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D E C I S I O N
of 23 June 1998

Case Number: T 0512/94 - 3.3.4

Application Number: 80304350.4

Publication Number: 0030815

IPC: C12P 1/00

Language of the proceedings: EN

Title of invention:
Hybrid cell line for producing monoclonal antibody to a human prothymocyte antigen, antibody, method of preparation of this antibody, diagnostic and therapeutic uses, and pharmaceutical compositions comprising this antibody

Patentee:
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Opponent:
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Becton, Dickinson and Company
Boehringer Mannheim GmbH Patentabteilung

Headword:
Monoclonal antibody (OKT10)/ORTHO PHARMACEUTICAL CORPORATION

Relevant legal provisions:
EPC Art. 83, 56

Keyword:
"Sufficiency of disclosure (yes)"
"Inventive step (no)"

Decisions cited:
T 0418/89, T 0495/89, T 0510/94, T 0513/94

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0512/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 23 June 1998

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Decision under appeal: Decision of the Opposition Division of the European Patent Office posted 22 April 1994 rejecting the opposition filed against European patent No. 0 030 815 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 030 815 with the title " Hybrid cell line for producing monoclonal antibody to a human prothymocyte antigen, antibody, method of preparation of this antibody, diagnostic and therapeutic uses, and pharmaceutical compositions comprising this antibody" was granted with 19 claims based on European patent application No. 80 304 350.4

Claims 1, 7 and 9 as granted read as follows:

"1. Mouse monoclonal antibody which reacts with

(i) approximately 95% of normal human thymocytes,

(ii) 5% of normal human peripheral T cells.

(iii) 10% of E^- peripheral mononuclear cells, and

(iv) 10-20% of bone marrow cells."

"7. Mouse monoclonal antibody produced by hybridoma ATCC CRL 8022 (OKT10)."

"9. Hybridoma ATCC CRL 8022 (OKT10)."

II. Notices of opposition were filed by four parties. Revocation of the patent was requested on the grounds of Article 100(a) to 100(b) EPC (exceptions to patentability under Article 53(a) EPC, lack of novelty, lack of inventive step, insufficiency of disclosure).

III. By a decision within the meaning of Article 106(3)EPC dated 22 April 1994, the Opposition Division maintained the patent unamended according to Article 102(2) EPC.

IV. The Opposition Division considered that the requirements of Article 53(a) EPC were satisfied for the reason that the invention which did not relate to the human body or parts thereof and which was achieved by techniques which had long been in use in the field of medicine, would not be abhorrent to the public.

- With regard to sufficiency of disclosure (Article 83 EPC), it was determined that the growing of the deposited hybridoma did not amount to undue burden of experimentation.

  The percentages of reactivity of the claimed monoclonal antibody with the different cell types had to be understood as mean values. None of the documents used by the Opponents in order to show that this reactivity pattern was wrong were relevant because the values they presented were not mean values or had not been determined by the same protocol as in the patent in suit.

- Novelty (Article 54 EPC) was acknowledged in the absence of any prior art document disclosing a monoclonal antibody with all of the claimed characteristics.

- With regard to inventive step (Article 56 EPC), it was found that the properties of the monoclonal antibodies already known in the art were so different from the properties of the claimed antibody that it could not have been obvious that an antibody with the claimed properties could be produced.

V. The Appellants (Opponents 4) lodged an appeal against this decision, paid the fee and submitted a statement of grounds of appeal. Opponents 2 sent a letter in support of the arguments provided by the Appellants.

VI. The Respondents (Patentee) answered the Appellants' submissions.

VII. A communication was sent by the Board according to Article 11(2) EPC of the Rules of Procedure of the Boards of Appeal setting out the Board's provisional, non-binding opinion.

VIII. Further submissions were sent by both parties.

IX. Amongst the more than 200 documents on file, the following documents are mentioned in the present decision:

(3): Barnstable, C.J. et al., Cell, vol. 14, 1978, pages 9 to 20,

(5): Williams, A. et al., Cell, vol. 12, 1977, pages 663 to 673,

(6): McMichael, A.J. et al., Eur.J.Immun., vol. 9, 1979, pages 205 to 210,

(37): Köhler, G. and Milstein, C., Nature, vol. 256, 1975, pages 495 to 497,

(76): Leucocyte typing, Edited by Bernard et al., Springer-Verlag, 1984, page 9 to 60, 114 to 116.

(99)(V): EP-A-0 033 578

(148): Experimental report by the Appellants submitted with the letter dated 1 August 1991,

(205): Leucocyte typing III, Edited by McMichael A.J. et al., Oxford University Press, 1987, page 309,

(206): Leucocyte typing IV, Edited by Knapp W. et al., Oxford University Press, 1989, pages 86 and 1084,

(232): letter from the ATCC submitted by the Appellants with the grounds of appeal,

(233): Kung, P.C. and Goldstein G., Monoclonal antibodies and T cell hybridomas, page 7, filed by the Appellants with letter dated 25 May 1998,

(234): Goldstein G. et al., Monoclonal Antibodies and T cell Products, pages 71 to 80, filed by the Appellants with letter dated 25 Mai 1998,

(235): Excerpt of Leucocyte typing VI, page 151, filed by the Appellants with letter dated 25 May 1998,

(236): Talle, M.A. et al., Blood, vol. 66, No. 5, 1985 pages 1124 to 1132,

(237): Nagel, J.E. et al., Immunological Comm., Vol. 12(2), 1983, pages 223 to 237,

(238): Terhorst et al., Cell, Vol. 23, 1981, pages 771 to 780.

X. Oral proceedings were held on 23 June 1998, at which no representative of the Respondents was in attendance.

XI. The submissions in writing and during oral proceedings by the Appellants can be summarized as follows:

(a) The new documents (233) to (238) were filed as a reaction to what seemed to be the Board's position at oral proceedings in the parallel case T 0510/94

of 21 April 1998 that a convincing way to challenge the claimed reactivity pattern of a monoclonal antibody (MAb) was to submit evidence from published documents as independent experts' findings that this reactivity pattern was wrong. The filing of the documents had been done within the time limit set by the Board.

(b) The deposition of the OKT10 producing hybridoma had not been achieved in a proper way, as a special medium was necessary in which to grow it, to be able to obtain a sufficient quantity of the OKT10 antibody. This medium was not mentioned in the patent specification which led the skilled person to use another unsuitable medium.

(c) In claim 1, the monoclonal antibody was defined quantitatively as reacting with a certain percentage of cells in given cell subsets. The reactivity with thymocytes was expressed in relative terms (approximately 95%) while that with T cells or E-rosette negative cells was given in exact terms (5% and 10% respectively). This meant that the first percentage had to be understood within a margin of error and the last two had to be seen as fixed numbers, with the following consequences that:

- feature (ii) was incorrect since the patent specification showed that OKT10 reacted with less than 5% of E-rosette positive cells (Table 1) and that it did not react with T cells (Table II). Alternatively, document

(148) showed that OKT10 reacted with 30.1% of T cells. Furthermore, OKT10 had been found to react with activated T cells (document (238)), and

- feature (iii) was incorrect because documents (233) and 99(V) showed that OKT10 reacted with more than 10% of E-rosette negative cells i.e. 13%.

Further evidence of OKT10 reacting with more than 10% of E-rosette negative cells could be obtained by combining the teachings of documents (236) to (238). Document (236) (page 1127) disclosed that 10% to 15% of all lymphocytes were null cells and document (237)(Table II,) that 30% to 35% of all lymphocytes were E-rosette negative cells. As all null cells were E-rosette negative, it followed that 30% to 50% of E-rosette negative cells were null cells. In addition, document (236)(page 1128) showed that about 75% of null cells reacted with OKT10. This implied that about 20% to 30% of E-rosette negative cells (in the form of null cells) reacted with OKT10. Moreover, document (238) disclosed that OKT10 also reacted with 5% to 10% of B lymphocytes. Thus, OKT10 reacted in toto with 25% to 40% of E-rosette negative cells.

