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D E C I S I O N
of 7 April 2005

Case Number: T 0877/03 - 3.3.4

Application Number: 96900937.2

Publication Number: 0805871

IPC: C12P 21/08

Language of the proceedings: EN

Title of invention:
Anti-CD30 antibodies preventing proteolytic cleavage and release of membrane-bound CD30 antigen

Patentee:
Roche Diagnostics GmbH

Opponent:
medac Gesellschaft für klinische Spezialpräparate mbH

Headword:
Anti-CD30 antibodies/ROCHE

Relevant legal provisions:
EPC Art. 54, 56, 83, 113(1), 123(2)(3)
EPC R. 88

Keyword:
"Added subject-matter (no)"
"Sufficiency of disclosure, novelty, inventive step (yes)"
"Violation of right to be heard (no)"

Decisions cited:
G 0011/91, G 0004/95, T 0019/90, T 0349/91, T 0585/92, T 0431/96

Catchword:
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Case Number: T 0877/03 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 7 April 2005

Appellant: (Proprietor of the patent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 28 March 2003 revoking European patent No. 0805871 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: M. Wieser
R. Moufang

Summary of Facts and Submissions

I. The appeal was lodged by the Patent Proprietors (Appellants) against the decision of the Opposition Division, whereby the European Patent No. 0 805 871 was revoked according to Article 102(1) EPC.

II. The patent has been granted with claims 1 to 10. Claims 1, 2 and 4 thereof read as follows:

"1. An antibody which binds to the CD30 antigen and

a) releases sCD30 from Hodgkin's disease cells to an amount of, or less than, 10%, referred to the release found without an addition of antibody;

b) does not bind to B cell non-Hodgkin's lymphomas or plasma cells in a manner which can be detected by immune precipitation.

2. Antibody according to claim 1, obtainable from cell line DSM ACC 2204.

4. Antibody according to claims 1 to 3, wherein the constant region of Ki-4 is modified in that part or all of the non-CD30 binding sequences of said antibody are replaced by the corresponding sequences from a human variable region."

Claim 3 referred to a preferred embodiment of the antibody of claims 1 or 2, claim 5 to the deposited cell line DSM ACC 2204. Claims 6 to 8 related to a method for producing the claimed antibody, claim 9 to the use of the antibody for the manufacture of a

therapeutic agent and claim 10 to a pharmaceutical composition containing the antibody.

III. The patent had been opposed by the Opponents (Respondents) under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), Article 100(b) EPC on the ground of lack of sufficient disclosure (Article 83 EPC) and Article 100(c) EPC on the ground of added subject-matter.

The Opposition Division decided that claims 1 to 10 of the only request before them, filed on 25 January 2001, did not involve an inventive step contrary to the requirements of Article 56 EPC. The claims were identical to claims 1 to 10 as granted, but for an amendment in claims 4 and 8, wherein the term "... the constant region of Ki-4 ..." has been amended to read "... the variable region of Ki-4 ...".

IV. The Board expressed their preliminary opinion in a communication dated 14 October 2004. In point (9) it was stated that Respondents' argumentation with regard to Article 83 EPC was not substantiated by experimental data, which were considered to be obtainable by carrying out routine experiments.

On 7 February 2005 the Respondents filed experimental data using the antibody obtainable from the deposited cell line DSM ACC 2204.

Oral proceedings were held on 7 April 2005.

V. The Appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 10 of the main request, or, alternatively, claims 1 to 6 of the first auxiliary request or claims 1 to 9 of the second auxiliary request or claims 1 to 7 of the third auxiliary request, all filed on 30 July 2003. Claims 1 to 10 of the main request were identical to claims 1 to 10 before the Opposition Division.

The Respondents requested that the appeal be dismissed, or, alternatively, that the proceedings be continued in writing.

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

(1) Blood, vol.74, no.5, 1989, pages 1678 to 1689

(2) Histopathology, vol.16, 1990, pages 409 to 413

(3) WO 91/07437

(4) The Lancet, vol.339, 1992, pages 1195 to 1196

(5) Annals of Oncology, vol.13, Supplement 1, 2002, pages 57 to 66

(6) Declaration of Dr Graziano, filed by the Respondents on 7 February 2005

VII. The submissions made by the Appellants as far as they are relevant for the present decision may be summarised as follows:

Omitting the limit of error of the conventional method of immune precipitation in claim 1 did not represent added subject-matter. The amendment of the term "constant" to "variable" in claims 4 and 8 was the correction of an obvious error according to Rule 88 EPC and did not contravene the requirements of Article 123 EPC.

The patent disclosed the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art as required in Article 83 EPC. The antibody obtainable from the deposited cell line had both characteristics as defined in items a) and b) of claim 1. Being in possession of this antibody a skilled person could have produced other antibodies having the same characteristics without undue burden.

An antibody having the technical feature of claim 1 a) was not disclosed in the prior art documents on file. The claims were therefore novel (Article 54 EPC). Contrary to what was stated in point (6.2) of the decision under appeal, the Appellants never had acknowledged that the antibody disclosed in document (1) had the feature of claim 1 a). From the fact that they had not contradicted this statement in their grounds for the appeal it could not be concluded that they agreed with it.

Starting from document (1) as representing the closest state of the art, the problem to be solved was to provide an improved pharmaceutically active compound for the treatment of Hodgkin's disease. The skilled

person could consider a plethora of possible strategies to achieve this goal. The one possibility chosen by the patent in suit, namely to find and use an antibody which decreases sCD30 shedding, could not be derived in an obvious way from the prior art documents on file. The claims therefore met the requirements of Article 56 EPC.

VIII. The submissions made by the Respondents as far as they are relevant for the present decision may be summarised as follows:

Contrary to the requirements of Article 123(2) EPC the application as originally filed did not contain a basis for a reference to the method of immune precipitation in claim 1 without indicating a limit of error of ≤5%. The amendment of claims 4 and 8 ("constant" to "variable") was not the correction of an obvious error as defined in Rule 88 EPC and thus violated Article 123(2) and 123(3) EPC.

As the Opposition Division had decided to revoke the patent, the burden of proof was shifted to the Appellants to demonstrate that the requirements of Article 83 EPC were met. These requirements were not fulfilled for two reasons. Firstly, the experimental data provided in document (6) proved that the antibody obtainable from the deposited cell line, which was the only antibody exemplified in the patent in suit, did not meet the requirement of claim 1 b). Secondly, the patent did not provide any disclosure extending beyond the preparation and analysis of the antibody obtainable by the deposited cell line. Generating other antibodies

having the same characteristics amounted to undue burden.

During the first instance procedure and in the written phase of the appeal procedure the issue of novelty of the claimed antibodies (Article 54 EPC) focussed on feature b) of claim 1. The Appellants, at oral proceedings before the Board of Appeal, for the first time argued that the claimed antibodies were novel over the disclosure in the prior art documents as those did not disclose an antibody having feature a) of claim 1. Up to that moment the Appellants had not contradicted the statement in point (6.2) of the decision under appeal wherein it was stated that the antibody disclosed in document (1) had feature a) of claim 1. The Respondents at oral proceedings were not prepared to argue against this "new case" resulting from a shifted line of argumentation. Therefore their right to be heard according to Article 113(1) EPC would be violated unless the procedure was continued in writing.

The reduction of sCD30 shedding was an obvious desideratum from a clinical view. A skilled person knowing the antibody disclosed in document (1) and looking for an antibody effecting a stronger reduction of the release of sCD30 from Hodgkin's disease cells would immediately have known how to achieve this goal, namely by producing monoclonal antibodies as described in document (1) and screening for the desired characteristic. The subject-matter of claims 1 to 10 did not involve an inventive step (Article 56 EPC), this all the more as clinical trials performed seven years after the priority date of the patent in suit (document (5)) did not show that the claimed antibodies

performed any better than the antibody disclosed in document (1).

Reasons for the Decision

Main Request

Added subject-matter and extension of protection
Article 123(2) and 123(3) EPC

1. Feature b) of claim 1 requires that the antibodies according to the invention do not bind to B-cell non Hodgkin's lymphomas or plasma cells in a manner which can be detected by immune precipitation.

According to page 3, third paragraph of the application as originally filed, the term "do not bind to a considerable extent", which was contained in claim 1 as originally filed, means that a binding cannot be detected by conventional methods. Immune precipitation is named as being customarily applied to determine such binding. It is moreover mentioned that the conventional limit of error in immune precipitation is about ≤ 5%. The description goes on to say that the term "do not bind to a considerable extent" means that a binding is not detectable by applying the conventional methods of immune precipitation having a limit of error of ≤ 5%.

2. It belongs to the common general knowledge of a person skilled in the relevant field of biochemistry that analytical methods have a limit of error. The reader of the patent in suit knows from the disclosure on page 3, that the detection of binding between an anti-CD30

antibody and B-cell non Hodgkin's lymphomas or plasma cells when determined by immune precipitation can be considered as being a reliable, true positive result only when it lies above 5%.

3. Thus, as the limit of error of ≤ 5% is an inherent feature of the conventional method of immune precipitation, the Board comes to the conclusion that the omission of the explicit mentioning of this error limit in claim 1 does not represent an amendment extending beyond the content of the application as filed.

4. The term "constant" in claims 4 and 8 as granted has been replaced during opposition procedure by the term "variable". While the Appellants consider this to be the correction of an obvious error according to Rule 88 EPC, the Respondents argue that the requirements of Article 123(2) and 123(3) EPC have been violated.

In order for correction under Rule 88 EPC to be allowable it must be obvious that there is an error and that it is immediately evident that nothing else would have been intended than what is offered as the correction.

5. Page 7, fifth paragraph, of the application as filed refers to antibodies wherein the **constant** region of Ki-4 is modified in that part or all of the non-CD30 binding sequences of said antibody are replaced by the corresponding sequences from human variable regions. This formulation is also used in claims 4 and 8 as granted. The description as filed continues to say that such antibodies are, for example chimeric or humanized

(CDR-grafted) antibodies, usually manufactured from a rodent monoclonal antibody.

It belongs to the general knowledge of a person skilled in the field of immunology that an antibody consists of two heavy and two light chains each comprising a constant and a variable region. The variable region of each chain comprises three hypervariable regions, the so called CDRs (Complementarity Determining Regions) which are the actual antigen-binding regions and which are embedded in the so-called framework regions. In order to reduce the antigenicity of mouse derived monoclonal antibodies when used in humans, methods have been developed wherein the non antigen-binding parts of the variable region of a mouse antibody, namely the framework regions, either partly or entirely, have been replaced by corresponding sequences from a human variable region. References to prior art documents disclosing these methods are given on page 7, lines 23 to 24 of the application as filed.

6. The Board concludes that the use of the term "constant" in claims 4 and 8 as granted will immediately be identified by a skilled reader as an error, whose correction to "variable" lies within the limits of what he/she would derive directly and unambiguously, using common knowledge, and seen objectively and relative to the date of filing, from the application as originally filed.

7. In the decision G 11/91 (OJ EPO 1993, 125) the Enlarged Board of Appeal stated that such a correction is of a strictly declaratory nature and thus does not infringe the prohibition of extension under Article 123(2) EPC.

8. If allowable, a correction under Rule 88 EPC has retrospective effect (see decisions J 4/85, OJ EPO 1986, 205, and T 219/86, OJ EPO 1988, 254). In other words it must be assumed (as a legal fiction) that the corrected text was in fact the text as originally filed.

In the light of the case law, establishing that corrections allowable under Rule 88 EPC are of strictly declaratory nature having retrospective effect, such corrections do not contravene the requirements of Article 123(3) EPC.

Sufficiency of disclosure - Article 83 EPC

9. The Respondents argue that according to the legal practice of the EPO the burden of proof in opposition proceedings with regard to the question of sufficiency of disclosure shifts from the Opponents to the Patent Proprietors when the Opposition Division has decided to revoke the patent. They refer to decision T 585/92 of 9 February 1995 and plead that the Board, in its communication of 14 October 2004, has disregarded this legal principle.

10. In the present case the Opposition Division decided that claims 1 to 10 before them, which were identical to Appellants' actual main request, met the requirements of Article 83 EPC (cf point (4.3) of the decision under appeal).

11. Therefore, the Board does not accept that the burden of proof with regard to sufficiency of disclosure (Article 83 EPC) is shifted to the Appellants (Patent

Proprietors), and holds that this burden remains resting on the Respondents' (Opponents') shoulders.

