July 1993

Case Number: T 0223/92 - 3.3.2

Application Number: 82305521.5

Publication Number: 0077670

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Human immune interferon

Patentee:
Genentech, Inc.

Opponent:
1) Roussel Uclaf
2) Biogen Inc.
3) Bioferon biochemische Substanzen GmbH & Co.

Headword:
HIF-Gamma/GENENTECH

Relevant legal norms:
EPC Art. 54, 56, 83, 114,
EPC R. 28

Keyword:
"Novelty (yes) - Larger protein in the state of the art not unambiguously identified as HIF"
"Inventive step (yes) - Expectation of success not likely by the method known for interferon-ß"
"Disclosure-enabling - by provision of DNA sequence"
"Late submitted material - admitted - confirmation of previous argument"
"Deposit of a micro-organism - no obligation"

Decisions cited:
T 0248/85, T 0205/83, T 0717/89, G 0001/92, T 0060/89, T 0081/87, T 0158/91, T 0500/91,

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0223/92 - 3.3.2

D E C I S I O N
of 25 March 1994 correcting error in the decision
of the Technical Board of Appeal 3.3.2
of 20 July 1993

Appellant 01: (Opponent 01)
Roussel Uclaf
35, Bd des Invalides
F-75007 Paris (FR)

Representative:
Bourgouin, André
Département des Brevets
Roussel Uclaf
B.P. no. 9
F-93230 Romainville (FR)

Appellant 02: (Opponent 02)
Biogen Inc.
14 Cambridge Center
Cambridge, Massachusetts 02142 (US)

Representative:
Vossius & Partner
Postfach 86 07 67
D-81634 München (DE)

Appellant 03: (Opponent 03)
Bioferon biochemische Substanzen GmbH & Co.
Erwin-Rentschler-Str. 21
D-88471 Laupheim (DE)

Representative:
Vossius & Partner

Respondent: (Proprietor of the patent)
Genentech, Inc.
460 Point San Bruno Boulevard
South San Francisco
California 94080 (US)

Representative:
Armitage, Ian Michael
Mewburn Ellis & Co.
2 Cursitor Street
London EC4A 1BQ (GB)

In application of Rule 89 EPC delete in the decision in Appeal case T 223/92 the word "laboratory" on page 19, third line from the bottom.

The Registrar: The Chairman:

P. Martorana P. Lançon

Decision under appeal: **Decision of the Opposition Division of the European Patent Office dated 13 January 1992 rejecting the opposition filed against European patent No. 0 077 670 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: P.A.M. Lançon
Members: U.M. Kinkeldey
S.C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 077 670 (application No. 82 305 521.5) was granted on the basis of 31 claims. By a decision notified on 13 January 1992 the Opposition Division maintained the patent as granted while rejecting three Oppositions.

II. Claims 1 and 9 read as follows:

"1. Human immune interferon of the amino acid sequence depicted in Figure 5 hereof and alleles thereof, free from other protein with which it is ordinarily associated.

9. A DNA isolate comprising a DNA sequence encoding human immune interferon having the amino acid sequence depicted in Figure 5 hereof or an allele or derivative of these having the function of human immune interferon."

Claims 2 to 8 relate to certain embodiments of the human immune interferon as claimed in Claim 1.

Claims 10 to 16 relate to cloning vectors, micro-organisms and cell cultures.

Claims 17 and 18 relate to compositions comprising human immune interferon.

Claims 19 and 25 relate to a process expressing in a recombinant host cell DNA encoding human immune interferon of the amino acid sequence depicted in Figure 5 and certain embodiments of this process.

Claims 20 to 24 and 26 to 30 are dependent on Claims 19 and 25 respectively and relate to embodiments of the processes.

Claim 31 relates to the use of the human immune interferon as claimed in Claims 1 to 8, or prepared by a process of any one of Claims 19 to 30, in preparing pharmaceutical compositions.

The terms "immune interferon" and "interferon-gamma" are synonyms. For the sake of simplicity, only the term "interferon-gamma" will be used in this decision, irrespective of which of these synonyms was actually used in a submission or a particular document.

