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 17 July 2002

Case Number: T 0282/01 - 3.3.4

Application Number: 92913153.0

Publication Number: 0584266

IPC: C12N 15/86

Language of the proceedings: EN

Title of invention:
Recombinant virus expressing carcinoembryonic antigen and methods of use thereof

Applicant:
THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by the SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

Opponent:
-

Headword:
Carcinoembryonic antigen/US GOVERNMENT

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request - inventive step - yes"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0282/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 17 July 2002

Appellant: (Applicant)
THE GOVERNMENT OF THE UNITED STATES OF AMERICA
as represented by the SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institute of Health
Office of Technology Transfer
Westwood Building
Box 0TT
Bethesda
MD 20892-9902 (US)

Representative:
Brown, David Leslie
Haseltine, Lake & Co.
Imperial House
15-19 Kingsway
London WC28 6UD (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 13 October 2000 refusing European patent application No. 92 913 153.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division to refuse the European patent application No. 92 913 153.0 (international publication No. WO 92/19266), publication No. 0 584 266, with the title "Recombinant virus expressing carcinoembryonic antigen and methods of use thereof".

Claim 1 as refused by the Examining Division read as follows:

"1. A recombinant virus comprising a vaccinia virus into which a carcinoembryonic antigen (CEA) gene is inserted which recombinant virus expresses CEA on the surface of cells infected therewith and which recombinant virus elicits an immune response in vivo directed against CEA and cells expressing CEA."

The Examining Division came to the conclusion that the subject-matter of this claim was obvious in view of the teaching of document (1):

(1): EP-A-0 263 933,

taken in combination with the teaching of either of documents

(2): Estin, C.D. et al., Proc.Natl.Acad.Sci.USA, Vol. 85, pages 1052 to 1056, 1988,

(3): Lathe, R. et al., Nature, Vol. 326, pages 878 to 880, 1987, or

(7): Bernards, R. et al., Proc.Natl.Acad.Sci.USA,

Vol. 84, pages 6854 to 6858, 1987,

II. The Board sent a communication under Article 11(2) of the Rules of Procedure of the Boards of Appeal, stating their preliminary non-binding opinion on the patentability of the claims refused by the Examining Division.

III. At oral proceedings which took place on 17 July 2002, the Appellants filed a new main request comprising 19 claims for all designated Contracting States except for ES and GR, corresponding method claims for ES and GR and a description adapted to these claims in replacement of the main request on file.

Claim 1 for all designated Contracting States except for ES and GR read as follows:

"1. A recombinant virus for use in the immuno-treatment of a carcinoma in a mammal, wherein the carcinoma cells express the mammal's carcinoembryonic antigen (CEA), the virus including an inserted CEA gene of said mammal whereby cells infected with the virus express said CEA on their surface and the virus is capable of eliciting in said mammal a humoral and /or cell mediated immune response directed against said mammal's CEA and cells expressing said mammal's CEA."

Claims 2 to 15 related to further features of the recombinant virus of claim 1. Claim 16 was directed to a pharmaceutical preparation comprising said virus and claims 17 to 19 related to the use of the recombinant virus for the manufacture of a medicament.

IV. The following further document is mentioned in this

decision:

(9): Mitchell, M.S., Journal of the National Cancer Institute, Vol.87, No.13, pages 949 to 951, 1995.

V. The Appellants' arguments with regard to inventive step were as follows:

The invention lay in the disclosure that, upon infection, a vaccinia virus carrying the carcinoembryonic antigen (CEA) gene of a mammal was able to elicit an immune response in said mammal, which response was directed against cells expressing CEA, such as carcinoma tumor cells.

Document (1) was to be considered as the closest prior art as it described the isolation and characterisation of the cDNA encoding CEA. It was not in any way concerned with eliciting an immune response **in vivo** against CEA-positive cells and there were no documents on file, the teachings of which could be combined with that of document (1) to render obvious a recombinant virus carrying the CEA gene as a mean for eliciting said immune response.

Document (3) reported the prevention and/or rejection of polyoma-induced tumors in rats using active immunisation of the rats with a recombinant virus including polyoma DNA encoding a range of proteins present in the tumor. These proteins which, contrary to CEA, were not naturally-occuring self-antigens were not to be taken as a close model for immuno-treatment of CEA-positive tumors. And, besides the results described in document (3) were highly inconclusive and inconsistent.

In a similar manner, document (7) showed that the expression of a recombinant virus carrying a rat oncogene in mice elicited an immunity response but, thereagain, the rat oncogene-encoded antigen was foreign to the mouse. The authors of document (7), when discussing their results as well as those in document (3), expressed doubts that the immunity would develop if the antigen differed only subtly from similar proteins found in the normal tissues of the tumor-bearing host (ie if it corresponded to a self-antigen).

Document (2) disclosed that a recombinant vaccinia virus expressing the human melanoma-associated antigen p97 induced immunity against p97-expressing melanoma cells transplanted in mice and in two monkeys. The experiments carried out in monkeys were essentially of the same kind as those which were described in the patent application to support claim 1 ie to support the finding that a recombinant vaccinia virus carrying the CEA gene worked as an anti-CEA immunity inducer. This apparent similarity, however, did not mean that by reading document (2), the skilled person would have come to the claimed invention in an obvious manner. Indeed, the expression of the p97 human protein in monkeys **would be expected** to elicit an immune response as human p97 was not a self-antigen for these animals. To the contrary, the expression of the human CEA protein in monkeys **would not be expected** to elicit much of an immune response, taking into account that the human and monkey CEA proteins were bearing similarities.

In document (9) written some five years after the priority date of the application, the findings by the

present inventors were described as not intuitively obvious, of profound theoritical and practical significance and as a challenge to conventional wisdom. This, of course, confirmed the unexpected character of the invention.

VI. The Appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of:

- claims 1 to 19 for all designated Contracting States except ES and GR and

- claims 1 to 19 for the Contracting States ES and GR,

both sets of claims filed on 17 July 2002.

Reasons for the Decision

Rule 86(3) EPC

1. At oral proceedings, the Appellants filed an entirely new set of claims as main request. This filing was said to be done in answer to the Board's communication under Article 11(2) of the Rules of Procedure of the Boards of Appeal. The amendments in the claims of the newly filed main request do take into account the concerns which the Board expressed in their communication about the inventive step of the former claims to recombinant viruses containing genes coding for an antigen which was foreign to the mammal into which it had been injected. Thus, the main request is found allowable under Rule 86(3) EPC.

Articles 123(2) and 84 EPC; formal requirements

2. The following passages of the application as filed provide support for the claims of the main request:

- claims 1 to 9: passage bridging page 8, line 34 to page 9, line 26,

- claim 10: page 10, lines 14 to 17,

- claims 11 to 16: claims 10 to 13, 18 and 23 as originally filed,

- claims 17 to 19: claims 8, 9 and 16 as originally filed.

The requirements of Article 123(2) EPC are fulfilled.

3. The claims are clear, concise and supported by the description (Article 84 EPC).

Articles 54 and 83 EPC; novelty, sufficiency of disclosure

4. In the course of examination, the Examining Division decided that the subject-matter of the claims then on file was novel over the prior art. The amendments introduced in the claims of present main request are not of such a nature as to change this conclusion.

5. The Board is of the opinion that, at the priority date, the claimed viruses could be reproduced on the basis of the teaching of the application as filed (examples 1 to 13), taking into account the common general knowledge in molecular biology which existed at the time.

6. The requirements of Articles 54 EPC and 83 EPC are fulfilled.

Article 56 EPC; inventive step

7. The closest prior art is document (1). It teaches that CEA is present during normal foetal development, in the normal adult intestinal tract at low concentrations, and that it is produced and secreted by a number of tumor cells. It discloses the cloning and characterisation of the cDNA encoding CEA, as well as the CEA antigen resulting from the expression of said cDNA. The antigenicity of CEA is made use of to isolate anti-CEA antibodies. A therapeutic method involving these antibodies is suggested (page 11, lines 7 to 12), namely, attaching radionuclides or toxins to them, introducing the complexes thus formed into the carriers of tumor cells so as to target the radionuclides or toxins to said cells and, thus, to eliminate them.

8. Starting from the closest prior art, the problem to be solved can be defined as providing a tool which enables the carriers of CEA-expressing tumors to develop an immune response against said cells and, thus, to eliminate these cells.

