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Case Number : T 299/86 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal
of 17 August 1989

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Decision under appeal : Decision of Examining Division 023 of the European Patent Office dated 25 March 1986 refusing European patent application No. 81 900 967.1 pursuant to Article 97(1) EPC

Composition of the Board :

Chairman : P. Lançon
Members : U. Kinkeldey
R. Schulte

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Bezeichnung der Erfindung: Monoclonal antibody
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : C12P 1/00

ENTSCHEIDUNG / DECISION

vom / of / du 17 August 1989

Anmelder / Applicant / Demandeur : Secher, D.S., Burke, D.C.

Patentinhaber / Proprietor of the patent /
Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence :

EPÜ / EPC / CBE Articles 83 and 84

Schlagwort / Keyword / Mot clé : "Clarity - reference to international standard"
"Sufficiency - identical repeatability of examples not required"

Leitsatz / Headnote / Sommaire

Summary of Facts and Submissions

I. PCT patent application PCT/GB81/00067 with the European application No. 81 900 967.1 and International publication No. WO 81/02899, having an international filing date of 13 April 1981 and published on 15 October 1981, was refused by a decision of the Examining Division dated 25 March 1986.

The decision was based on Claims 1-9, filed on 30 July 1984 and Claims 10 and 11 filed on 14 November 1983. Claims 1-3 read as follows:

1. A monoclonal antibody to human interferon-α characterised in that in a process for the immunopurification of a crude sample of extracellular medium from stimulated Namalva cells containing interferon-α at a specific activity of 2.4×10^4 U/mg, an increase in the specific activity of about 5000 fold is achieved in a single pass through a 0.5 ml immunoadsorbent column produced by coupling the monoclonal antibody to CNBr-activated Sepharose at 14 mg of monoclonal antibody per ml of Sepharose.

2. A monoclonal antibody to human interferon-α characterised in that, in a process for the immunopurification of a sample containing interferon-α at a specific activity of 1.6×10^6 U/mg, an increase in the specific activity of about 100 fold is achieved in a single pass through a 0.5 ml immunoadsorbent column produced by coupling the monoclonal antibody to CNBr-activated Sepharose at 14 mg of monoclonal antibody per ml of Sepharose.

3. A monoclonal antibody to human interferon-α characterised in that, in a process for the immunopurification of a sample containing interferon-α, wherein the sample is passed through an immunoadsorbent column produced by coupling the monoclonal antibody to a solid phase, the sample is purified to give interferon-α which is about 100% pure by specific activity.

Claims 4 - 6 relate to the processes by which the monoclonal antibody of Claims 1 - 3 are defined. Claim 7 is directed to a process in which about 100% pure (by specific activity) interferon-α is achieved by immunopurification, using the said monoclonal antibody. No objection was raised against Claims 8-11.

II. According to the Examining Division Claims 1-7 were not clear because of the term "specific activity". There were several methods for the determination of human interferon-α activity, for example, biological assay methods involving either the inhibition of nucleic acid synthesis (INAS) or the reduction in cytopathic effect (CPE) and furthermore interferon-α activity might, according to page 8, lines 31-33 of the specification, have been determined by yield reduction and plaque reduction assay.

Since, therefore, there existed several different methods for the determination of interferon-α activities, several different definitions of interferon-α activity units were possible so that for a man skilled in the art the above-cited term was not clear, and thus Claims 1 - 7 were not allowable under Article 84 EPC.

III. Further the Examining Division held that the application was not allowable according to Article 83 EPC because part of the specification, namely a process which leads to a

specific hybridoma, named NK2/13.35.6, was not repeatable.

IV. A notice of appeal was filed on 24 May 1986 together with the payment of the appeal fee, and a statement of grounds of appeal was filed on 26 July 1986. A first ground of appeal related to the right to oral proceedings. This has, however, been the subject of an interlocutory decision of this Board dated 23 September 1987.

V. A second ground of appeal related to Article 84 EPC. In support of the contention that Claims 1 - 7 satisfied the requirements of Article 84 EPC, the Appellant submitted that the term "specific activity", which was apparently the sole reason for the refusal under Article 84 EPC, had a definite meaning. The activity of human interferon-α was measured relative to an international standard reference sample of interferon in Reference Research Units (U) per unit mass (in mg) and there was no need for the definition of the international standard reference sample to be included in Claims 1-7. The various international standard reference samples of interferon were either identical to each other or had been rigorously calibrated against each other to ensure the true standard. Since the measurement of a specific activity was always relative to the international standard of activity per mg, by the assays must by definition be comparable in that respect.

Further, the characterising portions of the claims relied upon the results of performing immunopurification processes with the monoclonal antibody of the invention. Thus, in Claims 1, 2, 4 and 5 the process was defined in terms of a starting specific activity. Small alterations in the starting specific activity would not substantially affect the overall purification achieved. Claims 3 and 6

recited that the result of using the monoclonal antibody in an immunoadsorbent purification was to achieve a sample which was 100% pure by specific activity. The skilled person, reading the specification of the present application, would immediately have appreciated that human interferon-α having a specific activity of 1.2×10^8 or 1.6×10^8 U/mg was substantially pure.

VI. A third ground of appeal related to Article 83 EPC. As to the reason for refusal under this Article, the Appellant submitted that the position taken by the Examining Division with regard to the requirements of Article 83 EPC was fundamentally incorrect.

The Appellant submitted that it was only necessary that the specification taught how to prepare or to perform one or more embodiments falling within the scope of the claim and not necessarily the specific embodiment described in the specification. The present application, by exemplifying one preparation, taught the skilled addressee to prepare a wide range of hybridoma cell lines, each capable of producing a monoclonal antibody having the general characteristics defined in Claims 1 to 3. The specific immunogen needed for providing one of the cell types the fusion of which finally produced the hybridomas was the supernatant of Namalva cells challenged with Sendai Virus. This system was commonly used for producing human interferon-α, was widely available prior to the date of filing of the present application and was described in the specification.

A further starting material for preparing the necessary hybridomas, namely the NS 1 myeloma cell line was a publicly available cell line produced and maintained by the Medical Research Council in Cambridge, United Kingdom. All necessary starting materials were therefore available

to the public, which was further confirmed by a statutory declaration by Dr. Secher, who was one of the inventors of the present application, said declaration having been enclosed with the reasons for the appeal.

The instructions for testing for monoclonal antibodies having the characteristics of Claim 1 were clearly set out in the specification.

The Appellants acknowledged that the probability of obtaining a hybridoma **identical** in genotype to the one described as an example in the specification following the repeatable disclosures of the description, was very low. This would not, however, have been of any relevance to the repeatability requirement of Article 83 EPC with regard to the claimed subject-matter.

The Appellants furthermore complained that this objection, which had only been raised in the fourth communication by the Examining Division, more than two years after examination commenced, should have been raised in the first communication, and that a substantial procedural violation had occurred.

VII. The Appellants request that the decision of the Examining Division be set aside.

It is further requested that the following question of law be put before the Enlarged Board of Appeal:

"Does Article 83 EPC require that an embodiment described in the specification of a European patent or patent application be identically repeatable, where the claims are broader in scope than the embodiment?"

Further, reimbursement of the appeal fee pursuant to Rule 67 EPC is requested because the objections under Article 83 EPC were raised too late.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

2. **Article 123(2) EPC**

The only remaining questions at issue in this appeal are those of clarity (Article 84 EPC) and sufficiency of disclosure (Article 83 EPC). Other points, such as the allowability of Claims 3 and 7 under Article 123(2) EPC, were left undecided by the Examining Division. Because these points are not directly related to the issues under appeal, the Board will restrict its consideration to the issues and deal with the other points by exercise of its discretion under Article 111 EPC (see paragraph 14 below).

3. **Clarity (Article 84 EPC)**

3.1 All of the rejected Claims 1 to 7 contain terms relating to the specific activity of the interferon-α.

The wording of Claims 1 to 3 is chosen such that the claimed monoclonal antibodies are defined by their ability to bind to interferon-α in a way which allows the purification of interferon-α from a sample containing interferon-α. The affinity of the monoclonal antibody thereby obtained is defined in terms of the degree of purification of the interferon-α. In Claim 1, for

instance, if the specific activity of interferon-α of a starting material has a certain value, namely 2.4 x 10^4 U/mg, an increase in the specific activity of about 5 000 fold is achieved in a single pass through an immunoadsorbent column to which the claimed monoclonal antibody is bound. In Claim 2, the starting material has a specific activity of 1.6 x 10^6 U/mg and the increase in the specific activity is about 100 fold after passing the sample containing the interferon-α through said immunoadsorbent column containing the claimed monoclonal antibody. Thus, since it is related to a given starting activity, the increase of the specific activity amounts to a certain degree of purity of the obtained interferon-α (see Grounds of Appeal, 3.1, last paragraph). The monoclonal antibody of Claim 3 is defined by its affinity to interferon-α such that a sample can be purified to give interferon-α which is about 100% pure by specific activity.

3.2 The wording of Claims 4-6 corresponds to the process part of the product Claims 1-3. Claim 7 is directed to a process for immunopurification of interferon-α by using the monoclonal antibody.

4. The term "specific activity", used in all the rejected claims is explained in the description of the published application at page 8, lines 33-35. It is stated there that all human interferon titres are quoted in reference research units using the HuIFN-α reference research standard 69/19. This means that the activity of human interferon-α is measured relative to an international standard reference sample of interferon in Reference Research Units (U) per unit mass (in mg). The Board is satisfied that the standard sample to which reference is made (MRC69/19) is a publicly held international standard

maintained under an international treaty by the National Institute for Biological Standards and Control, Holly Hill, Hampstead, London, United Kingdom. The Board is thus of the opinion that for the skilled person it is clear that the term "specific activity" refers to an international standard and has a clear meaning. Therefore, it is not necessary to incorporate the definition of the feature into the claims, because the meaning of the feature is clearly defined by the description. According to Article 84 the claims shall define the matter for which protection is sought, but they need not give a perfect instruction how the invention is to be used. Moreover, pursuant to Article 84, second sentence, EPC conciseness is a special requirement for claims. One way to draft a concise claim is by making use of features which are clearly defined in the description. There are no objections to such a method, unless the clarity of the claim is so affected that a person skilled in the art would have difficulties understanding what is meant by the claim. No such difficulties arise in the present case.

5. The statement in the description that all human interferon titres are quoted in Reference Research Units using the human interferon-α reference research standard 69/19 (see page 8, lines 33 to 35) thus gives clear guidance to the skilled man as to how the term "specific activity" in the claims has to be interpreted.

6. In the decision T 68/85 "Synergistic herbicide", O.J. EPO 1987, 228, the Board already decided that functional features defining a technical result are permissible in a claim, if, from an objective viewpoint, such features cannot otherwise be defined more precisely without restricting the scope of the invention and if these features provided instructions which are sufficiently

clear for the expert to reduce them to practice without undue burden. This decision was confirmed by the decision T 292/85 "Polypeptide expression" dated 27 January 1988 (to be published in OJ EPO), where functional characteristics have been accepted in the field of biotechnology.

According to the Board's view, the prerequisites mentioned in the above decisions are fulfilled here. As to the first prerequisite (impossibility of more precise definition) the exact chemical structure of the claimed monoclonal antibody is not known and thus cannot serve as a basis for a proper definition of this antibody.

As to the second prerequisite (that the technical teaching of the chosen definition has to be clear and repeatable), it seems to be evident that the wording of a claim has to be understood in connection with the description. This principle is for example expressed in Article 69 EPC which states that the extent of the protection conferred by a European patent or a European patent application shall be determined by the terms of the claims, but the description and drawings shall be used to interpret the claims.

A common and clear way to define monoclonal antibodies is by their affinity to a certain substance. This affinity is expressed in the present claims by the ability to bind interferon-α in a certain sample to a certain degree and thus by their affinity to interferon-α. This feature can be understood as an indirect structural feature because the affinity of a monoclonal antibody depends on its stereochemical structure.

7. As to the term used in Claims 3 and 7, namely that the result of using the monoclonal antibody in an immunoadsorbent purification is to obtain an interferon-α

which is 100% pure by specific activity (Claim 3) or that the interferon used in an immunopurification process is about 100% pure by specific activity (Claim 7), it is clear for the skilled person that this means that the monoclonal antibody used binds monospecific for interferon-α.

8. Thus, the reasons for rejection of Claims 1-7 in view of Article 84 EPC cannot be upheld.

9. **Sufficiency of disclosure** (Article 83 EPC)

The second reason for the refusal of the present patent application was that one certain example of the description was not repeatable identically. The example in question forms part of the specification, described on page 7, lines 17 to page 13, line 3 and relates to the preparation of a hybridoma, defined as clone "NK2/13.35.6". The opinion of the Examining Division that this specific hybridoma is not repeatable without undue burden is correct because the production of hybridomas, which are the cell fusion products excreting the claimed monoclonal antibodies, is cumbersome and underlies a multiplicity of variations.

If an animal or human body is infected by a substance, called an antigene, an immune response of the body occurs during which **inter alia** antibodies against the antigene are produced. The cells producing these antibodies are isolated and fused with another cell type which is able to grow indefinitely. These are tumour cells, for example so called Myeloma cells. The fusion product is called a hybridoma and is able to produce indefinitely a monospecific and thus monoclonal antibody, the antibody having specificity to the antigene used as a stimulant for the production of the antibody in the animal or human body.

In the present case, the procedure presented here in summary is described in detail in the description of the patent application whereby as an antigene an interferon-α was used which in turn was produced by a certain procedure also described in detail. It is true that if the skilled person works according to the description many different antibodies against the interferon-α used may be produced; also, there may be differences in the interferon-α used as antigene. One reason for the diversity of the antibodies is that the antigene used, in the present case interferon-α, may have different so-called determinant regions in its molecular structure and antibodies may be produced at each different determination region. Further, the antibodies may be such that they differ in their affinity to certain determinants. It is thus unlikely that the one definite hybridoma described as an example in the present application and named NK2/13.35.6 could be reproduced identically. This clone, however, is an example in the specification and is not claimed.

10. In a previous decision, the Board has already held that "there is no requirement under Article 83 EPC to the effect that a specifically described example of a process must be exactly repeatable." It was further stated that variations in the constitution of an agent, for example a precursor, used in a process are immaterial to the sufficiency of the disclosure provided the process reliably leads to the desired product (T 281/86 "Preprothaumatin" dated 27 January 1988, (to be published in the O.J. EPO)(paragraph 6 of the reasons)).

In the present case in addition to the uncertainties described in paragraph 8 above there may be variations in the constitution of the starting material, namely the interferon-α, used as the stimulating antigene to provide

those cells producing the monoclonal antibody having affinity to the interferon-α so that a monoclonal antibody excreted by the hybridoma NK2/13.35.6 may not be exactly repeatable. The disclosure presented in the present case, however, provides detailed information for a reliable reproducibility of the process to produce hybridomas which excrete monoclonal antibodies having the specificity defined in the refused claims, measurable by the increase of the purity of a sample containing interferon-α as will be explained in the following:

11. The definition of the claimed monoclonal antibody in terms of the ability to bind to an interferon-α such that a purification to a degree of about $1,2 \times 10^8$ (Claim 1) or about $1,6 \times 10^8$ (Claim 2) is obtained comprises a group of antibodies whose members may be specific for different interferons of the α-type or different antigenic determinant areas of one interferon-α. Whilst the hybridoma NK2/13.35.6 excretes one specific "individual" monoclonal antibody, the monoclonal antibodies claimed represent a multiplicity of them. The wording of the claims, therefore, is broader than the example in question.

12. The Board confirms the view of the decision T 281/86 (Ibid) that the requirements under Article 83 EPC are not such that a specifically described example of a process must be exactly repeatable. The one definite clone NK2/13.35.6 demonstrates one example which leads to success when working according to the general description of the present patent application. From page 5, line 5 to page 14, line 20 there is sufficient information about details of the whole procedure which was described in general above and furthermore, details about the likelihood of being successful in screening for a hybridoma producing the desired monoclonal antibody. On

page 9, lines 20 to 25 it is said that 48 cell fusions were prepared successfully. It is then said on page 10, lines 33 to 37 and page 11, lines 1 to 17 that "several cultures" (page 10, line 36) showed interferon activity. Apparently, those cells from cultures which showed low levels of anti-interferon activity, when cloned further, produced clones which showed the desired anti-interferon activity (page 11, lines 15 to 18). Thus the description provides support for the view that hybridomas excreting the claimed monoclonal antibody are not so rare that the process as a whole would not lead reliably to the claimed substance. In the absence of evidence to the contrary it is thus the Board's position that the description provides a sufficient disclosure repeatably to produce the claimed monoclonal antibody reliably and there is thus no need to reproduce identically the example given in the specification.

13. The Appellant has suggested reference to the Enlarged Board of Appeal of the question mentioned under point VII. The Board sees no reason for taking up this suggestion since the appeal has been decided in favour of the Appellant and the question can be answered by reference to the EPC and the cited jurisprudence.

14. **Undecided issues**

As to the undecided issue whether Claims 3 and 7 are allowable under Article 123(2), the Board prefers to exercise its right to remit the case to the first instance in respect to this important outstanding issue.

There are also other basic issues for substantive examination such as novelty and inventiveness.

15. **Reimbursement of Appeal fee**

The two reasons for the request for reimbursement of fees submitted by the Appellants were that a request for oral proceedings had been refused and that the objection under Article 83 had been raised too late.

The fact that the objection under Article 83 was only raised in the fourth communication is not a substantial procedural violation justifying the reimbursement. These objections were already mentioned in the second communication under point 2. It is certainly desirable to raise all relevant objections as early as possible during the examination proceedings. If, however, an objection is only recognised later during the proceedings it is nevertheless the duty of the EPO to raise this question under Article 114(1) EPC. Therefore, a reimbursement of the appeal fee cannot be granted.

Order

For these reasons, it is decided that:

1. The decision of the first instance is set aside.

2. The requests to reimburse the Appeal fee and to refer the case to the Enlarged Board of Appeal are rejected.

3. The case is remitted to the Examining Division for further prosecution.

The Registrar: The Chairman:

F. Klein P. Lançon

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