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D E C I S I O N
of 22 April 1994

Case Number: T 0915/93 - 3.3.4

Application Number: 86308785.4

Publication Number: 0222617

IPC: A61K 39/395

Language of the proceedings: EN

Title of invention:
Monoclonal antibody therapy

Applicant:
Ortho Pharmaceutical Corporation

Opponent:
-

Headword:
Monoclonal antibody therapy/ORTHO

Relevant legal norms:
EPC Art. 56

Keyword:
"Inventive step (no) - obvious to try with reasonable expectation of success"

Decisions cited:
T 0249/88, T 0060/89, T0933/92

Headnote/Catchword:

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0915/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 22 April 1994

Appellant: Ortho Pharmaceutical Corporation
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Decision under appeal: **Decision of the Examining Division of the European Patent Office dated 21 April 1993 refusing European patent application No. 86 308 785.4 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U.M. Kinkeldey
Members: L. Galligani
S.C. Perryman

Summary of Facts and Submissions

I. European patent application No. 86 308 785.4 published under No. 0 222 617 was refused by the Examining Division.

The decision was taken on the basis of Claims 1 to 16 as originally filed.

Claim 1 read as follows:

"A product comprising at least two ligands for sequential use in therapy or diagnosis, wherein each ligand includes a monoclonal antibody antigen binding site which is functionally equivalent (as regards antigen binding) to the antigen binding site of each of the other ligand(s), and each ligand has a distinct idiotype."

Dependent Claims 2 to 14 related to specific embodiments of the product according to Claim 1.

Claims 15 and 16 related to the use of a ligand including a monoclonal antibody binding site in the preparation of a medicament or diagnostic composition.

II. The Examining Division refused the application under Article 97(1) EPC on the ground that the subject-matter of the application did not involve an inventive step within the meaning of Article 56 EPC, having regard to the following document:

(1) Transplantation Proceedings, Vol. XVII, No. 1, February 1985, pages 558 to 559.

The main reasons given for the decision were as follows:

(a) Document (1) dealt with the problem of the xenosensitisation in patients treated with the monoclonal antibody OKT3. On the basis of the observation in one unique patient, the conclusion was drawn in (1) that anti-idiotype antibodies were responsible for the abrogation of the therapeutic effect. Anti-isotype antibodies had no neutralizing capacity.

(b) In order to overcome the said problem, two suggestions were made in (1), one being the treatment of the patient with a combination of the monoclonal antibody with immunosuppressants, the other one being the use of a second monoclonal antibody with a different idiotype. The present application which proposed to use two or more monoclonal antibodies with distinct idiotypes in order to overcome host sensitisation lacked an inventive step *vis-à-vis* document (1). Neither the fact that the suggestion in (1) was based on the observation on a unique patient nor the fact that a second alternative was also suggested would have prevented the skilled person from trying the solution proposed therein in order to overcome the problem of host sensitisation. The skilled person would have been able to test without any difficulty the anti-T3 antibodies available in the prior art in order to find monoclonal antibodies which could be used as suggested in (1). There was a reasonable chance of success (see decision T 249/88 dated 14 February 1989, not published in the OJ EPO).

III. The Appellant lodged an appeal against this decision, paid the appeal fee and filed the Statement of Grounds.

IV. In a communication pursuant to Article 11(2) of the Rules of procedure of the Boards of Appeal, the Board invited the Appellant to oral proceedings and indicated a further question to be taken into consideration, namely the question of novelty of Claim 15.

V. With letter dated 18 April 1994 the Appellant withdrew unconditionally its request for oral proceedings and requested that the appeal be decided on the basis of its written submissions.

VI. The Appellant's main arguments are essentially as follows:

(a) reference (1) made assumptions and speculations on the basis of one patient who had an abnormal immune response. There were no data whatsoever to back up the suggestions made therein.

(b) Reference (1) provided a more concrete and simple proposal for using monoclonal antibodies in sensitised patients which the skilled person could have used, namely their use in association with conventional immunosuppressive drugs.

(c) In order to show that the invention was obvious, it should have been demonstrated not only that it was obvious to try, but also that there was a reasonable expectation of success (see decision T 60/89, OJ EPO 1992, 268). The speculative idea presented in (1) would not have provided a basis for such expectation for the skilled person because the mere availability of a number of monoclonal antibodies was not sufficient to establish that

they had different idiotypes or that their idiotypes, if different, were sufficiently different to avoid neutralisation by the original anti-idiotype antibody.

VII. The Appellant requested that the appealed decision be set aside and a patent be granted on the basis of the pending claims.

Reasons for the Decision

1. The appeal is admissible.

2. *Novelty (Article 54 EPC)*

Novelty was not contested by the Examining Division, nor does the Board see any objection to the novelty of the main claim.

In its communication the Board expressed some doubts as regards the novelty of use Claim 15. However, as oral proceedings did not take place (see Section V. above) at which the question of novelty of Claim 15 might have been clarified, the Board decided to postpone consideration of the novelty of this use Claim 15 until after deciding on whether lack of inventive step of the main claim would make it necessary in any case to dismiss the appeal. While it is usual to deal with the novelty of all claims of a request before considering inventive step, here examination of Claim 15 as to novelty would have involved waiting for the decision of the Enlarged Board of Appeal on the point of law relative to Article 110 EPC with respect to the following question: "Is the Board obliged or empowered to consider whether an application also fulfils those other requirements of the EPC which the Examining Division regarded as having been complied with and

therefore did not cite in its decision as grounds for refusing the application?" referred in decision T 933/92 dated 6 December 1993 (to be published in the OJ of the EPO) which is still pending under Ref. No. G 10/93.