9. The solution given is to recombine the CEA gene in the DNA of a virus known to trigger a strong immune response in the organism in which it is injected, the concomitant expression of the viral proteins and of CEA after injection of the virus into the host bearing tumor cells thereby eliciting from the host an immune response against its own CEA antigen present on the tumor cells (passage bridging page 1 and 2 of the application as filed, page 3, lines 8 to 14).

10. The therapeutic approach suggested in document (1) is conceptually quite different from that which may be carried out with the claimed virus and, thus, document (1) on its own does not render the subject-matter of claim 1 obvious.

11. The Examining Division came to the conclusion that the claimed subject-matter lacked inventive step over the combination of the teaching of document (1) with that of document (2), (3) or (7). In document (7), a recombinant vaccinia virus carrying the gene encoding the **rat** oncogen-encoded protein p185 is transferred into **mice** cells. The expression of p185 following injection is shown to result in a strong immune response against p185, as the transfected mice are fully protected against subsequent challenges with tumor cells expressing p185. Document (3) discloses that **rats** bearing tumors due to **polyoma** virus can be induced to reject these tumors by injection of a recombinant vaccinia virus expressing some of the polyoma-encoded proteins. Document (2) discloses that immunisation of **mice** with a recombinant vaccinia virus expressing the **human** melanoma-associated glycoprotein p97 induces humoral as well as cell-mediated immunity to p97. Mice so immunized reject transplants of melanoma cells expressing p97. The induction of immunity is also observed in **monkeys** although normal monkey cells express a low level of cross-reactive p97.

12. The common feature in the experiments presented in these three documents, involving rats or mice as hosts to the recombinant vaccinia virus is that the antigen resulting from the expression of this virus is **foreign** to the host (polyoma proteins in rats, rat oncogene-encoded p185 in mice, human melanoma p97 antigen in

mice). For this reason, the immune response is to be expected and cannot be considered as indicative of what might happen when an antigen is naturally produced by the mammal itself such as CEA, as is pointed out in document (7), where the results obtained by its authors and those in document (3) are discussed (page 6858, left-hand column): *"The present experiments show that vaccinia virus can serve as an effective vector for inducing immunity against antigen-bearing cells. A similar result was recently obtained by Lathe et al.(22) using polyoma virus-encoded antigens. The success of our experiments appears to stem from the allogeneic origin of the antigen that induced an immune response in the vaccinated host.* ***However, present results provide no assurance that such immunity will develop if the antigen in question differs only subtly from similar proteins found in the normal tissues of tumor-bearing hosts."*** (emphasis added by the Board)

13. It remains, however, the result in document (2) that an immunogenic response is elicited in monkeys which are said to naturally express a low-level of cross-reactive p97. During oral proceedings, the Board asked the Appellants why this experiment which is, in fact, of the same kind as that performed in the application (example 13) with the recombinant vaccinia virus carrying the CEA encoding gene, in order to show that an immune response could be elicited against an antigen naturally produced by the mammal itself, would not have suggested to the skilled person that such an immune response may be possible. The Appellants answered that the similarity between human and monkey p97 was much less than that between human and monkey CEA so that an immune response against human p97 would be expected

with the monkeys but would not be considered as indicative of the likelyhood of an immune response of the monkeys to human CEA. There is no evidence to the contrary on file and, thus, the Board considers this statement to represent a scientific fact which leads to the conclusion that also the disclosure in document (2) does not hint to the claimed invention. Accordingly, it is accepted that eliciting an immune response against CEA in a host which naturally expresses CEA was not obvious in the light of the disclosure of document (1) alone or in combination with either of that of document (2), (3) or (7).

14. In document (9) published some three years after the filing date of the present application, the findings by the Appellants are qualified as "*not intuitively obvious*" in the light of the existing prior art which is deemed either unconvincing or related to non-"self" antigens (page 949, passage bridging the left- and right-hand columns). It is also stated on page 951, left-hand column that the issues raised after these findings were known would not even have been posed had the Appellants not decided "*to defy conventional wisdom*".

15. For these reasons, inventive step is acknowledged.

16. The same reasoning also applies to the invention as claimed in claims 1 to 19 for ES and GR.

Order

For these reasons it is decided:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent in the following version:

   (a) claims 1 to 19 for all designated Contracting States except ES and GR,

   (b) claims 1 to 19 for the designated Contracting States ES and GR

   (c) description pages 1 to 44,

   (a) to (c) filed on 17 July 2002 and

   (d) drawings as originally filed.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey