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D E C I S I O N
of 3 September 2003

Case Number: T 0486/01 - 3.3.4

Application Number: 92917908.3

Publication Number: 0597033

IPC: A61K 38/30

Language of the proceedings: EN

Title of invention:
IGF-1 to improve the neural condition

Patentee:
GENENTECH, INC., et al

Opponent:
Cephalon, Inc.

Headword:
IGF-1/GENENTECH, INC., et al

Relevant legal provisions:
EPC Art. 123(2), 88(3), 54, 56

Keyword:
"Main request and auxiliary request 1 - novelty (no) - further medical use (no)"
"Auxiliary requests 2 and 3 - inventive step (no)"

Decisions cited:
G 0005/83, G 0279/93, T 0254/93, T 0892/94, T 0189/95, T 0019/86, T 0893/90

Catchword:
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Case Number: T 0486/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 3 September 2003

Appellant: (Proprietor of the patent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 1 March 2001 revoking European patent No. 0597033 pursuant to Article 102(1) EPC.

Composition of the Board:

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

Summary of Facts and Submissions

I. The appeal is *against* the decision of the opposition division revoking European patent No. 0 597 033 (application No. 92 917 908.3) filed on 3 August 1992 and claiming priority from NZ 239211 of 1 August 1991 (document (P)), which had been opposed by the respondent (opponent) on the grounds of Articles 100(a) (Articles 54 and 56) and 100(b) EPC. The patent relates to IGF-1 (insulin-like growth factor 1) to improve the neural condition. Independent claim 1 as granted read as follows:

"1. The use of IGF-1 and/or a biologically active analogue of IGF-1 in the manufacture of a medicament for treating central nervous system injury affecting glia or other non-cholinergic cells."

Claims 2 to 13 related to specific embodiments of the medical use of claim 1.

II. The reasons given for the refusal were that claim 1 of the main and third auxiliary requests lacked novelty, while claim 1 of the first and second auxiliary requests did not involve an inventive step.

III. With the Grounds of Appeal the appellant filed a new Main Request and Auxiliary Requests 1 to 3, of which independent claim 1 read as follows:

Main Request

"1. The use of IGF-1 and/or a biologically active analogue of IGF-1 in the manufacture of a medicament

for use in reducing the loss of glial cells or non-cholinergic neuronal cells suffered after a CNS insult."

Auxiliary Request 1

"1. The use of IGF-1 and/or a biologically active analogue of IGF-1 in the manufacture of a medicament for use in reducing the loss of glial cells suffered after a CNS insult."

Auxiliary Request 2

"1. The use of IGF-1 and/or a biologically active analogue of IGF-1 in the manufacture of a medicament for use in treating a CNS injury affecting glial cells or non-cholinergic neuronal cells and being the consequence of multiple sclerosis."

Auxiliary Request 3

"1. The use of IGF-1 and/or a biologically active analogue of IGF-1 in the manufacture of a medicament for use in reducing the loss of glial cells or non-cholinergic neuronal cells suffered as a consequence of multiple sclerosis.".

IV. Oral proceedings were held on 3 September 2003.

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

(C5) Principles of Neural Sciences, edited by E.R Kandel, J.H. Schwartz and T.M. Jessell, Appleton

& Lange, Norwalk, Connecticut, pages 244 to 257, 531 to 547, 609 to 625, 647 to 659, 711 to 730, 777 to 791, 974 to 986 and 1041 to 1049, third Edition 1991;

(C15) McMorris F.A. et al., Annals of the New York Academy of Sciences, Vol. 605, pages 101 to 109 (1990);

(C16) McMorris F.A. et al., Proc. Natl. Acad. Sci. USA, Vol. 83, pages 822 to 826 (February 1986);

(C17) WO-A-90/14838;

(C18) Mozell R.L. et al., Annals of the New York Academy of Sciences, Vol. 540, pages 430 to 432 (1988);

(C37) Gluckman P. et al., Biochem. Biophys. Res. Comm., Vol. 182, No. 2, pages 593 to 599 (31 January 1992);

(C38) Barres B.A. et al., Cell, Vol. 70, pages 31 to 46 (10 July 1992);

(C41) McMorris F.A. et al., Annals of the New York Academy of Sciences, Vol. 692, pages 321 to 334 (1993);

(C42) Knusel B. et al., J. Neurosci., Vol. 10, No. 2, pages 558 to 570 (1990).

VI. The submissions by the appellant can be summarized as follows:

Main Request and Auxiliary Request 1
Added subject-matter (Article 123(2) EPC)

- In claim 1 of the Main Request the wording "reducing the loss of glial cells **or** non-cholinergic neuronal cells" (emphasis by the board) was based on the application as filed, wherein glial cells and non-cholinergic neuronal cells were presented as alternative targets (see claim 1 of the published PCT application as filed: "glia **or** other non-cholinergic cells"; see also claims 5 and 6 thereof).

Right to priority (Article 88(3) EPC)

- Page 19, lines 12 to 13 ("neuronal loss was reduced") of priority document (P) (see Section I above) provided support for the entitlement of the IGF-1-based medical use of claim 1 of both requests to priority rights. A further support could be derived from page 19, lines 18 to 19 ("therapy reduced the neuronal death"), the tables on pages 20 and 21 (Experiments A and B), Figure 1D and its counterpart on page 14, lines 16 to 18 ("Astrocyte-like cells... express IGF-1 after insult").

Novelty (Article 54 EPC)

- The medical use of claim 1 did not relate to the treatment of a central nervous system (CNS)

disease with IGF-1 but rather to reducing (cf "rescue"), by means of IGF-1, the loss of glial cells or non-cholinergic neuronal cells (Main Request) or of glial cells (Auxiliary Request 1) after a CNS insult, such as eg Parkinson's disease. Even if the practical means of realisation were the same as in the prior art (document (C17)), the therapeutic effect ("rescue of glial cells or non-cholinergic neuronal cells after a CNS insult") was a functional feature which established novelty over the IGF-1-based medical treatment of central nervous system (CNS) diseases disclosed by document (C17), which described no such survival of glial/cholinergic cells.

- The above interpretation was supported by the experimental data in Experiment B of the patent in suit (see also page 5, lines 9ff), which showed that IGF-1 substantially reduced glial cell and non-cholinergic neuronal cell loss after a CNS insult.

- The skilled person would not take the teaching of document (C17) seriously, since it prescribed, for healing Parkinson's disease, the rescue of cholinergic neuronal cells (see page 8, central paragraph). However, this went against the teaching of document (C5), according to which the target cells to be rescued when treating Parkinson's disease should be the dopaminergic neuronal cells and, moreover, this disease had to be treated with anticholinergic agents (see page 654).

Article 52(4) EPC

- Since claims 8 to 10 were dependent on claim 1, drafted according to an acceptable second/further medical use format, they could not relate to methods of treatment excluded from patentability by the provisions of the above Article.

Auxiliary Requests 2 and 3
Added subject-matter (Article 123(2) EPC)

- The term "or" in claim 1 of the Auxiliary Request 3 did not represent added subject-matter (see Main Request).

Inventive step (Article 56 EPC)

- Documents (C15), (C16) and (C18) did not suggest a cure for treating MS. In fact, the experiments disclosed in these documents involved a transgenic mouse which was no acceptable model of remyelination. Further, these experiments merely showed the increase of myelin and of the number of oligodendrocytes *in vitro*. However, proliferation/stimulation of neuronal/glial cells by IGF-1 was not predictive of any *in vivo* activity of IGF-1 upon the enhancement of survival of glial/neuronal cells.

- This view was supported by post-published document (C41). The authors of this document (see page 330, first full paragraph) expressed their surprise that the in vivo tests achieved so little

difference in oligodendrocyte number between the control and the experiment, contrary to their expectations from the *in vitro* tests. Document (C41) provided an explanation of their surprising result, which explanation lay with the substantial differences between the *in vitro* and the in vivo experiments performed so far. In the *in vitro* tests of documents (C15), (C16) and (C18), the controls were performed in a serum-free medium in the absence of IGF-1 (condition of IGF-1 depletion) and the experiments were made under condition of IGF-1 restoration. In the *in vivo* experiments, however, the controls were normal mice expressing normal IGF-1 levels in the brain and the experimental conditions were ones of IGF-1 excess.

- As for document (C37), it discussed neuronal cell rescue in conjunction with endogenous IGF-1 and without identifying either non-cholinergic neurons or glial cells. The document used on page 598 a very cautious language "IGF-1 may have therapeutic potential".

- Document (C42) merely reported on the neurotrophic action (differentiation and proliferation) of IGF-1 on cholinergic and dopaminergic neurons in culture. Differentiation and proliferation in vitro of developing neurons, however, had nothing to do with rescue of injured mature neuronal cells *in vivo*.

- Document (C38) was irrelevant because it dealt with *in vitro* studies upon the

proliferation/stimulation on immature rat cells, wherein cell death (apoptosis) still occurred.

VII. The submissions by the respondent can be summarized as follows:

Main Request and Auxiliary Request 1
Added subject-matter (Article 123(2) EPC)

- The "or" in claim 1 of the main request ("for treating central nervous system injury affecting glial or other non-cholinergic cells") found no basis in the application as filed, wherein the expression read "loss of glial and other non-cholinergic cells" (see page 3, line 22 of the published PCT application as filed).

Right to priority (Article 88(3) EPC)

- Priority document (P) taught that IGF-1 healed a CNS injury by "reducing neuronal loss" in general (see eg page 19, lines 12 to 13). The medical use of claim 1 of both requests did not differ from the teaching of document (P). The reference to the mechanism of action being to IGF-1 healing CNS injury caused by "the loss of glial cells or non-cholinergic neuronal cells" (Main Request) or "the loss of glial cells" (Auxiliary Request 1), which mechanism of action was not disclosed in the priority document (P), was irrelevant to the subject matter of claim 1 of both requests, so these were thus entitled to priority.

Novelty

- According to decisions T 279/93 of 12 December 1996 and T 254/93 (OJ EPO 1998, 285), merely providing the previously unknown mechanism of action of a known compound/composition used for obtaining a known effect or in a known medical treatment, could not confer novelty. Therefore, the claims related to the medical use of IGF-1 in the treatment of a CNS insult, as the wording "reducing the loss of glial cells or non-cholinergic neuronal cells" was the mere explanation of the mechanism of action of IGF-1.

- However, document (C17) already disclosed the use of IGF-1 in the treatment of a CNS insult (see eg page 8, lines 26 to 33). Even if the claims were directed to "reducing the loss of non-cholinergic neuronal cells", document (C17) clearly disclosed the rescue of neuronal cells (see page 6, line 19).

Article 52(4) EPC

- Claims 8 to 10 related to methods of treatment excluded from patentability by the provisions of the above Article.

Auxiliary Requests 2 and 3
Added subject-matter (Article 123(2) EPC)

- The term "or" in claim 1 of the Auxiliary Request 3 represented added subject-matter (see Main Request).

Right to priority (Article 88(3) EPC)

- Priority could not be claimed as multiple sclerosis (MS) was not mentioned in the priority document.

Inventive step (Article 56 EPC)

- The subject-matter of the claims was obvious in view of document (C15), which taught that IGF-1 was a potent inducer of oligodendrocyte development and myelination (see page 105, end of first full paragraph), a process underlying the healing of demyelinating disorders and thus MS (see page 101, end of first paragraph). Documents (C16) and (C18) further confirmed IGF-1's effect of regenerating oligodendrocytes.

- Document (C37) was the publication by the authors of the patent in suit of experimental results, according to which IGF-1 reduced neuronal loss. In fact, the results obtained in the patent merely confirmed the results presented in document (C42), according to which IGF-1 had neuron protective activity (see page 8, line 58 to page 9, line 1 of the patent in suit).

- Document (C38) concluded on page 38, r-h column, first full paragraph that "IGF-1 and IGF-2 promote the survival of O-2A progenitor cells and oligodendrocytes" (the latter being glial cells). Page 32 thereof related to cell survival, not proliferation.

- Taken together or separately, these documents provided a clear teaching that IGF-1 could be used to rescue glia and non-cholinergic neurons in MS.

- Document (D41) being post-published, could not be used in the issue of the inventive step.

VIII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the Main Request or one of Auxiliary Requests 1 to 3, all submitted on 10 July 2001.

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

Reasons for the Decision

1. The appeal is admissible

Main Request and Auxiliary Request 1
Article 123(2) EPC

2. According to claim 1 of the published PCT application as filed ("glia **or** other non-cholinergic cells"; see also claims 5 and 6 thereof; emphasis by the board), the property by IGF-1 of exerting its loss-preventing activity occurs on both glial and non-cholinergic neuronal cells, either taken together ("and") or taken alone ("or"). The wording "or" in claim 1 of the main request thus does not infringe Article 123(2) EPC.

Right to priority

3. Priority document (P) teaches a medical use of IGF-1, namely that IGF-1 heals CNS injuries by "reducing neuronal loss" (see eg page 19, lines 12 to 13; see also ibidem, lines 18 to 19: "therapy reduced the neuronal death"). The subject-matter of claim 1 of both requests, worded in the form of second/further medical indications (see G 5/83, OJ EPO 1985, 64) differs therefrom in that the "neuronal loss" has been replaced with "the loss of glial cells or non-cholinergic neuronal cells" (Main Request) or "the loss of glial cells" (Auxiliary Request 1).

4. As explained in detail in points 5 to 12 infra in connection with the issue of novelty, the features "the loss of glial cells or non-cholinergic neuronal cells" (claim 1 of the Main Request) or "the loss of glial cells" (claim 1 of Auxiliary Request 1) do not confer novelty on the claimed medical use vis-à-vis any IGF-1-based treatment of a CNS injury, ie these features are ineffective for the board to consider the medical uses now claimed as novel (further) medical applications.

5. By implication, the claimed medical uses also do not go beyond, in terms of essential technical features, the medical use already disclosed in priority document (P), namely the treatment by IGF-1 of a CNS injury by "reducing neuronal loss". In conclusion, the subject matter of the claims of both requests is entitled to priority.

Novelty

6. The use of IGF-1 in the preparation of a medicament for use in the treatment of a CNS insult has already been proposed. Document (C17) indeed discloses such an application of IGF-1 in the treatment of eg Parkinson's disease (see eg page 8, lines 26 to 33). The mechanism of action underlying this therapeutic effect is, *inter alia*, the rescue by IGF-1 of neuronal cells, preferably non-mitotic neuronal cells and/or cholinergic neuronal cells (see page 6, lines 18 to 21). Claim 1 of both the Main Request and Auxiliary Request I are worded accordingly in the form suggested by the Enlarged Board of Appeal when more particularly considering the so-called second medical indication (see G 5/83, OJ EPO 1985, 64, point 9, 65), i.e. cases in which the medicament (IGF-1) of the claimed use is no different from a known medicament.

7. In its decision, the Enlarged Board of Appeal held that, provided the medicament is for a specified new and inventive application, "the required novelty for the medicament which forms the subject-matter of the claim is derived from the new pharmaceutical use" (ibidem, points 21 to 23). Consequently, the novelty of the subject-matter of claim 1 of both requests is intimately linked to whether the newly discovered effects "reducing the loss of glial cells or non-cholinergic neuronal cells" (claim 1 of the Main Request) or "reducing the loss of glial cells" (claim 1 of Auxiliary Request 1) can confer novelty on the claims vis-à-vis the known medical use disclosed by document (C17).

8. However, it must be pointed out that a new property of a known substance or a new technical effect achieved by a known molecule do not necessarily translate into a novel use (be it medical or otherwise) of that substance/ molecule (see eg decisions T 892/94, OJ EPO 2000, 1 and T 189/95 of 29 February 2000, both relating to the medical field). For a medicinal application to be construed as a "further medical use", this new technical effect would have to lead to a truly new therapeutic application, such as the healing of a different pathology or the treatment of the same disease with the same compound, however, when carried out on a new group of subjects distinguishable from the previously suggested subjects for such treatment (see eg T 19/86, OJ EPO 1989, 24).

9. Turning to the present situation, the appellant relied heavily during the proceedings, as novel features, on the target cells to be rescued by IGF-1, namely glial cells and non-cholinergic neuronal cells (claim 1 of the Main Request) or glial cells (claim 1 of Auxiliary Request 1), in contrast to the medical use disclosed in document (C17), based on rescuing neuronal cells in general, preferably non-mitotic neuronal cells and/or cholinergic neuronal cells.

10. As for the question of whether the claimed medical uses are directed to the treatment of new pathologies, such as eg a kind of "glial cell-dependent Parkinson's disease" or a "non-cholinergic neural cell-dependent Parkinson's disease", there is no evidence before the board that there exists such CNS injuries which affects **only** glia or non-cholinergic neurons, while leaving other populations of CNS cells unscathed. The

appellant's admission that "CNS insults such as Parkinson's disease represent quite complex physiological phenomena whose therapy certainly cannot be narrowed to the rescue of glial cells or non-cholinergic neuronal cells" (see submission dated 10 July 2001, page 3, Section 3.2), pleads rather to the contrary. Neither does it appear to be possible that a skilled person might practice an IGF-1-based therapy aiming at **selectively** rescuing glial cell or non-cholinergic neural cells, while taking care that other CNS cell populations, such as the non-mitotic neuronal cells and/or the cholinergic neuronal cells referred to in document (C17), be left unaffected. "Selective targeting" would indeed run against the teaching of the patent in suit that "IGF-1 has potent **nonselective** action on neurons" (see page 9, line 1; emphasis by the board).

11. For the same reasons the different physiological effects highlighted by the appellant do not allow the identification of a new sub-group of patients to be treated. It is true that two different mechanisms of action of a drug may end in the "splitting" of the group of patients being treated into two distinct sub-groups, as in the cases considered in T 19/86 (supra) and T 893/90 of 22 July 1993. However, that is clearly not the case here, as the patent in suit contains no such teaching. No new sub-groups of patients to be treated for, eg "glial cell-dependent Parkinson's disease" or "non-cholinergic neural cell-dependent Parkinson's disease" can be recognized as distinguishable from the subjects referred to in document (C17).

12. In conclusion, the board considers that, even deciding in the appellant's favour that the physiological effects emphasized by the appellant are not known in the state of the art, these can only be regarded as the discovery of additional items of knowledge about further mechanisms of action underlying the known therapeutic application of IGF-1 in the treatment of CNS insults, but cannot in themselves confer novelty over this known therapeutic application.

13. The appellant argues that the skilled person would not take the teaching of document (C17) seriously, since it prescribes, for healing Parkinson's disease via IGF-1, the rescue of cholinergic neuronal cells (see page 8, central paragraph). In the appellant's view, this goes against the teaching of document (C5), according to which the target cells to be rescued when treating Parkinson's disease should be the dopaminergic neuronal cells and, moreover, this disease has to be treated with anticholinergic agents (see page 654).

14. In the board's view, however, the teaching of document (C17) is confined neither to healing Parkinson's disease, which is only one example of the many CNS disorders referred to on page 8, central paragraph of document (C17), nor to rescuing cholinergic neuronal cells, i.e. one of the many aetiologies underlying Parkinson's disease (see point 10 supra). Document (C17) is rather concerned with the more general teaching that IGF-1 can heal a CNS disease by "enhancing the survival of neuronal cells" (see page 6, line 19). The skilled person has no reason to doubt this technical teaching. Finally, any feature relating to the target cells involved in a CNS-healing process via IGF-1 has no

bearing on the novelty issue since a novel insight into the drug's mechanisms of action (see point 12 supra) does not entail the novelty of the subject matter being claimed, as the same subjects are to be treated in the same way for the same disease.

15. In view of the foregoing, it is the board's view that document (C17) anticipates the subject-matter of claim 1 of both the Main Request and Auxiliary Request 1, neither of which can be allowed.

Article 52(4) EPC

16. In view of the negative finding in relation to novelty, no need arises for the board to decide the question of whether or not claims 8 to 10 relate to methods of treatment excluded from patentability by the provisions of the above Article.

Auxiliary Requests 2 and 3
Article 123(2) EPC

17. The wording "or" in claim 1 of Auxiliary Request 3 does not infringe Article 123(2) EPC, for the same reasons given under point 2 supra.

Right to priority

18. The parties agree that the subject-matter of the claims of these requests is not entitled to priority rights and the board agrees as well. These claims indeed relate to the treatment of MS, a pathology not disclosed in priority document (P).

Novelty

19. The claims at issue address the use of IGF-1 and/or an analogue thereof in the manufacture of a medicament for treating pathological situations resulting from MS. The parties agree that the claimed medical uses are directed to the treatment of pathologies not previously disclosed. Likewise, the board considers that the subject-matter of the claims of these requests is novel.

Inventive step

20. In view of the conclusions relating to priority rights (see point 17 supra), documents (C37) and (C38), published before the filing date of the patent in suit (3 August 1992), are prior art under Article 54(2) EPC, and can thus be relied on for assessing inventive step.

21. The claims at issue address the use of IGF-1 and/or an analogue thereof in the manufacture of a medicament for treating a CNS injury affecting *inter alia* glial cells, following MS (claim 1 of Auxiliary Request 2), or for reducing, *inter alia*, the loss of glial cells suffered as a consequence of MS (claim 1 of Auxiliary Request 3).

One of the aetiologies underlying MS involves oligodendrocyte (a glial cell) destruction and demyelination (see patent in suit, page 2, lines 18 to 19). That myelination is linked to the presence of oligodendrocytes is shown by document (C41), page 326 lines 1 to 3: "In most cases, the plaques eventually become devoid of oligodendrocytes and remyelination does not occur.[25,26]". This sentence is a summary of what was already known before the filing date of the patent

in suit from the there cited references "25,26" dated 1982.

22. The patent in suit describes *in vivo* studies in adult rats where IGF-1 is administered following a CNS insult (ischemic hypoxia) and illustrating the rescue of glial cells and non-cholinergic neurons, i.e. the loss of these cells is reduced (see eg Figure 3 and 4 and page 9, line 53 to 54). It is further confirmed on page 2, lines 18 to 19 of the patent that in the case of MS, the CNS insult is associated with the loss of myelin and oligodendrocytes (a sub-population of glial cells).

23. The closest prior art is represented by document (C15), relating to IGF-1, glial cells and MS. This document is concerned with in vitro investigations on the effects of IGF-1 on oligodendrocytes. IGF-1 turns out to be a potent inducer of oligodendrocyte development and accumulation of myelin (see page 105, end of first paragraph). A further experiment using transgenic mice overexpressing IGF-1 tests how IGF-1 affects myelination in the brain *in vivo*. The transgenic mice brains are found to contain twice as much myelin compared to those of the non-transgenic littermates (ibidem, first full paragraph). On page 101, end of the first paragraph of this document it is further stated that "this information may ultimately lead towards the development of treatment to promote remyelination in multiple sclerosis".

24. Compared to this prior art, the problem to be solved by the claimed subject-matter can be seen as being the provision of a medicament capable of in vivo reducing

the loss of glial cells or non-cholinergic neurons associated with a MS pathology. The question to be answered is whether or not it would have been obvious for the skilled person to arrive at something falling under the terms of these claims.

25. The appellant emphasizes that reducing the loss of a cell population, a property of IGF-1 not disclosed in any prior art document, has nothing to do with causing the cells to proliferate or with stimulating cell growth. However, in the board's view, document (C38) shows a further type of action by IGF-1, distinct from proliferation/stimulation, namely its behaviour as a survival factor for oligodendrocytes, ie IGF-1 reduces death/loss of the glial cells oligodendrocytes (see page 31, r-h column, last paragraph and page 32, r-h column, first full paragraph).

26. The board is thus of the opinion that in the light of the combined teachings of documents (C15) and (C38), it would have been obvious to a skilled person that IGF-1 would be an effective agent in rescuing/reducing the loss of glial cells associated with a MS pathology.

27. In a further line of argument the appellant maintains that the *in vitro* data of documents (C15), (C16) and (C18) are not predictive of the *in vivo* action of IGF-1. To buttress this view, the appellant draws attention to post-published document (C41). The authors of this document (see page 330, first full paragraph) express their surprise that the *in vivo* tests achieve so little difference in oligodendrocytes number between the control and the experiment, contrary to their expectations from the in vitro tests. Document (C41)

provides an explanation of this surprising result, which explanation lies with the substantial differences between the *in vitro* and the *in vivo* experiments performed so far (in brief, *in vitro* experiments: control = condition of IGF-1 depletion; experiments = condition of IGF-1 restoration; in vivo experiments: control = normal mice expressing normal IGF-1 levels; experiments: condition of IGF-1 excess).

28. However, since document (C41) is a post-published document, it cannot be used to show what was known to the skilled person at the filing date of the patent in suit, for the purpose of deciding the issue of inventive step. Further, since document (C41) compares proliferation/stimulation *in vitro* versus proliferation/stimulation *in vivo*, in the board's judgement, it is also irrelevant to a comparison of "rescuing" *in vitro* versus "rescuing" *in vivo*, the latter being the decisive issue (see point 25 supra).

29. Finally, the appellant argues that the *in vitro* studies according to document (C38) are not predictive of the behaviour of mature oligodendrocytes *in vivo* since they are carried out upon immature oligodendrocytes from the developing rat optic nerve, wherein cell death (apoptosis) still occurs.

30. Yet the board observes that the experiments described in document (C38) relate not only to immature oligodendrocyte "O-2A" progenitor cells. That more mature oligodendrocytes can be rescued by IGF-1 is shown on page 38, l-h column, second full paragraph ("for more mature oligodendrocytes, IGF-1 is sufficient"). Moreover, once the skilled person has

been taught by document (D38) that IGF-1 acts as a survival signal molecule for glial cells *in vitro*, in the board's opinion, he/she would reasonably expect that IGF-1 would achieve some survival in glia *in vivo*, especially if the experiment is carried out via an ICV (intracerebroventricular) injection as in Example "A" of the patent in suit (cf "ICV" on page 7, line 15).

31. The subject-matter of claim 1 of Auxiliary Requests 2 and 3 being obvious, none of them can be allowed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey