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D E C I S I O N
of 5 June 1997

Case Number: T 0856/94 - 3.3.4

Application Number: 90901328.6

Publication Number: 0449948

IPC: A61K 35/00

Language of the proceedings: EN

Title of invention:
Grafting genetically modified cells to treat diseases of the central nervous system

Applicant:
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

Opponent:
-

Headword:
Cell grafting/REGENT OF UC

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

Keyword:
"Clarity - claim 1 defined by functional features (yes)"
"Inventive step (yes - no reasonable expectation of success)"

Decisions cited:
T 0292/85, T 0296/93, T 0068/85, T 0694/92

Catchword:
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Case Number: T 0856/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 5 June 1997

Appellant: THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
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Decision under appeal: Decision of the Examining Division of the European Patent Office dated 3 June 1994 refusing European patent application No. 90 901 328.6 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

I. European patent application No. 90 901 328.6, filed as International Application No. PCT/US89/05557 and claiming priority from US 285 196 was published under the International Publication number WO 90/06757.

II. The application was refused by a decision of the Examining Division. That decision was based on a set of 29 claims as filed on 12 March 1993, replacing an originally filed set of 23 claims drafted as "methods of treatment" found by the Examining Division to be unacceptable, of which claim 1 read as follows:

"1. The use of genetically modified donor cells for the preparation of a therapeutic agent which produces a functional molecule in a sufficient amount to ameliorate defective, diseased or damaged cells in the mammalian central nervous system."

Dependent claims 2 to 29 were directed to specific embodiments of the use of claim 1.

III. One of the reasons for the refusal was that the subject-matter of claim 1 did not meet the requirements of Article 56 EPC in view of documents (1) and (4):

(1) Gage et al., Neuroscience Vol. 23, pages 795 to 807 (1987)

(4) Friedmann et al., Gene transfer and Gene Therapy, Alan Liss Inc., pages 409 to 416 (1989).

More specifically, the Examining Division came to the conclusion that the solution proposed in claim 1 of the application in suit to the problem of ameliorating defective, diseased or damaged cells in the mammalian

central nervous system (CNS) by using genetically modified donor cells which produced a functional molecule, was obvious in view of documents (1) and (4).

Document (1) recited (see the abstract): "We suggest that a combination of these two approaches, namely the grafting into the CNS of genetically modified cells, may provide a new approach toward the restoration of some functions in the damaged or diseased CNS. We present evidence of the feasibility of this approach including a description of some current techniques for mammalian cell gene transfer and CNS grafting, and several possible approaches to clinical application."

Document (4), which the Appellant did not dispute to be a post published transcript of an oral disclosure made at a public meeting before the priority date of the present application, recited on page 415, last paragraph: "The implantation of genetically modified cells into mammalian brain is likely to be an effective method of complementing some kinds of genetic or developmental defects...".

Thus the teachings of these documents would have led the skilled person not only to try treating patients suffering from cell damage of the CNS with genetically modified donor cells, but to do so with a reasonable expectation of success.

IV. Claim 1 was also found not to fulfil the requirements of Article 84 EPC because it was defined in terms of the result to be achieved rather than by means of technical features necessary for solving the problem which the present application intended to solve.

V. An appeal was filed, the fees paid and the written statement setting out the grounds of appeal comprised a new set of 34 claims. Claim 1 read as follows (amendments in respect of claim 1 as filed on 12 March 1993 are shown):

"1. The use of genetically modified donor cells **transfected with a vector comprising a gene encoding a functional therapeutic molecule**, for the preparation of a therapeutic agent ~~which produces a functional molecule in a sufficient amount to ameliorate~~ for ameliorating defective, diseased or damaged cells in the mammalian central nervous system."

Dependent claims 2 to 34 were directed to specific embodiments of the use of claim 1.

VI. During the oral proceedings held on 5 June 1997, the Board expressed its concern that claim 1 might not comprise a clear distinguishing feature vis-à-vis the teaching of document (1). In response thereto, the appellant submitted a new set of 33 claims, of which claim 1 was worded as follows (amendments in respect of claim 1 as filed on 12 March 1993 are shown):

"1. The use of genetically modified donor cells **transfected with a vector comprising a gene encoding a functional therapeutic molecule**, for the preparation of a therapeutic agent ~~which produces a functional molecule in a sufficient amount to ameliorate~~ for ameliorating defective, diseased or damaged cells in the mammalian central nervous system, **wherein said genetically modified donor cells after transplantation release either said encoded functional molecule or a product thereof which effect said amelioration.**"

The Appellant submitted that the expression newly introduced at the end of claim 1 included two technical features distinguishing claim 1 from the teaching of document (1), namely the therapeutic functional molecule was released and directly or indirectly exerted a therapeutic effect on the brain's diseased cells. The molecules expressed by the donor cells of document (1) were mere markers (labels) which were neither released, nor therapeutic agents.

VII. The Appellant essentially argued as follows:

Article 84 EPC

- Claim 1 now recited technical features and was clear. To further limit claim 1 to the exemplified molecules would unduly limit the scope of the claims given the impact of the invention on the art. It was requested that the same standard as in decision T 292/85 (OJ EPO 1989, 275) be applied to the present case.

Inventive step

- Document (1) was merely concerned with transplanted donor cells which expressed a marker. The document did not show that a functional molecule encoded by a gene could effectively be released in the CNS and be able to achieve a therapeutic effect. It was true that the authors of documents (1) and (4) envisaged using at some time in the future therapy strategies relating to the present invention, however, before the priority date of the present application, there was no clue as to whether said therapy might have worked. In other words, there was no expectation of success because the experimental findings of documents (1) and (4) did not answer the following

questions: (i) will the gene product be exported from the host cell?; (ii) will it interact with said target cell?; (iii) will it induce a therapeutically measurable effect on the brain's diseased cells?.

VIII. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the request submitted at the oral proceedings on 5 June 1997.

Reasons for the Decision

Article 123(2) EPC

1. New claim 1 differs from claim 1 as filed on 12 March 1993 by the additional features that the genetically modified donor cells are characterized by being "transfected with a vector comprising a gene encoding a functional therapeutic molecule". A basis for this wording is to be found in the application as filed (see page 15, lines 4 to 9 of the second paragraph) as well as in previous claim 5. The expression "wherein said genetically modified donor cells after transplantation release either said encoded functional molecule or a product thereof which effect said amelioration" finds a basis on page 15, lines 7 to 12 and page 29, lines 1 to 7 of the application as filed ("..uptake by target cells of secreted donor cell gene product or metabolite").

New claim 5 is based on previous claim 6 as filed on 12 March 1993, which has been amended in line with the amendments effected in new claim 1. Furthermore, the term "preferably" has been inserted before "retroviral" because the previous wording "...the group consisting

of viral, retroviral and neurotropic virus.." was confusing since, while retroviral and neurotropic viruses are sub-classes of viruses, no "viral" virus exists.

The remaining claims correspond to previous claims, with back references amended if necessary.

No objection according to Article 123(2) EPC thus arises.

Article 84 EPC

2. It has to be decided whether present claim 1 fulfils the requirements of Article 84 EPC. The Examining Division took the view that the skilled person had to overcome the series of technical problems listed on page 9 of the applicant's letter of 22 February 1991 submitted at the USPTO, in order that the therapeutic molecule recited in claim 1 be effective. These were:

1. Selection of an appropriate donor cell;

2. Development of growth conditions for the cell;

3. Selection of a vector and gene expression elements for modifying the donor cells;

4. Selection of the gene to be transferred to the donor cells and expressed in a host for amelioration of disease;

5. Determination of the assay time to detect expression of the gene transfer;

6. Selection of locations in the CNS for the implantation of the modified donor cell;

7. Determination of the number of modified donor cells to use in transplantation.

Claim 1 was, however, not drafted in terms of technical features which were necessary for solving the above technical problems but rather in terms of the result to be achieved.

3. The Board, however, is of the opinion that all these technical problems (1) to (7) listed on that page 9 have **already** been overcome through the experimental findings of document (1) dealing with investigations on grafting in the brain of cells genetically modified to express the markers hypoxanthine guanine phosphoribosyl transferase (HPRT) or luciferase and disclosing at a theoretical level the experiments on which the present application is based (the abstract of document (1) recites: "We present evidence... including a description of some current techniques for mammalian cell gene transfert and CNS grafting, and several possible approaches to clinical application.". As emphasized in point 7 infra, the technical contribution achieved by the application in suit is **not** a new technique for gene therapy in the CNS, but achievement of the experiments mentioned at a theoretical level by document (1). The means necessary for carrying out these experiments were already available either from the disclosure of document (1) and other pre-published documents, or from the general knowledge. For instance, Breakefield et al., Molecular Neurobiology, Vol. 1, pages 339 to 365 (1987) (document (7)) discloses on page 354 a genetically modified cell expressing nerve growth factor (NGF).

4. Thus, in the Board's view, claim 1, drafted in terms of functional features is allowable under Article 84 EPC since the skilled person knows, without exceeding his/her normal skills and knowledge, what has to be done in order to arrive at that result (see decision T 68/85, OJ EPO 1987, 228).

Novelty

5. Novelty was acknowledged by the Examining Division and the Board agrees with this finding.

Inventive step

6. Before the priority date of the application, implantation into mammalian brain of genetically modified cells expressing a therapeutical molecule was known to be one **potential** approach for complementing some kinds of genetic or developmental defects of the CNS. Document (1) disclosed at a **theoretical** level which steps the skilled person had to follow in order to achieve this goal. For instance, document (1) (see page 805, right hand column, first full paragraph) referred to the possibility of using a host cell expressing tyrosine hydroxylase (TH) and thus, indirectly, L-DOPA since TH is an enzyme capable of catalyzing the conversion of tyrosine to L-DOPA, for treating Parkinson's disease.

7. The skilled person was faced with document (1), which at a theoretical level states the steps necessary for arriving at ameliorating defective, diseased or damaged cells in the mammalian CNS by implanting donor cells genetically modified to express a therapeutic molecule in a sufficient amount to directly or indirectly ameliorate said defective, diseased or damaged cells in the mammalian CNS. Thus document (1) represents the most appropriate starting point for the evaluation of

inventive step in respect of the subject-matter of the claims at issue. In the light of this disclosure, the problem to be solved was to put into practice the theoretical proposal.

8. The technical contribution to the state of the art by the disclosure of the application consists of providing a technical solution to the treatment of diseases of the CNS by means of host cells expressing therapeutic molecules. The technical contribution achieved by the application is not a new technique for gene therapy in the CNS, but achievement of the technical result foreshadowed at a theoretical level by document (1). This situation is similar to the one dealt with in decision T 0694/92 (OJ EPO 1997, 408). The means necessary for carrying out these experiments were already available either from the disclosure of document (1) and other pre-published documents, or from the general knowledge. For instance, document (7) disclosed on page 354 a cell genetically modified to express NGF.

9. In view of Examples II and III disclosed in the application in suit, the Board is satisfied that the technical problem mentioned above has been solved. Example II shows that donor cells genetically modified to express NGF and implanted into the brains of rats with a surgical lesion of the fimbria-fornix, prevent the degeneration of cholinergic neurons that would die without treatment. Example III shows that cells genetically modified for expressing tyrosine hydroxylase (TH), an enzyme capable of catalyzing the conversion of tyrosine to L-DOPA, once implanted into the rostral-caudate striatum, significantly reduce drug-induced rotations, a rat model for Parkinson's disease.

10. The Board agrees with the Examining Division's conclusions (see paragraph II supra) that it would have been obvious for the skilled man to try the gene therapy as proposed at a theoretical level by document (1). But, even if an experiment is obvious to try for the skilled person, it is not necessarily true that this person would have any reasonable expectation of success when embarking on it. As already pointed out in decision T 296/93 (OJ EPO 1995, 627), "a reasonable expectation of success" should not be confused with the skilled person's "hope to succeed" (see *loc. cit.* point 7.4.4 of the Reasons).

11. Thus, the relevant question in respect of inventive step is whether the skilled person, starting from document (1), would have performed with a reasonable expectation of success or not the experiment referred to therein at a theoretical level of ameliorating defective, diseased or damaged cells in the mammalian CNS by implanting donor cells genetically modified to express a therapeutic molecule.

12. In order to answer this question, the Board first notes that the conceptual and methodological development of this theoretical objective disclosed in document (1) depended on the solutions to a great many questions and problems. These are listed in document (1) on page 796, left hand column, third full paragraph, page 797, left hand column, page 803, left hand column, second paragraph and right hand column, last paragraph.

13. It was with a view to elucidating these issues that the authors of document (1) undertook preliminary experiments consisting of grafting into the brain host **cells** modified to express the markers hypoxanthine guanine phosphoribosyl transferase (HPRT) or luciferase. It was found that these implanted modified

cells survived and continued to express the HPRT or luciferase genes at easily detectable levels for at least 7 weeks. Thus, a number of the fundamental questions mentioned previously could be elucidated, in particular an answer could be found to a number of the questions listed in document (1) on page 796, left hand column, third full paragraph and on page 797, left hand column, exception made for the issues dealt with in points 19 and 20 infra.

14. The Appellant submitted (see paragraph VI supra) that the critical features distinguishing the subject-matter of present claim 1 from the experiments disclosed in document (1) were to be seen in the fact that the molecules expressed by the donor cells referred to in claim 1 were **therapeutic agents** which were **released** into the brain.

15. As to the distinguishing feature "**therapeutic agent**", the Board agrees that NGF and L-DOPA (induced by TH) according to Examples II and III of the application in suit are therapeutic molecules, unlike HPRT or luciferase expressed by the genetically modified cells involved in the experiments disclosed in document (1), which are not therapeutic agents but only labels.

16. In connection with this, even if HPRT was known to be associated with the Lesh-Nyhan syndrome (see page 797, right hand column, third paragraph), it was not known whether the Lesh-Nyhan syndrome resulted directly from the absence of HPRT (page 804, right hand column, second paragraph). Thus, HPRT had been chosen by the authors of document (1) only because it was a good marker and, moreover, a very sensitive assay was available for the detection of this molecule. The Board thus acknowledges that the potential but unclear

pharmacological properties of HPRT were not the solution to the problem stated, and this view is also supported by the fact that these host cells expressing HPRT were transplanted into a **healthy** brain.

17. As to the distinguishing feature "**released**", there are no doubts that both molecules referred to in the Examples given in the specification of the patent application, namely NGF (see application in suit, page 41, line 5: "Assay for NGF Production and Secretion") and TH-induced L-DOPA (page 52, Table 2: "L-DOPA in cell media") are released from the genetically modified cells. As concerns the markers HPRT and luciferase referred to in document (1), it is not clear whether they are secreted into the extracellular space or not since this aspect has not been investigated at all by the authors of document (1). In fact, document (1) states in this respect that grafted cells expressing these molecules were dissected out, recultured and HRPT or luciferase were assayed **in the graft cells**, not in the extracellular space (see page 802, paragraph bridging left hand and right hand columns). Thus, the conclusion cannot be drawn that document (1) discloses the release in the brain's extracellular space of a product encoded by a gene.

18. In the Board's view, since HPRT and luciferase were not therapeutic agents and because document (1) did not deal with the issue of the release of the expressed molecules within the brain, the preliminary investigations disclosed by document (1) left unanswered the technical queries dealt with in details in points 19 and 20 infra. Nor did document (4) answer these queries since it is concerned with the same investigations as document (1), with the difference that the marker is β-galactosidase. Thus, in order to decide whether the skilled person had a reasonable

expectation of being successful in ameliorating defective, diseased or damaged cells in the mammalian CNS by means of implanted cells expressing a therapeutic molecule, it should be established whether these technical queries represented for the skilled person matter of high uncertainty or not.

19. The Board is of the opinion that a skilled person could not conclude, before the priority date of the application in suit, that if a cell secreted eg. NGF in vitro, it had necessarily to behave so once implanted into the brain, ie, in vivo. The mammalian brain is an extremely complex organ comprising equally complex interactive systems made of cells and biologically active molecules, which were and remain highly difficult to investigate, already given the difficulty in overcoming as a first step, the blood-brain barrier.

20. It is also decisive that the level of gene expression be sufficient to achieve the desired therapeutic effect but not so high as to be toxic to the diseased or healthy cells. More importantly, it is fundamental that the expression level remains more or less constant with time. All this could not have been foreseen by the skilled person since a shut down of transgene expression (see document (1), page 803, right hand column) or other hindrances could by no way be excluded. The preliminary experiments carried out with markers disclosed by document (1) could not cast any light on these issues since only qualitative but no quantitative assays for HPRT and luciferase had been performed.

Once the transgene therapeutic agent had been released from the cell at a constant rate, it had to diffuse within the brain to reach possibly distant diseased cells. However, nothing was known about how therapeutically active molecules diffuse within the

brain. Further, a brain's immunological response against the secreted molecule could not be excluded a priori (see page 803, right hand column, last paragraph of document (1)).

Finally, the transgene product must induce a therapeutically measurable effect upon interacting with said diseased cells. But this could not be taken for granted since the way brain cells took up biologically active molecules was and still is not fully understood.

In summary, the Board believes that the skilled person would not have considered that the effect of cells implanted in a brain could be equated to the effects observed in cells in a culture medium. This would have been an unreasonable oversimplification.

19. Thus, bearing in mind that the skilled person was faced with all these uncertainties, the Board has to conclude that documents (1) and (4) gave the skilled person no reasonable expectation of being successful in ameliorating defective, diseased or damaged cells in the mammalian CNS by means of implanted cells expressing a therapeutic molecule. The subject-matter of claim 1 and dependent claims 2 to 33 thus satisfies the requirements of Article 56 EPC.

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 the request submitted at the oral proceedings on 5 June 1997.

The Registrar: The Chairwoman:

D. Spigarelli U. Kinkeldey