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Datasheet for the decision of 5 September 2013

Case Number: T 1672/09 - 3.3.08

Application Number: 03739561.3

Publication Number: 1474521

IPC: C12N 15/86

Language of the proceedings: EN

Title of invention:
An herpes simplex virus complex

Patent Proprietor:
Virttu Biologics Limited

Opponent:
MediGene Aktiengesellschaft

Headword:
HSV Complex/ MEDIGENE

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

Keyword:
"Main request - added matter (no), inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1672/09 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 5 September 2013

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 16 June 2009 concerning maintenance of European patent No. 1474521 in amended form.**

Composition of the Board:

Chairman: M. Wieser
Members: B. Stolz
D. S. Rogers

Summary of Facts and Submissions

I. The patentee (appellant I) and the opponent (appellant II) each filed an appeal against the decision of the opposition division to maintain European patent No. 1474521 in amended form on the basis of the 3rd auxiliary request filed during oral proceedings on 22 April 2009.

II. With its grounds of appeal, appellant I submitted a main request and auxiliary requests 1 to 3.

In a further submission, dated 12 March 2010, appellant I responded to appellant II's arguments and filed an auxiliary request 4.

III. Appellant II filed its grounds of appeal, and, in a further submission, responded to appellant I's submissions.

IV. In a communication dated 3 May 2013, annexed to the summons to oral proceedings, the board informed the parties of its preliminary, non-binding opinion on some of the issues to be discussed at the upcoming oral proceedings.

V. With its final submissions before oral proceedings, appellant I withdrew the main request, renumbered previous auxiliary requests 1 to 3 as main request and auxiliary requests 1 and 2, respectively, and filed new auxiliary requests 3 to 7.

VI. Appellant II made its final submissions one month before oral proceedings.

VII. Oral proceedings were held on 5 September 2013. During the oral proceedings, appellant I filed a new main request consisting of claims 1 to 39.

VIII. Throughout this decision, reference is made to HSV which stands for herpes simplex virus.

IX. Independent claims 1, 12, 25, 34 to 37 and 39 of the main request read as follows:

"1. An HSV complex capable of targeting a specific cell type, said complex comprising an HSV modified in the terminal portion of R_L within BamH1 s (0-0.02 and 0.81-0.83mu) so as to lack neurovirulence, and a targeting agent linked to the modified HSV, wherein said targeting agent comprises an antibody binding domain and is linked to the modified virus via HSV glycoprotein gC.

12. An HSV which is capable of targeting a specific cell type, said HSV lacking an expressible γ34.5 gene so as to lack neurovirulence and wherein said HSV expresses a targeting agent as a fusion protein with HSV glycoprotein gC, wherein said targeting agent comprises an antibody binding domain.

25. A method of producing an HSV according to any one of claims 12 to 24 comprising the steps of

(a) modifying the HSV genome so as to prevent γ34.5 gene from expressing a functional protein;

(b) modifying the HSV genome by incorporating nucleic acid encoding a targeting agent so that said targeting

agent is expressed as a fusion protein with HSV glycoprotein gC, wherein said targeting agent comprises an antibody binding domain;

(c) expressing said modified HSV in a cell.

34. An HSV complex according to any one of claims 1 to 11 for use in a method of medical treatment.

35. An HSV according to any one of claims 12 to 24 for use in a method of medical treatment.

36. Use of an HSV complex according to any one of claims I to 11 in the preparation of a medicament for treating a disease associated with the proliferation of cells.

37. Use of an HSV according to any one of claims 12 to 24 in the preparation of a medicament for treating a disease associated with the proliferation of cells.

39. A pharmaceutical composition comprising an HSV complex according to any one of claims 1 to 11 or an HSV according to any one of claims 12 to 24 and a pharmaceutically acceptable carrier."

X. The following documents are cited in this decision:

D1: W096/03997

D2: WO 99/06583

D3: Galmiche M.C. et al., Expression of a functional single chain antibody on the surface of extracellular enveloped vaccinia virus as a step

towards selective tumour cell targeting, J. Gen. Virology (1997), 78:3019-3027.

D8: Laquerre S. et al., Recombinant herpes simplex virus type 1 engineered for targeted binding to erythropoietin receptor-bearing cells, J. Virol. (1998), 72:9683-97.

D13: Conner et al., A strategy for systemic delivery of the oncolytic herpes virus HSV 1716: redirected tropism by antibody-binding sites incorporated on the virion surface as a glycoprotein D fusion protein. Gene Therapy (2008), 1-14.

D15: Douglas J.T. et al., Targeted delivery by tropism modified adenoviral vectors, Nature Biotechnology (1996), 14:1574.

D16: Hammond A.L. et al., Single chain antibody dusplayed on a recombinant measles virus confers entry through the tumor associated carcinoembryonic antigen, J. Virol. (2001), 2087-2096.

D18: Grandi P. et al, Targeting HSV-1 virions for specific binding to EGF receptor VIII on tumor cells, Molec. Therapy (2006), 13: Suppl. 1.

XI. The arguments of appellant I, as far as relevant for the present decision, can be summarized as follows:

Article 123(2) EPC

Basis for the feature "wherein said targeting agent comprises an antibody binding domain and is linked to the modified virus via HSV glycoprotein gC" could be found on pages 4 and 5 of the patent application as filed.

Article 56 EPC

Starting from document D1 as closest prior art, the technical problem underlying the claimed invention consisted in providing an alternative HSV. The prior art cited by appellant II concerned different viruses and the teaching of this prior art was not applicable to HSV. The skilled person was a HSV virologist who knew from document D8 that the insertion of the 165 amino acid EPO sequence posed problems and that shorter peptides were considered more promising for altering target specificity. Document D2 (page 6, line 12) mentioned transferrin as a hypothetical ligand but made no mention of antibody binding domains.

XII. The arguments of appellant II, as far as relevant for the present decision, can be summarized as follows:

Article 123(2) EPC

The application as filed did not provide a basis for the linkage of an antibody binding domain specifically to glycoprotein gC.

Article 56 EPC

Document D1 represented the closest prior art and the technical problem to be solved consisted in providing an alternative HSV. The insertion of antibody binding domains into viral envelope proteins was known from documents D3, D15 and D16. Document D2 showed that the 165 amino acid sequence of EPO could be inserted into HSV glycoprotein C and the insertion of a much larger protein, transferrin, was also taught therein (page 6, line 12). There was no prejudice in document D8 against the insertion of longer sequences into glycoprotein gC. Therefore, the claimed solution was obvious.

XIII. Appellant I requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed at the oral proceedings.

XIV. Appellant II requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the decision

Admissibility of the main request

1. The main request, filed at the oral proceedings, is based on auxiliary request 3 filed with the grounds of appeal. The only difference is that all references to glycoprotein gD have been deleted. Appellant II had no objections to the introduction of the main request at this stage of the proceedings, and the board, in view of the fact that the amendments did not create any new issues, decided to admit it into the proceedings (Article 13(1) RPBA).

Article 123(2) EPC

2. Appellant II submitted that the limitation of claim 1 to a HSV complex comprising an antibody binding domain linked to glycoprotein gC represented a purposive selection from the broader disclosure of the application as originally filed.

3. The subject matter of the present application is a HSV complex with a modified tropism, capable of targeting particular cell types (e.g. page 4, lines 1 to 3; claim 1 of the application as filed). The targeting agent is conveniently an antibody or a component of an antibody linked to a viral envelope protein (page 4, last paragraph), and an antibody binding domain is a preferred embodiment (page 5, lines 16 to 17). Preferred envelope proteins are glycoproteins gB, gC, and gD (e.g. page 14, line 11). It is furthermore evident from the examples that fusions to glycoprotein gC represent the most preferred embodiments.

4. The limitation of the claimed subject matter to a HSV complex comprising an antibody binding domain linked to glycoprotein gC is therefore not the result of a purposive, previously undisclosed, selection but of a limitation to a preferred embodiment which was directly and unambiguously derivable from the application documents as filed.

5. The board is satisfied that the requirements of Article 123(2) EPC are met.

Articles 54, 83 and 84 EPC

6. Appellant II raised no objections under the provisions of any of Articles 54, 83 and 84 EPC, and the board sees no need to raise any on its own motion.

Article 56 EPC

7. Claims 1 and 12 relate to a modified HSV complex and a modified HSV, respectively, lacking neurovirulence and comprising an antibody binding domain linked to glycoprotein gC. The antibody binding domain allows the targeting of specific cell types. The intended use of the virus complex is in the treatment of cancer (e.g. page 4, line 8).

8. Document D1 relates to the use of HSV mutants for the treatment of cancer and represents the closest prior art. The mutants comprise a modification in the γ34.5 gene in the terminal portion of R_L such that neurovirulence is lost.

9. Starting from document D1, the technical problem underlying the present invention is seen in the provision of an alternative HSV for the treatment of cancer.

10. For the solution of this problem, the patent proposes the HSV complex of claim 1 and the HSV of claim 12. Example 1 shows that antibody binding domains fused to glycoprotein gC can be expressed and integrated into virus particles.

Wild-type HSV infects and replicates in both, terminally differentiated and dividing cells. HSV lacking neurovirulence is still capable of infecting and replicating in proliferating cells, e.g. in tumor cells (cf. document D1). There is no evidence that the modification of glycoprotein gC alters these properties, and post-published document D18 demonstrates infection of tumor cells in mice by a HSV comprising an antibody binding domain fused to gC.

The board is therefore satisfied that the above mentioned problem is solved by the subject matter of claims 1 and 12.

11. It remains to be established if the claimed solution involves an inventive step.

12. Appellant II submitted that the claimed solution was obvious in view of document D1 and the skilled person's general knowledge as exemplified by documents D3, D15 and D16. Furthermore, document D8 disclosed that HSV with differently modified surface glycoproteins could be obtained.

13. Both parties agreed that the general concept of linking an antibody binding domain to a viral surface protein in order to alter the tropism of a virus, in other words to target specific cell types, was known in the art. Known examples included modified Vaccina virus (document D3), modified Adenovirus (document D15) and modified Measles virus (document D16). The parties disagreed however whether it was obvious to link an antibody binding domain to surface glycoprotein gC of HSV.

14. Document D1 itself is silent about altering target specificity and thus neither provides a pointer nor an incentive to this effect.

15. Document D2 discloses modified HSV and its use in gene therapy applications. The target specificity of the HSV is altered by attaching polypeptides to glycoproteins gB or gC. Examples 2, 3, 5, 6, 12 and 13 all relate to modified gB and gC proteins respectively, comprising short amino acid sequence inserts of 13 or 14 amino acids to target the resulting vectors to specific cell types. Examples 4 and 11 disclose modified HSV comprising a 165 amino acid insert in order to target cells expressing the erythropoietin receptor. Examples 14 and 15 disclose that both types of modifications result in virus able to target specific cell types.

Document D8, the scientific publication corresponding to patent document D2, provides additional experimental data relating to the expression and incorporation into recombinant HSV of glycoprotein gC comprising the 165 amino acid erythropoietin insert. Of the three expression constructs tested, only construct gCEPO2 bound to and was internalized into erythropoietin receptor expressing cells (page 9693, left column, first paragraph). In view of the results obtained, the authors of document D8 refer to future studies with smaller erythropoietin binding peptides which "may be less perturbing than the full-length EPO" insert (page 9693, right column, 2nd full paragraph).

16. Thus, documents D2 and D8 show that it is possible to modify surface glycoproteins of HSV in order to alter

target specificity. However, with regard to the insertion of the 165 amino acids of the EPO sequence, the authors conclude that smaller sequences binding to the EPO receptor might be less perturbing and that future studies might be performed with shorter peptide sequences (very last paragraph of document D8).

17. In addition to the above mentioned technical information, document D2 (page 6) provides a list of potential ligands to be included in the HSV. This list encompasses a large protein, transferrin (line 12), of some 680 amino acids among many other potential ligands. The list is however only speculative (or suggestive) and not an enabling disclosure of the insertion of larger polypeptides. Importantly, there is also no mention of antibodies or antibody binding domains as potential ligands.

18. Documents D3, D15 and D16 disclose the successful integration of antibody binding domains and the skilled person trying to solve the above mentioned technical problem could have tried to do the same with HSV. However, since the skilled person is a person especially interested in the modification of HSV, it would also have taken documents D2 and D8 into consideration. Since these two documents, despite successful integration of one gC-EPO fusion protein into HSV (cf. Fig. 11 of document D8), point the skilled reader to further studies with amino acid sequences shorter than that of EPO, the skilled person trying to insert an antibody binding domain of about 250 amino acids into glycoprotein gC would not have had a reasonable expectation of success.

19. Given the absence of any pointers to the insertion of antibody binding domains into HSV glycoprotein gC in any of documents D1, D2 and D8, furthermore in view of pointers in document D8 towards the use of peptides shorter than EPO, the board concludes that the subject matter of all independent claims (cf. item IX above), involves an inventive step. The main request therefore meets 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 department of first instance with the order to maintain the patent as amended in the following version:

   Page 3 and pages 5 to 7 of the patent specification as granted. Pages 2 and 4 of the amended patent specification filed at the oral proceedings before the Board on 5 September 2013.

   Claims 1-39 of the Main Request filed at the oral proceedings before the Board on 5 September 2013.

   Figures 1 - 5 of the patent as granted.

The Registrar: The Chairman:

A. Wolinski M. Wieser