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**Datasheet for the decision
of 27 October 2009**

Case Number: T 0889/08 - 3.3.08

Application Number: 95115460.8

Publication Number: 0716148

IPC: C12N 15/86

Language of the proceedings: EN

Title of invention:
Recombinant alphavirus vectors

Patentee:
Novartis Vaccines and Diagnostics, Inc.

Opponent:
Bioption AB

Headword:
Alphavirus/NOVARTIS

Relevant legal provisions:
EPC Art. 56, 76(1), 84, 123(2)(3)

Relevant legal provisions (EPC 1973):
EPC Art. 54(3)

Keyword:
"Added matter (no)"
"Extension of the protection conferred (no)"
"Clarity (yes)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
G 0009/92

Catchword:
-



Case Number: T 0889/08 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 27 October 2009

Appellant: Novartis Vaccines and Diagnostics, Inc.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
22 February 2008 concerning maintenance of
European patent No. 0716148 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

- I. The patentee (appellant) lodged an appeal against the interlocutory decision of the opposition division dated 22 February 2008, whereby European patent No. 0 716 148, which had been granted on European application No. 95 115 460.8, was maintained in an amended form on the basis of the third auxiliary request (claims 1 to 25) filed during oral proceedings on 16 January 2008. The European application No. 95 115 460.8, claiming the priority dates of 15 September 1993 and 18 February 1994, was a divisional application filed on the earlier application No. 94 929 221.3 which had been published as the international application WO 95/07994. The main request (claims 1 to 24 as granted) and the second auxiliary request also filed on 16 January 2008 (claims 1 to 26) had been refused for lack of novelty over document D6 (see Section X *infra*) under Article 54(3) EPC. The first auxiliary request filed on 16 November 2007 had been refused for non-compliance with Article 123(2) EPC (presence of added matter).
- II. The patent had been opposed on the grounds as set forth in Article 100(a) EPC that the invention was neither new (Article 54 EPC) nor inventive (Article 56 EPC).
- III. The statement of grounds of appeal was filed on 2 July 2008. It was accompanied by a new main request (claims 1 to 28).
- IV. On 27 May 2009, in an annex to the summons to oral proceedings issued pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), the

board sent a communication containing its provisional opinion on a number of issues, including those of added matter and novelty. It also observed that, as the patentee was the sole appellant against the interlocutory decision under appeal, the board could not challenge the maintenance of the patent on the basis of claims 1 to 25 of the auxiliary request filed on 16 January 2008 (prohibition of *reformatio in peius*; see decision G 9/92 (OJ EPO, 1994, 875), point 1 of the Order).

- V. On 25 September 2009, in reply to that communication, the appellant made further submissions and filed a new main request and three auxiliary requests.
- VI. On 14 September 2009, the opponent (respondent) which had not yet made any submissions informed the board that it did not intend to attend the scheduled oral proceedings nor to file any further written submission.
- VII. On 15 October 2009, the board issued a second communication pursuant to Article 15(1) RPBA in which comments were made on the issue of inventive step.
- VIII. During the oral proceedings which took place on 27 October 2009 in the absence of the respondent, the appellant filed a new main request and withdrew all other pending requests.
- IX. The main request consisted of 14 claims of which claims 1 to 5 read as follows (emphasis added by the board):

"1. A DNA vector comprising:
(i) a 5' eukaryotic promoter;
(ii) a DNA sequence which upon transcription in a eukaryotic cell from said promoter provides an alphavirus RNA vector construct, and
(iii) a transcription termination site for termination of said transcription, wherein said alphavirus RNA vector construct is (a) capable of encoding non-structural proteins that enable said alphavirus RNA vector construct to self-replicate and (b) capable of expressing **one or more heterologous nucleotide sequences**,
wherein said alphavirus is Sindbis virus."

"2. A DNA vector comprising:
(i) a 5' eukaryotic promoter;
(ii) a DNA sequence which upon transcription in a eukaryotic cell from said promoter provides an alphavirus RNA vector construct, and
(iii) a transcription termination site for termination of said transcription, wherein said alphavirus RNA vector construct is (a) capable of encoding non-structural proteins that enable said alphavirus RNA vector construct to self-replicate and (b) capable of expressing **two or more heterologous nucleotide sequences**."

"3. A DNA vector comprising:
(i) a 5' eukaryotic promoter;
(ii) a DNA sequence which upon transcription in a eukaryotic cell from said promoter provides an alphavirus RNA vector construct, and
(iii) a transcription termination site for termination of said transcription, wherein said alphavirus RNA

vector construct is (a) capable of encoding non-structural proteins that enable said alphavirus RNA vector construct to self-replicate and (b) capable of expressing **a heterologous nucleotide sequence**, wherein the heterologous nucleotide sequence is from a virus selected from the group consisting of Human Papiloma Virus (HPV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Epstein-Barr Virus (EBV), Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Feline leukemia virus (FeLV), Feline immunodeficiency virus (FIV), Hantavirus, Human T-lymphotropic Virus (HTLV I), Human T-lymphotropic Virus (HTLV-II), and Cytomegalovirus (CMV)."

