Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 18 February 2014

Case Number: T 1710/10 - 3.3.07

Application Number: 04768829.6

Publication Number: 1670489

IPC: A61K33/00, A61P11/00

Language of the proceedings: EN

Title of invention:
USE OF XENON WITH HYPOTHERMIA FOR TREATING NEONATAL ASPHYXIA

Patent Proprietor:
Imperial Innovations Limited

Opponent:
L'AIR LIQUIDE, Société Anonyme
pour L'étude et L'exploitation
des procédés Georges Claude

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 1710/10 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 18 February 2014

Appellant: (Opponent)	L'AIR LIQUIDE, Société Anonyme pour L'étude et L'exploitation des procédés Georges Claude 75, Quai d'Orsay 75321 Paris Cedex 07 (FR)
Representative:	Pittis, Olivier L'Air Liquide, S.A. Direction de la Propriété Intellectuelle 75, Quai d'Orsay 75321 Paris Cedex 07 (FR)
Respondent: (Patent Proprietor)	Imperial Innovations Limited 52 Princes Gate Exhibition Road London SW7 2PG (GB)
Representative:	Clyde-Watson, Zöe D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 27 July 2010 rejecting the opposition filed against European patent No. 1670489 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman: J. Riolo
Members: A. Usuelli
P. Schmitz

Summary of Facts and Submissions

I. The appeal of the opponent (appellant) lies against the decision of the opposition division to reject the opposition against European patent No. 1670489.

The patent was granted with 22 claims. Independent claims 1 and 22 read as follows:

"1. Use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia in a neonatal subject, wherein said medicament is for use in combination with hypothermia."

"22. Use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said treatment comprises administering to a subject simultaneously, sequentially or separately xenon in combination with hypothermia."

II. An opposition was filed against the patent as a whole. It was based on Article 100(a) together with Articles 54 and 56 EPC. The opponent relied *inter alia* on the following documents:

D2: Pediatr. Res., 1998, 43(6):738-745 (abstract)
D3: Stroke, 1989, 20(7): 904-910 (abstract)
D4: US 6,559,190

III. In its decision, the opposition division came to the following conclusions:

a) The granted patent met the requirements of Article 54 EPC.
b) Starting from D4 as closest state of the art, and taking into account the experimental data of the

description which were considered to render credible the presence of a synergistic effect, the objective technical problem was seen as "how to adapt the closest prior art in order to achieve such synergistic effect". Since there was no hint in the cited documents to combine the use of xenon with hypothermia in order to obtain a synergistic effect, the patent was considered to comply with the requirements of Article 56 EPC.

IV. The appellant lodged an appeal against that decision. In the statement setting out the grounds of appeal it limited its arguments to the ground of lack of inventive step.

V. In the reply sent on 24 January 2011, the patent proprietor (respondent) requested as main request the maintenance of the patent as granted and submitted 2 sets of claims as first and second auxiliary requests.

VI. A communication was sent by the Board on 11 December 2013 in preparation for oral proceedings. Having regard to the assessment of inventive step, it observed that the experimental data of the patent appeared to corroborate the presence of a synergistic interaction between xenon and hypothermia.

VII. On 18 February 2014 oral proceedings were held before the Board.

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

a) Document D4 represented the closest state of the art for the assessment of inventive step. This document disclosed the use of xenon in the treatment of neurointoxications of various

origins, including oxygen deficiency during birth. The invention of the opposed patent differed from the disclosure of D4 in view of the additional use of hypothermia in combination with xenon.

b) During the written procedure, the significance of the experimental data disclosed in example 2 and figure 17A was contested. The objection was based on the observation that each value reported in the figure was affected by a high error of measurement, and that it was not clear whether the measurements were made at the same point of time for all the groups of animals. The alleged synergistic interaction between xenon and hypothermia was therefore not shown. This argument was not pursued at the oral proceedings, and the presence of a synergistic effect was acknowledged. The technical problem was defined as the provision of a method for the treatment of neonatal asphyxia resulting in an improved neuroprotection.

c) The solution of combining xenon with hypothermia was obvious in the light of the teaching of the closest prior art in combination with the teaching of D2 and D3 which disclosed the beneficial effects of hypothermia in rat models of hypoxia-ischemia and ischemia respectively. In particular, the indication in D3 that a treatment of hypothermia completely inhibited the release of glutamate, and the teaching of D4 (column 5) that xenon respiration prevented the negative effects of dopamine release, would have prompted the skilled person to combine the two treatments in order to minimise the negative effects of both glutamate and dopamine. The fact that D3 did not relate to the treatment of newborns was not

relevant, because the teaching that hypothermia inhibited the glutamate release would have been considered important also for the treatment of neonates suffering from hypoxia. Since there were no reasons for fearing any possible side-effect associated with the combined use of xenon and hypothermia and since no alternative treatments were suggested in the prior art, a skilled person would have tested said combination and necessarily observed the presence of a synergistic interaction.

d) For the same reason the subject-matter of the auxiliary requests was obvious in view of the state of the art.

IX. The respondent's arguments can be summarised as follows:

a) D4 represented the closest prior art. The claimed combination of xenon and hypothermia resulted in a synergistic effect which was supported by the experimental data of the description, in particular by figure 17A. The experimental results of example 2 were considered statistically relevant using the test described in paragraph [0137] of the patent. Furthermore, it was clear from paragraph [0142] that figure 17A provided a comparison at equivalent time points. The technical problem was therefore seen in the provision of an improved treatment for hypoxia-ischemia in neonates.

b) The prior-art documents did not suggest combining the uses of xenon and hypothermia with a reasonable expectation of synergy. The disclosure

of D4 was speculative because the experimental data were based on *in vitro* experiments. D3 was not concerned with the treatment of newborns. A skilled person would have considered that the brains of newborns and adults were different and therefore he would have not combined the teaching of D3 and D4. The effects of "combination" treatments were known as inherently unpredictable. Thus, even if the skilled person had considered the possibility of combining the teaching of D4 with D3 and D2, taking into account all the uncertainties, he would not have expected to obtain the results shown in the patent.

c) The same arguments applied to the subject-matter of the auxiliary requests.

X. The appellant requested that the decision under appeal be set aside and that European patent No. 1670489 be revoked.

XI. The respondent requested that the appeal be dismissed, alternatively that the decision under appeal be set aside and that the patent be maintained on the basis of the first or second auxiliary request filed with letter dated 24 January 2011.

Reasons for the Decision

Main Request

1. *Novelty*

The ground of novelty was no longer pursued by the appellant during the appeal proceedings. The Board sees no reasons for deviating from the conclusions of the

first instance. Accordingly, the subject-matter of the granted patent is considered to comply with the requirements of Article 54 EPC.

2. *Inventive Step*

2.1 The invention addresses the problem of providing a treatment for neonatal asphyxia (see [0006]).

2.2 The Board agrees with the decision of the opposition division and with the parties that D4 represents the closest state of the art. This document discloses the use of xenon for treating neurointoxications due to an uncontrolled release of neurotransmitters (column 1, lines 9-17). According to one of the embodiments, the neurointoxication is caused by oxygen deficiency during birth (column 3, lines 8-10). It was undisputed by the parties that the definitions "oxygen deficiency during birth" and "neonatal asphyxia" used respectively in D4 and in the opposed patent related to the same clinical condition.

2.3 The subject-matter of claim 1 differs from the disclosure of D4 in that the neonatal asphyxia is treated by the combined use of xenon and hypothermia instead of the use of xenon alone. This finding was uncontested by the parties.

2.4 In order to define the objective technical problem it is necessary to establish the effect achieved by the combination of xenon and hypothermia over the treatment using only xenon disclosed in D4. In this respect, particularly relevant are the results disclosed in example 2 and figure 17A of the patent, which concern a comparative study using an animal model of hypoxia-ischemia. It is explained in example 2 (see [0117]),

that the brain injuries in the animal model resemble hypoxic-ischemic injury in the human neonate.
Figure 17A shows that there is no neuroprotection when the animals are treated with 20% xenon alone or when they receive only a treatment of hypothermia at 35°C, because the percentage of viable cells for each group is not better than the corresponding percentage for the control group, i.e. animals who did not receive any therapeutic treatment. On the contrary, the combined use of 20% xenon and hypothermia at 35°C, produces a significant level of neuroprotection, as shown by the percentage of viable cells which is ca. 30% higher than the percentage for the control group. In the Board's opinion, the effect of protection provided by the combination of two treatments which are not effective when applied individually is evidence supporting the existence of a synergistic interaction between these treatments. The concerns expressed by the appellant in the written proceedings as to the statistical relevance of these data do not appear justified having regard to the indication to be found in the description that a "Data analysis was performed using one-way ANOVA... A $p<0.05$ was considered to be statistically relevant." ([0137]). The p values for the results of figure 17A are indeed below 0.05 (column 18, lines 20 to 38). Furthermore, in the light of the explanation given in paragraphs [0141] and [0142], it is clear that the data of figure 17A for the control group and for the groups treated only with xenon or only with hypothermia derive from measurements made after 16 hours. Concerning the animals receiving both treatments, figure 17A contains results of measurements made after 16, 24 or 48 hours. Thus, contrary to the position expressed by the appellant in the written proceedings, it is possible to compare data obtained at the same point of time, namely 16 hours, for all the

groups of animals. At the oral proceedings the presence of a synergistic effect was no longer disputed.

2.5 The experimental results of example 2 demonstrate therefore that the combined treatment according to the patent provides better neuroprotection over the treatment of D4 and that hypothermia and xenon act synergistically. In the light of these results, the technical problem is defined as the provision of an improved treatment for asphyxia in neonates.

