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Datasheet for the decision of 14 April 2010

Case Number: T 1022/08 - 3.3.04

Application Number: 03781200.5

Publication Number: 1569690

IPC: A61K 39/395

Language of the proceedings: EN

Title of invention:
Antilymphoma targeting agents with effector and affinity functions linked by a trifunctional reagent

Applicant:
Mitra Medical Technology AB

Headword:
Trifunctional reagent/MITRA

Relevant legal provisions:
EPC Art. 56
EPC Art. 123(2)

Keyword:
"Main request, auxiliary requests I to VI - added subject-matter (yes)"
"Auxiliary request VII - added subject-matter (no), inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1022/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 14 April 2010

Appellant: Mitra Medical Technology AB
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 13 November 2007 refusing European patent application No. 03781200.5 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: M. Wieser
B. Claes

Summary of Facts and Submissions

I. The appeal was lodged by the Applicant (Appellant) against the decision of the Examining Division to refuse under Article 97(1) EPC 1973 the patent application EP 03 781 200.5 (published as WO 2004/054 615), having the title: "Antilymphoma targeting agents with effector and affinity functions linked by a trifunctional reagent".

II. The Examining Division decided that claim 1 of the sole request before it, namely claims 1 to 21 filed with letter of 26 January 2007, did not meet the requirements of Articles 84 and 123(2) EPC and that its subject-matter did not involve an inventive step contrary to the requirements of Article 56 EPC.

III. In its statement of grounds of appeal, dated 20 March 2008, the Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of claims 1 to 21 filed therewith.

The Board expressed its preliminary opinion in a communication dated 29 January 2010 which was annexed to the summons to oral proceedings to be held on 14 April 2010.

By a letter dated 11 March 2010 the Appellant filed an amended set of claims 1 to 20 and requested "that if the grounds for the rejection still not would have been eliminated after the Board of Appeal's consideration of the present claim amendments and the arguments in favour of inventive step presented above, a further written Communication is issued or that [the Appellant's representative be] contacted via telephone".

Moreover, the Appellant informed the Board that it would not attend the scheduled oral proceedings.

On 18 March 2003 the Board issued a further communication wherein the Appellant was informed that claims 1 to 20, filed on 2 March 2010, did not meet the requirements of Articles 84 and 123(2) EPC. It was stated that the oral proceedings would be held as scheduled on 14 April 2010.

With a letter filed 12 April 2010 the Appellant submitted a new main request and auxiliary requests I to VIII and additional arguments concerning the requirements of Articles 84 and 123(2) EPC.

Oral proceedings were held on 14 April 2010 in the absence of the Appellant.

IV. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request or one of auxiliary requests I to VIII all filed with its letter filed 12 April 2010.

V. Claim 1 of Appellant's main requests read as follows:

"A medical agent comprising on average 1.5 to 4 reagents conjugated to an anti-CD20 antibody or variants thereof, wherein each reagent is 3-(13'-thioureabenzyl-(DOTA)trioxadiamine-1-(13''-biotin-Asp-OH)trioxamine-5-isothio-cyanato-aminoisophtalate, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, ibritumomab and tositumomab, and wherein the variant is an $F(ab')_2$, F(ab') or F(ab) fragment of said anti-CD20 antibody."

Claim 1 of auxiliary request I differed from claim 1 of the main request in so far as it referred to a medical agent comprising on average **1.5 to 3.5** reagents as defined in claim 1 of the main request.

Claim 1 of auxiliary request II differed from claim 1 of the main request in that it did not refer to variants of the anti-CD20 antibody.

Claim 1 of auxiliary request III differed from claim 1 of the main request in so far as it referred to a medical agent comprising on average **1.5 to 3.5** reagents as defined in claim 1 of the main request and that it did not refer to variants of the anti-CD20 antibody.

Claim 1 of auxiliary request IV differed from claim 1 of the main request in that the anti-CD20 antibody was defined as being rituximab.

Claim 1 of auxiliary request V differed from claim 1 of the main request in so far as it referred to a medical agent comprising on average **1.5 to 3.5** reagents as defined in claim 1 of the main request and that the anti-CD20 antibody was defined as being rituximab.

Claim 1 of auxiliary request VI differed from claim 1 of the main request in so far as the anti-CD20 antibody was defined as being rituximab and that it did not refer to variants of the anti-CD20 antibody.

Claim 1 of auxiliary request VII differed from claim 1 of the main request in so far as it referred to a medical agent comprising on average **1.5 to 3.5** reagents

as defined in claim 1 of the main request, that the anti-CD20 antibody was defined as being rituximab and that it did not refer to variants of the anti-CD20 antibody.

Dependent claim 2 of auxiliary request VII referred to a preferred embodiment of the medical agent of claim 1, claim 3 referred to a kit comprising the medical agent of claims 1 or 2.

Auxiliary request VIII consisted of one claim only which was identical to claim 1 of auxiliary request VII.

VI. The following documents are referred to in this decision:

(1) WO 00/02050

(2) US 2001/0023288

(5) WO 00/09160

(6) WO 01/80884

VII. The submissions made by the Appellant in writing, as far as they are relevant to the present decision, may be summarised as follows:

Article 123(2) EPC

The range "1.5 to 4 reagents" was based on a fusion of the two ranges 1.5 to 3.5 and 3 to 4 which were disclosed on pages 42, lines 3 to 7 and page 47,

lines 10 to 13, respectively, of the application as published.

Ibritumomab and tositumomab were stated to be effective as anti-lymphoma antibody in the claimed medical agent on page 42, lines 10 to 11 of the application as published.

$F(ab')_2$, F(ab') and F(ab) of CD-20 antibodies were disclosed in claim 5 of the application as published.

Article 56 EPC

Documents (D1) and (D2) disclosed trifunctional structures which were coupled via linkers to an "effector agent", an "affinity ligand" and to a "biomolecule reactive moiety". These structures were similar to the reagents conjugated to the anti CD-20 antibody (acting as the "biomolecule reactive moiety") in the medical agent of claim 1. Documents (D5) and (D6) disclosed the use of radiolabelled anti-CD20 antibodies for the treatment of tumours. None of these documents contained any hint that several trifunctional reagents could be bound to only one anti-CD20 antibody which led to the advantageous possibility to administer higher doses of the "effector agent" to a patient. Therefore, the claimed subject-matter involved an inventive step and met the requirements of Article 56 EPC.

Reasons for the Decision

Main request

1. Claim 1 refers to "a medical agent comprising on average **1.5 to 4** reagents conjugated to an anti-CD20 antibody or variants thereof" (emphasis added by the Board).

2. The Appellant argued that the requirements of Article 123(2) EPC were met, as the range 1.5 to 4 was based on a fusion of two ranges, namely 1.5 to 3.5 and 3 to 4, which were disclosed on page 42, lines 3 to 7 and page 47, lines 10 to 13, respectively, of the application as published.

3. Page 42, lines 3 to 7 of the application as published read:

"In the very most preferred embodiment, the rituximab conjugate contains 1.5 - 3.5 groups of 3-(13'-thioureabenzyl-(DOTA)trioxadiamine-1-(13''-biotin-Asp-OH)trioxamine-5-isothio-cyanato-aminoisophtalate".

The Board agrees that this passage clearly and unambiguously discloses medical agents containing 1.5 groups of the reagent specified in claim 1, which hereinafter is referred to as MitrTag-1033, conjugated to the anti-CD20 antibody rituximab.

4. Page 47, lines 10 to 13 forms part of example 5 of the application, starting on page 45. The example studies the influence of the conjugation process on the binding affinity of rituximab to the target antigen CD20 by

utilising a competitive inhibition assay. The results are shown in table 1 on page 46 and discussed on page 47 of the application as published. The affinity of four different rituximab-1033 conjugates, containing 1.6, 2.4, 3.4 and 4.6 groups of 1033, respectively, is measured and it is found that "the affinity for the 3.4- and 4.6-1033-riuximab conjugates is probably still high enough to obtain a proper tumour uptake". It is then stated that this assumption has been confirmed by clinical studies. This statement is immediately followed by the sentence which the Appellant considers as basis for the upper limit of the range in claim 1, which sentence reads:

"Therefore, it was concluded that conjugation of Rituximab with up to 3-4 conjugates per antibody would not diminish the binding properties of the antibody *in vivo*".

This sentence does not clearly and unambiguously disclose a medical agent according to claim 1 comprising four groups of MitraTag-1033 conjugated to rituximab. Rather it expresses an assumption based in part on the results of example 5 (shown in table 1, wherein reference is made to rituximab conjugates containing 1.6, 2.4, 3.4 and 4.6 groups of MitraTag-1033, respectively) and in part on separate (unidentified) clinical studies.

5. Accordingly, the Board arrives at the decision that the upper limit of the range indicated in claim 1 has no basis in the application as published. Thus, the main request does not meet the requirements of Article 123(2) EPC.

Auxiliary request I

6. Claim 1 refers to "a medical agent comprising on average **1.5 to 3.5** reagents conjugated to an anti-CD20 antibody or variants thereof" (emphasis added by the Board).

The indicated range is based on the disclosure on page 42, lines 3 to 7 of the application as published (see point (4) above).

7. The "anti-CD20 antibody or variants thereof" are defined at the end of claim 1 as follows:

"..., wherein the anti-CD20 antibody is selected from the group consisting of rituximab, ibritumomab and tositumomab, and wherein the variant is an $F(ab')_2$, F(ab') or F(ab) fragment of said anti-CD20 antibody."

8. As already shown with regard to the main request (see point (4) above), the only disclosure of the range 1.5 to 3.5 can be found on page 42, lines 3 to 7 of the application as published which refers to the "very most preferred embodiment" of the application which is a rituximab MitraTag-1033 conjugate.

9. The Applicant argued that the requirements of Article 123(2) EPC were met, as the antibodies ibritumomab and tositumomab were referred to on page 42, lines 10 to 11 of the application as published where it was said that they were "also effective as anti-lymphoma antibody in the medical agent". Moreover, $F(ab')_2$, F(ab') and F(ab) antibody fragments were disclosed in claim 5 of the application as published.

10. Since neither original claim 5 nor the citation on page 42, lines 10 to 11 refers to the range of 1.5 to 3.5 reagents conjugated to an anti-CD20 antibody, which feature is exclusively disclosed in connection with a rituximab MitraTag-1033 conjugate, claim 1 of auxiliary request I defines an intermediate generalisation of what is disclosed in the application as published, without there being a basis for this intermediate generalisation.

Therefore, auxiliary request I does not meet the requirements of Article 123(2) EPC.

Auxiliary requests II to VI

11. The decision taken by the Board with regard to the main request (see points (1) to (5) above) applies also to auxiliary requests II, IV and VI (see the respective claim 1).

The decision taken by the Board with regard to auxiliary request I (see points (6) to (10) above) applies also to auxiliary requests II, III, IV and V (see the respective claim 1).

Consequently, these auxiliary requests also do not meet the requirements of Article 123(2) EPC.

Auxiliary request VII

12. Claim 1 refers to "a medical agent comprising on average **1.5 to 3.5** reagents conjugated to an anti-CD20

antibody", wherein the reagent is MitraTag-1033 and the anti-CD20 antibody is rituximab.

The claim is based on page 42, lines 3 to 7 of the application as published (see point (3) above).

Claim 2 is based on claim 13 and page 42, lines 1 to 3, claim 3 is based on claim 34 of the application as published.

Auxiliary request VII meets the requirements of Article 123(2) EPC.

13. Claims 1 to 3 are clear and supported by the description and meet the requirements of Article 84 EPC.

14. Novelty of the claimed subject-matter was not objected to by the Examining Division in the decision under appeal. The Board also has no objection in this respect and finds that the subject-matter of claims 1 to 3 is novel over the disclosure in the prior art documents on file (Article 54 EPC).

15. The Board considers document (1) to represent the closest state of the art for the assessment of inventive step following the problem-and-solution approach.

Document (1) discloses a trifunctional reagent for diagnosis and treatment of tumours. Said reagent comprises a trifunctional linking moiety to which, via three linkers, an affinity ligand (for instance biotin), an effector agent (for instance a radionuclide binding moiety such as DOTA) and a biomolecule reactive moiety

(for instance a tumour binding monoclonal antibody) are coupled (see claims 1, 5 and 14 and page 5, lines 25 to 35). The reagent is administered to the blood circulation of a patient and reagent not attached to the target tissue or cells via the biomolecule reactive moiety is removed from the blood circulation by passing the blood through an affinity column absorbing the reagent by specific interaction with its affinity ligand.

16. In the light of this disclosure in document (1), the problem to be solved by the present application is considered to be the provision of a medical agent that allows the administration of higher doses of the effector agent with a view to treating the cancer disease more efficiently.

The medical agent according to claim 1 convincingly solves this problem by using rituximab, an anti-CD20 antibody as the "biomolecule reactive moiety", to which on average 1.5 to 3.5 reagents are coupled, each containing an affinity ligand (i.e. biotin) and an effector agent (i.e. DOTA). Despite the conjugation of up to 3.5 reagents to the antibody, its binding affinity to the target antigen CD20 was found to be high enough to obtain a proper tumour uptake in patients.

17. Neither document (1) itself, nor document (2), a published US patent application naming the same inventors as the present application, contain any information that would encourage a skilled person to modify the teaching of the closest prior art and to arrive at the claimed subject-matter in an obvious way.

Nor can such information be taken from document (5), which the Examining Division considered to represent the closest state of the art (see point (3.3) of the decision under appeal), or from document (6). These documents disclose the use of radiolabelled rituximab for the treatment of lymphoma (document (5), claims 1, 7 and 11; document (6), claims 19 and 20). They do not mention a trifunctional reagent containing an affinity ligand and accordingly do not envisage the possibility of conjugating more than one of such reagents to rituximab.

18. Therefore, the subject-matter of claims 1 to 3 of auxiliary request VII involves an inventive step and meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of claims 1 to 3 of auxiliary request VII filed on 12 April 2010 and a description and figures to be adapted thereto.

Registrar: Chairman:

P. Cremona C. Rennie-Smith