"4. A DNA vector comprising:

(i) a 5' eukaryotic promoter;
(ii) a DNA sequence which upon transcription in a eukaryotic cell from said promoter provides an alphavirus RNA vector construct, and
(iii) a transcription termination site for termination of said transcription, wherein said alphavirus RNA vector construct is (a) capable of encoding non-structural proteins that enable said alphavirus RNA vector construct to self-replicate and (b) capable of expressing **a heterologous nucleotide sequence**, wherein the heterologous nucleotide sequence encodes a protein selected from the group consisting of IL-1, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, α -IFN, β -IFN, γ -IFN, G-CSF, GM-CSF, tumor necrosis factor, CSF-1, ICAM-1, ICAM-2, LFA-1, LFA-3, an MHC class I molecule, an MHC class II molecule, β 2-microglobulin, a chaperone, CD3, B7/BB1, and an MHC linked transporter protein."

"5. A DNA vector comprising:
(i) a 5' eukaryotic promoter;
(ii) a DNA sequence which upon transcription in a eukaryotic cell from said promoter provides an alphavirus RNA vector construct, and
(iii) a transcription termination site for termination of said transcription, wherein said alphavirus RNA vector construct is (a) capable of encoding non-structural proteins that enable said alphavirus RNA vector construct to self-replicate and (b) capable of expressing **one or more heterologous nucleotide sequences**,
wherein said promoter is an inducible promoter."

Claims 6 and 7 were dependent on claims 2 to 5 and directed to particular embodiments thereof. Claim 8 was dependent on claims 1 to 7 and directed to particular embodiments thereof. Claim 9 was dependent on claim 8 and directed to a particular embodiment thereof.

Claim 10 was directed to *ex vivo* cells containing a DNA vector according to any one of claims 1 to 9.

Claim 11 was directed to a DNA vector according to any one of claims 1 to 9 for use in a method of therapeutic treatment.

Claim 12 was directed to a pharmaceutical composition containing a DNA vector according to any one of claims 1 to 9.

Claim 13 was directed to the use of a DNA vector according to any one of claims 1 to 9 for the preparation of a viral RNA vector construct.

Claim 14 was directed to a method of preparing a DNA vector according to any one of claims 1 to 9.

X. The following documents are referred to in the present decision:

(D2) WO 92/10578 (published on 25 June 1992)

(D3) WO 89/08145 (published on 8 September 1989)

(D6) WO 95/27044 (claiming a priority date of 31 March 1994 and published on 12 October 1995)

XI. The submissions made by the appellant, insofar as they are relevant to the present decision, may be summarised as follows:

The amendments contained in the main request found support in the application as filed. Of particular relevance in this respect was the Chapter of the description entitled "*Heterologous sequences*" (see page 12 of the application as published) which described alphavirus-derived DNA vectors containing one, two or more heterologous sequences.

The main request was new. Document D6, the only document cited during the opposition proceedings by the opponent in support of its objection of lack of novelty did not disclose any DNA vectors according to any one of claims 1 to 5.

Document D2 which represented the closest prior art described alphavirus-derived DNA expression vectors

comprising a 5' prokaryotic promoter and capable of expressing a heterologous sequence, the use of which implied the need of an *in vitro* transcription. The technical problem to be solved was regarded as the provision of an alternative system for expression of one or more heterologous sequences in eukaryotic cells. The solution thereto was a DNA vector according to any one of claims 1 to 5 of the main request which was capable of initiating the life cycle of a self-replicating alphavirus-derived RNA expression vector in a eukaryotic cell. That solution was neither taught nor suggested in the prior art. It would not have been obvious to the skilled person to substitute a 5' prokaryotic promoter for a 5' eukaryotic promoter in an alphavirus DNA vector construct.

XII. The respondent made no submissions at all during the appeal proceedings.

XIII. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed during the oral proceedings.

Reasons for the Decision

Compliance with Article 123(2) and (3) EPC

1. The main request being an amended version of the claims as granted, the board has the duty to assess whether it contains subject-matter which extends beyond the content of the application as filed.

2. Although not explicitly expressed in the application as filed, it is derivable from the disclosure that the expression "a 5' *eukaryotic promoter*", used in each of independent claims 1 to 5 to designate one of the components of the claimed DNA vectors, means a 5' promoter which, whatever its origin, is capable of driving transcription in eukaryotic cells. Such a promoter finds support on page 38, line 21 to 33.
3. A DNA vector according to claim 1, which comprises a DNA sequence providing an alphavirus RNA vector construct capable of expressing **one or more** heterologous nucleotide sequences and wherein said alphavirus is the Sindbis virus, is described on page 8, lines 14 to 25.
4. A DNA vector according to claim 2, which comprises a DNA sequence providing an alphavirus RNA vector construct capable of expressing **two or more** heterologous nucleotide sequences, is described on page 8, lines 14 to 23 taken together with page 23, lines 5 to 12.
5. A DNA vector according to claim 3, which comprises a DNA sequence providing an alphavirus RNA vector construct capable of expressing **a** heterologous nucleotide sequence and wherein **the heterologous nucleotide sequence is from a virus which is selected from a definite list of viruses**, is described on page 8, lines 14 to 23 read in the light of page 4, line 24 to 27.

6. A DNA vector according to claim 4, which comprises a DNA sequence providing an alphavirus RNA vector construct capable of expressing **a** heterologous nucleotide sequence and wherein **the heterologous nucleotide sequence encodes a protein selected from a definite list of lymphokines** including a number of immunomodulatory co-factors, is described on page 8, lines 14 to 23 taken together with the passage from line 15 on page 23 to line 12 on page 24.
7. A DNA vector according to claim 5, which comprises a DNA sequence providing an alphavirus RNA vector construct capable of expressing **one or more** heterologous nucleotide sequences and wherein the 5' eukaryotic promoter is an **inducible** promoter is described on page 8, lines 14 to 23 taken together with page 38, lines 30 to 33.
8. A DNA vector according to claim 6, i.e. a DNA according to any of claims 2 to 5 wherein the alphavirus is selected from the **Ross River virus** and the **Venezuelan equine encephalitis virus**, is described in the passages of the application as filed referred to at points 4 to 7 *supra* taken together with page 9, lines 10 to 12.
9. A DNA vector according to claim 7, i.e. a DNA according to any of claims 2 to 5 wherein the alphavirus is the **Sindbis virus**, is described in the passages of the application as filed referred to at points 4 to 7 *supra* taken together with page 8, lines 23 to 25.

10. A DNA vector according to claim 8, i.e. a DNA according to any of claims 1 to 7 wherein the transcription termination site is a **transcription termination sequence**, is described in the passages of the application as filed referred to at points 3 to 9 *supra* taken together with page 38, lines 21 to 29.
11. A DNA vector according to claim 9, i.e. a DNA according to claim 8 wherein the transcription termination site is a **termination/polyadenylation sequence** is described in the passages of the application as filed referred to at points 3 to 10 *supra* taken together with page 8, lines 28 to 29.
12. *Ex vivo* cells according to claim 10, which contain a DNA vector according to any one of claims 1 to 9 as described in the passages of the application as filed referred to at points 3 to 11 *supra* find support on page 9, lines 6 to 9 taken together with page 41, lines 22 to 33.
13. A DNA vector according to any of claims 1 to 9, as described in the passages of the application as filed referred to at points 3 to 11 *supra*, for use in a method of therapeutic treatment (see claim 11) finds support in the passage from line 27 on page 7 to line 13 on page 8.
14. A pharmaceutical composition containing a DNA vector according to any one of claims 1 to 9, as described in the passages of the application as filed referred to at points 3 to 11 *supra*, in association with a pharmaceutically acceptable carrier or diluent (see claim 12), finds support on page 42, lines 28 to 31

taken together with the Section entitled "*Pharmaceutical compositions*" on pages 54 to 57.

15. The use of a DNA vector according to any one of claims 1 to 9, as described in the passages of the application as filed referred to at points 3 to 11 *supra*, for the preparation of a viral RNA vector construct by transcription (see claim 13) finds support on page 39, lines 19 to 30.

16. A method of preparing a DNA vector according to any one of claims 1 to 9, as described in the passages of the application as filed referred to at points 3 to 11 *supra*, which comprises the step of inserting a cDNA corresponding to said viral RNA vector construct into an expression cassette (see claim 14) finds support on page 10, lines 24 to 28.

17. In view of the above remarks, it is concluded that the main request complies with Article 123(2) EPC. Furthermore, the board notes that none of the amendments results in an extension of the protection conferred by the claims as granted (compliance with Article 123(3) EPC) in view of their restrictive character.

Compliance with Article 76(1) EPC

18. As the patent in issue has been granted on a divisional application the board has the further duty to examine whether the main request complies with Article 76(1) EPC.

19. Corresponding appropriate support is found for each and every claim in the description of the earlier application as filed, the content of which is the same as that of the divisional application as filed. Thus, the main request complies with Article 76(1) EPC.

Compliance with Article 84 EPC

20. Having reviewed the amendments contained in the main request compared to the claims as granted, the board is satisfied that the main request complies with Article 84 EPC.

Compliance with Article 54 EPC

21. Document D6 is the only document on which the respondent based its objection of lack of novelty in the opposition proceedings. Thus, for the examination of novelty by the board, it is the only document to be taken into account.
22. Document D6 (WO 95/27044) is a Euro-PCT application, filed on 30 March 1995 and published on 12 October 1995, from which was derived the European application No. 95 914 666.3 with the publication number EP 0 753 053. It claims the priority date of 31 March 1994.
23. The subject-matter of the two priority documents of the patent-in-suit is limited to DNA vectors comprising a DNA sequence which provides a Sindbis virus RNA vector construct.

24. Thus, claim 1, which refers to the Sindbis virus as the only possible alphavirus, is entitled to the earlier priority date (15 September 1993) which is earlier than the priority date of document D6 (31 March 1994). Therefore, document D6 does not form part of the relevant state of the art with regard to claim 1.
25. In contrast thereto, claims 2 to 4, which refer to any alphaviruses, are not entitled to any one of the two priority dates but to the filing date of the European application (15 September 1994). Therefore, document D6 is to be taken into account in the examination of novelty under Article 54(3) EPC 1973 of claims 2 to 5.
26. As document D6 does not disclose DNA vectors wherein the alphavirus RNA vector is capable of expressing two or more heterologous nucleotide sequences, claim 2 is new over document D6.
27. As document D6 does not disclose DNA vectors wherein the RNA vector construct is capable of expressing a heterologous nucleotide sequence which is from a virus selected from the group referred to in claim 3 or which encodes a protein selected from the group referred to in claim 4, claims 3 and 4 are also novel over document D6.
28. As document D6 does not disclose DNA vectors wherein the 5' eukaryotic promoter is inducible, novelty of claim 5 is not affected by document D6.
29. As document D6 is the only document relied upon in support of a novelty objection, it is concluded that claims 1 to 5 are new. Since the subject-matter of

claims 6 to 14 refers back to claims 1 to 5, the main request as a whole complies with the requirements of Article 54 EPC.

Compliance with Article 56 EPC

30. As admitted by the appellant, document D2 is considered to represent the closest state of the art. It discloses DNA expression systems based on alphaviruses wherein a DNA expression vector is used which comprises a cDNA complementary to an alphavirus RNA located immediately downstream of the "prokaryotic" (in the sense that it is capable of driving transcription in a prokaryotic cell) SP6 RNA polymerase promoter (see the paragraph bridging pages 10 and 11). The vector further comprises an exogenous DNA fragment encoding a foreign peptide sequence (see claim 15). In these systems, the vector is used to produce recombinant RNA upon *in vitro* transcription driven by the prokaryotic SP6 promoter, this RNA transcript is then transfected into animal host cells and the transformed cells are cultured to express the RNA transcript, resulting in the production of the heterologous protein (see claim 32).
31. The technical problem to be solved in view of document D2 may be seen in the provision of an alternative alphavirus-derived expression system for the direct expression of a heterogeneous protein in eukaryotic cells. The solution thereto is an expression system wherein a DNA vector according to any one of claims 1 to 5 is used, i.e. an alphavirus-based DNA vector comprising a 5' eukaryotic promoter. In this system, the DNA is directly transfected into the eukaryotic host cell where the recombinant construct is

in vivo transcribed by the host RNA polymerase without the need for a first step of *in vitro* transcription.

32. The question to be answered is whether the skilled person would have found any incitation in the state of the art to replace in a DNA expression vector of document D2 the prokaryotic SP6 vector by a eukaryotic promoter.

33. In the decision of the opposition division in relation to inventive step no other prior art document than D2 has been referred to which could have been used in combination therewith. Having reviewed the documents on file (including document D3 which was cited by the respondent in written proceedings before the opposition division in combination with document D2), the board is indeed satisfied that the idea of using a DNA vector which, when transcribed within an eukaryotic host cell, produces a viral RNA expression vector which directs its own replication and also expresses a gene of interest, was not taught or suggested in the state of the art. Thus, the board is of the view that it would not have been obvious for the skilled person to substitute a 5' prokaryotic promoter for a 5' eukaryotic promoter in an alphavirus DNA vector construct of document D2.

34. The board concludes that claims 1 to 5 involve an inventive step. Since the subject-matter of claims 6 to 14 refers back to claims 1 to 5, the main request as a whole complies with the requirements of Article 56 EPC.

Concluding remarks

35. Although the main request provides a narrower scope of protection than that conferred by the auxiliary request of 16 January 2006 on the basis of which the opposition scope has maintained the patent, the appellant has indicated its approval of this only request. Thus, maintenance of the patent on the basis of the appellant's main request does not amount to a *reformatio in peius*.

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 with the order to maintain the patent on the basis of claims 1 to 14 of the main request filed during the oral proceedings and a description and figures to be adapted thereto.

The Registrar

The Chairman

A. Wolinski

L. Galligani