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D E C I S I O N
of 6 July 1998

Case Number: T 0279/96 - 3.3.4

Application Number: 89910391.5

Publication Number: 0432216

IPC: C12N 15/86

Language of the proceedings: EN

Title of invention:
Recombinant retroviruses with amphotropic and ecotropic host ranges

Applicant:
Whitehead Institute for Biomedical Research

Opponent:
-

Headword:
Retroviruses/WHITEHEAD INSTITUTE

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

Keyword:
"Inventive step (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0279/96 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 6 July 1998

Appellant: Whitehead Institute for Biomedical Research
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 24 July 1995 refusing European patent application No. 89 910 391.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
W. Moser

Summary of Facts and Submissions

I. European application No. 89 910 391.5 published as WO 90/02806 with the title "Recombinant retroviruses with amphotropic and ecotropic host ranges" was refused by the Examining Division.

II. The Appellants lodged an appeal against this decision, paid the appeal fee and filed a statement of grounds for the appeal together with a new main request and three auxiliary requests.

III. A communication was sent by the Board according to Article 11(2) of the Rules of Procedure of the Boards of Appeal setting out the Board's provisional, non binding opinion.

IV. The Appellants answered the Board's communication and filed a new main request and three auxiliary requests to replace all requests on file.

Claim 1 of the main request read as follows:

"1. A packaging cell line capable of generating helper-free recombinant retroviruses with amphotropic or ecotropic host ranges, wherein the genome of a cell of the packaging cell line comprises two mutant Moloney Murine Leukemia virus-derived proviral genomes, which genomes:

(a) carry complementary frame shift mutations which:

(i) are in the gag, pol or env genes, and
(ii) are such that the gross structure of the genome is substantially retained,

(b) carry a deletion of the Psi sequence,

(c) carry a deletion of the 3'-LTR sequence, and

(d) were introduced in the genome of the cell by sequential transfection, wherein a first proviral genome having one of the gag/pol or env gene frame shift mutations is introduced into the cell followed by the sequential introduction of a second proviral genome having the complementary gag/pol or env gene frame shift mutation."

Claim 1 of the first auxiliary request was identical to claim 1 of the main request except for step (d) which read:

"(d) were introduced into the genome of the cell by sequential transfection, which sequential transfection comprises the steps of:

(i) a first round of transfection with an env$^-$ genome followed by selection on the basis of reverse transcription activity;

(ii) a second round of transfection with a gag$^-$ genome followed by selection on the basis of packaging capacity."

Claim 1 of the second auxiliary request was identical to claim 1 of the main request except for step (d) which read:

"(d) were introduced into the genome of the cell by sequential transfection, which sequential transfection comprises the steps of:

(i) a first round of transfection with all or a portion of pCRIP-$\underline{env}^-$, as described in Fig.2 of the accompanying drawings followed by selection on the basis of reverse transcription activity;

(ii) a second round of transfection with all or a portion of pCRIPAM $\underline{gag}^-$ or pCRIPgag^{-2} as described in Fig.2 of the accompanying drawings followed by selection on the basis of packaging capacity."

In the three requests, the wording of claims 3 and 6 was adapted to the wording of claim 1. The other claims remained unchanged.

The third auxiliary request comprised one claim which read:

"1. The packaging cell line Psi CRIP having the identifying characteristics of ATCC CRL 9808, or the packaging cell line Psi CRE having the identifying characteristics of ATCC CRL 9807."

V. The state of the art comprised inter alia the following documents:

(1): UCLA Symposia on Molecular and Cellular Biology: Abstracts of the 17th Annual Meetings (Jan.30 to Feb.26, 1988), J. of Cellular Biochemistry, Supplement 12B, 1988,

(2): Markowitz, D. et al., J. of Virology, Vol. 62, No. 4, 1988, pages 1120 to 1124,

VI. The Appellants' arguments with regard to whether or not new matter was introduced, (Article 123(2) EPC) and with regard to inventive step (Article 56 EPC) were essentially as follows:

(a) In Claim 1 part (c) of the main request, the half sentence "e.g. a deletion spanning the entire 3' LTR sequence" had been taken out. In part (d), the sequential transfection had been described in detail. Support for these amendments could be found on page 20, line 5 and on page 22 of the application as filed. The requirements of Article 123(2) EPC were thus fulfilled.

(b) Document (1) was the closest prior art which disclosed packaging cell lines for helper free packaging of retroviral vectors. This document, when read in the context of the large body of prior art which indicated that helper genomes should be constructed by a process of deletion, provided no incentive to maintain the gross genomic structure of the helper genome. Yet, the retention of genomic-like structures (feature (a)(ii) of claim 1) provided benefits in that the packaging efficiency and cell line stability was improved. Furthermore, the sequential transfection as now defined in claim 1(d) was very important to inventive step. It eliminated the possibility of recombination between the constructs being used and hence the possibility of transfering packaging functions or yielding helper virus. Thus, inventive step had to be acknowledged.

The same arguments applied to the auxiliary requests.

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

(a) claims 1 to 10 filed on 8 June 1998 as main request; or

(b) claims 1 to 10 filed on 8 June 1998 as first auxiliary request; or

(c) claims 1 to 7 filed on 8 June 1998 as second auxiliary request; or

(d) single claim filed on 8 June 1998 as third auxiliary request.

Reasons for the Decision

1. The appeal is admissible.

Main request
Articles 123(2), 84 and 54 EPC

2. The claims and the description according to the main request meet the requirements of Articles 123(2), 84 and 54 EPC.

Article 56 EPC

3. The closest prior art document is document (1). The authors of this document are concerned with obtaining packaging cell lines carrying crippled helper genomes, for the production of recombinant retroviruses to be used in somatic gene transfer to large organisms. They point out that it is necessary to eliminate the transfer of packaging functions as well as the

possibility of formation of infecting helper virus starting from the crippled helper genomes. They describe the construction of packaging cell lines capable of generating helper free recombinant viruses with amphotropic or ecotropic host ranges, wherein the genome of a cell of the packaging cell lines comprises two proviral genomes, which genomes:

(a) carry non rescuable complementary frameshift mutations in the **gag-pol** or **env** genes.

(b) carry a deletion of the psi sequence,

(c) carry alterations in the cis acting sequences required for reverse transcription and integration.

The crippled genomes are constructed in vitro and introduced into the cell line "by two successive rounds of transfection/selection". Thus, fifteen different contructs are isolated which produce virus stocks with high titers (10^5 to 10^6 infectious particles/ml).

4. Starting from this prior art, the objective problem to be solved can be defined as the production of another packaging cell line which is safe for the somatic transfer of foreign genes by recombinant retroviruses.

5. The solution provided is a packaging cell line with the characteristics given in claim 1, which produces virus stocks with a titer of 10^6 infectious particles/ml (page 24, lines 17 and 18). The problem has thus been solved.

6. There are two differences in the way the packaging cell lines have been characterized in document (1) and in claim 1 of the main request now on file. Firstly, claim 1, feature (a)(ii) specifies that the frameshift

mutations introduced in the **gag-pol** or **env** genes are not such that the gross structure of the genome is altered. Secondly, the 3' LTR region is said to be deleted rather than the cis acting sequences required for reverse transcription and integration.

7. With regard to the first difference, the Appellants argued that the skilled person reading document (1) in the light of such prior art document as document (2) would have understood the term "frameshift mutation" as meaning extensive deletion resulting in the two DNA fragments on each side of the deletion being joined out of frame.

8. Document (2) describes one way to avoid the formation of helper viruses, which consists in transforming the packaging cell line with the DNA carrying the **gag-pol** gene on a plasmid vector and with the DNA carrying the **env** gene on another plasmid vector. A minimum of homology is kept between the two DNAs by deleting as much as possible of the sequences other than the **gag-pol** and **env** genes. It is nowhere specified that these deletions must engender a shift of frame in the remainder of the coding sequences. Thus, there is no reason why the skilled person reading document (2) would come to the conclusion that in these particular circumstances, deletions and frameshift mutations are necessarily to be considered as the same type of DNA alterations.

9. The method disclosed in document (1) comprises the construction of "two sets of complementary crippled genomes carrying mutations either in the $gp70^{env}$ coding sequences or in the gag-pol gene" and the term "frameshift" is found in the immediately preceding sentence defining the kind of mutations to be carried out. The skilled person reading this teaching would have no reason to doubt that the term "frameshift

mutation" was to be understood according to the basic terminology of classic genetics i.e. not as extensive deletion, since it is the env or gag-pol genes which are said to be affected by the frameshift and not the structure of the genomes as a whole.

10. Accordingly, the Board finds that feature (a)(ii) of claim 1 does not distinguish the subject-matter of the claim from the teachings of document (1) such that this feature would already impart inventive step to the whole claim.

11. With regard to the second difference (see point 5 above), it may be inferred from document (2) (page 1120, second column) that the deletion of the 3' LTR sequence which contains some of the cis acting sequences for reverse transcription and integration was a known mean to avoid the formation of infective helper virus. Therefore, it is not suited to impart inventive step to the claimed subject-matter.

12. The Board, thus, concludes that the features (a) and (c) of the packaging cell line of claim 1 taken alone or in combination do not impart inventive step on said cell line.

13. The Appellants further argued that the sequence of steps in the method given as feature (d) of claim 1 was important for inventive step. Yet, they were unable to provide any evidence that this specific sequence of steps led to any recognizable features in the claimed cell line. The Board would agree that the inventive step of the method disclosed as feature (d) could possibly have been based upon the sequence of steps comprised in this method, were it to be different from

that disclosed in document (1). From the plain description of the method in document (1), namely "These molecules were introduced in NIH 3T3 cells by two successive rounds of transfection/selection.", it would, however, be difficult to conclude that a successive order of steps is excluded.

14. In any case, it is not the inventive step of the method which is at stake but rather that of the producing cell line per se. In view of the fact that, as stated above, the specific sequence of steps was not shown to have any bearings on the features of the packaging cell line, it cannot be taken into account for the assessment of the non-obviousness of said cell line.

15. In view of what precedes, the Board decides that the subject-matter of the main request lacks inventive step.

First and second auxiliary requests

16. The features (a), (b) and (c) of the packaging cell lines of claim 1 in the first and second auxiliary requests are the same as in claim 1 of the main request. The claims differ from this latter claim in feature (d) since further details are provided on the method used to obtain the packaging cell line . Again, the Appellants did not produce any evidence that the method of feature (d), whether worded as in the first or in the second auxiliary request, would lead to recognizable technical features in the claimed packaging cell lines, in addition to features (a) to (c). As these last features were not found to impart inventive step to the claimed packaging cell line (see points 6 to 11 above), it is concluded that the subject-matter of the first and second auxiliary requests also lacks inventive step.

Third auxiliary request

17. The sole claim of this request relates to specific packaging cell lines deposited under numbers ATCC CRL 9808 and ATCC CRL 9807. On page 8 of the application these cell lines are said to produce recombinant retroviruses with high titers (10^6 infectious particles/ml). The viral producers derived from them do not transfer packaging functions or yield helper viruses.

18. These characteristics are the very characteristics of the 15 producer lines isolated in document (1). In the absence of any evidence that the claimed packaging cell lines have any other qualitative or quantitative properties which may not have been expected when reading document (1), they cannot be considered to be inventive.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

D. Spigarelli U. Kinkeldey