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D E C I S I O N
of 1 October 2002

Case Number: T 0747/01 - 3.3.4

Application Number: 96116202.1

Publication Number: 0768383

IPC: C12N 15/80

Language of the proceedings: EN

Title of invention:
Promoters of filamentous fungi and use thereof

Applicant:
DSM N.V.

Opponent:
-

Headword:
Filamentous fungi/DSM

Relevant legal provisions:
EPC Art. 76, 56

Keyword:
"Divisional application - extension beyond earlier application as filed (no) - after amendment"
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0747/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 1 October 2002

Appellant: DSM N.V.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 12 January 2001 refusing European patent application No. 96 116 202.1 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
S. C. Perryman

Summary of Facts and Submissions

I. The present patent application with title "Promoters of filamentous fungi and use thereof", which is a divisional application of the EP application 86 902 449.7, was refused by the examining division under Article 76 EPC as it was found that claims 1 and 2 then on file related to subject-matter which extended beyond the content of the earlier application as filed. In the view of the examining division, none of the passages relied upon by the applicants supported the general reference to starch-inducible promoters in the said claims which were directed to a method of producing a polypeptide in a filamentous fungus host cell.

II. The applicants (appellants) lodged an appeal against this decision. With the statement of grounds of appeal, they filed three auxiliary claim requests and requested accelerated treatment of the application in view of its filing date of 14 April 1986. They also requested a decision on the patentability requirements not yet examined by the first instance.

Their main argument against the finding of the examining division was that the application as a whole allowed to derive directly and unambiguously the feature "positively induced by starch" also in respect of a method claim with a more general outline, not only in respect to a method for polypeptide production that used the promoter region of the glucoamylase gene of Aspergillus niger. In this respect, they made reference to a number of decisions of the boards of appeal.

III. In the official communication dated 27 May 2002, the

board expressed the provisional opinion that the arguments put forward by the appellants in their statement of grounds of appeal were not considered to contribute any further elements which could convince the board to set aside the contested decision.

IV. In reply to said communication, the appellants filed as auxiliary request IV claims 1 to 5. They did not submit any comments on the preliminary position of the board.

V. Oral proceedings took place on 1 October 2002. After the discussion of the claim requests on file, the appellants filed claims 1 to 4 as a sole request in replacement of all the previous requests. A description adapted thereto was also filed.

Claim 1 read as follows:

" A method of producing a polypeptide in a filamentous fungus host cell which comprises:

(a) culturing a host cell in a culture medium comprising starch

(b) said host cell containing one or more copies of a DNA construct;

(c) said DNA construct comprising:

(i) a regulated DNA promoter region of the glucoamylase gene from *Aspergillus niger* which contains a DNA sequence active in regulation of gene transcription, said DNA sequence rendering the gene positively induced by starch; and

(ii) a DNA coding for a polypeptide operably linked to the promoter, said DNA coding for a polypeptide being foreign to the promoter;

(d) wherein said host cell is cultured under conditions in which the presence of starch induces the transcription promoting function of the promoter; and optionally

(e) recovering said polypeptide from the medium."

Dependent claims 2 and 3 related to embodiments of the method of claim 1 in which either Aspergillus nidulans or Aspergillus niger was the host. Claim 4 was directed to the use of a DNA construct of the preceding claims for transforming a filamentous fungus host cell.

VI. The appellants submitted that the subject-matter of the sole request on file complied with the requirements of Article 76 EPC being explicitly supported by the parent application as filed (cf in particular page 6, second full paragraph).

In their view, the claimed subject-matter enjoyed the priority date of CA 479 135 (ie 15 April 1985; this was erroneously indicated on the publication of the present application as 20 December 1985) and was novel and inventive having regard to the following documents:

(1) Van den Hondel C.A.M.J.J. et al., Abstract 1557, UCLA Symposia on Molecular & Cellular Biology, 14th Annual Meeting, April 6 - April 25 1985, J. Cell. Biochemistry Supplement 9C, 1985;

(2) EP-A-0 126 206.

(3) EP-A-0 215 594 (earliest priority date 29 August 1985)

Document (3) had been cited by a third party under Article 115 EPC against novelty under Article 54(3)(4) EPC.

VII. In addition to the above, the following two documents among the documents on file are referred to in this decision:

(6) Boel E. et al., The EMBO Journal, Vol. 3, No. 7, 1984, pages 1581 to 1585;

(8) Nunberg J.H. et al., Mol.Cell. Biol., Vol. 4, No. 11, November 1984, pages 2306 to 2315.

VIII. The appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of the following:

Description: pages 2 to 14 as submitted at oral proceedings on 1 October 2002;

Claims: 1 to 4 as submitted at oral proceedings on 1 October 2002;

Figures: 1A to 17 on sheets 1 to 25 as filed.

Reasons for the Decision

1. The subject-matter of the sole claim request on file is fully supported by the earlier application as filed, in particular on page 6, lines 6 to 19 and in Examples 3

to 5 which explicitly disclose the use of the promoter region associated with the glucoamylase gene in Aspergillus niger which is positively induced by starch in DNA constructs in a method for producing a polypeptide in a filamentous fungus host cell. Thus, the reasons which led to the rejection under Article 76 EPC are no longer applicable and the decision under appeal has to be set aside.

2. As for the question whether a complete examination of the patentability requirements should be carried out by the board in exercise of its discretion under Article 111(1) EPC, the board observes that the claims on file relate to subject-matter on the patentability of which the examining division had already expressed a negative opinion on inventive step during the prosecution of the case. Thus, the board, in consideration of the 1986 filing date, considers it more appropriate to re-examine all issues itself as requested by the appellants (cf Section II above), rather than remitting the case which might entail a further appeal and much delay.

3. During the prosecution of the case at the level of the first instance, the examining division, while acknowledging the sufficiency of disclosure of the narrower embodiment in relation to the use as starch-inducible promoter of the promoter region of the glucoamylase gene from Aspergillus niger, expressed in its communication dated 27 July 1999 a negative view on inventive step on a possible version of the claim restricted to such an embodiment. This view was based on the combination of the teachings of documents (1) and (2). It was maintained that document (1) made available the basic expression system to analyse

(Aspergillus) promoter sequences by combining them with a foreign gene and document (2), which elucidated the regulatory region of the glucoamylase coding region, made the choice of this promoter a preferred one. During prosecution before the first instance, a third party had also raised under Article 115 EPC, a lack of novelty objection vis-à-vis document (3).

4. As regards sufficiency of disclosure, the board considers that the description contains a clear and complete disclosure of all the elements which allow the skilled person to carry out the method of claims 1 to 4.

5. As the claimed subject-matter is entitled to the first priority date, ie 15 April 1985, being explicitly disclosed in the Canadian patent application CA 479 135 (cf eg page 4, second paragraph and claim 19), document (3) which enjoys a later priority (namely 29 August 1985) is not to be taken into account as prior art.

As none of the other documents presently on file discloses the same subject-matter as claimed, novelty is acknowledged.

6. As regards the issue of inventive step, the board considers that neither a combination of the teachings of documents (1) and (2) nor any other combination of documents on file renders the claimed subject-matter obvious for the skilled person for the following reasons:

(a) Document (1), which can be seen as the closest prior art since it is concerned with gene expression in the filamentous fungus Aspergillus

nidulans, describes a system for analysis of regulation signals in Aspergillus, said system consisting in fusing the E. coli lacZ reporter gene to a promoter or regulatory region of Aspergillus. In particular, the fusion of said reporter gene with the trpC gene of Aspergillus nidulans is disclosed. It is shown that the lacZ gene is expressed as a functional fusion protein, and the conclusion is drawn that the system can be used to analyse transcription-regulation signals of inducible Aspergillus genes.

(b) In view of document (1), the problem underlying the present application can be defined as being the provision of a method for producing in a filamentous fungus host cell a polypeptide under the regulation of an inducible promoter;

(c) The relevant question is whether it would have been obvious for the skilled person to propose as a solution a method based on the use of a DNA construct comprising a regulated DNA promoter region of the glucoamylase gene from Aspergillus niger, said DNA sequence rendering a gene, which is foreign to the promoter, positively induced by starch;

(d) As document (1) does not contain any suggestion as to the use of the promoter region of the glucoamylase gene of either, in general, Aspergillus, or, in particular, Aspergillus niger for fusions with the reporter gene lacZ, the question arises whether the skilled person would have derived such a suggestion from any other prior art document, in particular from document

(2);

(e) Document (2) discloses a DNA from Aspergillus awamori encoding glucoamylase and its use in the preparation of expression vectors for the production of glucoamylase in bacterial hosts, preferably E. coli, or in yeast, preferably Saccharomyces (cf page 3, lines 15 to 18, and page 13, lines 18 to 23). The promoter region within the sequence is identified. However, regulated expression of the DNA sequence by inducers such as starch is not envisaged. Nor are filamentous fungi mentioned as possible hosts. Actually, the document indicates that the promoter region has to be exchanged so that yeast will express the gene (cf page 12, lines 13 to 16). Thus, this document does not provide any incentive to use the inducible promoter region of glucoamylase of, in general, Aspergillus or, in particular, Aspergillus niger for expressing a polypeptide in filamentous fungi;

(f) Of the other documents on file, in the board's view, documents (6) and (8) would have been taken into closer consideration by the skilled person. Document (6) relates to a study of the glucoamylase-specific regions from the Aspergillus niger genome, the identification of the promoter region being one of the items described and discussed. However, the document makes no suggestion as regards the possibility either of using it in fusion with a foreign gene or of exploiting any inducibility properties. Document (8) is concerned with the molecular cloning and characterisation of the glucoamylase gene of

Aspergillus awamori. Although postulating that induction of glucoamylase is regulated transcriptionally, the document does not provide any suggestion in the direction of fusing a regulatory region of this gene or of an analogous gene from Aspergillus niger to a foreign gene.

7. For these reasons, an inventive step is acknowledged.

Adaptation of the description

8. There are no objections to the amendments to the description which have been effected to bring it into line with the claims.

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 grant a patent on the basis requested by the appellant.

The Registrar: The Chairperson:

P. Cremona U. Kinkeldey