2.6 The question to be answered is whether the proposed solution would have been obvious to a skilled person in the light of the prior art.

2.6.1 The closest prior art D4 teaches that xenon can reversibly suppress the release of neurotransmitter and in view of this property it is potentially useful in the treatment of a number of different disorders (column 3, lines 62 to 65 and column 4, lines 34-38). Although oxygen deficiency during birth is mentioned among the disorders, D4 does not contain any experimental data relating to the treatment of this specific condition. The two examples of this document relate to *in vitro* experiments and show the efficacy of xenon in inhibiting the release of dopamine (examples 1 and 2 and figures 1 and 2).

2.6.2 Results relating to the application of hypothermia treatments are disclosed in the abstracts D2 and D3. D3 relates to a rat model of ischemia. No reference is made in this document to the treatment of neonates. The results disclosed in D3 indicate that a treatment of hypothermia completely inhibits the release of glutamate and partly the release of dopamine. D2 describes the effects of moderate hypothermia in a rat

model of neonatal hypoxia-ischemia. It is stated *inter alia* that the neuroprotection offered by hypothermia in the cerebral cortex, hippocampus, basal ganglia and thalamus is between 25 and 35%, and that the sensorimotor function is not significantly improved when all the animals are considered.

2.6.3 The above remarks with regard to the teachings of D2, D3 and D4 underline the absence of conclusive results demonstrating the effectiveness of xenon or hypothermia in the treatment of neonatal asphyxia. In particular, the encouraging results disclosed in D3 and D4 with regard to the inhibition of the release of dopamine and glutamate are obtained in the context of experiments which do not concern the treatment of neonatal asphyxia. As to D2, certain conclusions set out in this document appear to cast some doubt on the efficacy of the use of hypothermia in a model of neonatal ischemia (see above).

2.6.4 In the Board's opinion, due to all these uncertainties as to the effectiveness of xenon and hypothermia the skilled person would not be motivated to combine the two treatments with any founded expectation of obtaining an improvement in the cure of neonatal asphyxia. Furthermore, synergy implies the existence of an interaction between xenon and hypothermia leading to an effect greater than the sum of the individual effects. However, nothing in the prior-art documents would suggest such behaviour of xenon and hypothermia when used in combination. The observation that according to D4 the use of xenon inhibits dopamine release and according to D3 a treatment of hypothermia completely inhibits glutamate release underlines the fact that the two treatments act on the release of neurotransmitters causing brain injuries. Yet, nothing

is said in these documents as to the existence of any possible link or interrelation between the biological mechanisms involved in the administration of xenon and in the use of hypothermia. However, in order for a synergistic effect to occur, there must be a mutual influence of the activities of the two individual treatments. It is precisely this information which appears missing in the prior-art documents.

2.6.5 The appellant's argument that the teaching of D3 and D4 concerning the effects of xenon and hypothermia on the release of dopamine and glutamate would have prompted the skilled person to combine these two treatments is also not convincing because it appears to be based on an over-simplification of the mechanisms involved in neonatal asphyxia. It is however clear from the description (see [0017] to [0019]) that when the blood supply becomes interrupted, as in the case of neonatal hypoxia, a number of metabolic changes occur which are not limited to the release of dopamine and glutamate. Mechanisms such as apoptosis and necrosis are involved too after hypoxic-ischaemic events (see [0020] to [0022]). Thus, also having regard to the complexity of the biological processes involved in neonatal asphyxia, the Board considers that the skilled person would have no reason for regarding the combination of xenon and hypothermia as a promising therapy for this pathology, not to mention a therapy involving a synergistic interaction between the two treatments.

2.6.6 The appellant has also argued that a skilled person would have no prejudice against the possibility of combining xenon and hypothermia since there were no reasons for fearing side-effects. However, this argument is not convincing because the absence of any indication in this respect does not mean that the

skilled person would combine xenon and hypothermia with the expectation of obtaining a synergistic effect.

2.6.7 The Board has also considered whether the skilled person would arrive at the combination of xenon and hypothermia for the sole reason that no other alternatives are suggested by the prior-art documents, i.e. whether a "one-way street" situation exists as argued by the appellant. It is considered however that an alternative to the use of xenon disclosed in the closest prior-art document could be its replacement with a treatment of hypothermia. Such alternative would possibly be considered even more straightforward and predictable than a combination therapy. Furthermore, it is stated in the description of the patent (see [0025]) that also NMDA antagonists have been investigated as a further alternative. The Board therefore sees no "one-way-street" situation in the present case.

2.7 In view of the above considerations, the Board concludes that the subject-matter of claim 1 meets the requirements of Article 56 EPC.

2.8 The appellant objected to claim 22 by merely relying on the same arguments as those submitted in respect to claim 1. This claim is therefore considered to meet the requirements of Article 56 EPC for the same reasons given in respect of claim 1.

In view of the above, the decision of the opposition division is to be maintained.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Fernández Gómez J. Riolo

Decision electronically authenticated