DECISION
of 2 March 2006

Case Number: T 0294/04 - 3.3.08
Application Number: 91915104.3
Publication Number: 0572401
IPC: C12N 15/87
Language of the proceedings: EN

Title of invention: Viral particles having altered host range

Patentees: The Regents of the University of California et al.

Opponent: Novartis AG

Headword: Viral particles/UNIVERSITY OF CALIFORNIA

Relevant legal provisions: EPC Art. 54, 56

Keyword: 
"- main request - novelty - yes"
"- main, first to third auxiliary requests - inventive step - no"
"- fourth auxiliary request - inventive step - yes"

Decisions cited: T 0202/95

Catchword: -
Case Number: T 0294/04 - 3.3.08

DECISION
of the Technical Board of Appeal 3.3.08
of 2 March 2006

Appellants: The Regents of the University of California
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 13 January 2004
revoking European patent No. 0572401 pursuant
to Article 102(1) EPC.

Composition of the Board:
Chairman: L. Galligani
Members: F. Davison-Brunel
C. Rennie-Smith
Summary of Facts and Submissions

I. European patent No. 0 572 401 with the title "Viral particles having altered host range" was granted with 18 claims for all designated Contracting States, based on European patent application No. 91 915 104.3.

II. An opposition was filed under Article 100(a) to (c) EPC for lack of novelty, lack of inventive step, insufficiency of disclosure and added subject-matter. The opposition division acknowledged compliance of the main request and the auxiliary request then on file with the requirements of Articles 123(2) and 54 EPC. The patent was revoked for lack of inventive step. Sufficiency of disclosure was not assessed.

III. The appellants (patentees) filed a notice of appeal, paid the appeal fee and submitted a statement of grounds of appeal together with a main request and four auxiliary requests.

IV. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal indicating its preliminary, non-binding opinion.

V. The appellants and the respondent (opponent) answered this communication.

VI. At oral proceedings, which took place on 2 March 2006, the respondent did not pursue the earlier objection of lack of novelty.
VII. The main request on file is the same main request as was considered by the opposition division. Claims 1, 3 and 10 read as follows:

"1. A packaging cell line capable of producing enveloped vector particles having a host range derived from vesicular stomatitis virus (VSV) and comprising:
   a first nucleic acid sequence encoding the production of a nucleocapsid protein having an origin from a retrovirus;
   a second nucleic acid sequence encoding the production of a heterologous membrane-associated protein which determines a host range being different from that of the retrovirus from which the first nucleic acid sequence is derived, said membrane-associated protein having an exterior receptor binding domain, a membrane-associated domain and a cytoplasmic domain, and wherein said membrane-associated protein is VSV G protein,
   said cells being stably transfected with said first and second nucleic acid sequences.

3. A mammalian packaging cell containing nucleotide sequences encoding gag, pol, and a heterologous chimeric membrane-associated protein which determines a host range, the chimeric membrane-associated protein comprising an exterior receptor binding domain, a membrane-associated domain, and a cytoplasmic domain, wherein the membrane-associated domain is the membrane-associated domain of VSV G and the cytoplasmic domain is the cytoplasmic domain of VSV G and wherein the exterior receptor binding domain is selected from any ligand/receptor to determine a host range which is
different from that of the virus from which the nucleotide sequence encoding gag and pol derives.

10. A stable mammalian packaging cell stably expressing a first nucleotide sequence encoding retroviral gag and pol and inducibly expressing a second heterologous nucleotide sequence encoding VSV G which determines a host range being different from that of the retrovirus from which said first nucleotide sequence derives, wherein said second nucleotide sequence is operatively linked to an inducible promoter."

Dependent claims 2, 4 and 5 respectively related to further features of the cell line/cell of claims 1 and 3. Claim 6 was directed to a recombinant vector particle comprising, in particular, a heterologous chimeric membrane-associated protein, and dependent claims 7 and 8 related to further features of the vector particle of claim 6. Claim 9 was directed to a method for producing a recombinant enveloped vector particle comprising a heterologous chimeric membrane-associated protein. Dependent claims 11 and 12 related to further features of the packaging cell of claim 10. Claim 13 was directed to a method of producing an enveloped vector from a mammalian packaging cell line inducibly expressing the envelope VSV G protein and dependent claims 14 to 16 related to further features of said method.

VIII. Claim 1 of the first auxiliary request corresponded to claim 1 of the main request with the further feature at the end of the last sentence "... and being tolerant to the production of the membrane-associated protein."

Claim 1 of the second and third auxiliary requests was
the same as claim 1 of the main request. The fourth auxiliary request comprised 14 claims corresponding to claims 3 to 16 of the main request.

IX. The following documents are mentioned in the present decision:


(13): Schubert, M. et al., Abstract P27-014, IUMS Symposium on New Developments in Diagnosis and Control of Infectious Diseases, August 26 to 31 1990;


X. The appellants' arguments in writing and during oral proceedings insofar as relevant to the present decision may be summarized as follows:
Article 56 EPC; inventive step
Main request, first to third auxiliary requests:
claim 1

The closest prior art was document (1) which described the transient production of pseudotype retroviral particles encapsidated in the VSV-G envelope protein of vesicular stomatitis virus.

The problem to be solved was the provision of a system for the long-term production of pseudotype retroviral/VSV-G vectors.

The solution provided was a cell line stably expressing proteins necessary for the formation of the pseudotype retroviral particles including VSV-G.

At no point did document (1) mention a cell line. A fortiori, it did not suggest that difficulties due to the toxic effects of VSV-G could be encountered when isolating a cell line. In fact, there were no documents in the prior art disclosing VSV-G as being toxic. In particular, document (5) would not be considered as providing such a teaching since it showed the isolation of stably transformed MDCK cells expressing VSV-G. Admittedly, the remark was made on page 385 that some transformed MDCK cells were lost during cultivation. Yet two explanations were proposed for the phenomenon: that the transformed cells grew slower that the untransformed cells; alternatively, that large amounts of VSV-G protein would be toxic to the cells. The skilled person would favour the first of these explanations.
It was the work done by the inventors which established for the first time in a surprising and unexpected manner that VSV-G was toxic. Before then, there would have been no reason to turn to document (5) as the provider of a stable cell line expressing VSV-G. Otherwise stated, the combination of the teachings of documents (1) and (5) could only be made with hindsight knowledge of the invention and, thus, it did not affect inventive step. The packaging cell line of claim 1 fulfilled the requirements of Article 56 EPC.

Fourth auxiliary request
Claim 1 (identical to claim 3 of the main request)

Denying inventive step to the packaging cell line expressing a chimeric envelope protein on the basis of the combination of documents (1) and (13) was unwarranted. Document (13) was not concerned with pseudotype retroviral particles but with pseudotype vesicular stomatitis viral particles. And, furthermore, the composition of the pseudotype viral particles which it described was significantly different from that of the now claimed particles: the envelope of the pseudotype VSV particle was of the same origin (VSV) as the encapsidated nucleotide sequence whereas, in the present case, the envelope of the pseudotype retroviral particle was of a different origin (VSV) than that of the encapsidated nucleotide sequence (retroviral). Even if the teachings of documents (1) and (13) were combined, that would not lead in an obvious manner to the claimed pseudotype retroviral particle.
Examples 9 and 10 provided evidence that retroviral vectors could be efficiently encapsidated in VSV-G and also that chimeric retroviral/VSV-G envelope could be used for encapsidation. Thus, there was a technical basis in the patent in suit for the effect underlying the inventive step of the invention.

Claim 8 (identical to claim 10 of the main request)

Inventive step was denied to the subject-matter of claim 8 for the reason that the use of an inducible promoter was an obvious precautionary measure to avoid the conventional problems which may occur upon expression of proteins in heterologous host cells. This assumption was false: inducible promoters would generally be avoided because they tended to give lower expression levels than constitutive ones. More specifically, they would be avoided in the present case because they would introduce a further complication into what was already a complicated expression system.

The opposition division had cited document (33) as an example of a case where an inducible promoter had been used to express a protein without knowing in advance that it was toxic. This, however, was not correct as the document taught that constitutive expression of the protein of interest was toxic and that the use of an inducible promoter would relieve toxicity. Here, even if one admitted that document (5) taught the VSV-G potential toxicity to cells, it nonetheless also taught the solution to this problem, namely to use a MDCK cell line. In the absence of any suggestion of yet another system for expressing VSV-G, the skilled person had no reason to develop such a system.
XI. The respondent's arguments in writing and during oral proceedings insofar as relevant to the present decision may be summarized as follows:

Article 56 EPC; inventive step
Main request and first to third auxiliary requests: claim 1

Starting from the teachings of document (1), the problem of establishing a system for the long-term production of retrovirus/VSV-G pseudotype retroviral vectors was obvious to solve by providing a stable cell line expressing VSV-G. Indeed, it was a matter of common general knowledge at the priority date that stable cell lines could be used to provide a viral vector with all proteins necessary for its multiplication and encapsidation.

At the priority date, the toxicity of VSV-G for the cells which produced it was already known from document (5) which, moreover, described a cell line that was able to sustain the expression of the VSV-G protein. The use of this cell line for solving the above mentioned problem was, thus, obvious. In addition, the application as filed (page 40) provided evidence that the patentees were aware of the existence of cell lines able to express VSV-G.
Fourth auxiliary request

Claim 1

The distinguishing feature of claim 1 over document (1) was that the heterologous membrane-associated protein was chimeric: VSV-G/ligand. The problem to be solved could be defined as modifying the host range of a VSV-G pseudotype retroviral vector. Document (13) disclosed VSV-G fusion proteins and also motivated the skilled person to determine whether it was possible to generate pseudotype viruses with a chimeric envelope. Accordingly, claim 1 lacked inventive step over the combined teachings of documents (1) and (13).

Claim 8

The use of inducible expression systems to produce proteins that showed toxic effects was common general knowledge at the priority date as shown, for example, in document (33). For this reason the skilled person, knowing from document (5) that VSV-G could be toxic, would find it obvious to produce it in an inducible manner in the packaging cell line.

XII. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of either the main request or one of the first to fourth auxiliary requests filed with the statement of grounds of appeal.

The respondent requested that the appeal be dismissed.
Reasons for the decision

Main request

Article 123(2) EPC; added subject-matter

1. The main request now under consideration is the same as the main request considered by the opposition division, which was found to have a basis in the application as filed. On appeal, this point was not challenged by the respondent. It is also the board's opinion that the requirements of Article 123(2) EPC are fulfilled.

Article 54 EPC; novelty of the subject-matter of claim 1

2. The claimed packaging cell line is disclosed in the priority document US 658632 of the patent in suit, Example 13, "Production of stable packaging construct in tolerated cell lines". Admittedly, the instructions for obtaining it are somewhat less detailed than in the corresponding Example 13 of the patent in suit. Yet, all necessary, specific steps are clearly identified. At oral proceedings, the respondent did not challenge priority. In the board's judgment, rights to priority may be acknowledged.

3. Accordingly, document (2) published between the priority and the filing dates of the patent in suit is not a piece of prior art to be considered when assessing novelty. There are no other documents on file relating to a packaging cell line such as now claimed. Novelty is acknowledged.
4. The closest prior art is document (1), an abstract relating to "Pseudotype formation of retrovirus vectors containing the glycoprotein of vesicular stomatitis virus", i.e. to the formation of retroviral particles encapsidated in the VSV-G envelope protein. The pseudotype retroviral particles are produced \textit{transiently} by co-transfection of BHK cells with a retroviral vector containing the gene encoding VSV-G and with a plasmid encoding the retroviral MoMLV gag and pol genes. It is stated that: "... VSV G protein alone in the absence of other VSV-encoded proteins is sufficient to interact with the nucleocapsid of MoMLV in the formation of MoMLV(VSV) pseudotypes, and G proteins can be incorporated into the virions of retrovirus as efficiently as MoMLV envelope proteins."

5. Starting from the closest prior art, the problem to be solved may be defined as providing a system for the \textit{long-term} production of pseudotype retroviral/VSV-G particles.

Providing such systems was part of the common knowledge at the priority date (cf. patent in suit, "Background part of the invention", [009]; document (6), a review on "Retroviral mediated gene transfer" published in 1990 and representing the common general knowledge, Section C). The formulation of the problem, thus, does not contribute to inventive step.
6. The solution provided is to use a packaging cell line which stably expresses the VSV-G gene as well as the necessary retroviral nucleocapsid proteins (gag and pol).

7. Cells expressing the VSV-G gene are disclosed in document (5) with the title "Immunoselection of Stably Transformed MDCK Cells Expressing the Vesicular Stomatitis Virus G-Protein at the Basolateral Surface".

8. The straightforward conclusion to be drawn from this prior art is that the combination of the teaching of document (1), namely that it is possible to obtain pseudotype retroviral/ VSV-G particles, with that of document (5) providing MDCK cells stably expressing VSV-G renders obvious the claimed stable cell line. No arguments were ever presented that any difficulties would arise from the cell line also having to express the retroviral gag and pol nucleocapsid proteins. The stated approach is indeed the one used in the patent specification.

9. According to the appellants, combining these teachings was per se not obvious because the prior art was wholly silent as to the VSV-G protein being toxic to the cells which produce it. Thus, the skilled person would have started from any cells at his/her disposal, in particular the BHK cells used in document (1), and would have failed to isolate the packaging cell line. Inventive step resided in the fact of having made the unexpected observation that VSV-G was toxic and of having nonetheless isolated cells which could stably express VSV-G.
10. In this respect, two remarks must be made. Firstly, there is some prior art suggesting that VSV-G could be toxic to the cells which produced it: document (5) itself, while disclosing transformed MDCK cells as stably expressing VSV-G nonetheless warned on page 385 against the possibility that: "... the expression of large amounts of G-protein could be toxic to the cells.". Secondly, the skilled person embarking on the project of producing a packaging cell line for the production of pseudotype retroviral/VSV-G particles would be aware not only of document (1) but also of document (5). Indeed, in accordance with the case law (eg T 202/95 of 21 July 1998), it is one of the attributes of the skilled person that he/she knows all of the state of the art pertaining to the field in question.

11. It can be accepted that for sake of convenience, the skilled person's first attempt at obtaining the desired packaging cell line would be carried out with any cell line then directly available to him/her but, nonetheless, this would be done in awareness of document (5). Thus, having encountered some difficulties and knowing from this document a possible explanation therefor and, also, most importantly, a solution thereto, he/she would obviously make use of this solution, ie would obviously make use of MDCK transformed cells. This is indeed what is exemplified in Example 13 of the patent in suit after the statement is made in paragraph [0111] that "One cell line, MDCK, (ATCC No. CCL34) has been reported ... to be capable of supporting long-term production of VSV-G".
For these reasons, the board concludes that the skilled person wanting to solve the above mentioned problem would have considered it obvious to combine the teachings of documents (1) and (5) to arrive at the claimed packaging cell line. As claim 1 of the main request does not fulfil the requirements of Article 56 EPC, the request cannot be allowed.

First to third auxiliary requests

Claim 1 is also present identically or in a slightly modified form (cf. section VIII supra) in the first to third auxiliary requests. Consequently, they also cannot be allowed for the same reasons given above.

Fourth auxiliary request

This request differs from the main request in that claims 1 and 2 have been deleted and claims 3 to 16 have been accordingly re-numbered claims 1 to 14. The positive findings regarding formal requirements and novelty in relation to the main request equally apply to this request.

Article 56 EPC; inventive step

Claim 1 (identical to claim 3 of the main request)

The closest prior art is document (1) which, as already mentioned at point 4 supra, discloses the transient production of pseudotype retroviral/VSV-G protein by co-transfection of BHK cells with a retroviral vector containing the VSV-G gene and with a plasmid encoding the gag and pol proteins also necessary for the production of the pseudotype retroviral particles.
Document (1), being a short abstract, does not disclose the aim of isolating these particles. Document (6), representing the common general knowledge at the priority date, teaches on page 103 that: "... in all packaging systems, the targeting of the vector is provided by the choice of envelope expressed by the packaging cells." Thus, reading document (1) in light of the common general knowledge, the skilled person would most probably understand the aim of the work it describes as being to enlarge the host range of retroviral vectors.

16. Starting from these premises, the problem to be solved may be defined as producing retroviral vector particles with an alternative host range.

17. The solution provided is a packaging cell enabling the long-term production of retroviral particles with a chimeric envelope whereby the membrane-associated and cytoplasmic domains originate from VSV-G whereas the exterior domain is from any ligand/receptor which determines a host range which is different from that of the retrovirus from which the nucleotide sequence encoding gag and pol derives. This solution, thus, amounts to isolating the pseudotype (retroviral vector/partial VSV-G/heterologous exterior domain) of a pseudotype (retroviral vector/VSV-G). This solution is different from the ones used in the prior art. Indeed, in accordance with the documents on file, the ways to alter the host range of a viral vector at the priority date were either to replace the viral envelope by that of another virus as disclosed in document (1) or, alternatively, to make the original viral envelope chimeric for an external domain specifying a different
host range as shown in document (13). In this latter case, it was intended to produce VSV particles with an altered host range and the VSV nucleotide sequence was encapsidated in a chimeric VSV envelope comprising the HIV receptor domain fused to the VSV-G membrane-associated and cytoplasmic domains. Thus, the solution provided by claim 1 is nowhere suggested in the prior art and is, therefore, not obvious.

18. In the patent in suit, there is no example of a packaging cell expressing a chimeric envelope such as now claimed, nor, of course, of the use of such an envelope for encapsidation. Yet, Example 9 discloses that retroviral particles may be encapsidated in chimeric retroviral/VSV-G envelopes. These data make it plausible that a chimeric protein could be created wherein the cytoplasmic and membrane-associated domains of VSV-G would be combined to the exterior receptor domain from a variety of unrelated proteins, which chimeric protein would serve to encapsidate the retroviral vector. Accordingly, it is accepted that the claimed packaging cell is a genuine solution to the problem of isolating retroviral vectors with alternative host ranges.

19. The inventive step of claim 1 is acknowledged.

Claim 8 (identical to claim 10 of the main request)

20. The closest prior art is document (1) (see point 4, supra) and the problem to be solved may be defined as previously (point 5 supra) as providing a system for the long-term production of pseudotype retroviral/VSV-G particles.
21. The solution in claim 8 is a stable packaging cell line which expresses VSV-G in an inducible manner.

22. As already mentioned in point 11 supra, the skilled person would find in document (5) a possible explanation of why difficulties may be encountered while trying to produce a cell line expressing VSV-G, but also and most importantly, document (5) gives a solution to these difficulties, namely MDCK cells transformed by the VSV-G gene and expressing the VSV-G protein. In the board's judgment, he/she would have no reason to look for a further solution to the problem created by the potential toxicity of VSV-G. The subject-matter of claim 8 represents a different, hitherto unsuggested approach to solving the above mentioned problem which solution is, thus, not obvious.

23. The opposition division denied inventive step for the reason that inducible expression would be chosen as a matter of precaution against the difficulties to be expected from heterologous gene expression, irrespective of whether or not any difficulties can be foreseen. As evidence therefor, they cited document (33) which describes the cloning and expression of the bovine herpesvirus I glycoprotein IV. It is doubtful that this document, which is in a different domain of virology, would be taken into consideration by the skilled person. In any case, it does not prove the point which it is intended to prove as, in fact, both constitutive and inducible expressions of the glycoprotein IV are tested before arriving at the result that only inducible expression is suitable. Document (33) is, thus, irrelevant for inventive step.
24. Inventive step is acknowledged for the subject-matter of independent claims 1 and 8. This is also the case for the subject-matter of independent claims 4, 7 and 11 respectively relating to recombinant viral particles encapsidated in a chimeric envelope, to a method for producing them and to a method for producing pseudotype retroviral vectors in an inducible manner. The fourth auxiliary request as a whole fulfils the requirements of Article 56 EPC.

25. Added subject-matter, novelty and inventive step were the three issues considered in the decision of the opposition division. Sufficiency of disclosure was not considered. The case is, thus, remitted to the first instance for further prosecution.

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 for further prosecution on the basis of the fourth auxiliary request filed with the statement of grounds of appeal.

The Registrar: A. Wolinski

The Chairman: L. Galligani