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Datasheet for the decision of 12 December 2012

Case Number: T 0947/09 - 3.3.08

Application Number: 98960976.3

Publication Number: 1038001

IPC: C12N 15/49, C12N 7/04, A61K 39/21

Language of the proceedings: EN

Title of invention:
Constitutive expression of non-infectious HIV-like particles

Patentee:
Sanofi Pasteur Limited

Opponent:
Bavarian Nordic A/S

Headword:
HIV-like particles/SANOFI PASTEUR

Relevant legal provisions:
EPC Art. 83, 54, 56

Keyword:
"Granted claims fulfil the requirements of the EPC - appeal dismissed"

Decisions cited:
T 0343/00, T 0753/00, G 0001/03

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0947/09 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 12 December 2012

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted on 26 February 2009 rejecting the opposition filed against European patent No. 1038001 pursuant to Article 101(2) EPC.

Composition of the Board:

Chairman: M. Wieser
Members: P. Julià
R. Moufang

Summary of Facts and Submissions

I. European patent no. 1 038 001 is based on European patent application no. 98 960 976.3 which was filed as International patent application PCT/CA1998/01164 and published as WO 99/31250. The patent claims the priority date of 16 December 1997 (US 991773) and was granted with 18 claims for the Contracting States AT, BE, CH, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE, FI and with 19 claims for the Contracting State CY. Claims 1 and 13 for all designated Contracting States except CY read as follows:

"1. A nucleic acid molecule, comprising a modified HIV genome devoid of long terminal repeats and wherein *vpr* and *tat* sequences are functionally disabled and a constitutive promoter operatively connected to said modified HIV genome for constitutive expression of said modified genome to produce non-infectious, non-replicating and immunogenic HIV-like particles, wherein said HIV genome is further modified to effect reduction in *gag*-dependent RNA packaging of the *gag* gene product."

"13. A method of obtaining a non-infectious, non-replicating, immunogenic HIV-like particle, comprising:

introducing an expression vector of claim 11 or claim 12 into mammalian cells, and
constitutively expressing the nucleic acid molecule in said expression vector in said cells to stably produce non-infectious, non-replicating, immunogenic HIV-like particles."

Claims 2 to 10 were preferred embodiments of claim 1. Claim 11 was directed to an expression vector comprising a nucleic acid molecule of any of claims 1 to 10. Claims 12 and 14 were embodiments of claims 11 and 13, respectively. Claim 15 was directed to a non-infectious, non-replicating, immunogenic HIV-like particle lacking Tat and Vpr and produced by the method of claims 13 or 14. Claim 16 was directed to an immunogenic composition comprising the HIV-like particle of claim 15 and a physiologically acceptable carrier. Claims 17 and 18 were directed to the HIV-like particle of claim 15 for use as a medicament (claim 17) or for use in the manufacture of a medicament for the treatment of retroviral disease, preferably by immunization (claim 18).

The claims for the Contracting State CY were essentially identical to those for the other Contracting States except for claim 1, which for CY did not contain the feature "*wherein said HIV genome is further modified to effect reduction in gag-dependent RNA packaging of the gag gene product*". This feature was the subject-matter of dependent claim 5, and the rest of the claims for CY were renumbered accordingly.

II. An opposition was filed on the grounds as set forth in Articles 100(a) (lack of novelty and of inventive step, Articles 54(3) and 56 EPC) and 100(b) EPC (insufficiency of disclosure, Article 83 EPC). The opposition division considered the patent to fulfil the requirements of the EPC and, accordingly, rejected the opposition.

III. A notice of appeal and a statement setting out the grounds of appeal were filed by the opponent (appellant).

IV. The patentee (respondent) did not reply to the appellant's grounds of appeal nor did it submit any request.

V. On 25 June 2012, the board summoned the parties to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed thereto, they were informed of the board's preliminary, non-binding opinion on the substantive issues of the case.

VI. In its letter of 16 October 2012, the respondent informed the board of its intention not to attend the oral proceedings. No submissions were made concerning the substantive issues and no request was formulated.

VII. In a letter dated 30 October 2012, the appellant replied to the communication of the board.

VIII. Oral proceedings took place on 12 December 2012 in the absence of the respondent.

IX. The documents cited in the present decision are:

D1: EP 0 904 392 B1 (priority dates: 17 October 1996 and 25 November 1996);

D2: US 5 439 809 A (publication date: 8 August 1995);

D4: W.A. Haseltine, FASEB J., 1991, Vol. 5, pages 2349 to 2360;

D6: M.E. Rogel et al., J. Virol., 1995, Vol. 69(2), pages 882 to 888;

D7: WO 96/11696 A1 (publication date: 25 April 1996);

D8: G.L. Stivahtis et al., J. Virol., June 1997, Vol. 71(6), pages 4331 to 4338;

D11: J.R. Haynes et al., AIDS Res. and Human Retroviruses, 1991, Vol. 7(1), pages 17 to 27.

X. Appellant's arguments, as far as relevant to the present decision, may be summarized as follows:

Article 100(b) EPC; Article 83 EPC

The invention defined in claim 1 could not be performed over the whole range claimed. The patent described only one way to stably produce the claimed nucleic acid, namely by use of the system described in Example 3. In this system, the nucleic acid contained mutations at specific sites and was linked to a specific promoter. The stable production of HIV-like particles was dependent on various parameters, in particular the cells used for passaging. Vero cells were used in Example 3 and evidence was on file showing that only these cells could be successfully used in the method of claim 13. However, claim 13 was not limited to Vero cells but contemplated all mammalian cells. The patent did not contain sufficient guidance for the selection

of those parameters which were important to provide a stable expression in any kind of mammalian cells.

Article 100(a) EPC; Article 54(3) EPC

According to the established case law (T 343/00 of 22 October 2002 and T 753/00 of 2 June 2003), examination of novelty over the prior art had to be based on the broadest interpretation of the claim. A broad interpretation of the expression "*devoid of long terminal repeats*" in claim 1 allowed that only parts of the long terminal repeats (LTR) were deleted. Claim 1 did not unambiguously require that "*any LTR*" was missing and thus, the HIV genome could also include, for instance, parts of the 5' and/or 3' LTRs. The more so because, by using the word "*comprising*", the presence of further elements in the nucleic acid molecule of claim 1 was not excluded.

Document D1 disclosed a HIV-genome based vector without the *vpr* and *tat* genes which was designed to prevent *gag* expression and thus produced non-replicating, non-infectious, immunogenic HIV-like particles. The HIV-genome based vector pH4Z shown in Figure 2 had a CMV promoter for constitutive expression replacing the 5' LTR, i.e. it was devoid of the 5'LTR. Thus, all the features characterizing the subject-matter of claim 1 were disclosed in document D1.

Article 100(a) EPC; Article 56 EPC

Documents D2 and D11 were both highly relevant; the latter could be taken as closest prior art since it disclosed the development of stable cell lines for

producing non-infectious, non-replicating, immunogenic HIV-like particles. Expression plasmids with a constitutive promoter were shown in Figures 1A and 1B. These constructs had the most relevant technical features in common with the subject-matter of claim 1, in particular the absence of any LTR in the HIV genome. Document D11 explicitly suggested further modifications in other regions of the HIV genome, such as in the RNA packaging signal and in those encoding *tat*, *vif*, integrase, etc. The disclosure of document D2 was similar and, according to this document, the deletion of both *vif* and integrase (*gag*, *pol*) genes did not affect the formation of HIV-like particles in inducible and in long-term expression. Thus, these two documents disclosed all elements characterizing the subject-matter of claim 1 except for the deletion or disablement of the *vpr* gene. Document D11 explicitly referred to the possible toxicity of a constitutive production of HIV-like particles and, in order to overcome this toxicity, to the replacement of the constitutive promoters by inducible promoters (Figure 1C).

Starting from document D11 and/or D2, the problem to be solved was the provision of alternative means and methods for overcoming the toxicity problem and stably produce non-infectious, non-replicating, immunogenic HIV-like particles. According to the patent, this was solved by the inactivation or disablement of the *vpr* gene.

The technical problem, however, was not solved over the whole breadth of the claims. Claim 1 was directed to a nucleic acid molecule comprising a modified HIV genome

functionally linked to any kind of constitutive promoter. The constitutive expression of the modified HIV genome was not limited to a certain type of host cell in the method of claim 13. Thus, claim 1 encompassed many different constructs with all kinds of constitutive promoters and all of them had to provide a stable expression of HIV-like particles in any possible mammalian cell type. The patent-in-suit was exemplified by a sole construct having a specific constitutive promoter (CMV) and enhancer elements in combination with *vpr* inactivation. This construct resulted in the expression of HIV-like particles over several passages in a very specific cell type (Vero) (Figures 2 and 3, Examples 2 and 3 of the patent-in-suit). There were prior art documents on file, such as documents D6 and D7, showing the importance of the host cell type used for a stable HIV production when the *vpr* gene was inactivated. According to this prior art, in particular document D8, the effect of disabling the *vpr* gene was cell-type specific, since *vpr* was only active in inhibiting cell proliferation of Vero cells but was inactive in human cells. Thus, it was not credible that any mammalian cell was suitable for a stable production of the nucleic acid molecule of claim 1.

According to the established case law, it was the normal task of the skilled person to be constantly occupied with furthering the state of the art. The use of inducible promoters for commercial production of recombinant products was known to be disadvantageous since it required to introduce an inducer(s) (expensive, toxic, difficult to eliminate, etc). Indeed, the inducible promoter used in the examples of documents D2 and D11 was commercially impractical in view of the

costs of the heavy metals employed and the toxic effect of such metals on the expression host cells. Thus, the skilled person had a strong incentive to avoid inducible promoters and to look for other alternative modifications of the HIV constructs while maintaining the constitutive promoter.

Whereas in 1991 and 1992, at the publication date of documents D2 and D11, the function of the *vpr* gene was not clearly known, the situation was different at the priority date claimed by the patent-in-suit (December 1997). The results reported in documents D6 (1995), D7 (1996) and D8 (June 1997), showing the effect of the expression of the *vpr* gene on cell proliferation, clearly established the function of this gene. In particular, document D6 showed that cell cultures infected with HIV stopped growing due to the presence of a functional *vpr* gene and the action of the *vpr* product, whereas HIV constructs with a disabled *vpr* gene led, after recovering from an initial cell-death phase, to continuous growing of the host cells and thus, to stable long-term cultures. The *vpr* gene and product alone were sufficient for obtaining this effect.

In the light of these disclosures, the disablement of the *vpr* gene was an obvious modification for a skilled person. The main function of the *vpr* gene in HIV strains, namely the ability to arrest host cell proliferation was known and thus, no hindsight was required to combine the teachings of documents D2 or D11 with the teaching of documents D6 or D8 and to arrive at the claimed subject-matter in an obvious manner. Moreover, in view of the results reported in these documents, showing the successful establishment

of long-term cell line cultures producing HIV-like particles, a reasonable expectation of success was also given. In the present case, which concerns a complex system, the "try-and-see approach" defined in the case law had to be applied, i.e. the skilled person had only to try to disable the *vpr* gene and to see whether the toxicity referred to in document D2 was overcome.

As for the additional disablement of the *tat* gene, the patent-in-suit did not report any advantage associated therewith. Both documents D2 and D11 referred to the presence of further modifications as additional safety measures including among others the modification of the *tat* gene. Thus, this feature did not provide an inventive contribution.

XI. As stated in Sections IV and VI *supra*, the respondent did not file any submissions on the substantive issues of the case.

XII. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

XIII. The respondent (patentee) did not file any request in appeal proceedings.

Reasons for the Decision

Article 100(b) EPC; Article 83 EPC

1. In the "*Notice of opposition*", the opponent/appellant raised an objection under Article 100(b) EPC concerning

the plasmid shown in Figure 2B and described in Example 2 of the patent-in-suit. A further objection concerned the subject-matter of claim 6 (cf. page 8, point 3 of the "*Notice of opposition*"). Both objections were addressed by the opposition division in its communication annexed to the summons to oral proceedings (cf. page 3, point 8 of the "*Summons to attend oral proceedings pursuant to Rule 115(1) EPC*"). In its reply to this communication, the opponent/appellant referred only to Article 100(a) EPC/Article 56 EPC and no comments were made on Article 100(b) EPC. According to the "*Minutes of the oral proceedings before the opposition division*" (hereinafter the "*Minutes*"), the parties had no comments under Article 100(b) EPC in addition to those filed in writing (cf. page 6, point 7 of the "*Minutes*"). As regards Article 100(b) EPC, the opposition division in the decision under appeal gave only reasons for the opponent/appellant's objections raised in the "*Notice of opposition*". The decision of the opposition division on these objections was not contested in the appellant's grounds of appeal and thus, it is not part of the present appeal proceedings.

2. In the statement of grounds of appeal, the appellant raised a new objection under Article 100(b) EPC based on an alleged lack of guidance of the patent-in-suit for performing the invention over the whole range claimed (cf. page 18, point VII of the grounds of appeal; Section X *supra*). Although this objection is new under Article 100(b) EPC, it is related to an objection originally raised under Article 100(a) EPC/Article 56 EPC, namely that it was not plausible that the technical problem had been solved over the

entire breadth of the claims (cf. paragraphs 15 to 18 *infra*). No reasons were given for justifying the introduction of this objection in appeal proceedings under Article 100(b) EPC and/or for explaining why it could not have been submitted in an earlier stage of the proceedings.

3. In its communication pursuant to Article 15(1) RPBA, the board - with reference to the function of an appeal proceedings as established in the case law (cf. "Case Law of the Boards of Appeal of the EPO", 6th edition 2010, VII.E.1, page 821) - questioned whether the appellant's objection was admissible under Article 100(b) EPC and referred to the discretion conferred on the board by Article 12(4) RPBA. In reply to this communication, the appellant maintained the new objection under Article 100(b) EPC and referred to the case law in support of its admissibility. At the oral proceedings before the board, the appellant referred to its written submissions and made no further submissions on this issue.

4. The subject-matter of claim 1 is directed to a product, i.e. a **nucleic acid molecule**, defined by several structural elements which are either present or absent (cf. Section I *supra*). The claim does not mention a technical effect or functional feature of said **nucleic acid molecule**. The board fails to see any technical problem or difficulty for a skilled person to achieve the defined nucleic acid molecule and there is no evidence on file to the contrary. According to decision G 1/03 (OJ EPO, 2004, page 413), "*... if the effect is not expressed in a claim but is part of the problem to be solved, there is a problem of inventive step ...*"

(cf. G 1/03, *supra*, point 2.5.2 of the Reasons). Thus, as regards the subject-matter of claim 1, appellant's objection is relevant only under the requirements of Article 100(a) EPC/Article 56 EPC.

5. The subject-matter of claim 13 is directed to a method of obtaining non-infectious, non-replicating, immunogenic HIV-like particles. It is required that the constitutive expression of the nucleic acid molecule of any of claims 1 to 10 (comprised in an expression vector of claims 11 or 12) in mammalian cells results in a stable production of these non-infectious, non-replicating, immunogenic HIV-like particles (cf. Section I *supra*). Thus, in line with decision G 1/03 (*supra*) which states that "*... (i)f an effect is expressed in a claim, there is lack of sufficiency of disclosure ...*" (cf. G 1/03, *supra*, point 2.5.2 of the Reasons), the appellant's objection as regards the subject-matter of claim 13 could be relevant under the requirements of Article 100(b) EPC. However, in view of the late filing of this objection (cf. point 2 *supra*) and of the prosecution history of the present case and, more importantly, of this particular objection during the first instance proceedings, the board, exercising its discretion under Article 12(4) RPBA, refrains to deal with this objection here and finds it more appropriate to consider it under the requirements of Article 100(a) EPC/Article 56 EPC (cf. points 15 to 18 *infra*).

Article 100(a) EPC; Article 54(3) EPC

6. Document D1 is the sole document cited in the decision under appeal with regard to the novelty of the claimed

subject-matter. According to the opposition division, whereas the nucleic acid molecule of claim 1 comprises a modified HIV genome "*devoid of long terminal repeat**s***", all the nucleic acid molecules disclosed in document D1 have a 3' LTR (cf. page 2, point 8 of the decision under appeal). Appellant's objection is based on an alleged ambiguity of the above sentence which, in combination with the word "*comprise*" present in claim 1, would allow, in the appellant's view, for a broad interpretation of this claim so as to embrace nucleic acid molecules with a modified HIV genome having a 3' LTR as disclosed in document D1 (cf. Section X *supra*).

7. According to the case law, the board is required to give an "*expression its broadest technically sensible meaning, while taking into account the whole disclosure of the patent and ruling out interpretations which are illogical or do not make technical sense*" (cf. T 343/00, *supra*, point 5 of the Reasons). In view of the whole disclosure of the patent-in-suit, in particular, the references to a fragment that "*lacks LTR elements*" and to "*a modified HIV genome lacking LTRs*" in combination with Figures 1 and 2B in which 5' and 3' LTR are deleted, the board considers that the appellant's interpretation actually runs counter to this disclosure and does not make therefore technical sense. Moreover, it is noted that the patent-in-suit, when it refers to the background of the invention refers to document US 5,439,809 (document D2 in the present proceedings) as disclosing "*... a modified retroviral genome deficient in long terminal repeats ...* " (underlining by the board) (cf. paragraph [0013] of the patent-in-suit). The expression in claim 1, "*devoid of long terminal repeats*", is used in this US document in

the same sense as interpreted by the opposition division in the decision under appeal.

8. Thus, the board agrees with the opposition division that the presence of a 3' LTR in the nucleic acid molecules disclosed in document D1 differentiates them from the nucleic acid molecules of claim 1. In view of this conclusion, there is no need to further examine whether this is the sole technical difference between the molecules of document D1 and those of claim 1 or whether other features, such as those cited on page 2, point 5.2 of the "*Minutes*", may also have to be considered.

9. Therefore, the requirements of Article 54(3) EPC are fulfilled.

Article 100(a) EPC; Article 56 EPC

The closest prior art and the technical problem to be solved

10. Documents D2 or D11 are equally considered to represent the closest prior art (see also page 4, point 9.3 of the decision under appeal). Both documents originate from the same authors, provide similar teachings and are contemporaneous (D11 published on 1991; D2 filing date 1992). They describe the engineering of cultured cells to produce immunogenic, non-infectious, non-replicating HIV-like particles by using HIV expression vectors devoid of LTR elements (cf. *inter alia* column 3, lines 30 to 33 and 50 to 54; column 4, line 65 to column 5, line 4 of document D2). These vectors include a heterologous promoter (cf. *inter alia* column 3, line 64 to column 4, line 5 of document D2) that may be a constitutive promoter, such as the SV40

virus early promoter or the adenovirus major late promoter (Ad-MLP) in COS cells (cf. column 5, lines 41 to 44; column 7, lines 19 and 41 to 42; columns 9 and 10, Examples 1 and 2; Figures 3 and 5 of document D2; Figures 1A and 1B of document D11).

11. It is stated in document D11 that "*(t)he possibility that constitutive viruslike particle production in COS cells was toxic ...*". In order to overcome this toxicity and improve the efficiency of the virus-like particle production, the use of expression vectors with an inducible promoter is exemplified (cf. page 22, right-hand column, last paragraph to page 23, left-hand column; Figure 1C of document D11). Although cell toxicity is not mentioned in document D2, it is nevertheless explicitly acknowledged that the use of an inducible promoter (human metallothionein II, Hu-MT IIa) improves the levels of non-infectious HIV particle production in engineered Vero cells lines (cf. paragraph bridging columns 7 and 8, column 14, Example 9 and Figure 10 of document D2).

12. From this it follows that the problem of cell toxicity resulting from the production of HIV-like particles is already disclosed in these prior art documents and that they also provide a solution that allows to improve the production of these HIV-like particles, namely the use of inducible promoters. The teachings of documents D2 and D11 are also intended to be applied to the large-scale production of HIV-like particles for use as a candidate vaccine, which is certainly of commercial interest (cf. *inter alia*, column 5, lines 37 to 41; column 8, lines 18 to 21 and 64 to 66 of document D2). In this context, the appellant argues that, in view of

the known disadvantages of inducible promoters in the large-scale commercial production of recombinant products, in particular of the Hu-MT IIa promoter (toxicity of expensive heavy metals and problems for their elimination in the final product), a skilled person would have looked for alternative solutions, avoiding the use of inducible promoters (cf. Section X *supra*).

13. The board is not convinced that a skilled person, starting from documents D2 and D11, would have reverted to a (constitutive expression) system that is clearly identified in these documents as being less efficient than the (inducible expression) system disclosed in these documents. On the contrary, as also acknowledged in the decision under appeal (cf. page 6, lines 3 and 4 of the decision under appeal), the board considers that a skilled person would have looked for improved alternative inducible expression systems to overcome the deficiencies referred to by the appellant. Nevertheless, even if the board follows the appellant's approach and considers that a skilled person, starting from documents D2 and D11, would have reverted to a less efficient constitutive expression system, the board cannot arrive at the appellant's conclusion that the claimed subject-matter would have been obvious to the skilled person.

14. In that case, starting from documents D2 and D11, the problem to be solved can be seen in the provision of an alternative system not containing an inducible promoter, capable of producing engineered, stable cell lines with high yield production of HIV-like particles and which overcomes the known cell toxicity problems. As a

solution to this problem, the patent-in-suit proposes the nucleic acid molecule of claim 1 and the method of claim 13. In view of the disclosure of the patent-in-suit, in particular Example 3, the board is convinced that the technical problem is solved.

Is the technical problem solved over the whole breadth of the claims?

15. The appellant argues, mainly based on document D8, that the problem is not solved over the whole breadth claimed, because the method of claim 13 is not limited to African green monkey cells, in particular not to Vero or COS cells, allegedly the sole cells in which the disablement of the *vpr* gene overcomes cell growth arrest (cf. Section X *supra*).

16. Document D8 is concerned with the conservation and host specificity of the Vpr-mediated cell cycle arrest of infected cells in the G_2 phase of the cell cycle. Vpr proteins from a wide variety of both tissue culture-passaged and uncultured human (HIV-1 and HIV-2), sooty mangabey (SIV_{SM}), African green monkey (SIV_{AGM}) and Sykes' monkey (SIV_{SYK}) isolates were used in these studies. Whereas SIV_{AGM} and SIV_{SYK} Vpr proteins were capable of arresting African green monkey cells, they were completely inactive in human cells. However, HIV-1, HIV-2, and SIV_{SM} Vpr proteins functioned in both simian and human cell types, albeit the SIV_{SM} Vpr protein was less efficient in human cells than in simian cells. Regardless of the origin, all Vpr alleles tested caused efficient cell cycle arrest in African green monkey cells (cf. *inter alia*, Abstract and page 4336, left-hand column, lines 7 to 5 from the bottom of

document D8). Although a certain degree of host-cell specificity for the Vpr protein, to achieve its effect on the cell growth of infected cells, is shown in document D8, the Vpr protein of both HIV-1 and HIV-2 - referred to in claim 1 - functions in all cell types tested, both simian and human. There is nothing to suggest that they may not function in other related mammalian cells, albeit admittedly at a lower efficiency. Thus, in the board's view, the prior art makes the skilled person aware of this host-cell specificity and, more importantly, of means and methods required to optimize the desired effect.

17. African green monkey cell lines, namely fibroblast-like COS and kidney Vero cell lines, are also used in document D2 which states that "*(i)nducible and long-term expression was not limited to monkey Vero cells. Metal-responsive expression of substantial amounts of particles was also observed in a human colon adenocarcinoma cell line. These data indicate that a wide variety of cell lines are suitable for the large-scale production of non-infectious virus-like particles*" (cf. column 8, lines 15 to 21 of document D2). Accordingly, there is no limitation to any type of mammalian cell in the method of claim 5 of document D2. Indeed, there are statements in document D7 confirming the general effect of the Vpr protein on cell growth arrest. In particular, it is stated that "*... Vpr protein can effect G2 arrest not only in cells infected with or susceptible to infection with HIV, but in any cell in which it is produced, assay systems can be designed ... which permit rapid measurement of the effect of the Vpr protein on cell growth in general*" (cf. *inter alia* page 5, last paragraph of document D7).

18. In the light of this prior art and the actual evidence on file, the board does not agree with the appellant and considers that the technical problem identified above is solved over the whole breadth of the claims.

Is the solution suggested by the patent-in-suit obvious?; Is a reasonable expectation of success present?

19. In view of the prior art on file, the board is not convinced by the appellant's argument that a skilled person would combine the teachings of document D11 and/or D2 with documents D6 or D8 in an obvious way and thus arrive at the claimed subject-matter with a reasonable expectation of success (cf. Section X *supra*). Firstly, at the priority date claimed by the patent-in-suit, the effect of the *vpr* gene on cell growth was not so well established in the prior art as argued by the appellant and, secondly, it is not correct that the skilled person did not face alternatives to the disablement of the *vpr* gene.

20. Already in document D8, it is stated that the ability of the Vpr protein to arrest infected cells in the G_2 phase of the cell cycle is less clearly understood than its role for targeting the viral pre-integration complex to the nucleus of non-dividing cells (cf. page 4331, left-hand column, second paragraph of document D8). Document D6 is concerned with the effect of the HIV-1 *vpr* gene - alone or in combination with the HIV-1 *nef* gene, another HIV-1 auxiliary gene - on the proliferation of the cell lines SupT1 and MT4, both derived from human T-cells and highly sensitive to the cytotoxic effects of HIV-1 (cf. page 883, paragraph

bridging left and right-hand columns and page 884, first full paragraph of document D6). Although it is reported in this document that "*... the effect of the Vpr ... in contrast to a previous report (25), is independent of the presence of Nef*" (cf. page 882, right-hand column, lines 8 to 11 of document D6), document D6 concludes that "*(a) minor effect of Nef on cytopathic effect (25) also cannot be excluded from our data*" (cf. page 887, left-hand column, second full paragraph of document D6). These comments and the disclosed results show the complexity of HIV and the functional interdependency of its genes, in particular of the six HIV auxiliary genes, which include the *vpr* and the *nef* gene (see in this context the title of the literature reference (25) in document D6, namely "*Context-dependent role of human immunodeficiency virus type 1 auxiliary genes in the establishment of chronic virus producers*"). The board considers that, at the priority date claimed by the patent-in-suit, the skilled person was well aware that "*(t)he auxiliary genes play a crucial role in viral replication and pathogenesis*" as stated in document D1 (filed on 17 October 1997 and claiming priority dates of 17 October 1996 and 25 November 1996). However, "(t)*he auxiliary genes have not been fully characterized nor their function defined*" and thus, "*... the roles of the auxiliary genes are not clear ...*", including that of the HIV *vpr* gene (cf. page 2, paragraphs [0008] and [0010] of document D1).

21. As also mentioned in document D1, some of the HIV auxiliary genes, i.e. *vif*, *vpu*, *vpr*, *nef*, *rev* and *tat* genes, were thought to be involved in the pathogenesis of HIV and the presence of cell cytotoxic effects was

known for some of them (cf. page 2, paragraph [0009] of document D1). It is also stated in documents D2 and D11 that, apart from the deletion of the LTR elements, "... *a number of additional genetic modifications in regions of the HIV nucleotide sequences which are necessary for infectivity but dispensable for particle production and immunogenicity*" may be made, including "*... the vif ... and tat genes*", albeit admittedly for eliminating heterologous recombination and a possible regeneration of an infectious virus, i.e. for safety reasons, and not for overcoming a possible cell cytotoxic effect (cf. column 9, lines 6 to 13 of document D2; page 25, left-hand column, third full paragraph of document D11). Importantly, it is also stated in document D2 that "... *the deletion in both the Integrase and the **Vif** genes did not affect particle formation*" (emphasis added by the board) (cf. column 9, lines 27 to 29; column 17, Example 15 and claims 3 and 12 of document D12).

22. In view of all these disclosures in the prior art and especially the references in documents D2 and D11 to other HIV auxiliary genes, the board is not convinced that the selection of the *vpr* gene for genetic modification and disablement would have been a straightforward and obvious strategy for the skilled person. The less so, since at least two other parameters - in addition to cell death toxicity - were of relevance, namely the ability to produce HIV-like particles, as explicitly mentioned in document D2, and the rate of recovery and cell growth after an initial cell death in the culture (see, for instance, Figures 1A-B of document D6).

23. In this context, it is of importance to take into account that the modified HIV genome comprised in the nucleic acid molecule of claim 1 is not limited to an HIV genome devoid of LTR elements and containing a *vpr* sequence functionally disabled, but that it contemplates further modifications, namely a modification to effect reduction in the *gag*-dependent RNA packaging of the *gag* gene product and a modification to functionally disable the *tat* sequence (cf. Section I *supra*). Although some of these modifications are mentioned in documents D2 and D11, the board fails to see any hint in these documents or in any other prior art on file to combine all these specific modifications and to arrive thereby at the claimed subject-matter. Additionally, in view of the complexity of the HIV and the interrelatedness of all its genes, there can be no expectation of success for a large-scale production of non-infectious, non-recombinant, immunogenic HIV-like particles according to claim 13. Moreover, the board is convinced that, in the absence of any hint in the prior art towards the specific combination claimed, the "try-and-see approach" as defined in the case law of the Boards of Appeal and referred to by the appellant (cf. Section X *supra*), is not applicable in the present case.

Conclusion on Article 100(a) EPC; Article 56 EPC

24. The board considers the subject-matter of the granted claims to fulfil the requirements of Article 56 EPC.

Claims for the Contracting State CY

25. Although the subject-matter of claim 1 granted for the Contracting State CY is broader than that of claim 1 for the other Contracting States, the modified HIV genome of the claimed nucleic acid molecule is defined as being devoid of LTR elements and as containing the specific combination of functionally disabled *vpr* and *tat* sequences with a constitutive promoter operatively connected thereto (cf. Section I *supra*). Thus, the reasons given above for the novelty and inventive step of the subject-matter of the claims granted for the other Contracting States apply also to the subject-matter of the claims granted for the Contracting State CY.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski M. Wieser