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Bezeichnung der Erfindung: Human Granulocyte Macrophage Colony Stimulating Factor and Muteines thereof
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement :

ENTSCHEIDUNG / DECISION

vom / of / du 15 September 1989

Anmelder / Applicant / Demandeur : Schering Biotech Corporation

Patentinhaber / Proprietor of the patent /
Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence : Human GM-CS-Factor

EPÜ / EPC / CBE PCT Article 17(3)(a) and Rules 13, 40.1

Schlagwort / Keyword / Mot clé : "Invitation to pay additional fees - Reasons confusing"

Leitsatz / Headnote / Sommaire

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Case Number : W 04/89
International Application No. PCT/US88/02334

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 15 September 1989

Appellant : Schering Biotech Corporation

Representative : Blasdale, John H.C.
Schering-Plough Corporation
One Giralda Farms
Madison, New Jersey 07940
USA

Subject of this decision: Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fee) of the European Patent Office (branch at The Hague) dated

Composition of the Board :

Chairman : P. Lançon
Members : U. Kinkeldey
R. Schulte

Summary of Facts and Submissions

I. On 15 July 1988 the Applicants filed the International patent application PCT/US88/02334 with the US Patent and Trademark Office. The application relates to a human granulocyte-macrophage colony stimulating factor and muteines thereof.

II. On 27 October 1988, the European Patent Office as competent International Searching Authority (ISA) issued, pursuant to Article 17(3)(a) PCT and Rule 40.1 PCT, an invitation to pay five additional search fees because it considered that the above identified application did not comply with requirements of unity of invention as set forth in Rule 13 PCT. In the said invitation it was stated that the general problem underlying the invention was not novel and solutions to it had already been found, as illustrated by W086/00639 and EP-0 228 018. The first citation disclosed unmodified human granulocyte-macrophage colony stimulating factors (GM-CSF), whose DNA sequence was identical with that of Claim 9, and unspecified muteins of the same. The second citation disclosed several muteins of GM-CSF. There was, therefore, no longer a general inventive concept for the claimed modified and unmodified GM-CSF. Thus, according to the ISA six subjects constituted separate inventive concepts which were separately identified as six groups of inventions. Inventions 1, 2 and 5 were the following:

1. "Claims: 9, 14, 16 completely; 17-20 partially:

   The protein of Claim 9, a pharmaceutical composition containing it, and an expression vector for its production."

2. "Claims: 15 completely; 17-20 partially:

A pharmaceutical composition containing the glycosylated protein of Claim 9, and an expression vector for its production."

5. "Claims: 1, 2, 5, 6, 13 completely; 21-23 partially:

The more than 2.4×10^{19} compounds which are covered by the definition of Claim 1 (2-fold-substituted GM-CSFs). Pharmaceutical compositions containing these compounds, nucleic acid cassettes for the construction of these muteins."

III. On 23 November 1988, the Applicants paid one additional search fee under protest (Rule 40.2(c) PCT) and requested the ISA to restrict the search to the expression vectors of Claims 17-20. The Applicants stated that they were prepared to delete, without prejudice, Claims 1-16 and 21-23 and further were of the opinion that Claims 17-20 clearly related to a single invention although, in its invitation, the ISA had regarded Claims 17-20 as two separate inventions numbered 1 and 2.

IV. Claims 1, 9 and 17 read as follows:

1. A protein exhibiting human granulocyte-macrophage colony stimulating factor activity comprising a glycosylated or unglycosylated 2-fold substituted polypeptide selected from the set defined by the formula:

H - X(Ala) - X(Pro) - X(Ala) - X(Arg) - X(Ser) - X(Pro) -
X(Ser) - X(Pro) - X(Ser) - X(Thr) - X(Gln) - X(Pro) -
Trp - X(Glu) - X(His) - X(Val) - X(Asn) - X(Ala) -
X(Ile) - X(Gln) - X(Glu) - X(Ala) - X(Arg) - X(Arg) -
X(Leu) - X(Leu) - X(Asn) - X(Leu) - X(Ser) - X(Arg) -
X(Asp) - X(Thr) - X(Ala) - X(Ala) - X(Glu) - X(Met) -
X(Asn) - X(Glu) - X(Thr) - X(Val) - X(Glu) - X(Val) -
X(Ile) - X(Ser) - X(Glu) - X(Met) - X(Phe) - X(Asp) -
X(Leu) - X(Gln) - X(Glu) - X(Pro) - X(Thr) - Cys -
X(Leu) - X(Gln) - X(Thr) - X(Arg) - X(Leu) - X(Glu) -
X(Leu) - X(Tyr) - X(Lys) - X(Gln) - X(Gly) - X(Leu) -
X(Arg) - X(Gly) - X(Ser) - X(Leu) - X(Thr) - X(Lys) -
X(Leu) - X(Lys) - X(Gly) - X(Pro) - X(Leu) - X(Thr) -
X(Met) - X(Met) - X(Ala) - X(Ser) - X(His) - X(Tyr) -
X(Lys) - X(Gln) - X(His) - Cys - X(Pro) - X(Pro) -
X(Thr) - X(Pro) - X(Glu) - X(Thr) - X(Ser) - Cys -
X(Ala) - X(Thr) - X(Gln) - X(Ile) - X(Ile) - X(Thr) -
X(Phe) - X(Glu) - X(Ser) - X(Phe) - X(Lys) - X(Glu) -
X(Asn) - X(Leu) - X(Lys) - X(Asp) - X(Phe) - X(Leu) -
X(Leu) - X(Val) - X(Ile) - X(Pro) - X(Phe) - X(Asp) -
Cys - Trp - X(Glu) - X(Pro) - X(Val) - X(Gln) -
X(Glu) - OH

wherein:

X(Ser) represents Ser, Ala, Thr, Gly, or Asn;
X(Arg) represents Lys or Arg;
X(Leu) represents Leu or Val;
X(Pro) represents Ala or Pro;
X(Thr) represents Thr, Ser, or Ala;
X(Ala) represents Pro, Ala, Ser, Thr, Gly, or Val;
X(Val) represents Val, Ile, Ala, or Leu;
X(Gly) represents Gly, Ala, or Ser;
X(Ile) represents Ile, Val, or Leu;
X(Phe) represents Phe or Tyr;
X(Tyr) represents Tyr or Phe;
X(His) represents His, Gln, or Asn;
X(Gln) represents Gln, Glu, or His;
X(Asn) represents Asn, Asp, Ser, or Lys;
X(Lys) represents Lys, Arg, or Asn;
X(Asp) represents Asp, Asn, or Glu;
X(Glu) represents Glu, Gln, or Asp; and
X(Met) represents Nle, Met or Leu.

9. The protein of Claim 8 wherein said polypeptide is unglycosylated and comprises the amino acid sequence defined by the formula:

Ala - Pro - Ala - Arg - Ser - Pro - Ser - Pro -
Ser - Thr - Gln - Pro - Trp - Glu - His - Val -
Asn - Ala - Ile - Gln - Glu - Ala - Arg - Arg -
Leu - Leu - Asn - Leu - Ser - Arg - Asp - Thr -
Ala - Ala - Glu - Met - Asn - Glu - Thr - Val -
Glu - Val - Ile - Ser - Glu - Met - Phe - Asp -
Leu - Gln - Glu - Pro - Thr - Cys - Leu - Gln -
Thr - Arg - Leu - Glu - Leu - Tyr - Lys - Gln -
Gly - Leu - Arg - Gly - Ser - Leu - Thr - Lys -
Leu - Lys - Gly - Pro - Leu - Thr - Met - Met -
Ala - Ser - His - Tyr - Lys - Gln - His - Cys -
Pro - Pro - Thr - Pro - Glu - Thr - Ser - Cys -
Ala - Thr - Gln - Ile - Ile - Thr - Phe - Glu -
Ser - Phe - Lys - Glu - Asn - Leu - Lys - Asp -
Phe - Leu - Leu - Val - Ile - Pro - Phe - Asp -
Cys - Trp - Glu - Pro - Val - Gln - Glu .

17. An expression vector for the production of human granulocyte-macrophage colony stimulating factor in a mammalian cell host, the expression vector comprising in sequence:

an SV40 origin of DNA replication;
an SV40 early region promoter;
an SRα promoter;
a splice junction and a nucleotide sequence capable of encoding human granulocyte-macrophage colony stimulating factor; and a polyadenylation site.

V. On 25 January 1989, the International Search Report covering inventions 1 and 2 in the order as listed by the ISA in the invitation was sent to the Applicants.

VI. By a letter of 3 February 1989, the Applicants informed the ISA that they were confused and were not able to understand what had been done by the ISA. They consequently asked for clarification. In its response the ISA informed the Applicants that "the main invention" (Claims 9, 14 and 16 fully and Claims 17-20 partially) had been searched. The second invention mentioned (Claim 15 fully and Claims 17-20 partially) had also been searched, this "in order to provide a full search of Claims 17-20 as was clearly the wish of the Applicant as stated in the letter of 23 November 1988." The ISA continued: "objection to lack of unity of invention is maintained, the case has been referred to the Technical Board of Appeal."

Reasons for the Decision

1. Pursuant to Article 154(3) EPC the Boards of Appeal of the EPO are responsible for deciding on protests raised by

Applicants against an invitation to pay additional search fees under Article 17(3)(a) PCT.

2. The protest complies with Rule 40.2(c) PCT and is admissible.

3. The Board considers, as did the ISA, that the additional fee was paid in view of the second invention quoted in the invitation. The second and the first invention, as stated in the invitation, cover Claims 17-20.

4. In Article 17 PCT, relating to the procedure before the ISA, there is clear wording in paragraph (3)(a) stating that "if the International Searching Authority considers that the international application does not comply with the requirement of unity of invention as set forth in the regulations, it shall invite the Applicant to pay additional fees. The International Searching Authority shall establish the International Search Report on those parts of the international application which relate to the invention first mentioned in the claims ("main invention") and, provided the required additional fees have been paid within the prescribed time limit, on those parts of the international application which relate to inventions in respect of which the said fees were paid" (emphasis added).

The reasons given by the ISA in its invitation to pay five additional fees are clear insofar as the second part of Article 17(3)(a) PCT has been correctly applied by the ISA, because Claims 17-20 apparently have been completely searched as "those parts of the international application which relate to inventions in respect of which the said fees were paid". This was undoubtedly requested by the Applicants.

5. Although the wording of the first part of Article 17(3)(a) PCT is, in the Board's opinion, unambiguous, the reasons given in the invitation with respect to it are confusing. Whatever the reaction of the Applicants may be to the invitation to pay additional fees because of alleged non-unity of the invention, in any case the ISA is obliged to establish the International Search Report on the basis of that part of the application which has been mentioned first in the claims. There seem to be no doubts that a "first invention" is defined in the first claim. If the first claim comprises more than one subject-matter to be considered as an invention, the Board interprets Article 17(3)(a) PCT as meaning that the first subject-matter mentioned in the first claim has to be considered as the "main invention" in the sense of the first part of said Article.

6. The reasons in the invitation given by the ISA established six inventions and defined these inventions in relation to certain claims. Inter alia one subject-matter of the claims is an unglycosylated protein exhibiting GM-CSF activity. Another subject-matter is said to be the same proteins in glycosylated form.

7. The "glycosylated" proteins are mentioned first in Claim 1 and thus have to be considered as the "main invention" which has to be searched by the ISA in any case, irrespective of whether or not the Applicants paid any additional fees.

In the reasons of the invitation to pay additional fees the ISA, however, considered Claims 9, 14, 16 completely and Claims 17-20 partially to be the first "reasonably searchable invention of this application". Claim 9 relates to one protein with a defined amino acid sequence in its "unglycosylated" form. This protein is comprised in the

second above defined subject-matter of Claim 1 and can, therefore, in the Board's opinion, not be considered as to be the "main invention" mentioned first in the claims. One may therefore draw the conclusion that the ISA did not act according to its obligation clearly defined in Article 17(3)(a) PCT.

8. Claim 1, which should have been searched by the ISA, is only mentioned in group five of the reasons for the invitation to pay additional fees. However, Claim 9, which forms the basis of the first invention mentioned in the invitation, is also a dependent claim referring back to Claim 1 and it is of the same category as Claim 1. Thus, Claim 9 is a particular embodiment of the invention claimed in Claim 1. Therefore, Claim 1 must have been the subject of at least a partial search. Nevertheless, Claim 1 is not mentioned in the first invention mentioned in the invitation.

As may become apparent from the above, the situation is not clear and indeed caused confusion to the Applicants as they stated in the letter of 3 February 1989.

In the view of the Board, there is an inconsistency between what the ISA should have done according to the clear wording of Article 17(3)(a) PCT, what the ISA in the reasons of the invitation states having done and what the ISA actually did. Thus, the ISA did not properly show what has been searched with the exception of Claims 17-20.

9. Rule 40.1 PCT stipulates that the invention provided for in Article 17(3)(a) PCT must specify the reasons for which the international application is not considered as complying with the requirements of unity of invention. The purpose of setting out reasons is to enable the Applicants and, in the case of a protest, the Board of Appeal as well, to examine

whether the request for the payment of additional fees owing to lack of unity of the invention is justified. The considerations behind the finding that the invention lacks unity and the consequences drawn by the ISA must be readily comprehended from the reasons given in the invitation of the ISA.

10. In several decisions the Boards of Appeal have consistently expressed the view that the existence of clear reasons is an essential prerequisite for an invitation to be legally effective (WO4/85, O.J. EPO 1987, 63; WO1/89 of 21 March 1989, unpublished). According to this jurisprudence, the basic considerations behind the finding that the invention lacks unity must be set out in a logical sequence. This requirement is not met in this case.

11. In the present case the Board considers the reasons in the invitation as not being sufficient because it is not possible to understand what has been searched and therefore for which reasons non-unity of the invention was established by the ISA. The Applicants' letter of 3 February 1989 confirms this view of the Board.

12. The situation is different as far as Claims 17-20 are concerned. The Applicants expressly requested in their letter of 23 November 1988 that the search should be restricted to the expression vectors of Claims 17-20. Because the ISA grouped these claims into two different groups of invention and thereby indicated non-unity of Claims 17-20, the Applicants paid one additional search fee. Payment was done under protest and reasons were submitted in the mentioned letter by the Applicants why they contended that Claims 17-20 clearly relate to one single invention.

13. Claim 17 relates to an expression vector for the production of human granulocyte-macrophage colony stimulating factors in a mammalian cell host, comprising five defined features. As far as it may be construed from the reasons given in the invitation, the ISA held that this expression vector did not belong to one single inventive concept because the use of this expression vector is for the production of glycosylated (invention 1) and unglycosylated (invention 2) human GM-CSF. In fact, the wording of Claim 17 makes it clear that the use of the expression vector is for an expression in a **mammalian cell host**. As it is known to the skilled person, expression in a mammalian cell host usually produces glycosylated proteins. This fact is also expressed in Claim 15, which has the wording "... wherein said protein has been glycosylated by a mammalian cell expression host". There is, therefore, no reason to object to unity of Claim 17 with regard to the production of glycosylated or unglycosylated proteins.

14. Furthermore, the Board wishes to mention an earlier decision WO1/83 of 12 July 1983 which considered plasmids (the "expression vectors" in the present case) **a priori** to belong to one single invention together with host bacterial strains in which these plasmids can be propagated and used in the sense of precursors. Further, patents have been granted comprising claims relating to precursors or intermediates and end products without questioning a priori the unity of invention (T 35/87, O.J. EPO 1989, 134). In the present circumstances, the Board sees no reason to depart from this established case law. Claims 18-20 are referred back to Claim 17 and relate to preferred embodiments of certain featurse of Claim 17. Therefore, even insofar, there is no internal a priori lack of unity to be found in Claims 17-20.

15. It is, therefore, the Board's conclusion that the reasons in the invitation to pay additional fees with regard to Claims 1-16 and 21-23 are not clear and thus not sufficient in the sense of Rule 40.1 PCT. With regard to Claims 17-20 there is no lack of unity. Under these circumstances, there was no sound basis to invite the Applicants to pay one additional search fee.

Order

For these reasons, it is decided that:

(1) The invitation to pay additional fees dated 27 October 1988 is set aside.

(2) The refund of the additional fee paid is ordered.

M. Beer
The Registrar

P. Lançon
The Chairman