BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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File Number: T 683/90 - 3.3.2

Application No.: 81 101 473.7

Publication No.: 0 035 265

Title of invention: Agent for tumor localization and therapy with labelled antibodies and antibody fragments

Classification: A61K 49/02

D E C I S I O N
of 5 May 1992

Proprietor of the patent: Goldenberg, Milton David

Opponent: 01 Hoechst Aktiengesellschaft, Frankfurt (Main)
02 Unilever PLC/Unilever N.V.
04 Hybritech Inc.

Headword: Tumor localisaton/GOLDENBERG

EPC Article 56

Keyword: "Inventive step - (no) - obvious solution - no unexpected superior effect"

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 683/90 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 5 May 1992

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Decision under appeal : **Interlocutory decision of the Opposition Division of the European Patent Office dated 25 April 1990, posted on 22 June 1990 concerning maintenance of European patent No. 0 035 265 in amended form.**

Composition of the Board :

Chairman : A.J. Nuss
Members : U.M. Kinkeldey
E.M.C. Holtz

Summary of Facts and Submissions

I. European patent application No. 81 101 473.7 was granted as European patent No. 35 265 with 12 claims.

II. Notices of opposition against the European patent were filed. Revocation of the patent was requested on the grounds of Articles 100(a), (b) and (c) EPC. During the procedure before the Opposition Division more than 100 documents were filed by the parties, out of which the following remained relevant in the appeal proceedings:

(8) Abstract No. 59c of the 7th Meeting Inter. Soc. Oncodev. Biol. a. Med., No. 21, Mach et al. "Demonstration of the in vivo tumour localisation of radiolabelled anti-CEA antibodies in patients with carcinomas"

(27) Cancer Research 40, August 1980, Goldenberg et al. "Radioimmunodetection of Cancer with Radioactive Antibodies to Carcinoembryonic Antigen"

(73) Science, Vol. 206, 16 November 1979, Ballou et al. "Tumour Localisation Detected with Radioactively Labelled Monoclonal Antibody and External Scintigraphy"

(78) Oncodevelopmental Markers, 1983, Chapter 9, page 167, Begent et al. "Radioimmunolocalisation of Cancer"

(84) Clinical Microbiology Newsletter, Vol. 2, No. 3, February 1, 1980, Sevier "Revolutionary Reagents: Monoclonal Antibodies from Hybridomas".

The Respondent submitted during oral proceedings before the Opposition Division several sets of new claims

according to a main request and three auxiliary requests. Claim 7 of auxiliary request III reads as follows:

"7. A sterile injectable composition, comprising:

(a) an antibody fragment specific to a tumor-associated intracellular or cell-surface marker, obtained by cleavage of an antibody specific to said marker substance, said fragment being radiolabeled with a pharmacologically inert radioisotope capable of external detection using an external photoscanning device, except a fragment of a polyclonal antibody, and

(b) a pharmaceutically acceptable injection vehicle; for use in humans in a method for detecting and localising a tumor which produces or is associated with an intracellular or cell-surface marker substance."

III. The Opposition Division maintained the patent on the basis of the claims of auxiliary request III, essentially for the following reasons:

(a) The requirements of Articles 83 and 123 EPC were met;

(b) none of the documents submitted by the parties described the subject-matter of any of the independent claims, in particular of Claim 7 and so far novelty of these claims was accepted (Article 54 EPC).

As far as written disclosures referring to subject-matter orally presented at the UICC workshop on radioimmunodetection of cancer, July 19-21, 1979,

Lexington, Kentucky were concerned, it was considered not to be necessary to take a decision on whether this oral disclosure represented a prior art within the meaning of Article 54(2) EPC, since the contested references were either equivalent or even less relevant than other references clearly published before the priority date. Nevertheless, for the purpose of the decision all these references had been taken into consideration as if they were comprised in the state of the art.

(c) All independent claims of auxiliary request III also involved an inventive step (Article 56 EPC). When regarding Claim 7, which disclaimed any fragments of polyclonal antibodies, it was established that the claim now contemplated only fragments of monoclonal antibodies. The advantages involved in the in vivo use of antibody fragments with regard to complete antibodies were well known to the skilled person (e.g. lower complement activation, higher ability to permeate the cell membranes).

Document (8), which was indicated by the parties as the closest state of the art, reported the external localisation of carcinoma by using inter alia $F(ab')_2$ fragments of carcinoembryonic antigen (CEA) antibodies. Although successful photoscanning could not be proved for all the patients, the results were considered by the authors of document (8) to be of importance for future research. According to document (8), therefore, the external imaging of carcinoma, making use of antibody $F(ab')_2$ fragments might be feasible; such a method would moreover take advantage of the favourable conditions resulting from the use of fragments instead of complete immunoglobulin.

