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D E C I S I O N
of 1 October 2004

Case Number: T 0210/02 - 3.3.2

Application Number: 96103701.7

Publication Number: 0732101

IPC: A61K 31/135

Language of the proceedings: EN

Title of invention:
Use of L-deprenyl for retarding age dependent deterioration of the immune system function in mammals

Patentee:
DEPRENYL ANIMAL HEALTH, INC.

Opponent:
CEVA SANTE ANIMALE

Headword:
Use of deprenyl in dogs/DEPRENYL ANIMAL HEALTH, INC.

Relevant legal provisions:
EPC Art. 56, 123

Keyword:
"Since the immune system is very complex, the mere allegation that an effect occurs is not sufficient to support an inventive step as required by Article 56 EPC"

Decisions cited:
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Catchword:
-

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Case Number: T 0210/02 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 1 October 2004

Appellant: (Proprietor of the patent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 27 December 2001 revoking European patent No. 0732101 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: M. Ortega Plaza
J. H. P. Willems

Summary of Facts and Submissions

I. European patent No. 0 732 101 based on application No. 96 103 701.7 was granted on the basis of five claims.

Independent claim 1 as granted read as follows:

"1. The use of the compound L-deprenyl, or a pharmaceutically acceptable form thereof, for the manufacture of a medicament for retarding the age-dependent deterioration of immune system function in mammals."

II. The following documents *inter alia* were cited in the proceedings:

(1) G. Renoux, Life Sciences, 1989, vol. 44, pp. 771-777
(5) J. Knoll, Advances in Pharmacological Research and Practice, 1985, vol. 3, pp. 7-26
(8) J. Knoll, The Mount Sinai Journal of Medicine, 1988, 55(1), pp. 67-74
(18) G. Le Fur, Life Sciences, 1980, vol. 26, pp. 1139-1148
(A1) Abstract of T. Muller, J. Neural Trans. Suppl. 1998, vol. 52, pp. 321-8
(A2) Abstract of K. Kitani, Ann. N. Y. Acad. Sci. 1998, vol. 854, pp. 291-306

III. Opposition was filed and revocation of the patent in its entirety was requested pursuant to Article 100(a) on the grounds of lack of novelty and lack of inventive step.

IV. The opposition division revoked the patent under Article 102(1) EPC.

The opposition division considered that the amended claims (main request and first and second auxiliary requests) met the requirements of novelty but did not meet the requirements of inventive step (Article 100(a) EPC). As regards the third auxiliary request, the opposition division considered that it contravened the requirements of Article 123(2) EPC.

In particular, the claimed subject-matter of the allowable requests was considered to be novel since none of the cited documents referred to the treatment of dogs.

With respect to inventive step, the opposition division considered that the problem to be solved was to provide a treatment for the age-dependent deterioration of the immune system function in dogs.

In view of the patentee's argumentation denying the extrapolation of the results from mice to dogs, the opposition division raised some doubts as to whether the problem referred to was actually solved. The experiments on dogs were of a prophetic nature as stated in the patent in suit.

The opposition division considered document (1) to represent the closest prior art. In the opposition division's opinion it was known from document (1) that deprenyl had a positive influence on the MPTP induced

fall in striatal dopamine, on the number of spleen B lymphocytes and on lymphoproliferation.

The opposition division further considered document (5), which disclosed that MPTP induced loss of striatal dopamine, was a useful model for mimicking premature age.

In view of this knowledge, the opposition division asserted that the skilled person would have known that L-deprenyl had an effect on age-dependent deterioration of the immune system in mice.

The opposition division also noted that document (18) taught that, among other mammals, dogs and rats had dopaminergic receptors on their lymphocytes. Therefore it was obvious to transfer the teaching of document (1) to dogs.

With respect to the first and second auxiliary requests, the opposition division considered that document (1) already used the same dosage and administration regime.

V. The appellant (patentee) lodged an appeal against the decision. The appellant maintained its main, first and second auxiliary requests and filed a new third auxiliary request. The appellant withdrew its previous third auxiliary request.

VI. The respondent (opponent) filed counterarguments. The respondent withdrew its opposition in a letter of 25 November 2003.

VII. Oral proceedings were held before the board on 1 October 2004.

The appellant (patentee) maintained its requests on file.

Claim 1 of the main request read as follows:

"1. The use of the compound L-deprenyl, or a pharmaceutically acceptable form thereof, for the manufacture of a medicament for retarding the age-dependent deterioration of immune system function in dogs."

Claim 1 of the first auxiliary request differed from claim 1 of the main request in that the following passage was added at the end of the claim:
"at a dosage level of from 0.1 to 5.0 mg/kg of body weight of the dog."

Claim 1 of the second auxiliary request differed from claim 1 of the first auxiliary request in that the following passage was added at the end of the claim:
", and at a frequency level of from one to five times weekly."

Claim 1 of the third auxiliary request differed from claim 1 of the second auxiliary request in that the following passage was added at the end of the claim:
"for a time of months to years."

VIII. The appellant's arguments may be summarised as follows:

The novelty of the subject-matter was based on the new effect on the immune system of dogs.

With respect to the requirements of inventive step (Article 56 EPC), the appellant acknowledged document (1) as the closest prior art. This document had been published one year before the priority date of the patent in suit.

The problem to be solved was the provision of a treatment for retarding the age-dependent deterioration of the immune system in dogs.

Questioned by the board about why it should be considered that the problem was plausibly solved, the appellant's submissions may be summarised as follows:

The opponent had never raised such a question; the opponent's analysis was an obviousness objection. The opponent had never suggested an objection as to lack of sufficiency under Article 83 EPC.

The experiments on dogs were prophetic in nature since to show a long life span would have meant waiting until the patent had expired, because a dogs life lasted over 14 years.

There had been a commercial success and there was no reason to think that the patent did not solve the problem. It was licensed to Pfizer in 1997 and had the trademark Anipryl.

The appellant cited paragraph 56 of the patent in suit where there was evidence of rats that had survived longer and appeared healthier. There were several reasons for a long span of life but the combination with the healthier appearance was clear evidence that the immune system functioned better. An animal with fewer infections appeared healthier.

Additionally, the appellant also cited paragraph 60 of the patent in suit where the scientific model for the dogs was explained.

Further to the inventive step issue, the appellant contended that the opposition division had interpreted the state of the art after having knowledge of the invention and that the opposition division had taken isolated parts of the documents out of their context. Moreover, documents (1) and (5) could not be combined since their contents were contradictory.

The correct test was, in the appellant's opinion, whether the skilled person would have gone forward in the expectation of advantages already achieved. This was not the case since the skilled person had to predict rationally. The more unexplored the field the more caution had to be shown by the skilled person. The immune system was very complex. The skilled person would have done routine experiments. He would not have done speculative experiments.

Document (1) was dedicated to sodium diethyldithiocarbamate (DTC) which protected against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced inhibition of immune responses in mice.

Document (1) did not, however, disclose that deprenyl counteracts the deterioration of the immune system. The disclosure of document (1) was that deprenyl had a similar effect to MPTP which mimicked Parkinson and negatively influenced the immune system.

The appellant made a summary of document (1) showing further that deprenyl had no effect on the concentration of striatal dopamine and its metabolites, decreased the T cell population, increased the B cell population, caused lymphoproliferation when no mitogen was employed but caused no lymphoproliferation when a T cell mitogen was used, and caused a high lymphoproliferation effect when a B cell mitogen was used. Moreover, deprenyl decreased the stimulation index in mixed lymphocyte culture (MLC). Finally, deprenyl did not, in contrast to DTC, restore the functions influenced by MPTP to their normal value. Deprenyl merely increased DA and its metabolite levels which were lowered by MPTP. Deprenyl had very different effects than DTC.

The skilled person would have concluded that deprenyl had negative effects on the immune system, since it mimicked the effects of MPTP. DTC was the molecule of choice. Deprenyl was only for comparative data. Additionally, document (1) taught a five-day treatment from which it was not possible to predict a long-term effect.

In the appellant's view, no skilled person would have thought, in the light of document (1), that deprenyl was obvious to treat the deterioration of the immune system.

Document (1) suggested that dopamine played an important role in the brain control of the T lymphocyte. This document showed how complex the pathways were and that the mechanisms of the influence of deprenyl in the immune response were still unknown.

The appellant also stated that extensive research would be required to investigate the effect of deprenyl in the immune system.

It would be a big leap to take the single results on the B cell population and forget the complete results of the document. Moreover, the appellant stated that there was no effect on B cells as mammals got older.

The appellant also argued that deprenyl did actually retard the deterioration of the immune system. The solution proposed by the patent in suit was a simple one. Deprenyl had a very beneficial effect on the dogs' life span even if complex mechanisms were involved. It did not matter which mechanisms were involved; what mattered was that they worked. The evidence was that the rats looked healthier and had longer lives. This made it plausible that the problem was solved.

Once one knew the solution, there were some pointers in document (1) that it might work (B cell proliferation and mitogen effect).

After a pause, the appellant filed two abstracts A1 and A2. It alleged that the late filing was due to the fact that the abstracts were the response to the question of plausibility raised during the proceedings. These

papers showed that deprenyl had the effect stated in the patent. A1 showed that deprenyl increased the interleukin level as foreseen by paragraph 60 of the patent in suit and A2 showed that the dogs treated with deprenyl had a long life.

It was extremely common to file patent applications with the clinical studies coming out some years later, and it was also common for patents to disclose drugs and uses without all data being available. Abstracts A1 and A2 showed that the problem had indeed been solved.

Additionally, the appellant argued that document (5) concerned a study on dopamine levels and its lowering with age. Deprenyl had a positive effect on this and hence had a positive effect on Parkinson's disease patients. There was no mention of the immune system in document (5). Document (5) taught that deprenyl could counteract the effects of MPTP. The teaching of document (5) was in contradiction to the teaching of document (1), since document (5) suggested that deprenyl had an effect *per se* on the dopamine (DA) levels in the brain. Document (5) was directed towards Parkinson's disease which was only relevant to humans and primates.

The appellant also argued that document (18) related to the identification of dopamine receptors in blood cells. It identified that the lymphocytes had dopaminergic receptors and suggested that dopaminergic receptors assisted in the lymphocyte response of the immune system. However, document (18) did not show how to assist the fact that deprenyl had an effect on age deterioration of the immune system.

Document (8) did not, in the appellant's opinion, mention the immune system. Furthermore this document was in contradiction of document (1), since it said that deprenyl caused high amounts of dopamine. Document (8) taught that deprenyl inhibited MAO activity in dogs and that it had an effect on dopamine level in the striatum, but this document did not teach anything with respect to the immune system.

In summary, the appellant put forward that none of the documents alone or in combination pointed to deprenyl as a solution to the problem. Moreover, no suggestion for a combination of documents was possible due to their contradictions.

With respect to the auxiliary requests, the appellant's arguments may be summarised as follows:

In addition to the statements already made concerning the main request, the three auxiliary requests were directed to dosage, frequency and life span, respectively.

As regards the first auxiliary request, the dosage was different from that given in Parkinson's disease. The dosage use in document (1) of 2 mg/kg concerned mice and not dogs. Both species would have a different level of treatment.

As regards the second auxiliary request, document (1) concerned a five-day treatment and again mice and not dogs were treated.

The third auxiliary request had its basis on pages 27, 28 and 29 of the application as filed.

With respect to inventive step, there was nothing in the prior art concerning a midlife treatment.

IX. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be granted on the basis of the set of claims of the main request, or on the basis of the first or second auxiliary requests (these three requests having served as basis for the first instance decision) or alternatively on the basis of the third auxiliary request which was filed with the grounds of appeal.

Reasons for the Decision

1. The appeal is admissible.

2. The late filing of the two abstracts A1 and A2 is admissible since it represents a due response to the discussion about plausibility of the solution which took place during the oral proceedings before the board.

3. The board agrees with the opposition division in that the main, first and second auxiliary requests meet the requirements of Article 123 EPC. With respect to the new third auxiliary request, the basis in the application as filed stated by the appellant is considered as acceptable (Article 123(2) EPC). Moreover, the claim relates to a restriction of the subject-matter claimed with respect to the claims as granted.

Hence, the requirements of Article 123(3) EPC have also been met.

4. Since claim 1 of the main request relates to a so-called second medical use claim, the novelty of its subject-matter can be formally accepted in view of the effect of retarding the age-dependent deterioration of the immune system function in dogs. This feature also appears in claim 1 of the three auxiliary requests which can also be considered as formally novel.

5. The board is satisfied that document (1) dealing with the MPTP-induced inhibition of immune response in mice and the treatment with DTC and deprenyl represents the closest prior art.

Document (1) discloses that DTC protects against MPTP-induced inhibition of immune response in mice. "The findings suggest a dopamine pathway could be involved in the brain-controlled immunostimulation afforded by DTC" (summary).

"The data obtained in MPTP- and DTC-treated mice indirectly confirm that brain structures control the T lymphocyte arm of the immune system (...), and suggest that dopamine may display an important role" (page 776, second full paragraph).

"In contrast to DTC, deprenyl modifies the immunological responses alike MPTP, and does not restore the MPTP-inhibited immune responses, yet it increases DA and metabolite levels that were significantly lowered by MPTP" (page 776, third full paragraph).

"The mechanism by which deprenyl depresses T-cell number and activity and augments B cell response is still unknown. It might be that a yet unknown deprenyl metabolite could influence the immune system, since deprenyl, an in vivo mitogen, have (*has*) no activity in vitro. Alternatively, it may be that tissue MAO activities, that are inhibited by deprenyl, display a role in the complex mechanisms regulating the immune system. Anyway more knowledge needs to be accumulated concerning MAO inhibitors before their effects on the immune system can be fully assessed" (page 776, third full paragraph).

The board agrees with the appellant that document (1) shows an effect of deprenyl on the immune system which at first glance does not look as positive and that it would require a research project to predict the effects of deprenyl on the immune system. It would not just be routine experimental work or routine trials since there is a very complex relationship between neurotransmitters and the numbers of T cells and B cells as well as antigens.

Document (1) clearly shows the complexity of the immune system and the difficulty in making a prognosis from the still unknown relationship of deprenyl with the immune pathways.

Accordingly, in the light of document (1) the problem to be solved can be seen in the provision of a further use of the medicament deprenyl.

The proposed solution according to the patent in suit lies in the treatment for retarding the age-dependent deterioration of the immune system function in dogs.

Therefore it first has to be examined whether this problem has indeed been solved by the proposed solution.

The appellant stated that there were two passages in the description of the patent in suit showing that it was plausible that the problem was actually solved.

Paragraph 56 reads as follows: "When compared with saline-treated controls, the L-deprenyl treated rats survived longer, appeared healthier, ...".

The appellant itself has acknowledged that several causes can be behind a longer survival. One of these causes is a better renal function which has been investigated in the patent in suit for rats by an examination of blood chemistry and in particular the level of blood urea nitrogen (BUN), which is a measure of waste product cleared from the body by the kidneys (paragraph 36).

The patent in suit states that "the only significant difference between the controls and L-deprenyl group at three months was in the measure of BUN" (paragraph 43).

The patent in suit also discloses that "The blood chemistry data were informative, and provide a possible explanation as to why animals treated with L-deprenyl survived longer than the controls. At 26 months, there was a significant difference in the measure of BUN, with the deprenyl group having a lower score than the

controls. BUN is a measure of a waste product which is cleared from the body by the kidneys. High levels are therefore indicative of ineffective renal function" (paragraph 44).

The patent in suit further discloses that "The significant drug effect at 26 months therefore is indicative of L-deprenyl treatment providing protection of the renal function" and "That such protection is associated with survival is further indicated by the significant correlation between BUN measure and days of survival in the 26 month group" (paragraph 45).

Accordingly, in the context of the patent in suit the most plausible cause for a longer survival is a better renal function. It is also well known that an injured renal function is linked with an unhealthy appearance and hence a better renal function will cause the animals to appear healthier.

Therefore the board concludes that paragraph 56 does not contain evidence that L-deprenyl has an influence in retarding the age-dependent deterioration of the immune system function in mammals.

As regards the content of paragraph 60, it belongs to the examples in dogs which are prophetic in nature as mentioned in paragraph 57. Paragraph 60 refers to some possible mechanisms of action of L-deprenyl in the immune system. The appellant has cited the abstracts A1 and A2 in order to show that the predictions of paragraph 60 were confirmed.

However, none of the abstracts relates to the experiments mentioned in paragraph 60. Both abstracts correspond to articles with a publication date of 1998. They are articles by different authors to the inventors of the patent in suit. The aim of the study referred to in abstract A1 was to characterise the influence of selegiline (deprenyl) on the biosynthesis of IL-1 beta (interleukin-1 beta), IL-6 and TNF (tumor necrosis factor alpha) in human peripheral blood mononuclear cells (PBMC). Therefore abstract A1 does not concern either cells from L-deprenyl treated dogs or experiments about IL-2 as foreseen by paragraph 60 of the patent in suit.

As regards abstract A2, it relates to a study assessing the effect of deprenyl on longevity but due to the antioxidant enzyme's activities as superoxide dismutase (SOD) and catalase (CAT) in selective brain regions. This study about oxidative stress has nothing to do with the immune system experiments foreseen in paragraph 60 (splenocytes mitogenically challenged and IL-2 experiments). A2 refers to another study on the aging of beagle dogs which showed a remarkable effect on longevity but it is not disclosed in the abstract whether the longer survival can be linked to the retarding of the age-dependent deterioration of the immune system function or not.

Since the immune system as shown by document (1) and acknowledged by the appellant is a very complex system, a mere allegation without any concrete evidence is not acceptable in the present case to support the plausibility of the claimed solution.

Accordingly, it matters whether the patent in suit makes it plausible to the skilled person that the proposed solution works. The skilled person reading document (1) would come to the conclusion that deprenyl has negative effects on the immune system. Therefore additional data would be required to make it plausible that deprenyl has a positive influence on the immune system as claimed. There are no such data in the patent in suit. The board is of the opinion that it is not necessary to explain the mechanisms, but the concrete evidence that deprenyl has the effect claimed is required.

Therefore, in the absence of any evidence, the board can only conclude that the claimed influence of deprenyl on the immune system in dogs has not been achieved.

With respect to the appellant's argumentation that the opponent had never raised a lack of plausibility objection, it has to be said that it was in fact part of the opposition's division decision and the opposition division was entitled to raise this objection within its discretionary power when examining for inventive step (Article 114(1) EPC).

In view of the fact that one of the aims of the appeal procedure may be seen in the revision of the first-instance decision, it is within the framework of the present appeal to investigate that issue.

In this context it is to be noted that the question as to whether the problem has been plausibly solved has nothing to do with the sufficiency of the disclosure,

which only requires that the skilled person is able to treat dogs with L-deprenyl.

Furthermore, it is generally not required to present in vivo experiments in cases of claimed subject-matter relating to the so-called second medical use. Moreover, long life in dogs is not proof of the effect on the immune system and experiments with rats would have also sufficed.

Finally, commercial success is not proof that the claimed solution does actually solve the problem, since the product may be sold for other purposes such as providing for a longer life. As said several times, a longer life may have to do with other effects than that on the immune system.

Consequently, the mere allegation that the claimed effect occurs is not sufficient to support an inventive step as required by Article 56 EPC.

Since the alleged effect on the immune system appears in all requests, the board comes to the conclusion that none of the requests meets the requirements of Article 56 EPC.

Finally it is to be noted that dogs have already been treated with deprenyl for investigating the MAO-B activity in the brain (document (8), page 69, left column) and since it is undisputed by the parties that deprenyl (selegiline) is a well-known medicament of the class of MAO-B (monoaminooxidase) inhibitors used in treating Parkinson's disease and that it is also known as an antidepressant (see for instance documents (1),

page 772 first paragraph and (8), pages 68 and 73), nothing else in the claim relating to the so-called second medical use of a known active substance and a known medicament remains allowing the definition of a problem not already solved by the same means in the state of the art.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

A. Townend U. Oswald