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Datasheet for the decision of 29 March 2007

Case Number: T 0176/06 - 3.3.08

Application Number: 97910794.3

Publication Number: 0932679

IPC: C12N 15/21

Language of the proceedings: EN

Title of invention:
Methods and compositions for delivery and expression of interferon-alpha nucleic acids

Applicant:
CANJI, Inc.

Opponent:
-

Headword:
Interferon delivery/CANJI

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

Keyword:
"- Main request - added subject-matter - no -"
"- Main request - inventive step - no -"
"First to fourth auxiliary requests - clarity - no"

Decisions cited:
T 0363/99

Catchword:
-

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Case Number: T 0176/06 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 29 March 2007

Appellant: CANJI, Inc.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 19 August 2005 refusing European application No. 97910794.3 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: F. Davison-Brunel
T. J. H. Mennessier

Summary of Facts and Submissions

I. European patent application No. 97 910 794.3 published as WO 98/17801 with the title "Methods and compositions for delivery and expression of interferon-α nucleic acids" was refused by the examining division pursuant to Article 97(1) EPC.

A main request and four auxiliary requests were considered.

Claim 1 of the main request read as follows:

"A recombinant vector for expression of an interferon alpha polypeptide, said vector comprising a nucleic acid sequence enconding *[sic]* an interferon alpha polypeptide operably linked to a promoter functional in a mammalian cell;

wherein said vector is a viral vector derived from the genus adenoviridiae;

wherein said interferon alpha polypeptide is interferon alpha 2b; and

wherein said nucleic acid sequence enconding *[sic]* an interferon alpha polypeptide is operably linked to a nucleic acid encloding *[sic]* an interferon alpha secretion leader."

II. In its decision dated 19 August 2005, the examining division refused the main request and the first auxiliary request for lack of inventive step of claim 1 of either request over the teachings of document (2)

(infra). The second to fourth auxiliary requests were refused as they did not comply with the requirement of Article 123(2) EPC.

III. The appellant (applicant) filed an appeal, paid the appeal fee and submitted a statement of grounds of appeal together with a new main request and three auxiliary requests.

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 11(1) of the Rules of Procedure of the Boards of Appeal stating its preliminary, non-binding opinion.

VI. The appellant sent a further submission in answer to this communication together with a new main request and an auxiliary request to replace the requests on file.

Claim 1 of the **main request** read as follows:

"A recombinant adenoviral vector for expression of an interferon alpha 2b polypeptide, said vector comprising a nucleic acid sequence encoding an interferon alpha 2b polypeptide operably linked to a constitutive promoter functional in a mammalian cell."

Claim 2 related to further features of the recombinant vector of claim 1 and claim 3 related to a pharmaceutical formulation comprising said vector. Claims 4 to 6 related to various uses of the recombinant vector according to claim 1 or 2.

Claim 1 of the **first auxiliary request** read as follows:

"A recombinant adenoviral vector for expression of an interferon alpha 2b polypeptide, said adenoviral vector being a vector disclosed in Wills et al., Human gene Therapy 5: 1079-1088 (1994) and comprising a nucleic acid sequence encoding an interferon alpha 2b polypeptide operably linked to the promoter of said vector."

Claims 2 to 6 were identical to claims 2 to 6 of the main request.

VII. Oral proceedings took place on 29 March 2007. Three auxiliary requests were filed in addition to the main and the first auxiliary requests. The principal differences between claim 1 of these requests and of the first auxiliary request are shown in bold below.

Claim 1 of the **second auxiliary request** read as follows:

"1. A recombinant adenoviral vector for expression of an interferon alpha 2b polypeptide, said adenoviral vector being a vector disclosed in Wills et al., Human gene Therapy 5: 1079-1088 (1994) and comprising a nucleic acid sequence encoding an interferon alpha 2b polypeptide operably linked to the **constitutive** promoter of said vector."

Claim 1 of the **third auxiliary request** read as follows:

"1. A recombinant adenoviral vector for expression of an interferon alpha 2b polypeptide, **wherein** said adenoviral vector **is the** vector disclosed in Wills et al., Human gene Therapy 5: 1079-1088 (1994) and comprising a nucleic acid sequence encoding an interferon alpha 2b polypeptide operably linked to the promoter of said vector."

Claim 1 of the **fourth auxiliary request** read as follows:

"1. A recombinant adenoviral vector for expression of an interferon alpha 2b polypeptide, comprising a nucleic acid sequence encoding an interferon alpha 2b polypeptide **inserted into the adenovirus vector** disclosed by Wills et al., Human gene Therapy 5: 1079-1088 (1994)."

In all these requests, claims 2 to 6 were identical to claims 2 to 6 of the main request.

VIII. The following documents are mentioned in this decision:

(2): Zhang, J-F. et al., Proc.Natl.Acad.Sci.USA, Vol.93, pages 4513 to 4518, April 1996;

(3): Zhang, JF. et al., Cancer Gene Therapy, Vol.3, No.1, pages 31 to 38, 1996;

(4): Ferrantini, M. et al., Cancer Research, Vol.53, pages 1107 to 1112, 1 March 1993;

(7): Hochkeppel, H.K. et al., Drugs of the Future, Vol.17, No.10, pages 899 to 914, 1992;

(8): Goeddel, D.V. et al., Nature, Vol. 290, pages 20 to 26, 5 March 1981;

(9): Benedict, W.F. et al., Molecular Therapy, Vol.10, No.3, pages 525 to 532, September 2004;

(10): Wills, K.N. et al., Human Gene Therapy, Vol. 5, pages 1079 to 1088, September 1994;

(13): Iqbal Ahmed, C.M. et al., Cancer Gene Therapy, Vol.8, No.10, pages 788 to 795, 2001;

(14): Iqbal Ahmed, C.M. et al., Human Gene Therapy, Vol.10, pages 77 to 84, 1 January 1999.

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

Main request: claim 1
Article 123(2) EPC; added subject-matter

There was an explicit basis for a recombinant vector comprising a constitutive promoter on page 10, lines 5 to 9 of the application as filed. Furthermore, an implicit disclosure was also provided insofar as the application made reference on page 11 to the vectors of Wills et al., and adenoviral vectors described therein comprised constitutive promoters.

Article 56 EPC; inventive step

Document (2) was the closest prior art as it disclosed a replication-proficient adenoviral vector for expression of the con 1 interferon (IFN-con 1) gene in tumor cell lines.

Starting from document (2), the problem to be solved could be seen as the provision of an alternative adenoviral expression vector for tumor treatment.

The solution provided was the adenoviral vector of claim 1. The claimed vector differed from the vector of the prior art by the use of the IFN-α2b expressed from a constitutive promoter instead of the IFN-con 1 gene.

First, document (2) taught that the recombinant construct which it described was well-suited for obtaining the desired anti-tumor effect and thus did not provide any incentive for the skilled person to isolate another recombinant vector for the same purpose. If nonetheless the skilled person thought it worthwhile to construct some other recombinant vectors for tumor treatment, he/she had multiple choices available such as using vectors and toxic genes other than adenovirus and the IFN-α2b gene.

Secondly, none of the prior art references which may have been combined with document (2) suggested the IFN-α2b gene for gene therapy (e.g. documents (4), (7) or (8)).

Finally and importantly, the use of the IFN-α2b gene in the background of an adenoviral vector was associated

with a surprising effect as evidenced by the post-published documents (9), (13) and (14).

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

First auxiliary request
Article 84 EPC; clarity

In the application as filed, page 11 of the description, reference was made to **the** adenovirus vector disclosed by Wills et al., Hum. gene Therapy 5: 1079 to 1088 - document (10) in these proceedings - as being a particularly advantageous vector. The skilled person would readily understand the expression "**the** adenovirus vector..." as meaning "**the kind** of adenovirus vector...", i.e. as representing any one of the four vectors disclosed in this scientific article.

For this reason, he/she would find it unambiguous that claim 1 - to a recombinant adenoviral vector being **a** vector disclosed in Wills et al.,... - was in fact directed to one of the four vectors disclosed in Wills et al.,... comprising the IFN-α2b gene.

The vectors themselves were described in a very clear manner in document (10) (page 1080, left-hand column "Construction of recombinant adenoviruses"). The parts of the vectors relevant to IFN-α2b expression were mentioned as being in a pML2 background. The fact that no information was given as to what this meant did not introduce any ambiguity because the technical meaning of the term "a pML2 background" would be part of the skilled person's knowledge. Furthermore, the board's

observation that there existed two kinds of vectors differing by the promoters which they carried (inducible or constitutive) did not have any bearing on clarity because the two promoters had been clearly identified and were, in fact, both constitutive.

Indirect evidence that the skilled person would have had no difficulty in understanding what the "Wills" vectors were could be seen in the fact that they had been used in the post-published documents (9), (13) and (14).

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

Further requests
Articles 123(2) and 84 EPC

Claim 1 of the second auxiliary request differed from claim 1 of the first auxiliary request in that it made clear that, of the "Wills" vectors, the one which had to be used was that which contained a promoter which was undoubtedly constitutive.

Claim 1 of the third and fourth auxiliary requests reproduced the wording which was used on page 11 of the application as filed to define a particularly advantageous vector. The requests fulfilled the requirements of Article 123(2) EPC and also those of Article 84 EPC for the same reasons as had been given in respect of the vectors of the first auxiliary request.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted in the following version:

the main request as filed with the letter of 28 February 2007, the first auxiliary request as filed with the same letter or one of the three further auxiliary requests filed during the oral proceedings.

Reasons for the decision:

Main request; claim 1
Article 123(2) EPC; added subject-matter

1. The question of added subject-matter arose in relation to the feature of the recombinant vector of claim 1 that it comprises a constitutive promoter. On page 10, the application as filed provides the generic teaching that recombinant gene expression may be achieved by linking the gene to be expressed to a promoter which is either constitutive or inducible. Furthermore, mention is made on page 11 that a particularly advantageous vector for carrying out the claimed invention is described in the scientific article by Wills et al. which is cited. A vector is indeed disclosed therein which comprises the constitutive human cytomegalovirus promoter (CMV). The board thus accepts that the above mentioned generic teaching is meant to apply in particular to the recombinant vectors according to the invention, i.e. that there is a basis in the application as filed for a recombinant vector expressing the IFN-α2b gene from a constitutive

promoter. The requirements of Article 123(2) EPC are fulfilled.

Article 56 EPC; inventive step

2. The closest prior art is document (2) which teaches a recombinant adeno-associated virus (ad5/IFN) containing the human consensus IFN gene (IFN-con 1). When breast cancer tumors established in nude mice are transduced with the ad5 vector as such or with the ad5/IFN-con 1 vector, partial tumor regression is observed, the effect being more pronounced with the latter vector. When human leukemia tumors or hamster melanoma tumors established in nude mice are injected with either one of these vectors, partial tumor regression is observed with the ad5/IFN-con 1 vector . The authors propose that tumor regression is at least partially, if not totally, due to the very high levels of interferon produced by the recombinant virus (see discussion, pages 4516 and 4517).

3. Starting from the closest prior art, the problem to be solved can be defined as providing an alternative vector for inducing cancer tumor regression. It is readily apparent from some of the documents on file (e.g. document (3), last paragraph) that, at the priority date, much effort was being put into developing gene therapy of cancer. Therefore, the formulation of the problem per se does not contribute to inventive step.

4. The solution provided is a recombinant adenoviral vector expressing the gene encoding the natural IFN-α2b interferon from a constitutive promoter.

5. Like document (2), document (3) is concerned with determining the effect on tumor cells of a recombinant adeno-associated vector expressing IFN-con 1 - from the inducible mouse metallothionein promoter. It shows that when injected into nude mice, tumor cells which have been transduced in vitro by this vector fail to develop into tumors. On page 37, it is mentioned that:

"These results suggest that therapy with genes such as IFN type I might be useful in the treatment of human cancers, ..."

6. In the board's judgment, the combination of the teachings of documents (2) and (3) renders obvious the use of IFN-α2b as the skilled person would be well aware that this interferon is a type I interferon - a point which was mentioned in the board's communication and was not thereafter disputed by the appellant. In the written proceedings, documents (4), (7) and (8) were cited as evidence that the skilled person would not have considered using the IFN-α2b gene. Documents (7) and (8) are not concerned with gene therapy, one of them being a review on IFN-α hybrids, the other reporting the cloning of leucocyte interferon cDNAs and, for this reason, they are not relevant. Document (4) is an example of "gene therapy" using a retroviral vector expressing an interferon identified as IFN-α/β. In the board's view, the fact that one interferon gene was previously used for studying tumor regression is not sufficient to conclude that the skilled person would not envisage using another, such as, for example, the IFN-α2b gene.

7. In the same manner, it was argued that it was not obvious to use an adeno-associated viral vector. This argument is, however, not convincing taking into account that it is just such a vector which is used in document (2) and that the advantages of using it are clearly described in that same document (passage bridging the right- and left- hand columns, page 4513).

8. Finally, inventive step was said to be due to the characterising feature of the recombinant vector that the IFN-α2b gene was expressed from a constitutive promoter. In this respect, reference was made to post-published documents (9), (13) and (14) as evidence that such vectors were particularly advantageous for tumor therapy. The recombinant adenoviral vector described in document (9) - which, in any case, is said to be effective against human bladder cancer **only** in the presence of the gene transfer enhancing agent Syn 3 - is the same as that used in document (13) (see document (9), bibliographical reference 9 cited on page 530, in "Cell lines, vectors and Syn 3"). Although somewhat different, this vector and the one used in document (14) comprise the same adenovirus backbone and the same features relevant to gene therapy, namely those which are also present in the vector pACN described in Wills et al., (see document (13), reference 13 on page 789, left-hand column and document (14), page 78). For this reason, the three vectors are, in fact, the same vector insofar as the features relevant to tumor therapy are concerned: their features relative to gene therapy are **very specific**: they express the IFN-α2b gene from the **strong constitutive** cytomegalovirus promoter and are **replication-deficient**.

9. In contrast, claim 1 is of such a scope that it comprises, for example, replication-proficient vectors wherein the IFN-α2b gene is expressed from a constitutive promoter of any strength. The patent application does not provide any evidence that such vectors would be advantageous. In fact, it does not provide any evidence whatsoever that any of the claimed vectors would induce tumor regression. In this situation, the only conclusion which may be drawn is that inventive step due to an advantageous effect linked to the features of the claimed vector has not been demonstrated over the scope of the claim.

10. For these reasons, inventive step is denied to the subject-matter of claim 1 and the main request is rejected for failing to fulfil the requirements of Article 56 EPC.

First auxiliary request; claim 1
Article 84 EPC; clarity

11. In claim 1 of this request, the recombinant vector is characterised by reference to a document of the state of the art (Wills et al., Human Gene Therapy 5 : 1079-1088 (1994): see document (10) on file). A similar case was dealt with in decision T 363/99 of 19 April 2004 wherein it was requested that a patent be granted to, in particular, a process for cleaning contact lenses whereby the rinsing solution was defined in the claim as being that described in the earlier patent document DE 3 315 974 ("Verfahren nach Anspruch 1, a) und b) Abspülen der Linsen wie nach c) mit einer wässrigen Lösung nach DE 3 315 974 ...). The then competent board decided that this wording rendered the claim unclear as

the publication number of a referenced document did not amount to a technical feature as must be used for a proper definition of a claimed subject-matter (see Section B of the decision).

12. The fact that the presently claimed subject-matter is in a quite different field of expertise from the claimed subject-matter in the earlier decision does not detract from the findings in this decision as regards clarity. Claim 1 could be refused on this basis alone (and see also Rule 29(1) EPC, first sentence).

13. Assuming for the sake of discussion that it would not be, it remains to be assessed whether the claimed subject-matter is clear in substance. A number of observations must then be made:

(a) Whereas the application as filed, page 11, teaches that "a particularly advantageous vector is **the** adenovirus disclosed in Wills et al. ..." (emphasis added), this scientific article in fact discloses four vectors: pNL3C, pNL3CMV, A/M/N/53 and A/C/N/53 (page 1080, *"Construction of recombinant adenoviruses";* the last two vectors are recombined with the p53 gene). The appellant argued that the skilled person would understand that any one of these vectors would be suitable, especially since the data presented showed that they all had equivalent effects on tumor regression when expressing the p53 gene.In that case, one is left wondering why the application as filed did not teach that particularly advantageous vector**s were** the adenoviru**ses** disclosed by Wills et al.

(b) pNL3C and pNL3CMV are characterised as "kindly provided by Dr. Robert Schneider". No bibliographic reference is provided which the skilled person could consult. They are also said to carry the regulatory elements necessary for expression "in a pML2 background". No explanation is given as to what this background may be. The appellant argued that "a pML2 background" would be matter of common general knowledge but failed to provide evidence in this respect.

(c) A/M/N/ and A/C/N are respectively derived from pNL3C and pNL3CMV by deletion of the adenoviral gene encoding protein IX. If (which was not the case) a reason had been given for this deletion, that might have been of help in evaluating the relevance of using these vectors rather than the parental ones.

(d) The promoters for the expression of the relevant gene - here, the IFN-α2b gene - differ in pNL3C and pNL3CMV. One of them is the Ad2 major late promoter (MLP), the other one is the human cytomegalovirus immediate-early promoter (CMV). At oral proceedings, the board made the remark that the MLP promoter being a late promoter, it would probably be considered as an inducible promoter, whereas the CMV promoter which is immediate early should not require to be induced i.e. would be considered as a constitutive promoter, and that this difference may leave the skilled person to wonder which one of these vectors, if any, is the advantageous one mentioned in the description. The

appellant argued that, under the circumstances, the MLP promoter would be regarded as a constitutive promoter yet did not provide any evidence in this respect.

In the board's judgment, the skilled person reading the section "*Construction of recombinant viruses*" in document (10) would not find there a clear and unambiguous description of the vectors (point (b), supra). Furthermore, he/she would not know which one to choose (points (c) and (d), supra). Consequently, claim 1 which refers to this document is unclear.

14. It was also argued that the skilled person must have been able to understand what the Wills vectors were on the basis of the description in document (10), since these vectors or derivatives thereof had been used later on in post-published work (documents (9), (13) and (14)). The board cannot accept this argument as the three documents are, at least in part, either authored by Wills or by research workers at the same laboratory, who would inevitably have known the vectors.

15. For these reasons, the first auxiliary request is refused for failing to comply with the requirements of Article 84 EPC.

Second to fourth auxiliary requests

16. Claim 1 of the second auxiliary request differs from claim 1 of the first auxiliary request in that it specifies that the vector carries the constitutive promoter of a vector of Wills et al., (see Section VII, supra). In the appellant's view, all vectors therein

described carry a constitutive promoter. In the board's opinion, it is possible that only the vectors with the CMV promoter do so. Thus, the amendment either adds nothing to the subject-matter of claim 1 or it offends Article 123(2) EPC by relating to a specific choice amongst the Wills et al., vectors which was not disclosed in the application as filed. Accordingly, the requirements of Article 123(2) EPC may not be complied with by claim 1 of the second auxiliary request (see also point 18 below regarding clarity).

17. In claim 1 of the third and fourth auxiliary requests, the same language is used as in the application as filed, namely the claimed vector is defined as being the vector disclosed in Wills et al. These requests fulfil the requirements of Article 123(2) EPC.

18. Nevertheless, for the reasons given above in respect of the claim 1 of first auxiliary request, the reference to Wills et al., in claim 1 of any of the second to fourth auxiliary requests does not provide a clear and unambiguous disclosure of the claimed vectors. These auxiliary requests do not fulfil the requirements of Article 84 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski C. Rennie-Smith