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D E C I S I O N
of 3 June 2004

Case Number: T 0199/02 - 3.3.4

Application Number: 91308438.0

Publication Number: 0476953

IPC: A61K 48/00

Language of the proceedings: EN

Title of invention:
Targeted destruction of neoplastic cells by retroviral vector-producing packaging cells

Patentee:
THE GENERAL HOSPITAL CORPORATION

Opponent:
Chiron Corporation

Headword:
Targeted destruction of neoplastic cells/THE GENERAL HOSPITAL CORPORATION

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Main request: novelty (yes) - Inventive step (no)"
"Auxiliary request: novelty (yes) - Inventive step (no)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0199/02 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 3 June 2004

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 20 December 2001 revoking European patent No. 0476953 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
G. E. Weiss

Summary of Facts and Submissions

I. European Patent No. 0 476 953 (application No. 91 308 438.0) filed on 16 September 1991, claiming priorities from 14 September 1990 (US 582055) and 16 August 1991 (US 746655) and relating to targeted destruction of neoplastic cells by retroviral vector-producing packaging cells was granted on the basis of 18 claims.

II. A notice of opposition was filed by the opponent (respondent) requesting the revocation of the European patent on the grounds of lack of novelty and inventive step (Articles 54, 56 and 100(a) EPC). By their decision the opposition division revoked the patent because the subject-matter of the claims as granted (main request) and of the first auxiliary request then on file was not novel or lacked an inventive step.

III. Claim 1 as granted read as follows:

"1. The use of retroviral vector-producing packaging cells in the preparation of an anti-neoplastic cell agent or of a sensitizing agent against neoplastic cells already existing in a patient, wherein the retroviral vector produced by said packaging cells can infect neoplastic cells, and wherein said retroviral vector contains a gene whose gene product is capable of:

1) killing the neoplastic cells, or

2) sensitizing the neoplastic cells so that they can be killed by additional chemical treatment or radiation."

Claims 2 to 7 related to specific embodiments of the medical use of claim 1. Claims 8 to 11 were addressed to retroviral vector-producing packaging cells capable, inter alia, of infecting neoplastic cells. Claims 12 to 14 were directed to pharmaceutical compositions. Claims 15 to 17 were directed to products comprising retroviral vector-producing packaging cells and claim 18 was for a process for preparing the pharmaceutical composition.

In the claims of the first auxiliary request, the "neoplastic cells" were limited to "neoplastic cells of a nervous system tumour".

IV. The appellant (patentee) filed an appeal against the decision of the opposition division.

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

(D1) EP-A-0334 301;

(D2) EP-B1-0334 301;

(D3) The approved text for grant of divisional application 95115441.8 derived from (D1) (internal document);

(D4) WO-A-91/02805;

(D5) WO-A-90/07936.

VI. As previously announced, neither the appellant nor the respondent attended oral proceedings held on 3 June 2004.

VII. The submissions by the appellant in writing, insofar as they are relevant to the present decision, can be summarized as follows:

Main request
Novelty

- Documents (D2) and (D3) did not form prior art according to Article 54(2) EPC.

- The passage in column 15, lines 36-46 of document (D1) merely related to packaging cells in the context of an immune response based approach, while claim 1 of document (D1) related to recombinant retroviral vectors per se. Therefore, document (D1) did not destroy the novelty of any of the claims of this request.

- Document (D4) related to on an immune response approach. The reference to Herpes simplex virus thymidine kinase (HSVTK) on page 54 of this document was made in the context of killing the packaging cells, not the target cells.

- Document (D5) also did not relate to the use of packaging cells in the preparation of an anti-neoplastic medicament. The passage on page 32, last paragraph to page 33, first paragraph,

referred to removing lymphocytes or bone marrow cells from a subject, converting them into retrovirus-producing packaging cells, and then reintroducing them into the subject in the context of anti-viral therapies.

Inventive step

– Neither document (D1) nor (D5) taught or suggested the claimed approach.

– The skilled person would not inevitably depart from the teaching of documents (D1) or (D5) to arrive at the claimed subject-matter.

Auxiliary request
Novelty

– Compared with those of the main request, the claims of this request were a fortiori novel over the disclosure of the mentioned documents.

Inventive step

– The medical use of claim 1 of this request was based on the unique environment of nervous system tumours, e.g. CNS or brain tumours, which had a dividing cell population within a population of non-dividing normal brain cells. Thus, the retroviral vectors produced by the packaging cells of the invention could be selectively targeted to tumours of the nervous system. None of the cited documents gave any indication of this particular

advantage, which was thus not obvious to the skilled person.

– Column 22, paragraph [0088] of the patent in suit showed that the claimed approach performed very well.

– Given that documents (D1) and (D5) did not even disclose the use of packaging cells for treating cancer in general, there was no incentive for the skilled person to go from the disclosure of these documents to using the cells to treat nervous system tumours.

VIII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or, in the alternative, on the basis of the set of claims filed on 8 October 2001 before the opposition division (first auxiliary request).

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Main request

Novelty

2. Claim 1 of the main request is directed to the "first medical use" of retrovirus-producing packaging cells for treating a tumour in general.

Documents (D1), (D2) and (D3)

3. Document (D2), is the publication of the granted patent EP-B1-0 334 301 which was published on 23 December 1998, i.e. about seven years after the filing date of the patent in suit. Document (D3) is an internal document relating to the approved text for grant of a divisional application derived from document (D1). These documents thus do not form prior art according to Article 54(2) EPC. Document (D1), however, is the published application EP-A1-0 334 301 with publication date 27 September 1989, i.e. prior to the first priority date of the patent in suit, and thus forms prior art under Article 54(2) EPC.

4. The passage in column 15, lines 36-46 forms part of Example 2 of document (Dl), which is entitled "Immune Response to Retroviral Vector-Encoded Antigens" and relates to using retrovirus-producing packaging cells as an alternative to using the retroviral vector, in the context of this specific example dealing with an immunologic response based approach. Claim 1 of document (Dl) (see also column 22, lines 38-51) relates to recombinant retroviral vectors for use in treating inter alia cancerous cells.

However, the conclusion cannot be drawn that document (D1) discloses the use of retrovirus-producing packaging cells for treating cancerous cells, i.e. the medical use of present claim 1, in the absence of a pointer in document (D1) to this specific (packaging cells/cancer) combination.

Document (D4)

5. There is a reference on page 54 of this document (see first paragraph) to injecting packaging cell lines expressing Herpes simplex virus thymidine kinase (HSVTK) to a patient with the purpose of killing the packaging cells, not the target cells. The rationale behind this expedient is to remove the packaging cells post-injection, to avoid issues related to immune reactions. In fact, the document as a whole deals with immune response-based diseases with no reference to treating cancer. Thus, document (D4) does not teach the medical use of claim 1.

Document (D5)

6. Document (D5) (see page 32, last paragraph) relates to converting lymphocytes or bone marrow cells to packaging cells by inserting a construct capable of expressing the viral genes encoding gag-pol and env, followed by the insertion of a "vector of the invention". Page 14, lines 13-14 of this document further relates to the use of a "DNA construct" (see page 11, line 16) for the treatment of "hyperproliferative disorders (especially cancers)".

However, no conclusion can be drawn that document (D5) discloses the use of retrovirus packaging cells for treating cancer, i.e. the medical use of present claim 1, in the absence of any pointer in document (D5) to this specific (packaging cells/cancer) combination.

7. In conclusion, there is no direct and unambiguous disclosure in the prior art of retroviral vector-producing packaging cells in the context of treating neoplastic disorders. There is also no evidence before the board that any of the retroviral vector-producing packaging cells disclosed by documents (D1), (D4) and (D5) are capable of infecting neoplastic cells. The claims of the main request thus satisfy the requirements of Article 54 EPC.

Inventive step

Closest prior art

8. According to document (D1) (see e.g. column 22, lines 27-51), a retroviral vector is used to selectively target and kill neoplastic cells by expression of a gene product. An example of this construct is the thymidine kinase gene (TK) of Herpes simplex type 1 virus (HSV-1), i.e. HSV-1-TK, inserted into a retroviral vector under the transcriptional control of the enhancer-promoter element of the Moloney murine leukemia virus long terminal repeat. Once expressed, HSV-1-TK does not kill the cell directly but by "activating" the co-administrated nucleoside analogs acyclovir or gancyclovir (ibidem, column 23, lines 46-56). The sensitivity of a cell expressing HSV-1-TK to the toxic effect of acyclovir or gancyclovir is significantly increased, compared with an uninfected

cell (comprising mammalian TK which cannot "activate" these nucleoside analogs). Thus the retroviral vector is used to selectively kill essentially all infected cells while sparing uninfected ones.

Problem to be solved

9. Direct injection of the retroviral vectors at the site of the neoplastic growth has proven to be ineffective owing to the low infection rate and the limited life span of the retroviral vectors in vivo (see patent in suit, column 22, paragraphs [0087] and [0088]). Therefore, the objective problem to be solved in the light of this is seen by the board in the improvement of this technique. The solution proposed according to claim 1 is a retrovirus-producing packaging cell, placed into the tumour to deliver the vectors. Column 22, paragraph [0088] of the patent in suit shows that the above problem has indeed been solved.

10. In the board's view, however, using a packaging cell producing the retroviral vector is a known method for delivering the vector. Document (D1) (see column 15, lines 36-46) indeed teaches that this expedient is used in order to infect a larger number of target cells and to increase the viral vector's life span in vivo. It is true that the above passage is concerned with using retrovirus-producing packaging cells as an alternative to using the retroviral vector, in the context of an immunologic response-based approach, however, the board is convinced that the skilled person would be motivated to apply this expedient to any target cells such as tumour cells.

11. In conclusion, claim 1 of the main request does not fulfil the requirements of Article 56 EPC. This request must thus be refused.

First auxiliary request
Novelty

12. In claim 1 of this request, the neoplastic cells to be treated have been limited to cells of a nervous system tumour. The conclusions arrived at under paragraph 7 supra that the claims satisfy the requirements of Article 54 EPC also apply to the claims of this request.

Inventive step
Closest prior art and problem to be solved

13. The problem-solution approach adopted in relation to claim 1 of the main request (see points 8 and 9 supra) also applies to claim 1 of this request by replacement of the term "tumour" (main request) by the expression "nervous system tumour" (first auxiliary request).

14. It is argued by the appellant that the retroviral vector-producing packaging cells prove useful in the selective delivery of e.g. the HSV-1-TK killer gene to quickly dividing tumour cells in the dividing nervous system, where most endogenous cells, except glial cells, are not dividing (e.g., in the case of glioblastoma) and that this particular advantage was not obvious to the skilled person.

15. The relevant question to be answered in the context of the inventive step issue is whether the prior art would direct in an obvious manner the skilled person to treat

nervous system cancer by means of retrovirus-producing packaging cells. The answer is in the affirmative, since there was already an incentive to treat any type of cancer by means of retrovirus-producing packaging cells (see point 10 supra), regardless of whether the particular advantages pointed out by the appellant of selecting the treatment of nervous system cancers among all possible neoplasia might not have been known/evident to the skilled person.

16. In conclusion, claim 1 of the auxiliary request also fails to fulfil the requirements of Article 56 EPC. Therefore, this request must also be refused.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey