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Datasheet for the decision of 23 November 2006

Case Number: T 1229/03 - 3.3.02

Application Number: 95901795.5

Publication Number: 0799041

IPC: A61K 31/565

Language of the proceedings: EN

Title of invention:
Estrogen compositions and method for neuroprotection

Applicant:
UNIVERSITY OF FLORIDA

Opponent:
-

Headword:
Estrogen compounds for treating neurodegenerative disorders/UNIVERSITY OF FLORIDA

Relevant legal provisions:
EPC Art. 123(2), 84, 54, 111

Keyword:
"Main (sole) request: Novelty (yes); Functional feature brings novelty to the use claimed"
"Remittal"

Decisions cited:
G 0002/88, G 0005/83

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1229/03 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 23 November 2006

Appellant: UNIVERSITY OF FLORIDA
RESEARCH FOUNDATION, INC.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 10 July 2003 refusing European application No. 95901795.5 pursuant to Article 97(1) EPC.**

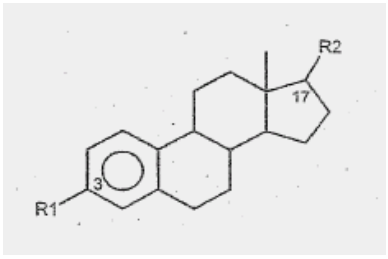
Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
H. Preglau

Summary of Facts and Submissions

I. European patent application No. 95 901 795.5 based on international patent application WO 95/12402 was filed with 46 claims. Claim 1 read as follows:

"1. A method of protecting a population of nerve cells from death, comprising: administering to a nerve cell population in an animal subject, an effective dosage of an estrogen compound sufficient to cause the nerve cell population to be protected from progressive cell damage leading to the death of the cells otherwise occurring without any intervention, the compound having a general structure:



a tautomer thereof, or a pharmaceutically acceptable salt thereof."

II. The following documents have been cited inter alia during the examination and appeal proceedings:

(1) L. L. Wright, Int. J. Dev. Neurosci., 5(4), 1987, 305—311
(2) K. Mizoguchi, Neurosci. Lett. 138, 1992, 157—160
(3) J. W. Simpkins, Adv. Behav. Biol., 36, 1989, 197-212
(4) US(B) 4 897 389

(5) K. J. Jones, Metabolic Brain Disease, 3(1), 1988, 1-18

(6) C. S. Emerson, Brain Res., 608, 1993 (publication date, 9 April 1993), 95-100

(7) A. Matsumoto, J. Compar. Neurol. 197, 1981, 197-205

(8) H. Honjo, J. Steroid. Biochem. Mol. Biol., 41, 1992, 633–635

III. The appeal lies from a decision of the examining division refusing the patent application under Article 97(1) EPC pursuant to the requirements of Article 54 EPC.

IV. The examining division considered that the subject–matter claimed in the main and sole request (set of claims, filed with the letter of 5 April 2001) concerned the treatment of all thinkable neurodegenerative conditions. Hence, according to the examining division's findings, document (4), which disclosed the use of estrogen compounds for attaining reversal of symptoms in patients suffering from a neurodegenerative disease (e.g. Alzheimer's disease), anticipated the subject–matter claimed.

Claim 1 of the set of claims filed with the letter of 5 April 2001 read as follows:

"1. Use of an estrogen compound in the manufacture of a pharmaceutical composition for protecting a population of nerve cells in an animal subject from progressive cell damage leading to the death of the cells."

V. The appellant (applicant) lodged an appeal against said decision and supported it with arguments.

VI. A communication from the board dated 12 June 2006 conveyed the board's preliminary opinion.

VII. The appellant filed with its response of 18 August 2006 a new main request and five auxiliary requests.

VIII. A communication from the board was sent as an annex to the invitation for oral proceedings in which the board raised an objection within the meaning of Article 123(2) EPC against some of the claims of the various requests.

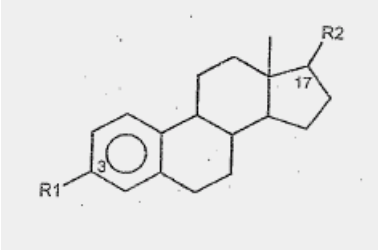
IX. The appellant filed with its letter of 19 October 2006 a new main request and five auxiliary requests.

