BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 14 July 2003

Case Number: T 1120/01 - 3.3.8

Application Number: 92107060.3

Publication Number: 0510691

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
DNA coding for human cell surface antigen

Applicant:
OSAKA BIOSCIENCE INSTITUTE

Opponent:
-

Headword:
Cell surface antigen/OSAKA BIOSCIENCE

Relevant legal provisions:
EPC Art. 123(2), 83, 54, 56

Keyword:
"Formal allowability - yes"
"Sufficiency of disclosure - yes"
"Novelty - yes"
"Inventive step - yes"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1120/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 14 July 2003

Appellant: OSAKA BIOSCIENCE INSTITUTE
Applicant: 2-4, Furaedai 6-chome
Suita-shi
Osaka 565 (JP)

Representative: Jaenichen, Hans-Rainer, Dr.
VOSSIUS & PARTNER
Postfach 86 07 67
D-81634 München (DE)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 12 April 2001 refusing European application No. 92107060.3 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
M. B. Günzel

Summary of Facts and Submissions

I. European application No. 92 107 060.3 published under No.0 510 691 with the title "DNA coding for human cell surface antigen" was refused by the Examining Division.

The reasons for refusal were failure to fulfill the requirements of Article 123(2) EPC (main request), lack of novelty over the teachings of either of documents (1), (4) or (6) (see infra, first and second auxiliary requests), lack of inventive step (third auxiliary request).

II. Claim 1 of the third auxiliary request read as follows:

"1. A DNA encoding a protein selected from the group consisting of:

(i) a Fas antigen having the amino acid sequence from amino acid number -16 to 319 or from amino acid number 1 to 319 in Figures 1 and 2 which is capable of inducing apoptosis when recognized by an antibody specific to human Fas antigen;

(ii) a protein comprising the protein as identified in (i); and

(iii) a protein having an amino acid sequence which is derived from the amino acid sequence as recited in (i) through the deletion, substitution, addition or insertion of 1 to several amino acids, and maintaining a function substantially the same as the protein identified in (i)."

The reasons which led the Examining Division to deny inventive step to the subject-matter of this claim may be summarized as follows:

Document (1) provided a method for the purification of the membrane protein APO-1 involved in apoptosis and, therefore, albeit implicitly, the amino acid sequence of said protein. A skilled person had a reasonable expectation of success of isolating the cDNA encoding the Fas antigen (claim 1), by selecting the positive recombinant clones with oligonucleotide probes devised on the basis of the APO-1 amino acid sequence.

Alternatively, it would be obvious to select positive recombinant clones by the panning method described in document (2). Cells which did not naturally undergo apoptosis would, in principle, be suitable host cells for the Fas cDNA, since, once they were transformed with said cDNA and expressed the Fas antigen, they could be selected for their ability to undergo apoptosis in the presence of an anti-Fas monoclonal antibody (Mab). In the opinion of the Examining Division, the skilled person would not have expected the cells which did not naturally undergo apoptosis to fail to synthesize any proteins (other than the Fas protein) which may also be necessary for apoptosis to occur.

III. The Appellant (Applicant) lodged an appeal against this decision, paid the appeal fee and filed a statement of grounds of appeal together with a new main request and an auxiliary request.

IV. The Board sent a communication pursuant to Article 11(2) of the Rules of Procedure of the Boards of Appeal, conveying its preliminary, non-binding opinion on some of the issues to be decided.

V. The Appellant answered to the Board's communication, filing a new main request and an auxiliary request.

VI. At oral proceedings which took place on 14 July 2003, the Appellant filed a main request in replacement of all of the previously filed claim requests.

Claims 1 to 4, 8 to 11 and 13 read as follows:

"1. A DNA encoding a protein selected from the group consisting of:

(i) a Fas antigen having the amino acid sequence from amino acid number -16 to 319 or from amino acid number 1 to 319 in Figures 1 and 2 which is capable of inducing apoptosis when recognized by an antibody specific to human Fas antigen;

(ii) a protein comprising the protein as identified in (i); and

(iii) a protein having an amino acid sequence which is derived from the amino acid sequence as recited in (i) through the deletion, substitution, addition or insertion of 1 to several amino acids, and which is capable of inducing apoptosis when recognized by an antibody specific to human Fas antigen."

"2. A DNA encoding a protein selected from the group consisting of:

(i) a protein consisting of:

(a) the signal peptide and the extracellular domain in Figures 1 and 2 having the amino acid sequence from amino acid number -16 to 157; or

(b) the extracellular domain of the Fas antigen having the amino acid sequence from amino acid number 1 to 157 in Figures 1 and 2;

and

(ii) a protein comprising the protein identified as in (i)."

