BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

| A | | B | | C | X |
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File Number: T 349/91 - 3.4.2

Application No.: 81 900 044.9

Publication No.: 0 040 628

Title of invention: Monoclonalhybridoma antibody specific for high molecular weight carcinoembryonic antigen

Classification: G01N 33/574, G01N 33/577, A61K 39/00

# D E C I S I O N
of 10 March 1993

Applicant: The Wistar Institute

Opponent: F. Hoffmann-La Roche & Co. Aktiengesellschaft

Headword:

EPC Articles 54, 56, 83

Keyword: "Sufficient disclosure - no; rectified by limitation of subject-matter of the patent to the antibody by the deposited hybridoma cell line" - "Novelty, inventive step - confirmed"

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number** : T 349/91 - 3.4.2

# D E C I S I O N
## of the Technical Board of Appeal 3.4.2
## of 10 March 1993

**Appellant** : (Opponent)
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**Decision under appeal** :
**Decision of the Opposition Division of the European Patent Office dated** 27 September 1990, **posted on** 20 February 1991 **rejecting the opposition filed against European patent No.** 0 040 628 **pursuant to Article 102(2) EPC.**

**Composition of the Board** :

**Chairman** : E. Turrini
**Members** : C. Black
. L.C. Mancini

**Summary of Facts and Submissions**

I. The appeal lies against the decision of the Opposition Division to reject the present Appellant's opposition to European patent No. 0 040 628 and maintain the patent on the basis of Claims 1 to 4 then under consideration.

II. The gist of the Opposition Division's argumentation is as follows: The antibody according to Claim 3 recognises an epitope on carcinoembryonic antigen (CEA) not recognised by other monoclonal antibodies to CEA. Since the said antibody enables more sensitive diagnostic tests to be made, without false positive results, the antibody, and the hybridoma ATCC = CRL-8019 producing it, are novel and inventive. Moreover the patent teaches for the first time that there is an epitope on the component of CEA having a molecular weight of 180 000 Daltons (hereinafter 180 kD CEA). The Patentee is therefore entitled to protection not only for the antibody produced by the said hybridoma but also for any antibody which has the same specificty for the said epitope, that is, in the wording of Claim 3, an antibody corresponding to said antibody. The patentability of Claims 1 and 2 derives from that of Claims 3 and 4.

III. Documents cited in the Opposition Division's decision which will be referred to in this decision are as follows:

D1 = XXVII Annual Colloquium of the Protides of the Biological Fluids, Brussels (BE), Abstract 8, (30.04 to 03.05.1979)

D2 = As above showing the programme for Monday, 30 April, 1979

D3 = Protides of the Biological Fluids, 1980, p. 31 ff

D4 = PNAS USA, Vol. 77 (1), pp. 563 to 566 (01.1980)

P1 = Cancer Research 44 (245-253), 1984

P2 = Cancer Research 43 (3857-3864), 1983
P3 = Hybridoma, Vol. 2 (3), 1983, pp. 329 ff.

IV. Oral proceedings were held, during which the Respondent (Patentee) submitted amended claims in which the word "corresponding" in Claims 1 and 3 was supplemented by a definition derived from page 7 of the description (main request) or replaced by said definition (alternative request I). The word corresponding is however a convenient label for the antibodies it is intended to designate and it will be used for this purpose in this decision. The Respondent further submitted a second auxiliary request.

V. At the end of the oral proceedings the Appellant requested that the decision under appeal be set aside and the patent revoked, this request however being restricted to the Respondent's main request and first auxiliary request (alternative request I).

The Respondent requested that the appeal be dismissed and a patent granted in amended form on the basis of sets of claims reading as follows:

Main request:

1. A diagnostic method for detecting the presence of colorectal carcinoma which comprises contacting blood serum with an antibody having a specificity for 180,000 dalton molecular weight carcinoembryonic antigen and measuring materials bound by the antibody, characterized in that an antibody corresponding to the antibody produced by hybrid cell ATCC # CRL-8019 is used, which antibody attaches to the same site of the 180,000 dalton molecular weight CEA and is not reactive with the other components of CEA.

2. The method of Claim 1 wherein

   (a) an aliquot of 180,000 molecular weight $^{125}$I-carcinoembryonic antigen is contacted with the antibody and the antibody is agglutinated;

   (b) a second aliquot of 180,000 molecular weight $^{125}$I-carcinoembryonic antigen is mixed with blood serum and the mixture is contacted with the antibody and the antibody is agglutinated; and

   (c) the radioactivity of the bound material of step (b) is compared with the radioactivity of the bound material step (a), a decrease in the radioactivity of bound material in step (b) indicating the presence of 180,000 carcinoembryonic antigen in the blood serum.

3. An antibody having a specificity for 180,000 dalton molecular weight carcinoembryonic antigen and corresponding to the antibody produced by hybrid cell ATCC # CRL-8019, which antibody attaches to the same site of the 180,000 dalton molecular weight CEA and is not reactive with the other components of CEA.

4. Hybrid cell, ATCC # CRL-8019.

First auxiliary request (alternative request 1):

1. A diagnostic method for detecting the presence of colorectal carcinoma which comprises contacting blood serum with an antibody having a specificity for 180,000 dalton molecular weight carcinoembryonic antigen and measuring materials bound by the antibody, characterized in that an antibody attaching to the same site of the 180,000 dalton molecular weight CEA as the antibody

produced by hybrid cell ATCC # CRL-8019 and being not reactive with the other components of CEA is used.

2. The method of Claim 1 wherein

   (a) an aliquot of 180,000 molecular weight $^{125}$I-carcinoembryonic antigen is contacted with the antibody and the antibody is agglutinated;

   (b) a second aliquot of 180,000 molecular weight $^{125}$I-carcinoembryonic antigen is mixed with blood serum and the mixture is contacted with the antibody and the antibody is agglutinated; and

   (c) the radioactivity of the bound material of step (b) is compared with the radioactivity of the bound material step (a), a decrease in the radioactivity of bound material in step (b) indicating the presence of 180,000 carcinoembryonic antigen in the blood serum.

3. An antibody having a specificity for 180,000 dalton molecular weight carcinoembryonic antigen and attaching to the same site of the 180,000 dalton molecular weight CEA as the antibody produced by hybrid cell ATCC # CRL-8019 and being not reactive with the other components of CEA.

4. Hybrid cell, ATCC # CRL-8019.

Second auxiliary request (alternative request 2)

1. A diagnostic method for detecting the presence of colorectal carcinoma which comprises contacting blood serum with an antibody having a specificity for 180,000 dalton molecular weight carcinoembryonic antigen and

measuring materials bound by the antibody, characterized in that an antibody produced by hybrid cell ATCC # CRL-8019 is used.

2. The method of Claim 1 wherein

(a) an aliquot of 180,000 molecular weight $^{125}$|-carcinoembryonic antigen is contacted with the antibody and the antibody is agglutinated;

(b) a second aliquot of 180,000 molecular weight $^{125}$|-carcinoembryonic antigen is mixed with blood serum and the mixture is contacted with the antibody and the antibody is aggluntinated; and

(c) the radioactivity of the bound material of step (b) is compared with the radioactivity of the bound material step (a), a decrease in the radioactivity of bound material in step (b) indicating the presence of 180,000 carcinoembryonic antigen in the blood serum.

3. An antibody having a specificity for 180,000 dalton molecular weight carcinoembryonic antigen and produced by hybrid cell ATCC # CRL-8019.

4. Hybrid cell, ATCC # CRL-8019.

VI. The written and oral submissions of the Appellant relating to his request may be summarised as follows:

D1 discloses a monoclonal antibody VII-23e hereinafter Mab 23, which is specific for CEA. As is clear from D4, communicated before the priority date of the patent in suit, CEA is a glycoprotein of molecular weight 180 kD (page 563, first paragraph). The Appellant has obtained

from Professor Mach, co-author of D1, cell residues originating from the clone which produced Mab 23 (certified by Professor Mach's letter of 4 June 1991). The experiments of Dr Maurer (details accompanying grounds of appeal) show that Mab 23 is corresponding to the antibody produced by ATCC # CRL-8019 (hereinafter Mab 3d) because peroxidase-marked Mab 3d is shown to be completely inhibited by Mab 23 using the Western Blot technique. This is confirmed by cross-inhibition experiments using Gold epitopes Gold 1 to Gold 5. The Respondent's argument that Mab 23 and Mab 3d are not corresponding because Mab 23 recognises the same determinant as does Mab 202 (P2) and Mab 202 has a different epitopic specificity from Mab 3d (P3) is not valid; only experiments in which both antibodies to be compared take part can provide a reliable conclusion. The Respondent's further argument that D1 is not an enabling disclosure because it has not been proved that Professor Mach would supply the cell line producing Mab 23 to anyone requesting it is also not valid; the authors of P2 (under acknowledgements) were also able to obtain the cell line from Professor Accolla.

VII. The gist of the Respondent's counterargumentation is as follows:

The specificity of the claimed antibody Mab 3d for 180 kD CEA means that it recognises a determinant found on 180 kD CEA but not on any of the other lower molecular weight constituents of CEA. D1 and D3 say nothing of the molecular weight of CEA, but in any case the specificity of Mab 23 for CEA means only that it does not cross-react with non-CEA antigens such as the glycoproteins NGP, NCA purified from normal lung. As is shown in P1, page 249, chart 4A, 180 kD CEA has a number of epitopes, of which only one, specific for Mab 3d, is not found on any of the lower molecular weight constituents. Moreover P2 (chart 4) shows

that Mab 23 recognises the same antigenic determinant as does Mab 202, whereas P3 (Table 9) shows that Mab 202 has a different epitopic specificity from Mab 3d. Mab 23 and Mab 3d therefore cannot be corresponding. As to the Maurer report, the quality of the photographs is such that no conclusion can be drawn. The Gold epitope experiments were only explained at the oral proceedings and no protocol for these has been provided; these should be disregarded. Moreover D1 is not an enabling disclosure because it relies on Professor Mach making available the hybridoma which produces Mab 23. There is no certainty that he would have done so, as is evidenced by the fact that the Appellant only acquired the cell residues after several attempts. That the authors of P2 received samples is not surprising, since P2 is a publication originating from Professor Mach's laboratory.

**Reasons for the decision**

1. The appeal is admissible.

2. As compared with the granted patent, Claims 1 and 3 according to the main and first auxiliary requests now include a definition of the term "corresponding" derivable from page 7, lines 2 to 12 of the description and also from the original application documents. The claims according to the second auxiliary request have been limited to the antibody produced by the hybrid cell ATCC # CRL-8019. No objection therefore arises under Articles 123(2) and (3) EPC.

3. It is convenient first of all to dispose of the second auxiliary request, because the Appellant stated at the end of the oral proceedings that the request for revocation of the patent did not apply to this request. This is in accord

with a corresponding statement made during the opposition procedure to the effect that the objections under Articles 54, 56 and 83 EPC were maintained only in connection with the expression "corresponding to" (paragraph 11 of Facts and Submissions in the Opposition Division's decision). Moreover the Board sees no reason to disagree with the Opposition Division's decision, to the extent that it relates to the part of the subject-matter of the granted claims covered by the second auxiliary request, which is therefore allowable.

4. The main and first auxiliary requests have substantially the same scope and can be dealt with together. Claim 3 of these requests covers, in addition to the antibody produced by the hybrid cell ATCC # CRL-8019 (Mab 3d), antibodies which attach to the same site of 180 kD CEA as does Mab 3d and are not reactive with other components of CEA, that is, antibodies designated as corresponding antibodies in the granted patent. The Board has noted the conflicting evidence adduced by the parties as to whether the antibody Mab 23 corresponds to Mab 3d or not, but finds it unnecessary to take a position on this issue or for that matter on whether D1 is an enabling disclosure, because the requests are not allowable for another reason.

5. The Board recognises that the production of hybridoma cell lines and the monoclonal antibodies they secrete by the technique of Köhler and Milstein involves (or at least did so at the priority date of the patent in suit) a laborious and time-consuming operation requiring skilled personnel, which in appropriate circumstances justifies the grant of a patent for the hybridoma and the secreted monoclonal antibody. This is the case in the patent in suit, because the unique specificity of Mab 3d for 180 kD CEA provides an improved tool for diagnosing colorectal carcinoma. The question arises whether the Patentee, having disclosed this

monoclonal antibody, and also taught for the first time that there is an antigenic determinant on 180 kD CEA, not shared by other components of CEA, for which Mab 3d is specific, is entitled to claim any monoclonal antibody having this same property (that is, a corresponding antibody). It was argued during the oral proceedings that once you had the monoclonal antibody, the screening process for obtaining hybridomas secreting corresponding monoclonal antibodies was facilitated. Moreover Mab 3d could be used in affinity chromatography for separating CEA components and obtaining a pure component which could be used in a secondary inoculation in carrying out the Köhler and Milstein technique thereby increasing the chances of obtaining the desired hybridoma. However methods for purifying CEA were already known - cf. the patent in suit, page 3, lines 17 to 20 - and as regards facilitation of screening no details were given. Moreover in this respect the description merely says that once it has been determined that the specific antibody exists, corresponding antibodies can be made from hybrid cells obtained from animals other than mice (page 7, lines 3 to 7). The Board is therefore not convinced that the invention, to the extent that it relates to corresponding antibodies, is described in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, who would have to carry out substantially the same laborious screening process to produce a hybridoma cell line secreting a corresponding antibody even with the assistance of Mab 3d. This is equivalent to the exercise of inventive ingenuity. Accordingly, contrary to the view taken by the Opposition Division, the main and first auxiliary requests are not allowable because of non-compliance with Article 83 EPC. For completeness, it is noted that in the opposition proceedings the Opponent's objection under Article 83 was treated to some extent under lack of clarity. However the

Opposition Division's reasoning in paragraphs 7 and 8 of the Reasons for the Decision clearly falls under Article 83.

**Order**

**For these reasons, it is decided that:**

1. The decision under appeal is set aside.

2. The case is remitted to the Opposition Division with the order to maintain the patent on the basis of Claims 1 to 4 of alternative (auxiliary) request 2 and description to be adapted.

The Registrar: The Chairman:

P. Martorana E. Turrini