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**Datasheet for the decision
of 13 December 2007**

Case Number: T 0805/06 - 3.3.04

Application Number: 94929665.1

Publication Number: 0733643

IPC: C07K 14/435

Language of the proceedings: EN

Title of invention:

Membrane protein polypeptide having function of supporting
pre-B cell growth and gene therefor

Patentee:

HIRANO, Toshio

Opponent:

OXFORD GLYCOSCIENCES (UK) LTD

Headword:

Membrane protein/HIRANO TOSHIO

Relevant legal provisions:

EPC Art. 54(1), (2), (3) and (4)

Relevant legal provisions (EPC 1973):

EPC Art. 54(4) and (5), 83, 111(1)

Keyword:

"Main request (granted claims): novelty (yes)"

"Inventive step (yes)"

"Sufficiency of disclosure (yes)"

Decisions cited:

T 0301/87

Catchword:

-



Case Number: T 0805/06 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 13 December 2007

Appellant:
(Patent Proprietor)

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(Opponent)

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Decision under appeal:

Decision of the Opposition Division of the
European Patent Office posted 30 March 2006
revoking European patent No. 0733643 pursuant
to Article 102(1) EPC 1973.

Composition of the Board:

Chair: U. Kinkeldey
Members: R. Gramaglia
D. S. Rogers

Summary of Facts and Submissions

In this decision articles and implementing rules under the EPC 2000 will be referred to in the form "Article X EPC"; and articles and implementing rules under the EPC 1973 will be referred to in the form "Article X EPC", if the text of Article X is the same under both the EPC 1973 and the EPC 2000, or as "Article X EPC 1973", if the text of the article in the EPC 1973 differs from the text of the article in the EPC 2000.

- I. European Patent No. EP-B-0 733 643 (application No. 94 929 665.1) having the title "Membrane protein polypeptide having the function of supporting pre-B cell growth and gene therefor" was granted with the following 7 claims:

"1. A polypeptide containing an amino acid sequence shown in sequence No. 1 of the sequence table or a part of the amino acid sequence having the function of supporting pre-B cell growth."

"2. A DNA encoding a polypeptide containing an amino acid sequence shown in sequence No. 1 of the sequence table or a part of the amino acid sequence having the function of supporting pre-B cell growth."

"3. The DNA according to Claim 2, characterised by containing a base sequence which hybridizes the base sequence shown in sequence no. 2 of the sequence table or a base sequence derived from said base sequence having at least one amino acid residue substituted, removed or added partially, said base sequence encodes

an amino acid sequence having the function of supporting pre-B cell growth."

"4. A recombinant vector containing the DNA according to Claim 2 or 3."

"5. A prokaryotic or eukaryotic host cell, characterised by being transformed with the recombinant vector according to Claim 4."

"6. A method for producing the polypeptide containing an amino acid sequence shown in sequence No. 1 of the sequence table or a part of the amino acid sequence, characterised by culturing the host cell according to Claim 5."

"7. A monoclonal antibody recognising a polypeptide containing an amino acid sequence shown in sequence No. 1 of the sequence table or a part of the amino acid sequence having the function of supporting pre-B cell growth."

II. Notice of opposition was filed by the opponent requesting the revocation of the European patent on the grounds of Article 100(a) and (b) EPC on the grounds that the claims did not fulfil the requirements of Articles 54, 56 and 83 EPC 1973.

III. The opposition division revoked the patent. This decision was taken on the basis of the claims of the main request and of the first to third auxiliary requests then on file.

IV. The appellant (patentee) filed an appeal against the decision of the opposition division.

V. The board expressed its provisional opinion in a communication dated 22 October 2007.

VI. Oral proceedings were held on 13 December 2007.

VII. The following documents are cited in the present decision:

D1 Goto T. et al., Jpn. J. Clin. Immunol.,
Vol. 15(6), pages 688-691 (1992);

D1a English language translation of D1;

D2 Ohtomo T. et al., Biochem. Biophys. Res.
Comm., Vol. 258, pages 583-591 (1999);

D3 EP-A-0 997 152;

D4 Goto T. et al., Blood, Vol. 84(6), pages
1922-1930 (1994);

D5 EP-A-0 725 135.

VIII. The submissions by the appellant (patentee), insofar as they are relevant to the present decision, can be summarized as follows:

Main request

Novelty (Article 54 EPC)

Document D1

- Document D1 represented a non-enabling disclosure because the KPC32 and MHB cells were not available to the public and document D1 did not teach which cells had actually been used for performing the screening.

Document D5

- Even if the technique described in document D5 for selecting the hybridomas/antibodies involved the same immunogen as in the patent in suit, the screening method was different and led to a different hybridoma/antibody recognising a protein of 318 amino acids.

Inventive step (Article 56 EPC)

- The patent in suit was concerned with inhibition of pre-B cell proliferation by identifying a protein associated with pre-B cell proliferation. The approach taken by the authors of document D1 was that of identifying a protein associated terminal differentiation of B cells.

Sufficiency of disclosure (Article 83 EPC)

- The patent provided all the necessary information (see the test of paragraph [0097]) for the skilled person to carry out the invention.

IX. The submissions by the respondent (opponent), insofar as they are relevant to the present decision, can be summarized as follows:

Main request

Novelty (Article 54 EPC)

Document D1

- The subject-matter of present claims 1 and 7 lacked novelty in view of document D1.

- Document D1 indeed disclosed the "HM1.24 antigen" of molecular weight of approximately 30 kDa and antibody HM1.24 recognising this antigen.

- The "HM1.24 antigen" referred to in document D1 was the same (and thus inherently possessed the same amino acid sequence) as the polypeptide according to present claim 1 (hereafter: the BST2 antigen) having "the amino acid sequence SEQ ID No 1".

- The identity between the "HM1.24 antigen" (document D1) and the BST2 antigen (claim 1) could be derived from the following facts and evidence:
 - In post-published document D2, co-authored by the patentee/joint inventor of the patent in suit, it was admitted that the HM1.24 antigen was the bone marrow stromal cell antigen BST2 (see page 588, column 2, first full paragraph, in conjunction with Fig. 4).

 - It was also stated on page 5, lines 5-9 of later European patent application D3 that the HM1.24 antibody could be raised using as sensitising antigen a protein having the amino acid sequence set forth in SEQ ID NO. 1 of that document,

which was identical to SEQ ID NO. 1 of the patent in suit.

- On page 2, lines 36-37 of document D3, there was a cross-reference to later published document D4 dealing with the anti-HM1.24 antibody.
- Both document D2 (see paragraph bridging page 583 and page 584) and document D3 (see page 2, lines 36-37 and lines 51-54) referred to post-published document D4 as disclosing the HM1.24/BST2 antibody and antigen.
- The data presented in document D4 in relation to the HM1.24/BST2 antibody and antigen were identical to that disclosed in document D1 (compare Figure 1 of document D1 with Figure 1A of document D4 and Figure 2 on page 690 of document D1 with Figure 4A of document D4).
- The skilled person was in a position to perform the screening against the publicly available cell line RPMI 8226 in order to select an antibody having the binding profile shown in Fig. 2 of document D1 and/or having the capacity of precipitating a "broader band of MW30kD".

Document D5

- This document pursuant to Article 54(3) EPC disclosed a method for the generation of monoclonal antibodies using the synovial cell line SynSV6-14, the latter being identical to that used in the patent in suit to generate antibodies recognising

the BST2 antigen. Therefore, the skilled person following the instructions in document D5 would inevitably generate the same repertoire of hybridomas/antibodies, including a hybridoma expressing a monoclonal antibody that recognised the BST2 antigen.

Inventive step (Article 56 EPC)

- The features in present claim 1 "containing an amino acid sequence shown in sequence No. 1 of the sequence table" and "having the function of supporting pre-B cell growth" were inherent properties of the BST2 antigen disclosed in document D1. However, determining the amino acid sequence and activity of this protein did not involve any inventive step.

- An alternative obvious route to the claimed monoclonal antibody/BST2 antigen could be taken from document D1, namely using the publicly available RPMI 8286 cell as an immunogen and selecting an antibody binding to a 30 kDa protein. The antibody could be used for purifying the antigen.

Sufficiency of disclosure (Article 83 EPC)

- Claim 1 covered fragments of the polypeptide having the amino acid sequence defined by SEQ ID NO. 1 which had the function of supporting pre-B cell growth. However the patent gave no guidance as to how to modify the native sequence, or how to obtain fragments, all achieving the desired function.

- Nor did the patent provide any guidance as to how to select monoclonal antibodies according to claim 7 different from the exemplified antibody.
- X. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained as granted.

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

Reasons for the Decision

Main request

Novelty (Article 54(1)(2)(3) and (4) EPC; Article 54(4) and (5) EPC 1973)

1. The respondent maintains that the subject-matter of claims 1 and 7 lacks novelty in view of document D1, disclosing the "HM1.24 antigen" of molecular weight of approximately 30 kDa (see document D1a, page 6, end of first paragraph) and antibody HM1.24 recognising this antigen (ibidem, page 3, end of first paragraph).
2. For a prior publication to take away the novelty of a claim, according to the jurisprudence of the boards of appeal, the subject-matter of the claim must be clearly and unambiguously disclosed in the prior publication, and also in a manner which enabled the skilled person to carry it out. The question thus arises whether or not document D1 provided sufficient technical information for the skilled person to arrive, without

exercise of undue burden, at the "HM1.24 antigen" and monoclonal antibody HM1.24 recognising this antigen.

Enabling or non-enabling character of document D1 for the monoclonal antibody of claim 7

3. Many years after Köhler and Milstein's 1975 publication of the results of their pioneer work concerning the production of monoclonal antibodies by using the hybridoma technique, the production and screening of hybridomas secreting a monoclonal antibody with specific, desired features consisted basically of a sequence of widely known routine technical steps where all that was normally called for was perseverance. However, as transpires from the analysis below (see points 4 and 5 infra), the selection of the immunogen used to raise the antibodies as well as the screening method for selecting the hybridoma secreting a monoclonal antibody with a desired specificity still remained critical steps.

4. As regards the immunogen, the authors of document D1 (see document D1a, page 2, last full paragraph), used KPC32 and MHB cells. These were in-house cell lines established in the laboratory of the authors of document D1 (see document D4, page 1922, r-h column, under "Material and Methods"). Therefore, serious doubts arise as to public availability of the immunogen (i.e., the KPC32 and MHB cells) to the skilled person wishing to reproduce the teaching of document D1. The skilled person using cells other than KPC32 and MHB cells (possibly not bearing the "HM1.24 antigen" on their surface) would of course possibly miss the hybridoma/antibody ("HM1.24") looked for.

5. As for the screening method, this is a fundamental step allowing the selection of a hybridoma secreting a monoclonal antibody characterised by a well defined spectrum of binding activities from a great number of hybridomas. The authors of document D1 (see the passage bridging pages 2 and 3 of document D1a) indeed collected 248 hybridomas (termed "antibodies" in document D1a) and applied "FCM and an enzymatic antibody method" to various cell lines in order to arrive at the 4 kinds of antibodies (HM series) shown in Table 1 of document D1, of which antibody HM1.24 exhibited the highest specificity to unfixed plasma cells surface antigens (see page 3, lines 7-9 of document D1a).

However, the skilled person was not taught which specific cell(s) among the many possible cells (see *ibidem*: "peripheral blood cells, bone marrow cells, lymph nodes of normal individuals and hematopoietic tumor patients") have actually been selected for performing the screening. Moreover, the cells listed in Table 2 of document D1, taken from patients ("T.K.", "H.M.", etc) suffering from lymphoid malignancies, were also not available to the skilled person wishing to reproduce the teaching of document D1. Therefore, in the absence of the above critical information as to how the screening method had to be carried out, the skilled person was prevented from arriving at the four antibodies ("HM series") referred to in Table 1 of document D1, let alone isolating a monoclonal antibody designated HM1.24.

6. The respondent argues that the skilled person was in a position to perform the screening against the publicly available cell line RPMI 8226 in order to select an antibody having the binding profile shown in Fig. 2 of document D1 and/or having the capacity of precipitating a "broader band of MW30kD". However, while the RPMI 8226 cell line was publicly available from the Japanese Cancer Research Resources Bank (see document D4, page 1922, lines 13-14 from the heading "Materials and Methods"), in the board's view, the skilled person would have to establish a binding curve (7 different concentrations of ^{125}I -labeled free antibody in abscissa vs. the bound form) for each of the 248 hybridomas/antibodies referred to on page 2, line 3 (from the bottom) of document D1a, which borders on undue burden. This conclusion extends to the possibility of using the antibody's capacity of precipitating a "broader band of MW30kD", which would require that an autoradiography of immunoprecipitates (as shown in Fig. 5, lane 1 of document D4) be performed for each of the 248 hybridomas/antibodies.
7. Furthermore, binding to RPMI 8226 cells and/or precipitating a "broader band of MW30kD" were necessary but not sufficient conditions for arriving at monoclonal antibody HM1.24. This is shown by post-published document D4, cited by the respondent for questioning the novelty. On page 1924 of this document (see under "Results") it is stated that the screening for obtaining monoclonal antibody HM1.24 had to be made not only against RPMI 8226 cells but also against KPC-32, Raji, CEM and THP-1 cells. After this first screening, three hybridomas were selected for their specificity for plasma cells. Of the three, two antibodies

- (implicitly binding inter alia to RPMI 8226 cells) were discarded and only moab HM1.24 was retained for its best behaviour in cytometric analysis and its cytolytic activity against RPMI cells. The skilled person, however, could not derive all this critical information from document D1.
8. Finally, the board observes that the skilled person could not make use of hybridoma FERM BP-5233 producing monoclonal antibody HM 1.24 because this hybridoma had been deposited on 14 September 1995 (see document D3, page 6, lines 13-17), i.e., after the publication date of document D1 (1992) and after the priority date (15 October 1993) of the patent in suit.
9. In conclusion, the board considers document D1 as a non-enabling disclosure for the skilled person wishing to obtain monoclonal antibody HM1.24, which the respondent argues falls under the definition of present claim 7.

Enabling or non-enabling character of document D1 for the polypeptide of claim 1

10. As regards the antigen recognised by monoclonal antibody HM1.24, which the respondent argues falls under the definition of present claim 1, the only technical information which can be taken from document D1a is that "the antigens were immunoprecipitated by a lactoperoxidase method as a broader band of HM1.24 of MW30KD from dissolved RPMI8226 cells labeled with ¹²⁵I" (see document D1a, page 6, end of first paragraph). More details about this way to proceed are given in document D4, page 1924, r-h column, under

"Immunoprecipitation": the "broader band of HM1.24 of MW30KD" was the result of the following operations: (i) RPMI 8226 cells were surface-labeled with ^{125}I (which bound to any antigen on the cells' surface); (ii) the cells were solubilised; (iii) monoclonal antibody HM1.24 was added (whereby only the antigen recognized by this antibody could precipitate from the clear solution); (iv) a SDS-PAGE and an autoradiography were performed on the (re-dissolved) immunoprecipitate yielding an autoradiography as shown in Fig. 5, lane 1 of document D4.

11. The above steps (i) to (iv) show that the only route open to the skilled person towards the "broader band of HM1.24 of MW30KD" occurred via the obligatory monoclonal antibody HM1.24 (cf. step (iii)). This is because simply lysing RPMI 8226 cells (with or without ^{125}I -labeling), electrophoresing (SDS-PAGE) and taking from the gel a band around 30 kDa would have resulted in a preparation contaminated with a great number of proteins having a molecular weight around 30 kDa, but which failed to bind to monoclonal antibody HM1.24 and hence to undergo immunoprecipitation.
12. But since document D1 did not enable the skilled person to arrive at monoclonal antibody HM1.24 (see point 9 supra), the board must conclude that this document was also non-enabling for the skilled person wishing to isolate the "HM1.24 antigen" of molecular weight of approximately 30 kDa, which the respondent argues falls under the frame of present claim 1.

Document D5

13. In a different line of argument, the respondent maintains that the skilled person following the instructions in document D5, representing prior art pursuant to Article 54(3) EPC, would inevitably generate a hybridoma expressing a monoclonal antibody that recognised the BST2 antigen, given that the immunogen was the same in both document D5 and in the patent in suit.

14. The board agrees that document D5 discloses a method for the generation of monoclonal antibodies using the synovial cell line SynSV6-14 as an immunogen, the latter being identical to that used in the patent in suit to generate antibodies recognising the BST2 antigen (compare page 7, line 10 of document D5 with page 7, line 45 of the patent). It is also conceded that immunisation with the cell line SynSV6-14 as an immunogen would generate a great number of hybridomas (cf. the 248 hybridomas referred to in document D1) possibly including a hybridoma expressing a monoclonal antibody that recognises the BST2 antigen.

15. However, the idea that said collection of hybridomas/antibodies itself would anticipate an invention relating to a well defined hybridoma/antibody which may be contained therein somewhere, cannot be sustained. Rather, this well defined hybridoma/antibody would only become part of the state of the art if its existence had recognisably been made publicly available (see decision T 301/87, OJ 1990, 335, point 5.8 concerning a DNA contained somewhere in a cDNA gene bank).

16. As regards the question whether or not document D5 provides instructions as to how a hybridoma expressing a monoclonal antibody that recognises the BST2 antigen has to be isolated from said collection of hybridomas/antibodies, it is stated on page 8, lines 5 of this document that the clones were screened against RASV5-5 and NFSV-1 cells to yield hybridomas RF3 and SG2 (ibidem, page 7, line 49) secreting antibodies RF3 and SG2. The latter antibodies differ from the antibody referred to in present claim 7 because they recognise a protein of 318 amino acids (ibidem, page 10, line 22) which is clearly different from the 180 amino acid-long BST2 antigen of present claim 1 (see SEQ ID No 1). Accordingly, the above question about the teaching by document D5 of means for isolating the hybridoma/antibody against the BST2 antigen, has to be answered in the negative. Hence document D5 does not render publicly available this well defined hybridoma/antibody.
17. In view of the foregoing, the subject-matter of granted claims 1 to 7 is new in the sense of Article 54(1) EPC 1973.

Article 56 EPC

18. The question to be answered is whether or not the claimed subject-matter (including the polypeptide having the amino acid sequence defined by SEQ ID NO. 1 according to claim 1 and the monoclonal antibody according to claim 7) is obvious in the light of the prior art.

19. As emphasised under points 8 and 12 supra, following the instructions in document D1 did not provide by itself an enabling disclosure for obtaining the claimed subject-matter. Stated otherwise, the lack of sufficient information in document D1 prevented the skilled person starting from document D1 from arriving at the claimed subject-matter.

20. Nevertheless, it is the respondent's view that starting from document D1 as closest prior art, the skilled person could derive from this document supplemented by the common general knowledge an alternative and obvious way to the claimed monoclonal antibody/BST2 antigen, which route consisted in using the publicly available RPMI 8286 cells as an immunogen, and selecting a hybridoma secreting an antibody binding to a 30 kDa protein. The antibody, in the respondent's opinion, could be used for purifying the antigen.

21. The board firstly notes that the approach taken by the authors of document D1 was that of identifying a protein associated with the terminal differentiation of B cells, whereas the claimed subject-matter purports to identify and isolate a protein associated with pre-B cell proliferation. Doubts thus arise whether the skilled person looking for a protein associated with pre-B cell proliferation would have turned to document D1, dealing with a protein associated with the terminal differentiation of B cells.

22. However, even assuming in the respondent's favour that the skilled person would have turned to document D1, the board is not convinced by the respondent's line of argument that an alternative obvious route to the

claimed subject-matter existed (i.e., using the publicly available RPMI 8286 cells as an immunogen, and selecting a hybridoma secreting an antibody binding to a 30 kDa protein). This is because selecting hybridomas/antibodies on the basis of their capacity of binding to a band around 30 kDa in a gel afforded no certainty that the "right" hybridoma/antibody had been selected, owing to the great number of proteins having a molecular weight around 30 kDa (see point 11 supra). Moreover, once a protein of 30 KD had been purified via this antibody, no amino acid sequence information or biological test were available to confirm that the "right" protein (and hence antibody) had been picked up.

23. Therefore, the claimed subject-matter (including the polypeptide having the amino acid sequence defined by SEQ ID NO. 1 according to claim 1 and the monoclonal antibody according to claim 7) is not obvious from document D1 and/or any other prior art document before the board.

Sufficiency of disclosure (Article 83 EPC)

24. Sufficiency of disclosure was also cited as a ground of opposition. In the decision of the first instance, it was not assessed in respect of the subject-matter now claimed on appeal since the appellant filed new claims before the opposition division. Taking into account the length of the proceedings, the board decides to make use of the provisions of Article 111(1) EPC to evaluate by itself whether or not the claimed invention is sufficiently disclosed.

25. The board firstly observes that the hybridoma secreting antibody RS38 had been deposited according to the Budapest Treaty (see paragraph [0079] of the patent in suit). The respondent never argued that the patent did not provide sufficient information for the skilled person to obtain antibody RS38 or to isolate the intact protein of claim 1.

26. Rather, the respondent argues that the patent gives no guidance as to how to modify/truncate the amino acid sequence defined by SEQ ID NO. 1 and still achieve the function of supporting pre-B cell growth.

27. Methods for obtaining modified or truncated proteins by chemical and/or genetic engineering methods were part of the common general knowledge of the skilled person at the priority date of the patent in suit (see e.g., paragraphs [0051] to [0056] of the patent). A technique for monitoring/measuring pre-B cell growth is disclosed in paragraphs [0097] and [0098] of the patent. There is thus no reason to believe that the selection of modified/truncated forms of the amino acid sequence defined by SEQ ID NO. 1 still achieving the function of supporting pre-B cell growth could be achieved only with an undue burden of experimentation. No evidence to the contrary has been submitted by the respondent.

28. As for the respondent's argument that the patent provides no guidance as to how to select monoclonal antibodies according to claim 7 different from the exemplified antibody (RS38), once monoclonal antibody RS38 and the intact or modified/truncated protein were in the skilled person's hands, it would have been common practice to use these molecules as immunogens

and means for screening hybridoma panels for isolating further hybridomas secreting antibodies binding to these molecules. This situation is quite different and not comparable to that encountered by the skilled person attempting to reproduce the teaching of document D1 without having either the antibody or the protein at hand (see points 8, 12 and 22 supra).

29. The board concludes that no case of insufficiency of disclosure has been made out.

Order

For these reasons it is decided that:

1. The decision under appeal be set aside.
2. The patent is maintained as granted.

Registrar:

Chair:

P. Cremona

U. M. Kinkeldey