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Datasheet for the decision of 3 April 2008

Case Number: T 0113/07 - 3.3.08

Application Number: 90910074.5

Publication Number: 0431135

IPC: C12N 15/87

Language of the proceedings: EN

Title of invention:
Particle-mediated transformation of animal somatic cells

Patentee:
Powderject Vaccines, Inc.

Opponent:
Vical Incorporated

Headword:
Animal cells transformation/POWDERJECT VACCINES

Relevant legal provisions:
EPC Art. 123(2), 56, 83
RPBA Art. 12

Relevant legal provisions (EPC 1973):
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Keyword:
"Main request - added subject-matter -no"
"Inventive step - yes"
"Sufficiency of disclosure - yes"

Decisions cited:
G 0010/91, T 0606/89, T 0455/91

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0113/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 3 April 2008

Appellant: (Patent Proprietor)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 6 November 2006 revoking European patent No. 0431135 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
C. Heath

Summary of Facts and Submissions

I. European patent No. 0 431 135 with the title "Particle-mediated transformation of animal somatic cells" was granted with 4 claims based on the International patent application No. PCT/US90/03522 published as WO 91/000359.

Granted claims 1 to 4 read as follows:

"1. Carrier particles for use in a method of therapy by genetic transformation *in vivo* of somatic cells in the skin of a living animal, wherein the particles are of dense material, are small relative to the size of the said cells, and are coated with copies of an exogenous genetic construction that includes a protein-coding DNA sequence and flanking regulatory sequences effective to express the protein in the said cells.

2. Particles according to claim 1, which are of gold.

3. Particles according to claim 2, which are 1-3 μm in size.

4. Particles according to any preceding claim, wherein the living animal is a human being."

II. An opposition was filed under Article 100(a) to (c) EPC. The opposition division revoked the patent pursuant to Article 102(1) EPC for failing to fulfil the requirements of Article 123(2) EPC (main request) and for lack of inventive step (Article 56 EPC; first auxiliary request).

III. The appellant (patentee) filed a notice of appeal and submitted a statement of grounds of appeal which was accompanied by a main request and seven auxiliary requests in replacement of the requests on file.

The **main request** comprised two claims which read as follows:

"1. Gold particles for use in a method of therapy by genetic transformation *in vivo* of somatic cells in the skin of a living animal, wherein the particles are 1-3 μm in size and are coated with copies of an exogenous genetic construction that includes a protein-coding DNA sequence and flanking regulatory sequences effective to express the protein in the said cells.

2. Particles according to claim 1, wherein the living animal is a human being."

IV. The respondent (opponent) filed a written submission in answer to the statement of grounds of appeal.

V. The board sent summons to oral proceedings to take place on 3 April 2008 together with a communication indicating its preliminary, non-binding opinion.

VI. On 3 March 2008, the appellant and the respondent informed the board that they would not take part in the oral proceedings. The respondent also withdrew its request for oral proceedings.

VII. The oral proceedings were cancelled on 31 March 2008.

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

(13) : Sanford, J.C. et al., Particulate Science and Technology, Vol. 5, pages 27 to 37, 1987;

(14) : Sanford, J.C., Tibtech, Vol.6, pages 299 to 302, December 1988;

(18) : Zelenin, A.V. et al., FEBS Letters, Vol. 244, No. 1, pages 65 to 67, February 1989;

(27) : Cline, M.J., The American Journal of Medicine, Vol. 83, pages 291 to 297, August 1987;

(28) : Ulmanen, I and Kallio, A., Annals of Clinical Research, Vol. 18, pages 316 to 321, 1986.

IX. The appellant's arguments insofar as relevant for the present decision may be summarized as follows:

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

There was a basis in the application as filed for the use of coated gold particles in the absence of mention of physical acceleration and of a specific apparatus. The "field of invention" and the "background of the invention" sections disclosed transformation in general without any limitation. The fact that the particles of

the invention could be used in transformation in general was also apparent from page 4, lines 11 to 15 and page 6, lines 23 to 26.

Article 56 EPC, inventive step

According to the opposition division, the closest prior art was document (14), a review article on biolistic delivery which discussed initial work on plants and mentioned the possibility that the technique might be applicable to living animals in the future.
The technical problem to be solved from document (14) could be formulated as the provision of a new way to transform somatic cells in the skin of a living animal.
The solution to the technical problem was to employ gold particles coated with an exogenous genetic construction that included a protein-coding DNA sequence and flanking regulatory sequences effective to express the protein in the cells.
The skilled person who was conservative and cautious in nature would not have found it obvious to try applying biolistic delivery to somatic animal cells, all the more so that the central paradigm at that time as regards animal transformation was to remove cells from the body, introduce genes and then return them to the body (documents (27) and (28)). The structural differences between plant cells and the skin of an animal would also imply that no reasonable expectation of success existed in carrying out such a process.
Furthermore, the suggestions in documents (13) and (14) of transferring the technique of biolistic delivery from plants to animals would have been considered as wildly speculative. These documents themselves

demonstrated a lack of reasonable expectation of success for such a transfer.
For these reasons, inventive step should be acknowledged.

Article 83 EPC; sufficiency of disclosure

The examples in the patent showed that it was possible to safely and effectively transform somatic cells in the skin of a living animal, achieving successful expression of genes. No evidence had been provided that the claimed subject-matter could not be put into practice. The requirement of sufficiency of disclosure was satisfied.

X. The respondent's arguments insofar as relevant for the present decision may be summarized as follows:

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

The subject-matter of claim 1 of the main request represented an intermediate generalisation for which there was no direct and unambiguous disclosure in the application as filed. The general disclosures referred to by the patentee were not sufficient to meet the requirements of Article 123(2) EPC.

Article 56 EPC, inventive step

The claimed subject-matter represented nothing more than an obvious approach for the skilled person given the disclosure of document (14), bearing in mind also document (13). In relation to the "plant vs. animal"

discussion in the proprietor's submissions, it must be said that while plants used to be considered "special" in patent circles and a number of patents had initially been granted for work in patents that bore a strong analogy with prior work in animals, the EPO had seen through this some years ago and many of those patents were revoked (eg. T 455/91, OJ EPO 1995, 684).
The prior art itself (cf. documents (13) or (14)) explicitly suggested applying to animals the technique which had been successfully applied in plants, making the requisite modification or adjustment to allow application to the skin. In the patent, the only modification brought to the transformation was precisely to adapt the transforming device for delivery to the skin.
Furthermore, documents (13) and (14) referred to other techniques in the art. Knowledge of variation in efficiency of other techniques would indicate that the skilled person would not be required to expect "spectacular" success in order to be motivated to try the ballistic approach taught in the prior art.

Article 83 EPC, sufficiency of disclosure

The claim extended beyond the specifically disclosed means for delivery of particles. The nature of the particles was only vaguely defined. There was no limitation as to how the particles were coated with copies of an exogenous genetic construction. There was no teaching or demonstration as to how to apply the biolistic technique to particles other than those experimentally exemplified. There was no teaching or demonstration as to how to achieve genetic transformation in somatic cells without ensuring that

the particles entered the cells. There was no technical basis for any route of administration to result in genetic transformation of somatic cells in the skin - all routes being comprised within the claim. In short, the claim extended significantly beyond any possible contribution to the art, even on the proprietor's own assertions of patentability of its ballistic delivery of gold particles using electric discharge. The requirements of Article 83 EPC were not fulfilled.

XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained with the claims of the main request or, in the alternative, the claims of one of auxiliary requests 1 to 7 filed with the statement of grounds of appeal.

The respondent requested that the appeal be rejected and the patent be revoked.

Reasons for the decision:

Main request
Article 123(2) EPC; amendments

1. The application as filed discloses as follows:

- page 4, lines 28 to 30: "The present invention is directed towards the transformation of the somatic cells of animals or human beings ..."
- page 5, lines 2 and 3: "Preferred target tissues include skin..."

- page 5, lines 31 to 33: "The invention is directed towards the introduction of exogenous, often chimeric , genetic constructions into animal somatic cells."
- page 5, line 38 to page 6, line 4 : "The exogenous DNA construction would normally include a coding sequence for a transcription product or a protein of interest, together with flanking regulatory sequences effective to cause the expression of the protein..."
- page 7, lines 15 to 20: "In its use, the exogenous foreign gene construct intended to be transformed into the animal somatic cells is [....] dried onto small particles of a durable dense material such as gold, the particles typically being 1 to 3 microns in size."

2. It can also be understood from the following statement on page 2, lines 6 to 12: " The genetically engineered somatic cells offers the ability to make genetic corrections for inherited genetic disorders [...]. It is also possible that such genetic transformations of somatic cells, and not germ line cells, may be desirable for certain therapeutic applications.", that the gold particles are for use in a method of therapy. The application to humans is disclosed on page 2, lines 2 to 5.

3. Accordingly, in the board's judgment, the application as filed discloses gold particles for use in a method of therapy as is now claimed in claims 1 and 2.

4. The respondent's argument that the claimed "subject-matter is an intermediate generalisation for which there is no direct and unambiguous disclosure in the application as filed" is understood as meaning that the requirements of Article 123(2) EPC are not fulfilled

because the feature that the gold particles are delivered to their target by means of an electric discharge is not included in the claim. Whereas the latter is true, it remains nonetheless that the application as filed discloses gold particles for use for the transformation in vivo of somatic cells in the skin of a living animal as is now claimed (see supra). In fact, the argument rather seems to be an argument under Article 84 EPC that the feature of using an electric discharge to propel the gold particles would be an essential feature. This feature is, of course, not a characterising feature of the gold particles per se. And besides, in opposition and appeal proceedings, objections under Article 84 EPC may only be raised in relation to amendments **then** brought into the claims (see Enlarged Board's decision G 10/91, (OJ EPO 1993, 420)). Omitting the mode of delivery is not one such amendment as the feature already failed to be present in the granted claims. The argument is, thus, not valid. The requirements of Article 123(2) EPC are fulfilled.

Article 56 EPC

5. In accordance with the case law, the closest prior art is a 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 (eg. T 606/89 of 18 September 2000).

6. Document (18) discloses tungsten particles coated with DNA expressing a protein, for the biolistic transformation of animal cells, namely **cultured** NIH 3T3

mouse cells. For this reason, it is considered as being the closest prior art.

7. Starting from document (18), the problem to be solved can be defined as applying biolistic transformation to further animal cells.

8. The solution provided is to use gold particles coated with DNA expressing the relevant protein to transform **somatic** cells of a **living** animal, this being expressed in the form of a "first medical use" type of claim.

9. At the priority date, the field of animal transformation was already well developed. Several methods had been tried which are reviewed in documents (27), pages 292 to 295, and document (28), pages 316 to 318. Both these documents identify the most promising transformation system as being the use of retroviruses. Calcium phosphate precipitation, DEAE dextran, liposome transformation, electric shock are cited as transfection methods with lower efficiency. In document (27), chromosome mediated gene transfer and microinjection of DNA into the nuclei of the target cells are also discussed. However, none of these documents refer to the use of DNA coated particles.

10. In fact, the suggestion to use biolistic transformation with live animal cells comes from an entirely different field, namely that of plant transformation (documents (13) and (14)).
Document (13) describes the concept of a macron accelerator as a biological delivery system and teaches how onion cells may be transformed by using such a

device (pages 29 and 30). In the conclusion part of the article, pages 35 and 36, it is mentioned that:

"The particle bombardment process **may** play a vital role in several areas of research including [...] human gene therapy.". "The particle gun process [...] **might** provide the unique capability of transforming human tissues, in situ." (emphasis added by the board).

Document (14) also discloses the application of the biolistic process to plants. Under the headings "Current research needs" and "Expected developments" (page 302), it is said:

"There are important applications for the biolistic process which appear feasible, **but have not yet been demonstrated**: [...], intact animal tissue transformation, [...]". "Some key proof-of-concept experiments, such as animal epidermal delivery, **may** take place during the next twelve months." (emphasis added by the board).

11. Yet, under the first of these headings, the following observation is also made:

"There is a great need for refinement and optimization of the process. Currently, there is poor control over size, aggregation, coating, quantity dispersal and velocity of particles [...]. This will require substantial further efforts in engineering."

12. In the board's judgment, both these documents are merely speculative in nature. They at best convey the assumption that biolistics might be used on cells of a

living animal. At worst, they give a clear warning that much improvements are needed before it can even be envisaged to use biolistics for other purposes than plant transformation. Thus, taking into consideration that the person skilled in the art of transforming live animal cells did not consider biolistics as a possible means for transformation (see documents (27) and (28) supra), the board doubts that the teachings in documents (13) or (14) on their own could be regarded as making obvious that animal cells transformation by biolistics ought to be tried.

13. If for the sake of argument, one accepts that the documents (13) and (14) provide the required incentive, then there remains to be assessed whether the skilled person would have a reasonable expectation of success when trying the experiment. Document (14) clearly points out to the shortcomings of biolistics as a method of transformation (supra). Furthermore, the skilled person would be well aware of the structural differences between plant cells and the skin of a living animal and, also, between animal cells in culture and normal animal tissue. In the board's judgment, these differences will shed doubts as to the possibility of a successful transfer of the biolistic technology to animal tissues.

14. In its answer to the appellant's grounds of appeal, the respondent mentioned the decision T 455/91 (supra) as evidence that the technology transfer from one organism to another should be regarded as non-inventive. In this earlier decision, the then competent board concluded that the skilled person working in one field would regard a means conveniently adapted in a neighbouring

field as being readily usable also in that field, if this transfer of technical knowledge involved nothing out of the ordinary. Inventive step was, thus, denied to a DNA vector suitable for expression in yeast cells having features equivalent to a known DNA vector for expression in E.coli because the skilled person knew how to adjust the technical teaching from the adjacent neighbouring field. The present situation is, however, different, insofar as the skilled person has no prior knowledge of how to adjust the technical teaching of transforming plant cells. Indeed, as already above mentioned, the structural differences between the different types of cells involved may affect the transformation process in an hitherto unforeseeable manner.

15. For the reasons given in points 6 to 12, supra, inventive step is acknowledged.

Article 83 EPC; sufficiency of disclosure

16. On appeal, the respondent did not provide any arguments as regards sufficiency of disclosure/lack thereof, simply referring to "our written submissions in the Opposition proceedings, including the original Opposition Statement and our letter of 1 September 2006".

17. The Rules of Procedure of the Boards of Appeal (RPBA) require under Article 12 (formerly Article 10a)), paragraph (2) that:

"The statement of grounds of appeal and the reply shall contain a party's complete case. They shall set out

clearly and concisely the reasons why it is requested that the decision under appeal be reversed, amended or upheld, and should specify expressly all the facts, arguments and evidence relied on".

18. In the board's judgment, the mere cross-reference to written submissions which were made in the opposition proceedings cannot amount to a "complete case" and it certainly does not set out clearly all the facts, arguments and evidence relied on. Since the respondent's reply does not comply with said article of the RPBA which, in paragraph (4) also states that "without prejudice to the power of the Board to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the first instance proceedings, everything presented by the parties under (1) shall be taken into account by the board **if and to the extent it relates to the case under appeal and meets the requirements in (2).**" (emphasis added by the board), the board is not required to take into account the scant reference to the opposition proceedings made by the respondent.

19. Nonetheless, as this point has not been raised earlier on, the board did consider the respondent's submissions in the opposition statement of 12 December 2003 and the letter of 1 September 2006. The earlier submissions (see section X supra) were made in relation to a much broader claim than present claim 1 and do not apply to this claim. As for the latter submission, it solely contains the objection that "the Proprietor argues for an (alleged) invention that it is not claiming". The board does not see this remark as being meaningful to sufficiency of disclosure.

20. Quite to the contrary, the patent in suit provides detailed examples of how to produce the relevant genetic constructs and how to transform somatic cells in vivo with DNA-coated gold particles (mouse, amphibian, rat cells).

21. For this reason, and in the absence of any evidence to the contrary, the board concludes that the requirements of Article 83 EPC are fulfilled.

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 and 2 filed as main request with the grounds of appeal on 16 March 2007 and a description and figures to be adapted thereto.

The Registrar The Chairman

A. Wolinski L. Galligani