Document (8) was thus considered to contain a clear suggestion for the skilled person to persist in that direction by trying fragments of polyclonal antibodies specific for other important tumour markers. Since, however, Claim 7 of auxiliary request III (different from Claim 7 of all other requests) involved only monoclonal antibody fragments an important qualitative difference was recognised.

The peculiar features of a monoclonal antibody were a very high specificity but of course a very low avidity. The low avidity might strongly affect the level of the radioemission and the efficacy of the resolution of a method of external imaging. Thus, the efficacy of the composition according to Claim 7 of auxiliary request III for external imaging by photoscanning was regarded as completely unpredictable. This position was taken in the light of the disclosure of document (73), dealing with monoclonal antibodies applied in an animal model for tumour localisation by external scintigraphy. It was not accepted that results obtained in animals may, in the specific present case, render obvious the result eventually obtained in humans. Thus, the combination of document (73) with, for example, document (8) was not regarded as able to render obvious the efficacy of monoclonal antibody fragments in external imaging.

IV. The Appellants lodged appeals against this decision.

(a) Oral proceedings took place on 5 May 1992.

(b) During the appeal proceedings several documents were filed with letters of 25 October 1990 and 31 March

1992 by Opponents 01 and of 6 April 1992 by Opponents 04, to provide evidence that the firstly named author of document (8), Professor Mach, orally disclosed, that monoclonal antibodies and fragments were suitable to be used in the method described in document (8) when presenting this document in Surrey, United Kingdom, at the 7th Meeting of the International Society for Oncodevelopmental Biology and Medicine held on 14 September 1979.

(c) The Appellants argued essentially as follows:

(i) The Opposition Division was wrong to consider Article 83 EPC not to be an issue.

(ii) As to Claim 7, relating to a sterile injectable composition comprising an antibody fragment from monoclonal sources, it was submitted that the provision of these antibodies did not involve an inventive step with regard to the disclosure of document (8), a printed abstract presented at the meeting in Surrey, in combination with either document (73), which disclosed the application of radioactively labelled monoclonal antibodies for the purpose of tumour location by external scintigraphy, i.e. the location in mice of murine teratocarcinomas, or document (84) where there was disclosed the revolutionary aspects of monoclonal antibodies, including all their advantages, in particular in connection with cancer, for example their usefulness in the study of cell surface antigens, such as tumour markers, so that by labelling and injecting an in vivo imaging of tumours could be carried out.

Thus, the facts of the present case were comparable with those upon which an earlier decision was based (T 499/88 of 11 January 1990, not published in the OJ EPO), where the replacement of monospecific polyclonal antibodies by monoclonal antibodies in an immunopurification process was considered to be obvious.

(d) During the oral proceedings the Respondent filed three sets of new claims as a first, second and third auxiliary request respectively. Each set of claims contains Claim 7 of the main request, being renumbered as Claim 6 in the first auxiliary request, Claim 4 in the second auxiliary request and Claim 3 in the third auxiliary request.

(e) The Respondent argued essentially as follows:

It was strongly contested that Professor Mach proposed orally at the Surrey meeting the use of monoclonal antibodies or fragments to improve the imaging of tumours by photoscanning. Evidence had been filed as to this point with letter of 31 July 1991.

The disclosure of document (8) was ambiguous since a clear correlation between successful and unsuccessful detection by complete antibodies or antibody fragments of tumours by photoscanning was not possible. Further, the warning contained in document (8) that the described method had only limited usefulness for tumour detection and had not yet been proven to be clinically useful actually led away from the technical teaching given in Claim 7.

Although it was agreed that document (73) described tumour location detection with radioactively labelled monoclonal antibodies and external scintigraphy, it was pointed out that the monoclonal antibodies described there belonged to the antibody class of IgM and not to the class of IgG, as described in the patent in suit. Moreover, there was a sentence in the patent in suit pointing out that the IgM described elsewhere were not suitable in the system of the patent in suit.

Thus, neither document (73) nor document (84) suggested that radiolabelled monoclonal antibody fragments, being specific for tumour markers, could be used to improve the photoscanning method described in document (8), which used polyclonal antibody fragments.

In particular it was pointed out and illustrated by a chart submitted during oral proceedings, which indicated possible directions for the improvement of imaging, that the choice of monoclonal antibody fragments was by no means a "one-way-street" situation, and thus unlike that of decision T 499/88 (see above paragraph IV(c)(ii)). Rather, the skilled person could have considered various alternatives for the improvement of the imaging described in document (8), for example improved subtraction, better radiolabelling, the application of a higher amount of antibodies applied, the application of a mixture of antibodies, use of specific hybrid antibodies and improved background clearance. To use monoclonal antibody fragments was thus only one out of many possibilities and the prior art did not provide any hint that monoclonal antibody fragments would be the preferred means for improving tumour detection.

Further, there was no reliable positive inference to be drawn from the results of animal tests as to the possible success of an application in human beings.

The unexpected effect of radiolabelled, tumour-markers-specific monoclonal antibody fragments was demonstrated by the newly filed comparative tests according to which metastases as small as 5 mm were detected. In particular the test called "Case 3" compared - while otherwise all conditions were the same - complete monoclonal antibodies with monoclonal antibody fragments. The improvement when using the latter was evident.

V. The Appellants 01 and 02 (Opponents 01 and 02) requested that the decision under appeal be set aside and that the European patent No. 35 265 be revoked with regard to the subject-matter of Claim 7 as mentioned in the decision under appeal. Appellant 04 (Opponent 04) requested that the decision under appeal be set aside and that European patent No. 35 265 be revoked with regard to the subject-matter of Claims 1 to 3 and 6 to 10 as maintained in the decision under appeal.

The Respondent requested that the appeal be dismissed and that the patent be maintained in accordance either with the main request or auxiliary requests I to III, each as submitted in writing in the oral proceedings.

Reasons for the Decision

1. The appeals are admissible.

2. Claim 7 of the main request

2.1 The subject-matter of Claim 7 is a composition which contains as essential element an antibody fragment specific to a tumour marker except a fragment of a polyclonal antibody. Therefore, this claim is limited to a composition containing monoclonal antibody fragments. This claim corresponds to Claim 7 considered by the Opposition Division.

The Board has no reason to disagree with the Opposition Division's opinion that the claim meets the requirements of Article 123(2) and (3) EPC (see point 3 of the reasons of the contested decision).

Novelty

2.2 The oral disclosure by Professor Mach at the Surrey meeting in September 1979 is contended by the Appellants to be novelty destroying (see point IVb) above).

The Board cannot agree to this opinion because the alleged oral disclosure would not have related to a composition containing as essential element a monoclonal antibody fragment, as claimed in Claim 7. It can, therefore, be left undecided, whether or not the disputed oral disclosure in fact took place.

Since undisputedly no other document on file comes closer to the claimed subject-matter, novelty can be accepted.

Problem and Solution

2.3 In order to define the problem underlying Claim 7, the Board considers document (8) to be the closest prior art. Document (8) relates to the demonstration of the in vivo tumour localisation of radiolabelled anti-CEA antibodies in patients with carcinomas. Immunoabsorbent purified ^{131}I labelled goat antibodies against the tumour marker carcinoembryonic antigen (CEA) were injected into 24 patients with various types of carcinoma. Two other patients were injected with a whole IgG anti-CEA fraction and five additional patients with $F(ab')_2$ fragments prepared from specific anti-CEA antibodies. All 31 patients were tested by external photoscanning with a gamma camera 4, 24, 36 and 84 hours after injection. In 13 patients with colorectal carcinoma the previously diagnosed tumour could be detected by photoscanning 36 to 84 hours after injection. In 9 other patients the interpretation of the scanning pictures was difficult and in 9 additional patients there was no increased ^{131}I radioactivity in the tumour area. To study the specificity of the tumour localisation, the radioactivity present either in tumours or in normal adjacent tissue recovered after operation was measured. The results in 8 patients showed that the concentration of antibody radioactivity was 3.6 times higher ranging from 1.5 to 5.3 in tumour as compared to normal colon mucosa.

It is concluded at the end of document (8) that, although this demonstration was of importance for future research in tumour immunology and nuclear medicine, the photoscanning results gave a word of warning concerning the limitations of this method of tumour detection, which had not yet been proven to be clinically useful. While it is true, as the Appellants state, that there is no direct connection disclosed between the application of radio-

labelled, tumour specific polyclonal antibody fragments and the successful detection of tumours, document (8) nevertheless discloses the use of radiolabelled tumour specific polyclonal antibody fragments for the external detection using an external photoscanning device.

2.4 Starting from document (8) the problem underlying the subject-matter of Claim 7 thus can be seen in providing a means for improving tumour detection in human beings.

This problem is solved by the provision of a composition according to Claim 7 comprising a radiolabelled tumour specific monoclonal antibody fragment capable of external detection by means of an external photoscanning device.

The description of the patent in suit does not provide in its examples any particular data relating to the use of monoclonal antibody fragments; however, the Board can accept that in view of the general information provided in connection with the detection of tumours, it is plausible that the underlying problem was solved by the claimed composition (see in particular column 6, line 61 to column 7, line 57 of the patent in suit).

Inventive step (Article 56 EPC)

2.5 The question is whether or not, starting from document (8), the composition claimed in Claim 7 containing as essential element a monoclonal antibody fragment was obvious to a skilled person.

2.6 When trying to find a solution to the above-stated problem the skilled man indeed, as pointed out by the Respondent, could have thought of influencing several parameters in order to improve the quality of the detection of tumours. This fact becomes already apparent by providing in the

patent in suit a plurality of solutions embodied in several independent claims whose subject-matter represents different solutions. These are hybrid antibodies (Claim 1), the addition of boron atoms to the antibodies (Claim 4), improvement of the subtraction technique (Claim 6) or the use of monoclonal antibody fragments (Claim 7). The skilled person is, therefore, not confronted with a "one-way street" situation.

The decisive question in the present case is whether a skilled person would have considered the claimed composition in expectation of an improvement or advantage in respect of the closest prior art represented by document (8) in the light of the teaching of document (73).

2.7 Document (73) discloses tumour location detected with radioactively labelled monoclonal antibodies and external scintigraphy. Here it is stated that the use of specific antibodies for tumour localisation and treatment had been suggested and attempted for some time with little success until recently, the main difficulties having been the preparation and purification of specific antibodies to tumours and the need for suppression of background noise caused by unbound antibodies or circulation of antibody-antigen complexes. Reference is then made to prior art which had disclosed that it was possible to image successfully both primary tumours and metastases in man by using ^{131}I-labelled immunoglobulin IgG from absorbed goat antiserums to human renal carcinomas. In this prior art, problems had been noted, which were caused by the presence of radioactive background due to a large excess of radioactively labelled non-specific antibody (see page 844, first three paragraphs).

This citation (73) then goes on to describe an improved method for cancer imaging, which had been published by the Respondent himself, who combined ^{131}I-labelled affinity purified goat antiserum to CEA with a second radiolabel that remained in the general circulation. This second radiolabel was distinguishable from the first by certain means. Its image could be subtracted from that of the radiolabelled tumour-specific antibody to provide a correction for unbound or metabolised antibodies.

In particular it is stated there: "A more incisive approach is made possible by the recent development of monoclonal tumor-specific antibodies (...). Such antibodies, derived from lymphocyte hybridomas (...), are homogenous, require little labour for purification, and can be reproducibly prepared in large quantities. It should then be possible to use a monoclonal, nonselected antibody of the same class as the tumor-specific antibody for background subtraction. If both antibodies were labelled in similar fashion with different radioisotopes of the same element, metabolism of the two should be similar, except for binding to tumors. We here report results that indicate that tumor imaging by radiolabelled monoclonal antibodies is feasible, with and without such background subtraction." (see page 844, right column, last paragraph bridging to page 845, left column, first paragraph).

In this document it is finally stated that the purity of monoclonal antibodies permits the use of a minimum amount of radiolabel for tumour detection, since potentially all of the antibody is tumour-directed (see page 845, right column, last sentence of the first paragraph).

2.8 While it is true that the man skilled in the art would have realised that there existed more than one possibility

to solve the underlying problem, in the Board's judgment, however, document (73) provides a strong incentive to solve the problem arising from the short-comings of the polyclonal technique described in document (8), by making use of the technically superior monoclonal antibodies. He would, therefore, certainly have tried to replace the polyclonal antibody fragments by monoclonal ones. Under these conditions the Board considers the improvement to correspond to what was to be expected by the skilled person. Consequently the claimed solution cannot be regarded as surprising.

2.9 The above conclusion still holds good when taking into account the experimental data submitted by the Respondent at the stage of appeal intending to prove an unexpected superior result of the use of monoclonal antibody fragment. These experiments merely concern comparisons with state of the art which is more remote from the claimed invention than the closest state of the art, i.e. document (8). According to the established jurisprudence of the Boards of Appeal, such evidence cannot be a substitute for the demonstration of an inventive step with regard to the closest state of the art (see decision T 199/86 of 15 September 1987, point 9.3 of the reasons).

Case 3 provides a comparison of the use of complete monoclonal antibodies and monoclonal antibody fragments, showing the superiority of the latter. This superiority, however, was to be expected in view of what was already proposed in document (8), although there polyclonal antibody fragments are described. The obvious advantages to use antibody fragments, lacking the Fc-arm of the antibody are namely that unspecific binding by the Fc-arm is avoided, that there is lower complement activation, that the antibody molecules are smaller and thus more easily distributed in the body when injected and that they

have a higher ability to permeate the cell membrane. These known advantages were already correctly pointed out in the decision of the Opposition Division (paragraph 4.3.5.2).

Moreover, the experimental results relating to cases 1, 2, 4 and 5 compare data obtained by injection of labelled monoclonal antibody fragments with results obtained by computed XCL tomography (CAT scans), which intends to show that a single photon emission computed tomography (SPECT) after injection of radiolabelled monoclonal antibody fragments shows a better resolution of cancer occurrences; for example in case 1 metastases having a size of between 0.5 and 1.0 cm in diameter could be imaged.

However, these recent results lie far beyond what was considered at the time the patent in suit was filed to be feasible in the art. According to document (27) (page 2984 "Abstract" and page 2990, right column, last full paragraph) and document (78) (page 180, last paragraph) the smallest tumours detectable were considered to have a size of about 2 cm. It is to be noted that the Respondent himself was one of the authors of document (27), so that the Board has no reason to consider such expert opinion as tendentious. The striking discrepancy could well be due to improved instrumentation or computer processing or to other technical progress in that technology achieved in the past decade. Therefore, in the absence of clear evidence that the results submitted to the Board are exclusively due to the use of monoclonal antibody fragments as claimed, they cannot be accepted as a convincing piece of evidence demonstrating an effect going beyond the expectation of the man skilled in the art. Moreover, at the oral proceedings the Respondent conceded that this evidence only confirmed that the claimed composition leads to a positive improvement, a fact the

Board has duly taken into account as can be seen from points 2.3 to 2.8 above.

In view of the above the Board sees no reason to examine the ambiguous result of case 5, where apparently the used radiolabelled monoclonal antibody fragments bound heavily to the spleen for reasons unknown, i.e. although the spleen might not have been cancerous.

2.10 The fact that the monoclonal antibodies actually prepared in document (73) are of the class IgM and not of the class IgG, i.e. those of the examples of the patent in suit, does not change the conclusion as to inventive step, because Claim 7 does not differentiate between the two classes of antibodies. The Board has thus no reason to consider the use of IgM monoclonal antibody fragments as an essential feature of the claimed composition (see decision T 215/85 of 20 January 1987, not published in the OJ EPO, in particular point 4.4, last paragraph). The sole reference in the patent specification in column 7, lines 30-33, that the IgM monoclonal antibodies of Koprowski in U.S. patent 4 172 124 were unsuitable for the use in the present method seem to be contradicted by the disclosure of document (73) which described successful localisation by antibodies of this class. At least one cannot consider this statement in the patent in suit as a prejudice to use monoclonal antibody fragments of the whole class of IgMs.

2.11 Finally, the Respondent strongly contests that the teaching of document (73) is relevant because the experiments described there were carried out with murine teratocarcinomas and there is no reliable extrapolation possible from animal models to the application in human beings. Although this may be correct, the relevant question in the present case is whether a skilled person

would be encouraged to try a composition in humans with a reasonable expectation of success when advised that a first trial in animals provided a positive result. It may very well turn out that in the human system one encounters pitfalls or difficulties which could not be foreseen from the animal model. However, the Board is not convinced that the man skilled in the art would automatically disregard animal tests as a preliminary step before deciding whether or not it would be worthwhile to carry out the more complex clinical trials needed on humans. One might conclude that, if a test carried out in an animal provides negative results and somebody nevertheless against any reasonable expectation of success tries this method in human beings with success, this could be considered as being surprising, which is clearly not the case here. Consequently the Board cannot see any sound reason why a skilled person, faced with the underlying technical problem would not have arrived at the solution of Claim 7.

2.12 It follows from all this that the subject-matter of Claim 7 of the main request does not involve the required inventive step.

3. Since each of the auxiliary requests contain the subject-matter of Claim 7 of the main request, namely as Claim 6 in the auxiliary request I, Claim 4 in auxiliary request II and Claim 3 in auxiliary request III all these requests contain subject-matter which contravenes the requirements of the EPC. Thus none of the auxiliary requests is allowable either.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. European patent No. 35 265 is revoked.

The Registrar: The Chairman:

E. Görgmaier A. Nuss