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 418/89 - 3.3.2

Application No.: 80 300 829.1

Publication No.: 0 017 381

Title of invention: Monoclonal antibody to human T cells, method for preparing it, hybrid cell line producing it, therapeutic composition comprising it and diagnostic method using it.

Classification: C12P 1/00

D E C I S I O N

of 8 January 1991

Proprietor of the patent: Ortho Pharmaceutical Corporation

Opponent: 01) Behringwerke Aktiengesellschaft
02) Sandoz AG
03) Becton, Dickinson and Company
04) 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

I. A disclosure provided by a deposit according to Rule 28 EPC is not regarded as being sufficient within the meaning of Article 83 EPC, if and when it is only possible to reproduce the invention after repeated requests to the depository institution and by applying techniques being considerably more sophisticated than those recommended by the depository institution (cf. point 3.14 of the reasons for the decision).

II. A mere deposit number 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 (cf. point 5.3 of the reasons for the decision).

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Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 418/89 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 8 January 1991

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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
Decision under appeal :	**Interlocutory decision of the Opposition Division of the European Patent Office dated 7 June 1989 concerning maintenance of European patent No. 0 017 381 in amended form.**

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. 80 300 829.1, European patent No. 17 381 was granted with seventeen claims. Claims 1, 4, 5, 8, 11, 13 and 15 read as follows:

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

4. Monoclonal antibody according to any one of claims 1 to 3, which reacts with from 5% to 10% of normal human thymocytes.

5. Monoclonal antibody according to any one of Claims 1 to 4, which reacts with leukemic cells from humans with T-cell chronic lymphoblastic leukemia but does not react with leukemic cells from humans with T-cell acute lymphoblastic leukemia.

8. Monoclonal antibody which is produced from hybridoma ATCC CRL 8000 (OKT1).

11. Hybridoma ATCC CRL 8000 (OKT1).

13. A method for preparing a monoclonal antibody according to any one of claims 1 to 7, 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 1-7;

(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 the hybridoma ATCC CRL 8000 in a suitable medium and recovering the antibody from the supernatant above said hybridoma.

II. Notices of Opposition were filed against the European patent by four 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.

The Respondents submitted, during the proceedings before the Opposition Division, a new set of claims which were then subject-matter of the main request before the Opposition Division and wherein Claims 7, 13 and 14 were amended as follows (amendments emphasised by the Board):

"7. Monoclonal antibody according to any one of Claims 1 to 6, which is produced by a hybridoma formed by fusion of spleen cells from a mouse previously immunized with **E-rosette positive purified normal**

human peripheral T-cells and cells from a mouse myeloma line."

Claims 13 and 14 were amended accordingly such that mice were to be immunized with "E-rosette positive purified normal human peripheral T-cells."

III. The Opposition Division maintained the patent on the basis of the amended claims.

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 8, and the monoclonal antibody described in late published documents. 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 8 did not show the reactivity pattern as stated in the claims 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 I, II and IV lodged an appeal against the decision and submitted Statements of Grounds. Oral proceedings took place on 8 January 1991.

A. During the appeal proceedings further documents were filed by all parties, for instance:

Versuchsbericht, filed by Appellants I,

Statutory declaration by Professor Janossy, filed by Appellants II,

Versuchsbericht filed by Appellants IV.

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 late published documents, that the monoclonal antibodies produced by the deposited hybridomas had binding characteristics different from those disclosed in the patent in suit both in the description and in the claims. 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, all three Appellants submitted, together with their grounds for the appeals, experimental data which showed firstly that it was only with undue burden possible to isolate monoclonal antibodies from the deposited hybridoma, if at all; secondly, the very poor yield of monoclonal antibodies finally achieved did not show the characteristics of the invention described in the patent in suit. In particular, it was emphasised that all three of the Appellants had not been successful in producing monoclonal antibodies from the deposited hybridoma from the first sample they had requested from the depository institution. On the contrary, only after repeated requests and repeated discussions with responsible persons at the depository institution and a considerable amount of own skill going far beyond the common general knowledge was it finally possible for two of the Appellants to produce a minimal amount of monoclonal antibodies from the deposited hybridoma. However, the monoclonal antibodies then achieved showed characteristics which were in contradiction to the 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 a further document

Declaration of Dr. Patricia E. Rao

and argued essentially as follows:

(a) As to the submissions of the Appellants that it was not possible to produce the monoclonal antibody from the deposited hybridoma, the Respondents referred to the declaration of Dr. Rao which stated that the procedure used by the Appellants was a standard procedure which would have been carried out by any person of ordinary skill in the art presented with a batch of a hybridoma from a source such as the depository institution ATCC. Professor Janossy's declaration showed that a skilled person could, without undue experimentation, produce the monoclonal antibody from the hybridoma deposited at the ATCC. A large number of people had requested samples of the hybridoma from the depository institution, had received such samples and had apparently produced the respective monoclonal antibody from these samples since no-one had up to this time indicated to the depository institution or the patentee that they had been unable to produce the monoclonal antibody from the deposited hybridoma. The depository institution never asked the patentee to deposit a new sample of the hybridoma, which would have been necessary within the meaning of Rule 28 EPC, in the case that the depository institution had any knowledge that the deposited hybridoma for whatever reason no longer produced the monoclonal antibody.

(b) 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.

(c) All of the Appellants failed to prove the alleged insufficiency because all of them 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.

(d) 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.

(e) 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 8000 as shown by the experimental data submitted by the Appellants II and IV 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: on the basis of the claims as maintained by the decision under appeal; second auxiliary request: on the basis of Claims 8, 11, 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 amended Claims 7, 13 and 14 of the first auxiliary request had been submitted before the Opposition Division, who did not object to these amendments under the above

mentioned Article. The Board does not see any reasons to raise objections as to this point.

The claims which are subject-matter of the second 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 T-cells, but does not react with any of the normal human peripheral cells in the group comprising 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 II:

(i) the sample of monoclonal antibodies produced by the hybridoma as deposited under the deposition No. ATCC 8000 (OKT1) reacted with 55 to 61% of E-rosette positive T-cells;

(ii) OKT1 reacts with 65 to 66% with normal thymocytes;

(iii) OKT1 reacts with 79% of T-cell acute lymphoblastic leukemia.

The characteristics found by the Appellants IV were the following:

(i) OKT1 reacts with about 72% of normal human peripheral T-cells;

(ii) OKT1 reacts with about 15% of B-cells;

(iii) OKT1 reacts 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. Reinherz et al., Eur. J. Immunol. 1980. 10: 758 "A monoclonal antibody blocking human T-cell function"). 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 ATCCCRL 8000, are different from those mentioned in Claim 1 and further from those mentioned in Claims 4 and 5.

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 Furthermore, the Appellants have submitted convincing evidence that it was not possible to produce monoclonal antibodies from the deposited hybridoma in a first assay using techniques recommended by the depository institution. Only after requesting second or even third samples from the depository institution and using special skill could minimal amounts of the antibody be produced by two of the Appellants. The expert of Appellants II, Professor Janossy, commented during oral proceedings on the experiments described in his Statutory Declaration and explained that he carried out a cell cloning at a cell density of 3 to 6 cells per well, which could not be regarded as a routine practice of standard technique.

Questioned by the Board during oral proceedings, Appellants IV answered that they had not been able to produce any antibodies from the deposited hybridoma following the instructions given by the depository institution. They repeatedly discussed the problem with responsible persons of the depository institution who could not provide further advice. Only after having received a further sample were they able to produce minimal amounts of the desired antibody by applying the same technique as the Appellants II.

Appellants I also successively requested new samples of the hybridoma and were not able to produce any antibodies at all.

Although the Declaration of Dr. Rao filed by the Respondents contested the Appellants' submissions and evidence, it was nevertheless stated under point 15 of the said declaration that the technique used by Appellants II and IV "... may not be the procedure of first choice. Obviously it would be much easier to carry out batch culture from the original batch or to carry out successfully single cell cloning. However, if these two options did not work, then the skilled man would as a matter of course turn to multiple density cloning."

3.13 The Board believes that the amount of effort applied by the Appellants had only been invested in response to the reasons of the impugned decision. It was felt necessary to produce at any rate the monoclonal antibodies to provide evidence and, by determination of their characteristics, to show that they are different from those mentioned in the main claim and description in the patent in suit. The repeated requests for the hybridoma and the techniques of the kind used by the Appellants were thus provoked by the particular circumstances of the case. One can assume that in other circumstances a third party would have given up earlier its attempts to produce the monoclonal antibodies from the deposited hybridoma.

3.14 Thus, in consideration of the above in connection with what has been set out under point 3.2, the Board is of the opinion that a disclosure provided by a deposit of a hybridoma according to Rule 28 EPC is not regarded as being sufficient within the meaning of Article 83 EPC, if and when it is only possible to reproduce the invention after repeated requests to the depository institution and

by applying techniques being considerably more sophisticated than those recommended by the depository institution.

3.15 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. **First auxiliary request**

The claims of the first auxiliary request do not differ from those of the main request in a way which could provide a basis for a different evaluation of the sufficiency of the disclosure of the main claim. The above reasoning, therefore, applies.

5. **Second auxiliary request**

5.1 The second 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 8, 11, 15 and 16.

5.2 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.

5.3 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.

5.4 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 17 381 is revoked.

The Registrar: The Chairman:

P. Martorana P. Lançon