X. Oral proceedings took place on 23 November 2006.

XI. During the oral proceedings before the board the appellant filed an amended set of claims as main and sole request.

Claim 1 of the main and sole request reads as follows:

"1. Use of an estrogen compound in the manufacture of a medicament for treating a neurodegenerative disorder in an animal subject by protecting a population of nerve cells from death, the estrogen compound having the following general structure:



a tautomer thereof, or a pharmaceutically-acceptable salt thereof;

wherein

R1 is selected from hydrogen, hydroxyl, methyl, methyl ether, acetate, ethyl ether, benzoate, benzyl ether, glucuronide, valerate, cyclopentylpropionate, propionate, hemisuccinate, palmitate, enanthate, and stearate;
and
R2 is selected from hydrogen, hydroxyl, oxo, methyl, methyl ether, acetate, ethyl ether, 17, 17—dimethyl ketal, ethynyl-α, benzoate, benzyl ether, glucuronide, valerate, cyclopentylpropionate, propionate, hemisuccinate, palmitate, enanthate, and stearate."

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

The main request filed during the oral proceedings met the requirements of Article 123(2) EPC, since it had been amended by deletion and/or replacement of those terms and claims objected by the board. In particular, claim 1 of the main request was based on originally filed claim 1, which had been redrafted in "Swiss-type form", and pages 8, 9 and 12 of the description, as well as claims 4 and 5 (with the corresponding substituent lists shown in figures 9A and 9B).

Claim 1 concerned, in "second medical use claim" form, the use of an estrogen compound (depicted and defined in the claim) for the therapeutic treatment of neurodegenerative disorders in an animal subject, by protecting a population of nerve cells from death.

The protection of a population of nerve cells from death in an animal subject was the ultimate form of neuroprotection and clearly excluded "systemic neuroprotection", which was linked to the cardiovascular system (and increase of blood flow), as well as reparative and mitogenic cell growth.

This feature of the claim, namely "by protecting a population of nerve cells from death", concerned a functional feature which was linked to the therapeutic treatment of the neurodegenerative disorders when using an estrogen compound and could not be read separately or isolated from the therapy. Said feature was neither an explanatory feature nor concerned the discovery of a mode of action of an established therapeutic practice. Therefore, it had a delimiting effect in the subject-matter claimed.

As regards the assessment of novelty in the light of the cited prior art, the appellant referred to its written submissions filed with the grounds of appeal and with its letter of 18 August 2006.

Basically, document (4) concerned a non-enabling disclosure because its author had been proven to be non-reliable (as shown by the documents submitted during appeal proceedings, which concerned legal

actions brought against the author) and since the document's contents were nonsensical and not credible. The experiments (one male and one female treated) reported in document (4) had no scientific value, since it is not possible to contra-produce long term degeneration such as that caused by Alzheimer's disease on the basis of one week or one month of treatment. Hence, the statements given in document (4) had no more merit than those given by a non-technical person, without any scientific basis and they lacked substance and proof. Furthermore, document (4) alleged that neurodegenerative diseases can be treated by compounds that make nerve cells grow, which is a different treatment to that of the present invention. Document (4) made no distinction with respect to the use of the hormones linked to the sexual effects. The anabolic effect mentioned in document (4) relates to growth of nerve.

Therefore, in the appellant's view, the skilled person faced in document (4) an insufficient disclosure as regards neuroprotection and, in particular, neuroprotection at cellular level.

Document (5) did not anticipate the subject-matter claimed since it referred to neurotrophism (inter alia in cholinergic system), which had to do with repair of the nerve system, but not with the function of protection of nerve cells from death. Moreover, the trial studies mentioned on post-menopausal women with Alzheimer's disease concerned the use of estrogen as feminising hormone, as for instance to enhance mood. There was no disclosure in document (5) concerning the treatment of neuronal loss by estrogen.

Therefore, the application in suit opened a new strategy for therapy which had to do with protection of the nerve cells from death, i.e. preserving nerve cells from dying and protecting the status quo, whereas neurotrophism had to do with cell growth. When a cell was damaged it triggered certain reparatory effects but eventually it died. Neuroprotection at cellular level meant preserving the nerve cells from death. Hence, the proposed therapy addressed the cause instead of the symptoms of the disease in a patient.

According to the appellant's submissions, document (1)'s experiments on postnatal mice, which relate to normal development pathways, were not an adequate model for dealing with the treatment of neurodegenerative disorders, including aging.

Furthermore, document (2)'s experiments which related to stress-induced neuronal death in the hippocampus of castrated rats were not an appropriate model either. Stress-induced neuronal death was an acute condition with a very different physiology to neurodegenerative disorders. Hence, document (2) did not anticipate the subject–matter claimed. Moreover, this would presuppose the person undergoing the stress to know in advance when the acute stress was going to occur.

As regards document (3), the appellant stated that one of the authors of the scientific publication (3), namely Mr Simpkins, was one of the inventors of the present application and at the time of its publication he did not know about neuroprotective effects by estrogen compounds. Therefore, one should avoid reading

document (3) with hindsight after being aware of the teaching of the application in suit. Moreover, analogous arguments to those given in respect of document (5) also applied.

In the appellant's view, apart from the fact that the estrogen activity disclosed in document (6) was exclusively to be linked to the sexual functionality of the hormone, the experiments discussed in document (6) were not scientifically conclusive, as acknowledged by the authors of said document (page 98, right column). Hence, there was no clear teaching which could be considered as novelty destroying for the subject—matter claimed.

Document (8) dealt with growth promotion which was distinct from neuroprotection of nerve cells, preserving them from death.

XIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims 1 to 13 as filed during the oral proceedings (main and sole request).

Reasons for the Decision

1. *Admissibility*

1.1 The appeal is admissible.

1.2 The late-filed main request (sole request) is admitted into the proceedings since the amendments introduced at the oral proceedings represent a clear and direct

response to the discussion which took place previous to their filing during the oral proceedings.

2. *Main (and sole) request*

Claim 1 of the main request meets the requirements of Article 123(2) EPC since it is based on originally filed claim 1 redrafted in a "Swiss–type form" in the light of the description as originally filed (WO 95/12402), in particular pages 8, 9 and 12. As regards the specific definitions of the substituents appearing in the generic formula, they correspond to those of originally filed dependent claims 4 and 5 (also appearing in figures 9A and 9B), with the deletion of those options which contravened the requirements of Article 84 EPC (clarity, conciseness).

Additionally, the amendments which were objected to by the board as contravening the requirements of Article 123(2) EPC have been deleted from the set of claims filed during the oral proceedings before the board.

Consequently, the set of claims of the main and sole request meets the requirements of Articles 123(2) and 84 EPC.

2.1 Novelty

As expressed in the "Order" (point (iii)) of the decision of the Enlarged Board of Appeal G 2/88, OJ EPO 1990, 093:

"(iii) A claim to the use of a known compound **for a particular purpose**, which is based on a technical effect which is described in the patent, should be interpreted as including that technical effect as a **functional technical feature**, and is accordingly not open to objection under Article 54(1) EPC provided that such technical feature has not previously been made available to the public." (*emphasis added*)

Moreover, the well established jurisprudence of the boards of appeal confirms that a new function (corresponding to a technical effect) may confer novelty on the use of known compounds.

Additionally, a "European patent may be granted with claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application". (G 5/83, OJ EPO, 1985, 064)

Claim 1 of the main request has been drafted in a "Swiss-type form" and concerns the use of an estrogen compound (as defined in the claim) *in the manufacture of a medicament* for treating a neurodegenerative disorder in an animal subject by protecting a population of nerve cells from death.

Therefore, before acknowledging the feature "by protecting a population of nerve cells from death" as a functional feature on which the novelty of the claimed use may be based, it first has to be assessed whether the said feature can be directly linked, on the one hand, to the therapeutic application "for treating a neurodegenerative disorder in an animal subject" and,

on the other, to the estrogen compound(s) for which the use is claimed. Additionally, when doing so, it has also to be assessed whether the intended technical effect is disclosed in the application in suit in a technically meaningful and plausible manner.

The board is satisfied about the definition of "neurodegenerative disorder" given on page 9, lines 12-15, of the application in suit, which reads "a disorder in which **progressive loss of neurons** occurs either **in the peripheral nervous system or in the central nervous system**". (*emphasis added*)

Hence, it is plausible and technically meaningful that "protecting a population of nerve cells from death" can be directly linked to the therapeutic application "treating a neurodegenerative disorder in an animal subject".

An inspection of the application in suit immediately makes apparent that the protection of nerve cells against neuronal loss by estrogen (α and ß) and by estrogen benzoate (a compound representative of the covalent derivatives encompassed by claim 1) has been proven by a handful of technical data obtained from several *in vitro* and *in vivo* (animal models) experimental tests.

The board is satisfied that the application in suit contains data which make credible, inter alia, the effect of cytoprotection on nerve cells caused by the estrogen compounds as defined in claim 1.

In particular, the increase in viability of nerve cells by using estrogen (α and ß), or estrogen benzoate, has been proven in a credible way by the *in vitro* experiments of examples la, 1b; longer survival of nerve cells has been proven by the experiments of example 1c; cytoprotection of nerve cells against cytotoxicity induced by hypoglycaemia has been proven by the *in vitro* experiments of examples 2a, 2b and the *in vivo* experiments of example 6; protecting effect on nerve cells against cytotoxicity induced by excitatory amino acids has been proven by the experiments of example 2c.

Therefore, the feature "by protecting a population of nerve cells from death", appearing in claim 1, can be acknowledged as a functional feature linked to the therapeutic application and to the compounds defined in the claim.

2.2 It remains now to determine whether the claimed use is novel over the cited prior art.

2.2.1 Leaving aside the question concerning the non-reliability of the author of document (4) in view of the legal actions pursued against her before US courts, the primary question which has to be answered, in order to decide whether or not the disclosure of document (4) is a non-enabling disclosure, is whether the skilled person could make a meaningful reading of document (4)'s content at its publication date. The following can be read under the heading "Detailed description of the invention" in column 3 of document (4).

"To **reverse the degenerative nature** of central nervous disorder disease, such as Parkinson's disease, Senile Dementia, Alzheimer's disease, senile tremor, and the like, and diseases especially associated with dementia, it has been discovered that treatment methods utilizing the synthesizing, metabolic effects of androgens, estrogens, and anabolic hormones **have reversed the degenerative nature** of the diseases, and have **restored patients suffering from the diseases to more normal and productive lives, with alleviation of many of the symptoms of the diseases**." (*emphasis added*)

Document (4)'s experimental basis for these statements is given in the bridging paragraph of columns 3 and 4, which reads:

"In one patient suffering from diagnosed Alzheimer's disease and early stage Parkinson's disease, which patient was sixty years old and weighed one—hundred eighty pounds, he was given 10mg. of fluoxymesterone USP daily. In conjunction with the fluoxymesterone, the patient was given 1 mg. of ergolid myselates four times a day; and acetyl salicylic acid enteric coated, four times a day, all taken orally. **Within one week of the start of this treatment, the patient experienced noticeable improvement, including the cessation of Parkinsonism tremor, and a wider span of attentiveness**. In about one month from the start of the treatment, the patient stopped bed-wetting, and was able to concentrate on television and other mentally—stimulating activities. Within about two months, the patient's intellectual capacity increased so that he could carry on a conversation with another person...". (*emphasis added*)

Apart from the fact that in the above-cited case the combination therapy refers to a synthetic androgen and not to an estrogen compound, it becomes apparent from the above-quoted and marked passages that it is highly questionable and can only be seen as scientifically unfounded to claim that any serious conclusion can be attained in respect of the therapeutic activity concerning the treatment of severe long-acting degenerative diseases on the basis of one single patient and several weeks' treatment!

Surprisingly enough, document (4) extrapolates this "teaching" about anabolic male sex hormones and proposes the use of estrogen in female patients: "For women, estradiol, a major anabolic sex hormone in a female is needed. For men, androgen, a major anabolic sex hormone in a male is needed." (column 5, lines 22-25)

Document (4) further reports: "Thus, **in one case history** of a female patient 78 years of age, weighing approximately one-hundred fifty pounds, diagnosed as having Alzheimer’s disease, the patient was given the following, orally: 1.25mg. conjugated estrogen once a day; 10mg. methyltestosterone once a day; 1mg. ergoloid myselate USP four times a day; dipyridamole four times a day; and 300mg. acetyl salicylic acid enteric coated four times a day...Just as in the case of the male patient noted above, this female patient experienced marked and fast rejuvenation, dissipation of dementia, increased mental alertness, and a general vitalization such that many of her Alzheimer’s disease symptoms by conventional diagnosis, but senile dementia disappeared

by new biochemical diagnosis in FIG. 3 and 4." (column 5, lines 25–33, 37–44) (*emphasis added*)

Figure 3 concerns a graphic "Venous blood fluctuation" versus time (0 to 120 minutes) and figure 4 concerns a graphic "Proportional concentration of brain neuro–transmitter acetyl choline esterase in ng/ml versus time (0 to 120 minutes).

Besides the fact that the treatment of one single female reported in column 5 relates to a combined therapy, there is a lack of scientific validity for the two (one male and one female) **one patient/short term treatment**(s) as a credible basis for the therapeutic application concerning the treatment of the severe long–acting diseases mentioned in document (4).

In view of the above, the disclosure of document (4) is considered as non-enabling.

Therefore, document (4)'s allegation that "for female patients suffering from the above-named central nervous system degenerative diseases, the use of estradiol alone in suitable dosage provides sufficient anabolic effect, so that the use of an anabolic hormone supplemental to the female sex hormone is not needed" (which corresponds to the subject–matter of claim 1 of document (4)), amounts to a speculative statement without any scientific basis.

Correspondingly, such a non–enabling disclosure cannot be considered as part of the state of the art.

Therefore, document (4) does not anticipate the subject—matter claimed in the main request.

2.2.2 The studies disclosed in document (1) deal with developmental neuron death in postnatal mice and the studies disclosed in document (2) relate to stress-induced neuronal death. The board is satisfied that the appellant's submissions in respect of these two documents are well-founded and scientifically sound. Therefore, it is considered that the studies of documents (1) and (2) cannot serve as valid experimental models for the treatment of neurodegenerative disorders. Hence, documents (1) and (2) do not anticipate the subject—matter claimed.

2.2.3 As regards document (5), it clearly concerns a review article which deals with neurotrophism and does not account for protection of a population of nerve cells from death. The information given in document (5) under the heading "Gonadal steroid hormone use in the damaged nervous system" concerns the promotion of neural plasticity which has to do with **reparation** mechanisms concerning growth-like effects (*inter alia*, increase of synapses, cell density) but cannot be considered as an anticipation of the **treatment of neurodegenerative disorders by protecting a population of nerve cells from death.**

Furthermore, although positive results are reported in the above-mentioned section of document (5) in relation to trial studies with estrogen in post-menopausal women with Alzheimer's disease, they concern improved performance scores on a number of psychometric tests including mood, attention, orientation and social

interaction, but they do not reveal more than the effects of a feminizing hormone replacement therapy, without any teaching concerning protection of nerve cells from death.

Therefore, document (5) cannot be considered to destroy the novelty of the subject–matter claimed in the main request.

2.2.4 Analogous arguments to those given in point 2.2.3 above in respect of post-menopausal women also apply to the trial studies reported in document (3) for "estrogen compounds". (page 207, first full paragraph)

Additionally, it has to be said that the estradiol ester derivative E_2–CDS depicted on page 200 of document (3) is not encompassed by the definitions of estrogen compounds given in claim 1 of the main request.

Therefore, document (3) does not anticipate the subject–matter claimed in the main request.

2.2.5 The scientific studies disclosed in document (6) which relate to the biochemical and neurological outcome following traumatic brain injury in male rats, but not in females, are not conclusive and they are statistically non-significant, as acknowledged in document (6) itself (end of right-hand column, page 98). Hence, the content of document (6) cannot be considered to anticipate the subject–matter claimed in the main request.

2.2.6 Document (8) discloses studies concerning estrogen as a growth factor for central nervous cells, using

estradiol valerate, but does not disclose the technical effect of protecting of a population of nerve cells from death.

2.2.7 Document (7) is not relevant for the assessment of novelty.

2.3 In conclusion, the subject—matter claimed in claim 1 of the main request is novel over the cited prior art, since it does not concern an explanatory mode of action of an established therapy, but addresses a new therapeutic application by achieving the technical effect of protection of nerve cells from death in an animal subject.

Additionally, claims 2 to 13 are dependent claims. Consequently, the subject-matter claimed in the main request meets the requirements of Article 54 EPC.

3. *Remittal to the department of first instance*

3.1 The set of claims on which the first—instance decision was based related to very broadly defined use claims whereas the set of claims of the main request filed during the oral proceedings before the board relates to second medical use claims in "Swiss—type form", with specifically defined subject—matter.

Therefore, the board has decided to make use of its discretionary power under Article 111(1) EPC to remit the case to the first-instance department in order not to deprive the applicant of two instances for dealing with the issue concerning inventive step.

The department of first instance is reminded of the fact that since the case is remitted for further prosecution that department is bound by the *ratio decidendi* of the board of appeal (Article 111(2) 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 for further prosecution.

The Registrar | The Chairman

A. Townend | U. Oswald