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D E C I S I O N
of 29 October 2003

Case Number: T 0891/02 - 3.3.8

Application Number: 92901887.7

Publication Number: 0563201

IPC: C12N 15/56

Language of the proceedings: EN

Title of invention:

Genetically engineered modification of potato to form amylose-type starch

Applicant:

BASF Plant Science GmbH

Opponent:

-

Headword:

Potato starch/BASF

Relevant legal provisions:

EPC Art. 83

Keyword:

"Sufficiency of disclosure (no)"

Decisions cited:

T 0158/91, T 0612/92, T 0694/92, T 0639/95

Catchword:

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Case Number: T 0891/02 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 29 October 2003

Appellant: BASF Plant Science GmbH
D-67056 Ludwigshafen (DE)

Representative: Bieberbach, Andreas, Dr
BASF Aktiengesellschaft
Patentabteilung GVX - C6
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 7 March 2002
refusing European application No. 92901887.7
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
C. Rennie-Smith

Summary of Facts and Submissions

- I. European Patent Application No. 92 901 887 was published as international application WO 92/11375 (EP A 0 563 201) with the title "Genetically engineered modification of potato to form amylose-type starch". In a decision issued on 7 March 2002 the examining division refused the application pursuant to Article 97(1) EPC on the grounds of lack of sufficient disclosure (Article 83 EPC) and lack of clarity (Article 84 EPC) of the main and auxiliary requests. The examining division questioned also the novelty of the subject-matter of claim 8 of the second auxiliary request.
- II. With respect to Article 83 EPC, the examining division decided that the patent application did not describe the claimed subject-matter in such sufficient detail as to enable a person skilled in the art to carry out the invention without being dependent on pure chance. In particular, it was found that the application did not provide sufficient information on the so-called "potato branching enzyme (BE) protein" in order for the skilled person successfully to purify this enzyme and obtain partial protein sequences that would allow the design of oligonucleotides suitable for the identification of a cDNA encoding this protein. Further, the examining division held that the application provided neither sequence information for the promoter of the branching enzyme gene, nor data that clearly demonstrated that the expression of the BE gene would be inhibited by the use of an antisense construct. With regard to Article 84 EPC, the examining division regarded the use

of the terms "tuber-specific promoter" and "branching enzyme" in eg claim 1 of all requests as arbitrary.

III. On 19 March 2002 the appellant lodged an appeal against the decision of the examining division and with the statement of grounds, filed on 11 July 2002, it submitted a new main request with claims 1 to 12 that corresponded essentially to claims 1, 2, 5 to 8 and 10 to 15 of the main request as rejected by the examining division and a new auxiliary request with claims 1 to 7.

Claims 1 and 2 of both the new main and auxiliary requests read:

"1. A method of increasing the formation of amylose-type starch in potato plants by suppressing formation of amylopectin-type starch, characterised by introducing into the genome of the potato tissue a gene construct, comprising a tuber-specific promoter, a transcription start site and the first exon of the gene coding for branching enzyme (BE gene) in potato, said exon being inserted in the antisense direction.

2. A method of producing amylose-type starch, characterised in suppressing formation of amylopectin-type starch in potato plants by introducing into the genome of a potato tissue a gene construct, comprising a tuber-specific promoter, a transcription start site and the first exon of the gene coding for branching enzyme (BE gene) in potato, said exon being inserted in the antisense direction, and subsequently extracting the amylose-type starch from the tubers."

Claims 3 to 6 of the main request concerned antisense constructs, and claims 7 to 12 were directed to, respectively, a vector, a potato plant cell, a potato plant, potato tubers, a seed and microtubers from potato plants, all comprising an antisense construct as claimed in one of the claims 3 to 6.

Claims 3 to 7 of the auxiliary request corresponded in principle to claims 8 to 12 of the main request, except that they were formulated as "product-by-process" claims.

- IV. The appellant requested oral proceedings if the board considered confirming the decision of the examining division.

- V. Oral proceedings were summoned. In a communication annexed to the summons the board expressed the provisional opinion that the application was seriously insufficient in its disclosure of the claimed invention, and that this objection would apply equally to both the main and auxiliary requests.

- VI. In preparation for the oral proceedings, the appellant filed certified translations of correspondence with the Swedish Department of Agriculture on field trials carried out in 1993/1994, as well as an opinion of Prof. Steup and a list of additional documents. Copies of the documents cited in either the list and/or the opinion were also filed.

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

D1: G.H. Vos-Scheperkeuter et al., Plant Physiol., 1989, Vol. 90, pages 75 to 84;

D2: S.A. Jobling et al., The Plant Journal, 1999, Vol. 18(2), pages 163 to 171.

VIII. In writing and during oral proceedings the appellant argued that the use of antisense constructs in order to inhibit a gene encoding branching enzyme was a straightforward technique at the priority date of the present application. In the description, starting on page 5, line 23, it was disclosed how appropriate cDNA clones were prepared, said clones being used for isolation of the branching enzyme gene from a genomic library. The appellants maintained that the content of Sambrook et al., "Molecular Cloning. A laboratory manual", 1989 (a later version of the laboratory manual referenced in the specification of the application in suit, but published before the priority date of the same) showed that technologies related to molecular cloning were firmly established in the art. By following the description the person skilled in the art would arrive at the result as claimed without undue burden and without needing inventive skill. Later experimental evidence showed that the concept and methods described in the specification yielded microtubers that contained substantially more high-amylose starch material than the non-transformed controls.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or the auxiliary request as filed on 11 July 2002.

Reasons for the Decision

Article 83 EPC

1. The question at issue is whether the subject-matter of claims 1 to 12 of the main request or claims 1 to 7 of the auxiliary request is sufficiently disclosed in the application as filed.

2. The disclosure of the invention for which protection is sought is one of the fundamental requirements for the grant of a patent. This requirement is based on the legal principle according to which the inventor is granted a temporary exclusivity to the invention in return for the disclosure of the technical teaching to the public. In the European Patent Convention the disclosure requirement is formulated in Article 83 EPC, which states that a European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

3. In the assessment as to whether a European application fulfils the requirement of Article 83 EPC, it is a well-established principle in the case law of the boards of appeal that, for the disclosure of an invention to be sufficiently clear and complete, the skilled person, on the basis of the information

provided in the application itself and by using the common general knowledge at the application date (or the priority date, if applicable), has to be able to achieve the desired result without undue burden and without exercising any inventive skill (see eg decisions T 694/92 OJ EPO 1997, 408 and T 612/92 of 28 February 1996).

The examination as to the sufficiency of a disclosure in a patent application has to be conducted in each case on its own merits, and it depends on the correlation of the facts of the case to certain general parameters, eg the amount of reliable technical details disclosed in the application, the time when the disclosure was presented to the public and the corresponding common general knowledge, as well as the character of the technical field and the average amount of effort necessary to put into practice a certain written disclosure in that technical field (see decision T 158/91 of 30 July 1991, point 2.3 of the reasons; and T 639/95 of 21 January 1998).

4. The question at issue in the present case is whether, taking into account the guidance provided by the application as filed and the common general knowledge at the time the disclosure was presented, the skilled person could have arrived at the invention as claimed without undue burden and without exercising any inventive skill.

5. The aim of the method as claimed in claim 1 of both the main and auxiliary requests is to increase the formation of amylose-type starch in potato cells by suppressing the synthesis of amylopectin-type starch.

To achieve this aim the inventors propose to inhibit the transcription of the potato branching enzyme gene by introducing into the potato cell genome a construct comprising a tuber-specific promoter, a transcription start and the first exon of the gene coding for branching enzyme in potato, the exon being inserted in the antisense direction.

6. It follows from the above that, in order to carry out the claimed invention the skilled person would first have to prepare a construct with a transcription start and the first exon of the potato gene coding for branching enzyme inserted in the antisense direction with respect to the tuber-specific promoter. The appellant acknowledged that the DNA sequence encoding the first exon could not be derived from the amino acid sequence of peptides obtained by proteolytic digestion of the BE protein, because in potato the branching enzyme is processed and the amino acid sequence corresponding to the first exon is lost. Thus, the availability of the full-length cDNA and genomic sequence of the potato gene encoding branching enzyme is essential for carrying out the invention.

7. However, the DNA sequence of the potato BE gene was not publicly available at the priority date of the application, nor was it disclosed in the application as filed. The examples in the present application fail to provide any information on a DNA sequence that encodes potato branching enzyme, but only refer the reader to the antisense constructs depicted in Figure 2. In this figure an antisense fragment of the BE gene is represented as a "black box" inserted between a promoter (CaMV 35S, patatin 1 or GBSS promoter) and the

NOS terminator. Thus, in the absence of any DNA sequence information for the potato branching enzyme gene, the skilled person willing to prepare the gene construct required to carry out the invention as claimed would first have to isolate the BE gene from potato. This has been admitted by the appellant.

8. Hence the question arises whether the quantity and quality of experimentation required for a person of ordinary skill to isolate the potato BE gene, based on the guidance provided in the application as filed and on common general knowledge, was undue.

9. For specific technical details concerning the isolation of the BE gene, the appellant referred to the paragraph entitled "Isolation of Genomic BE Gene in Potato" on page 5 of the application. In this paragraph the skilled person is informed that:

"Based on a known peptide sequence from the BE gene (sic) in potato, two synthetic oligonucleotides overlapping one another are produced. The oligonucleotides (produced at the Institute for Cell Biology, Uppsala, Sweden, at the applicant's request) are used for identification of cDNA clones from a cDNA library in lambda gt 11 (produced on the applicant's behalf by Clontech, USA). The cDNA clones are used for isolation of the genomic BE gene from a genomic library in EMBL 3 (produced on the applicant's behalf by Clontech, USA)." (emphasis added by the board)

10. Thus, if the skilled person, following the instructions provided in the application, intended to isolate the DNA encoding the potato branching enzyme, he or she

would first have to know at least part of the amino acid sequence of the BE protein. However, the application fails again to provide any information on the amino acid sequence of the protein or a peptide derived therefrom, and the appellant has admitted that such sequences were not publicly available at the priority date.

11. The appellant submitted that the fact that the required peptide sequence was neither disclosed in the application nor known in the art would not have been a hindrance, since the skilled person could have purified the BE protein following the indications given in the application as filed and, with the pure protein in his or her hands, obtained at least partial amino acid sequences that would serve as a basis to prepare synthetic primers for screening a potato cDNA library for the BE gene.

The board notes that the only information provided in the application with respect to the purification of the BE protein is found on page 3, lines 16 to 22. There it is stated that the potato branching enzyme is a monomer protein with a molecular weight that varies between 79 and 103 kD, depending on the purifying process used. It is further stated on page 3, lines 19 to 21 of the application that:

"There are indications that potato BE should consist of several forms, but presumably several forms are degradation products from the actual protein (Vos-Scheperkeuter, 1989; Blennow & Johansson, 1990)."

12. At the priority date the article by Blennow & Johansson referenced in the application was still in press and was not published even until 1991 (ie after the priority date of the present application). As to the referenced article by Vos-Scheperkeuter et al. (document D1), upon which the appellant relied in its submissions, it describes the purification of starch branching enzyme from potato tubers using several cycles of chromatography on three different types of columns, as well as the preparation of antibodies against the purified potato enzyme, both in its native and denatured form. According to document D1 the behaviour of potato branching enzyme on all chromatography columns tested would strongly suggest that the enzyme occurs as a single protein entity. However, the authors noted that a close examination of the SDS-gel profile showed that the purified BE protein did not run as a single sharp band, but rather as a diffuse and broad band, which, in some cases, appeared to consist of two very closely running bands. The authors concluded that the observation of a double band opens up the possibility that potato plants, like many other plants, contain multiple forms of branching enzyme, and therefore additional evidence had to be obtained for the definite identification of this double band (see document D1, page 82, right column, second paragraph from the bottom). The possibility contemplated in document D1 was confirmed by the finding, after the priority date of the application, of a second potato starch branching enzyme with a similar molecular weight (see document D2 filed by the appellant in the appeal proceedings). The two potato branching enzymes are only 55% identical on the amino acid level.

13. Thus, the skilled person, when trying to obtain pure branching enzyme protein from potato tubers by the purification method of document D1, would be confronted with the uncertainty as to whether the protein preparation obtained contained one or more protein species with branching enzyme activity. In this situation the skilled person would have to decide whether to obtain partial peptide sequences from this protein preparation, taking the risk of sequencing peptides originating from different proteins, or whether he or she should perform additional purification steps not described in document D1. In this respect the skilled person would not be able to rely on any guidance from the application or the prior art, and it would be up to him or her to find a way to further purify BE protein in order to obtain reliable peptide sequence data that could serve as a basis for the design of oligonucleotide primers.

14. During oral proceedings the appellant argued that, alternatively, the skilled person could have tried to isolate the BE gene by immunoscreening of a potato cDNA library using the anti-BE antibodies described in document D1. However, the board notes that the application not only does not offer any experimental guidance in this respect, but also fails to suggest such an approach.

15. In the board's judgement the choice of one of the above mentioned possible alternatives, ie purifying the potato BE protein and obtaining partial amino acid sequences as basis for oligonucleotides primers or cloning the BE gene directly by immunoscreening, is far

from being clear and straightforward, and the amount of necessary effort is considerable, especially taking into account the scarce technical details provided in the application. Even if, as argued by the appellant, all the molecular cloning techniques required were well established in the art at the priority date of the present application, the board considers that to devise a feasible method for the cloning of the potato gene for branching enzyme represented an undue burden for the person of ordinary skill, and it cannot be excluded that this would even require the application of inventive skills.

16. The experimental data and reports of results from field trials submitted by the appellant in support of the issue of sufficiency cannot change the view of the board on this matter. The board notes that the technical information and data provided by the appellant *a posteriori* in its statement of grounds of appeal, including both the full-length cDNA sequence of the potato BE gene and a fragment of a genomic clone corresponding to the first exon, ought to have been disclosed in the application as filed. A failure in the disclosure of essential information for carrying out the invention in the application as filed cannot be remedied by filing the said information at a later stage.

17. As to the opinion of Prof. Steup submitted by the appellant, it does not provide any further arguments in support of disclosure sufficiency, but rather confirms the uncertainties that the skilled person would have had to face with respect to the existence of different forms of potato branching enzyme. It also mentions a

further problem that the skilled person would be confronted with, namely the unpredictability of a selective antisense inhibition of the desired biochemical function when different isozymes are involved in this function.

18. In conclusion, the arguments and evidence put forward by the appellant in support of a sufficient disclosure of both the cDNA and the genomic sequence of the potato gene encoding branching enzyme are not convincing. In the judgement of the board the amount of experimentation required in order to carry out the claimed invention based on the guidance provided by the application as filed and the common knowledge at the time the disclosure was presented, was undue for a person of ordinary skill.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani