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D E C I S I O N
of 6 March 2002

Case Number: T 0224/99 - 3.3.4

Application Number: 85112852.0

Publication Number: 0177957

IPC: C12N 15/10

Language of the proceedings: EN

Title of invention:
Expression of biologically active platelet derived growth factor analogs in eucaryotic cells

Patentee:
ZymoGenetics, Inc.

Opponent:
Beiersdorf Aktiengesellschaft

Headword:
PDGF/ZYMOGENETICS

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Novelty -yes -"
"Inventive step - yes -"

Decisions cited:
G 0009/92

Catchword:
-

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Case Number: T 0224/99 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 6 March 2002

Appellants: (Proprietors of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 23 December 1998 concerning maintenance of European patent No. 0 177 957 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. The appeal lies from the interlocutory decision of the Opposition Division to maintain in amended form the patent No. 0 177 957 with the title "Expression of biologically active platelet derived growth factor analogs in eucaryotic cells" which was granted with 19 claims for all Designated Contracting States other than Austria (non-AT States), with 27 claims for Austria (AT) and with priority dates of 12 October 1984 and 25 February 1986.

II. Claim 1 of the sixth auxiliary request (non-AT States) accepted by the Opposition Division read as follows:

"1. A method of preparing biologically active PDGF analogs, comprising:

introducing into a eucaryotic host cell a DNA construct capable of directing the expression and secretion of biologically active PDGF analogs in eucaryotic cells, said DNA construct containing a transcriptional promoter followed downstream by a gene encoding a protein having substantially the same structure and mitogenic activity as PDGF, and a signal sequence capable of directing the secretion of the protein from the eucaryotic host cell;

growing said eucaryotic host cell in an appropriate medium; and

isolating the protein product of said gene from said eucaryotic host cell,

wherein the eucaryotic host cell is a yeast cell, and the promoter and signal sequence are of yeast origin."

Claims 2 to 4 were directed to further features of the method of claim 1. Claims 5 to 7 related to a specific yeast cell, DNA construct and plasmid, respectively. Claim 8 was directed to a method for preparing PDGF (platelet-derived growth factor) analogs substantially homologous to the PDGF B chain in yeast cells.

The corresponding claims 1 to 8 were allowed for AT.

III. The Opposition Division came to the conclusion that the subject-matter of these claims was novel and inventive since "*the prior art does not refer to or suggest the expression of PDGF analogs in yeast cells*".

IV. The Appellants (Patentees) filed an appeal. At oral proceedings which took place on 6 March 2002, they submitted as sole request, a request which comprised 14 claims for the non-AT States and 21 claims for AT.

Claims 5 to 8 and 10 to 12 of this request for non-AT States are identical to claims 1 to 7 as maintained by the Opposition Division.

Claim 1 is identical to claim 2 as granted while claims 2 to 4, 9, 13 and 14 correspond to granted claims 3 to 5, 12, 17 and 18 when restricted to yeast.

Claim 1 reads as follows:

"A DNA construct capable of directing the expression and secretion of biologically active PDGF analogs in

eucaryotic cells, said DNA contruct containing a transcriptional promoter followed downstream by a gene encoding a protein having substantially the same structure and mitogenic activity as PDGF, and a signal sequence directing the secretion of the protein from the eucaryotic cell,

wherein the eucaryotic cell is a yeast cell, and the promoter and signal sequence are of yeast origin."

Claims 2 to 4 are directed to further features of the DNA construct of claim 1 and claim 9 is directed to a yeast cell transformed with any one of said constructs. Claim 13 is directed to a DNA construct capable of directing in yeast cells the expression and secretion of biologically active analogs of the B chain of PDGF, wherein the promoter and signal sequence are of yeast origin. Claim 14 relates to a method for preparing such analogs from a DNA construct with the features recited in claim 13.

In the corresponding set of claims for AT, claims 1 to 14 are identical to claims 1 to 14 for the non-AT States. Claims 15 to 21 are directed to methods for preparing constructs having the features recited in claims 1 to 4 and 11 to 13, respectively.

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

(2): Devare, S.G. et al., Proc.Natl.Acad. Sci.USA, Vol. 80, pages 731 to 735, 1983,

(7): Owen, A.J. et al., Science, Vol. 225, pages 54 to 56, June 1984,

(9): Deuel, T.F. et al., Science, Vol. 221, pages 1348 to 1350, 1983.

VI. The Appellants' arguments insofar as they relate to the set of claims filed at oral proceedings may be summarized as follows:

As the prior art failed to disclose the use of yeast as host cells for the expression of PDGF analogs, the subject-matter of claims 1 to 4, 9, 13 and 14 which were directed to constructs, cells and methods specific for the expression of PDGF analogs in yeasts was novel.

At the priority date, the skilled person knew from documents (7) and (9) that PDGF or analogs thereof were heavily processed in the higher eucaryotic cells where they were naturally produced. It would not have been expected that **yeast** could produce these analogs in biologically active form. Inventive step could, thus, be acknowledged.

VII. The Respondents (Opponents) did not express any objections against this set of claims.

VIII. The Appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of:

claims: sets of claims filed at oral proceedings on 6 March 2002,

description: pages 3,4,6,7 and 8 as submitted at oral proceedings on 6 March 2002, pages 5,9 to 18 as granted,

Figures: as granted.

The Respondents made no request.

Reasons for the Decision

1. Claims 5 to 8 and 10 to 12 (non-AT States) are the claims on the basis of which the Opposition Division took the decision of maintaining the patent and only the Patentees appealed this decision. Thus, in accordance with the decision of the Enlarged Board of Appeal G 9/92 (OJ EPO 1994,875) that "*if the patent proprietor is the sole appellant against an interlocutory decision maintaining a patent in amended form, neither the Board of Appeal nor the non-appealing opponent as a party to the proceedings as of rights under Article 107, second sentence, EPC may challenge the maintenance of the patent as amended in accordance with the interlocutory decision,* the patentability of claims 5 to 8 and 10 to 12 need not be investigated.

2. Claim 1 corresponds to granted claim 2. Claims 2 to 4, 9, 13 and 14 corresponding to granted claims 3 to 5, 12, 17 and 18 have been amended in such a way as to be restricted to yeast. These claims fulfill the requirements of Article 123(2) EPC as the expression in yeast of PDGF analogs is described in the application as filed. The requirements of Article 123(3) EPC are also fulfilled as the amendment does not amount to a broadening of the scope of the claims. This amendment does not introduce unclarity (Article 84 EPC).

3. None of the documents on file are concerned with the

expression of PDGF DNA constructs in yeast so that the constructs as well as the yeast cells containing them and the method for the production of PDGF analogs in yeast, which are the subject-matter of claims 1 to 4, 9, 13 and 14 are novel.

4. The closest prior art to the subject-matter of these claims is document (7). This document is a **research article** which discloses that normal rat kidney cells (NRK) transformed by simian sarcoma virus (SSV) release into the culture medium a biologically active mitogen with properties identical to those of PDGF (abstract). On page 56, left-hand column, the mitogen is tentatively identified as being the product of the SSV v-sis gene. The v-sis protein is said to be a 28Kd protein that dimerizes to a 56Kd protein. In the rat cells, the 56Kd protein is then processed by proteolysis at the amino- and carboxy-terminals to yield dimeric proteins of 46-, 34-, 30- and 24- Kd.

5. Starting from the closest prior art, the problem to be solved may be defined as the production of PDGF analogs **in high quantities**.

6. At the priority date, the skilled person knew from document (9) that "*PDGF is well suited to mediate inflammatory and repair processes at sites of blood vessel injury and may play an important role in the genesis of artherosclerosis in humans*" and also, that it was only possible to purify it in relatively small quantities. In addition, he/she knew from the closest prior art that PDGF analogs existed which exhibited the same properties as PDGF (see above). Thus, it would have been obvious to formulate the problem of finding some means to produce the PDGF analogs in such

quantities as might help understanding the role of PDGF. The formulation of the problem per se is not inventive.

7. As a solution, methods and means are proposed for expressing a gene encoding PDGF analogs, in particular, the v-sis protein in yeast. This includes yeast host cells as well as DNA constructs carrying a yeast promoter and a yeast signal sequence upstream from the v-sis gene.

8. The cloning of the v-sis gene per se in any known expression system did not involve more than routine work as the sequence of this gene was known from document (2).

9. In the Board's judgment, however, the choice of yeast as the host for expressing the PDGF analogs in a recombinant manner is in itself non-obvious. Indeed, as shown in document (7) (see above) but also in document (9), the natural v-sis gene product undergoes quite a number of post-translational modifications in higher eucaryotic cells where it is thought to have mitogenic properties. It could not have been expected that such modifications would take place in yeast which is a lower eucaryote and, therefore, does not necessarily carry out the same post-translational modifications. Otherwise stated, the skilled person could not expect that in using a yeast expression system, a biologically active PDGF analog would be produced. Thus, the requirements of Article 56 EPC are fulfilled.

10. For these reasons, which also apply to the subject-matter of the claims for AT filed at oral proceedings,

the requests are allowed.

11. There are no objections to the adaptation of the description.

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 as requested by the Appellants.

The Registrar: The Chairman:

P. Cremona L. Galligani