12. The Board considers that the conclusion drawn in point (3.2) of decision T 585/92 cannot be applied in the present case as the circumstances are fundamentally different. In the case underlying decision T 585/92 the Opposition Division has decided that the requirements of Article 83 EPC were not met by Appellant's (Patent Proprietor's) main request, as the description of the patent disclosed six examples of the claimed compositions, while it gave little or no guidance how to select other compositions lying within the broad ambit of the claimed subject-matter (cf point (3.1) of the reasons). The Board in decision T 585/92 found that the burden of proof is shifted to the proprietor of the patent to demonstrate on appeal that the reasons for revoking the patent under Article 83 EPC were not justified.

13. Claim 1 refers to an antibody characterised by the two functional features defined in items a) and b). Claim 2 relates to an antibody according to claim 1, obtainable from the deposited cell line DSM ACC 2204. This is the only antibody exemplified in the patent in suit.

Feature b) of claim 1 requires that the claimed antibody does not bind to B cell non-Hodgkin's lymphomas or plasma cells in a manner which can be detected by immune precipitation. The Appellants contended that this "non-binding" results from the fact that the CD30 antigen, which is the specific target of the claimed antibodies, is not present on said cells. Thus, when considering that the claim is directed to an

anti-CD30 antibody, the feature required in item b) is a matter of course and could be seen as an "over-definition" of the claimed subject-matter.

14. Nonetheless the respondents argued that the antibody obtainable by the deposited cell line does not meet the criteria as set out in claim 1 b) and that the invention therefore is not disclosed in a manner sufficiently clear and complete for it to be carried out by a skilled person.

To substantiate their argument they provided experimental data as part of document (6), which was filed two month before oral proceedings. The Board, exercising its discretion under Article 114 EPC, decides to allow document (6) and the experimental data contained therein, into the proceedings. The Appellants did not object to this.

15. Document (6) reports the results of a series of experiments examining the binding of the antibody Ber-H2, which is disclosed in document (1), and Ki-4, the antibody obtainable from the deposited cell line DSM ACC 2204 according to claim 2 of the patent in suit, to various cells. The binding was studied by flow cytometry using fluorescence activated cell sorting (FACS analysis) using Hodgkin's disease cell line L540, three B-cell non-Hodgkin's lymphoma (NHL) cell lines and isolated human plasma cells. In FACS analysis the cells are mixed with an antibody carrying a detectable label and the number of cells carrying the label is determined. This method, which is different from immune precipitation as required in claim 1 b), has been chosen accordingly by the Respondents as it is

routinely performed in their laboratory and the experiments had to be carried out under high time pressure.

16. Description sheets of the three NHL cell lines used in the tests, namely GRANTA-519, KARPAS-1106P and SU-DHL-4, are annexed to document (6). Two thereof, KARPAS-1106P and SU-DHL-4, are described as being CD30-negative. The third cell line, GRANTA-519, is described as being indifferent with regard to the presence of the CD30 antigen. According to the Respondents this has to be interpreted such that the CD30 antigen is present on GRANTA-519 cells from time to time depending on the circumstances, which due to the fact that it is a cancer cell line, are not always precisely predictable.

The results of two independent binding experiments are shown in figures 1 and 2 and tables 1 and 2 of document (6). In both experiments the CD30 specific antibodies Ber-H2 and Ki-4 bound strongly to the Hodgkin's disease cell line L540. The two antibodies failed to bind to one of the three NHL cell lines (SU-DHl-4) in both experiments. In the first experiment both antibodies showed very low binding to GRANTA-519 and no binding to KARPAS-1106P, in the second experiment both antibodies showed the opposite binding behaviour, namely very low binding to KARPAS-1106P and no binding to GRANTA-519. The geometric mean fluorescent intensity (geo MFI) measured for the binding of the antibodies to NHL cell lines lies between 1,7% and 3,8% of the Geo MFI values measured for the binding with the Hodgkin's disease cell line L540, as can be calculated from the values indicated in tables 1 and 2 of document (6).

17. In a further set of tests (points (9) to (10) of document (6)) FACS analysis was performed with human plasma cells, using a different experimental set up. Figure 4A shows that approximately 2% of cells were Ber-H2+, figure 4B shows that approximately 5% of cells were Ki-4+. The penultimate sentence on page 3 of document (6) reads: "The 2-5% of cells reacting with Ber-H2 or Ki-4 is a level of binding that is within experimental error and thus this binding may or may not be true binding".

18. In summary, the examples rely on an analytical method different from the one required in claim 1 b). This method, FACS analysis, is described on page 3 of document (6) as having a limit of error which does not allow to determine if binding of 2-5% of cells to an antibody represents true binding or not. The results of binding experiments with three NHL cell lines according to tables 1 and 2 show that both, the antibody of the patent in suit and the antibody disclosed in document (1), in each of two independent experiments showed very low levels of binding to a different NHL cell line to which they did not bind in the other experiment. In none of these cases of very low level binding the measured Geo MFI, which corresponds to the number of cells carrying the labelled antibody, was higher than 3,8% of the Geo MFI measured as a result of the binding of the antibodies to the Hodgkin's disease cell line L540.

19. The Board, considering that feature b) of claim 1 requires that the claimed antibody does not bind to NHL cell lines or plasma cells in a manner which can be detected by an analytical method which is known and

described in the patent to have a limit of error of ≤ 5%, does not see that the experiments described in document (6) prove that Ki-4 obtainable from cell line DSM ACC 2204, the only antibody exemplified in the patent in suit, does not have this feature formulated in negative terms.

20. According to a second line of argumentation, the Respondents pleaded that the breadth of claim 1 was based on the assumption only that the method of generating and screening antibodies could be repeated without undue burden by one of ordinary skill in the art. The patent did not provide any disclosure extending beyond the preparation and analysis of Ki-4. They argued that one could not prepare other antibodies, besides Ki-4, which meet the requirements of claim 1 without undue burden, which contravened the requirements of Article 83 EPC.

21. Reference was made to decision T 349/91 of 10 March 1993, dealing with the question if a patent which discloses for the first time the existence of an antigenic determinant on 180kD CEA (carcinoembryonic antigen), not shared by other components of CEA, and moreover discloses an antibody (Mab 3d) specific for this epitope, is entitled or not to claim any monoclonal antibody having this property. In this case the competent Board came to the conclusion that a skilled person when trying to find antibodies corresponding to the one obtainable from a deposited cell line would have to carry out substantially the same laborious screening process as described in the patent under consideration, which is equivalent to the

exercise of inventive ingenuity (cf T 349/91, point (5) of the reasons).

22. The present Board notes that the patent being the subject of decision T 349/91 has the priority date 21 November 1979 which is only four years after Köhler and Milstein in 1975 published the results of their pioneer work concerning the production of monoclonal antibodies by using the hybridoma technique. The patent referred to in decision T 349/91 can therefore be attributed to an early phase of this technology. This is also acknowledged in the first sentence of point (5) of the reasons of decision T 349/91.

23. The patent in suit claims the priority date 18 January 1995, which is more than sixteen years later.

The technique for the production and screening of hybridomas secreting a monoclonal antibody with specific, desired features has been developed in the meantime and consists basically of a sequence of widely known routine technical steps where all that is normally called for is perseverance. As the claimed monoclonal antibody is characterised by its ability to bind the CD30 antigen and to reduce shedding of sCD30 from Hodgkin's disease cells, thus by features readily testable in an assay, the skilled person seeking to reproduce the invention and to produce antibodies different from Ki-4 having the features required by claim 1, will have to produce monoclonal antibodies by routine methods and test them singly in an assay. This may possibly involve some tedious and time-consuming work, but nothing out of the ordinary since the techniques for the production and selection of

hybridomas were common routine techniques at the priority date of the patent in suit.

In decision T 431/96 of 23 February 1999 this Board in a different composition has come to the same conclusion when considering a patent with a priority date of 17 March 1983 (cf point (6) of the reasons).

24. The objection based on lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts. The mere fact that a claim is broad is not in itself a ground for considering the patent as not complying with the requirement of sufficient disclosure under Article 83 EPC (cf decision T 19/90 OJ EPO 1990, 476, point (3.3) of the reasons).

25. As no such verifiable facts leading to serious doubts are identified by the Board in the present case, the requirements of Article 83 EPC are met.

Novelty - Article 54 EPC

26. According to claim 1 a), the antibody when added to Hodgkin's disease cells reduces the release of sCD30 from Hodgkin's disease cells to an amount of, or less than 10%, when compared with release without an addition of antibody.

It is acknowledged on page 18, end of second full paragraph of the application as filed, that Ber-H2, the monoclonal antibody (mAb) disclosed in document (1), inhibits the release of sCD30 from L540 cells. However, it is mentioned that the reduction of sCD30 by mAb Ki-4

seemed reproducibly slightly stronger than that induced by Ber-H2.

According to page 3, lines 4 to 11 of the patent in suit (corresponding to page 3, lines 7 to 15 of the application as filed), it was found that, using the antibodies according to the invention, the release of sCD30 from Hodgkin's disease cells could be reduced to 10% or less, as tested by a method known in the art. It was found that up to 16 hours the shedding was nearly completely inhibited, i.e. less than 1%,. Thereafter, the amount of sCD30 could increase to maximally 10% compared to that of untreated control cells.

Neither document (1) nor any other cited document discloses that one of the antibodies described therein has the technical feature of claim 1 a), namely reduction of sCD30 shedding to a value of or less than 10%, referred to shedding found without addition of the antibody.

Thus, claim 1, and in consequence claims 2 to 10, are novel and meet the requirements of Article 54 EPC.

27. The Respondents objected that the Appellants for the first time at oral proceedings argued in favour of novelty of claim 1 on the basis of feature 1 a), and requested that the procedure shall be continued in writing as their right to be heard (Article 113(1) EPC) otherwise would be violated (see section (IX) above).

28. The substantive submissions of the Appellants during opposition procedure, where no oral proceedings were held, and the written phase of the appeal procedure

consist of two letters, the first one from 22 January 2001 (pages 1 to 4), the second one from 30 July 2003 (pages 1 to 2). Nowhere in these two short letters a statement can be found that the Appellants acknowledge that Ber-H2, the antibody of document (1) meets the requirement of claim 1 a), as declared in point (6.2) of the decision under appeal. This is not disputed by the Respondents, who, however, stated that the Appellants by not contradicting the statement of the Opposition Division, at least in their view, seemed to have accepted it.

29. The Board notes that the Appellants have not submitted new facts and/or evidence during appeal proceedings, except document (5), a post published article, which should prove the clinical superiority of the claimed antibody. The Board moreover notes that it is evident from the title of the patent in suit ("Anti-CD30 antibodies preventing proteolytic cleavage and release of membrane-bound CD 30 antigen") that the reduction of sCD30 shedding is a highly relevant feature of the underlying invention, and that it therefore cannot be regarded as surprising that the Appellants argue on the basis of this feature.

The Enlarged Board of Appeal decided in decision G 4/95 (OJ EPO 1996, 412) that arguments on the basis of previously submitted facts and evidence are allowed at any stage of opposition or opposition appeal proceedings, under the discretion of the EPO (cf point (4b) of the reasons).

30. Consequently, the Board, not seeing that Respondents' right to be heard has been violated contrary to the

requirements of Article 113(1) EPC by the new argument presented by the Appellants at oral proceedings, decides to reject the Respondents' request to continue the present procedure in writing.

Inventive step - Article 56 EPC

31. Document (1), describing the production and characterization of a mAb designated Ber-H2 directed against the CD30 antigen and having improved features for clinical use when compared with prior art mAb's (cf abstract), is considered to represent the closest state of the art.

32. In the light of the disclosure in document (1) the problem to be solved by the patent in suit is considered to be the provision of an improved pharmaceutically active compound for the treatment of Hodgkin's disease.

This problem is solved according to claim 1 by providing an anti-CD30 antibody which reduces shedding of sCD30 more effectively than prior art antibodies.

33. Shedding of sCD30 from the surface of Hodgkin's disease cells by proteolytic cleavage results in an elevated level of the soluble antigen in the sera of Hodgkin patients, which can be used as a diagnostic indicator of the severity and the clinical stage of the disease. However, as mentioned on page 1, fourth paragraph of the present application as filed, it weakens or even makes obsolete the pharmaceutical use of anti-CD30 antibodies, especially in the form of immunotoxins in

the treatment of Hodgkin's disease, as the antibodies bind to cell surface bound CD30 as well as to sCD30.

According to the Appellants this shortcoming can be overcome by the provision of a mAb specifically binding to an epitope of the CD30 antigen on the surface of Hodgkin's disease cells which at the same time masks the binding site of the protease responsible for shedding the antigen from the cell surface.

34. The Respondents argue that reduction of sCD30 shedding was an obvious desideratum from a clinical point of view at the priority date of the patent in suit. They refer to page 2, second paragraph of the application as filed, where reference is made to a workshop on "Leucocyte Differentiation Antigens" in Vienna 1989. The following sentences, from which it is not clear whether or not they refer to a disclosure made at said workshop, report of co-cultivation experiments by the inventors of L540 Hodgkin's lymphoma cell line, revealing that the release of sCD30 was most strongly increased by a prior art antibody designated Ki-1, while being strongly inhibited by the antibody Ber-H2.

The Respondents conclude that it was obvious for a skilled person how to perform in order to obtain antibodies having an even more increased ability to prevent sCD30 shedding. He/she would have produced anti-CD30 antibodies and would have screened for the desired property by using standard screening techniques. Both working steps, namely production of mAb's and screening procedures are standard processes and are described in document (1) (pages 1679 to 1680) and document (3) (example I).

35. The Board notes that a skilled person being confronted with the problem underlying the present invention at the claimed priority date was not in a one-way situation. On the contrary he/she could chose between different strategies possibly leading to the desired goal, namely obtaining an improved pharmaceutically active compound for the treatment of Hodgkin's disease. Increasing antigen specificity and/or sensitivity, eliminating unwanted residual cross-reactivity or targeting an epitope as close as possible at the cell membrane would have been some possible ways to proceed.

The Appellants chose a different way by providing an antibody with the ability to reduce sCD30 shedding more effectively.

36. Neither document (1) nor document (3), with the title "improved CD-30 antibodies and fragments thereof" mention sCD30 shedding and its detrimental role on treatment of Hodgkin's disease by mAb-immunotoxin conjugates . The same applies to documents (4), investigating the therapeutic role of an immunotoxin covalently linked to Ber-H2, and document (2), referring to the diagnostic significance of the CD30 antigen.

It is the patent in suit whose disclosure reveals that the reduction of sCD30 shedding would have a positive effect on immunotoxin treatment of Hodgkin's disease.

No document referring to the disclosure made at the workshop in Vienna in 1989, mentioned in point (34) above, is on file. Also in this respect it is the

patent in suit which for the first time reports of comparative experiments wherein the influence of different anti-CD30 mAb's on sCD30 shedding was investigated (page 18, second full paragraph, of the application as filed). Although the prior art mAb Ber-H2 (document (1)) was found to inhibit the release of sCD30 from L540 Hodgkin's disease cells, the reduction of sCD30 by mAb Ki-4, the antibody according to claim 2, seemed reproducibly slightly stronger than that included by Ber-H2.

37. The Board concludes that the subject-matter of claims 1 to 10 cannot be derived in an obvious way from the disclosure in the cited prior art documents, either if taken alone or in any combination.

38. Following a different line of argumentation, the Respondents argue that it has not been proven that the posed problem has been solved as the claimed antibody cannot be considered as being an improved pharmaceutically active compound for the treatment of Hodgkin's disease.

They refer to post-published document (5) from which they conclude that a Ber-H2 containing immunotoxin demonstrated a much higher efficacy for the treatment of Hodgkin's disease than an immunotoxin containing Ki-4 (page 59 and table 1).

Document (5) describes Ki-4.dgA (deglycosylated Ricin A-chain) as the most effective immunotoxin for the treatment of Hodgkin's disease and describes a clinical phase I trial in 17 patients in the passage bridging left and right column on page 59. In the following

paragraph a clinical trial in twelve patients with Ber-H2-Sap6 is described. Sap6 is a toxin derived from *Saponaria officinalis.* The results of the trials are shown in lines 4 and 5 of table 1.

The Board notes that document (5) discloses clinical trials with Hodgkin's disease patients, using two immunotoxins each containing a different toxin component, one containing the mAb according to claim 2, the other one the mAb of document (1). The document does not refer to shedding of sCD30 and does not mention that this may weaken or even make obsolete immunotoxin treatment of Hodgkin's disease.

The Board does not agree that it can be inferred from the teaching in document (5) that the problem underlying the patent in suit has not been solved.

39. In summary, the Board decides that claims 1 to 10 involve an inventive step and meet the requirements of Article 56 EPC.

Order

For these reasons it is decided:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent in amended form on the basis of the following documents:

   – Claims 1 to 10 of the main request filed on 30 July 2003.

   – Description: pages 2 to 3 and 5 to 13, line 7, as granted and amended page 4 as filed at the oral proceedings.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey