Case Number: T 0710/05 - 3.3.08
Application Number: 90914299.4
Publication Number: 0486621
IPC: G01N 33/50
Language of the proceedings: EN
Title of invention: NMDA oxidizing agents for protecting neurons from injury
Applicant: The Children's Medical Center Corporation
Opponent: -
Headword: NMDA oxidizing agents/ THE CHILDREN'S MEDICAL CENTER
Relevant legal provisions: EPC Art. 84, 56
Keyword: "Main and first auxiliary requests - clarity - no"
"Second and third auxiliary requests - inventive step - no"
Decisions cited: T 0292/85, T 0923/92, T 1329/04
Catchword: -
Case Number: T 0710/05 – 3.3.08

DECISION
of the Technical Board of Appeal 3.3.08
of 22 February 2007

Appellant: The Children's Medical Center Corporation
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 20 December 2004
refusing European application No. 90914299.4
pursuant to Article 97(1) EPC.

Composition of the Board:
Chairman: L. Galligani
Members: F. Davison-Brunel
         C. Rennie-Smith
Summary of Facts and Submissions

I. European patent application No. 90 914 299.4 published as WO 91/02810 with the title "NMDA oxidizing agents for protecting neurons from injury" was refused by the examining division pursuant to Article 97(1) EPC.

A main request and two auxiliary requests were then considered.

Claims 1 and 3 of the main request read as follows:

"1. Use of an agent capable of oxidising an N-methyl-D-aspartate receptor in the manufacture of a medicament for use in therapy or prophylaxis of neuronal injury.

3. Use of glutathione in the manufacture of a medicament for use in therapy or prophylaxis of neuronal injury resulting from toxicity mediated at N-methyl-D-aspartate receptors."

Dependent claims 2 and 5 related to the use in accordance with claim 1 involving specific oxidising agents/categories of agents. Dependent claim 4 related to the use of glutathione in the manufacture of a medicament for use in therapy or prophylaxis of specific diseases.

Independent claims 6 and 7 were respectively directed to the use of putrescine and diamine oxydase, and to the use of substrates for various oxidases in the manufacture of a medicament for use in therapy or prophylaxis of neuronal injury.
Claims 1 and 3 of the *first auxiliary request* read as follows:

"1. Use of an agent capable of oxidising an N-methyl-D-aspartate receptor in the manufacture of a medicament for use in therapy or prophylaxis of stroke, anoxia, ischemia, hypoglycemia, seizures, epilepsy, Huntingdon's disease, Alzheimer's disease, or amyotrophic lateral sclerosis-Parkinsonism-dementia complex.

3. Use of glutathione in the manufacture of a medicament for use in therapy or prophylaxis of stroke, anoxia, ischemia, hypoglycemia, seizures, epilepsy, Huntingdon's disease, Alzheimer's disease, or amyotrophic lateral sclerosis-Parkinsonism-dementia complex resulting from toxicity mediated at N-methyl-D-aspartate receptors."

The *second auxiliary request* comprised two claims which read as follows:

"1. Use of an agent comprising a superoxide or peroxide capable of oxidising an N-methyl-D-aspartate receptor in the manufacture of a medicament for use in therapy or prophylaxis of stroke, anoxia, ischemia, hypoglycemia, seizures, epilepsy, Huntingdon's disease, Alzheimer's disease, or amyotrophic lateral sclerosis-Parkinsonism-dementia complex.

2. Use of an agent as specified in claim 1, wherein said agent comprises potassium superoxide, or hydrogen peroxide."
II. During examination, the claims of the second auxiliary request were considered patentable. On 3 May 2004, the examining division issued a communication under Rule 51(4) EPC to inform the applicant of its intention to grant a patent on this basis. In its letter dated 25 August 2004, the applicant refused to agree to that version of the text and requested a decision on the main request.

III. In its decision dated 20 December 2004, the examining division refused the main request and the first auxiliary request pursuant to Article 97(1) EPC for non-compliance with Articles 54, 56, 83, 84, 123(2) EPC and Rule 86(4) EPC. The requirement of clarity was found not to be fulfilled, in particular, in relation to the term "agent capable of oxidising an N-methyl-D-aspartate receptor" present in claim 1 of both requests. It was also determined that the subject-matter of claims 1, 2 and 5 of the main request (claims 1, 2 and 4 of the first auxiliary request) did not involve an inventive step because there was no evidence that the problem underlying the application had been solved over the scope of the claims.

IV. The appellant (applicant) filed an appeal, paid the appeal fee and submitted a statement of grounds of appeal together with a main request and two auxiliary requests corresponding to the requests considered by the examining division with a minor amendment in claims 7 and 6 of, respectively, the main and first auxiliary requests.
V. The examining division did not rectify the contested decision and referred the appeal to the board of appeal (Article 109 EPC).

VI. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal stating its preliminary, non-binding opinion.

VII. The appellant sent a further submission in answer to this communication together with a new main request and two auxiliary requests.

Claim 1 of the main request read as follows:

"1. Use of an agent capable of oxidising an N-methyl-D-aspartate receptor in the manufacture of a medicament for use in therapy or prophylaxis of neuronal injury mediated at N-methyl-D-aspartate receptors."

Claim 1 of the first auxiliary request was identical to claim 1 of the first auxiliary request considered by the examining division and the second auxiliary request was identical to the second auxiliary request which had been found patentable (see I, supra).

VIII. During the oral proceedings which took place on 22 February 2007, the appellant filed a third auxiliary request comprising one claim which read as follows:

"1. Use of glutathione in the manufacture of a medicament for use in therapy or prophylaxis of stroke, anoxia, ischemia, hypoglycemia, seizures, epilepsy, Huntingdon's disease, Alzheimer's disease, or
amyotrophic lateral sclerosis-Parkinsonism-dementia complex."

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


(12) : Choi, D.W., Neuron, Vol. 1, pages 623 to 634, October 1988;


X. The appellant's arguments in writing and during oral proceedings which are relevant to the present decision may be summarized as follows:

Main and first auxiliary requests

Article 84 EPC, clarity

- The skilled person would have no problems in understanding the term "an agent capable of oxidising an N-methyl-D-aspartate receptor". The N-methyl-D-aspartate (NMDA) receptor was a known receptor at the priority date and the concept of "oxidation" was, of
course, well-understood. Furthermore, the application (Example 4) provided a test for determining whether or not an agent was capable of oxidising the (NMDA) receptor.

- The present invention opened an entirely new field of investigations. For this reason, as already established by the case law (T 292/85, OJ EPO, 1989, 275), a functional definition - here, "capable of oxidising" - was allowable. It was also allowable under such circumstances that the claim encompassed a great number of compounds, some of which had not yet been identified.

- Finally, the board's concern that the claim may be unclear, insofar as it comprised the use of agents which caused the in vivo level of an oxidising agent of the NMDA receptor to be increased, was not justified because the causative agent could be tested for this effect by the test described in Example 4.

Second auxiliary request
Article 56 EPC; inventive step

- The closest prior art was document (1) relating to the selective modulation of the NMDA receptor responses to NMDA by reduction and oxidation. It established that the electrophysiological responses to NMDA were subject to a modulatory redox mechanism and, in particular, that oxidation with DTNB decreased the magnitude of the responses. Yet, it only speculated that an in vivo mechanism that could strongly regulate NMDA-activated functions by oxidation may exist and it did not suggest
at any time that advantage could be taken of this mechanism for a therapeutic use such as now claimed. In contrast, the present application provided evidence (Example 4) that the oxidizing agent DTNB protected neuronal cells by interfering with the NMDA-NMDA receptor interactions. To conceive of exploiting the potential of oxidising agents by manufacturing a medicament required an inventive step.

- The board was concerned that the only oxidising agent exemplified in the application was toxic and that, therefore, it could not be a solution to providing a medicament, i.e. it was concerned that no evidence had been provided that the claimed subject-matter was a solution to a technical problem. Yet, the requirements for patentability were different from the requirements for the medical authorisation of a therapeutic product. In particular, it was not required for a medical invention to be patentable that it must comply with the standards necessary for such authorisation. Thus, the board had no cause for concern. As with most other drugs, the toxicity of the oxidising agents would very much depend on the amount that was administered. Furthermore, the diseases they would be fighting against were so severe that the toxicity of the medicament became secondary.

- For the same reasons, the statement in post-published document (10) that "a non-toxic agent that down-regulates this site has yet to be described" did not constitute evidence that the problem of using oxidising agents in the manufacture of a medicament had not been solved in the application.
- Document (22) was the closest prior art as it related to glutathione-induced inhibition of Na\(^+\)-independent and dependent bindings of L-[\(^3\)H] glutamate in rat brain. It taught that the binding of glutamate to neurons was significantly reduced in the presence of oxidised glutathione. Yet, the possible consequences of this tripeptide preventing glutamate binding were only vaguely speculated upon.

In contrast, the present application unambiguously taught on page 7 that both reduced and oxidized glutathione could protect against toxicity mediated at the NMDA receptors. For this reason, using glutathione against diseases involving neuronal injury was inventive.

- The following two observations also supported an inventive step. Firstly, the mechanisms by which glutathione (in reduced or oxidized forms) worked were not relevant and in any case, it would be expected to work as DTNB in Example 4 of the application. Secondly, post-published documents (10) and (11) provided evidence of the effects of glutathione on NMDA mediated receptor toxicity.

The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or auxiliary request 1 filed on 22 January 2007 or auxiliary request 2 filed on 29 April 2005 or auxiliary request 3 filed during the oral proceedings.
Reasons for the decision

Main and first auxiliary requests
Article 84 EPC; clarity of the expression "an agent capable of oxidising an N-methyl-D-aspartate receptor".

1. This expression is found in claim 1 of both requests. Although the NMDA receptor was known at the priority date and the oxidation reaction belongs to basic chemistry, it remains a fact that this characteristic of the agent does not help in identifying which compounds are intended for the claimed use. Corroborating evidence for this is found in the application itself since no less than three pages (pages 3 to 5 but also page 7, lines 12 to 16, 26 to 32) are devoted to describing such compounds:

(a) - oxidising agents, eg. DTNB, superoxydes, peroxydes);

(b) - agents which need not be oxidising agents in their own right but will be acted upon in vivo to produce oxidising agents at the in vivo site of the NMDA receptors, eg. putrescene, substrates for various oxydases, tyramine-containing food or drugs ...;

(c) - agents which prevent the removal of oxidising agents which occur naturally in vivo such as, but not exclusively, yet to be identified inhibitors of enzymes known to break down oxidising compounds (page 5, lines 10 to 29);
(d) - agents which cause the in vivo level of an oxidising agent of the NMDA receptor to be increased (page 7, lines 12 to 16);

(e) - reduced and oxidised glutathione.

2. This list contains an almost limitless number of compounds of unspecified structures and having any unspecified function in - for some of them undefined - biological mechanisms eventually leading to oxidation of the NMDA receptor. In the board's judgment, this does not amount to a clear definition of the agents which may be made use of in the manufacture of a medicament in accordance with the claims.

3. This conclusion is fully in agreement with the existing case law on clarity, for example, T 923/92 (OJ EPO 1996, 564). This earlier decision relates to a case where a claimed group of compounds was defined by the functional feature "has tissue plasminogen activator function". The then competent board remarked (points 25 and 27 of the decision) that this feature was vague and ambiguous, relating to "a vast catalogue of derivatives of human t-PA of unspecified structure having any unspecified function of human t-PA" and concluded therefrom that "the area covered by the claim is not clearly defined, which is contrary to the provisions of Article 84 EPC".

4. In its submissions under Article 84 EPC, the appellant relied on the findings in decision T 292/85 (supra, points 3.1.2 and 3.1.5 of the decision) that in appropriate cases such as the one then dealt with, it was only possible to define the invention in a way
which gave a fair protection having regard to the nature of the invention which had been described, by using functional terminology in the claims and that in such cases the requirements of Article 84 EPC were fulfilled even if as yet undiscovered components may fall within the scope of the claim.

5. This earlier case was concerned with an invention corresponding to the first ever disclosure of recombinant DNA plasmids for the heterologous expression of proteins. The invention paved the way to a vast majority of subsequent inventions in the domain of genetic engineering. In contrast, the work described in the present application clearly belongs to the already developed area of research concerned with the importance of the NMDA receptor function in neuronal diseases (see eg. the prior art review article document (12)). There is, thus, no room for arguing that, as in T 292/85 supra, it opens an entirely new field of investigations. The findings in T 292/85 do not apply.

6. The argument was also presented that the patent application provided in Example 4 a test system for identifying the relevant agents, which put the skilled person in a position to determine which agents were adequate for the claimed use. However, the test described in Example 4 is an in vitro test of the effect of an oxidizing agent per se (DTNB). There is no evidence that it could be helpful in identifying any of the agents of categories (b) to (d) in point 1, supra, the last such category being in any case defined by a function only to be tested in vivo.
7. For these reasons, it is concluded that the subject-matter of claim 1 of both the main and first auxiliary requests is unclear and, therefore, both requests are rejected for failing to fulfil the requirements of Article 84 EPC.

Second auxiliary request; claim 1
Article 84 EPC; clarity, support in the description

8. The person skilled in the art would have no problems in understanding which compounds are superoxides or peroxides as these two terms correspond to defined chemical structures. Furthermore, the compounds could be tested for their capacity of oxidising an NMDA receptor in the test described in Example (4). The claimed subject-matter is clear and supported by the description.

Article 56 EPC; inventive step

9. The closest prior art is document (1) which is concerned with the effect of the oxidising agent DTNB on the activation of NMDA receptors by NMDA. It teaches that in the presence of NMDA, neuronal preparations are activated at the level of the NMDA receptor, which activation results in electrophysiological responses which are, in turn, involved in neurotoxicity (summary and introduction). It shows, in particular, that when the NMDA receptors are oxidised by DTNB, their response to NMDA is either substantially diminished or completely abolished (page 1257, right-hand column and Fig.1C). The authors remark on page 1262, left-hand column that "the experiments presented here introduce a new process whereby the NMDA response can be altered"
and also that "A more complete characterization of the NMDA receptor channel complex would be of extreme interest due to the involvement of these receptors in many important physiological and pathological processes in the central nervous system." (emphasis added by the board)

10. Starting from the closest prior art, the problem to be solved can be defined as finding a practical use for the mode of regulation of NMDA receptor activation therein disclosed.

11. The solution provided is to manufacture oxidising agents comprising peroxides and superoxides (eg.DNTB) as medicaments for use in the therapy or prophylaxis of specific diseases known to involve neuronal injury.

12. In the years prior to the priority date, the skilled person had been actively seeking strategies to fight diseases of the nervous system and one such favoured strategy was to take advantage of the existence of NMDA antagonists to interfere with NMDA-NMDA receptor interactions, as reflected in document (12), a review of neurotoxicity (page 629, "Strategies for Therapeutic Intervention"). In the light of the teaching in document (1) that an oxidising agent existed which interfered with NMDA-NMDA receptor interaction, the skilled person would have found it obvious to propose this agent as a medicament for treating diseases of the nervous system. This is all the more true in that, as already mentioned at point 9 supra, document (1) itself refers at the same time to the involvement of the NMDA receptor in neurotoxicity and to the potential use of oxidation to alter its activation in response to NMDA.
13. At oral proceedings, a discussion took place on the question of whether or not Example 4 in the application showing the beneficial effect of DTNB on neuronal survival was adequate to illustrate the claimed subject-matter taking into account that the inherent toxicity of DTNB most probably made it unsuitable as a medicament. Another question which was also discussed was whether or not the application could be considered as providing a bona fide solution to the problem to be solved taking into account the teaching in post-published document (10) - of which the present inventor is also an author - that two years after the priority date, "a nontoxic oxidising agent that down-regulates this site [the NMDA receptor] has yet to be described." [added by the board].

14. In accordance with the case law (T 1329/04 of 28 June 2005), there can only be an invention if the application makes it at least plausible that its teaching indeed solves the problem it purports to solve (see also point 20, infra). Here, any negative outcome to the above mentioned discussion may have led to a negative conclusion in terms of inventive step (no plausible solution of a technical problem provided). However, there is not need to decide this issue in view of the conclusion reached above of lack of inventive step (points 9 to 12, supra).

15. The second auxiliary request is rejected for failing to fulfil the requirements of Article 56 EPC.
Third auxiliary request

Article 56 EPC; inventive step

16. The sole claim of this request is limited to the use of glutathione in the manufacture of a medicament for use in therapy or prophylaxis of a number of diseases involving neuronal injury (see VIII supra).

17. The closest prior art is document (22) published three years before the priority date. This document teaches that glutamate is a potential excitatory neurotransmitter in the central nervous system (page 2411). It demonstrates that glutathione inhibits the binding of glutamate to neuronal cells (page 2415). In the discussion part of the article, it is speculated that "glutathione may play some important physiological roles in synaptic neurotransmission at putative central Glu neurons through interacting with the receptor sites and/or uptake sites which are sensitive to this tripeptide".

18. Starting from the closest prior art, the problem to be solved can be defined as finding a practical application for the observed effect of glutathione on glutamate binding to neuronal cells.

19. At the priority date, the formulation of this problem was obvious taking into account that the properties of glutamate to excite virtually all neurons and to be responsible at least in part for anoxia, ischemia, seizures, epilepsy, amyotrophic lateral sclerosis-Parkinsonism-dementia complex etc..., were already well-established, as reflected in document (12) (page 623, left-hand column, pages 626 to 629).
Furthermore, as already above mentioned (point 12, supra), the necessity for developing strategies for therapeutic interventions against neuronal diseases was strongly felt.

20. The proposed solution is to manufacture glutathione as a medicament for treating specific diseases involving neuronal injury. Whether or not the application provides evidence that the problem has indeed been solved needs to be investigated.

21. The unique passage in the application relating to glutathione reads as follows: "Applicants have also discovered that both reduced and oxidised glutathione (0.5-10mM) can protect against toxicity mediated at the NMDA receptors by a mechanism not related to the site of oxidation discussed above. Thus, glutathione can be used in vivo or in vitro as discussed in this application for those agents which act to oxidise the NMDA receptor." (emphasis added by the board)

No evidence of any kind is given in support of the latter statement. The appellant argued that the evidence given in relation to the oxidising agent DTNB in Example 4 could well serve to illustrate the efficacy of glutathione against neuronal toxicity. This argument, however, is not convincing since the above mentioned passage teaches that a different mechanism of action is involved which, of course, leaves entirely open the possibility that glutathione may not protect neuronal cells from toxicity. The application as filed, thus, does not make plausible that glutathione may be used as a medicament against diseases due to neuronal injuries. At a later date, the two post-published
documents (10) and (11) (to be taken as expert's opinions) show that oxidised glutathione inhibits responses mediated by activation of the NMDA receptor.

22. This situation is analogous to the one encountered in the case dealt with in T 1329/04 (supra). There, a polypeptide was claimed as a member of the TGF-β family whereas the application provided no satisfactory evidence that it was so. Post-published evidence established that the polypeptide was a growth differentiation factor. The then competent board established that: "The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve"

and came to the conclusion that the requirement of inventive step was not fulfilled as no plausible solution to the technical problem had been provided.

23. In the board's judgement, these findings apply by analogy to the present case for the above mentioned reasons (point 21, supra). It is, thus, concluded that the provisions of Article 56 EPC are not fulfilled.
Order:

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar

The Chairman

A. Wolinski

L. Galligani