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D E C I S I O N
of 5 October 2000

Case Number: T 0333/97 - 3.3.4

Application Number: 86307850.7

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Title of invention:

Effecting somatic changes in plants through the use of
negative strand RNAs

Patentee:

MONSANTO COMPANY

Opponent:

Novartis AG
Calgene Inc.

Headword:

Somatic changes/MONSANTO

Relevant legal provisions:

EPC Art. 56

Keyword:

"Inventive step (no)"

Decisions cited:

T 0296/93, T 0207/94, T 0386/94, T 0923/92

Catchword:

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Case Number: T 0333/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 5 October 2000

Appellant: MONSANTO COMPANY
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 20 January 1997
revoking European patent No. 0 223 399 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
V. Di Cerbo

Summary of Facts and Submissions

- I. The appeal lies from the decision of the opposition division issued on 20 January 1997 whereby the European patent No. 0 223 399, which had been opposed by two parties, was revoked under Article 102(1) EPC.

Claim 1 therein read:

" A method for effecting somatic changes in higher plants comprising the step of:

introducing into a plant a DNA sequence including a promoter normally operable in plant cells and a coding sequence located 3' of the promoter, the orientation of the coding sequence being reversed relative to the promoter from its normal reading direction, which coding sequence causes transcription of a negative strand RNA having sufficient complementarity to an endogenous target RNA strand; or

introducing into a plant a DNA sequence which causes the transcription of a negative strand RNA having sufficient complementarity to a target pathogenic RNA strand;

sufficient complementarity being such that the negative strand RNA will effectively bind to the target RNA strand to inhibit target RNA strand activity in vivo."

Claims 2 to 6 concerned embodiments of the method of claim 1. Claims 7 and 8 were directed to a chimeric gene construction operable in plants; claim 9 was directed to a plant comprising in its genome the said

construction; claim 10 was directed to the seed of the said plant.

II. The opposition division decided that, while the claims as granted met the requirements of Articles 54 and 83 EPC, they lacked an inventive step having regard to following documents:

(2) Science, Vol. 229, 26 July 1985, pages 345 to 352;

(6) Nature, Vol. 315, 13 June 1985, pages 601 to 603.

III. With the statement of grounds of appeal, the appellants (patent proprietors) filed the expert opinions of Dr Kenneth A. Barton and Prof Dr Joachim Messing together with the documents referred to therein. Among them, the following are referred to in the present decision:

(12.1) Oxford Surveys of Plant Molecular & Cell Biology, Vol. 6, 1989, pages 221 to 246;

(12.2) Cell, Vol. 30, 1982, pages 763 to 773;

(12.4) Plant Physiol., Vol. 81, 1986, pages 86 to 91;

(12.5) Gene, Vol. 28, 1984, pages 113 to 118.

IV. On 9 June 1997, opponents 02 withdrew their opposition.

V. The respondents (opponents 01) replied to the statement of grounds of appeal and filed therewith the expert opinion of Dr Mary-Dell Chilton together with the documents referred to therein, namely:

(13.1) Nature, Vol. 304, 14 July 1983, pages 184 to 187;

(13.2) Nature, Vol. 310, 12 July 1984, pages 115 to 120;

(13.3) Bio/Technology, Vol. 3, March 1985, pages 241 to 246;

(13.4) Proc. Natl. Acad. Sci. USA, Vol. 82, May 1985, pages 3320 to 3324.

VI. On 7 July 2000, the board issued a communication with preliminary observations on the case.

VII. On 2 October 2000, the appellants withdrew their request for oral proceedings, informed the board that they would not attend the hearings and requested that the board decide the appeal on the basis of the written submissions.

VIII. Oral proceedings took place on 5 October 2000 and were attended only by the respondents.

IX. In addition to the documents already mentioned above, the following citations are referred to in the present decision:

(1) Bio/Technology, Vol. 2, June 1984, pages 520 to 527;

(9) Cell, Vol. 32, April 1983, pages 1033 to 1043.

X. The appellants submitted in writing essentially that, although document (6) could be seen to suggest that the

antisense approach might be tried in plants, the required "reasonable expectation of success" (cf decision T 296/93, OJ EPO 1995, 627) was missing and could not be provided by evidence of success or partial success in animal cells in culture, eg by document (2). This was because:

- (a) In 1985, the introduction and expression of foreign gene constructs in plants was still a relatively unexplored technical area and there were uncertainties as to which particular genes or genetic elements, techniques or strategies which worked in bacteria or animal cells would also work in plant cells;
- (b) There were significant differences between the mechanisms of expression and regulation of genes in plants and animal cells. This was demonstrated, for example, by the fact that:
 - (i) Promoters which worked in animal cells did not work in plant cells and, viceversa, plant promoters did not necessarily work in animal cells (cf documents (12.2) and (12.4));
 - (ii) Transposable elements of drosophila DNA inserted into plant cells would not transpose;
 - (iii) Plants and animals differed at a cellular level and in their DNA splicing and processing activities, so that mammalian genes, such as human growth hormone, had been found not to be expressible in plant

cells;

(iv) Document (9) had shown that the yeast ADH gene could not be expressed in transgenic plant cells.

(c) Document (2) suggested to the reader that in mammalian cells a large excess of anti-sense RNA was required to achieve any meaningful decrease in the transcription of the genes sought to be down-regulated. The skilled person would not have expected to be able to provide such excess amounts in plants as there were reports (cf document (12.5)) that non-translatable transcripts were not likely to accumulate at normal levels. Only later work (cf document 12.1) had shown that the mechanism of anti-sense inhibition of genes in plant cells seemed to be different from that in animal cells.

(d) There were further uncertainties with regard to the use of anti-sense technology in plant cells for conferring virus resistance as there were dramatic differences between animal and plant DNA viruses, as the latter, for example, were not capable of integration into the genome.

XI. The respondents argued essentially that, although plant biotechnology was a relatively new area of research, in 1985 some knowledge about chimeric gene constructions and about the ways for introducing in plants regulatory regions linked to coding genes and expressing said genes was already available (cf documents (1), and (13.1) to (13.4)). From document (6), which in a "Note added in proof" made reference to the results of the

work described in document (2), the skilled person knew that the anti-sense RNA strategy was a promising, universally applicable technology, and was explicitly motivated to apply it to plants for the purpose of providing immunity against plant viruses. Document (2) confirmed by way of various experiments that this strategy could be used for the constitutive and conditional suppression of exogenous and endogenous genes. Thus, since there were in 1985 genes and genetic elements as well as techniques and strategies which worked in plants, the skilled person would have been quite optimistic about the applicability of the known anti-sense strategy to plants. In accordance with the criteria established in decision T 207/94 (OJ EPO 1999, 273), the assessment of the "reasonable expectation of success" required a scientific evaluation of the facts at hand. None of the alleged difficulties put forward by the appellants amounted to a prejudice against the use of the anti-sense strategy in plants as they were either irrelevant or not substantiated. In particular, the allegation that the need of excess levels of anti-sense RNA for achieving an effect would have dissuaded the skilled person, was based on a misreading of document (2), which referred to ratios anti-sense/sense RNA only in respect of experiments in which two vectors were used. No such ratios were mentioned in the transformation experiments wherein one anti-sense DNA expression vector was used, these being the experiments that were closest to those carried out in the example of the patent in suit.

XII. The appellants requested that the decision under appeal be set aside and the patent be maintained as granted.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The only point at issue in the present case is inventive step (Article 56 EPC).
2. Claim 1 at issue concerns a method for effecting somatic changes in higher plants which can be performed in two different ways, namely:
 - (a) by introducing into a plant a DNA sequence which causes transcription of a negative strand RNA having sufficient complementarity to an endogenous target RNA strand; or
 - (b) by introducing into a plant a DNA sequence which causes transcription of a negative strand RNA having sufficient complementarity to a target pathogenic RNA strand.

The term "sufficient complementarity" is further defined in the claim as resulting in that the negative strand RNA will effectively bind to the target RNA strand to inhibit target RNA strand activity in vivo.

3. When the method according to embodiment (b) is taken into consideration, document (6) constitutes the most appropriate starting point for the evaluation of inventive step. This document describes a particular application in E.coli of the known strategy of introducing in the cells a DNA construct encoding a messenger-interfering-complementary RNA (micRNA), which blocks bacteriophage or virus infection by binding to transcripts of a given gene. This micRNA system is said to provide an effective way of preventing viral

infection as well as the expression of harmful genes in both prokaryotes and eukaryotes. The document states in its final part on page 603: "Combined with existing technology, the present report provides a promising prospect for the application of the micRNA immune system to both plants and animal cells. [M]icRNA immune systems directed against plant viruses can be introduced into the genomes of plant protoplasts which can subsequently be regenerated into mature fertile plants." In a "Note added in proof", the document also makes reference to similar results obtained by other groups using the same technology and, among them, to the results to be reported ("in press") in document (2).

4. Having regard to document (6), the underlying technical problem can be defined as the **actual** provision of a method for blocking in plants a given pathogenic target RNA strand activity.
5. As a solution, claim 1 proposes introducing into plants a DNA sequence which causes the transcription of a negative strand RNA having sufficient complementarity to the target pathogenic RNA strand (cf embodiment (b), point 2 above). Example 1 of the patent in suit provides the corresponding experimental support therefor.
6. Since there is agreement between the parties that document (6) would have indeed suggested to the skilled person trying the anti-sense strategy in plants (cf section X, first sentence and section XI above), the key question here is whether the skilled person would have had a reasonable expectation that the anti-sense strategy, which was known to work in bacterial

and mammalian cell systems (cf documents (6) and (2), respectively), would have worked also in plants.

7. According to established case law (cf eg T 296/93, T 207/94, supra, T 386/94 OJ EPO 1996, 658, T 923/92, OJ EPO 1996, 564), in cases where the prior art provides suggestions or incentives to do something and thus it may seem obvious for the skilled person to follow the indicated path, the question may arise whether the said skilled person, based on a scientific evaluation of the facts at hand, would thereby have had a "reasonable expectation of success". Generally speaking, the more unexplored a technical field of research is, the more difficult is the making of predictions about the successful conclusion of a given endeavour and, consequently, the lower the expectation of success (cf T 296/93 supra). However, as stated eg in T 207/94 (supra), in order to be considered, any allegation of factors putting in jeopardy the reasonable expectation of success must be based upon technical facts and an absence of evidence that a given factor might be an obstacle to carrying out an invention would not be taken as an indication that this invention could not be achieved, nor that it could.

8. In the present case, the appellants put forward a number of factors which, in their view, would have induced the skilled person to believe that the anti-sense strategy would not have worked in plants by simple analogy with the bacterial and animal cell systems and, consequently, to be pessimistic about the possibility of achieving any result. It has thus to be examined whether and in which measure such factors would have had an impact on the skilled person's expectations.

9. In the appellants' view, one of the difficulties was represented by the fact that in 1985 plant genetic engineering was a relatively unexplored technical field (cf section X, item (a)). In the board's judgment, although it is true that this area of research was relatively new, it is also a fact that there was already sufficient knowledge about elements and techniques which could be used in order to successfully achieve the insertion and expression in plants of foreign genetic information (cf eg documents (1), (13.1) to (13.4)), so that the skilled person would not have groped in the dark for finding out how to introduce into a plant a DNA sequence which could be transcribed into an RNA strand.
10. The appellants alleged also that the significant differences between plant and animal cells would have negatively affected the expectation of success by the skilled person (cf section X, item (b), subitems (i) to (iv)). In the board's view, apart from the fact that some of the statements in this respect are unsubstantiated (cf eg subitems (ii) and (iii)), the factors referred to would not have had a negative impact on the skilled person's expectations because they are either not technically related to the problem to be solved (cf the allegation under subitem (ii)) or too specific to be of any relevance (cf subitem (iv)). As for differences and uncertainties in relation to the promoters, in the board's view the skilled person was well aware of the necessity to use "a promoter normally operable in plant cells" (it is noted in passing that such a feature is proposed in claim 1, embodiment **(a)**). Such promoters were available (cf documents (1), (13.1) to (13.4)), and thus the skilled person would have had no technical difficulties in this respect.

11. As regards the appellants' argument that, based on the findings in document (2), the skilled person would have expected to be unable to achieve the necessary excess amount of anti-sense RNA for downregulating a gene, the board does not consider it to be of decisive relevance. This is because:

- The skilled person was aware of the fact that in order to be effective in blocking a given target RNA the anti-sense RNA transcribed from the DNA introduced into a plant had to have a certain stability and a sufficient concentration, and had no reasons to doubt that this could be achieved, in the light of the state of knowledge in the area of plant engineering (cf point 9 supra). Nothing in the art indicated that an anti-sense RNA strand would have been particularly unstable in plants or that an inserted DNA encoding an anti-sense RNA would not have been transcribed into an RNA strand;

- Specific ratios of anti-sense RNA to sense RNA were mentioned in document (2) in relation to experiments in which co-transformation with two vectors, one containing the sense sequence, the other one the anti-sense sequence, were carried out. From these experiments the skilled person would not have concluded that there was an absolute necessity to achieve any specific fold excess of anti-sense in order to block a given target pathogenic RNA.

12. In the board's judgement, also the alleged differences between animal and plant viruses would not have had a negative influence on the skilled person's expectations

because the said differences, insofar they actually exist, would have been recognised as irrelevant to the applicability in plant cells of anti-sense technology for blocking an intruding target viral RNA by means of an anti-sense DNA transcript.

13. In summary, the board concludes that, when judged based on the technical facts, none of the factors referred to by the appellants would have been considered by the skilled person as creating a prejudice or constituting a real obstacle to carrying out anti-sense experiments in plants.

The suggestion in document (6) and the optimistic tone of both documents (6) and (2) would have given the skilled person an incentive to try to introduce in a plant a DNA to be transcribed into a negative strand RNA having sufficient complementarity to a given target pathogenic RNA strand. These are exactly the measures proposed in claim 1 at issue (cf embodiment (b)) as a solution to the underlying technical problem, and performing them merely required the application of techniques and knowledge available at the time of the invention, no particular ways or strategies being proposed by the patent in suit. In the absence of evidence of real difficulties which would be encountered, the skilled person, when following the indicated route, would have had either some expectations of success, or, at worst, no particular expectations of any sort, but merely the curiosity to see whether a result could be achieved. The latter situation, however, does not equate with an absence of reasonable expectation of success.

14. In view of these findings an inventive step is denied

to embodiment (b) of claim 1. Under these circumstances, there is no need to examine inventive step in relation to embodiment (a) because, if an embodiment (here: embodiment (b)) falling under the scope of the claim lacks inventive step, the claim as a whole and the request containing it fail.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

U. Bultmann

L. Galligani