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D E C I S I O N
of 16 September 2003

Case Number: T 0127/02 - 3.3.8

Application Number: 95907356.0

Publication Number: 0739414

IPC: C12N 7/04

Language of the proceedings: EN

Title of invention:
Herpesvirus replication defective mutants

Applicants:
PRESIDENT AND FELLOWS OF HARVARD COLLEGE, et al

Opponent:
-

Headword:
Herpesvirus mutants stromal keratitis/HARVARD

Relevant legal provisions:
EPC Art. 123(2), 84, 83, 54, 56

Keyword:
"Added subject-matter - no"
"Clarity - yes"
"Sufficiency of disclosure - yes"
"Novelty - yes"
"Inventive step - yes"

Decisions cited:
-

Catchword:
-

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Case Number: T 0127/02 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 16 September 2003

Appellants: PRESIDENT AND FELLOWS OF HARVARD COLLEGE et al
17 Quincy Street
Cambridge
Massachusetts 02138 (US)

Representative: Kirkham, Nicholas Andrew
Graham Watt & Co.
St. Botolph's House
7-9 St. Botolph's Road
Sevenoaks
Kent TN13 3AJ (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 9 July 2001 refusing European application No. 95907356.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julia
J. H. P. Willems

Summary of Facts and Submissions

I. An appeal was lodged by the applicants (appellants) against the decision of the examining division dated 9 July 2001 whereby the application No. 95 907 356.0, published as WO 95/18852 (European publication No. 0 739 414) with the title "Herpesvirus replication defective mutants", was refused pursuant to Article 97(1) EPC on grounds of lack of an inventive step (Article 56 EPC), insufficiency of disclosure (Article 83 EPC) and lack of clarity of the claims and lack of support of the claims by the description (Article 84 EPC).

II. The decision of the examining division was based on a request consisting of claims 1 to 8 filed on 31 July 1996, wherein independent claim 1 read as follows:

"1. The use of a herpesvirus having a mutation in one or more genes encoding a protein essential for viral replication to render the herpesvirus replication defective, said mutant herpesvirus having an ability to effect an antibody subclass shift of IgG2a/IgG1 upon *in vivo* administration to a mammal for the manufacture of a medicament for the treatment of an immunopathologic, immunomodulatory or immunoregulatory disease."

Claims 2 and 3 were formulated essentially as claim 1 except that the manufacture of the medicament was for the treatment of herpetic stromal keratitis or latent herpesvirus infection (claim 2) or the mutant herpesvirus was defined as having an ability to induce production of IFN- γ upon administration (claim 3). Claims 4 and 5 were dependent on claims 1, 2 and 3 and

defined the type of herpesvirus and the mutated genes respectively. Claim 6 was essentially as claim 2 but the defective herpesvirus was defined as in claim 3. Claims 7 and 8 were as claims 1 and 3 respectively with the additional proviso that the herpesvirus was not d301, n504 or a gH deletion mutant.

III. With the statement of grounds of appeal the appellants filed a main request (claims 1 to 6) which was essentially limited to the use of the defined replication defective HSV-1 mutants for the treatment of herpetic stromal keratitis.

IV. The examining division did not rectify the decision under appeal and remitted the appeal to the board of appeal (Article 109(2) EPC).

V. The board sent a communication pursuant to Article 11(2) of the Rules of procedure of the Boards of Appeal stating its preliminary, non-binding opinion.

VI. With their letter of 15 August 2003, the appellants replied to the board's communication and filed a new main request and a first and second auxiliary requests. The main request only contained three claims which read:

"1. The use of HSV-1 having a mutation in one or more genes encoding a protein essential for viral replication to render the herpesvirus replication defective, said mutant herpesvirus having an ability to effect an antibody subclass shift of IgG2a/IgG1 upon *in vivo* administration to a mammal for the manufacture of a medicament for the treatment of herpetic stromal keratitis."

"2. The use of HSV-1 having a mutation in one or more genes encoding a protein essential for viral replication to render the herpesvirus replication defective, said mutant herpesvirus having an ability to induce production of IFN- γ upon administration for the manufacture of a medicament for the treatment of herpetic stromal keratitis."

"3. The use of claim 2 wherein the mutation is in the gene or genes encoding the proteins ICP8 or ICP27."

