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D E C I S I O N
of 19 October 1999

Case Number: T 1112/96 - 3.3.4

Application Number: 86900439.0

Publication Number: 0205564

IPC: C12P 21/00

Language of the proceedings: EN

Title of invention:
Method for the production of erythropoietin

Patentee:
Genetics Institute, Inc.

Opponent:
Janssen-Cilag GmbH
Hoechst Aktiengesellschaft
Johnson & Johnson
Elanex Pharmaceuticals Inc.
Merckle GmbH Chem.-pharm. Fabrik

Headword:
Erythropoietin production/GENETICS INSTITUTE

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

Keyword:
"Added subject-matter (no)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
T 0412/93

Catchword:

-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1112/96 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 19 October 1999

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 11 October 1996 revoking European patent No. 0 205 564 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: R. E. Gramaglia
W. Moser
F. Davison-Brunel
C. Holtz

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division issued on 11 October 1996 whereby the European patent No. 0 205 564 was revoked under Article 102(1) EPC. The patent had been granted on the basis of European patent application No. 86 900 439.0 claiming priority from three US applications dated 4 December 1984, 3 January 1985 and 22 January 1985 respectively, and it had been opposed by five parties on grounds of Article 100(a) to (c) EPC. The patent as granted contained twenty-two claims for all designated contracting states except Austria (non-AT states) and fourteen claims for AT. Claim 14 for the non-AT states (corresponding to claim 2 for AT) read as follows:

"A method for the production of human erythropoietin comprising culturing in a suitable medium eucaryotic host cells containing a DNA sequence as shown in Table 3 operatively linked to an expression control sequence, and separating the erythropoietin so produced from the cells and the medium."

II. Seventy-five documents were quoted during the proceedings before the opposition division. The opposition division decided that the two requests then on file failed to comply with the requirements of the EPC because they contained claims which either offended against Article 123(2) EPC or did not satisfy the requirements of novelty and inventive step.

III. With the statement of grounds of appeal, the appellants (patentees) filed a main request and three auxiliary requests together with further documents in support of

their arguments. Respondents I and III (opponents 01 and 03) filed jointly comments to the statement of grounds of appeal.

IV. The board issued a communication pursuant to Article 11 of the rules of procedure of the boards of appeal. The appellants, respondents I and III (jointly) and respondents II (opponents 02) sent comments in reply to the board's communication. The appellants replaced all previous requests with a new main request and one auxiliary request. Respondents I and III submitted jointly further comments thereupon.

V. Oral proceedings took place on 18 and 19 October 1999. Respondents V (opponents 05), although duly summoned, did not attend them. The appellants filed a new main request and an auxiliary request during oral proceedings in substitution of all previous requests on file.

Claim 1 of the **main request** reads as follows:

"A method for the production of human erythropoietin comprising culturing in a suitable medium eukaryotic host cells containing the DNA sequence as shown in Table 3 from the sequence ATG encoding initial Met through AGA encoding the terminal Arg operatively linked to an expression control sequence, and separating the erythropoietin so produced from the cells and the medium."

Dependent claims 2 to 7 of the main request concern particular embodiments of the method according to claim 1.

VI. The following documents are referred to in the present decision:

(5) Lawn R.M. et al., Cell, 1978, Vol. 15, pages 1157 to 1174;

(6A) EP-A-0 148 605;

(15) Miyake T. et al., J. Biol. Chem., 1977, Vol. 252, pages 5558 to 5564;

(17) Seki T. el al., Fed. Proc., 1982, Vol. 41, page 365, Abstract No. 563;

(18) Sue J. M. and A. J. Sytkowski, Proc. Natl. Acad. Sci. USA, 1983, Vol. 80, pages 3651 to 3655;

(19) Suggs S. V. et al., Proc. Natl. Acad. Sci. USA, 1981, Vol. 78, pages 6613 to 6617;

(30) Hunkapiller M. et al., Nature, 12 July 1984, Vol. 310, pages 105 to 111;

(33) Lin F-K et al., Exp. Hemat., July 1984, Vol. 12, page 357;

(73) Lee-Huang S., Proc. Natl. Acad. Sci. USA, May 1984, Vol. 81, pages 2708 to 2712.

VII. In the appellants' view, the conflicting European patent application document (6A) does not affect the novelty of the claimed method because it does not disclose the DNA sequence of Table 3 referred to in claim 1. Moreover, they submit that none of the pre-

published prior art documents, taken alone or in combination with other prior art, contains information which could render obvious the claimed method. In particular:

- Document (15) is confined to the purification of urinary erythropoietin, nothing being said about any DNA sequence encoding it;

- Document (18) reports the amino terminal sequence of human erythropoietin and contains two errors which would have rendered impossible for the skilled person the construction of successful probes;

- Documents (17) and (33) are two abstracts with no enabling information;

- Document (73) is a publication which, as recognised later by the author, contains many errors and which could not lead the skilled person to the isolation of cDNA encoding human erythropoietin.

VIII. In the respondents' view, the amendment introduced in claim 1, namely the feature "from the sequence ATG encoding initial Met through AGA encoding the terminal Arg", results in the creation of subject-matter which extends beyond the content of the application as filed where the said specific portion of the DNA sequence of Table 3 is not disclosed, nothing being said about the exclusion from the latter sequence of the 3' and 5' ends.

The respondents maintain that the subject-matter now claimed is entitled only to the second priority date.

The respondents, in particular respondents IV, argue that the method of claim 1, in consideration of the wording of the claim, which does not exclude the presence of a larger DNA sequence, is not novel under Article 54(3) and (4) EPC having regard to document (6A). This document discloses erythropoietin production in eukaryotic cells containing a DNA sequence (cf Table VI) which contains a sequence identical to that now referred to in claim 1.

As regards inventive step, on the one hand, respondents I and III do not see any prior art document which renders obvious the claimed method. On the other hand, respondents II and IV dispute the presence of an inventive step on the basis of the following considerations:

- Respondents II consider that the report in document (33) of the successful cloning and expression of human erythropoietin via the genomic route, which confirmed the validity of the probing strategy (mixed short probes) illustrated in document (17) (in this respect reference was made to the statement in decision T 412/93 dated 21 November 1994, point 124 of the reasons), would have given the skilled person a reasonable expectation of achieving erythropoietin expression with cDNA by way of routine experimentation, the N-terminal amino acid sequence of the protein being known in the art eg from document (18).

- Respondents IV maintain that at the priority date the short probe and the long probe techniques were available to the skilled person for cloning a gene. Starting from document (15), which disclosed substantially purified human erythropoietin from urine, it was obvious for the skilled person, faced with the problem of producing sufficient quantities of the protein, to try the one or the other approach in order to express human erythropoietin in a recombinant system. This had been done already with a number of other proteins. The short probe approach would have required three basic steps, namely (i) digesting and sequencing the available protein by known means (cf eg document (30)); (ii) designing suitable probes (cf eg document (19)); and (iii) either screen a cDNA library, which would have provided directly the sequence of Table 3, or proceed via a genomic library (cf document (5)) as done eg in document (17), and engineer out the introns. Although the latter document provided no guarantee of success, nothing in the art indicated that the approach was unlikely to work. The disclosure of document (33) provided the crucial motivation for persevering and thus a reasonable expectation of success. The long probe approach was equally obvious to try for the skilled person based on the partial amino acid sequences disclosed in document (18). The success reported in document (33), where this approach was used, provided also in this case the substantial motivation and expectation that cloning and expression would be achieved. The disclosure of document (73) would have contributed to the general expectation of success.

IX. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the following documents submitted during oral proceedings: a) claims 1 to 7 as main request, or b) claims 1 to 8 as auxiliary request.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

The main request

Amendments: Article 123(2) and(3) EPC

1. Claim 1 derives from claim 14 as granted for non-AT states by way of introduction in the latter of the feature "from the sequence ATG encoding initial Met through AGA encoding the terminal Arg". This feature has a restrictive effect on the extent of protection conferred. Dependent claims 2 to 7 are identical to granted claims 16 to 21 which were correspondingly dependent from granted claim 14. Thus, the amendment complies with the requirements of Article 123(3) EPC.

2. The board does not share the respondents' objections under Article 123(2) EPC to the said amendment (cf Section VIII, first paragraph supra) for the reasons given hereinafter. In addition to reporting Table 3, the application as filed points specifically on page 16, lines 21 to 30 to the cDNA portion starting at the initial ATG codon encoding Met and to the amino acid sequence of erythropoietin of Table 2 which starts with Met and terminates with Arg. Moreover, claim 19 as

filed refers to a DNA sequence encoding the amino acid sequence 1-166 with the leader sequence starting with Met as illustrated in Table 3. This provides fair support for the reference in claim 1 to the DNA sequence as shown in Table 3 from the sequence ATG encoding initial Met through AGA encoding the terminal Arg. Thus, no offence against Article 123(2) EPC is seen by the board.

The right to priority (Articles 87 and 88 EPC)

3. Although the sequence of Table 3 can be found already in the first priority document, only the second priority document provides the information which points to the specific portion of the said sequence which starts at the ATG encoding initial Met and terminates at the AGA encoding the terminal Arg, this information being the same which justifies the amendment under Article 123(2) EPC (cf point 2 supra; cf second priority document page 17, lines 11 to 19 and claim 47). Consequently, the effective date for the claims at issue is that of the second priority, namely 3 January 1985.

Novelty (Article 54 EPC)

4. While it is true that Table VI of the conflicting European patent application document (6A) contains a DNA sequence which comprises in different places **portions** of the sequence now referred to in claim 1, it is a fact that neither the table itself nor the document as a whole disclose explicitly or implicitly the latter sequence on its own as an uninterrupted nucleotide sequence, ie as a single chemical compound

with no other sequences inserted therein, as requested by present claim 1. Thus, there can be no question of document (6A) affecting the novelty of claim 1.

No other document was cited by the respondents as being prejudicial to the novelty of claim 1. Nor does the board find any such document. Thus, claim 1 satisfies the novelty requirement of Article 54 EPC.

Inventive step (Article 56 EPC)

5. The DNA sequence referred to in claim 1 is the coding portion of the human erythropoietin cDNA. Preparation of a cDNA requires the availability of a suitable cDNA library, and thus a suitable source of mRNA, and the availability of suitable probes for screening it. The only prior art document dealing with the cloning and expression of human erythropoietin cDNA is document (73). Notwithstanding this, none of the respondents considered this document to represent the closest prior art. They rather saw in it a disclosure which contributed to the general expectation of success in expressing human erythropoietin cDNA, said expectation, in their view, being based on the combination of the teachings of other documents, namely documents (17) and (33) or documents (15) and (18). However, the latter documents are concerned either with genomic DNA or with human erythropoietin itself.

6. Contrary to the respondents' view, the board sees in document (73) the closest prior art because it is the document which comes closest to disclosing the claimed invention as it concerns the development of a method for producing human erythropoietin in sufficient

quantities in a recombinant system **via cDNA**. The document, taken at its face value (thus, independently from any alleged later recognition of its invalidity; cf Section VII, last paragraph supra), describes the cloning of human erythropoietin cDNA in E. coli by using pBR322 as a vector and the identification of three clones expressing the protein as fusion protein as detected by radioimmunoassay. No sequence data whatsoever are reported in the document in relation to either the probes or the cDNA inserts or the protein. The document points to the many difficulties encountered in preparing human erythropoietin mRNA (cf page 2709, left-hand column). In the conclusions, it is stated that two of the three isolated cDNA inserts are too short for encoding human erythropoietin and the third "is probably close to the coding size".

7. In the light of document (73) the problem to be solved by the present invention is defined as being the isolation of a complete cDNA sequence encoding human erythropoietin and its expression in eukaryotic cells.

8. The solution is represented by the method of claim 1 which relies on the sequence of Table 3 which, as shown in the examples, indeed results in the expression in eukaryotic host cells of biologically active human erythropoietin.

9. The skilled person, faced with the technical problem as defined above, knew that a first important obstacle was the finding of a source of mRNA encoding human erythropoietin abundant enough to enable the preparation of a suitable cDNA library. This was by no means facilitated by the disclosure of document (73)

which provided no useful technical information in this respect as the information therein was either incomplete or missing.

Another hindrance was the lack of sufficient information on the amino acid sequence of human erythropoietin to enable the preparation of suitable probes. In this respect, document (73) was completely silent, while documents (15) and (18) provided either no sequence data or only partial data. Neither was document (33) of any use, because, although it related to the cloning and expression of genomic clones encoding human erythropoietin, it provided no technical information about the amino acid sequence of the protein, about the probes which had been used, or about the genomic DNA clones which had been isolated. The skilled person knew that the isolation of a genomic clone such as obtained in document (33) could provide a useful probe for screening a cDNA library, but document (33), also read in combination with the extremely generic teaching of the abstract (17), left the skilled person entirely to his or her own resources to find ways to solve the several experimental problems which could be reasonably expected in view of the scarce information available about human erythropoietin. This was not simply a matter of routine as this area of research was quite unexplored at the priority date of the patent in suit.

10. In view of the many uncertainties, the skilled person would have concluded that the task of cloning and expressing in eukaryotic host cells the complete cDNA encoding human erythropoietin was very difficult and that it was not possible to predict a successful

conclusion of the project.

11. For these reasons, the board concludes that the method of claim 1 (and, thus, that of dependent claims 2 to 7) which relies on the specific DNA sequence of Table 3, was not obvious. The presence of an inventive step is thus acknowledged.

12. Adapted description pages were submitted in the oral proceedings with the main request. The respondents had no formal objections to the amendments made. Nor does the board have any objections thereto. The respondents wished the introduction in the passages of the description dealing with the isolation and the expression of genomic clones, of a statement that this aspect of the description was not claimed. However, such a statement is not necessary because the claims are unambiguously directed and limited to the use of the specified DNA sequence of claim 1. Moreover, the description explicitly states on page 14, lines 18 to 19 that the true scope of the invention is set forth in the appended claims.

13. As the patent is to be maintained on the basis of the main request, it is not necessary to discuss the auxiliary request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the following documents:

(a) claims 1 to 7 submitted during oral proceedings as main request, and

(b) description: pages 3, 4, 13, 14, 34, 35 submitted during oral proceedings; and pages 5 to 12, 15 to 33 as granted, and

(c) drawings: Figures 1 to 4, 5A, 5A', 5B, 5B', 5C, 6 to 8 as granted.

The Registrar: The Chairman:

U. Bultmann L. Galligani