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D E C I S I O N
of 24 November 2005

Case Number: T 0871/04 - 3.3.08

Application Number: 94901544.0

Publication Number: 0668913

IPC: C12N

Language of the proceedings: EN

Title of invention:
Adenovirus-mediated Gene Transfer To Cardiac And Vascular Smooth Muscle

Patentee:
Arch Development Corporation

Opponent:
Collateral Therapeutics Inc.

Headword:
Gene transfer/ARCH

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main, first auxiliary and second auxiliary requests: inventive step (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0871/04 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 24 November 2005

Appellant: (Proprietor of the patent)	Arch Development Corporation 1101 East 58th Street Chicago, IL 60637 (US)
Representative:	Bublak, Wolfgang Bardehle, Pagenberg, Dost, Altenburg, Geissler Galileiplatz 1 D-81679 München (DE)
Respondent: (Opponent)	Collateral Therapeutics Inc. 11622 El Camino Real San Diego, CA 92130 (US)
Representative:	Armitage, Ian Michael Mewburn Ellis LLP York House 23 Kingsway London WC2B 6HP (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 3 May 2004 revoking European patent No. 0668913 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
U. Tronser

Summary of Facts and Submissions

I. The patentee (appellant) lodged an appeal against the decision of the opposition division of 3 May 2004 revoking the European patent No. 0 668 913. The patent, entitled "Adenovirus-mediated gene transfer to cardiac and vascular smooth muscle", was granted on European application No. 94 901 544.0 which originated from an international application published as WO 94/11506.

II. The patent had been opposed on the grounds as set forth in Article 100(a) EPC that the invention was not susceptible of industrial application within the meaning of Article 52(4) EPC, that it was not new and not inventive (Articles 54 and 56 EPC), and on the ground as set forth in Article 100(b) EPC that it was not sufficiently disclosed (Article 83 EPC).

III. Basis for the decision under appeal were a main request (namely, the claims as granted with two sets of claims, one for AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL and SE, and the other for PT) and a first and a second auxiliary request (each with two sets of claims as for the granted claims) then on file. The requests had been refused for the reasons that
(i) claim 1 of each set of the main request was not new under the provisions of Article 54(3) EPC and did not involve an inventive step (Article 56 EPC),
(ii) claim 1 of the set for all designated Contracting States except PT of the first auxiliary request contained added-matter (Article 123(2) EPC), and
(iii) claim 1 of the set for all designated Contracting States except PT of the second auxiliary request did not involve an inventive step (Article 56 EPC).

IV. With its statement of grounds of appeal, the appellant confirmed that the claims as granted were still its main request. The respondent (the opponent) filed observations to the patentee's appeal.

V. A communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal presenting some preliminary and non-binding views of the Board was sent to the parties.

VI. On 19 October 2005 the appellant submitted two auxiliary requests (in the two versions for all designated Contracting States except PT and for PT) which exactly corresponded to the first and second auxiliary requests on which the decision under appeal was based and filed two sets of new documents in support of its views, namely D16 to D20 and D21 to D31.

VII. Further submissions regarding the format of the second medical use claims were filed by the appellant. The respondent put forward a list of decisions of the Boards of Appeal on which it could rely.

VIII. Oral proceedings took place on 24 November 2005, at which a new main request and two auxiliary requests were filed by the appellant to replace all the previous requests.

Claim 1 of the main request for all designated Contracting States except PT read:

"1. Use of an adenovirus vector construct, comprising a coding sequence that encodes a gene product desired for

introduction into a cardiac muscle cell, for manufacturing a medicament for effectively inducing expression of said gene product in said cardiac muscle cell, wherein said medicament is for infusion into a coronary artery."

Claim 1 of the first auxiliary request for all designated Contracting States except PT read:

"1. Use of an adenovirus vector construct, comprising a coding sequence that encodes a gene product desired for introduction into a cardiac muscle cell, for manufacturing a medicament for the treatment of a cardiovascular disorder by effectively inducing expression of said gene product in said cardiac muscle cell, wherein said medicament is for infusion into a coronary artery." (emphasis added by the Board to show the difference with respect to claim 1 of the main request)

Claim 1 of the second auxiliary request for all designated Contracting States except PT read:

"1. Use of an adenovirus vector construct, comprising a coding sequence that encodes a gene product desired for introduction into a cardiac muscle cell for manufacturing a medicament for the treatment of cardiac diseases by effectively inducing expression of said gene product in said cardiac muscle cell, wherein said medicament is for infusion into a coronary artery." (emphasis added by the Board to show the difference with respect to claim 1 of the main request)

IX. At the oral proceedings it was decided to admit documents D16 to D20 into the procedure whereas no decision was taken as to the admissibility of documents D21 to D31 into the procedure as the appellant refrained from relying on those documents.

X. The following documents are cited in the present decision:

(D1) Leslie D. Stratford-Perricaudet et al., J. Clin. Invest., Vol. 90, August 1992, pages 626 to 630

(D5) Melissa A Rosenfeld et al., Science, Vol. 252, 19 April 1991, pages 431 to 434

(D8) Melissa A. Rosenfeld et al., Cell, Vol. 68, 10 January 1992, pages 143 to 155

(D9) Leslie D. Stratford-Perricaudet et al., Hum. Gene Ther., 1990, Vol. 1, pages 241 to 256

(D10) H.A. Jaffe et al., Nature Genetics, Vol. 1, August 1992, pages 372 to 378

(D11) L. D. Stratford-Perricaudet et al., Bone Marrow Transplant., Vol. 9, Suppl. 1, 1992, pages 151 and 152

(D13) Chang S. Lim et al., Circulation, Vol. 83, No. 6, June 1991, pages 2007 to 2011

(D16) Cindy L. Grines et al., Circulation, Vol. 105, 2002, pages 1291 to 1297

(D17) Cindy L. Grines et al., Vol. 42, No. 8, 2003, pages 1339 to 1347

(D18) Cindy Grines et al., Am. J. Cardiol., Vol. 92 (suppl), 2003, pages 24N to 31N

(D19) Mei Hua Gao et al., Human Gene Therapy, Vol. 15, June 2004, pages 574 to 587

(D20) WO 98/50079 (published on 12 November 1998)

XI. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Inventive step (Article 56 EPC)

Document D1 described a gene delivery protocol which in reality would not be applicable to the treatment of cardiac diseases. This was because only such a small percentage as 0.2% of the cardiac cells had undergone gene transfer after intravenous injection of 10^9 pfu of virus. Moreover, it remained unclear how many of the cardiac muscle cells, namely the myocytes, compared to the other types of cells present in the heart, had been actually infected. When entering the heart ventricle the virus attached not to cardiac muscle cells which were located within the myocardium but to endothelial cells of the endocardium. Thus, the technical problem could not be defined as the provision of an alternative route of administration of an adenovirus to target the heart other than the intravenous administration.

In the patent for the first time a clinically applicable technique for the *in vivo* gene transfer and

expression into the myocytes using a recombinant adenovirus was disclosed. This technique relied on an infusion of the adenovirus into a coronary artery.

Document D11 was a document discussing experimental results reported in previous documents only. Insofar as the heart was concerned, it stated nothing more than that the intravenous route of administration had been found to allow a distribution of the adenovirus vector throughout the different tissues of the tested mice, including the heart, and that using this administration route the cardiac muscle would be amenable to gene transfer.

XII. The respondent's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Inventive step (Article 56 EPC)

Reading document D11 which, when commenting on the experiments of document D1 (see bottom of page 151 of D11), stated that a substantial percentage of cells from lung, liver, intestine, heart, and skeletal muscle were infected, the skilled person would have understood that a number of cardiac muscle cells sufficient to render plausible a gene therapy had been infected.

From the mentioning of myocardial cells expressing the transferred gene on page 629 of document D11, it was clear that cardiac muscle cells were infected by the adenovirus and the protein expressed in those cells.

Example 2 of the patent described nothing more than what was already known in the state of the art. Only a marker protein, not a protein of therapeutic interest had been expressed in the infected cells. No level of expression had been measured.

XIII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of either the main request or auxiliary request 1 or 2 all filed during the oral proceedings.

XIV. The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

Procedural matters

Admissibility of "late filed" documents into the procedure

1. The appellant has filed *inter alia* documents D16 to D20 on 19 October 2005, i.e. within the time limit fixed in the Board's communication accompanying the summons to oral proceedings scheduled on 24 November 2005. The respondent argued that none of those documents, which were all published years after the filing date of application WO 94/11506, should be introduced into the proceedings for the only reason that they had been late filed.

2. Although, in principle, an appeal should be essentially based on facts and evidence which were already

available to the department of the first instance, parties in their effort to make a full statement of the grounds why the revision of the contested decision is requested often rely on additional evidence. Such evidence is not necessarily defined as being "late-filed". Much depends on its *prima facie* relevance, the Board being empowered essentially either (i) to disregard it under Article 114(2) EPC or (ii), having admitted it, either to remit the case to the department of first instance under Article 111(1) EPC for further prosecution, or to decide on the case.

3. In the present case, the Board, exercising its discretion, decided in the course of the oral proceedings to admit documents D16 to D20 for the following reasons:

4. Documents D16 to D18 report on randomized, double-blind, placebo controlled clinical trials of intracoronary injection of an adenovirus vector construct (Ad5FGF4) in patients with stable angina pectoris to determine the effect on myocardial perfusion. Document D19 is a study providing preclinical data on a model of myocardial ischemia in pigs that supported the initiation of the clinical trials of intracoronary administration of Ad5FGF4 reported in documents D16 to D18. Document D20 describes similar preclinical assays also using porcine models. As a whole, these documents illustrate with great detail how the use of an adenovirus vector construct of claim 1 had been reduced into practice on the basis of the teaching of the patent. Therefore, although not being decisive for the outcome of the present appeal, they were considered of

interest for a better understanding of the claimed invention.

5. As for the further documents D21 to D31, no decision as regards their admissibility had be taken since the appellant, who had filed them, refrained from relying on them.

Key issue to be dealt with

6. The Board finds it expedient to deal with the key question whether the use of an adenovirus vector construct of claim 1 involves an inventive step in the light of the state of the art and to leave aside the issue of compliance of the request with the requirements of Articles 52(4) and 123 EPC.

Inventive step (Article 56 EPC)

7. The claimed invention, whatever the requests on file, is primarily concerned with gene therapy applied to the treatment of cardiac diseases, the methodology involved relying on the infusion into a coronary artery of an adenovirus vector construct comprising a coding sequence that encodes a gene product to be introduced and expressed into cardiac muscle cells. Claim 1 of each request is in the format of a second medical use claim wherein the way of administration, i.e. infusion into a coronary artery, constitutes the main characterising feature. Claim 1 of the second auxiliary request being precisely centred on the treatment of cardiac diseases and falling under the scope of claim 1 of each of the main and the first auxiliary requests,

the reasoning on inventive step will be made on the basis of claim 1 of the second auxiliary request.

8. Document D11 is regarded as the closest state of the art. It is a review compiling findings made in the scientific literature, including in particular documents D1, D5, D8 and D9, cited as references 3, 6, 7 and 4 respectively in the document, regarding the feasibility of adenovirus-mediated gene transfer *in vivo*. It reports that several routes of administration have been explored, in particular the intravenous (see D1 and D9) and the intratracheal (see D5 and D8) routes.

8.1 Regarding the experiments reported in document D1, document D11 states that using the intravenous route of administration allowed a distribution of the viral vector throughout the different cells of the injected neonatal mice and that the extent of blue staining marking the expression of the transfected gene encoding β-galactosidase had revealed that a substantial percentage of cells from lung, liver, intestine, **heart** and skeletal muscle had been infected. Furthermore, document D11 stresses that it had been proved that using this route a single injection of the recombinant virus had sufficed to obtain efficient gene transfer and to target the muscle tissues, **heart** included, and that this had serious implications for therapeutic applications.

8.2 Regarding the experiments reported in document D9, document D11 states that these experiments, conducted on mice having an inherited defect on ornithine transcarbamylase (OTC) protein synthesis, were the first documenting the feasibility of using adenovirus

for the direct *in vivo* long-term delivery of a gene resulting in the restoration of an impaired metabolism.

8.3 Regarding the experiments of documents D5 and D8, document D11 states that two adenovirus vectors, the one having a gene encoding the human α1-antitrypsin (α1AT) and the other a gene encoding the human cystic fibrosis transmembrane conductance regulator (CFTR), had been used to specifically evaluate pulmonary gene transfer. After tracheal instillation of the recombinant viruses, it had been demonstrated that gene delivery to the rat respiratory epithelium *in vivo* was possible and that expression of the encoded protein lasted at least six weeks.

9. Thus, document D11 would have offered the skilled person a broad panorama of the use of adenovirus vector constructs in gene therapy with preliminary hopeful results. Not only would the skilled person have noticed that such vectors could be successfully administered using a plurality of routes, he/she also would have been impressed by the successful targeting of an organ as the result of an administration in the direct proximity to that organ (as initially reported, for example, in the cited document D5 which shows the transfection of lungs upon intratracheal instillation).

10. In view of this state of art, the technical problem to be solved by the invention may be regarded as being the provision of an alternative administration route, other than the intravenous one, to transfer a gene encoding a gene product of therapeutic interest into the cardiac muscle cells. The solution of this technical problem is the use of an adenovirus vector construct according to

claim 1 of the second auxiliary request which relies on an infusion into a coronary artery.

11. The question to be answered is whether the use of such an administration route would have been obvious to the skilled person.

12. From document D11, the skilled person facing the aforementioned technical problem would immediately have derived the notion that the targeting of a specific organ could be achieved by introducing an adenovirus-vector carrying a gene encoding a protein of therapeutic interest in close proximity to that organ. As this notion is also supported by an additional document of the state of the art, namely document D10, which reports the adenovirus-mediated *in vivo* gene transfer and expression in rat liver upon intraportal administration, the skilled person would definitely have decided to look for a point of injection in close proximity to the heart.

13. Thinking of an appropriate point of injection in close proximity to the heart the skilled person would readily have had in mind the coronary arteries, i.e. those vessels which supply the blood to the heart. These were not an unusual way of delivering a gene construct also in view of the treatment of cardiovascular disease as shown e.g. by prior art document D13 which describes the successful liposome-mediated gene transfer and expression into segments of the left anterior descending **coronary artery** in the dog achieved by flushing the lumen of these segments with a transfection solution made of a luciferase plasmid DNA plus a liposome preparation. Therefore, the skilled

person would have found in the state of the art an incentive to conceive that administration of a vector carrying a gene encoding a protein of therapeutic effect into a coronary artery in close proximity to the heart would have allow the precise targeting of the cardiac muscle cells. Thus, arriving at the solution proposed in claim 1 does not involve the exercise of inventive skill, as this was one of the obvious options open to the skilled person.

14. The appellant has argued that the technical problem could not be defined as the provision of an alternative route of administration of an adenovirus to target the heart because the intravenous administration presented *per se* problems which still had to be solved before looking for alternatives. In fact, as reported in document D1 and thereafter commented in document D11, this route would not have permitted an effective induction of expression of a protein of therapeutic interest in the cardiac muscle cells, because only a small percentage of those cells would have been transfected. In support of its view, the appellant has pointed to the admission made in document D1 that approximately 0.2% of cardiac cells had undergone gene transfer after iv injection of 10^9 pfu of virus (see the sentence bridging the columns of page 527), notwithstanding the fact that, moreover, among these cardiac cells many of them were not myocytes.

15. This argument by the appellant is not tenable as it imposes to the prior art a standard different from that applied to the own patent specification. In fact, the only working example illustrating in some way the use of claim 1 is Example 2 (see paragraphs 0081 to 0083),

which essentially relies on the observation of some **unquantified** β-galactosidase activity in the coronary vascular smooth muscle (in the vasculature associated to the heart) and in cardiac muscle cells in rabbits killed 5 to about 21 days after the intracoronary infusion of an adenovirus carrying a gene encoding that marker protein, a protein which, moreover, as such is not capable of any therapeutic effect.

16. The appellant has also argued that the approach reported in document D13 would not be applicable to humans. This is considered irrelevant as document D13, irrespective of the experimental details, which of course were specifically tailored to a veterinary experiment, is merely indicative of prior art suggestive of the feasibility of the *in vivo* gene transfer into coronary arteries aiming at the localised production of therapeutically important proteins for the treatment of cardiovascular diseases.

17. Therefore, the Board comes to the conclusion that claim 1 of the second auxiliary request does not involve an inventive step within the meaning of Article 56 EPC.

18. As claim 1 of the second auxiliary request falls under the scope of claim 1 of each of the main and the first auxiliary requests, also those two requests do not meet the requirements of Article 56 EPC.

19. Thus, none of the three requests on file could form a basis for the maintenance of the patent in an amended form.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani