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D E C I S I O N
of 13 July 2004

Case Number: T 0857/01 - 3.3.4

Application Number: 91303387.4

Publication Number: 0453242

IPC: A61K 48/00

Language of the proceedings: EN

Title of invention:
Transfer and expression of gene sequences into central nervous system cells using herpes simplex virus mutants with deletions in genes for viral replication

Patentee:
THE GENERAL HOSPITAL CORPORATION

Opponents:
01. University College London
02. ARCH Development Corporation
03. British Technology Group Limited

Headword:
Herpes simplex virus/GENERAL HOSPITAL

Relevant legal provisions:
EPC Art. 83

Keyword:
"Sufficiency of disclosure (no)"

Decisions cited:
T 0158/92, T 0612/92, T 0694/92, T 0639/95

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0857/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 13 July 2004

Respondent: (Proprietor of the patent)
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Appellant III: (Opponent 03)	British Technology Group Limited 101 Newington Causeway London SE1 6BU (GB)
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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 28 May 2001 concerning maintenance of European patent No. 0453242 in amended form.**

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: M. Wieser
R. Moufang

Summary of Facts and Submissions

I. Appeals were lodged by Opponents 1 to Opponents 3 (Appellants I to Appellants III) against the decision of the Opposition Division, whereby the European patent No. 0 453 242 was maintained in amended form pursuant to Article 102(3) EPC.

II. The Opposition Division had decided that claims 1 to 4 of the second auxiliary request before them met the requirements of the EPC

III. The Board expressed their preliminary opinion in a communication dated 11 August 2003.

IV. The Patent Proprietors (Respondents) replied on 28 November 2003 and filed a new main request and three auxiliary requests. Claims 1 of these requests read:

Main request:

"1. The use of a herpes simplex virus 1 (HSV-1) vector having a mutation in the immediate early gene that encodes infected cell protein (ICP) 0, 4, 22, 27, and/or 47 and having a gene sequence operably linked to a promoter sequence, the vector allowing the gene sequence to be expressed in a central nervous system cell so that the expressed gene product complements a neurological deficiency, in the preparation of an agent for treating a neurological deficiency of the central nervous system, ..."

This wording was followed by a disclaimer, excluding the disclosure in prior art document (1), (cf section VII below).

Auxiliary requests 1 to 3:

"1. The use of a herpes simplex virus 1 (HSV-1) vector having a mutation in the immediate early gene that encodes infected cell protein (ICP) 4 and/or 27 and having a gene sequence operably linked to a promoter sequence, the vector allowing the gene sequence to be expressed in a central nervous system cell so that the expressed gene product complements a neurological deficiency, in the preparation of an agent for treating a neurological deficiency of the central nervous system."

V. The board summoned for oral proceedings which were held on 13 July 2004 in the absence of Appellants II, Appellants III and the Respondents.

VI. The Appellants I to III requested that the decision under appeal be set aside and the patent be revoked.

The Respondents requested that the patent be maintained on the basis of the main request (claims 1 and 2), or auxiliary request 1 (claims 1 to 4), or auxiliary request 2 (claims 1 and 2), or auxiliary request 3 (claim 1), all filed on 28 November 2003.

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

(1) EP-A-0 487 611

(2) J. Virology, vol.63, 1989, pages 4579 to 4589

(4) J. Virology, vol.63, 1989, pages 3714 to 3728

(11) Science, vol.244, 1989, pages 1275 to 1281

(14) Mol. Cell. Biology, vol.8, 1988, pages 457 to 460

(29) The New Biologist, vol.2, 1990, pages 739 to 746

(31) Cell, vol.25, 1981, pages 227 to 232

(36) J. Virology, vol.68, 1994, pages 6347 to 6362

(37) J. Virology, vol.66, 1992, pages 2952 to 2965

(38) J. Virology, vol.70, 1996, pages 6358 to 6369

(40) Gene Therapy, vol.5, 1998, pages 1593 to 1603

VIII. The submissions by the Appellants as far as they are relevant to the present decision may be summarized as follows:

Many vectors in which any one of any combination of immediate early genes were mutated were unsuitable for the treatment of neurological deficiencies of the central nervous system. In particular HSV-1 vectors in which just one immediate early gene was disrupted were not satisfactory in practice. This had been disclosed in a number of post-published documents, which have appreciated that "minimisation" of all immediate early genes was needed to give an acceptable vector for the

claimed purpose. The patent in suit not only gave no guidance as to how to overcome the shortcomings and essential negative side effects caused by vectors falling within the scope of claim 1, but failed to disclose a single vector suitable for performing the stated purpose. Both immediate early gene mutated vectors disclosed in the patent ("7143" and "GAL4") fell outside the definition of the viruses of claim 1 of all requests, as they did not contain a gene expressing a protein complementing a neurological deficiency, but only a marker gene, e.g. the E.coli lacZ gene.

To put the invention into effect, the skilled person had to engage in a program of research to determine safe and suitable vectors for the claimed purpose, thus he was forced to make a greater technical contribution to the art than the inventor of the patent in suit.

IX. The submissions by the Respondents as far as they are relevant to the present decision may be summarized as follows:

Even if assuming that some of the vectors falling under the scope of claim 1 of all requests have toxic effects, the skilled reader, a physician, would select appropriate vectors according to the disease to be treated. In certain circumstances, such as the treatment of a brain tumour, a vector with a higher toxicity would be tolerated.

The objection that the patent in suit did not disclose the claimed invention in sufficient detail to be carried out by a skilled person, ignored the fact that

the patent demonstrated for the first time that certain mutated HSV-1 vectors caused expression of a heterologous protein in cells of the central nervous system *in vivo*.

Reasons for the Decision

Article 83 EPC

1. The disclosure of an invention for which protection is sought is one of the fundamental requirements for the grant of a patent. In the European Patent Convention the disclosure requirement is laid down in Article 83 EPC, which states that a European patent application must disclose the invention in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

2. In the assessment as to whether a European application fulfils the requirement of Article 83 EPC, it is established case law of the Boards of Appeal that, for the disclosure of an invention to be sufficiently clear and complete, the skilled person, on the basis of the information provided in the application itself and by using general knowledge, has to be able to achieve the desired result without undue burden and without exercising any inventive skill (cf decisions T 694/92, OJ EPO 1997, 408 and T 612/92 of 28 February 1996).

3. The examination as to the sufficiency of a disclosure in a patent application has to be conducted in each case on its own merits, and it depends on the correlation of the facts of the case to certain general

parameters, e.g. the amount of reliable technical details disclosed in the application, the time when the disclosure was presented to the public and the corresponding common general knowledge, as well as the character of the technical field and the average amount of effort necessary to put into practice a certain written disclosure in that technical field (see decision T 158/91 of 30 July 1991, point 2.3 of the reasons; and T 639/95 of 21 January 1998).

4. The question at issue in the present case is whether, taking into account the above considerations, the skilled person could have arrived at the invention as claimed without undue burden and without exercising any inventive skill.

5. Claim 1 of all requests refer to the use of a mutated HSV-1 virus in the preparation of an agent useful for gene therapy in the central nervous system ("The use of a herpes simplex virus 1 ... in the preparation of an agent for treating a neurological deficiency of the central nervous system"). The mutation of the virus vectors is situated in one or more immediate early genes selected from the following genes that encode infected cell proteins (ICP):

- ICP 0, 4, 22, 27, 47 (main request),
- ICP 4, 27 (auxiliary requests 1 to 3).

The vector is required to contain a gene encoding a protein that complements a neurological deficiency, which gene is to be expressed in a central nervous system cell.

6. The patent mentions only two vectors having a mutation in an immediate early gene encoding an ICP (see examples). These are the vectors "7134", possessing lacZ substitutions in both copies of the HSV-1 ICP 0 gene, which is known from document (2), and "GAL4", possessing lacZ substitutions in both copies of the HSV-1 ICP 4 gene, which is known from document (4).

Expression of β-galactosidase is observed in cortical neurons following stereotactic inoculation of the mutant viruses in adult rat brains (page 6, lines 40 to 41, lines 54 to 56; page 7, lines 18 to 21).

7. Both vectors contain a single gene deletion, "7134" in both copies of the ICP 0 gene, "GAL4" in both copies of the ICP 4 gene. None of them contains a gene sequence that upon expression results in a gene product complementing a neurological deficiency.

8. The interest in vectors for gene therapy derived from classes of nonintegrating viruses, such as HSV-1, resulting from the need for high-titer vectors for transduction and expression of foreign sequences in nonreplicating or fully differentiated postmitotic cells, such as neurons, is described in the art (document (11), page 1277, left column). Moreover, it has been considered, in order to improve the efficiency of vector delivery *in vivo*, to take advantage of tissue or organ tropism, for example to use vectors derived from neurotropic viruses, such as HSV, for gene transfer into the central nervous system (document (11), page 1279, right column).

The use of a recombinant HSV-1 virus vector for expressing human HPRT cDNA in HPRT-deficient rat neuroma cells *in vitro* has been disclosed in document (14) (see abstract).

9. However, viral vectors for use in gene therapy, either for *in vitro* gene transfer followed by cell implantation or for direct vector delivery *in vivo*, have to fulfil various, specific conditions.

10. Clinical applications require faithful regulation of the foreign gene expression. Too much or too little caused by a too strong or too weak promoter, inappropriately timed, or transient gene expression, may prevent disease correction (document (11), page 1280, left column). The regulation of gene expression of a heterologous gene encoding a therapeutically active protein contained in a virus vector is not a straightforward task that can routinely be carried out by a skilled person. On the contrary, it is considered to be a complex problem, being different for each and every gene of interest and asking for extensive research and experimental work.

11. The infection of target cells with replication defective mutated viral vectors for transfer of a heterologous gene must not be associated with cytopathic effects, as viral cytotoxicity limits practical application even in the absence of viral replication.

The disclosure in a number of post-published documents (see below) shows that many of the vectors falling within the scope of claim 1 of all requests, including

the only two vectors explicitly disclosed in the patent in suit, are associated with cytopathic effects and are thus not suitable for the claimed purpose.

The inventors of the patent themselves state in document (29), page 744, right column, that the replication-deficient mutants "7134" and "GAL4" appear to be relatively nonpathogenic to animals, but still may cause substantial cell damage around the injection site. They go on to say that mutants, such as "7134", may be somewhat pathogenic, as some cell death will result from productive infections.

According to document (36) (see abstract) mutations in only one or two immediate early genes encoding ICPs would not result in safe HSV-1 mutants. In order to reduce virus induced cytopathic effects it is necessary to mutate or reduce the expression of nearly all HSV-1 immediate early genes. Document (40) arrives at the same conclusion (abstract).

Moreover, documents (37), (38) and (40) disclose that mutant viruses in which the immediate early gene ICP 4 only is deleted are toxic, rapidly destruct many cell types in culture and cause chromosomal aberrations and rapid cell death ((37) abstract;(38) page 6359, left column; (40) abstract).

Document (31) discloses that an intact gene for ICP 22 is not essential for the replication of HSV-1. This means that a virus bearing a single mutation in this gene only would be replicative and thus unsuitable for the purpose of claim 1, as it would invariably kill the cells in which it multiplies.

12. The Respondents have argued that in certain circumstances a vector with higher toxicity would be tolerated, and that a skilled person upon reading the patent in suit would be able to select appropriate vectors according to the neurological deficiency to be treated. This view has been shared by the Opposition Division in point (VIII) of the reasons for their decision.

13. The Board, however observes that a skilled person, like a physician, reading the patent in suit is confronted with the explicit disclosure of two virus vectors, "7134" and GAL4", which apparently are not suitable for the claimed purpose. He/she is not provided with further information that would allow him/her to find out which modifications of these vectors are necessary to make them safe tools for gene therapy.

14. The Board agrees to the Respondent's position that the actual contribution to the art provided by the patent is to show that said two mutated HSV-1 vectors can cause expression of a heterologous protein in central nervous cells in vivo (see examples). However, the only heterologous protein for which such expression is shown is β-galactosidase, encoded by E.coli lacZ, the marker gene used in the state of the art disclosing the vectors ("7134" in document (2) and "GAL4" in document (4)). This, however, is not a protein as mentioned in claim 1, supposed to be able to complement a neurological deficiency.

15. Starting from this disclosure in the patent in suit, the skilled person, in order to finally arrive at the

claimed subject-matter, which at a theoretical level is already anticipated in the prior art (documents (11) and (14), see point (8) supra), has, therefore, to engage in a research program to find vectors which are safe and suitable for the purpose of claim 1 without any guidance as to how to achieve this goal. Further, the skilled person not being provided with a vector suitable for the use of claim 1, is confronted with the problem of faithful gene regulation of a therapeutically active protein which is an indispensable requirement for a clinical application, and which is considered as being a complex technical problem (see point (10) above).

16. According to established case law of the Boards of Appeal, where an invention relates to the actual realisation of a technical effect anticipated at a theoretical level in the prior art, a proper balance must be found between, on the one hand, the actual technical contribution to the state of the art by said invention, and, on the other hand, the terms in which it is claimed, so that, if patent protection is granted, its scope is fair and adequate (cf T 694/92, supra).

17. No such proper balance is considered to be given in the present case. On the contrary, the skilled person being provided with his general knowledge and the technical contribution to the art of the patent in suit is not in the position to arrive at the subject-matter of claim 1 without performing an extensive research program, possibly even requiring inventive activity, which amounts to undue burden.

18. Therefore, the Board decides that the patent does not disclose the invention according to claim 1 of the main request and of auxiliary requests 1 to 3 in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, contrary to the requirements of Article 83 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey