BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Publication in the Official Journal ~~Yes~~ / No

File Number: T 495/89 - 3.3.2

Application No.: 80 301 356.4

Publication No.: 0 018 794

Title of invention: Monoclonal antibody to human helper T cells, method of preparing it, hybrid cell line producing it, its diagnostic and therapeutic uses and diagnostic and therapeutic compositions comprising it.

Classification: C12P 1/00

# D E C I S I O N
of 9 January 1991

Proprietor of the patent: Ortho Pharmaceutical Corporation

Opponent:
01 Biotest-Serum-Institut GmbH
02 Behringwerke AG
03 Becton, Dickinson and Company
04 Sandoz AG
05 Boehringer Mannheim GmbH

Headword: Monoclonal antibody/ORTHO

EPC Article 83, Rule 28

Keyword: "Sufficient disclosure (no)" -
"Culture deposit not corresponding to the written disclosure"

## Headnote

Case Number : T 495/89 - 3.3.2

# D E C I S I O N
## of the Technical Board of Appeal 3.3.2
## of 9 January 1991

Appellant : (Opponent 04)
Sandoz AG
Lichtstrasse 35
CH-4002 Basel

Appellant : (Opponent 05)
Boehringer Mannheim GmbH
Sandhofer Strasse 116
Postfach 31 01 20
D-6800 Mannheim 31

Representative :
Weickmann, Heinrich, Dipl.-Ing.
Patentanwälte Dipl.-Ing. H. Weickmann
Dipl.-Phys. Dr. K. Fincke
Dipl.-Ing. F.A. Weickmann
Dipl.-Chem. B. Huber
Dr.-Ing. H. Liska
Dipl.-Phys. Dr. J. Prechtel
Postfach 86 08 20
D-8000 München 86

Respondent : (Proprietor of the patent)
Ortho Pharmaceutical Corporation
U.S. Route 202
P.O. Box 300
Raritan
New Jersey 08869-0602 (US)

Representative :
Jones, Alan John
Carpmaels & Ransford
43 Bloomsbury Square
London, WC1A 2RA (GB)

Other party : (Opponent 01)
Biotest-Serum-Institut GmbH
Flughafenstrasse 4
D-6000 Frankfurt/Main 71

Representative :
Vossius & Partner
Siebertstrasse 4
P.O. Box 86 07 67
W-8000 München 86

.../...

**Other party :** (Opponent 02)
Behringwerke Aktiengesellschaft
Postfach 11 40
W-3550 Marburg 1

**Other party :** (Opponent 03)
Becton, Dickinson and Company
Mack Centre Drive
Paramus, New Jersey 07652 (US)

**Representative :**
Ruffles, Graham Keith
Marks & Clerk
57-60 Lincoln's Inn Fields
London WC2A 3LS (GB)

**Decision under appeal :**
**Decision of Opposition Division of the European Patent Office dated 4 April 1989 posted on 5 July 1989 rejecting the opposition filed against European patent No. 0 018 794 pursuant to Article 102(2) EPC.**

**Composition of the Board :**

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

**Summary of Facts and Submissions**

I. In respect of European patent application No. 80 301 356.4, European patent No. 18 794 was granted with 25 claims. Claims 1, 4, 5, 10, 12, 13, 15 and 16 read as follows:

1. Mouse monoclonal antibody which (i) reacts with essentially all normal human peripheral helper T cells (being about 55% of all normal human peripheral T cells), but (ii) does not react with any of the normal human peripheral cells in the group comprising non-helper T cells, B cells, null cells and macrophages.

4. Monoclonal antibody according to any one of claims 1 to 3, which reacts with about 80% of normal human thymocytes.

10. Monoclonal antibody which is produced from hybridoma ATCC CRL 8002.

12. Hybridoma ATCC CRL 8002.

13. A method for preparing a monoclonal antibody according to any one of claims 1 to 9, which comprises the steps of:

(i) immunizing mice with E rosette positive purified human T cells;
(ii) removing the spleens from said mice and making a suspension of spleen cells;
(iii) fusing said spleen cells with mouse myeloma cells in the presence of a fusion promoter;

(iv) diluting and culturing the fused cells in separate wells in a medium which will not support the unfused myeloma cells;

(v) evaluating the supernatant in each well containing a hybridoma for the presence of an antibody having the properties specified in any one of claims 1-9;

(vi) selecting and cloning hybridomas producing the desired antibody; and

(vii) recovering the antibody from the supernatant above said clones.

15. A method for preparing a monoclonal antibody which comprises culturing hybridoma ATCC CRL 8002 in a suitable medium and recovering the antibody from the supernatant above said hybridoma.

16. A method of preparing a monoclonal antibody, which comprises injecting into a mouse hybridoma ATTCC CRL 8002 and recovering the antibody from the malignant ascites or serum of said mouse.

II. Notices of Opposition were filed against the European patent by five parties. Revocation of the patent was requested on the grounds of Article 100(a) and (b) EPC. During the proceedings before the Opposition Division about 160 documents were considered altogether.

III. The Opposition Division maintained the patent on the basis of the claims as granted, because the requirements of Articles 83, 54 and 56 EPC were said to be met.

As far as Article 83 EPC was concerned, the Opposition Division was not convinced of the identity of the monoclonal antibody deposited by the Respondents and claimed in claim 10, and the monoclonal antibody described

in a late published document having different features from that monoclonal antibody claimed. The Appellants thus did not provide the necessary evidence that the characteristics of the deposited monoclonal antibody were different from those mentioned in claim 1 and the patent specification. The arguments of insufficiency based on this allegation had, therefore, to be rejected.

The Appellants did not submit experimental data of their own showing that the monoclonal antibody according to claim 10 did not show the reactivity pattern as stated in claim 1 and in the patent specification. Consequently, the patent provided at least one way for carrying out the patented invention and thus the requirements of Article 83 EPC were met.

IV. Appellants IV and V lodged an appeal against the decision and submitted statements of grounds. Oral proceedings took place on 9 January 1991.

A. During the appeal proceedings further documents were filed by all parties. In particular:

Statutory declaration by Professor Janossy, filed by Appellants IV;

Versuchsbericht, filed by Appellants V.

B. The main arguments submitted by the Appellants with regard to Article 83 EPC were as follows:

(a) It was known that it was generally cumbersome and, in addition, not very likely to reproduce a monoclonal antibody having certain characteristics according to a written description. An attempt to reproduce the

invention merely by following the written disclosure of the patent specification would mean undue burden for the skilled person to achieve the desired result if at all. A deposit of the monoclonal antibody producing hybridoma according to Rule 28 EPC as one example for carrying out the invention, therefore, was necessary. However, the monoclonal antibody produced by the hybridoma did not correspond to the written disclosure.

(b) Evidence was already filed before the Opposition Division as a late published document, that the monoclonal antibodies produced by the deposited hybridomas had binding characteristics different from those disclosed in the patent in suit in the description and in claim 1 as well. Because of the position taken by the Opposition Division in its decision that this evidence was not sufficient to show convincingly the identity of the respective monoclonal antibodies, both Appellants submitted, together with their grounds for the appeals, experimental data which showed that the monoclonal antibodies purified from the deposited hybridomas did not show the characteristics of the invention described in written form in the patent in suit. The monoclonal antibodies achieved showed characteristics which were in contradiction to the written specification.

C. The Appellants further contested the existence of an inventive step within the meaning of Article 56 EPC.

V. In reply, the Respondents filed as a further document a

Declaration of Dr. Patricia E. Rao

and argued essentially as follows:

(a) As to the submission that the deposited hybridoma was not able to produce antibodies showing the characteristics as described in the description and in Claim 1, it was necessary to look at the description as it would have been looked at by a person skilled in the art at the priority date. It was not permissible to use techniques and machines which were developed later than the relevant date of the patent application to test whether the disclosure in a patent was sufficient. If this were not the case, then it would be impossible to judge whether a patent was valid during its lifetime. It was pointed out that the results presented in the patent in suit were obtained using the best machine available at the priority date and the best judgement of the operators of the machine to interpret the data. The patentee made a bona fide effort to present the best results possible at that time. Thus, the patent at the date of its filing met all the requirements of Article 83 EPC.

(b) Both Appellants failed to prove the alleged insufficiency because they used techniques and machines which were not available at the priority date of the patent in suit. As they were much more sensitive and sophisticated it was not surprising that the results obtained using them were not exactly the same as those obtained using the machines available at the priority date. Any comparison between the results was thus meaningless.

(c) As to this question in general, the Respondents submitted as evidence a decision of 1910 issued by the Court of Appeal of Great Britain -"Z" Electric Lamp Manufacturing Company Limited v. Marples, Leach & Co. Limited (Reports of patent cases, Vol. XXVIII, 1910, page 737) - where it was found that the patentee's obligations were not to be omniscient; the patentee's obligation was to put the public in the possession of his invention, and if he did that bona fide in such a way that they knew its advantages and they could obtain those advantages practically the fact that he had formed an erroneous view in theory of that which procures those advantages, or the state of things in which those advantages occurred, did not, in the court's opinion, militate against him. These principles were not restricted to the United Kingdom but rather generally applicable to patent law all over the world.

(d) Questioned by the Board during oral proceedings, the Respondents did not deny that the characteristics of the monoclonal antibody produced by a hybridoma as deposited under No. ATCC 8002 as shown by the experimental data submitted by the Appellants IV and V and those being apparent from late published documents were correct.

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

The Respondents requested that the appeals be dismissed and that the patent be maintained on the basis of the claims as granted, auxiliary request: that the patent be maintained on the basis of claims 10, 12, 15 and 16 as granted.

The requests to submit questions to the Enlarged Board of Appeal were withdrawn.

## Reasons for the Decision

1. The appeals are admissible.

2. **Amendments (Article 123(2) and (3) EPC)**

The claims which are subject-matter of the main and auxiliary request have not been amended. No objections with regard to Article 123(2) and (3) EPC, thus, arise.

3. **Sufficiency of the disclosure (Article 83 EPC)**

**Main request**

3.1 The main claim of the main request refers to a mouse monoclonal antibody which is characterised by certain reactivities, namely that it reacts with essentially all normal human peripheral helper T-cells, (being about 55% of all normal human peripheral T cells) but does not react with any of the normal human peripheral cells in the group comprising non-helper T cells, B cells, null cells and macrophages. The Respondents, thus, describe their invention by functional features. According to established case law of the Boards of Appeal, functional features defining a technical result are permissible in a claim, if, from an objective viewpoint, such features cannot otherwise be defined more precisely and if these features provide instructions which are sufficiently clear for the experts to reduce them to practice (T 68/85 OJ EPO 1987, 228 Synergistic herbicides/CIBA-GEIGY; T 292/85 OJ EPO 1989, 275 Polypeptide expression/GENENTECH I).

3.2 Sufficiency of disclosure within the meaning of Article 83 EPC requires not only that an invention can be carried out

at all but rather that this can be done without undue burden. This requirement follows from Article 83 EPC stating that the disclosure of an invention must be in a sufficiently clear and complete manner. If the description of the invention leaves the skilled person in doubt, so that he cannot carry out the invention by applying his skill and a reasonable amount of experiments, then the disclosure is not sufficient.

3.3 In the present case the first question with regard to sufficient disclosure within the meaning of Article 83 EPC is, whether or not the written description of the patent in suit provides sufficient detailed information so that the acknowledged random and cumbersome process to produce a hybridoma producing a monoclonal antibody as claimed may be carried out under the mentioned circumstances without undue burden to reproduce the invention as claimed in Claim 1.

3.4 The description of the patent in suit provides information concerning a general process for the production of hybridomas and monoclonal antibodies whereby the only feature being particularly directed to the present case is the use of E-rosette positive purified normal human peripheral T-cells as the antibody stimulating antigen. However, this fact alone is not sufficient to make the process reproducible as to monoclonal antibodies having the characteristics of claim 1. To select a hybridoma of the desired kind in any case means a huge amount of effort and, above all, it is not certain that this hybridoma can be selected at all. Working according to the written description would mean producing a great number of different monoclonal antibodies, each defined solely by its antigene.

3.5 The technique to produce monoclonal antibodies was first described in 1975 in Nature, Vol. 256, 495 by Köhler and Milstein. It is essentially based on the following knowledge and fundamental process steps:

An animal or human body, infected by a substance, called an antigene, develops an immune response of the body, 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, i.e. 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.

3.6 If the skilled person works according to the present description, a multiplicity of antibodies against the T-cells used as the stimulating antigene will be produced. One reason for the diversity of the antibodies is that the T-cell has a variety of different so-called antigenic determinants or epitops at its cell surface and antibodies may be produced at each different antigenic determinant. Further, the antibodies may be such that they differ in their affinity to certain antigenic determinants.

3.7 The Board considers that in the circumstances of the present case, where the written description of how to produce a hybridoma is basically the known cumbersome and random general process and a specific technical teaching is provided only by identifying the type of the antigene, being E-rosette positive purified normal human peripheral T-cells, the requirements of Article 83 EPC are not met.

3.8 The second question is whether or not the deposited hybridoma enables the skilled person to carry out the invention as claimed.

