BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 22 September 2004

Case Number: T 1198/01 - 3.3.4

Application Number: 94916500.5

Publication Number: 0728014

IPC: A61K 39/00

Language of the proceedings: EN

Title of invention:
Vaccines expressed in plants

Applicant:
PRODIGENE, INC.

Opponent:
-

Headword:
Vaccines expressed in plants/PRODIGENE, INC.

Relevant legal provisions:
EPC Art. 123(2), 84, 54, 56

Keyword:
"Main request, first auxiliary request and second auxiliary request: added subject-matter (no)"
"Clarity (yes)"
"Novelty (yes)"
"Inventive step (no)"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1198/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 22 September 2004

Appellant: PRODIGENE, INC.
1716 Briarcrest, Suite 507
Bryan
Texas 77802 (US)

Representative: Thomson, Paul Anthony
Potts, Kerr & Co.
15, Hamilton Square
Birkenhead
Merseyside CH41 6BR (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 31 May 2001 refusing European application No. 94916500.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
R. Moufang

Summary of Facts and Submissions

I. European patent application No. 94 916 500.5 published as WO 94/20135 with the title "Vaccines expressed in plants" was refused by the examining division for lack of novelty or inventive step of the claims of the main and auxiliary requests, respectively, then on file.

II. The appellant (applicant) lodged an appeal against this decision. The statement of Grounds of Appeal comprised a new main request and a first auxiliary request. With the letter dated 6 September 2004, the appellant submitted a second auxiliary request.

Claim 1 of the **main request** read as follows:

"1. A transgenic plant intended for human or animal consumption expressing a recombinant viral antigen protein."

Claim 1 of the **first auxiliary request** read as follows:

"1. A transgenic plant intended for human or animal consumption including an edible part expressing a recombinant viral antigen protein.

Claim 1 of the **second auxiliary request** read as follows:

"1. A transgenic plant expressing a recombinant viral antigen protein, wherein at least part of said plant is intended for human or animal consumption and such part represen[t]s a substantial proportion of the whole plant accumulation of said protein."

III. The following documents are cited in the present decision:

(D1) Mason H.S. et al., Proc. Natl. Acad. Sci. USA, Vol. 89, pages 11745-11749 (December 1992);

(JH2) Declaration made by Dr. John Howard before the USPTO in relation to US patent application Serial No. 08/481,291 (14 January 1998).

IV. Oral proceedings were held on 22 September 2004.

V. The appellant's arguments were essentially as follows:

Main request
Formal admissibility

– The wording "intended for human consumption" did not offend Article 84 EPC and had a basis on page 17, line 30 and page 8, lines 15-21 of the published WO-A-94/20135 application.

Novelty

– All the claims relied on the novel distinguishing feature "plant intended for human or animal consumption".

Inventive step

– Document (Dl) represented the closest prior art. This document disclosed a transgenic tobacco plant not intended for human or animal consumption that

expressed Hepatitis B surface antigen (HBsAg). The objective technical problem was the provision of an alternative production system for recombinant viral antigens, the solution as claimed being the use of edible plants as such a system.

– One of the main advantages of utilising such a production system was that an immune response could be elicited by merely consuming the "edible" transgenic plant or edible part thereof.

– Document (D1), when read as a whole, would in no way prompt the skilled person to attempt to utilise edible plants as an alternative production system for recombinant viral antigens, as it reported that the maximal levels of HBsAg expressed by the transgenic plants were too low. The present invention lay in having nevertheless continued on this route and arrived at vaccines that were in vivo active (see Exhibit A to document (JH 2)).

– Moreover the following prejudices known to the skilled person would dissuade him/her from attempting to express a recombinant viral antigen in an "edible" plant:

– The expression of heterologous DNA in a plant was unpredictable.

– There was no reasonable certainty that the expressed protein would fold properly, especially since the plant's intracellular environment

differed from the intracellular environment where the protein was normally expressed.

– Membrane bound proteins, such as those of transmissible gastroenteritis virus (TGEV), were more difficult to express than other types of proteins and as such, achieved only very low expression levels.

– Many of the factors which made the expression of the S-protein of TGEV unpredictable were also applicable to HBsAg.

Auxiliary request 1
Formal admissibility

– There was a basis for the feature "edible part" on page 7, line 15 and page 8, lines 11-13 of the published WO-A-94/20135 application.

Inventive step

– The arguments submitted in relation to the main request were equally applicable, mutatis mutandis, to the expression of a recombinant viral antigen in the edible part of a plant, for example, the fruit.

Auxiliary request 2
Formal admissibility

– There was a basis for claim 1 on page 10, lines 20-22 and page 32, lines 6-30 of the published WO-A-94/20135 application.

Inventive step

– The higher expression in the fruit explained why the invention worked (see Example III on page 32).

VI. The appellant (applicant) requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 21 of the main request or claims 1 to 21 of the first auxiliary request, both filed with the grounds of appeal, or claim 1 to 21 of the second auxiliary request, filed with the letter dated 6 September 2004.

Reasons for the Decision

1. The appeal is admissible.

Main Request
Article 123(2) EPC

2. The feature "plant intended for human or animal consumption" in the claims of this request finds a basis on page 6, line 26; page 7, lines 4-5; page 8, lines 15-21; page 10, lines 20-32; page 11, lines 1-3; page 15, lines 32-35; page 18, lines 10-16 of the published WO-A-94/20135 application. The claims thus satisfy the requirements of Article 123(2) EPC.

Article 84 EPC

3. The feature "plant intended for human or animal consumption" is clear in the light of e.g. page 8, line 14 ("food plant") of the application.

Novelty

4. Owing to the features "plant intended for human or animal consumption", the claims are novel over document (D1) disclosing the expression of a recombinant viral antigen protein (HBsAg) in tobacco, a plant which is not intended for human or animal consumption within the meaning of the present case.

Inventive step

5. Document (Dl) represents the closest prior art. This document discloses the transformation of tobacco with an Agrobacterium strain transformed with plasmids pHB101 or pHB102 (see page 11746, l-h column, lines 2-4). The transgenic tobacco plant expresses hepatitis B surface antigen (HBsAg). This HBsAg exhibits physical and antigenic properties similar to those of HBsAg found in human serum (see the Abstract: "recombinant HBsAg and human serum-derived HBsAg have similar physical properties"). The levels of expressed HBsAg in the leaves of the transformants were quantified as 2-6 ng/mg of soluble proteins for plasmid pHB101 and up to 66 ng/mg for plasmid pHB102 (see page 11748, l-h column, lines 3-7). It is stated on page 11749, l-h column of this document that "Presently, the maximal levels of HBsAg we have found in transgenic plants represent about 0.01% of the soluble leaf protein. This is an

inadequate level for the efficient use of plants as production systems for rHBsAg for vaccine use. Further studies must be done to increase the accumulation of HBsAg...".

Problem to be solved

6. The concept of administrating a vaccine by means of an edible plant expressing a recombinant viral antigen is already suggested on page 11745, r-h column, lines 3-5 of document (D1). Moreover, page 6, lines 27-28 of the application ("...purified and partially purified plant derived antigen...") and claim 16 of this request also contemplate the isolation and purification of the recombinant viral antigen from the transformed plants. Therefore, finding a new method of administration for antiviral vaccines (and its "edible plant"-based solution) is, in the context of the problem-solution approach, not the proper problem to be solved.

7. The present application also does not purport to solve the problem referred to on page 11749, end of l-h column of document (D1) of remedying to the too low levels of viral antigen expressed in the plant. This can be derived from a comparison between the expression levels referred to in Table 1 on page 32 of the application for the tomato fruit (43 ng/mg total protein (0.0043%)) and those of Fig. 2 of document (D1) (see also page 32, lines 14-18 of the application).

8. The only difference worth being noted upon comparison of the claimed subject matter with the disclosure of document (D1) is that the recombinant viral antigen is expressed in an edible plant instead of the tobacco as

described in document (D1). The board thus agrees with the appellant that the objective technical problem is to provide an alternative production system for recombinant viral antigens, the solution, as claimed, being the use of edible plants as such a system.

9. In the board's judgement, once the skilled person has been taught by document (D1) that HBsAg could be stably expressed in tobacco, a model for other plants (see document (JH2), paragraph 11), he/she would prima facie have a reasonable expectation of success that other plants such a tomato or potato could be transformed as well and would yield similar results.

10. The appellant, however, argues that there was no reasonable expectation of success in expressing viral antigens in e.g. tomato or potato because the expression of heterologous DNA in these plants was unpredictable as to whether the expressed protein would fold properly. However, the experimental results arrived at in document (D1) demonstrated that the antigen (HBsAg) expressed in tobacco exhibited physical and antigenic properties similar to those of the native HBsAg circulating in human serum, i.e., that it had the correct conformation. Therefore, similar results could be expected by replacing tobacco with tomato or potato, without any evidence on file that these systems would pose particular problems. The board also observes that this appellant's line of argument does not find any support in the broadness of the present claims, which relate to any monocot/dicot plant, and also goes against the proposition by the appellant (see section 11 of document (JH2)) that once successful plant transformation has been shown for tobacco, tomato and

potato, other monocot and dicot plant species may be transformed as well.

11. It was the appellant's view that membrane bound proteins, such as the S-protein of TGEV, were more difficult to express than other types of proteins and achieved very low expression levels (see paragraph 6 of document (JH2)) and that these unpredictable factors were also applicable to HBsAg (see ibidem, paragraph 9). However, in the board's view, the reverse is also true that the disclosure by document (D1) of HBsAg expressed in a plant cell with the correct conformation was predictive of similar results with the S-protein of TGEV. Moreover, since the claims presently before the board are not restricted to these membrane bound viral proteins, this above appellant's argument cannot assist his case on inventive step.

12. The appellant also relied on Exhibit A to document (JH2) for arguing that the claimed edible vaccines have turned out to be active in vivo. However, this document pertains to US patent No. 08/481,291 filed three year later than the present application, which is not concerned with demonstrating that plant vaccines work in vivo once they are eaten. Therefore the later evidence provided by the appellant cannot be taken into account for showing that the presently claimed subject matter is inventive.

13. Therefore claim 1 does not satisfy the requirements of Article 56 EPC and the main request has to be refused.

First Auxiliary Request
Article 123(2) EPC

14. There is a basis for the feature "edible part" on page 7, line 15 and page 8, lines 11-13 of the published WO-A-94/20135 application.

Inventive step

15. According to claim 1 of this request, the transgenic plant should include an edible part expressing the recombinant viral antigen. However, there is nothing inventive in the additional feature that an edible transgenic plant includes edible transgenic parts expressing the recombinant viral antigen. The contrary would rather be surprising. Therefore, claim 1 does not satisfy the requirements of Article 56 EPC and this request must also be refused.

Second Auxiliary Request
Article 123(2) EPC

16. According to claim 1 of this request, the edible part of the transgenic plant represents a substantial proportion of the whole plant accumulation of the viral antigen. There is a basis for claim 1 on page 6, line 28, relating to an edible part of the plant (e.g. fruits), taken in combination with page 32, lines 6-30 of the published WO-A-94/20135 application (more antigen in more dense fruits).

Inventive step

17. The feature in claim 1 of this request, according to which the edible part of the transgenic plant represents a substantial proportion of the whole plant accumulation of the viral antigen is an obvious consequence due not to surprisingly higher levels of expression therein, as the appellant maintains (in fact they are lower: see page 32, line 19) but to the higher density of the fruit (ibidem, lines 20-21), a feature obvious to the skilled person. Therefore, claim 1 of this request also does not satisfy the requirements of Article 56 EPC. This request cannot be allowed either.

Other "in-the-air" requests

18. At the end of the oral proceedings, the appellant suggested the possibility of filing further auxiliary requests including the limitation vis-à-vis claim 1 of the main request "wherein the plant is tomato, potato or corn" or "wherein the plant is tomato". However, the filing of these further auxiliary requests would not have healed the deficiency pointed out above that no problem is solved by this newly claimed subject matter other than that of providing an alternative plant system for the expression of viral antigens, whose solution has been found to be obvious.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey