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Datasheet for the decision of 23 May 2007

Case Number: T 0516/06 - 3.3.08

Application Number: 98907702.9

Publication Number: 1007715

IPC: C12N 15/86

Language of the proceedings: EN

Title of invention:
Adenovirus vectors containing heterologous transcription regulatory elements and methods of using same

Applicant:
CELL GENESYS, INC.

Opponent:
-

Headword:
Adenovirus/CELL GENESYS

Relevant legal provisions:
EPC Art. 56
RPBA Art. 10a and 10b

Keyword:
"Fourth main request - inventive step - no"
"Fifth main request - admissibility - no"

Decisions cited:
G 0010/93, T 0016/87, T 0794/94, T 0397/01

Catchword:
-

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Case Number: T 0516/06 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 23 May 2007

Appellant: (Applicant)
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 12 October 2005 refusing European application No. 98907702.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: F. Davison-Brunel
Members: P. Julià
C. Heath

Summary of Facts and Submissions

I. European patent application No. 98 907 702.9 published as WO 98/39464 with the title "Adenovirus vectors containing heterologous transcription regulatory elements and methods of using same" was refused by the examining division pursuant to Article 97(1) EPC.

Claims 1, 8, 47 to 49 as originally filed read as follows:

" 1. An adenovirus vector comprising a first adenovirus gene under transcriptional control of a first heterologous transcriptional regulatory element (TRE) and at least a second gene under transcriptional control of a second heterologous TRE, wherein the first heterologous TREs is cell-specific, the first heterologous TRE is different from the second heterologous TRE, and the heterologous TREs are functional in the same cell.

8. The adenovirus vector of claim 1, wherein the first and second genes are essential for adenovirus replication.

47. A method for suppressing tumor growth comprising contacting a target cell with an adenovirus vector according to claim 1 such that the adenovirus vector is introduced into the target cell.

48. A method according to claim 47, wherein the target cell is a mammalian cell.

49. A method according to claim 48, wherein the mammalian cell is a prostate cell."

II. The reason for refusal was that the claimed subject-matter lacked inventive step. In the decision, it was also mentioned that although several claims had been objected earlier on for lack of novelty, this objection was no longer maintained. The decision of the examining division was based on a set of claims filed on 9 May 2005. Claim 1 read as follows:

"1. A replication-competent adenovirus vector for selective cytolysis of a target cell, comprising a first adenovirus gene essential for replication under transcriptional control of a first heterologous transcriptional regulatory element (TRE) and at least a second adenovirus gene under transcriptional control of a second heterologous TRE, wherein the first and second heterologous TREs are cell-specific, the first heterologous TRE is different from the second heterologous TRE, and the heterologous TREs are functional in the same cell."

III. The appellant (applicant) filed an appeal against the decision of the examining division, paid the appeal fee and submitted a statement of grounds of appeal together with a new main request and three auxiliary requests. The main request was identical to the request on which the decision under appeal was made, except for the addition of new claim 17 directed to a "second medical use" of the claimed vector. The first auxiliary request was identical to the main request except that it was further limited by the feature that the TREs were derived from different genes.

IV. The examining division did not rectify the contested decision and referred the appeal to the board of appeal (Article 109 EPC).

V. The board sent a communication pursuant to Article 110(2) EPC to inform the appellant that in accordance with the findings in decision G 10/93 (OJ EPO 1995, 172) that when the examining division has refused an application, the board has the power to examine whether the application fulfils the requirements of the EPC even those which had been regarded as fulfilled, the board intended to re-consider the novelty issue. It also provided its preliminary, non-binding opinion as regards this issue and that of inventive step.

VI. The appellant filed further submissions in answer to this communication together with a new main request.

VII. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA) indicating, in particular, that any further submissions should reach the board no later than one month before the oral proceedings and also, that the new main request apparently suffered from the same deficiencies under Article 54 EPC as the earlier main request.

VIII. On 8 May 2007, two weeks before the oral proceedings, the applicant filed further submissions together with a new main request and a new first auxiliary request to replace all previous requests, also indicating its willingness that the oral proceedings be cancelled if

the board felt in a position to allow either one of them.

IX. In a telephone conversation which took place on 14 May 2007, the rapporteur informed the appellant that oral proceedings were maintained and drew attention to such case law which it deemed particularly relevant in the framework of assessing whether or not the subject-matter of claim 1 of the first auxiliary request fulfilled the requirements of Article 123(2) EPC.

X. Oral proceedings took place on 23 May 2007. After the main request filed on 8 May 2007 was rejected for lack of clarity, the appellant requested from the board that a new main request be taken into consideration. After this second main request was found to lack novelty, the appellant requested that a third main request and two auxiliary requests be introduced in the proceedings. The board refused the third main request for failing to fulfil the requirements of Article 123(2) EPC and indicated to the appellant that it would be given one more chance to file a last main request. The appellant then filed a fourth main request together with a new first auxiliary request in replacement of all requests on file. As this main request was found to lack inventive step and the accompanying auxiliary request was found not to fulfil the requirements of Article 123(2) EPC, the appellant filed a fifth main request and indicated that it would withdraw the fourth main request if the fifth one was found admissible. The auxiliary request was withdrawn.

XI. Claim 1 of the fourth main request read as follows:

"1. Use of a replication-competent adenovirus vector in the manufacture of a medicament to treat prostate cancer by selective cytolysis of a target cancer cell, said adenovirus vector comprising a first adenovirus gene essential for replication under transcriptional control of a first heterologous transcriptional regulatory element(TRE) and at least a second adenovirus gene essential for replication under transcriptional control of a second heterologous TRE, wherein the first heterologous TRE is prostate tumor cell specific and the second heterologous TRE is prostate cell-specific, the first heterologous TRE is different from the second heterologous TRE, and the heterologous TREs are functional in the same cell."

Dependent claims 2 to 8 related to further features of the claimed use.

Claim 1 of the fifth main request read as follows:

"1. Use of a replication-competent adenovirus vector in the manufacture of a medicament to treat prostate cancer by selective cytolysis of a target cancer cell, said adenovirus vector comprising a first adenovirus gene essential for replication under transcriptional control of a first heterologous transcriptional regulatory element (TRE) and at least a second adenovirus gene essential for replication under transcriptional control of a second heterologous TRE, wherein the first heterologous TRE is prostate tumor cell specific and the second heterologous TRE is prostate cell-specific, the heterologous TREs are derived from the transcriptional regulatory regions of

different genes, and the heterologous TREs are functional in the same cell."

Dependent claims 2 to 8 remained unchanged.

XII. The following document is mentioned in this decision:

(2): WO 97/01358 (publication date: 16 January 1997)

XIII. The appellant's arguments during oral proceedings insofar as relevant to the present decision may be summarised as follows:

Fourth main request (request maintained at the end of oral proceedings); claim 1
Article 56 EPC; inventive step

The closest prior art was document (2) which described adenoviral vectors ultimately to be used for the purpose of killing prostate cancer cells (page 36). One such vector comprised two genes essential for viral replication, each of them being independently under the control of the **same** heterologous PSE TRE which TRE was functional in malignant prostatic cells (page 33).

Starting from the closest prior art, the problem to be solved could be defined as providing improved adenoviral vectors for the treatment of prostate cancer. The formulation of this problem was per se inventive insofar as it reflected the appellant's unexpected findings that, while exhibiting a high level of cell specificity, vectors wherein the **same** heterologous TREs controlled the transcription of two

adenoviral genes were intrinsically unstable and suffered polynucleotide rearrangements.

The provided solution was adenoviral vectors wherein **different** heterologous TREs were used to control transcription of each of the relevant adenoviral genes. The same high level of cell specificity was, thus, achieved while retaining genome stability. This result was clearly advantageous for the contemplated use.

For these reasons, the subject-matter of claim 1 was inventive.

Fifth main request; admissibility

This request should be admitted into the proceedings for the following reasons:

- It was only a small change which had been introduced into claim 1 as compared with claim 1 of the fourth main request.

- It was immediately obvious that claim 1 was allowable under Articles 123(2) and 84 EPC.

- The request had been filed in direct reaction to an objection raised for the first time during the oral proceedings.

XIV. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the new main request last filed in oral proceedings, in the alternative, on the basis of the main request as filed in oral proceedings and already admitted.

Reasons for the Decision

1. At the end of the oral proceedings, the appellant withdrew all claim requests filed up till then, except for two of them, the fourth and fifth main requests. The first question which arises in respect of these requests - which had been filed during the oral proceedings - is that of their admissibility.

Admissibility of the "fourth" and "fifth" main requests

2. In accordance with the Rules of Procedure of the Boards of Appeal (Articles 10a(2) and 10b(1) RPBA), the statement of grounds of appeal shall contain a party's complete case. Any amendments filed thereafter may be admitted at the board's discretion. One observes that, although the belated filing of claim requests is inherently fraught with the risk that they be disregarded, the situation is, nonetheless, rather frequently encountered. Accordingly, there is a plethora of decisions by the boards of appeal which define the circumstances which may arise, and the criteria which should be fulfilled, to justify that these requests be admitted (see "Case Law of the Boards of Appeal of the European Patent Office", 5th Edition 2006, Chapter VII.D.14, pages 640 to 649).

3. The principles applicable to the admission in the appeal proceedings of new requests filed at a late stage are referred to in very broad terms in Article 10b(1) RPBA:

"The *[board's]* discretion shall be exercised in view of inter alia the complexity of the new subject-matter

submitted, the current state of the proceedings and the need for procedural economy." (*[added by the board]*)

They are reviewed in, for example, T 397/01 of 14 December 2004:

- the amendments must be filed in response to objections or comments which were raised during the appeal proceedings.

- they do not extend the frame of discussion as determined by the decision under appeal and by the statement of grounds of appeal.

- they are clearly allowable and can easily be dealt with.

In decision T 794/94 of 17 September 1998, it is remarked that in the field of genetic engineering, the necessity of filing different independent claims to appropriately reflect the invention can make formulation of a suitable request difficult and may, thus, justify late submissions of requests in accordance with the principles just enounced.

4. While the board agrees with this long- and well-established practice of the boards of appeal, it is also of the firm opinion that the belated filing of claim requests at oral proceedings must have its limits. In this respect, it fully concurs with the statement made in T 794/94 (supra, point 2.1.4 of the decision):

"However, there is no right to file an endless succession of new requests in substitution for requests

found inadmissible or unallowable by the board. Proceedings must come to an end some time."

5. Indeed, if the contrary was true, oral proceedings could easily be misused, in particular in ex-parte cases, to test the board's opinion as to what subject-matter might be patentable and to tailor claims accordingly. In such cases, while not "holding the pen", the board would nonetheless be the ghost-writer of what is ultimately claimed. This is simply not one of the duties of a board of appeal.

6. It is in the light of these considerations that the admissibility of the requests filed as fourth and fifth main requests during oral proceedings was assessed.

7. The fourth main request was the one-before-last in a line of requests filed in reply to the board's opinion at oral proceedings that the claimed subject-matter lacked clarity (main request filed in writing, withdrawn), was not novel (second main request, withdrawn), or was not allowable under Article 123(2) EPC (third main request and first auxiliary requests, withdrawn). At this point in time, the board was already concerned by the number of requests filed in the proceedings and informed the applicant accordingly. Then, the fourth main request was submitted. The board made a comparison of the claims of this request with claims 1, 8, 47 to 49 as originally filed (see Sections I and XI, supra) and came to the conclusion that they encompassed essentially the same subject-matter. For this reason, it was decided to admit the fourth main request in the proceedings.

8. After this fourth main request was refused for lack of inventive step, the fifth main request was filed. The board readily accepts that the feature introduced in claim 1 had a formal basis in the application as filed and that the amendment had undoubtedly been carried out to take account of what was perceived as the board's reasons for denying inventive step to the fourth main request. Yet, in accordance with the findings in T 794/94 (point 4, supra) and, in view of the numerous re-shuffles of claim requests which had already taken place both in the written and in the oral parts of the proceedings - which, if one was to take a strict stance, could even be regarded as tactical abuse -, the board used its discretion under Article 10b(1)RPBA in order not to admit the fifth main request in the proceedings.

9. The following remarks can also be made. Firstly, the appellant argued that the change in claim 1 of the fifth auxiliary request compared to claim 1 of the fourth auxiliary request was small - thus, implying that the claim request should be accepted. The board is not convinced by this argument. The important point in this specific case is not the nature of the change but the sheer number of them. Secondly, it is always the appellant's responsibility to decide at which stage of the proceedings to file a new request. It is to be expected that the filing of a new request might give rise to new issues and considerations. The later its introduction into the proceedings, the greater the risk that issues might have to be faced without further preparation. Here, it is also worth keeping in mind that the feature introduced in claim 1 of the fifth auxiliary request was already present in claim 1 of the first auxiliary request filed on appeal (see Section

III supra), yet had been abandoned in all subsequent requests, raising doubt as to the appellant's own perception of its relevance to the invention. Finally, although the case is in the field of genetic engineering, the findings in T 794/94 (point 3, supra) that this may constitute a circumstance in which additional claim requests may be filed at oral proceedings do not apply here, because there is no need to accommodate a multiplicity of independent claims, as was the case in the cited decision.

10. At the end of oral proceedings, the appellant requested that if the fifth request was not deemed admissible, a reasoned decision be issued in this respect and also in respect of the patentability of the fourth main request. Since the fifth main request cannot be admitted, this decision will concern the patentability of the fourth main request admitted to the proceedings.

Fourth main request (sole request on file); claim 1
Articles 123(2), 84 and 54 EPC

11. The subject-matter of claim 1 of the main request amounts to a combination of originally filed claims 1, 8 and 49 (Section I, supra), the additional feature that the first heterologous TRE is prostate tumor cell specific and the second heterologous TRE is prostate cell specific being found, for example and not exclusively, on page 10 of the application as filed. The subject-matter of the remaining dependent claims finds a basis in particular, in originally filed claims 4 to 7, 10, 21, 54 to 62 (Article 123(2) EPC).

12. The claimed subject-matter is clear and supported by the description (Article 84 EPC).

13. There is no document on file teaching the now claimed use of an adenoviral vector which comprises two different, prostate tumor cell specific and prostate cell specific, heterologous TREs in the manufacture of a medicament to treat prostate cancer. Novelty is, thus, acknowledged (Article 54 EPC).

Article 56 EPC; inventive step

14. The closest prior art is document (2) which is concerned with providing, in particular, replication-competent adenoviral vectors for use for selective cytolysis of target cells, with special reference to prostate cancer cells (page 7, lines 9 to 14, page 8, lines 19 to 28 ...). An adenovirus is described in which the two adenoviral E1a and E1b genes, which are essential for replication, are independently under the control of the **same** heterologous TRE (PSE TRE) which is functional in a limited population of cells (prostate cell-specific), yet is preferably active in prostate cancer cells (prostate tumor cell specific) (page 33; CN 716, PSE-E1A, PSE-E1B).

15. Starting from the closest prior art, the problem to be solved can be defined as the provision of improved adenoviral vectors for the intended use.

16. Document (2) does not suggest at any time that there would be the necessity to isolate other vectors than those which it describes. Yet, from reading the small review of the state of the art provided on pages 1 to 4

of this document, it is clear that at the priority date, treatment of target cells with viral DNA (gene therapy) was very much an on-going field of research and that adenoviruses were considered advantageous over other viruses (eg. retroviruses). It is also clear that the skilled person was aware of potential disadvantages which, of course, would lead him/her to try and develop further - and possibly better - adenovirus vectors for gene therapy. Thus, the formulation of the problem does not in itself contribute to inventive step.

17. The provided solution is adenoviral vectors having the same features as those of the vector CN 716 described in document (2) except for the fact that the two adenoviral genes essential for replication are transcriptionally controlled by heterologous TREs which are **different** from each other.

18. According to the appellant, inventive step lay in the unexpected properties of the claimed vectors. In this context, reference was made to the passage on page 10, lines 13 to 20 of the application as filed:

"Previous attempts to achieve this level of specificity through the construction of adenovirus vectors with the **same** heterologous TRE controlling transcription of two adenoviral vector genes appear to have resulted in unstable genomes and undesirable polynucleotide sequence rearrangements... Without wishing to be bound by theory, such genome instability may be the result of homologous recombination through the duplicated TRE sequences."(emphasis added by the board)

The use of two different TREs was said to relieve the observed instability of the vectors of the prior art.

19. The application as filed, page 11, lines 16 to 19 provides, in particular, the following definition of the term "different TREs":

"In the context of adenovirus vector(s), a first heterologous TRE is "different" from a second (or another) heterologous TRE when the polynucleotide sequence identity between the two heterologous TREs is less than about 95%, preferably less than about 90%, preferably less than about 85%, preferably less than about 75%. Generally, "different TREs" are derived from the transcriptional regulatory regions of different genes. "Different TREs" may also be derived from the transcriptional regulatory region of the same gene, as long as the sequence identity between them is less than the values listed above (i.e., less than about 95%, preferably less than about 90%, more preferably less than about 85%, more preferably less than 80%, preferably less than about 75%)."

From this statement, the board understands that the claimed subject-matter covers the use of adenoviral vectors carrying two TREs with a sequence identity of "from 0% to about 94%".

20. At oral proceedings, the board made the remark that if inventive step was to be acknowledged on the basis of some unexpected advantages of the vectors, then all vectors comprised within the claim should share these advantages. Accordingly, the appellant was asked whether all vectors comprised within the claim would be

expected to be genetically stable; i.e. whether one would expect that vectors comprising TREs with as much sequence identity as eg.94% would undergo **significantly less** homologous recombination than that occurring between two strictly identical TREs.

21. To this point, it was answered that the skilled person would understand the term "different heterologous TREs" as meaning TREs originating from different genes and that the presence of these TREs in the adenoviral vectors would certainly be beneficial to genomic stability.

22. The board accepts that enhanced stability may be observed with vectors comprising TREs from different genes having low sequence identity irrespective of whether or not the observed effect would be unexpected. Yet, the difficulty is otherwise: in accordance with the case law (e.g. T 16/87 (OJ EPO 1992, 212), the description may be used to interpret the claims when assessing inventive step. Here, it is unambiguous from the description that TREs with a very high level of identity fall within the definition of "different heterologous TREs" and it was not denied that these TREs could undergo homologous recombination. Thus, not all constructs comprised within the claim possess the property - genomic stability - which would possibly justify acknowledging inventive step. In other words, the advantageous effect argued to impart inventive step is not obtained over the scope of the claim.

23. The appellant also argued that inventive step lay in the fact of having found out that the vectors of the prior art were unstable. This, however, could only

serve to back up a conclusion of inventive step as regard the proposed solution if the claimed subject-matter entirely consisted of vectors which had lost this undesirable property.

24. For these reasons, it is concluded that the subject-matter of claim 1 lacks inventive step and the claim request is refused for failing to fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chairman

A. Wolinski F. Davison-Brunel