Finally, document (148) showed that OKT10 reacted with 61.6 % of CD3 negative cells comprising B cells and null cells.

(d) Document (205) presented a compilation of data involving monoclonal antibodies recognizing the same antigen (CD38) as OKT10. The reagents used were common to all groups. The cell purification was achieved in most laboratories by the same method of E-rosetting which was also the method used in the patent in suit. The data were mostly analysed by the same method. The results showed that the antibodies reacted with on average 15% of peripheral T cells and 22% of E-rosette negative cells. Furthermore, documents (234) and (235) showed that the CD38 antigen recognized by OKT10 was to be found on B cells. Thus, the definition of OKT10 as reacting with 5% of peripheral T cells and 10% of E-rosette negative cells had to be erroneous

(e) The facts of this case were analogous to those of decisions T 0418/89 (OJ EPO 1993, 20) and T 0495/89 (of 9 January 1991) where the patents were revoked as the claimed hybridoma could not be grown without undue burden of experimentation (T 0418/89) and the properties of the claimed specific antibodies did not correspond to the written description (T 0418/89 and T 0495/89).

(g) The closest prior art document was document (6) which disclosed the production by the technique of Köhler and Milstein (document (37)), using human thymocytes as immunogen, of a monoclonal antibody highly specific for human thymocytes (NA1/34). This antibody bound very weakly to a population of peripheral blood lymphocytes (Figure 3). It did not recognize T lymphocytes or bone marrow cells.

The problem to be solved was the production of another monoclonal antibody specific for thymocytes.

The solution provided was the claimed MAb. It was also obtained by the method of document (37). Its properties were not significantly different from those of NA 1/34. Thus, it could not be considered inventive.

XII. The Respondents replied essentially as follows:

(h) The newly filed documents (233) to (238) should not be allowed into the proceedings at so late a stage.

(i) The medium necessary to grow the OKT10 producing hybridoma was identified in the letter from ATCC accompanying the delivery of the hybridoma. The composition of this medium was part of the state of the art since 1978. Adding serum to the growth medium of hybridomas was also common practice. As for a different medium being disclosed in the patent, the skilled person would readily have recognized that the recommended medium was to be used for cell fusion, not for the culture of hybridomas. Alternatively, the hybridoma could always be grown in ascites.

(j) The reactivity of OKT10 with less than 5% of T cells as determined in the patent specification and with 13% of E-rosette negative cells as determined in document (233) or 99(V) were in accordance with the claimed reactivity pattern of 5% and 10% respectively, taking into account unavoidable experimental variations.

The protocol followed in document (148) to test the reactivity pattern of OKT10 with regard to T and B cells was flawed and, thus, no conclusion could be drawn that the reactivity pattern of OKT10 was not that described in the patent specification.

The fact that OKT10 had been shown in document (238) to react with activated T cells was irrelevant as the definition of the antibody of claim 1 did not comprise the reactivity pattern of OKT10 with activated T cells but with normal T cells.

In document (237), the reactivity pattern of OKT10 with T cell populations isolated by the rosetting technique was determined. It could not be seen as indicative of the ability of OKT10 to react with T cells as using the E-rosetting technique did not lead to pure T cell populations.

In document (236), the relationship of null cells to other cell subsets was studied. Yet, the number of E-rosette negative cells (null cells and B cells) was not given, which would have been indispensable to show that the reactivity pattern of OKT10 with E-rosette negative cells was not as claimed.

(k) Document (205) provided information on the average reactivity pattern of antibodies recognizing the same antigen as OKT10. This average reactivity pattern was in no way indicative of the reactivity pattern of a specific MAb like OKT10. A large number of laboratories participated in the tests.

No standardized procedure was used: the cell populations tested were not always isolated by the same protocols. The compilation of the results to arrive at the average reactivity pattern did not exclude stray values.

(l) The facts of this case were not at all analogous to those of the cases dealt with in decisions T 0418/89 and T 0495/89 (see supra) because there was no problem in growing the hybridoma and also because, in these latter cases, there existed post-published documents representing independent experts' findings which showed that the then claimed antibodies did not have the reactivity pattern to be expected from reading the patent.

(m) At the priority date of the application, the technique of making monoclonal antibodies was still very much in its infancy. It would not necessarily lead to a particular desired monoclonal antibody. Proof thereof could be found in document (3) which showed that the same protocol which led to the production of monoclonal antibodies against a specific antigen present on rat thymocytes and T cells using rat thymocytes membranes as immunogen (document (5)) did not lead to the isolation of monoclonal antibodies specific for human thymocytes using human thymocyte membranes as immunogen. In the same manner, although the avowed goal of document (6) had been defined as the production of monoclonal antibodies to subclasses of human T lymphocytes, the monoclonal antibody which was produced was specific for thymocytes.

The antibody (NA 1/34) disclosed in document (6) had a different reactivity pattern from that of the claimed antibody. Thus, the claimed antibody was not obvious.

XIII. The Appellants (Opponents 4) requested that the decision under appeal be set aside and that the European patent No. 0 030 815 be revoked.

The Respondents requested that the appeal be dismissed.

Reasons for the Decision

Late filing of documents

1. One of the grounds for the appeal is that the requirements of Article 83 EPC are not fulfilled, more specifically, that the reactivity pattern with T cells and E^- cells, of OKT10 as claimed in claim 7 and secreted by a hybridoma as claimed in claim 9 is different from that described in the patent specification and in claim 1. The Appellants filed six new documents in support of this ground of appeal only a month before the oral proceedings. It was explained that the necessity for filing them had only become evident after the oral proceedings and decision in the parallel case T 510/94 of 21 April 1998 made it likely that they could have a determining influence on the Board's decision in this case.

2. The documents deal directly or indirectly with the reactivity pattern of OKT10 with T cells or E-rosette negative cell populations. Their potential relevance to the assessment of whether OKT10 as deposited has the reactivity pattern defined in claim 1 cannot be ignored. The Board, thus, decides on the basis of Article 114(2) EPC to admit them into the proceedings.

Article 53(a) EPC

3. Opponent 2 raised objection under this Article at the opposition stage. He did not appeal. Nor did he attend oral proceedings before the Board of Appeal as a "party as of right" (Article 107 EPC). The Board agrees to the findings of the Opposition Division on the matter (see section IV above).

Article 83 EPC; claims 7 and 9

Deposition of the hybridoma

4. The Appellants argued that the written description of the patent specification was not sufficient for the skilled person to be able to reproduce the invention and that thus a deposition of the OKT10 producing hybridoma with a recognized depositary institution was necessary for sufficiency of disclosure. This deposition had not been achieved in the proper way as the medium in which to grow the hybridoma was not disclosed in the patent as filed and also because IL-6 needed to be added to the growth medium in order to make the monoclonal antibody in sufficient quantities.

5. The patent as filed teaches in example IB to multiply the hybridoma in ascites. Furthermore, when delivering the hybridoma upon request, the ATCC recommended a specific growth medium "because it had been published", supplemented with 20% fetal bovine serum (document (232)). Thus, there are two ways available to grow the deposited OKT10 hybridoma.

6. The objection that the hybridoma could not be grown in such a way that OKT10 could be obtained in sufficient quantities leaves entirely open, which purpose the quantities of OKT10 should be sufficient for. However, it should at least be possible to make the antibody in such quantities that its properties can be tested. It is apparent from document (148) that the Appellants themselves were able to test these properties; one of the preparations of OKT10 then used being produced in ascites. Thus, the impossibility of producing OKT10 "in sufficient quantities" by culturing the deposited hybridoma has not been proved in a convincing manner.

7. The Appellants submitted that because the patent taught that the RPMI 1640 medium was the medium suitable for cell fusion, the skilled person would have assumed that it was a proper growth medium as well, whereas, in fact, the hybridoma did not satisfactorily grow in RPMI 1640. This argument is not convincing since the depositary ATCC had given advice in which medium to grow said hybridoma.

8. Thus, the facts of this case are different from the ones dealt with in decision T 0418/89 (see supra) where there was evidence on file that the then claimed hybridoma could only be grown after repeated requests by many recipients had been made and by applying techniques considerably more sophisticated than those recommended by the depositary institution.

9. For all of these reasons, the Board sees no evidence that the hybridoma was not properly deposited.

The reactivity pattern of OKT10 secreted by the deposited hybridoma as disclosed in the state of the art

10. The hybridoma ATCC CRL 8022 which produces OKT10 was deposited for the purpose of ensuring that the claimed invention was adequately disclosed. OKT10, thus, should show the reactivity pattern defined in claim 1. In particular, it should react with *approximately 95%* of human thymocytes (feature i)), *5%* of T cells (feature ii) and *10%* of E-rosette negative peripheral mononuclear cells (feature iii)). The Appellants argued that, following the wording of the claim, the earlier figure had to be seen as somewhat variable, whereas the latter figures were to be seen as fixed numbers.

11. The Board would agree that the claim should be so understood if it was to be read in isolation, on a purely formal level. Yet, a claim should be read in the light of the description (Article 69(1) EPC). The description makes it clear that the invention is an antibody, the specificity of which is to human thymocytes (page 5 column 5, lines 1 to 4, page 10 column 16 lines 5 to 8). With regard to its reactivity pattern with other kinds of cells, it is stated on page 5, column 6, lines 5 to 10: "The antibody...**may** also exhibit the pattern of reactivity to peripheral T cells shown in Table 2" and, in the same manner on page 9, column 13 lines 60 to 64: " ..it appears that as the thymocyte is exported into the peripheral cell compartment, it loses the OKT10 marker since this antigen is lacking on **virtually** all T lymphocytes" (emphasis added). Furthermore, in Table 1, the reactivity pattern of OKT10 with T cells is given as less than 5%. Such statements and data will lead the

skilled person to the understanding that the reactivity pattern of OKT10 to cells other than thymocytes should be very low, but not that it should necessarily be identifiable by a fixed number. Besides, figures representative of a biological phenomenon such as the binding of OKT10 with T cells or E-rosette negative cells should never be understood as straight figures, seeing that experimental variability is technically unavoidable.

12. Accordingly, the argument by the Appellants that, since OKT10 was found to react with less than 5% of T cells (Table 1, patent in suit) and 13% of E rosette negative cells (documents (233) and 99(V)), it did not show the reactivity pattern given in claim 1 ii)(reactivity with 5% of T cells) and iii)(reactivity with 10% of E-rosette negative cells), is not convincing.

13. At oral proceedings, the Appellants also reasoned as follows with regard to the reactivity pattern of OKT10 with E-rosette negative cells:

- from document (236)(Figure 3, second vertical panel and page 1127), it could be calculated that OKT10 reacted with at least 6 to 9% of all peripheral E-rosette negative blood lymphocytes in the form of null cells, and

- from document (237)(Table IV), it could be deduced that 30% to 35% of all lymphocytes were E-rosette negative cells,

- from the combination of both documents, it could thus be concluded that OKT10 reacted with at least 20 to 30% of the E-rosette negative cells in the form of null cells.

Furthermore, document (238)(page 776) showed that OKT10 reacted with 5 to 10% of B lymphocytes. Accordingly, OKT10 reacted with 25 to 40% of E-rosette negative cells (null cells + B cells), which was not the reactivity pattern given in claim 1 (iii).

14. The Board, however, is not convinced that combining the results of documents (236) and (237) is meaningful. Document (237) is a study of the percentage of T cells present in peripheral blood cell populations from many different donors, where the T cells are identified by their ability to bind to OKT3. This percentage is found to be around 65% to 70%. Whether the remaining population, which does not bind OKT3, is entirely composed of E-rosette negative cells is not shown. There is, thus, no evidence that the E-rosette negative population makes up 35% to 30% of all cells present in the blood sample tested. Furthermore, document (237) discloses that the percentage of T cells differs depending on the blood sample tested. It is, thus, doubtful whether any estimation of the percentage of E-rosette negative cells in the blood samples tested in document (237) can be seen as a valid estimation of the percentage of E-rosette negative cells in the blood samples used in document (236). Accordingly, the above calculation fails and the conclusion cannot be reached that OKT10 reacts with 25% to 40% of E-rosette negative cells.

15. Finally, the fact that OKT10 reacts with activated T cells (document (238)) is not relevant for the reactivity pattern given in claim 1 (ii) which relates to the capacity of OKT10 to react with **normal** T cells.

Experimental report

16. Document (148) is an experimental report from the Appellants on the ability of OKT10 to bind to T cells and non-T cells. It was found that OKT10 bound to 30.1% of T cells and to 61.7% of non-T cells in a population of peripheral blood lymphocytes, when these two groups of cells are identified by their ability/inability to react with the monoclonal antibody OKT3.

17. The Board has difficulty in understanding how it can simultaneously be argued (see point XI c)) that OKT10 does not show the claimed reactivity pattern because it reacts with less than 5%, or with about 30.1% T cells, and with 13%, or 25 to 40%, or 61.7% of E-rosette negative cells. These mutually exclusive or widely differing results could possibly be explained by differences in the protocols used to obtain them. In this context, the Board remarks that the protocol used in document (148) is internally inconsistent. It is specified on page 3 that 100 µl of OKT10 were used which amounted to 10 µg of the antibody. Yet the concentrations of the three preparations of OKT10 which were then available were defined as 26 µg/ml, 53.5 µg/ml and 4.4 mg/ml. It is impossible that 100 µl of anyone of these preparations would contain 10 µg of the antibody. Uncertainty as to how much of the antibody was effectively used does not permit to draw the conclusion that the results of document (148) are meaningful and serve the purpose of showing that the reactivity of the deposited MAb is not as claimed.

The Leukocyte Typing Workshops

18. Documents (205), (206) and (235) contain excerpts of the post-published Leukocyte Workshops III, IV and VI. These workshops disclose studies on an international scale of monoclonal antibodies for the characterisation

of normal and malignant leukocyte populations. Their purpose was defined in the first volume in the series (Leukocyte Workshop; document (76)): a joint effort was to be made "to prevent that the rapidly increasing number of monoclonal antibodies being produced would result in a plethora of individual systems of nomenclature being adopted which "would create complete confusion and render impossible any coherent dialog...". Thus, the monoclonal antibodies were regrouped in clusters, the clusters being defined statistically, a monoclonal antibody being classified to one of the already delineated clusters if its distance to the furthest monoclonal antibody in the group was the least (passage bridging pages 29 and 30). Both parties agree that OKT10 falls within the CD38 cluster.

19. In document (205), it is disclosed that the monoclonal antibodies of the CD38 cluster recognize on average 15% of the peripheral T cells. In document (206), it is disclosed that the HB7 monoclonal antibody which is one of the antibody of this cluster binds to 31% of T cells. These results show that the average reactivity of the CD38 cluster is not necessarily representative of the reactivity of each antibody of the cluster taken on its own. Accordingly, as the reactivity pattern of OKT10 per se was not investigated in the Leukocytes Worshops, it is also not possible to draw the conclusion from these studies that OKT10 does not show the claimed reactivity pattern.

20. Documents (206) (page 1084), (234) (page 78) and (235)(page 151) also disclose that in addition to its main reactivity to thymocytes, plasma cells and activated T cells, OKT10 is capable of reacting with B cells at defined stages in their maturation. As the extent of this reactivity is not specified in documents

(206) and (234) or specified as being weak (document (235)), the disclosure of these post-published documents is no evidence that the reactivity pattern of OKT10 given in claim 1 (iii) is wrong.

21. In view of the findings in paragraphs 9 to 20 above, the Board decides that there is no insufficiency of disclosure with regard to the properties of the specific hybridoma and monoclonal antibody of claims 7 and 9. Because of this, claim 1 is also reproducible since claims 7 and 9 are embodiments thereof.

22. The requirements of Article 83 EPC are fulfilled.

Article 56 EPC

23. The closest prior art document is document (6) which discloses a monoclonal antibody NA1/34 which predominantly recognizes an antigen detectable on human thymocytes. Figure 3 shows the binding capacity of NA1/34 to peripheral blood lymphocytes or to bone marrow cells to be about 8% of its capacity to bind to thymocytes.

24. Starting from this prior art, the objective problem to be solved is the production of another monoclonal antibody specific for human thymocytes.

25. An antibody is provided in claim 1 which reacts with approximately 95% of thymocytes, 5% of T cells, 10% of E-rosette negative cells and 10 to 15 % of bone marrow cells. The binding capacity of this antibody to cells other than thymocytes is not so high that the antibody could not serve to distinguish the thymocytes from other types of cells. The problem has, thus, been solved.

26. The method used in the patent in suit for producing the antibody is as in document (6), that of Köhler and Millstein (document (37)), with the difference that the immunogen is human leukemic T-ALL cells rather than human thymocytes. This difference was never argued to impart inventive step on the monoclonal antibody per se. As for the properties of the claimed antibody, they are not different in any meaningful manner from those of NA1/34. The question which thus remains to be answered is whether the skilled person would have had a reasonable expectation that, when working according to the teachings of document (6), one could arrive at another MAb with similar or the same features.

27. In this context, the Respondents cited documents (3) and (5). Document (3) published in 1978 describes a failed attempt to produce monoclonal antibodies characteristics of specific antigens on human leukocytes, using human immunogens. Document (5) published in 1977 showed, on the contrary, that monoclonal antibodies specific for rat thymocytes and T cells could be isolated using rat thymocytes membranes as immunogens. According to the Respondents, these results would have been taken by the skilled person as indicative that success should not necessarily be expected while reproducing the experiment of producing monoclonal antibodies to specific antigens.

28. This argument, however, fails to take into account the difference between the present situation where it is known from document(6) that a monoclonal antibody as it is desired to be produced has already been obtained, and the situation at the time documents (3) and (5) were published, when there existed no state of the art describing the production of monoclonal antibodies to specific antigens on **human** leukocytes. In that latter case, it would be legitimate for the skilled person to

wonder if monoclonal antibodies to specific antigens on human leukocytes could be isolated at all. Yet, once a monoclonal antibody with essentially the same properties as desired had been isolated, the skilled person would consider the isolation of another equivalent antibody as reasonably feasible, if only by following the very same method.

29. In the parallel cases T 513/94 of 23 April 1998 and T 510/94 of 21 April 1998, inventive step was acknowledged to the monoclonal antibodies OKT3 and OKT5. Case T 513/94, however, dealt with the situation described in the paragraph 27 where the production of monoclonal antibodies to specific antigens of human peripheral blood lymphocytes or thymocytes had not yet been achieved at the priority date. At the priority date of the patent dealt with in case T 510/94, document (6) which as already stated describes the production of an antibody specific for thymocytes was already state of the art. Yet, no monoclonal antibodies specific of the T cells populations of peripheral blood lymphocytes had ever been obtained, let alone to a subgroup of this population, as was then the subject-matter of the patent in suit. The facts of the present case are therefore different from the facts of these two earlier cases in such a way that a different conclusion has to be drawn in terms of inventive step.

30. The Board concludes that the subject-matter of claim 1 lacks inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

A. Townend U. Kinkeldey