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D E C I S I O N
of 10 May 2001

Case Number: T 0606/96 - 3.3.4

Application Number: 87200081.5

Publication Number: 0234612

IPC: G01N 33/574

Language of the proceedings: EN

Title of invention:
Method and kit for compounding radiolabeled antibodies for in vivo cancer diagnosis and therapy

Patentee:
Rhomed, Incorporated

Opponent:
Akzo Nobel Pharma B.V.

Headword:
Radiolabeled antibodies/RHOMED INC.

Relevant legal provisions:
EPC Art. 57, 54, 56

Keyword:
"Methods of treatment of the human body (no) - novelty (yes)"
"Inventive step (yes)"
"Referral (no)"

Decisions cited:
T 0082/93, T 0532/96

Catchword:
The limiting effect of the features of the sequence of manufacturing steps leading to a medicament prevails on that

of intended medical use.

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0606/96 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 10 May 2001

Appellant: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 7 May 1996 rejecting the opposition filed against European patent No. 0 234 612 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
V. Di Cerbo

Summary of Facts and Submissions

I. The appeal lies against the decision of the opposition division rejecting the opposition against European patent No. 0 234 612 (application No. 87 200 081.5) with the title "Method and kit for compounding radiolabeled antibodies for in vivo cancer diagnosis and therapy". The patent was granted on the basis of 4 claims, of which claim 1 read as follows:

"1. A method for selecting at least one monoclonal antibody component, the monoclonal antibody component comprising at least one member from the group consisting of whole monoclonal antibodies and monoclonal antibody fragments, for use in preparing a patient specific monoclonal antibody-based compound for use in **in vivo** cancer detection or therapy of a specific patient, comprising the following steps:

(a) preselecting a panel of at least two monoclonal antibody components, the monoclonal antibody components predetermined to be specific to tumor associated antigens of a cancer type to be detected or treated;

(b) obtaining a solid tumour specimen, which has been obtained from a specific patient, of the cancer type to be detected or treated;

(c) allowing the preselected panel of monoclonal antibody components to bind to tumor associated antigens present in the specific patient's solid tumour specimen;

(d) independently determining which, if any, of the monoclonal antibody components in the preselected panel bind to tumor associated antigens present in the specific patient's solid tumor specimen; and

(e) selecting at least one monoclonal antibody component, if the selected monoclonal antibody is determined in step d) to bind to tumor associated antigens present in the specific patient's solid tumor specimen, for use in preparing a compound for use in **in vivo** cancer detection or therapy for the specific patient.

Claim 2 related to a specific embodiment of the method of claim 1. Claims 3 and 4 covered an apparatus for carrying out the method of claims 1 or 2.

II. The following documents are cited in this decision:

(1) EP-A-0 151 030;

(6) Hellström K.H. et al. in Monoclonal Antibodies for Cancer Detection and Therapy, Baldwin et al. editors, Academic Press Inc., London, pages 17 to 51 (1985);

(10) Abrams P.G. et al. in Monoclonal Antibody Therapy of Human Cancer, K.A. Foon and A.C. Morgan Editors, Martinus Nijhoff Publishing, Boston, pages 103 to 120 (1985).

III. None of the parties requested oral proceedings.

IV. The submissions by the appellant can be summarized as follows:

Lack of industrial applicability (Article 52(4) EPC)

- Insofar as the Opposition Division considered the intended use in claims 1 and 2 at issue: "for use in preparing a patient specific monoclonal antibody-based compound for use in **in vivo** cancer detection or therapy of a specific patient" as a distinguishing feature over the prior art, infringement was determined by a mental act of the doctor deciding to use the antibody cocktail known from document (1) to treat the patient from whom it was generated. But the novelty of a **process** claim could not reside in non patentable therapeutic/diagnostic steps, unlike the case of industrially produced **means** for use in therapy/diagnostics of the human body, for which Article 54(5) EPC made an exception.

- The claimed methods and the product obtained therethrough were therapeutic procedures, not industrial ones since they had a specific rather than a general applicability. The product was derived from tissue taken from a specific patient and was used only for that specific patient. It did not make sense setting up an industrial plant to the extemporaneous preparation of the product (the cocktail of selected monoclonal antibodies) to be used for treating only one patient. In fact, Article 27 of the Community Patent Convention (CPC) excluded from patentability the extemporaneous preparation in a pharmacy of a medicine for individual cases.

Novelty (Article 54 EPC)

- Reference was made to a passage bridging pages 118 and 119 of document (10):

  "If one uses a single antibody or a combination of a few antibodies that together bind to only a small portion of the tumour cells, or if the small percentage of the true replicating cell (stem cell) is not eliminated, eventual recurrence of the tumour, perhaps with resistant cells, will result. It seems logical, therefore, to "type" human tumours with a panel of antibodies and to deliver toxic substances utilizing "cocktails" of antibodies sufficient to bind strongly to all the tumour cells for each patient. This approach requires a considerable amount of testing for each patient, and a "typing" of one or more tumours from each patient."

  The appellant maintained that said passage was a clear instruction to treat individual patients by "typing" at least one tumour from each patient with a panel of antibodies and using the result of such "typing" to prepare a "cocktail" of antibodies to be used for treatment of that patient.

- The expression in claim 1 "for use in in vivo cancer detection or therapy of a specific patient" qualified the selected monoclonal antibodies as "suitable for that use" without being itself an actual step of the claimed method. However, document (1) disclosed a method for selecting monoclonal antibodies which were in any case suitable for treatment of individual patients, even if the main intention was that they should be

useful for treating a range of patients. Therefore, what allegedly distinguished the claimed method from that of document (1) was either the mental intention of the selector to use selected monoclonal antibodies in therapy practised on an individual patient or the application of the claimed method to that individual patient, neither of which was a proper distinguishing feature to confer novelty over document (1).

- Document (1) anticipated the claimed method. Figure 2 of this document showed in a grid the results of challenging tumours from 15 patients with 10 antibodies. As a result of these tests, an antibody cocktail comprising antibodies 6a3-1 and 7a2 was proposed. This selection process met all the requirements stated in claim 1 of the patent in suit.

Inventive step (Article 56 EPC)

- The claimed method was obvious in view of the common general knowledge alone since the step of checking for binding of therapeutic monoclonal antibodies to the patient's tumour cells before starting treatment was trivially obvious (see document (6), page 30, lines 4 to 7 and page 39, lines 7 to 10).

- The claimed method was obvious by combining document (1) teaching testing of panels of antibodies against a number of tumours from different patients with the above quoted passage bridging pages 118 and 119 of document (10),

giving instruction to treat individual patients by "typing" at least one tumour from each patient.

- There was in Figure 2 of document (1) a special case, namely that of patient No. 9, whose tumour did not react with any of antibodies 6a3-1 and 7a2 forming the cocktail proposed by this document. In the appellant's view, it was obvious to any reader of this document wishing to cure this patient to use one or both of monoclonal antibodies 12-38 and 12-42 reactive with the tumour of patient # 9, thus applying the claimed method.

- There is no evidence of an improved effect over the method of document (1).

Referral of a question of law to the Enlarged Board of Appeal (Article 112 EPC)

- Should the board be doubtful about accepting the appellant's contention that a method claim for preparing a therapeutic agent cannot be distinguished from the prior art by the intended use to which the agent is to be put, the board was invited to refer this question of law to the Enlarged Board of Appeal in the context of Article 54(2) EPC.

IV. The submissions by the respondent can be summarized as follows:

Lack of industrial applicability (Article 52(4) EPC)

- The claimed method did not comprise any step of treatment of the human body.

- The claims at issue did not inhibit doctors from treating anybody, but only manufacturers of custom cocktails from applying steps (a) to (e) of claims 1 and 2 at issue.

- Preparing the custom-selected antibody-drug according to the patent in suit was not a therapeutic procedure but a manufacturing one.

- It was not an extemporaneous preparation made in a pharmacy.

Novelty (Article 54 EPC)

- Document (10) taught that only an approach involving raising monoclonal antibodies against **all** the tumour antigens of a given patient would work. Therefore it did not disclose step (a) of claim 1 directed to the preselection of a panel of antibodies predetermined to be specific to tumour associated antigens of a cancer type to be detected or treated.

- According to claim 1 of the patent in suit, the ultimate criterion that determined the inclusion of a monoclonal antibody in a variable formula composition was its binding to a specific patient's tumour. Therefore, the intended use of the product of the claimed process was not the only difference from the prior art: while document (1) provided means and methods for carrying out step (a) of claim 1, there was no disclosure of the remaining steps.

- The selection process of Figure 2 of document (1) did not meet all the requirements stated in claim 1 of the patent in suit because the last step, namely further selection based on binding to the patient's own tumour, was still missing. This process yielded antibodies which were not suitable for treating a particular patient but rather groups of patients.

Inventive step (Article 56 EPC)

- Document (1) disclosed fixed-formula cocktails of monoclonal antibodies for treating each and every patient, and therefore taught away from the claimed method, which required selection of monoclonal antibodies reactive to tumour antigens from a specific patient to select tailor-made cocktails.

- Better results were obtained with the claimed method since no antibody was used which was not specific to the patient's tumour antigens. Therefore, background or systemic toxicity were thereby minimized and specific toxicity was maximized.

  As for document (10), the passage on page 118, line 28 to page 119, line 14 was concerned with antigenic diversity within the same tumour of the same patient. This passage suggested that only an approach involving developing monoclonal antibodies to all the tumour antigens of a given patient would work.

V. The appellant (opponent) requested that the decision

under appeal be set aside and that European patent No. 0 234 612 be revoked.

The respondent (patentee) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Lack of industrial applicability (Article 52(4) EPC)

2. The appellant in essence argues that claims 1 and 2 at issue relate to unpatentable methods for treatment/diagnosis of the human body if they are interpreted the way the Opposition Division did, namely by considering the intended medical use as a distinguishing feature.

3. In the board's view, however, it has first to be noted that a multi step process is considered to relate to a method for treatment/diagnosis of the human body if it comprises at least one such step (see decision T 0082/93 (OJ EPO 1996, 274). That this does not occur for the method of claim 1 under consideration, has been acknowledged by the appellant (see page 7, paragraph 7 of the submission of 17 September 1996). The board agrees as well that none of steps (a) to (e) of claim 1 is a step of treatment/diagnosis of the human body.

4. Secondly, even if the appellant's view expressed under point 2 supra were correct, the following should be noted. In the case of a sequence of manufacturing steps leading to a medicament/diagnostic agent, the possible

attribution of novelty by virtue of an intended therapeutic/diagnostic use does not detract by itself from the limiting effect of the **remaining features** of the process claim (see decision T 0532/96 of 13 July 1999, points 2.2.3 to 2.2.5). Upon applying the rationale of this decision to claim 1 of the patent in suit, the board observes that the claimed method differs from that disclosed in document (1) in that the latter does not include the step of further selecting the monoclonal antibodies according to whether they react with a particular tumour of a specific patient. Therefore, the intended medical/diagnostic use is not the sole critical distinguishing feature, contrary to the appellant's line of argument. Hence, the conclusion cannot be drawn that infringement is determined by a mental act of the doctor deciding to use the antibody cocktail known from document (1) to treat the patient. Rather, claim 1 at issue only inhibits manufacturers of custom antibody cocktails from selecting the components of such cocktails in accordance with steps (a) to (e) of claim 1, regardless of the intended medical use thereof.

5. As for the appellant's proposition that it does not make sense setting up an industrial plant to the extemporaneous preparation of the product (the cocktail of selected monoclonal antibodies) to be used for treating only one patient, the board observes firstly that it cannot see a legal basis for not granting a patent on such a ground, and secondly assumes that the claimed method can be performed on a large scale in, eg, hospitals' laboratories to which hundred of patients' specimens are sent and the cocktails compounded. This does not amount to the extemporaneous preparation in a pharmacy of a medicine for an

individual case.

6. In conclusion, claim 1 at issue does not relate to a method of treatment/diagnosis of the human body, which pursuant Article 52(4) are regarded as not susceptible of industrial application and therefore unpatentable. This conclusion also extends to claims 2 representing a specific embodiment of claim 1.

Novelty (Article 54 EPC)

7. The appellant considers the passage bridging pages 18 and 119 of document (10) as a clear instruction to treat individual patients by "typing" at least one tumour from each patient with a panel of antibodies and using the result of such "typing" to prepare a cocktail of antibodies to be used for the treatment of that patient. In the board's judgement, this passage reflects the problem arising from the known heterogeneity of cancer and the ability of cancer cells to mutate and how it can be overcome. It is stated in the cited passage that only an approach involving developing monoclonal antibodies to **all** the antigens of a patient's tumour (cf the term "all" at the bottom of page 118), including those belonging to the true replicating cells (stem cells) would work, however, this approach presents formidable practical and economical obstacles. The board notes that this problem of cancer heterogeneity is also referred to on page 9, second full paragraph of document (1): "Without a standardized vaccine [prepared according to document (1)], only a vaccine prepared for each individual patient **from his own tumour tissue** could be used in therapy" (emphasis added). In view of these facts, the board comes to the conclusion that the cited passage of document (10) relates to a kind of "fully customized" approach which requires raising monoclonal antibodies against each patient's tumour(s), typing these antibodies to make a cocktail having the property that **each** of the patient's tumour cell reacts with an antibody in the cocktail.

8. Claim 1 at issue, however, relates to a "semi-customized" approach, namely a method for selecting the

monoclonal antibodies for use in in vivo diagnosis or therapy for a specific patient by reacting a **preselected** panel of antibodies with the antigens present in a tumour specimen from a specific patient and selection of the antibodies which bind to said antigens. The difference between the claimed methods and the "fully customized" approach of document (10) lies in that the panel of monoclonal antibodies of step (a) of claim 1 is a panel of pre-fabricated antibodies known to react with a certain type of tumour (eg, colorectal cancer), while the monoclonal antibodies in the panel of document (10) come from the patient's own tumour(s), against which they have been raised.

9. The appellant argues that claim 1 lacks novelty because it is the intended medical/diagnostic use which distinguishes the method of claim 1 from that of document (1) and the monoclonal antibodies selected according to method of document (1) are in any case suitable for the treatment of individual patients. Yet, the board has to disagree to this proposition because the intended medical/diagnostic use is not the sole critical feature distinguishing the claimed method from that disclosed in document (1): the latter does not include the step of further selecting the monoclonal antibodies according to whether they react with a particular tumour of a specific patient (see point 4 supra).

10. The experiments tabulated in Figure 2 of document (1), showing in a grid the results of challenging tumours from 15 patients with 10 antibodies and leading to the selection of a cocktail comprising antibodies 6a3-1 and 7a2 (see page 34, lines 14 to 15 of document (1)), meet, according to the appellant, all the requirements

stated in claim 1 of the patent in suit. The board, however, notes that upon applying the method of claim 1 at issue to the tumour antigens of patient No. 3 (taken by the appellant as an example), one arrives, by virtue of step (e) of claim 1 (ie, antibodies binding to patient No. 3's tumour must be selected from the panel of the 10 listed under the term "ANTIBODY" in Figure 2) at a cocktail containing the 7 monoclonal antibodies 6a3, 7a2, 12-38, 12-42, 16-4, 16-58 and 16-88 rather than to the cocktail 6a3-1 and 7a2. Since the process of document (1) and the claimed one lead to discrepant results, they cannot be identical in their steps. The selection process according to document (1) in fact comprises a critical step of selecting only those monoclonal antibodies that are statistically significant and discarding the others. Consequently, the above appellant's proposition is not convincing.

11. In conclusion, the subject-matter of claim 1 and of its dependent claim 2 satisfies the requirements of Article 54 EPC. This conclusion also extends to claims 3 and 4 since none of the documents before the board discloses an apparatus having the features stated in these claims.

Inventive step

12. The closest prior art is the passage on page 9, second full paragraph of document (1) and its counterpart in document (10) (paragraph bridging pages 118 and 119) relating to the problem faced by the skilled person wishing to make cocktails of antibodies for use in the treatment/diagnosis of cancer, which problem arose from cancer heterogeneity and the ability of cancer cells to mutate. It is suggested in the cited passages of

documents (1) and (10) that the only effective approach would be developing monoclonal antibodies to **all** the antigens of a patient's tumour, however, this approach presents formidable practical and economical obstacles (see eg, document (1), page 9, lines 29 to 33: "It would not have been possible to make individual preparations for treating the approximately 139,000 cases of colorectal cancer that are discovered in the United States every year"). Document (1) purports to overcome these practical and economical obstacles linked with a "fully customized" approach by proposing a "standardized vaccine" (page 9, line 22) obtained by selection of only those monoclonal antibodies that are statistically significant, ie which bind to most cancers of a certain type.

13. When viewed against this framework, the problem to be solved by the patent in suit is to provide another method for compounding monoclonal antibody cocktails, as an alternative to that disclosed by document (1), which method also intends to overcome the obstacles linked with the unapproachable "fully customized" technique. This method proposed by claim 1 at issue is the "semi-customized" approach, based in essence on the selection from a preselected panel of antibodies known to be each specific to a certain type of tumour, of those monoclonal antibodies which bind to the antigens present in a tumour specimen from a specific patient. Despite no in vitro/in vivo tests on cancer patients are reported in the patent in suit, there is no evidence before the board showing that the method of claim 1 is not a good substitute for the "fully customized" approach. The board is thus satisfied that the method of claim 1 solves the above problem.

14. The relevant question is whether or not the method of claim 1 at issue follows in an obvious manner from the prior art.

15. The appellant maintains that the claimed method is obvious in view of the common general knowledge alone since the step of checking for binding of therapeutic monoclonal antibodies to a patient's tumour cells before starting treatment is trivially obvious (see document (6), page 30, lines 4 to 7 and page 39, lines 7 to 10). However, the fact that a process step as such is trivial does not mean that the whole process comprising a succession of steps is also trivial. As for document (6) dealing with anti-melanoma antibodies, the board observes that the problem of cancer heterogeneity does not arise at all since it is stated on page 29, Chapter A that "every tested, consecutive sample of histologically diagnosed metastatic melanoma could be stained by antibodies to at least one of the three major melanoma antigen". Therefore, document (6) does not motivate a skilled person to go in the direction of the claimed method, given that it conveys the impression that a "universal" antibody cocktail for melanoma is already available.

16. According to the appellant, the claimed method is obvious by combining document (1), teaching testing of panels of antibodies against a number of tumours from different patients with the passage bridging pages 118 and 119 of document (10), giving instruction to treat individual patients by "typing" at least one tumour from each patient. This passage, though, relates to the "fully customized" approach (see point 7 supra). Combining documents (1) and (10) therefore does not lead to the claimed method.

17. The special case of patient No. 9 in Figure 2 of document (1), whose tumour does not react with any of antibodies 6a3-1 and 7a2 forming the cocktail proposed by this document, would, in the appellant's view, induce the skilled person reading this document and wishing to cure this patient to use one or both of monoclonal antibodies 12-38 and 12-42 reactive with the tumour of patient No. 9, thus applying the claimed method. In the board's judgement, however, the skilled person having patient No. 9's health at heart is not faced with a "one-way street" situation necessarily leading him/her to adopt the claimed method. This is because other possibilities are also open for treating patient No. 9: for instance adding one or both of monoclonal antibodies 12-38 and 12-42 to the cocktail (6a3-1 + 7a2 + 12-38/12-42), exceptionally applying the "fully customized" approach or turning to traditional chemotherapy/ surgery using no antibodies.

18. Finally, the appellant relies on the lack of evidence of an improved effect in carrying out the claimed method vis-à-vis the method of document (1). The board's position is that, while an unexpected improved effect might be an indication of inventive step, the decisive question is always whether it would have been obvious for the skilled person to arrive at something falling under the terms of a claim at all. This is not the case here.

19. In view of the foregoing, the claimed method does not follow from the prior art in an obvious manner. The subject-matter of claims 1 and its dependent claim 2 therefore satisfies the requirements of Article 56 EPC. This conclusion also extends to claims 3 and 4 relating

to an apparatus specifically designed for carrying out the method of claim 1 and 2.

Referral of a question of law to the Enlarged Board of Appeal (Article 112 EPC)

20. Since the claimed methods can be distinguished from the prior art by features **other** that the intended medical use (see points 4 and 9 supra), the question whether or not "a method claim for preparing a therapeutic agent can be distinguished by the intended use to which the agent is to be put" does not arise in the present case and referral of this question to the Enlarged Board of Appeal is refused.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

U. Bultmann U. M. Kinkeldey