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D E C I S I O N
of 12 November 1998

Case Number: T 0380/94 - 3.3.4

Application Number: 86300291.1

Publication Number: 0193259

IPC: C12N 15/82

Language of the proceedings: EN

Title of invention:
Modifying plants by genetic engineering to combat or control insects

Patentee:
Plant Genetic Systems N.V.

Opponent:
Novartis AG Patent and Trademark Dept.
The Lubrizol Corporation

Headword:
Insect control/PGS

Relevant legal provisions:
EPC Art. 56, 123(2), 87-89

Keyword:
"Right to priority (no)"
"Main request - inventive step (no)"
"Auxiliary requests 1 to 4 - added matter (yes)"

Decisions cited:
T 0081/87, G 0001/98

Catchword:
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Case Number: T 0380/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 12 November 1998

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 18 February 1994 revoking European patent No. 0 193 259 pursuant to Article 102(1) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division issued on 18 February 1994 whereby the European patent No. 0 193 259, which was based on the European patent application No. 86 300 291.1 filed on 17 January 1986, was revoked pursuant to Article 102(1) EPC. The priority date of the patent was 18 January 1985. The patent had been opposed by two parties under the terms of Article 100(a) and (b) EPC.

II. The opposition division decided that the subject-matter of the main request as well as that of the auxiliary request then on file lacked an inventive step having regard to the combined teachings of the following two documents:

(D1) EP-A-0 142 924, published on 29 May 1985;

(D12) WO-A-84/02920, published on 2 August 1984.

The opposition division was satisfied that the formal requirements as well as the requirements of novelty and sufficiency of disclosure were met.

The main request on file consisted of claims 1 to 23 of which claims 1 and 20 read as follows (in bold-type characters the additions and in square brackets the deletions in comparison with claims 1 and 20 as granted):

"1. A transformed plant cell **capable of being regenerated into a morphologically normal transformed plant** containing a chimeric gene which: is stably integrated in the genome of said cell, is capable of being expressed in differentiated cells of **said plant** [a plant derived from said cell], and comprises:

(a) a promoter region derived from a gene which is naturally expressed in a plant cell; and

(b) a DNA fragment obtained by truncation of a DNA coding for a crystal protein produced by Bacillus thuringiensis or having substantial sequence homology thereto;

said truncated fragment (b) coding for at least a polypeptide toxin of said crystal protein and providing an insect controlling amount of said polypeptide toxin in said cell as a result of intracellular expression of said truncated fragment (b)."

"20. A **morphologically normal** plant or differentiated plant cell progeny which comprises the plant cell as claimed in any of claims 1 to 19."

III. Both respondents (opponents 01 and 02) replied to the statement of grounds of appeal filed by the appellants (patentees). Respondents I filed the following document:

(L11) Wakibo et al, Appl. Environm. Microbiol. Vol. 49(3), March 1985, pages 706 to 708.

IV. With letter dated 11 August 1995, the appellants filed a new main request (claims 1 to 23) and a declaration by Dr. J. Leemans.

The claims of this new main request differed from the claims as granted only in respect of claim 1 which read as follows (in bold-type characters the additions and in square brackets the deletions in comparison with claim 1 as granted):

"1. A transformed plant cell containing a chimeric gene which[:] is stably integrated in the genome of said cell, is capable of being expressed in differentiated cells of a plant derived from said cell, and comprises:

(a) a promoter region derived from a gene which is naturally expressed in a plant cell; and

(b) a DNA fragment obtained by truncation of a DNA **encoding** [coding for] a crystal protein produced by Bacillus thuringiensis, **and encoding a polypeptide toxin of approximately 60 to approximately 80 kD,** or **a DNA fragment** having substantial sequence homology thereto;

wherein said **DNA** [truncated] fragment (b) [coding for at least a polypeptide toxin of said crystal protein and providing] **provides** an insect controlling amount of said polypeptide toxin in said cell as a result of intracellular expression of said truncated fragment (b)."

V. The board outlined the issues to be discussed at oral proceedings in the communication dated 6 August 1998. As the board had drawn the parties' attention inter alia to the fact that questions related to the patentability under Article 53(b) EPC of the claims directed to plants and seeds might have to be examined, the appellants with letter dated 14 August 1998 requested that two questions be referred to the Enlarged Board of Appeal and that the proceedings be suspended until Decision G 1/98 (cf. OJ EPO 1998, page 509) became available.

VI. In the communication dated 2 September 1998 the board indicated that, in view of the fact that the patent had been revoked for lack of inventive step, the requests by the appellants for referral of questions to the Enlarged Board of Appeal, or for suspension of the proceedings, would only become relevant if a set of claims was considered by the board to meet other requirements of the EPC.

VII. With letter dated 12 October 1998, the appellants responded to the board's communications and filed further documents.

VIII. Both respondents made further submissions and filed additional documents.

IX. Oral proceedings took place on 12 November 1998. Four new auxiliary claim requests were submitted. All consisted of claims 1 to 15 of which claim 1 differed from claim 1 of the main request (see Section IV supra) in respect of item (b) which in the respective requests read as follows:

Auxiliary request 1

"..

b) a DNA fragment obtainable by truncation of a DNA encoding a crystal protein of Figure 13, and encoding a polypeptide toxin of approximately 60 to approximately 80 kD, wherein said DNA fragment b) provides an insect controlling amount of said polypeptide toxin in said cell as a result of intracellular expression of said DNA fragment b), said insect controlling amount resulting in mortality of 75 to 100% of insects feeding on differentiated cells of a plant derived from said cell."

Auxiliary request 2

"..

b) a DNA fragment encoding a truncated version of the crystal protein of Figure 13, and encoding a polypeptide toxin of approximately 60 to approximately 80 kD, wherein said DNA fragment b) provides an insect controlling amount of said polypeptide toxin in said cell as a result of intracellular expression of said DNA fragment b), said insect controlling amount resulting in mortality of 75 to 100% of insects feeding on differentiated cells of a plant derived from said cell."

Auxiliary request 3

"..

b) a DNA fragment obtainable by truncation of a DNA encoding the crystal protein of Figure 13, and encoding a polypeptide toxin with an amino acid sequence of Figure 13 from amino acid position 1 to an amino acid position between positions 607 and 725, wherein said DNA fragment b) provides an insect controlling amount of said polypeptide toxin in said cell as a result of intracellular expression of said DNA fragment b), said insect controlling amount resulting in mortality of 75 to 100% of insects feeding on differentiated cells of a plant derived from said cell."

Auxiliary request 4

"..

b) a DNA fragment encoding a truncated version of the crystal protein of Figure 13, and encoding a polypeptide toxin with an amino acid sequence of Figure 13 from amino acid position 1 to an amino

acid position between positions 607 and 725, wherein said DNA fragment b) provides an insect controlling amount of said polypeptide toxin in said cell as a result of intracellular expression of said DNA fragment b), said insect controlling amount resulting in mortality of 75 to 100% of insects feeding on differentiated cells of a plant derived from said cell."

X. In addition to the documents already mentioned in Sections II and III supra, the following documents are referred to in the present decision:

(D2) Schnepf H. E. et al., J. Biol. Chem., May 1985, Vol. 260, No. 10, pages 6273 to 6280;

(D3) Adang M. J. et al., 1985, Vol. 36, pages 289 to 300;

(D4) Bulla L. A. et al., March 1981, Vol. 256, No. 6, pages 3000 to 3004;

(D8) Barnes W. M., "A Bifunctional Gene for Insect and Kanamycin Resistance", Abstract OR-21-10, First International Congress on Plant Molecular Biology, 1985, Savanna, Georgia, USA;

(D9) Nagamatsu Y. et al., Agric. Biol. Chem., 1984, Vol. 48, No. 3, pages 611 to 619;

(D10) Whiteley H. R. et al., in "Molecular Biology of Microbial Differentiation", Proceedings of the 9th International Spore Conference, Asilomar, California, USA, 3 to 6 September 1984, J. Hoch and P. Setlow eds., 1985, American Society for Microbiology, pages 225 to 229.

XI. The appellants submitted that the claimed subject-matter was entitled to the priority date because the priority document explicitly described a KpnI fragment, which corresponded to a truncated Bt (Bacillus toxin) gene encoding a protein with a molecular weight falling withing the range 60 to 80 kD (see in particular Figure 11).

As for inventive step, they argued essentially that, if document (D1) was to be considered as prior art, it had to be taken into account that this document was merely hypothetical. Its technical teaching was manifestly deficient in many respects and common general knowledge would not have been sufficient to complete the missing information. The skilled person would have, for example, immediately recognized that there was no teaching as to the technical effect of obtaining insect resistance in plants cells and plants because the examples given were either scientifically not credible (inconsistencies and implausibility of the relevant examples) or incomplete as no data were presented and no comparisons were made. Thus, the teaching of document (D1) was no more than an invitation to experiment. In any case, the document in question described the transformation of plant cells with either a full-length Bt gene or with the Hind III fragment. There was no motivation for the skilled person to modify the teaching of document (D1) by using a 60-80 kD encoding fragment. This was because there was no demonstration in the prior art that Bt expression could be achieved in plants and work on recombinant Bt expression in E. coli had shown that the truncated gene products were less toxic than full-length gene products (cf. eg documents (D2)-(D4)). Moreover, the complex mechanisms of Bt toxicity indicated that many factors could lead to uncertainty as to the effect, if any, in plants (solubility of the expressed Bt protein, their toxicity to plant cells etc.). Data obtained from the

expression in E. coli (cf. eg document (L11)), which were based on the testing of solubilised extracts, would not have allowed a prediction of the effect of expression in plant cells or plants. Consequently, there could not be a reasonable expectation of success. The inventive merit of the patent in suit was the demonstration that the approach suggested in document (D1) based on the use of the full-length gene product was ineffective in plants and that the technical effect of insect resistance could instead be obtained by choosing truncated Bt genes encoding 60-80 kD polypeptides.

XII. The respondents raised some formal objections under Articles 84 and 123(2) EPC to the amended claims, in particular to claim 1 of the main request. In their view, there was no basis in the application as filed for the creation of a range of "approximately 60 to approximately 80 kD" and for its generalisation to any polypeptide toxin from any Bacillus thuringiensis expressed in any plant cell. This was because the stated values were disclosed in relation to one specific fusion protein of a size within this range and there was no disclosure of the concept of a range as such of proteins that would provide the desired effect. Moreover, there was no experimental support whatsoever for a gene encoding a 60kD toxin, even less so for such a gene in a plant cell or in a plant. Furthermore, the lack of a reference in the claim to the method of determination of molecular weight and the expression "substantial sequence homology" rendered the amended claim unclear.

Objections under Article 123(2) EPC were also raised against all auxiliary requests because in claim 1 thereof inter alia mortality data taken from a specific example had been introduced and unduly generalised.

The respondents submitted further that the claimed subject-matter of all requests was not entitled to the priority date and thus also documents published between the priority date and the filing date constituted relevant prior art under Article 54(2) EPC which had to be taken into account for the inventive step analysis. In their view, the provision of alternative truncated crystal protein genes did not involve an inventive step having regard to the teaching of document (D1), which indicated the approach for preparing insect resistant plant cells (and plants) via transformation with a construct comprising either the entire gene or a truncated form thereof, in combination with prior knowledge that truncated forms of the crystal proteins had insecticidal activity (cf. eg documents (D2), (D3) and (L11)).

XIII. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request submitted on 14 August 1995 or one of the auxiliary requests 1 to 4 submitted at the oral proceedings on 12 November 1998 and also requested that two questions as set out in the letter dated 14 August 1998 be referred to the Enlarged Board of Appeal and that the proceedings be suspended until Decision G 1/98 (supra) becomes available.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

The main request

Formal objections

1. The approximate upper and lower values for the molecular weight of the subject polypeptide toxin which are found on page 54, line 7, and page 62, line 1, respectively, of the application as filed, together with the general indication in the same application of truncated forms of the gene encoding it and the various examples of truncation in the search of the minimal toxin encoding fragment (cf. eg Figure 20) provide as a whole a fair basis for the amendment in claim 1. Thus no objection under Article 123(2) EPC is seen.

2. As for the objections raised by the respondents under Article 84 EPC (see Section XII supra), it seems indeed to be questionable whether this requirement is met in view of the lack of a reference to the method of determination of the stated molecular weight as well as in view of the expression "a DNA fragment having substantial sequence homology" in the context of the amended claim 1. However, in view of the conclusions on the inventive step issue (cf. points 5 to 14 infra), there is no need to further investigate these matters.

Allocation of the priority date

3. In support of their priority claim for the subject-matter of the claim 1 at issue, the appellants refer to Figure 11 of the priority document. While it is true that the said figure as well as the text of the priority document (cf. eg page 8, lines 19 to 23, and page 34, lines 10 to 22) refer to deletions in the Bt gene, nowhere in this document reference is made to the

specific range of "approximately 60 to approximately 80kD" which constitutes an essential characterising technical feature of the subject-matter of claim 1 at issue. Thus, in line with established case law (cf. eg T 81/87 OJ EPO 1990, 250), the claim cannot be entitled to the priority date, but only to the filing date of the European application, ie 17 January 1986 (cf. Articles 87 to 89 EPC).

Novelty

4. Novelty was not disputed by the respondents at the oral proceedings. The board is also of the opinion that none of the documents on file affects the novelty of the claimed subject-matter.

Inventive step

5. The closest prior art document is represented by document (D1) which relates to the preparation of insect resistant plants. The document outlines in some detail (cf. pages 23 to 35) the experimental approach to be used therefor. This essentially consists in isolating a DNA fragment encoding an insecticidal protein or an insecticidally active portion thereof and inserting it under the control of a plant expressible promoter into a plasmid construct suitable for the stable integration into plant cells and plants. The examples, which - as stated on page 35, last paragraph - utilise known techniques, report the application of such a strategy to a Hind III fragment of the gene encoding the Bacillus thuringiensis (BT) insecticidal protein (cf. Examples 1 to 6) or to the complete protoxin gene (cf. Example 11).

As for the results:

- Example 2.4 (relating to the Hind III gene fragment) reports that "transformed tobacco tissue is lethal to tobacco hornworms" and that "..regenerated plants and their insecticidal protein-containing de[s]cendants are resistant to infestation by larvae of insects such as tobacco hornworm by virtue of the toxic effect such larvae experience when eating tissue from such plants". No specific direct information is given as regards the size of the truncated toxin encoded by the DNA fragment finally transferred to the plant cells. Data based on the product translated in E.coli (cf. Examples 1.2 and 1.3) indicate a size in the range from less than 130 kD to more than 67 kD. The partial DNA sequence and the deduced partial amino acid sequence of the crystal protein are reported in Figure 1.

- Example 11 (relating to the complete gene) reports that "Tobacco hornworms fed on transformed tobacco callus tissue containing the plant expressible full-length insecticidal protein gene were observed to display symptoms att[r]ibutable to B. thuringiensis crystal protein toxicity".

6. In the light of document (D1), the problem to be solved was the provision of further insect resistant plant cells or plants.

7. As a solution thereto, claim 1 proposes in quite general terms a plant cell transformed so as to contain stably integrated in its genome a DNA fragment encoding a BT polypeptide toxin of approximately 60 kD to approximately 80 kD, said protein being expressed by

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the cell in an insect controlling amount. The patent specification reports examples of plants, which having been transformed with plasmid constructs encoding a polypeptide in this molecular weight range, indeed acquired insect resistance.

8. The relevant question is whether the proposed solution would have readily occurred to the skilled person as a feasible way to solve the underlying technical problem.

9. In seeking an answer to the above question, account should be taken of the following facts:

(a) It was known in the art that only part, namely the N-terminal part of the BT protoxin was necessary for insecticidal activity (see documents (L11), (D2) to (D4), (D8) to (D10)). This was known also for BT subspecies berliner 1715 which is the specific strain used in the examples of the patent in suit (cf. document (L11)).

(b) Experiments of synthesis of toxic peptide in recombinant E.coli strains had shown (cf. eg (D10), page 229, Summary) that DNA sequences located between codons 10 and 50 at the 5'-end and between codons 603 and 645 at the 3'-end were required. These encoded a toxic peptide with a molecular weight within the range recited in claim 1 (cf. ibidem, page 228, left-hand column, first paragraph).

(c) The technology for achieving plant cell (and plant) transformation was available in the art (cf. eg documents (D1) and (D12)). In this respect, the patent in suit makes in particular reference to EP-A-0116 718 (cf. page 9 lines 18 to

20). As already stated (cf. point 5 supra), prior art document (D1) outlined the experimental approach for transforming plants with the entire BT gene or a truncated form thereof encoding toxic polypeptides.

10. In the appellants' view, the prior art information of point 9, items a) and b) supra, would not have encouraged the skilled person to try to transform plant cells or plants with a truncated form of the BT gene, firstly, because of the reported lower toxicity of the truncated toxin in comparison with the full-length toxin and, secondly, because the data were in relation to E.coli extracts, not in relation to plant leaves on which the insects actually fed.

11. The board does not share the appellants' view for the following reasons. The fact that more than one prior art document reported insecticidal activity for given truncated forms of the toxin, in particular for truncated forms expressed in E.coli, would have rather encouraged the skilled person to try the effect thereof in plant cells or plants. As a matter of fact, this was the next logical step to carry out as the testing in E.coli was known to be an intermediate step in the framework of transformation of plant cells or plants. This step could be carried out according to known techniques available in the art (cf. point 9, item c) supra). The reports about a lower activity of the truncated forms would not have dissuaded the skilled person from trying because he or she knew that the lower activity (here: only a slightly lower activity), which in any case did not mean loss of activity, might be compensated by the better handling of the product or by its more direct effect, if, like in the present case, the untruncated product is a precursor which has to be metabolised (cf. document (2), page 6273, left-hand column). In any case, it should also be noted that

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eg document (L11) reported for the truncated form expressed in E.coli a toxicity "virtually identical to that of native protoxin" (cf. page 706, left-hand column, second paragraph).

12. As for the appellants' submissions in relation to the merely hypothetical value of the disclosure of document (D1), it is the board's view that the skilled person was likely to take the teaching and the experiments reported in document (D1) at their face value. Nothing in document (D1) or in the other available documents would have led the skilled person away from accepting the contents of document (D1) without scrutinizing it in every detail, as pretended by the appellants. The fundamental information that the skilled person would have derived from document (D1) was that it was technically feasible to transform plant cells and plants with a BT gene with the view of preparing insect resistant plants. In this respect, document (D1) provided more than just a mere invitation to experiment, as - on the background of existing knowledge - it outlined in some detail the experimental plans, to which the skilled person could refer when designing, also based on common general knowledge, a strategy for transforming plant cells or plants. Although lacking concrete data and comparative examples, the said document reported, although in vague terms, positive results which the skilled person had no reasons to doubt. These would have fostered his or her expectations of success. Thus, the fact that the technology for achieving plant cell and plant transformation was available in the art (cf. point 9, item c) supra) in combination with the positive statements in document (D1) in respect of the results that were or could be achieved (cf. point 5 supra) would have been sufficient to encourage the skilled person to proceed with it. Knowing that truncated DNA sequences encoded an active peptide, the skilled person

would have readily used them in such an experimental plan in the reasonable expectation of achieving the desired technical effect of conferring insecticidal activity to the plant cells or plants. Prior art was not dissuasive in this respect and nothing suggested that this would inevitably have led to a failure. The motivation therefor was, in the board's view, provided by the many prior art documents pointing to the toxic effect of truncated BT toxin having a molecular weight in the range recited in claim 1 at issue. Of course, there were, as always in this area of technology, some uncertainties such as the level of expression and toxicity in the plant cells or plants, however this was nothing out of the ordinary that would not be expected to be solved by way of routine testing or of an acceptable amount of trial and error experimentation.

13. The alleged difficulties that in the appellants' view the skilled person would have envisaged when reading the examples of document (D1) derive from an over-meticulous examination of the experimental details provided by the document. Such an attentive examination is unnecessary in the technical circumstances of this case (cf. point 12 supra). Firstly, in spite of some possible inaccuracy or incompleteness, document (D1) does not contain any misleading or dissuasive information. Secondly, and more importantly, the relevant question here is not whether the skilled person would have been able to repeat exactly the experimental plans outlined in document (D1), but rather whether the skilled person, starting from the document (D1) taken at its face value, would have thought of the solution proposed in claim 1 at issue as a feasible way to solve the underlying technical problem. For the reasons already given above (cf. point 12 supra), the board is of the view that this would have been the case.

14. For these reasons, in the board's judgement the subject-matter of claim 1 at issue does not involve an inventive step and consequently the main request of which it is part is not allowable under Article 56 EPC.

Auxiliary requests 1 to 4

15. Claim 1 of all auxiliary requests contains in item b) the feature "..said insect controlling amount resulting in mortality of 75 to 100% of insects feeding on differentiated cells of a plant derived from said cell." . The said mortality rate is that recorded in Experiment II of Example 13.4 in relation to plants transformed with the plasmid pGS1151 which codes for a fused truncated form of the toxin (see application as filed, page 115, line 19). This was a test involving larvae of Manduca sexta on some of the plants used in Experiment I, following procedure 1 outlined on page 110. As nothing in the application as filed indicates that such a mortality rate is generally obtained with any plasmid construct encoding any truncated form of the toxin, in any plant, with any insect independently from the specific conditions of testing, the generalisation of this feature, which is taken from the said specific experiment, results in subject-matter which extends beyond the content of the application as filed. This contravenes the provisions of Article 123(2) EPC and for this reason all the auxiliary requests must be refused.

Questions to the Enlarged Board of Appeal

16. The requests by the appellants for referral of questions to the Enlarged Board, which were in relation to possible objections under Article 53(b) EPC to claims directed to plants or seeds, would have become relevant only if a set of claims had been considered by

the board to meet the other EPC requirements. Such is not the case here, as none of the requests on file can be allowed. Thus, there is no need to deal with the matter.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairperson:

D. Spigarelli U. K. Kinkeldey