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Datasheet for the decision of 15 April 2014

Case Number: T 0165/11 - 3.3.01

Application Number: 97925571.8

Publication Number: 1021084

IPC: A01N1/02, A61M1/00, A61M31/00

Language of the proceedings: EN

Title of invention:
SOLUTION AND PROCESS FOR RESUSCITATION AND REPARATION OF ISCHEMICALLY DAMAGED TISSUE

Patent Proprietor:
Breonics, Inc.

Opponent:
Vitrolife Sweden AB

Headword:
Repair of ischemical damage/BREONICS

Relevant legal provisions:
EPC Art. 123(2), 100(a)

Keyword:
Main request and auxiliary request 1: amendments - added subject-matter (yes)
Auxiliary request 2: inventive step (yes)

Decisions cited:
G 0010/91

Catchword:

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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 0165/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 15 April 2014

Appellant: (Opponent)	Vitrolife Sweden AB Faktorvägen 13 43437 Kungsbacka (SE)
Representative:	Dean, John Paul Withers & Rogers LLP 4 More London Riverside London SE1 2AU (GB)
Respondent: (Patent Proprietor)	Breonics, Inc. W.A. Harriman Campus Drive Building 7A, Suite 310 Albany, NY 12206 (US)
Representative:	Griffin, Philippa Jane Mathys & Squire LLP 120 Holborn London EC1N 2SQ (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 26 November 2010 concerning maintenance of the European Patent No. 1021084 in amended form.**

Composition of the Board:

Chairman: A. Lindner
Members: C. M. Radke
D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 021 084 relates to a process restoring the integrity, function and viability of an ischemically damaged organ, and to a solution which is perfused into this organ during this process.

The solution contains compounds called **chemical energy substrates** which will be referred to in the following as **CES**.

II. Independent claims 1 and 5 of the patent as granted read as follows:

"1. A process for inducing repair of an ischemically damaged organ to the degree that impairment of organ function can be reversed, said process comprises flushing the organ at a temperature of about 28°C to about 37°C with a buffered physiological solution to remove blood and acidotic products which have accumulated in the organ during blood flow deprivation;

and perfusing the organ at a temperature of about 28°C to about 37°C with a buffered physiological solution which further comprises a vasodilator for dilating blood vessels within the organ, trophic factors for reestablishing cellular integrity and cellular function thereby restoring organ function, and at least one chemical energy substrate selected from the group consisting of AMP, UTP, coenzyme A, β-nicotinamide adenine dinucleotide (Nad^+), β-nicotinamide adenine dinucleotide phosphate (NADP), flavin adenine dinucleotide (FAD), diphosphopyridine nucleotide, **tri-phosphopyridine nucleotide monosodium** and cocarboxylase for re-establishing oxidative metabolism in the organ in readapting the organ to an oxygenated environment."

"5. A resuscitation solution for inhibiting ischemic damage, and for inducing repair of ischemic damage to a degree that impairment of organ function is reversed in an organ deprived of blood flow, said resuscitation solution comprises a buffered physiological solution and further comprises:

vasodilators in a physiologically effective amount for dilating vasculature of the organ;

at least one chemical energy substrate selected from the group consisting of AMP, UTP, coenzyme A, β-nicotinamide adenine dinucleotide (Nad^+), β-nicotinamide adenine dinucleotide phosphate (NADP), flavin adenine dinucleotide (FAD), diphosphopyridine nucleotide, **tri-phosphopyridine nucleotide monosodium** and cocarboxylase, in a physiologically effective amount to reestablish oxidative metabolism lost during organ blood flow deprivation; and

trophic factors in a physiologically effective amount to promote one or more cellular repair processes to reestablish cellular function lost during organ blood flow deprivation."

(Emphasis added by the board)

III. The opposition against the patent in suit was directed against the patent as a whole and was based on grounds under Article 100(a) (lack of inventive step), (b) and (c) EPC.

IV. The opponent appealed against the interlocutory decision of the opposition division that the patent in

suit amended according to the auxiliary request meets the requirements of the EPC.

The opposition division had decided that the feature "tri-phosphatopyridine nucleotide monosodium" mentioned in claims 1 and 5 as granted (main request) had no basis in the application as filed.

V. The documents cited during the opposition proceedings include the following:

(D1) WO-A-95/31 897
(D2) WO-A-94/21 116
(D12) L. Brasile et al., Transplantation Proceedings, vol. 29 (1997), 3422-3423
(D13) B. M. Stubenitsky et al., Transplantation, vol. 70, no. 8 (27 October 2000), 1254-1258
(D14) L. Brasile et al., American Journal of Transplantation, 2001, no.1, 316-320
(D16) L. Brasile et al., Transplantation, vol. 73, no.6 (27 March 2002), 897-901
(D18) L. Brasile et al., Transplantation Proceedings, vol. 34 (2002), 2624
(D19) L. Brasile et al., American Journal of Transplantation, 2005, no. 5, 300-306
(D20) R. W. Jamieson and P. J. Friend, Transplantation Reviews, vol. 20 (2006), 172-178
(D40) A. Kawamura et al., The International Journal of Artificial Organs, vol. 17, no. 1 (1994), 053-060
(D47) E-mail dated 11 May 2001 of Abbott Laboratories to C. Neuland of the FDA, five pages.

VI. In the appeal proceedings, the following document was additionally cited:

(D49) L. Brasile et al., Transplantation Proceedings, vol. 32 (2000), 177-178.

VII. The present claims are those filed under cover of the letter dated 14 October 2011, i.e.

- claims 1 to 10 of the main request,
- claims 1 to 10 of auxiliary request 1,
- claims 1 to 10 of auxiliary request 2, and
- claims 1 to 9 of auxiliary request 3.

a) The claims of the main request are identical with the claims of the auxiliary request the opposition division deemed to be allowable in the decision under appeal.

Claim 1 and 5 of the main request read as follows:

"1. An ***ex vivo*** process for inducing repair of an ischemically damaged organ to the degree that impairment of organ function can be reversed, said process comprises:
flushing the organ **through the arterial system** at a temperature of about 28°C to about 37°C with a resuscitation solution to remove blood and acidotic products which have accumulated in the organ during blood flow deprivation; and

perfusing the organ at a temperature of about 28°C to about 37°C with a resuscitation solution;

wherein the resuscitation solution comprises a buffered physiological base solution and further comprises the following combination of supplements:

(i) vasodilators in a physiologically effective amount, for dilating blood vessels within the organ, wherein the vasodilators comprise from 1% to 50% by volume (w/v) of the combination of supplements added to the base solution;

(ii) trophic factors for reestablishing cellular integrity and cellular function thereby restoring organ function, and

(iii) a combination of chemical energy substrates selected from the group consisting of AMP, UTP, coenzyme A, b-nicotinamide adenine dinucleotide (Nad+), b-nicotinamide adenine dinucleotide phosphate (NADP), flavin adenine dinucleotide (FAD) and cocarboxylase, in a physiologically effective amount, for re-establishing oxidative metabolism in the organ in readapting the organ to an oxygenated environment, wherein the chemical energy substrates comprise from 0.01% to 90% by volume of the combination of supplements added to the base solution."

"5. A resuscitation solution for inhibiting ischemic damage, and for inducing repair of ischemic damage to a degree that impairment of organ function is reversed in an organ deprived of blood flow, said resuscitation solution comprises a buffered physiological base solution and further comprises the following combination of supplements:

(i) vasodilators in a physiologically effective amount for dilating vasculature of the organ; wherein the vasodilators comprise

from 1% to 50% by volume (w/v) of the combination of supplements added to the base solution;

(ii) a combination of chemical energy substrates selected from the group consisting of AMP, UTP, coenzyme A, b-nicotinamide adenine dinucleotide (Nad+), b-nicotinamide adenine dinucleotide phosphate (NADP), flavin adenine dinucleotide (FAD) and cocarboxylase, in a physiologically effective amount to reestablish oxidative metabolism lost during organ blood flow deprivation, wherein the chemical energy substrates comprise from 0.01% to 90% by volume of the combination of supplements added to the base solution; and

(iii) trophic factors in a physiologically effective amount to promote one or more cellular repair processes to reestablish cellular function lost during organ blood flow deprivation."

b) Auxiliary Request 1

The claims of this request differ from the ones of the main request in that in the definition of the CES in claims 1 and 5 "selected from the group consisting of ... and cocarboxylase" has been replaced by "comprises ... and cocarboxylase".

c) Auxiliary Request 2

The claims of this request differ from the ones of auxiliary request 1 in that in the definition

of the CES in claims 1 and 5 "comprises AMP, UTP, coenzyme A, b-nicotinamide adenine dinucleotide (Nad+), b-nicotinamide adenine dinucleotide phosphate (NADP), flavin adenine dinucleotide (FAD) and cocarboxylase" has been replaced by "comprises **pyruvate**, **glucose**, **ATP**, AMP, UTP, coenzyme A, b-nicotinamide adenine dinucleotide (Nad+), b-nicotinamide adenine dinucleotide phosphate (NADP), flavin adenine dinucleotide (FAD), cocarboxylase, **chloride**, **adenosine and magnesium**" (emphasis added by the board).

d) Auxiliary Request 3

The claims of this request differ from the ones of the auxiliary request 2 in that "organ" has been replaced by "kidney" and claim 10 has been deleted.

VIII. The arguments of the appellant (opponent), as far as relevant for this decision, may be summarised as follows:

Article 123 EPC

The list of the (chemically not related) CES which has been restricted with respect to the one disclosed on page 16, lines 13-20, has no basis in the application as filed.

Article 100(b) EPC

The patent only discloses one specific resuscitation solution. It is not credible that the person skilled in the art could work the invention over the whole scope of the claims, especially as glucose, which is not

mentioned in the claims of the main request, seems to be essential as it is the supplement added in the largest quantity. As kidneys are the least sensitive organs (see document (D2)) the results obtained with kidneys cannot be transferred to other organs.

Novelty

The subject-matter of claim 1 lacks novelty in view of document (D1).

Inventive step

The subject-matter of claims 1 and 5 is not inventive in view of document (D40).

The examples of the patent in suit cannot show an advantage over the prior art for the following reasons:

- It is not clear whether the solution disclosed in Table 1 of the patent in suit was also used in the examples;
- the examples do not disclose the kidney function over time; they only indicate the function at the end point; hence, the function of the kidneys prior to the perfusion treatment is not known;
- the solution disclosed in documents (D14) and (D16) performs well although it does not contain a CES as defined in claims 1 and 5 of the main request.

IX. The respondent's arguments, as far as relevant for this decision, may be summarised as follows:

Article 123 EPC

The combination of CES is properly based on page 16, lines 3-5 and 13-20 of the application as filed.

Article 100(b) EPC

The appellant's objection is unsubstantiated. Glucose is present in many base solutions. The liver, not the kidney is the organ least sensible to warm ischemic damage. As to the test on livers, see document (D49).

Novelty

Novelty was neither raised as a ground for appeal, nor admitted into the proceedings by the opposition division, nor does the patent proprietor give its consent to admit this fresh ground.

Inventive step

In document (D40), the urine production of undamaged kidneys is increased, which means that the solution causes leakage and thus damages the kidneys. Hence, this document does not show a positive effect on the kidneys, let alone the reversal of the damages. The problem to be solved was to repair ischemically damaged organs. The examples in the patent in suit show that this problem was solved. This is confirmed by post-filed evidence (see documents (D12)-(D14), (D16) and (D18)-(D20)). The tables in documents (D14) and (D16) referred to the base solution and did not include all the supplements. The appellant has not shown that the problem is not solved over the whole breadth of the claims. Neither (D40) (which only cites glucose as CES, which, however, does not prime the organ to prepare for

the restoration of oxidative metabolism), nor any other prior art cited, renders the subject-matter of the present claims obvious, as

- the flushing step in (D40) is performed with lactated Ringer's solution, not with the perfusion solution; and
- the temperature in (D40) is lower than that required in the present claims.

X. The appellant and opponent had been duly summoned but was absent at the oral proceedings before the board, as announced in its letter dated 18 February 2014.

The proceedings were thus held in the absence of the duly summoned appellant in accordance with Rule 115(2) EPC.

XI. The appellant (opponent) requested in writing that the decision under appeal be set aside and that the European patent No. 1 021 084 be revoked.

The respondent (patent proprietor) requested that as a Main Request, the appeal be dismissed, or alternatively that the decision under appeal be set aside and the patent be maintained upon the basis of the claims of any of Auxiliary Requests 1 to 3, all submitted under cover of a letter dated 14 October 2011.

XII. At the end of the oral proceedings the chairman announced the decision of the board.

Reasons for the Decision

1. The appeal is admissible.

2. Article 100(b) EPC

In opposition appeal proceedings each party bears the burden of proof for the facts it relies on.

The appellant did not provide any evidence in support of its argument that the person skilled in the art could not work the invention over the whole scope of the claims.

Hence, it is to be concluded that the ground for oposition under Article 100(b) EPC does not prejudice the maintenance of the patent.

3. Novelty

Lack of novelty was neither raised as a ground for opposition nor introduced as such by the opposition division. It was raised for the first time in the statement setting out the grounds of appeal.

"Fresh grounds for opposition may be considered in appeal proceedings only with the approval of the patentee" (G10/91, OJ EPO 1993, 420, point 3 of the opinion).

The patent proprietor (respondent) has not given its consent to the introduction of this new ground for opposition.

Hence, the board may not consider this fresh ground of opposition.

4. Main Request and Auxilary Request 1

4.1 The appellant considered that the limitation of the list of CES in claims 1 and 5 of both requests with respect to those disclosed on page 16 of the application as filed contravened the requirements of Article 123(2) EPC (see point VIII above).

This limitation has the effect that the following compounds mentioned on page 16, lines 13-20, as examples of CES are no more among those listed in the claims mentioned above:

Pyruvate, glucose, ATP, chloride, adenosine and magnesium.

4.2 Furthermore, the concentration of the CES has been limited by the range disclosed on page 16, lines 24-28 of the application as filed.

This second limitation requires that "the chemical energy substrates comprise from 0.01% to 90% by volume of the combination of supplements added to the base solution".

4.3 During the oral proceedings before the board it was discussed whether the combination of these two limitations introduces subject-matter which extends beyond the content of the application as filed.

4.4 The respondent argued that it was evident from the application as filed that the concentration range of the CES (i.e. the second limitation) referred to the CES in general and thus could be combined with any limited definition of the compounds to be considered as

CES. As stated on page 17, lines 14-22, of the application as filed, compounds such a magnesium or glucose did not only function as CES but could, and would in the limited claims be considered as vasodilators (magnesium) or trophic factors (glucose).

4.5 The board agrees with the respondent in that concentration range of the CES indicated on page 16, lines 24-28, of the application as filed refers to the CES in general. It is, however, evident from the examples of CES given in the same paragraph that any pyruvate, glucose, ATP, chloride, adenosine and magnesium added to the base solution might be considered as forming part of the range of from 0.01% to 90% by volume.

In the present claims, this range refers to a more limited set of compounds. This does, however, not mean that pyruvate, glucose, ATP, chloride, adenosine and magnesium may no more be present in the resuscitation solution claimed nor used in the claimed process. The wording "and further **comprises** the following combination of supplements" (emphasis added) in claims 1 and 5 of both requests permits the presence of any additional compounds.

This has the consequence that a basic solution supplemented by more than 90 % by volume of CES as defined in the application as filed could be considered as containing less than 90 % by volume in the amended claims (where pyruvate, glucose, ATP, chloride, adenosine and magnesium are no more considered as CES). That this is not just a hypothetical case is illustrated by Table 1 on pages 20-21 of the application as filed. According to this table, more than 50 % by weight of the supplement consists of

glucose, i.e. of a compound no more considered to be a CES.

Hence, the combination of the limited list of CES with the concentration range disclosed on page 16, lines 24-28 in claims 1 and 5 of both requests adds subject-matter beyond that contained in the application as filed, contrary to the requirements of Article 123(2) EPC.

For these reasons, the main request and auxiliary request 1 are found not to comply with the requirements of Article 123(2) EPC.

5. Auxiliary request 2

5.1 Article 123(2) EPC

The independent claims of this request refer to the complete list of CES disclosed on page 16 of the application as filed (see claims 1 and 5). Therefore, neither the conclusions drawn under point 4 above nor the appellant's objections under Article 123(2) EPC apply to the claims of this request (see point VIII above). Nor has the board found any other reason for an objection under Article 123(2) EPC.

5.2 Inventive step

5.2.1 The board agrees with the parties that document (D40) is to be considered as the closest prior art.

This document relates to a conditioning system which permits to condition and to evaluate the viability of kidneys which have been damaged by warm ischaemia following cardiac arrest (see the abstract). The

perfusion fluid used contains glucose, sodium chloride, adenosine and magnesium sulfate (see Table 1 on page 54, left column).

These ingredients are CES according to present claim 1.

The subject-matter of the present claims differs from the disclosure of document (D40) in that the present claims require the following CES to be additionally present: pyruvate, ATP, AMP, UTP, coenzyme A, β-nicotinamide adenine dinucleotide (Nad+), β-nicotinamide adenine dinucleotide phosphate (NADP), flavin adenine dinucleotide (FAD) and cocarboxylase.

5.2.2 The problem addressed in the application as originally filed was to provide a "process and solution which can overcome, rather than only inhibit, the effects of ischemia in organs or tissues during the prelethal phase, and support a repair process in organs or tissues in the very early stages of lethal ischemia" (see page 5, lines 13-17).

The respondent argued that the treatment with the perfusion solution disclosed in document (D40) damages the kidneys. Indeed, the document mentions that the urine production of undamaged kidneys (i.e. of the control group WI-0) during perfusion decreased from 5.5 ml/h during the first two hours to a total of 45.4 ml in the first twelve hours (which corresponds to 3.8 ml/h; see the chapter "*Urine volume (Fig.3)*" on page 55). Furthermore, the kidneys which underwent warm ischemia for 40 min (WI-40) either had no excretion of urine during perfusion or excreted urine which became turbid, which was associated with a leakage of the glomerulus (see the paragraph bridging pages 56 and 57).

The examples of the patent in suit show that kidneys which had undergone 60 minutes of warm ischemia excreted urine after perfusion with the claimed solution whereas untreated kidneys after 30 minutes of warm ischemia did not (see example 4). Hence, the organs treated with the claimed solution were initially more severely damaged than the ones of the control. At least in this case the board does not share the view of the appellant that the test was not meaningful as the function of the kidneys prior to perfusion was not indicated (see point VIII above). Moreover, example 5 demonstrates that kidneys suffering two hours of warm ischemia had reestablished their cellular integrity after the claimed treatment.

Furthermore, the appellant argued that it was not evident that the solution containing the supplements specified in Table 1 was used in the examples. This argument is based on the fact that the examples do not refer to the supplements listed in Table 1 but to "the resuscitation solution according to the present invention" (see, e.g., page 10, lines 10-12 and 41-44 of the patent in suit). However, it has to be taken into account that the types and concentrations of the supplements listed in Table 1 of the patent in suit correspond exactly to those of the marketed product "Exsanguineous Metabolic Support (EMS) System" (see the table on the last page of document (D47)). Therefore, it is most probable that the solution containing the supplements listed in Table 1 represented the best mode known at that time for carrrying out the invention and was used in the examples in order to demonstrate the advantages of the claimed invention.

The appellant argued that the solutions disclosed in documents (D14) and (D16) performed well although they

did not contain the combination of CES claimed. The appellant referred to table 1 in both documents. The content of both tables is identical. Their heading reads as follows "Table 1 ... Composition of basal EMS medium". The word "**basal**" supports the argument of the respondent that these tables disclosed the **base** solution only and that they do not indicate all the ingredients of the perfusion solution used. Therefore, a direct comparison of the claimed solution with that disclosed in the tables of documents (D14) and (D16) is not meaningful.

The board also does not share the appellant's argument that the results obtained from kidneys could not be transferred to other organs, as document (D49) demonstrates the use of these results in livers.

For these reasons the subject-matter of the present claims solves the problem in view of document (D40) to provide an ex vivo process and a solution for repairing ischaemic damage in organs. Due to the explicit listing of the combination of the CES in the present claims and taking into account that the CES play a vital role in that they provide means for reestablishing oxydative metabolism (see paragraph [0033] of the patent in suit) the board is satisfied that this problem is solved over the whole breadth of the claims.

5.2.3 Document (D40) mentions that "the preparation of the perfusate is most important and difficult" (see page 58, the first sentence under the heading "DISCUSSION"). This implies that the composition of the solution is critical. Therefore, document (D40) rather discourages the person skilled in the art from modifying the solution by adding the CES mentioned in the last

paragraph under point 5.2.1 above in order to yield the claimed solution to be used in the claimed process.

Hence, document (D40) as such cannot render the subject-matter claimed obvious.

5.2.4 The only other prior art mentioned in the discussion on inventive step is document (D1). It discloses a specific preservation solution for organs in Table 1 on pages 11-13; this solution contains 70 compounds including ATP and pyruvate (see page 12, lines 10 an 51). However, the following CES required in the solution of present claim 5 are disclosed neither in (D1) nor in (D40): AMP, UTP, coenzyme A, β-nicotinamide adenine dinucleotide (Nad+), β-nicotinamide adenine dinucleotide phosphate (NADP), flavin adenine dinucleotide (FAD) and cocarboxylase. Therefore, even the combined teachings of these documents cannot render the subject-matter of claim 5 obvious. The same applies to claims 6-10 which are dependent from claim 5, and to claims 1-4 which are directed to a process wherein this solution is used.

5.2.5 Hence, the subject-matter of the claims of auxiliary request 2 is based on an inventive step.

5.3 Other objections against the claims of this request were not raised. Nor did the board find any deficiency which contravenes the maintenance of the patent on the basis of these claims. Hence, there was no need to deal with auxiliary request 3.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent with the claims of Auxiliary Request 2, filed under cover of a letter dated 14 October 2011, and a description to be adapted.

The Registrar: The Chairman:

G. Nachtigall A. Lindner

Decision electronically authenticated