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Case Number: T 0288/08 - 3.3.08

Application Number: 96921468.3

Publication Number: 0844887

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Language of the proceedings: EN

Title of invention:
AAV transduction of myoblasts

Applicant:
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

Opponent:
-

Headword:
AAV transduction/UNIV. NORTH CAROLINA

Relevant legal provisions:
-

Relevant legal provisions (EPC 1973):
EPC Art. 56

Keyword:
"Main request - inventive step - yes"

Decisions cited:
G 0010/93, T 0606/89

Catchword:
-

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Case Number: T 0288/08 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 9 June 2009

Appellant: UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 30 August 2007 refusing European application No. 96921468.3 pursuant to Article 97(2) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
T. Karamanli

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division dated 30 August 2007 to refuse the European patent application No. 96921468.3 published under the international publication No. WO96/40272 with the title "AAV transduction of myoblasts".

Claim 1 of the first auxiliary request then on file read as follows:

"1. Use of a recombinant AAV vector comprising a non-AAV gene capable of expressing a gene product, ligated into an AAV vector, for the preparation of a pharmaceutical composition for the treatment of a disease caused by a deficiency of said product, which is required to be produced and/or secreted in an animal, wherein the composition is administered into muscle tissue of an animal."*(Note by the board: AAV stands for adeno-associated virus)*

Claims 2 to 12 related to further features of the use of claim 1.

II. The examining division came to the conclusion that the main request then on file failed to fulfil the requirements of Article 123(2) EPC 1973 and that the subject-matter of claim 1 of the first auxiliary request lacked inventive step over the teachings of document (4) (infra) which suggested the claimed use. In its opinion, the alleged invention was a mere reduction to practice of this suggestion. The skilled person would have had no reason to doubt that the gene

product of interest would be stably expressed after being administered into the muscle tissue of an animal.

III. The appellant (applicant) lodged an appeal against this decision, paid the appeal fee and submitted a statement of grounds of appeal.

IV. The examining division did not rectify its decision and the case was remitted to the board of appeal (cf. Article 109(2) EPC 1973).

V. On 3 December 2008, the board sent a communication pursuant to Rule 100(2) EPC, making known its preliminary, non-binding opinion that the subject-matter of claim 1 of the request on file may not be inventive in view of the teachings of a further document introduced by the board as document (21) (see infra). The appellant was given three months to answer to this communication.

VI. On 13 March 2009, the appellant filed further submissions.

VII. The documents mentioned in the present decision are the following:

(2) : Xiao, X. et al., Advanced Drug Delivery Reviews, Vol. 12, pages 201 to 215, 1993;

(4) : Kourtis, A.P. et al., Modern Pathology, US, Baltimore, MD, Vol.8, No.1, page 33A, Abstract 178, 1995;

(9) : Jooss, K. et al., Journal of Virology, Vol.72, No.5, pages 4212 to 4223, May 1998;

(10) : Fisher, K. J. et al., Nature Medicine, Vol.3, No.3, pages 306 to 312, March 1997;

(21) : Flotte, T.R. et al., Proc.Natl.Acad.Sci.USA, Vol.90, pages 10613 to 10617, November 1993;

(24) : Doherty, P.C., The Journal of Immunology, Vol.155, pages 1023 to 1027, 1995;

(26) : Flotte, T.R., Journal of Bioenergetics and Biomembranes, Vol.25, No.1, pages 37 to 42, 1993.

VIII. The appellant's submissions in writing insofar as relevant to the present decision may be summarized as follows:

- The examining division reached a negative conclusion as regards inventive step on the basis of document (4) as closest prior art. This document was concerned with the problem of heart allograft rejection and reported the **in vitro** transfection of avian embryonic cardiac explants with recombinant AAV-LacZ constructs. The transfected explants still expressed β-galactosidase after 48 hours in culture. In contrast, the present application aimed at providing means and methods for **in vivo** gene therapy. This was a substantially different technical problem and, thus, document (4) did not qualify as closest prior art.

If document (4) was nonetheless taken as the closest prior art, then it should be kept in mind that at the priority date there was a general perception that any observations relating to gene transfer and expression mediated by AAV **in vitro** (as in document (4)) could not be translated **in vivo**. Not only the vector component was the subject of significant concerns, but also the transgene. It was believed that host immune responses would be raised against the transgene product. The 48 hours of β-galactosidase gene expression disclosed in document (4) would not have been regarded by the skilled person as a long-term in vitro expression, let alone as representative of a long term gene expression in vivo.

Even if one would accept that it was obvious to formulate the problem of achieving in vivo gene therapy in muscle tissue with recombinant AAV on the basis of the information provided by document (4) - which it was not -, it remained that the skilled person would have had no reasonable expectation of success in attempting to do so.

As further evidence of inventive step, post-published documents (9) and (10) should be cited which disclosed that the long-term expression in muscle tissue of the transgene carried by the AAV recombinant vector was, indeed, surprising.

- Document (21) was regarded by the board as the closest prior art because it described an **in vivo** experiment wherein a recombinant AAV vector carrying the normal cystic fibrosis transmembrane conductance regulator (CFTR) cDNA was directly delivered in the

lobe of a rabbit lung and the CFTR protein was expressed in the airway epithelium for up to six months after vector administration. However, there was no suggestion in document (21) to transfer the technology to other tissues. Furthermore, such a transfer to muscle tissue would not have come to mind because of the differences between airway epithelium and muscle tissues, the earlier cells being highly specialized with distinct characteristics and being of a different origin (endodermal) from that of muscle cells (mesodermal). And besides, AAV was known to exhibit a tropism to the respiratory epithelium and the skilled person would have had no reason to expect that it would also have tropism for muscle.

Even if the transfer of technology was considered to be obvious, there remained that the skilled person would have had no reasonable expectation of success in carrying AAV gene therapy in muscle. On the contrary, the skilled person would have expected that host-defence mechanisms such as immune responses would block long-term expression in muscle tissue. More specifically, the long-term expression of the CFTR gene in the airway epithelium would not have suggested a successful outcome of the same experiment in muscle tissue because it was known at the priority date that different immune responses would occur in different microenvironments in the body. In fact, the post-published documents (9) and (10) were proof that the observed long-term expression of the transgene carried by the AAV vector in muscle tissue **in vivo** was surprising.

For these reasons, and irrespective of whichever document was taken as the closest prior art, the requirement of inventive step was fulfilled.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 12 filed on 2 October 2006 during the oral proceedings before the examining division. As an auxiliary measure oral proceedings were requested if the board could not follow the appellant's argumentation in favour of the claimed subject-matter being inventive.

Reasons for the decision

1. Claims 2 to 11 correspond to originally filed claims 2 to 11. The subject-matter of claim 1 finds a basis in originally filed claim 1 together with the passage on page 12, lines 7 to 12 and that on page 9, lines 28 and 29 of the application as filed. Claim 12 finds a basis on page 12, lines 8 to 10 of the application as filed. The claims are clearly drafted. The requirements of Article 123(2) EPC 1973 and Article 84 EPC 1973 are fulfilled. Novelty was never at stake (Article 54(1) EPC 1973). The claimed subject-matter is reproducible on the basis of the information given in the description, in particular in the examples (Article 83 EPC 1973). Industrial applicability is in the field of pharmacology (Article 57 EPC 1973).

2. The issue to be decided is that of inventive step. Using the problem-solution approach, it is firstly necessary to identify the document which is the closest

prior art. In its decision, the examining division considered that document (4) was the closest prior art. In its communication pursuant to Rule 100(2) EPC, the board pointed out to the relevance of another document, document (21), which was introduced into the proceedings in accordance with the principle established in the Enlarged Board's decision G 10/93 (OJ EPO, 1995, 171) that in an appeal from a decision of an examining division in which a European patent application is refused, the board of appeal has the power to examine whether the application or the invention to which it relates meets the requirements of the EPC. This implies that any document deemed relevant may be taken into account irrespective of whether or not it had been previously cited.

3. Document (4) is an abstract relating to cardiac gene therapy with AAV as a means of achieving graft-specific immunosuppression. It teaches that avian embryonic cardiac explants (**smooth muscle tissue**) which are infected **in vitro** with AAV constructs carrying the LacZ reporter gene exhibit β-galactosidase activity for at least 48 hours. It is concluded that:

"This virus has distinct advantages as a vector for gene therapy because of the high rate of infection in terminally differentiated cells and because it does not promote an immune response. The application of these techniques to allografted hearts is expected to provide a means for achieving graft-specific immunosuppression."

4. Document (21) describes the stable **in vivo** expression of the normal cystic fibrosis transmembrane conductance

regulator (CFTR) cDNA carried by an adeno-associated virus. The recombinant vector is delivered in vivo to the lobe of a rabbit lung. The CFTR RNA and protein are detected in the airway epithelium (**not a muscle tissue**) of the infected lobe for up to 6 months after vector administration (abstract). It is concluded that:

"In summary, these observations show that a normal CFTR gene can be delivered in an AAV vector with high efficiency and result in stable expression in the relevant cell types both ***in vitro*** and ***in vivo***. AAV-CFTR vectors may hold promise as a gene therapy for CF ***(cystic fibrosis)***, since their potential for stable expression could make it possible to correct the basic pathophysiologic defect in the airway epithelium from an early age, prior to the onset of irreversible lung injury." ***(expression in brackets added by the board)***

5. In accordance with the case law, the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common (see e.g. T 606/89 of 18 September 1990).

6. Document (21) describes experiments which are directly aimed at gene therapy i.e. in vivo experiments whereas in document (4), the recombinant AAV vector is used in vitro in order to modify the properties of a means (the allograft) which will ultimately be used in vivo for "classical" therapy (grafting). In this respect, document (21) best fits the definition of the closest prior art. The teachings of both documents relate to a

recombinant AAV vector. The methods which they described each have a different essential technical feature in common with the claimed subject-matter. In case of the method of document (4), it is the use of a muscle tissue as recipient, although this tissue comes from smooth muscle whereas the gist of the present invention as described in the application is primarily to carry out gene therapy in striated muscle. In case of the method of document (21), the common feature is the mechanism of gene therapy per se which involves the direct transfer and expression of the relevant gene in the living organism.

Under these circumstances and taking into account the principle established in the case law, the board decides that the closest prior art is document (21).

7. Starting from the teachings of document (21), the problem to be solved can be defined as how to use recombinant AAV for the treatment by gene therapy of other diseases than cystic fibrosis.

8. The provided solution is to use recombinant AAV as a therapeutic means which is expressed in vivo from muscle tissue.

9. The board is satisfied that this is a bona fide solution to the above mentioned problem as the application (pages 13 to 16 of the originally filed document) shows that the injection of recombinant AAV carrying the LacZ gene in muscle tissue in vivo leads to the production of β-galactosidase (as a reporter protein) for as long as it was tested, namely five months (page 15 of the originally filed document), and

furthermore, it is to be expected that the protein will be delivered to other parts of the body by the host's vascular system.

10. Was it obvious or not to transfer the teachings of document (21) which concerns airway epithelium to muscle tissue? Here, it must be observed that the document itself contains no suggestion to this effect. On the contrary, as already mentioned in point 4, supra, the authors limit the promise held by the experiments which they describe to the treatment of cystic fibrosis. Furthermore, although AAV had been shown to display a broad host range including chicken, rodent, monkey and human cells (document (2), page 210), it was also known as a virus with a natural tropism for the upper respiratory system (document (26), page 38, Table 1, page 40, col.1, lines 7 to 9). In this framework, the appellant pointed out that airway epithelium comprises specialized polarized cells with distinct apical and basolateral membrane characteristics which were so different from the "otherwise specialized" muscle cells that the results obtained with the earlier kind of cells would not have suggested to the skilled person that they could be duplicated with the latter. Thus, the prior art did not make obvious to try a transfer of technology from airway epithelium to muscle cells.

11. If, for the sake of discussion, the opposite view is held, then it is necessary to assess whether or not the skilled person would have a reasonable expectation of success in using the recombinant AAV vector in gene therapy carried out in muscle tissue.

12. As regards the introduction and expression of the recombinant vector in muscle tissue, document (4) certainly provides a positive answer to this question since heart muscle tissue was indeed transfected with a recombinant AAV vector and the product of the LacZ reporter gene was expressed in the explants. Yet, this is not sufficient as a basis for acknowledging a reasonable expectation of success for the corresponding gene therapy. Indeed, the clinical situation created by gene therapy is different from the situation described in document (4) since a further most critical parameter comes into play, that is, the reaction of the living organism to the presence of the recombinant vector and the expression of, at least, the recombinant protein.

13. At the priority date, it was a matter of common general knowledge that the introduction of a "foreign" entity into a higher organism would necessarily trigger host defence mechanisms such as host immune responses which may ultimately destroy it. Thus the long-term transgene expression observed after transfection of recombinant AAV in muscle tissue (up to five months, page 15 of the application) was undoubtedly surprising. Indeed, this is reflected in post-published document (9), (page 4212):

"It was particularly surprising that AAV failed to elicit immune responses to highly expressed neoantigenic transgene products when injected into muscle (11,23, 45) whereas other vector systems expressing the identical transgene, such as adenovirus (52) and naked DNA, do."

and document (10), (abstract):

"Remarkably, no humoral or cellular immune responses are elicited to the neoantigenic transgene product *E.coli* β-galactosidase."

to be taken as experts' evidence.

14. Of course, one may then wonder why the sustained transgene expression (up to six months; document (21), abstract)) observed in the airway epithelium of a living organism should not be regarded as evidence that sustained transgene expression could equally take place in the muscle tissue. Here, appellant cited document (24), a review published in August 1995 summarising the existing state of the art around the priority date. In this review entitled "Anatomical Environment as a Determinant in Viral Immunity", it is mentioned on page 1023 that:

"..., the characteristics of the anatomical environment in which lymphocytes encounter Ag, then lodge after the phase of Ag elimination (or during Ag persistence), will influence the phenotype of both the acute phase and memory components of immunity",

Thus, a lack of immune response in airway epithelium would not necessarily be considered as indicative that the same lack of immune response would occur in muscle tissue.

15. For at least the reasons given in points 12 and 13, supra, the skilled person attempting to achieve gene therapy in muscle tissue with a recombinant AAV vector would not have had a reasonable expectation of success.

16. Twenty-six documents form the available state of the art in relation to the present application. Seventeen of them are intermediary or post-published documents. Four out of the nine prior art documents have been taken into account in this decision. The others relate to various aspects of gene therapy, to lung cells, to the AAV viral vector system or to experiments corresponding to those disclosed in document (4). While providing the necessary background to the understanding of the invention and the assessment of inventive step, they do not bring any further information likely to affect the above finding that the claimed subject-matter is inventive over the teachings of document (21) alone or in combination with those of document (4).

17. In view of the above, the requirements of Article 56 EPC 1973 are fulfilled. In the absence of any further objections the application and the invention to which it relates meet the requirements of the EPC. Thus, the appellant's request is allowable.

18. Oral proceedings were requested as an auxiliary measure if the board could not follow the appellant's argumentation regarding inventive step. Since the board concluded that the present invention involves inventive step, there was no need to appoint oral proceedings.

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 grant a patent on the basis of claims 1 to 12 filed as auxiliary request 1 on 2 October 2006 during oral proceedings before the examining division, and the description as originally filed.

The Registrar The Chairman

A. Wolinski L. Galligani