VII. Oral proceedings were held on 16 September 2003. As announced in their letter of 15 August 2003, the appellants did not attend the oral proceedings.

VIII. The appellants requested that the decision under appeal be set aside and a patent be granted on the basis of the main request or one of the two auxiliary requests all filed on 15 August 2003.

Reasons for the Decision

Main request
Article 123(2) EPC

1. Claims 5 and 11 as originally filed explicitly refer to the use of the disclosed replication-defective herpesvirus mutants for the treatment of herpetic stromal keratitis. Similar references are found in the description of the application as originally filed, such as *inter alia* on page 2, lines 12 to 15, page 3, lines 28 to 34, page 4, lines 1 to 3, page 13, line 30

to page 14, line 4 and page 14, lines 22 to 27. Passages referring to HSV-1 and to mutations in the ICP8 and IPC27 genes are found *inter alia* on page 3, lines 5 to 10 and page 8, lines 6 to 17. Thus, the requirements of Article 123(2) EPC are met.

Article 84 EPC: clarity

2. The claimed subject-matter is limited to the use of the disclosed replication-defective HSV-1 mutants for the manufacture of a medicament for the treatment of a specific disease, namely herpetic stromal keratitis, which is a well-known disease and clearly defined in the prior art. Thus, the requirements of Article 84 EPC in respect of clarity of the claimed subject-matter are considered to be fulfilled.

Article 84 EPC: support by the description

3. As stated in point 1 *supra*, there is a formal support for the claimed subject-matter. However, it has been established jurisprudence of the Boards of Appeal that a formal support is not sufficient for fulfilling the requirements of Article 84 EPC. For these requirements to be met, the claimed subject-matter must necessarily have a technical support in the description too, in the sense that it has to reflect the applicant's effective contribution to the art (cf Case Law of the Boards of Appeal, 4th edition 2001, II.B.3, pages 166 to 168). The question therefore arises whether or not the application provides such a technical support for the claimed subject-matter.

4. The board notes that in the application as filed there are no data concerning an ocular infection with HSV-1 let alone the effect of the disclosed replication-defective HSV-1 mutants on herpetic stromal keratitis. The application, however, provides technical evidence that these replication-defective HSV-1 mutants induce a subclass shift of IgG2a/IgG1 similar to the wild-type HSV-1 herpesvirus (cf page 51 lines 9 to 31, Table 7 on page 54 and Figure 10) as well as the effect of IFN- γ on this IgG subclass shift (cf page 52, lines 1 to 20 and Figure 11). This IgG subclass shift is identified as being associated with Th1-mediated responses (cf page 13, lines 30 to 33 and page 54, line 7 to page 55, line 2).

5. Prior art document S. Jayaraman et al., J. Immunol., 1993, Vol. 151(10), pages 5777 to 5789 (filed with appellant's letter of 27 December 1999 and cited on page 2, lines 14 to 15 in the application) refers to the protective role of Th1-mediated responses and the exacerbation of herpetic stromal keratitis by Th2-mediated responses. In the light of this background knowledge, the elucidation of the effect of the replication-defective HSV-1 mutants on the IgG subclass shift and the associated Th1-mediated responses makes technically plausible for the skilled person to use these HSV-1 mutants for the treatment of herpetic stromal keratitis, ie the reference to this specific disease in the application as filed is not seen as a hypothetical suggestion but as a technically informed one.

6. Thus, the requirements of Article 84 EPC in respect of support by the description of the claimed subject-matter are met.

Article 83 EPC

7. The replication-defective HSV-1 mutants as defined in the claimed subject-matter were known in the prior art and easily available to the skilled person. No undue burden can be seen in their preparation. Moreover, as stated in point 2 *supra*, the specific disease herpetic stromal keratitis was also well-known in the prior art. Thus, the board fails to see any particular technical problem or special difficulty that could have prevented or hindered the skilled person from putting into practice the teachings disclosed in the application, ie preparing a medicament for the treatment of herpetic stromal keratitis. The fact that no specific experimental data are given does not render the teaching insufficient. In fact, as stated above in points 3 to 6, the claimed subject-matter is considered to be supported by the description.

8. Moreover, there is technical evidence on file corroborating this assumption. In particular, document L.A. Morrison and D.M. Knipe, J. Virol., February 1994, Vol. 68(2), pages 689 to 696 (taken as expert evidence) discloses indeed a protective effect against HSV-1 corneal inoculation and further development of keratitis by immunization of mice with replication-defective HSV-1 mutants.

9. Thus, the requirements of Article 83 EPC are considered to be fulfilled.

Article 54 EPC

10. The claimed subject-matter is entitled to the priority date of the first priority document, ie US 08/179,106 of 10 January 1994, which explicitly refers to the **same subject-matter** (cf eg pages 3 and 4). Thus, the sole cited prior art referring to herpetic stromal keratitis, namely L.A. Morrison and D.M. Knipe, J. Virol., February 1994 (cf point 8 *supra*), is not relevant for the assessment of novelty. None of the other documents of the cited prior art refers to herpetic stromal keratitis. Therefore, the claimed subject-matter is novel.

Article 56 EPC

11. It is well-known that herpes simplex virus causes a wide variety of pathogenic symptoms and considerable morbidity in man (cf "Notes on Medical Virology", 8th edition, 1986, Morag C. Timbury, Chapter 10, pages 80 to 83, filed with appellant's letter of 8 January 2001). Document L.H. Nguyen et al., J. Virol., 1992, Vol. 66(12), pages 7067 to 7072, which is considered to be the closest prior art, refers to these infections and to the considerable efforts made for producing herpesvirus-specific vaccines (cf page 7067, first paragraph in the left-hand column). This document discloses the induction of humoral and cellular immunity by known replication-defective HSV-1 mutants (d301 with a deleted ICP8 gene, n504R with a nonsense mutation in the ICP27 gene and d120 with a deleted ICP4 gene) as well as their protective effect against a subsequent lethal infection with wild-type HSV-1

(lethal HSV-1 challenge) (cf Figure 4). These replication-defective HSV-1 mutants are the same referred to in the application (cf page 51, line 15 and Figure 10 in the application).

12. Starting from the closest prior art, the objective technical problem underlying the present application is finding a specific therapeutic application for these replication-defective HSV-1 mutants. The solution proposed in the main claim request is their use in the manufacture of a medicament for the treatment of herpetic stromal keratitis. The board is satisfied that the claimed solution solves the above mentioned technical problem (cf point 8 *supra*).

13. There is an explicit reference in the L.H. Nguyen et al. document to animals inoculated with the HSV-1 mutants by cornal scarification (cf page 7070, full paragraph in the right-hand column). However, this inoculation is only performed in order to show the unability of the replication-defective HSV-1 mutants to spread by retrograde transport to neurons located in the peripheral nervous system (trigeminal ganglion tissue). There is no suggestion that this inoculation or an immunization by intraperitoneally injection (cf page 7067, last full paragraph in the right-hand column) could result in a protective effect against a localized ocular infection by wild-type HSV-1.

14. Prior art document WO 92/05263, which refers to herpes simplex virus as causing "a *wide range of pathogenic symptoms in man, including recurrent facial and genital lesions*" (cf page 17, lines 13 to 16), discloses the use of HSV-1 mutants for immunization against wild-type

HSV-1. However, these HSV-1 mutants are said to be preferably not prevented from replication (cf page 7, lines 13 to 15), as the exemplified gH-deleted HSV-1 (cf page 8, line 25 to page 9, line 2), and the protective effect is only shown in cervical ganglia (cf Tables 1 to 4). There is neither a reference nor a suggestion to any ocular infection.

15. In the light of this prior art and bearing in mind that herpetic stromal keratitis was thought to be an immune-mediated disease and thus, any immunization had the potential to elicit possible immune-responses that could actually exacerbate the corneal disease (cf S. Jayaraman et al., *supra*), the board considers that proposing the use of replication-defective HSV-1 mutants, let alone the use of a specific type of replication-defective HSV-1 mutants, namely having the ability to effect a IgG subclass shift or to induce the production of IFN- γ, for the manufacture of a medicament for treating herpetic stromal keratitis was not obvious to the person skilled in the art.

16. Therefore, the claimed subject-matter fulfils the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of the main request filed on 15 August 2003 and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski

L. Galligani