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D E C I S I O N
of 7 February 2000

Case Number: T 0338/97 - 3.3.4

Application Number: 86905070.8

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Language of the proceedings: EN

Title of invention:
Molecular farming

Patentee:
Calgene LLC

Opponent:
Groupe Limagrain Holding
Mogen International N.V.

Headword:
Molecular farming/CALGENE LLC

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - no"

Decisions cited:
T 0694/92

Catchword:
-



Case Number: T 0338/97 - 3.3.4

DECISION
of the Technical Board of Appeal 3.3.4
of 7 February 2000

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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 20 January 19972000
revoking European patent No. 0 233 915 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

- I. The appeal lies against the decision of the opposition division to revoke the patent in suit under Article 102(1) EPC for lack of inventive step.
- II. Exchanges of submissions took place between the Appellants (Patentees) and the Respondents (Opponents) and a communication was sent by the Board to express their provisional non-binding opinion. The Appellants filed one main request and five auxiliary requests with their last written submission. During oral proceedings, the main request and auxiliary requests 1 to 3 were replaced by a new main request and new auxiliary requests 1 to 3.

Claim 1 of the main request read as follows:

"1. A method for producing a **physiologically active** mammalian peptide which comprises:
growing plant cells containing an integrated sequence comprising,
a first expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells (2) a structural gene coding for said mammalian peptide and (3) a termination region
whereby said structural gene is expressed to produce said **physiologically active** mammalian peptide;
and
isolating said **physiologically active** mammalian peptide substantially free of plant cell components.

Claims 2 to 6 related to further features of the method of claim 1. Independent claim 7 corresponded to method claim 1 but was restricted to physiologically active interferon. Claims 8 and 9 were dependent on claim 7

and related to further embodiments. Claims 10 to 12 were addressed to the expression cassette itself and claim 13 related to a DNA construct which contained in addition to the expression cassette, a second expression cassette carrying a gene coding for an enzyme imparting antibiotic resistance to plant cells.

Auxiliary request 1 was as the main request but for the omission of the cassette/construct claims.

Auxiliary request 2 was as the main request except that claim 1 contained the additional following paragraph:

"...wherein the structural gene is a mammalian viral pathogen gene, an α -, β - or γ -interferon gene, a gene for a light or heavy chain of an immunoglobulin, a lymphokine gene, a growth factor gene, a blood factor gene, a histocompatibility antigen gene or an enzyme gene."

Auxiliary request 3 was as auxiliary request 2 but for the omission of the cassette/construct claims.

Auxiliary request 4 was as the main request but the method claims were confined to the expression of interferon.

Auxiliary request 5 was as auxiliary request 4 but for the omission of the cassette/construct claims.

III. The following documents are referred to in this decision:

(2) WO 84/02913,

(4) Fraley, R.T. et al., Biotechnology, Vol. 3, No. 7, pages 629 to 635, 1985,

- (5) WO 84/02919,
- (6) Rogers, S. G. et al., in *Biotechnology in Plant Science, Relevance to Agriculture in the Eighties*, Edited by Zaitlin, Day and Hollaender, Academic Press, Inc., pages 219 to 225, 1985,
- (8) Odell, J. T et al., *Nature*, Vol. 313, pages 810 to 812, 1985,
- (9) Eichholtz et al., *Somatic Cell and Molec. Genetics*, Vol. 13, No. 1, pages 67 to 76, 1987,
- (21) Konez, C. et al., *The EMBO Journal*, Vol. 3, No. 5, pages 1029 to 1037, 1984.

IV. The submissions in writing and during oral proceedings by the Appellants can be summarized as follows:

In the present case, it was not satisfactory to rely wholly on published documents to assess inventive step as the result of unsuccessful experiments would not be published. There was a declaration on file from a scientist working in the field at the time, stating that there was genuine uncertainty as to whether a stable and functional active mammalian protein could be produced in plants. Post-published document (9) referred to documents (21) and (8) where transformation failed to yield functional proteins.

The problem to be solved was to be defined as providing a method for the expression of a **physiologically active mammalian peptide** in plant cells.

Document (2) or (5) were cited as closest prior art. In document (2), host/gene incompatibility barriers between the kingdoms was discussed at length on pages 6 to 9. In particular, it was stated on page 8, lines 33 to 35: "It is very unlikely that a gene from a cell of one kingdom...could be expressed in cells from another kingdom." Having so informed the skilled person of the potential difficulties, the authors of document (2) failed to provide any experimental proof that the gap between kingdoms could be bridged. Indeed, document (2) described the introduction of the bacterial gene for kanamycin resistance in plant cells but the enzyme responsible for the breakdown of kanamycin was not isolated, nor was its activity tested directly. Document (2) also provided chimeric constructs containing the structural gene encoding bovine growth hormone. Yet the polypeptide was neither expressed nor purified.

Without this experimental confirmation, the doubts in the skilled person's mind would not be resolved.

The opposition division combined document (2) or (5) with document (4) or (6) to arrive at their conclusion of lack of inventive step. This combination could only be done with hindsight and besides, the thrust of document (6) was not towards mammalian gene expression in plant cells and document (4) only contained unsustained allegations that mammalian genes could be expressed. They were not relevant to inventive step.

The key point in the assessment of inventive step was that the Appellants had made the relevant constructs and were able to isolate mammalian peptides in active form from the plant cells.

The fact that it was interferon- γ which the Appellants had expressed in plant cells, whereas this protein was notoriously difficult to obtain by recombinant means, justified acknowledgment of inventive step to the broadly formulated claim 1 of the main and first auxiliary requests, but also to the claim 1 of the second and third auxiliary requests relating to the expression of further specific mammalian peptides and, of course, to claim 1 of the fourth and fifth requests which related to interferons.

- V. The submissions in writing and during oral proceedings by the Respondents can be summarized as follows:

From document (2) or (5), it could be seen that it was possible to express a heterologous gene in plants. It was reasonable to expect that also mammalian genes could be expressed, especially in view of the information given in document (4) that a variety of mammalian genes including those encoding mouse dihydrofolate reductase and human chorionic gonadotropin had been successfully expressed, and, in document (6), that the CaMV35S promoter had been used for that purpose.

It was true that document (2) discussed host/gene incompatibility across kingdoms but document (2) also suggested the measures to be taken to deal with the incompatibility problem and documents (4) and (6) clearly stated that it was possible to cross the barriers between the plant and animal kingdoms.

The patent in suit did not disclose that the expression of interferon- γ in plant cells required any specific measures to be taken. Therefore, it did not look especially difficult to achieve and inventive step could not be based on having obtained and purified the protein in an active state.

VI. The Appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the main request or one of the auxiliary requests 1, 2, 3, all submitted at the oral proceedings on 7 February 2000, or of the claims of one of the auxiliary requests 4 or 5 submitted on 7 January 2000.

The Respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.
2. No objections were raised against any of the claims now on file for reasons other than lack of inventive step. The Board agrees that inventive step is the only issue to be discussed.

Claim 1, main and first auxiliary requests;

3. Document (2) describes an attempt to overcome gene/host incompatibility barriers between the plant kingdom (plant cells as host) and the other kingdoms (genetic material to be expressed). It is shown that a chimeric construct containing the bacterial gene encoding neomycin phosphotransferase (NPT II) under the control of regulatory signals which are recognized by plant cells can be transformed and expressed in said cells which then become resistant to the antibiotic kanamycin. The expression of a mammalian coding sequence is also contemplated (page 19, lines 19 to 22). The construction of a chimeric gene comprising the

coding sequence for bovine growth hormone (BGH) coupled to a plant promoter and a termination signal from *Agrobacterium tumefaciens* is described. Document (2) is, thus, considered as the closest prior art.

4. Starting from document (2), the problem to be solved may be defined as providing a method for the expression and, thus, for the production of a physiologically active mammalian polypeptide in plant cells.
5. The solution provided is to grow transformed plant cells containing a chimeric gene whereby the coding sequence for the mammalian peptide is linked to transcriptional and translational regulatory regions recognized by plant cells, to express, to extract and to purify the mammalian peptide therefrom, the activity of which is thereafter tested.
6. The differences between the teachings of document (2) and the claimed method consist firstly in the origin of the foreign gene to be expressed: a gene out of the animal kingdom rather than out of the protista kingdom, and, secondly, insofar as a mammalian gene is referred to, in that this gene is expressed, and its product is extracted and purified from the plant cells before being tested for activity.
7. By showing that a bacterial coding sequence can be expressed in plant cells, document (2) provides evidence that the gene/host incompatibility barriers between kingdoms need not be insurmountable:

- the foreign DNA is not necessarily destroyed upon entry into the plant cells,

- the problem posed by the recognition of the regulatory sequences by the plant cells can be settled by constructing chimeric genes,
- the foreign mRNA (at least when transcribed from a bacterial gene) can be translated into a protein which is physiologically active, as shown by the fact that the plant cells acquire a phenotype due to said protein.

8. The question to be answered is, therefore, whether this teaching with regard to bacterial genes will lead the skilled person to have a reasonable expectation that mammalian genes will also be expressed under the same conditions ie when the mammalian coding sequence is inserted into a chimeric construct of the same type as disclosed in document (2) with respect to the bacterial NTP II gene and the mammalian BGH gene, and the chimeric construct is transformed into the plant cells.

9. It is, thus, of much relevance that there existed in the state of the art at the priority date, documents in which it was stated (although not experimentally shown) that the expression of mammalian genes in plant cells had been achieved from chimeric constructs containing regulatory signals recognized by plant cells, for example: document (6), page 225: "We are currently using the CaMV35S promoter for expression of new chimaeric genes using coding sequences derived from the mammalian genes in plants. These coding sequences include one for a mouse dihydrofolate reductase gene and one for the α subunit of human chorionic gonadotropin".

10. Furthermore, and contrary to the Appellants' opinion, neither document (8) nor document (21) show failure to express chimeric genes containing regulatory signals recognized by plant cells: in document (21), no chimeric constructs of the kind has been tested, in document (8), the translation of the mRNA obtained from a chimeric construct has not been attempted.

11. In the Board's judgment, the combined teachings of documents (2) and (6) would lead the skilled person at the filing date to think that by introducing chimeric mammalian genes into plants, there existed a reasonable expectation of success that the corresponding protein will be produced in active form. This conclusion is comforted by the results announced in document (4) that two genes had been successfully expressed in plants, although document (4) is silent on the type of constructs which were used. As for the fact that the mammalian protein is extracted and purified before being tested for activity, this only seems to require the use of known techniques, which is not susceptible to impart inventive step to the method of claim 1.

12. The Appellants have expressed the view that published documents gave a distorted picture of the expectations of the scientific community at the filing date because, as a general rule, results of unsuccessful experiments were not published and that, in fact, there was great uncertainty that mammalian genes would be expressed in plant cells. In this respect, it should be kept in mind that the term "mammalian genes" covers coding sequences which may contain introns or not. Those which do not contain introns are not distinguishable in structure from bacterial DNA sequences ie their origin does not provide them with a distinctive character susceptible to alter any expectation of success, the skilled person may have acquired from learning that the expression of bacterial genes in plant cells was possible. As to

whether the skilled person may have had doubts that mammalian genes containing introns would be expressed in plant cells, this need not be taken into account while assessing inventive step because these doubts are not resolved by the patent in suit wherein the feasibility of expressing intron-containing genes is not demonstrated.

13. The Appellants also argued that the skilled person knowing from document (2) of the host/gene incompatibility between kingdoms would not have expected that the expression of mammalian genes into plant cells would be feasible. Furthermore, it was only with hindsight that document (2) could be combined with document (6) or (4) in an attempt to justify reasonable expectation of success. These arguments, however, are not convincing. Whilst it is true that document (2) discusses incompatibility problems, it is also readily apparent that this very same document teaches means to overcome said problems (pages 18 and 19). In fact, Figure (2) shows a scheme for expression of foreign genes into plants (with reference to the NTPII gene) which comprises the same technical steps as the method of claim 1 and no further critical step is disclosed in the patent in suit which would be missing in document (2). The combination of document (2) with documents (4) or (6), which can be done without hindsight as these documents are all concerned with setting up systems for the expression of foreign genes into plants, does not serve to give extra technical information necessary to implement the teachings of document (2). It is merely relied on as telling the skilled person that any doubts he might have had as to the feasibility of what is suggested in document (2) are groundless, and that there is a reasonable expectation of success using the method of document (2).

14. Finally, the further argument was also presented that a broadly formulated claim to the expression of mammalian proteins in plant cells should be allowed because the patent in suit showed the expression in plant cells of human interferon- γ , a protein notorious for being difficult to produce by recombinant DNA techniques. As regards the main claims of the main and auxiliary requests discussed here, the only logical line of reasoning on which this would be an argument for their validity would appear to require acceptance of the premise that the sole acceptable evidence which should give rise to a reasonable expectation of success that an expression cassette will work for mammalian proteins, in general, is the proof that this expression cassette works for obtaining expression of as difficult a mammalian protein to express as is interferon- γ . This premise is impossible to justify, as the board can see no reason why a reasonable expectation of success should not already exist when the expression cassette has been shown to work in some test. Reasonable expectation of success does not require certainty: certainty will only exist once a particular cassette has been shown to work for a particular mammalian protein and, then, it will be limited to what has been shown to work. A reasonable expectation of success, however, can exist for an expression cassette suggested in the prior art, even though it turns out that for expression of some mammalian proteins, problems arise with that expression cassette, to overcome which either a different expression cassette would be needed, or supplementary measures not suggested in the prior art. Accordingly, the only premise which the Board can accept as correct in the present case is that once the skilled person had an indication that the method suggested in the prior art worked for some mammalian proteins, his/her expectation would be that it could be

got to work for all mammalian proteins in the absence of proof to the contrary. Here it has never been shown that the expression cassette suggested in the prior art would fail for any mammalian protein.

15. In accordance with the case law (cf Decision T 694/94 (OJ EPO 1997, 408) a proper balance must be found between the actual technical contribution, if any, to the state of the art disclosed in a patent or patent application and the scope of protection claimed. A patentee cannot ask the board to disregard prior art as giving rise to no reasonable expectation of success, while at the same time asking for protection of much broader scope than has been proved to work according to the information in his own patent, when he has made no technical contribution beyond showing that the prior art suggestion actually works in one case.
16. The main and first auxiliary requests are rejected for lack of inventive step.

Further requests

17. In all further requests, the method of claim 1 involves the same steps as the method of claim 1 of the main request, the claims being restricted to the expression of specific genes including those encoding interferon- α , - β and - γ in auxiliary requests 2 and 3, and to the expression of the genes encoding said interferons (which are different from each other in structure) in auxiliary requests 4 and 5. The patent in suit does not show the expression in plant cells of any of these genes with the exception of the gene encoding interferon- γ .

18. On the premise that a skilled person even knowing of documents (2), (4) and (6) would still have no reasonable expectation of success for expression of the genes mentioned in the auxiliary requests with the expression cassette suggested in document (2), then the evidence given in the patent that expression of γ -interferon was possible would not remove this lack of reasonable expectation as to the possibility of expression of the other mentioned genes including those which encode interferon- α or - β . Nevertheless the appellants are asking the board to grant them a claim covering interferon- α , interferon- β , for which the patent provides no greater reasons for assuming a reasonable expectation of success than the prior art. As stated in point 15 above the board is not prepared to adopt such inconsistent reasoning. Rather it finds that the skilled person knowing of documents (2), (4) and (6) will have a reasonable expectation of success for the expression of all mammalian proteins, unless there is actual evidence that the prior art cassette does not work. There is no evidence here that the prior art cassette does not work for interferons, and thus inventive step cannot be acknowledged for auxiliary requests 2 to 5.

Order

For these reasons it is decided that:

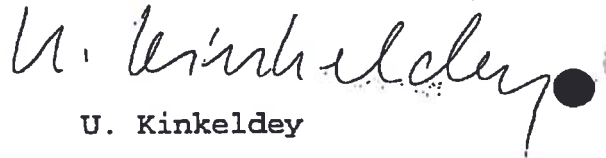
The appeal is dismissed.

The Registrar:



M. Beer

The Chairwoman:



U. Kinkeldey