III. The Opposition Division maintained the patent essentially for the following reasons:

Objections under Articles 83 and 88 EPC were held to be unfounded because the whole text of the patent, apart from a few sentences of no particular importance, could be found in the priority document. This priority document also already contained a sufficient disclosure which enabled the skilled man at the priority date to carry out the invention essentially by provision of the DNA-sequence of Figure 5. Taken together with the pre-existing technical capabilities of the skilled man, the "making available" of the DNA sequence *de facto* served the same function as a deposit of a clone containing this sequence. For this reason the objection that there was insufficient disclosure in the patent itself was unfounded.

As for novelty and inventive step, out of fifty prior art documents the following were considered to be relevant:

(21) Yip et al., Proc. Natl. Acad. Sci. USA 78 (March 1981), p. 1601 - 1605;

(22) Wallace et al. Biochem. Biophys. Res. Comm. 100 (May 29, 1981) p.865 - 871;

(23) Taniguchi et al. (Taniguchi III), Proc. Natl. Acad. Sci. USA 78 (June 1981), p. 3469 - 3472;

(31) EP-A 28 033 published 1 May 1981

(47) McGraw-Hill's Biotechnology Newswatch, Vol. 2, No. 19, p. 4 - 5 (Oct. 1982), and Genetic Engineering letter, Vol. 2, No. 17 (Sept. 1982);

With regard to human interferon-gamma, document (21) was considered as closest prior art. From the point of view of the nucleotide sequences, document (23) was considered to be the closest prior art. In relation to this the technical problem to be resolved was said to be twofold:

On the one hand it consisted in the purification and unambiguous identification of human interferon-gamma and, on the other hand, in the preparation of a nucleotide sequence coding for said interferon in order to produce substantial amounts of said protein by genetic engineering. Document (21) did not disclose the amino acid sequence of human interferon-gamma and the same applied to all the documents cited. As a consequence it could not be concluded that the prior art had unambiguously identified and isolated human interferon-gamma. Therefore, the subject matter of Claims 1 to 8 was considered novel. Since document (23) did not disclose an isolated mRNA coding for human

interferon-gamma also Claim 9, directed to the DNA-sequence coding for this substance, and Claims 10 to 31 were considered as novel.

An inventive step was acknowledged firstly, because the mRNA population described in document (23) was recognisably for the skilled man still rather impure, present in trace amounts and thus unsuitable for insertion into a vector. Secondly, the skilled person would not have considered the genetic engineering method applied to interferon-beta, as described in document (31), as applicable to the production of interferon-gamma. This was so because the method of providing the mRNA in the patent was different from that of document (23). Therefore, the skilled man would not have contemplated the use of a mRNA as described in document (23) in a method as disclosed in document (31) with a reasonable expectation of success. Claims 1 to 31 thus fulfilled the requirement of Article 56 EPC.

IV. Notices of Appeal and Grounds of Appeal were filed by all Opponents and the required fees were paid.

V. During the proceedings and after the summons for the oral proceedings had already been issued by the Board of Appeal, Appellants II and III filed submissions and a statement by an expert, Prof. Schmieger. The Respondents objected to these, but in a communication the Board stated that it was inclined to admit them as being merely an elaboration of the arguments already presented. Five days before the oral proceedings, the Respondents filed by telefax statements by two experts, Prof. Taniguchi and Mr. Rabbitts and excerpts of the transcript of the cross-examination of a Prof. Brammar during the hearing of a case in the High Court of Justice in London, during which he answered questions relating to a screening method similar to that stated to

have been used in the present patent. Appellants II and III objected to the admission of this evidence filed on behalf of the Respondents.

VI. Oral proceedings took place on 20 July 1993.

VII. During the proceedings essentially the following arguments were submitted by the Appellants:

(a) Appellants I maintained objections based on Articles 83 and 88 EPC stating that it would be an undue burden on the skilled person to find which elements in the description were essential to carry out the invention when they are contained only implicitly. The provision of the DNA-sequence coding for human interferon-gamma was in itself not sufficient and it amounted to an undue burden to repeat the invention on the basis of this knowledge. This view was confirmed by the document (47) which provided evidence that the synthesis of a gene producing human interferon-gamma in E. coli amounted to two months' work. Further, there was a later published document

(53) EP-B 0 095 350,

a granted European patent on the synthesis of the gene in question, which was evidence that inventive skill was necessary to carry out the present invention based on the knowledge of the DNA-sequence according to Figure 5, which would not be considered as having the same function as a deposit. The requirements of Article 83 EPC were fulfilled neither by the priority document nor by the application as filed. The absence of the paragraph appearing on page 15, lines 21 to 27 of

the European patent specification from the priority text was a further reason why the latter did not contain an adequate disclosure.

(b) Objections to novelty (Article 54 EPC) were raised by all Appellants. The substance as defined in Claim 1 was not novel over the disclosure of document (21). The provision of the amino acid sequence as a new parameter of a substance already described would not render the substance novel (decision T 248/85, OJ EPO 1986, 261); a higher degree of purity of the substance is also not suitable for distinguishing that substance from an already known one in lesser purity (decision T 205/83, OJ EPO 1985, 363); the substance being unaccompanied by undesired contaminants as well was not to be considered novel as such (decision T 717/89 of 25 March 1992, not published in the OJ EPO).

Finally, the claimed product could have been analysed by the man skilled in the art in the composition described in document (21) (decision G 1/92, OJ EPO 1993, 277).

(c) Inventive step was denied by all Appellants on the basis that arriving at the claimed subject matter by carrying out the method of document (31), using the mRNA preparation described in document (23), was obvious. A sufficient amount of mRNA could be expected by following the route of stimulation and purification of mRNA in the combined teaching of document (23) and (22), and the method of the production of interferon-beta by recombinant DNA technique described in document (31) did not involve such difficulties as to put off the skilled person from trying it in the reasonable expectation

of success (cf. decision T 60/89, OJ EPO 1992, 268). In particular the so-called +/- screening method was the method of choice in the circumstances given and routinely used at the time of priority. In support of this argument there were submitted the statements of the expert Prof. Schmieger who exhibited a bundle of prior art documents (Annexes A-F to his statements) disclosing the use of this method for other purposes, to support the argument that the method in question was within common general knowledge.

The method of cloning a gene starting from an available mRNA similarly was routine work at the time of priority. Particular emphasis was put on a statement in document (31) which described the method of the recombinant DNA production of interferon-beta, that this method could equally well be used to produce interferon-gamma.

VIII. The Respondents argued essentially as follows:

(a) The invention as described in the patent was reproducible as required by Article 83 EPC by providing the complete and correct DNA-sequence coding for interferon-gamma. Equipped with this knowledge the skilled man could without undue burden of experimentation follow different known routes for cloning and expressing the gene to obtain the desired protein. This was equally true for the priority document and consequently the objection that the application was not entitled to the claimed priority should be rejected.

(b) Novelty of the interferon in question as such was given because the state of the art before the priority date described no more than an elusive

substance which was not as such available to the public. Thus the *ratio decidendi* of decision G 1/92 (see above paragraph VII(b) was not applicable to the present case.

(c) As to the requirement of an inventive step (Article 56 EPC) in view of all the independent claims it was decisive that, given the circumstances that (i) the product to be produced by recombinant DNA technique was elusive and not at all sufficiently known, (ii) the reports in documents (22) and (23) about the quality and quantity of the mRNA did not give reliable guidance which could be used to establish a starting point for the cumbersome method and (iii) the +/- screening method described in document (31) in case of interferon-beta could not simply be transposed to interferon-gamma with its apparently different properties, the skilled man could have combined the teaching of documents (23) and (31) but he would not have done so, because there was no reasonable expectation of success. This position was further underlined by the arguments that each and every case of isolating a gene, characterising and cloning it and finally expressing it to produce the respective protein contained its own difficulties which were as a rule not predictable. The less that was known about the protein in question the less reliable was the application of the known process steps for its production by recombinant DNA technique. Finally, it was known to those skilled in the art that lengthy and complex biological processes such as the preparation by recombinant DNA-technique never were reliably identically reproducible. Inventive modifications were necessary in the present case. In addition, the

outcome of the procedure, namely the unexpectedly low molecular weight of interferon-gamma, was surprising.

IX. The Appellants requested that the decision under appeal be set aside and that European patent No. 0 077 670 be revoked.

The Respondents requested that the appeals be dismissed and the patent be maintained.

Reasons for the Decision

1. The appeals are admissible.

2. *Procedural matters (Article 114(2) EPC)*

The Respondents filed (by telefax) five days before the Oral Proceedings a letter to the Board of Appeal enclosing statements of two experts, Professor Taniguchi and Mr. Rabbitts, and excerpts of the transcript of the cross-examination of a Prof. Brammar during the hearing of a case in the High Court of Justice in London, in which he answered questions relating to a screening method allegedly similar to that stated to have been used in the present patent.