"3. A DNA encoding a protein selected from the group consisting of:

(i) a protein consisting of the cytoplasmic domain of the Fas antigen as defined in claim 1 having the amino acid sequence from amino acid number 175 to 319 in Figures 1 and 2; and

(ii) a protein comprising the protein as identified in (i)."

"4. The DNA of any one of claims 1 to 3, which is selected from the group consisting of:

(i) a DNA having a nucleotide sequence selected from (a) to (f) *(sic)*:

(a) from position 1 to 2534 in Figures 1 and 2;

(b) from position 195 to 1199 in Figures 1 and 2;

(c) from position 243 to 1199 in Figures 1 and 2;

(d) from position 195 to 713 in Figures 1 and 2;

(e) from position 243 to 713 in Figures 1 and 2;

(f) from position 765 to 1199 in Figures 1 and 2;

(g) from position 195 to 1202 in Figures 1 and 2; and

(ii) a DNA comprising the DNA as identified in (i)."

"8. A method of preparing the protein encoded by a DNA of any one of claims 1 to 4, comprising culturing a transformant of claim 6 or 7 under suitable conditions."

"9. A protein obtainable by the method of claim 8."

"10. Use of a protein of claim 9 as an antigen in the preparation of an antibody specific thereto."

"11. Use of a DNA of any one of claims 1 to 3 in the induction of apoptosis in a cell in vitro, which comprises introducing the DNA into said cell such that it is expressed."

"13. Use of a DNA of any one of claims 1 to 4 or a vector of claim 5 for the preparation of a pharmaceutical composition for inducing apoptosis of cells."

Claim 5 related to a vector comprising a DNA of any one of claims 1 to 4. Claims 6 and 7 related to transformed cells comprising said vector. Claim 12 related to a pharmaceutical composition comprising the Fas antigen of claim 9.

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

(1): Oehm, A. et al., Abstract No. A.15 presented at the XXIst Meeting of the Society of Immunology, Immunobiology, Vol. 181, No. 2/3, page 127, 1990;

(2): EP-A-0 330 191;

(3): Oehm, A. et al., The Journal of Biological Chemistry, Vol. 267, No. 15, pages 10709 to 10715, 1992;

(4): WO 91/10448;

(6): Trauth, B.C. et al., Science, Vol. 245, pages 301 to 305, 21 July 1989.

VIII. The Appellant's arguments in writing and during oral proceedings may be summarized as follows:

Article 123(2) EPC; added subject-matter

Claim 3 related to the DNA encoding the Fas antigen cytoplasmic domain characterized by its amino acid sequence. The application as filed (page 14) defined the invention as comprising DNAs encoding fragments of the Fas protein. One such fragment was identified on page 10 as being the cytoplasmic domain. It was unambiguously shown in Figures 1 and 2 that the amino acid sequence of said domain started at amino acid 175 to finish at amino acid 319. The subject-matter of claim 3, thus, had a basis in the application as filed.

Claim 4 related to specific DNAs identified by their sequences. DNAs (b), (d) and (f) were disclosed in the application as filed by the combination of the DNA sequence given in Figures 1 and 2 with the disclosure on page 10 of the mature protein, the extracellular and the cytoplasmic domains, respectively. DNAs (a), (c), (e) and (g) were disclosed in Figures 1 and 2 and on pages 5 and 22, respectively.

Article 54 EPC; novelty of the full length Fas protein (claim 9)

Neither of documents (1), (4) or (6) described the protein APO-1 (corresponding to the Fas antigen) in such a way that the novelty of the subject-matter of claim 9 could be affected.

The APO-1 purification process disclosed in document (1) involved an affinity chromatography step using anti-APO-1 antibody, yet the document failed to describe how to obtain this antibody.

Document (4) disclosed the preparation of an anti-APO-1 monoclonal antibody but the corresponding hybridoma had not been deposited, ie it was not publicly available. Moreover, the anti-APO-1 antibody was not used for the purification of APO-1 but to show that more than one protein in a cellular lysate could be detected by immunoprecipitation with said antibody.

The disclosure content of document (6) corresponded to the teaching of document (4) and was irrelevant for the same reasons as given in relation to this last document. It did not make available the anti-APO-1 monoclonal antibody as the description of a molecule in a scientific journal did not imply that it would be freely distributed to the members of the scientific community. It also did not describe any purification process for APO-1.

Article 56 EPC; inventive step (claim 1)

The closest prior art was document (6).

Starting from this document, the technical problem to be solved could be regarded as providing means for the recombinant production of the Fas antigen.
The solution to this technical problem was the DNA sequence encoding said antigen.

At the priority date, the role of the APO-1 antigen in apoptosis had not yet been well defined. Thus, the skilled person would have had no incentive to clone the APO-1 gene in order to solve the above mentioned problem. Moreover, there was no reasonable expectation of success in obtaining the DNA encoding the Fas antigen by hybridisation to a probe derived from the amino acid sequence of the APO-1 protein for a number of reasons: the APO-1 N-terminal amino acid sequence could not be determined. There was no evidence that enough APO-1 protein might be obtained to make possible the sequencing of an internal APO-1 peptide. The Fas mRNA abundancy was unknown. There was no suitable assays for identifying Fas antigen positive clones.
For all these reasons, an inventive step had to be acknowledged.

IX. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims and the amended pages of the description of the main request filed during the oral proceedings.

Reasons for the decision

Article 123(2) EPC; admissibility of amendments

1. The subject-matter of claim 1 (i) to (iii) finds a basis in the application as filed, in claims 1, 15 and 16 together with Example 2, claim 4, and page 13, second paragraph, respectively. The subject-matter of claim 2 (i)(a), 2 (i)(b) and (ii) finds a basis in the application as filed in claims 1 and 17, claims 1 and 18, and claim 4, respectively.

2. The subject-matter of claim 3 (i) and (ii) finds a basis in the application as filed on page 10 where the number of amino acids in the different domains is reported in combination with Figures 1 and 2 and claim 4, respectively. The subject-matter of claim 4 finds its basis in the application as filed, in Figures 1 and 2 (DNA(a)), in Figures 1 and 2 and page 10 (DNAs (b),(d),(f)), on page 5 (DNAs(c),(e)) and page 22 (DNA (g)).

3. The subject-matter of claim 10 finds a basis on page 11, that of claim 11 finds a basis in the experimental Example 2, that of claim 13 finds a basis on page 30.

4. Claims 5 to 9 and 12 correspond to claims 8 to 10, 12 and 13 considered by and not objected to by the Examining Division. The Board shares the view that there is support for the subject-matter of these claims in the application as filed.

5. The requirements of Article 123(2) EPC are fulfilled.

Article 83 EPC

6. The patent in suit provides the sequence of the DNA encoding the Fas antigen (Figures 1 and 2). It also teaches how to assay for the induction of apoptosis (Experimental Example 2). In the Board's judgment, the skilled person would be able to reproduce the claimed subject-matter (section VI supra) by routine work involving a reasonable amount of trial and errors on the basis of this information and of the common general knowledge available in 1991. Sufficiency of disclosure is acknowledged.

Article 54 EPC; novelty

7. Documents (1), (4) and (6) were considered by the Examining Division to be novelty destroying for the Fas antigen (claim 9). Insofar as the protein involved in apoptosis is concerned, the disclosure content of document (4) (a patent application relevant under Article 54(3)(4) EPC) is essentially the same as that of document (6), a scientific article which is prior art under Article 54(2) EPC. In the following assessment of novelty, reference will solely be made to documents (1) and (6).

8. Claim 9 comprises, in particular, the Fas antigen having the sequence shown in Figures 1 and 2. Documents (1) and (6) are concerned with a membrane protein identified as APO-1. Post-published document (3) (to be taken as an expert opinion) shows that APO-1 and the Fas antigen having the sequence shown in Figures 1 and 2 are the same molecule. Thus, either of documents (1)

or (6) could be novelty destroying for the subject-matter of claim 9 if its teaching was enabling with regard to the isolation of the APO-1 protein.

9. Document (1) is an abstract which briefly discloses the purification of APO-1 from SWK6.4 cells. It gives a list of the steps to be carried out but does not provide any technical detail. One of these steps is an affinity chromatography on an anti-APO-1 Mab, yet how to obtain this Mab is not described.

10. Document (6) is concerned with the isolation of an anti-APO-1 Mab. This Mab is said to react "with a 52-Kilodalton antigen (APO-1) on a set of activated human lymphocytes...". The protein per se is seen as a band on a denaturing SDS-polyacrylamide gel after immunoprecipitation of the supernatant of a cell lysate with the Mab. It is not the object of any further studies, let alone of any purification.

11. In the Board's judgment, the purification of APO-1 could not be achieved without undue burden on the basis of the very scanty information given in document (1) or on the basis of that given in document (6) (or document (4), cf point 7 supra). For these reasons, documents (1), (4) and (6) are not considered to provide an enabling disclosure of APO-1. Consequently, they are not relevant to novelty.

12. The requirements of Article 54 EPC are fulfilled.

Article 56 EPC; inventive step

13. The closest prior art is document (6). It teaches that cells carrying the APO-1 protein at their surface will undergo apoptosis when challenged with an anti-APO-1 antibody. APO-1 is identified as a 52 Kd protein on a denaturing SDS-polyacrylamide gel. It is stated on page 304, middle column: "*It is conceivable..., that several distinct surface antigens with a different tissue distribution are involved in the induction of apoptosis. Elucidation of the structure of APO-1, its possible connection to the cytoskeleton and the molecular events following anti-APO-1 binding might resolve some of these issues.*"

14. Starting from the closest prior art, the objective technical problem to be solved may be defined as providing the means for producing a protein involved in apoptosis.

15. The solution given to this problem is the DNA of claim 1 defined by its ability to encode a specific protein, and its use for producing said protein capable of inducing apoptosis.

16. The recovery of the claimed DNA requires, of course, that the recombinant clones which contain it be ultimately identified as such, ie., according to the claim, that they be identified as producing a protein capable of inducing apoptosis when recognized by an antibody specific to human Fas antigen. Cells which naturally undergo apoptosis cannot, of course, be chosen as host cells since one would not know whether the cellular death observed in the presence of the Mab

is due to the natural phenomenon or to the expression of the recombinant Fas antigen. The only cells which may, in principle, be suitable as host cells are cells which do not naturally undergo apoptosis, the recombinant clones expressing the Fas antigen then being discernable by their ability to undergo apoptosis in the presence of an anti-Fas Mab. This selection method will, however, only work if the expression of the Fas gene carried by the recombinant DNA is **enough on its own** for apoptosis to take place in these host cells which do not naturally undergo apoptosis.

17. Document (6) (page 304, bottom of left-hand column) published in 1989 teaches that APO-1 "might be a receptor for cytotoxic molecules or for autocrine growth factors. Alternatively, it could be a molecule essential for vertical or lateral growth signal transduction...". There is no document on file published between 1989 and the priority date and concerned with apoptosis. It must, thus, be taken that, at the priority date, the molecular mechanisms involved in cellular death by apoptosis were not yet understood and that many molecules were thought to be involved. In addition, the genetic background of cells which did not undergo apoptosis had not been investigated. In the Board's judgment, the skilled person had, thus, no reasons to expect that amongst these cells, some would carry and express all genetic determinants necessary for apoptosis to occur, **with the exception of the Fas gene**, so that they would be likely to undergo apoptosis once they had received the recombinant Fas gene and upon challenge with the anti-Fas antibody.

18. In this context, the post-published document (3) may be referred to, where it is stated on page 10715: "The APO-1 cDNA was introduced into the human Burkitt's lymphoma line BL60-P7, and APO-1 expressing transfectants were found to be susceptible toward anti-APO-1 mediated apoptosis. Thus, these cells **seem to provide all cellular components necessary for signalling through APO-1.**", which statement clearly indicates that even after the filing date of the patent, concerns still existed as to which host cells might be suitable.

19. Accordingly, and contrary to the opinion expressed by the Examining Division (Section II, supra), the Board concludes that the skilled person had no reasonable expectation of success in choosing the host cells appropriate for the identification of the clones carrying the Fas cDNA.

20. The Examining Division also concluded that the cloning of the cDNA encoding the Fas antigen defined by its amino acid sequence (claim 1) was obvious in view of document (1) which made the amino acid sequence of the APO-1 protein implicitly available as well as, consequently, the hybridisation probes necessary to detect the Fas recombinant clones (Section II, supra). However, the conclusion that hybridisation probes constructed on the basis of the amino acid sequence of the APO-1 protein can be used in an obvious manner to retrieve the Fas cDNA is a conclusion which can only be reached under the assumption that the APO-1 protein is the same protein as the Fas antigen since, otherwise, the encoding DNAs would not be expected to hybridize with each other. Yet, it is only with the hindsight

knowledge of the Fas amino acid sequences shown in Figures 1 and 2 of the patent in suit and of the APO-1 amino acid sequence shown in the post-published document (3) that the identity of the two proteins can be established. As this sequence information was not available at the filing date of the patent in suit, the skilled person had no reasonable expectation of success that by using "APO-1 hybridisation probes", he/she would retrieve the cDNA of claim 1 encoding the **specific** protein **defined by its sequence** in Figures 1 and 2.

21. For these reasons, inventive step is acknowledged.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division with the order to grant the patent with the following documents: Claims of the main request filed during the oral proceedings, description pages 5, 6, 8 and 22 of the main request filed during the oral proceedings, remaining of pages of the description and figures as originally filed.

The Registrar: The Chairman:

A. Wolinsky L. Galligani