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Datasheet for the decision of 5 October 2006

Case Number: T 0937/02 - 3.3.04

Application Number: 91905894.1

Publication Number: 0521156

IPC: C07K 14/00

Language of the proceedings: EN

Title of invention:
DNA Coding for granulocytic colony stimulating factor receptor

Patentee:
OSAKA BIOSCIENCE INSTITUTE

Opponent:
01) Monsanto Company
02) Immunex Corporation

Headword:
G-CSF/OSAKA BIOSCIENCE

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

Keyword:
"Main request - added subject-matter (yes)"
"Auxiliary request I - inventive step (no)"
"Auxiliary request II - inventive step (yes)"

Decisions cited:
G 0009/92, T 0021/81, T 0181/82, T 0383/88, T 0329/99, T 0823/96, T 0280/00

Catchword:
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Case Number: T 0937/02 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 5 October 2006

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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 22 May 2002 concerning maintenance of European patent No. 0521156 in amended form.

Composition of the Board:

Chair: U. Kinkeldey
Members: M. Wieser
G. Weiss

Summary of Facts and Submissions

I. The appeal was lodged by the Patent Proprietor (Appellant) against the interlocutory decision of the Opposition Division, whereby the European patent No. 0 521 156, claiming priority from JP 74539/90; 23 March 1990 and JP 176629/90; 3 July 1990, could be maintained in amended form pursuant to Article 102(3) EPC.

II. The patent had been opposed by Opponent 01 (Respondent I) and Opponent 02 (Respondent II) under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) and (c) EPC.

III. The Opposition Division had decided that the main request and auxiliary request I before them did not meet the requirements of Articles 123(2) and 83 EPC, that the claims of auxiliary request II before them were not novel, contrary to the requirements of Article 54 EPC, and that the claims of auxiliary request III before them did not involve an inventive step and contravened Article 56 EPC.

However, they decided that claims 1 to 13 for all designated Contracting States except GR and ES, claims 1 to 13 for GR and claims 1 to 14 for ES according to auxiliary request IV met all requirements of the EPC.

IV. The Board expressed its preliminary opinion in a communication dated 23 January 2006.

Oral proceedings were held on 5 October 2006 in the absence of Respondent I, who had informed the Board with letter dated 10 February 2006 that he will not attend the oral proceedings.

V. The Appellant requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of claims 1 to 17 of the new main request, which corresponds to auxiliary request I filed on 15 October 2001, or alternatively, on the basis of auxiliary requests I or auxiliary request II (versions A to C) filed at the oral proceedings.

Respondents I and II requested that the appeal be dismissed.

VI. Claims 1 of Appellant's new main request read as follows:

"A DNA encoding a protein having the biological properties of murine G-CSF receptor having the amino acid sequence from amino acid No. 1 to 812 presented in Figure 1 or fragments thereof, said fragments having the ability to bind specifically to G-CSF."

The phrase "... a protein having the biological properties of ..." was also contained in claims 3, 5, 7, 12 and 13 of the new main request. These claims referred to DNA encoding a human G-CSF receptor and to murine and human G-CSF receptor.

VII. Claims 3 and 5 of auxiliary request I read as follows:

"3. A DNA which encodes a human G-CSF receptor having the amino acid sequence from amino acid No. 1 to 813 presented in Figure 8(a),(b).

5. A DNA which encodes a human G-CSF receptor having the amino acid sequence from amino acid No. 1 to 598 presented in Figure 8(a),(b) and that from amino acid No. 599 to 748 presented in Figure 8(c),B."

Dependent claims 4 and 6 referred to the nucleotide sequences of the DNA of claims 3 and 5 respectively.

Claims 1, 2 and 7 to 17 of auxiliary request I corresponded to claims 1 to 13 of auxiliary request IV before the Opposition Division. In the decision under appeal it had been decided that the patent could be maintained on the basis of this request pursuant to Article 103(2) EPC.

VIII. Claims 1 to 15 of auxiliary request II for all designated contracting states except GR and ES (version A) differed from claims 1 to 17 of auxiliary request I in so far as claims 3 and 4 of auxiliary request I had been deleted.

These claims had also been deleted from the claims of auxiliary request II for GR (version B; claims 1 to 15) and of auxiliary request II for ES (version C; claims 1 to 16). The wording of claim 3 is identical in versions A, B and C of auxiliary request II.

If not otherwise specified, the present decision when referring to a specific claim means the claim for all designated contracting states except GR and ES.

IX. The present decision refers to the following documents:

(7) Blood, vol.74, no.1, July 1989, pages 56 to 65

(10) Proc. Nat. Acad. Sci. USA, vol.86, 1989, pages 9323 to 9326

(14) Cell, vol.61, April 1990, pages 341 to 350

X. The submissions made by the Appellant, as far as relevant to the present decision, may be summarised as follows:

The phrase "... or a protein having the biological properties of ...", contained in the claims of the new main request had a basis in column 11, lines 28 to 39; column 11, line 58 to column 12, line 5 and claims 2 and 4 as originally filed. Thus, the requirements of Article 123(2) were met.

The subject-matter of claim 3 of auxiliary request I, a DNA encoding a human G-CSF receptor having the amino acid sequence presented in Figure 8(a),(b), could not be derived in an obvious way from the disclosure in the cited prior art documents. The skilled person reading document (14), which disclosed a DNA encoding murine G-CSF receptor, had no reasonable expectation of success to obtain the human receptor, let alone the human receptor with the specific amino acid sequence indicated in the claim.

The problem to be solved by the present invention according to claim 3 of auxiliary request II was the provision of a soluble form of human G-CSF receptor, which was applicable as a ready-to-use G-CSF antagonist. As neither document (14) nor any other of the cited prior art documents were concerned with the same technical problem, the subject-matter of claim 3 of auxiliary request II involved an inventive step (Article 56 EPC).

XI. The submissions made by the Respondents, as far as relevant to the present decision, may be summarised as follows:

The phrase "... or a protein having the biological properties of ..." had no basis in the application as filed. The claims of the new main request therefore did not meet the requirements of Article 123(2) EPC.

The skilled person, equipped with the detailed information disclosed in document (14), would have followed the suggestion made in this document and would have used the mouse G-CSF receptor cDNA as probe to screen for the human counterpart. By doing so he would have arrived at the subject-matter of claim 3 of auxiliary request I in an obvious way, contrary to the requirements of Article 56 EPC.

In the same obvious way the skilled person would have arrived at the DNA according to claim 3 of auxiliary request II. The fact that this DNA encoded a soluble form of the human G-CSF receptor lacking the transmembrane domain had to be considered as bonus

effect, which according to the case law of the Boards of Appeal could not confer inventiveness on an obvious solution.

Reasons for the decision

New Main Request
Amendments - Article 123(2) EPC

1. Claim 1 refers to "[a] DNA encoding **a protein having the biological properties of** murine G-CSF receptor..." (emphasis added by the Board) having the specific amino acid sequence presented in Figure 1, or fragments thereof. (The same language is used in claims 3, 5 and 7 referring to DNA encoding human G-CSF receptor and in claims 12 and 13 referring to the protein encoded by the claimed DNA.)

   By using the phrase emphasised above, the claim encompasses DNA molecules encoding proteins having the desired biological properties, namely those of murine G-CSF, but being structurally different, i.e. having a different amino acid sequence, in comparison to the protein having the amino acid sequence presented in Figure 1. The extent to which these proteins may be structurally different from the protein presented in Figure 1 is not defined.

2. The Appellant argues that a basis for such claim can be found in the following passages of the application as originally filed:

Column 11, lines 28 to 39:

"The nucleotide sequence of cDNA encoding murine G-CSF receptor is shown in Figs. 1(a), 1(b) and 1(c), and that of cDNA encoding human G-CSF receptor is shown in Figs. 8(a), 8(b) and 8(c). Persons ordinary skilled in the art will appreciates that it is easy to obtain derivatives having a similar activities by modifying said sequence using conventional methods, such as site specific mutation of DNA which comprises the insertion, substitution or deletion of nucleotide(s). Thus obtained DNA derivatives also fall within the scope of the present invention."

Column 11, line 58 to column 12, line 5:

"It is possible to isolate a DNA encoding G-CSF receptor from cells of various animals using the DNA of the invention, construct an expression vector containing said DNA, transform said expression vector into an appropriate cultured cell, and make the resultant transformant produce G-CSF receptor."

Claims 2 and 4:

"2. The DNA of Claim 1, wherein said granulocyte colony-stimulating factor receptor is the murine granulocyte colony-stimulating factor receptor.

4. The DNA of Claim 1, wherein said granulocyte colony-stimulating factor receptor is the human granulocyte colony-stimulating factor receptor."

3. None of these cited passages contains an explicit disclosure of the phrase in question (a protein having the biological properties of).

According to the established case law of the Boards of Appeal in order to determine whether an amendment does or does not extend beyond the subject-matter of the application as filed, it is necessary to examine if the overall change in the content of the application originating from an amendment results in the skilled person being presented with information which is not directly and unambiguously derivable from that previously presented by the application, even when account is taken of matter which is implicit to a person skilled in the art in what has been expressly mentioned (see decision T 383/88 of 1 December 1992; point 2.2.2).

The term "implicit disclosure" should **not** be construed to mean matter that does not belong to the **content** of the technical information provided by a document but may be rendered **obvious** on the basis of that content. The term "implicit disclosure" relates solely to matter which is not explicitly mentioned, but is a clear and unambiguous consequence of what is explicitly mentioned (cf decision T 823/96 of 28 January 1997; point 4.5).

4. Column 11, lines 28 to 39 of the application as originally filed refers to derivatives of the murine and humane proteins having the amino acid sequences shown in Figures 1 and 8 and having similar activities. These derivatives are described as being obtainable by "using conventional methods, such as site specific

mutation of DNA which comprises the insertion, substitution or deletion of nucleotide(s)".

Thus, contrary to the subject-matter of claim 1, the extent to which these proteins may be structurally different from the proteins presented in the Figures is defined (see point (1) above).

The passage bridging columns 11 and 12 of the application as originally filed describes the possible use of "the DNA of the invention" in a method to isolate other DNA's encoding G-CSF receptors. When assuming that "the DNA of the invention" defines the DNA presented in Figures 1 and 8, the Board does not see a basis, neither explicit nor implicit, for a claim referring to a DNA encoding a protein having the biological properties of a specific, defined protein, which is not a derivative obtainable from the amino acid sequences of Figures 1 or 8 by the methods disclosed in column 11, lines 28 to 39 of the application as originally filed.

The same holds true for original claims 2 and 4, which refer to DNA encoding murine, respectively humane G-CSF, without being restricted to a specific sequence.

5. A technical embodiment may be rendered obvious on the basis of the content of an application as filed without, however, belonging to its explicit or implicit disclosure and, therefore, without serving as a valid basis for amendments complying with the requirements of Article 123(2) EPC (cf decision T 329/99 of 5 April 2001; point 4.5).

6. Consequently the Board judges that at least claim 1 of Appellant's new main request has been amended in such a way that it contains subject-matter which extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

Auxiliary Request I

7. Claims 1, 2 and 7 to 17 of this request correspond to claims 1 to 13 of auxiliary request IV before the Opposition Division. In the decision under appeal it had been decided that the patent could be maintained on the basis of this request pursuant to Article 103(2) EPC.

The Patent Proprietor is the sole Appellant against this interlocutory decision. Considering the principle of prohibition of reformatio in peius as elaborated by the Enlarged Board of Appeal in decision G 9/92 (OJ EPO 1994, 875), the Board, in the present case, is concerned with the examination of claims 3 to 6 only.

8. The Respondents had no objections to claims 3 to 6 under Articles 123(2), 54 and 83 EPC. The Board has neither.

Inventive step - Article 56 EPC

9. Claim 3 relates to a DNA encoding human G-CSF receptor having the amino acid sequence presented in Figure 8(a), (b).

The amino acid sequence of Figure 8 is not disclosed in the first priority document JP 74539/90; 23 March 1990.

Claim 3 is therefore not entitled to the first but only to the second priority date claimed, namely JP 176629/90, 3 July 1990.

As a consequence, document (14), published April 1990, belongs to the state of the art according to Article 54(2) EPC. Its content has to be considered when assessing inventive step of claim 3 as required by Article 56 EPC.

10. Document (14) is considered to represent the closest state of the art. It discloses the cloning and the sequence analyses of murine G-CSF receptor. The document describes the examples of the present patent insofar as related to the murine receptor. On page 348, left column, last paragraph, document (14) reads:

"Under low-stringency hybridization, mRNA for the human G-CSF receptor could be detected in some human myeloid leukemia cells ... using mouse G-CSF receptor cDNA as a probe. Availability of cDNA for the human G-CSF receptor would be valuable in the screening of various leukemia cells from human patients for the expression of the G-CSF receptor before treatment of the patients with G-CSF ..."

Document (14) teaches to use the 2,5 kb HindIII-XbaI fragment of clone pJ17 as probe (page 349, left column, fourth paragraph). The patent uses the 2,5 kb HindIII-XbaI fragment of clone pI62 under low-stringency hybridization conditions as described in example 4, in columns 18 and 19.

The two sequences were found to be identical within the coding regions (document (14), page 343, left column, lines 1-2). Figure 4 on page 343 shows that the HindIII-XbaI fragment does not exceed the coding region. Thus, the probe used in the patent, derived from clone pI62, and the probe used according to document (14), derived from clone pJ17, have the same sequence.

Document (14) suggests several sources a skilled person could have used for establishing a human cDNA library for conducting the screening for a sequence coding for G-CSF receptor. Page 341, right column, first full paragraph, discloses that several reports suggested that the expression of the G-CSF receptor in mouse and human is restricted to progenitor and mature neutrophils and various myeloid leukemia cells. Among the documents cited there is "Park et al., 1989" which corresponds to document (7) in the present case. Document (14) continues to disclose that G-CSF receptor has also recently been found in non-hemopoietic cells such as placenta, and refers in this respect to "Uzumaki et al., 1989", which is document (10) in the present case.

Document (7) demonstrates the binding of human G-CSF to U937 cells in Figure 3 on page 59. Document (10) shows the binding of KW-2228, an I-labelled mutein of human G-CSF to placental membranes in Figure 1 on page 9324.

The human cDNA libraries screened in example 4 of the patent in suit are derived from U937 cells and human placenta. cDNA clones coding for human G-CSF receptor according to claim 3, which are designated in the

patent in suit as "Class 1" receptors (see column 19, line 57 to column 20, line 30) were obtained from U937 and placenta cells respectively.

11. In the light of the disclosure in document (14), the problem to be solved by the present invention according to claim 3 of auxiliary request 1, is the actual provision of a DNA encoding human G-CSF receptor.

12. The Appellant argued that U937 cells were known to contain only a very low amount of human G-CSF receptor mRNA as shown in Figure 11 of the patent. Thus, the skilled person would not have been encouraged to use this cell line to prepare a cDNA library in order to screen for human G-CSF receptor.

The Appellant referred to the decision T 280/00 of 6 February 2003, wherein the competent Board in a case dealing with humane and porcine inhibin accepted that the knowledge of a hypothetical homology would have given the skilled person some hope that he/she might succeed in isolating a mammalian gene by cross-species hybridisation. Yet this hope did not amount to a reasonable expectation of success, in the absence of any indication/suggestion in the prior art that some degree of homology could be expected to exist between the human inhibin gene to be cloned and its presumed already known counterpart in another species (point (22) of the reasons).

The Appellant argued that in the present case it was not even known whether there was some similarity at the amino acid level between the murine and human G-CSF receptor.

Moreover, the Appellant pointed to the fact that claim 3 referred to a DNA encoding a human G-CSF receptor having the particular sequence shown in figure 8. Following the teaching of the patent in suit it was possible to separate three different classes of human G-CSF receptors. Even clones deriving from the same cell line contained different forms of the human G-CSF receptor; for example using U937 cells as source, cDNA's encoding class 1 and class 2 human G-CSF receptors could be obtained and when using placenta cells as source, class 1 and 3 human G-CSF receptors were obtained. Therefore, the provision of a DNA sequence encoding a human G-CSF receptor characterised by a particular amino acid sequence could not be regarded as being obvious in the light of a combination of the disclosure in document (14) with either of documents (7) or (10).

13. As stated in point (10) above, document (14) discloses several sources that a skilled person could have used for establishing a human cDNA library for conducting the screening for a sequence coding for G-CSF receptor. A skilled person knowing that one of these possible sources (U937 cells) contained only a very low amount of human G-CSF receptor mRNA when compared to another possible source (placenta) would not have been discouraged to follow the suggestions in document (14) which refers to both cell types.

The question whether or not there existed a reasonable expectation of success that the desired aim might be achieved has to be answered on the basis of the

available prior art (cf decision T 280/00 supra; point (19) of the reasons).

In the case underlying decision T 280/00 (supra), only documents (2) and (8) could be taken into account for the assessment of inventive step of claims relating to human inhibin (point (14)). Both documents did not mention human inhibin chains at all (point (20)).

This situation differs in essence from the situation in the present case, where the closest prior art, document (14), discloses a suitable probe, the conditions to be used for screening and possible sources of cDNA libraries for screening for the human G-CSF receptor.

14. In the light of the present factual situation this Board judges that a person skilled in the art would have carried out the cloning of the human G-CSF receptor with a reasonable expectation of success and, upon screening of the cDNA libraries, as suggested by document (14) would have arrived at the DNA specified in claim 3 in an obvious way.

The subject-matter of claim 3 of auxiliary request I does not involve an inventive step contrary to the requirements of Article 56 EPC.

Auxiliary Request II

15. In the light of what has been said in points (7) and (8) above with regard to the claims of auxiliary request I, the only issue the Board has to decide with regard to auxiliary request II is the question of inventive step

of the subject-matter of claim 3 and of claim 4 dependent thereon.

Inventive step - Article 56 EPC

16. The DNA according to claim 3 encodes a specific form of human G-CSF receptor, which is designated in the patent in suit as "Class 2" receptor and which is a secreted and soluble form of the receptor (see patent, column 20, lines 31 to 46). Compared to the DNA coding for "Class 1" receptors, which were the subject of claim 3 of auxiliary request I, this DNA lacks 88 nucleotides. This deletion includes the transmembrane domain and results in an altered translation reading frame that encodes additional 150 amino acids after the deletion point (see Figure 9). The DNA is isolated from a U937 cell (column 20, line 31).

17. Cell-bound G-CSF receptor, by binding to its ligand G-CSF, is involved in the stimulation of growth and differentiation of neutrophilic granulocytes, the regulation of neutrophils and the stimulation of the growth of tumour cells such as myeloid leukemia cells (column 1, lines 38 to 56).

Contrary to this, the secreted and soluble form of G-CSF receptor, which due to the lacking of a transmembrane domain is not anchored in a cell surface, does not stimulate and/or regulate the above biological activities. Thus, a secreted and soluble form of G-CSF receptor, which competes with cell-bound G-CSF receptor for the ligand G-CSF, acts as a G-CSF antagonist.

18. None of the prior art documents on file refers to a secreted and soluble human G-CSF receptor.

The problem to be solved by the present invention according to the embodiment of claim 3 is therefore the provision of a secreted and soluble form of human G-CSF receptor.

This problem has been solved convincingly by the provision of the DNA of claim 3 encoding a human G-CSF receptor having the amino acid sequence from amino acid No. 1 to 598 presented in Figure 8(a),(b) and that from amino acid No. 599 to 748 presented in Figure 8(c), B.

19. Neither document (14) nor any other document on file contains information that would have encouraged a skilled person to screen a cDNA library obtained from U937 cells, which are known to contain only a very low amount of human G-CSF receptor mRNA (Figure 11 of the patent), in order to isolate a secreted and soluble form of human G-CSF receptor.

20. Respondent II argued that a skilled person when following the teaching in document (14) will automatically and inevitably arrive at the DNA according to claim 3. The fact that the G-CSF receptor encoded by this DNA is a soluble receptor is therefore a bonus effect, which according to the established case law of the Boards of Appeal cannot contribute to an inventive step.

21. An effect which may be said to be unexpected can be regarded as an indication of inventive step (cf decision T 181/82, OJ EPO 1984, 401). However, if,

having regard to the state of the art, it would already have been obvious for a skilled person to arrive at something falling within the terms of a claim, because an advantageous effect could be expected to result from the combination of the teachings of the prior art documents, such claim lacked an inventive step, irrespective of the circumstance that an extra effect (possibly unforeseen)was obtained (cf decisions T 21/81, OJ EPO 1983, 15). Thus, an unexpected bonus effect does not confer inventiveness on an obvious solution.

22. As already stated in point (18) above the solution to the underlying problem according to claim 3 cannot be considered as being obvious.

Document (14) suggests several sources that a skilled person could have used for establishing a human cDNA library for the purpose of screening for a sequence encoding human G-CSF receptor. Among these suggested sources are U937 cells, which are known to contain only a very low amount of human G-CSF receptor mRNA. The isolation of a secreted and soluble form of human G-CSF receptor is not referred to in document (14) or in any other prior art document on file.

23. The patent in suit discloses the isolation from a U937 cell cDNA library of a DNA sequence encoding a soluble human G-CSF receptor having the specific amino acid sequence indicated in claim 3.

The subject-matter of claim 3, and of claim 4 dependent thereon, involves an inventive step and meets 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 department of first instance with the order to maintain the patent in the following version:

Claims: Claims 1 to 15 of version (A) for all designated contracting states except GR and ES, and claims 1 to 15 of version (B) for the contracting state GR, and claims 1 to 16 of version (C) for the contracting state ES, according to auxiliary request II filed during oral proceedings;

Description: Pages 2 to 7 and 14, filed during oral proceedings, and pages 8 to 13 as granted;

Drawings: Figures 1 to 14 as granted.

Registrar: Chair:

P. Cremona U. Kinkeldey