3. *Inventive step (Article 56 EPC)*

3.1 The closest prior art

Document (1) represents the closest prior art.

In this document it is stated that, when renal allograft patients were treated with the monoclonal antibody OKT3 to prevent rejection, xenosensitisation occurred due to the production in the patients of anti-OKT3 antibodies. It was observed that these antibodies exhibited two types of specificity: i) **anti-isotypic** and ii) **anti-idiotypic**.

On the basis of the results obtained with a unique patient, the authors concluded that the anti-isotypic antibodies did not have neutralizing capacity and, consequently, assumed that "only anti-idiotypic anti-OKT3 antibodies are detrimental to the immunosuppressive capacity of OKT3". As a first suggestion, the authors hence proposed that a second monoclonal antibody with a different idiotype could be used in patients sensitised to the monoclonal antibody OKT3. Alternatively, as a second suggestion, the authors proposed that the sensitization obstacle could be circumvented by the association of low-dose conventional immunosuppressive drugs to the treatment protocol.

3.2 The underlying technical problem and the solution proposed

In the light of document (1) the technical problem underlying the present application can be seen in the provision of a product and method for overcoming the xenosensitisation which occurs during the administration of monoclonal antibodies.

As a solution thereto Claim 1 provides a product which comprises at least two functionally equivalent (as regards antigen binding) monoclonal antibodies for sequential use in therapy or diagnosis, wherein each monoclonal antibody has a distinct idiotype.

3.3 The difference between the disclosure of document (1) and the solution proposed

The solution proposed in Claim 1 is the practical realisation in the form of a product of the first suggestion offered by document (1) to use, subsequent to the monoclonal antibody OKT3, a second monoclonal antibody with a different idiotype in sensitised patients. The present application merely confirms that in fact said suggestion is feasable.

3.4 Assessment of inventive step

3.4.1 The question to be asked in respect of inventive step in the present case is whether the skilled person would have tried to put into practice the first suggestion made in document (1) with a reasonable expectation of success, and could have done so without difficulty.

3.4.2 The problem of the sensitisation of patients treated with monoclonal antibodies, in particular with the monoclonal antibody OKT3, was well known in the art (see introductory part of the present application) and was recognised also in document (1). The latter, after an analysis of the possible causes thereof, indicated two possible solutions, one of them being the use in sensitised patients of a second monoclonal antibody with a different idiotype (first suggestion).

3.4.3 The Board agrees with the view of the Examining Division that both the fact that the conclusions and suggestions in document (1) were based on a unique patient and the fact that a second, more simple alternative was proposed would not have deterred the skilled person from trying the suggested approach. Firstly, in biomedical research data obtained from unique or unusual cases often provide - through the formulation and testing of working hypotheses and suggestions - an important insight into unsolved problems and the line so suggested would be adopted by the skilled person with a reasonable expectation of success. Secondly, the presence in a scientific article of a second suggestion does not necessarily lessen the incentive of the skilled reader to try the first one, even if the second is presented as being more simple. With only two suggestions, it would not be unusual to try both and to compare their effectiveness in fact, as opposed to in theory.

The Board additionally observes that the second alternative suggested in document (1) involves a treatment with immunosuppressive drugs. In view thereof, the Board thinks it most likely that the skilled person, being aware of the numerous side effects of such drugs (see also present description page 4, lines 19 to 20), would have given careful (or even preferential) consideration to the first suggestion.

3.4.4 For these reasons, the Board is of the opinion that document (1), far from being a bar, would have constituted for a skilled person, who was attempting to find a solution to the problem of xenosensitisation of patients treated with a first monoclonal antibody, a strong incentive to try the suggestions offered therein.

3.4.5 It remains to be established whether the putting into practice of the said first suggestion would have been readily possible for an average skilled person in a reasonable expectation of success.

A number of anti-T3 monoclonal antibodies was available in the prior art (see, for example, the list given in Table I of the present application). To find among them idiotypically distinct anti-T3 monoclonal antibodies to use in *seriatim* administration as indicated in document (1) would have involved for the skilled person nothing out of the ordinary in the field of biomedical research as this would have merely required the carrying out of routine immunological determinations. In particular, it was not necessary to go through the cumbersome route of preparing the monoclonal antibodies in question by the hybridoma technique.

In view of the quite straightforward nature of the approach indicated by document (1) and of the routine nature of the techniques to be used in order to put it into practice, the Board is of the opinion that the average skilled person would not have encountered particular technical difficulties or obstacles in order to put the suggested approach into practice and thus would have had a reasonable expectation of success.

3.5 Conclusion

The Board, therefore, concludes that it would have been obvious for the skilled person to try the first suggestion offered by document (1) and that he or she would have readily done so with a reasonable expectation of success thereby arriving in a straightforward manner at something falling within the terms of present Claim 1. Thus, Claim 1 lacks an inventive step and the request is not allowable so that the appeal must be dismissed.

4. Given the above conclusion, there is no need to go further into the question of the novelty of the use Claim 15 (see point 2. above).

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar:

A. Townend

The Chairwoman:

U. Kinkeldey