Actually, in the present case, the Respondents deposited a hybridoma with an acknowledged depository institution according to the requirements of Rule 28 EPC. The Appellants consider this deposition as one working example within the meaning of the general description provided in the patent in suit in written form. It is normal that an example of a general description provides a certain embodiment of this description and thus corresponds to it; however, it must be examined whether the deposited hybridoma truly represents such a working example in the present case.

According to the statutory declaration filed by the Appellants IV and the "Versuchsbericht" filed by Appellants V, the sample of monoclonal antibodies produced by the hybridoma as deposited under the deposition No. ATCC 8002 (OKT 4) reacted with macrophages (monocytes).

3.9 These results indicate that the characteristics of the monoclonal antibody produced by the deposited hybridoma are different from those mentioned in claim 1 and in the description of the patent in suit. The information given by these experiments corresponds to that disclosed in late published documents (among other relevant documents e.g. Wood G.S. et al., J. Immunol., 131, 212-216, 1983). The Respondents did not contest these differences in the characteristic features of the monoclonal antibodies to be compared. The Board is, thus, convinced that the characteristics of monoclonal antibodies produced by the hybridoma deposited with deposition number ATCC CRL 8002, are different from those mentioned in claim 1.

3.10 The Board fully agrees with the decision mentioned by the Respondents (see paragraph V(d) above), that the disclosure of a patent is sufficient, provided that during its lifetime the technical teaching can be repeated; if the theory, assumed to be the basis of the technical effect, turns out to have been incorrect, the disclosure can still be regarded as sufficient as long as the invention as such can nevertheless be reproduced. Quite different is the present case.

3.11 The Respondents emphasised during the proceedings that when the patentees described their invention at the priority date to their best knowledge and ability with techniques and machines then available, this description of the invention could not have been set out in a better manner and should, therefore, be regarded as sufficient within the meaning of Article 83 EPC. The fact that this description later turned out to be wrong, could not affect the sufficiency of the disclosure at the priority date. The Board cannot accept this argument. In the present case the written description of the invention was wrong right from the beginning. For both reproducing and examination of the invention without undue burden the Respondents had deposited the hybridoma as an example of the invention and had made it available to the public as required by Rule 28 EPC. It has now been shown that the characteristics of the monoclonal antibody produced by the deposited hybridoma did not correspond to "the invention" described in written form in the patent in suit. It is, thus, apparent that the Respondents themselves were not able to carry out "the invention" according to their own written disclosure. It must be concluded that the "example" constituted by the deposition does not correspond to the written description.

3.12 In these circumstances the patent in suit, neither by the written description nor by a deposition according to Rule 28 EPC, provides a sufficient disclosure within the meaning of Article 83 EPC.

4. **Auxiliary request**

4.1 The auxiliary request is restricted to claims which are directed to monoclonal antibodies and hybridomas and methods for preparing the monoclonal antibodies based merely on the deposited hybridoma, i.e. claims 10, 12, 15 and 16.

4.2 The deposited hybridoma and its corresponding claims have to be seen in the whole context of the description of the patent in suit which describes what the Respondents thought to be their invention. By way of the publication of the written disclosure of the patent in suit, the public is informed about the invention as described therein. The deposited hybridoma also has to be publicly available at the same time and can be requested for the purpose of reproducibility of the invention by third parties. If now, as in the present case, the characteristics of the deposited hybridoma differ from the written disclosure in the patent, this will not be apparent to the public unless the requested hybridoma has been analysed by determining its corresponding monoclonal antibodies. This means that the true characteristics of the said monoclonal antibodies are not in fact made public by the corresponding written description.

4.3 Thus, even if one could have considered the possibility of restricting the scope of the patent to what had been deposited and thus leaving aside any information provided in the written disclosure of the patent in suit, including the discussion of the state of the art, the problem and

the solution, and the industrial application which would not at all correspond to the characteristic of the "invention" represented by the deposited hybridoma, the said "invention" would not be sufficiently disclosed because the true characteristics of the monoclonal antibodies produced by the deposited hybridoma were nowhere described and thus not available to the public. Therefore, no technical teaching is provided which would allow an examination of patentability. Thus, a mere deposit of a hybridoma without any corresponding written description does not provide a sufficient disclosure of a technical teaching within the meaning of Article 83 EPC.

4.4 Accordingly, the claims directed to the deposited hybridoma or its monoclonal antibodies do not meet the requirements of a sufficient disclosure within the meaning of Article 83 EPC.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The European patent 18 794 is revoked.

The Registrar: The Chairman:

P. Martorana P. Lançon

23.7.91

02981

23.7.91