Appellants II and III objected to these statements as having been filed too late and argued that therefore they should not be admitted into the proceedings. Further they objected to the admission of the excerpt of the shorthand transcript as no assessment of this isolated evidence was possible in the absence of any knowledge of the case in which it was made as a whole.

The Board considers this evidence from the Respondents to be merely a reaction to the submissions and statements filed by the Appellants II and III after the date for oral proceedings were fixed, i.e. on May 17 and June 11 1993 and the Communication issued by the Board stating that it intended to accept them.

The statements of Professor Taniguchi and Mr. Rabbitts were made specifically for the purpose of these proceedings and relate directly to the issues involved. Their evidence does not introduce new issues or arguments going beyond those already put forward by the Respondents in their answer to the Grounds of Appeal, but merely provides confirmation of arguments already put forward.

The excerpt of the shorthand transcript on the other hand is not admitted into the procedure, as the context in which the statements were made and the weight that can be attributed to them are quite unclear.

3. *Sufficiency of the disclosure of the European application and of the priority application (Articles 83 and 88 EPC)*

3.1 The subject matter of the application falls into the technical field of recombinant DNA technique. It is acknowledged that at the time of priority the average amount of time and effort needed to produce, clone and express a gene was high. However, in the priority application the DNA-sequence, coding for interferon-gamma is already fully disclosed. The Board is well aware of the fact that even with this technical teaching, reproducibility of the whole process of expressing the gene to produce the desired interferon-gamma was still a difficult, complex and time consuming task in 1981. The Board is nevertheless

convinced that the provision of the DNA-sequence in 1981 enabled those skilled in the art to reproduce the invention. Knowledge of the DNA-sequence opened up other routes for cloning and expressing the gene than that proposed in the priority application. For example the DNA-sequence could be prepared by synthesis.

An example of this situation is provided by document (53). This is a patent application on which a patent was granted which makes use of the knowledge of the DNA-sequence published by the Respondents and prepares by the method of chemical synthesis DNA-sequences adapted to special circumstances in varying host-cell-systems but still coding for interferon-gamma. Appellants I considered this document and the fact that a patent was granted to be a proof that inventive skill was necessary to reproduce the present invention. The Board does not agree with this position but rather is convinced that this document is evidence for the opposite position that, based on the knowledge of the DNA-sequence, provided by the Respondents already in their priority application, use of this invention was possible, as were methods of using it to develop further inventions.

The Board is thus convinced that the application provides a reliable technical teaching which placed those skilled in the art in a position to reproduce the production, cloning and expression of interferon-gamma, possibly in a time consuming and cumbersome way, but, in the given circumstances, without undue burden of experimentation and without needing inventive skill.

3.2 Finally, there is no legal requirement in the EPC which would force the Respondents to deposit a micro-organism, containing the gene coding for interferon-gamma ready for production. Rule 28 EPC, relating to the

requirements of European patent applications relating to micro-organisms clearly states in paragraphs (1) and (1)(a) that in the cases where an invention concerns a microbiological process or the product thereof and involves the use of a micro-organism which cannot be described in a manner as to enable the invention to be carried out by a person skilled in the art, the invention shall only be regarded as being disclosed as prescribed in Article 83 EPC if a culture of the micro-organism has been deposited with a recognised depository institution. This prescription cannot be interpreted such that there is an obligation to deposit material to facilitate the reproduction if the invention can be repeated on the basis of the written description, even if this should be a much more cumbersome way than by merely growing the deposited micro-organism.

3.3 The priority application differs from the European application text only in that the latter contains two additional paragraphs. Of these the one appearing on page 15, lines 21 to 27 of the European patent specification deals with the method of purification of the expressed interferon-gamma. It is on this addition to the matter appearing in the priority application that Appellant I relies in support of an argument that even if the application text fulfilled the requirements of Article 83 EPC the priority application does not. However the Board finds that this additional information contained in the European application is not essential for carrying out the invention because it merely makes explicit what the priority document would in any case have suggested to the man skilled in the art at the priority date.

The Board thus finds that both the European patent application as filed, and the priority document disclose the invention in a manner sufficiently clear and

complete for it to be carried out by a person skilled in the art. It is, therefore, not necessary to consider what consequences, if any, there would be if this were not the case for the priority document.

4. *Novelty (Article 54 EPC)*

4.1 Claim 1 is a product claim and relates to the interferon-gamma *per se*, defined by the DNA-sequence coding for it and its amino-acid-sequence deduced from the DNA-sequence, both being depicted in Figure 5 of the patent. It also relates to alleles, i.e. proteins with different amino acids but nevertheless having the same function as interferon-gamma. A further feature of the product claimed is that it is free from other protein with which it is ordinarily associated.

4.2 The parties and the Board all shared the view that out of all documents on file, only the disclosure of document (21) need be considered for the purpose of assessing the novelty of Claim 1. This document describes an attempt to purify a protein whose existence and several of whose properties were known. As is stated on page 1601, left hand column, this protein represented one of three groups of proteins which were called interferons. The primary basis for differentiation among these three interferon species, called alpha, beta and gamma, was formed by major antigenic differences. While interferon-alpha and interferon-beta had been purified to homogeneity and their amino acids had been determined first partially by direct amino acid sequence determination and later more completely by analysis of cloned cDNA sequences, much less information was available about the protein called interferon-gamma. The definition of this elusive protein rested on two major criteria: (i) unlike interferon-alpha and interferon-beta the biological activity of

interferon-gamma is largely destroyed by exposure to pH2, and (ii) antiserums prepared against interferon-alpha and interferon-beta did not cross-react with interferon-gamma. Further it was known that interferon-gamma induced the anti-viral state much more slowly than the other interferons.

Under the heading "Materials and Methods" (pages 1601 - 1602) the attempt to produce, purify and characterise the third protein in the group of different interferons is described. Human lymphocytes were induced by phytohemagglutinin (PHA) and 12-O-Tetradecanoylphorbol 13-acetate (TPA). The culture media were collected and by testing for pH2 instability and for inability of antiserums against interferon-alpha and interferon-beta to neutralise antiviral activity, it was established that interferon-gamma was present.

To further purify the desired protein from the crude, interferon containing culture fluid, CPG chromatography and Con A-Sepharose Chromatography were applied sequentially and an attempt was made to determine the molecular weight on a molecular weight scale constructed by using bovine serum albumin (68,000), ovalbumin (43,000), chymotrypsinogen A (25,000) and RNase A (13,700) (page 1602, Figure 1 description, two lines from the bottom). From the elution profile shown in Fig. 1C it was deduced that interferon-gamma was homogenous in molecular size and that the estimated molecular weight was 58,000 +/- 3,000.

Although under the heading "Discussion" (page 1603, right hand column) it is stated that the procedure described provided an improvement with regard to the only few earlier attempts to purify and determine the least-well-characterized interferon species, there remained obstacles as regards the identity and

availability of the protein. Because of the lack of a generally accepted standard for establishing the activity of the substance, no objective determination of an improved method for production was possible. Thus the authors of document (21) only made the cautious statement that their method "appears" to produce a yield that was superior to other published methods. Differences between the molecular weight determined by these authors and those published earlier were said to be attributable to different stimulation methods, resulting in different materials (page 1604, left hand column, first paragraph). In any case, the authors conclude that the protein they tried to purify and characterise was significantly larger than interferon-alpha and interferon-beta.

4.3 In contrast to this, Claim 1 relates to a protein called interferon-gamma defined by its amino acid sequence with the number of 146 amino acids from which the molecular weight of 17 400 can be calculated. This protein is not that characterised in document (21).

Appellants II and III emphasised that it turned out later that interferon-gamma appears as dimers or trimers and that the substance characterised in document (21) may well have been a glycosylated dimer. This may or may not be the case, but it was not possible for the skilled man at the time of priority to recognise this. What was available to the public within the meaning of Article 54 (2) EPC by document (21) was the information that in a culture fluid of induced lymphocytes after certain purification steps a protein is contained that has properties differing from those of the well characterised interferon-alpha and interferon-beta and has a molecular weight of 58 000.

4.4 Appellants II and III considered that Claim 1 as worded covered also the oligomers, and the Respondents agreed that this was so. However, this does not provide an argument against novelty, because at the priority date neither the monomer, nor any oligomer was available as such, but merely infinitesimal amounts of something that included a compound showing activity typical of interferon gamma.

4.5 Appellants II and III underlined their novelty objections on three decisions of the Boards of Appeal (see above paragraph VII). In decision T 248/85 it was held that a known product cannot be rendered novel merely by defining it by its process, i.e. by formulation of the so-called product-by-process claim. The situation in the present case is obviously different, because there is neither a known protein nor a product-by-process Claim involved. Even though a known product is not rendered novel merely by means of further definition, this does not apply in the present case because Claim 1 does not further define an already known product.

Decision T 205/83 also deals with the problem of product-by-process claims. It was held in this decision (point 3.2 of the reasons) that a known product does not necessarily acquire novelty merely by virtue of the fact that it is prepared in purer form. Although the wording of present Claim 1 "...free from other protein with which it is ordinarily associated" may suggest similarity, because in the present case the product was not "known" the reasoning of T 205/83 is not applicable.

In decision T 717/89 referred to by the Appellants, it was held that on the facts there existing it was obvious to obtain a product free from proteins normally

associated with it when made by the recombinant DNA technique. This reasoning has no scope for application where, as here, the product itself is novel.

Finally decision G 1/92 deals with the situation where a product is known and publicly available on the market and can be freely and successfully analysed by anyone who should want to do so. The circumstances of the present case are obviously quite different, as there was no interferon-gamma which was made publicly available for known methods of analysis on the basis of the teaching document (21).

The Appellants have thus failed to show that the protein claimed in Claim 1 of the patent in suit lacks novelty.

4.6 The other independent product Claims 2, 5 and 6 relating to the interferon-gamma are directed to more narrowly defined preferred embodiments of the protein defined in Claim 1, and no objections to their novelty have been made out.

4.7 No objections to the novelty of the claims directed to the DNA-sequence, the vectors and the host cells and the genetic engineering process for the production of interferon-gamma were raised by the Appellants or the Opposition Division, and the Board sees none.

5. *Inventive step (Article 56 EPC)*

5.1 Product Claim 1 being novel, it is necessary to examine whether the invention claimed in it involves an inventive step. The Board considers the following further documents to be relevant for this purpose:

(26) L.B. Epstein, Interferon 1981, Vol. 3, p. 13 - 44;

(30) Yip et al., Proc. Natl. Acad. Sci. USA Vol 79 (March 1982), p. 1820 - 1824;

(35) L.B. Epstein, Nature Vol. 295 (11 February 1982) p. 453 - 454;

5.2 The Board considers document (21) to be the closest prior art. In the light of the technical teaching of this document (see above point 4.2), the technical problem can be seen in the provision of the authentic substance interferon-gamma. The problem is solved by providing a product as claimed in Claim 1, a DNA sequence as claimed in Claim 9, and a process as claimed in Claims 19 and 25.

5.3 When examining whether the provision of authentic interferon-gamma, free from other proteins with which it is ordinarily associated constitutes an inventive contribution to the art the first question seems to be whether the skilled person would have contemplated an improvement of the method described in document (21) to achieve the desired result. From this document and from the teaching of others as well (documents (26) and (35)) the skilled person knew that all attempts of stimulation of lymphocytes, purification and characterisation of the desired interferon-gamma were not sufficient to provide the protein in a quantity and quality which would have put him in a position to identify unambiguously the substance as such, let alone to provide a sufficient amount of it for medical purposes. It seems, however, to be remarkable that the authors of document (21) in a later publication of March 1982 (document (30)), i.e. after the priority date of the present patent, still applied the same method of stimulation and purification with the addition of a further purification step. There were reported two subspecies of this protein with

molecular weights of 20 000 and 25 000 respectively (cf. p. 1820, left hand column "Abstract", line 13). From this the Board concludes that the "classical" method for isolating this protein was still a method favoured by skilled persons at that time.

5.4 Since, however, interferon-alpha and interferon-beta had already been produced by the recombinant DNA technique as stated in document (21) (page 1601, left hand column, first paragraph) the Board believes that this method would in practice also have been considered as a possible route to make interferon-gamma available. There is no ready answer to the question of whether or not the skilled person in view of all particular circumstances of this case would have considered this route as something obvious to try with a reasonable expectation of success (cf. T 60/89 see above paragraph VII).

5.5 In the present case the relevant date at which the knowledge and capabilities of the notional skilled person in the art needs to be considered is October 1981, i.e. more than one year later than was the case for decision T 500/91. In October 1981, a considerably greater number of genes had been made the subject of cloning and expressing methods, and skills and experience in this technical field were developing rapidly. The knowledge of the notional skilled person in the art must be considered as that of a team of the appropriate specialists, who know all the difficulties still to be expected when considering cloning a new gene. However the skilled person must be assumed to lack the inventive imagination to solve problems for which there do not exist already routine methods of solution, the appropriate comparison here being not with a team but with a highly skilled ~~laboratory~~ technician carrying out a project where the initial instructions received are already adequate to tell the technician how to

overcome any problems likely to arise. This notional skilled person, with a practical orientation, would have to weigh up carefully the amount of time and effort required by any technique in general against the probability of success that could reasonably be expected from it, in each case based on its own technical facts and without having to perform scientific research in areas not yet explored.

5.6 The Board believes that in this situation the skilled person would have considered closely the teachings of documents (23) and (31).

Document (23) discloses a partial characterisation of interferon-gamma mRNA extracted from human lymphocytes. If, as in the present case, the amino acid sequence of a protein is not known, the provision of the mRNA of the corresponding gene is one important step in the whole complex process. After stimulation of cells with PHA and TPA a relatively uniform and enhanced yield of interferon-gamma (page 3470, left hand column "Results", (line 9) is achieved. The corresponding mRNA is extracted from these cells (page 3470, right hand column, paragraph 2). Then the sedimentation coefficient is calculated 15 S, corresponding to a length of mRNA of about 14,000 nucleotides. This is in contrast to the molecular weight of interferon-gamma, reported in document (21) to be 58,000 which would correspond to a much larger mRNA. The authors of document (23) speculated about possible reasons for this discrepancy (page 3471, right hand column, second paragraph) leaving the skilled person with uncertainties.

One may, therefore, assume that the skilled person would have considered further scientific exploration to define a more reliable mRNA population. On the basis of a promising mRNA population the skilled person would then

have to consider how to select that mRNA among others of the same or very similar size which actually codes for interferon-gamma, i.e. to choose the most promising and appropriate screening method.

5.7 The Board follows Appellants' II and III argument that in the difficult situation where the amino-acid-sequence - at least a short part of it - is not known, the knowledge about a reliable and sufficient provision of the mRNA in question plays a key role for answering the question whether the skilled person would have contemplated trying the whole cumbersome enterprise. Appellants II and III calculated the amount of mRNA to be expected if the method of document (23) was applied and concluded that this amount would have encouraged the skilled person to start the work. When looking closely at the actual technical disclosure of document (23) the Board has doubts whether this is really so. The fact that document (23) describes an "enhancement" of interferon-gamma and thus mRNA production does not necessarily mean that the total amount is already encouraging. Rather the skilled person would compare this amount with that of other selectively expressed proteins which were already subject to recombinant DNA processes to estimate reasonable expectation of success.

5.8 Here one can assume that the skilled person would have looked at document (31). There, the recombinant DNA process in case of interferon-beta is described. As in the present case the amino acid sequence was not known and it was, therefore, equally decisive to start the process with a reliable pool of mRNA. Nowhere in document document (31) is there any remark that the preparation of the mRNA, be it its stimulation, its purification, its unambiguous characterisation or its amount was hampered by difficulties. The total amount mentioned in the Example was 5 µg.

5.9 Document (31) further describes a method wherein an unscreened population of mRNA of a size estimated to relate to the desired gene is transcribed into cDNA by reverse transcriptase, the cDNA is used for the preparation of a gene bank and the gene bank is screened by hybridisation with mRNA of induced and uninduced cells and transcribed into cDNA, which is labelled radioactively. Those clones in the gene bank which do not hybridise with cDNA derived from uninduced mRNA are selected and investigated further as to whether the inserted gene codes for interferon-beta. The method is one type of general screening called the +/- method. Appellants II and III filed together with Professor Schmieger's statement prior art documents published in 1979 and 1980 supporting the argument that this method was routinely applied in cases where selective activity of gene expression takes place.

5.10 The Board agrees that this method was one possibility in the given situation. The Board believes, however, that the skilled person knew that this method is beset with possible traps and difficulties which are to be expected in such an extremely lengthy and complex method.

One example that shows that success of this method, which is itself only one of many steps in the whole process of producing interferon-gamma by the recombinant-DNA route, is by no means certain is provided by document (53). This is a European patent application filed at the European Patent Office before the present patent application and claiming priorities earlier than those of this patent. It relates to the production of "interferon-gamma" and its mRNA. On pages 54 and 55 of the published application under the heading "Transformants Screened for Ability to Express IFN-gamma" a +/- screening method is described for selecting clones from a collection which should contain

the gene coding for interferon-gamma. However, the skilled workers in that case did not achieve success. Rather they disclosed two different species of "interferon-gamma" with molecular weights of 20,000 and 25,000 (page 20, line 33 and page 21, line 9 of the published application), and the amino acid composition of these proteins is different from that finally determined by the present patentees and now generally accepted (page 50, Table III).

5.11 If one now imagines the position of a skilled person who wants to produce and identify interferon-gamma, he would be confronted with the situation that (i) little was known about the protein as such and actually contradictory data had been published making the situation particularly confusing (see above point 5), (ii) despite the fact that an improved stimulation method was known, the quantity and quality of the mRNA available from this was extremely poor making the prospects of success for the recombinant-DNA-technique route look very poor if nothing better than this known method could be found and (iii) the decisive screening method was not to be considered as a reliable way to find what could only be described as "a needle in a haystack".

5.12 The Board is convinced that there is no sufficient certainty that the skilled person in this situation would have tried this method with any reasonable expectation of success. In other words, while someone might have chosen the route of the recombinant-DNA-technique, he would only have attempted it despite success being very uncertain, for example because he trusted in his own luck, skill and inventive ingenuity to overcome the known and the as yet unknown problems involved, even though these problems were such that the average skilled person would expect to fail.

5.13 The Board agrees with the arguments as such submitted by Appellants II and III in answer to the reasons given in the decision of the Opposition Division for maintaining the patent, but for the reasons given above still does not consider that invalidity on the ground of lack of inventive step has been made out. It is correct that

(i) pure mRNA was not necessary for the procedure - if pure mRNA had been available, the whole screening method would not be necessary and the corresponding DNA could be directly cloned,

(ii) document (23) described an improved method for preparing the mRNA coding for interferon-gamma, but still the level achieved was very low,

(iii) any degradation or interruptive events on the long way to expression are not specific to interferon-gamma, nevertheless those hampering events are to be expected,

(iv) the skilled person was aware of the problem of differing S-values of the mRNA reported in different publications, but still the discrepancies would have to be clarified, and

(v) the +/- screening method for isolating a clone containing the interferon-beta gene was successful (document (31)), but still there was no indication that it would function in the same way for a poorly described protein.

5.14 In particular the latter argument was emphasised by Appellants II and III and, therefore, the Board would like to remark that it was common general knowledge at the time of priority that the cloning of each and every gene coding for a certain protein depends on many

technical details which are particular to each single gene, for example the size, the existence or non-existence of introns or pre- or pro- sequences and the existence and location of necessary restriction enzyme sites. A reasonable extrapolation from the successful cloning of one gene to another was, therefore, only in rare cases possible at that time. From the analysis given above of the technical facts in the present case it is evident that this case is not one where such an extrapolation would be reliably possible. In fact, there is no evidence on file that the method of document (31) had been applied successfully in any other case.

5.15 The method used by the Respondents differs from that used in document (31). The Respondents used a different substance to produce stimulation, a different purification method for the mRNA and a modified +/- screening method. The goal of the Respondents can be likened to wanting to reach the peak of a mountain which is permanently covered by cloud so that the correct approach route cannot be seen. Whilst it cannot be said with certainty that the differences in the route chosen by the Respondents over known routes were decisive, the Respondents successfully reached this peak, not knowing when they started to climb whether known and as yet unknown difficulties on their chosen route might not force them to give up and try some other route. By identifying the DNA-sequence, the Respondents so to speak provided a guide rope to the peak which enabled others to be certain of getting to the same peak with much less trouble. It was for the Appellants to show that this peak could have been reached by a route which involved no invention, and they have failed to do so.

5.16 It follows that the Board is satisfied that no objection to Claim 1 of the patent on the basis of lack of inventive step (Article 56 EPC) has been made out.

5.17 Independent product Claim 9, relating to the DNA-sequence coding for interferon-gamma and Claims 19 and 25, being independent process claims for the production by recombinant DNA technique of the products of Claims 1 and 9 have novelty and inventive step for the same reason as Claim 1, as do the other claims dependent on these independent claims.

Order

For these reasons, it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

P. Martorana P.A.M. Lançon

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