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# D E C I S I O N
# of 7 April 2003

**Case Number:** T 0919/99 - 3.3.4

**Application Number:** 89900042.6

**Publication Number:** 0343217

**IPC:** A61K 35/14

**Language of the proceedings:** EN

**Title of invention:**
Isolation and preservation of fetal and neonatal hematopoietic stem and progenitor cells of the blood

**Patentee:**
PharmaStem Therapeutics, Inc.

**Opponents:**
Stichting Eurocord Nederland Foundation
ThermoGenesis Corp.
Hiltrud Breyer (MdEP) Die Grünen im Europäischen Parlament
Christoph Then et al
ASTA Medica AG Arzneimittelwerk Dresden GmbH

**Headword:**
Neonatal hematopoietic stem cells/PHARMASTEM THERAPEUTICS

**Relevant legal provisions:**
EPC Art. 123(2)(3), 54, 106, 107, 108
EPC R. 57a, 64

**Keyword:**
"Sole request: novelty (no)"

**Decisions cited:**
T 0224/96

**Catchword:**
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0919/99 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 7 April 2003**

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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 21 July 1999 revoking European patent No. 0 343 217 pursuant to Article 102(2) EPC.**

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey
**Members:** R. E. Gramaglia
S. C. Perryman
M. R. J. Wieser
S. U. Hoffmann

## Summary of Facts and Submissions

I. European Patent No. 0 343 217 (application No. 89 900 042.6; published by the WIPO under the number WO 89/04168) was filed on 10 November 1988. The patent relates to the isolation and preservation of fetal and neonatal hematopoietic stem and progenitor cells of the blood and was granted on the basis of 68 claims, of which claims 32 and 34 to 36 read as follows:

"32. A composition comprising a plurality of viable cryopreserved human neonatal or fetal hematopoietic stem cells derived from the blood for use in a method for hematopoietic or immune reconstitution of a human.

34. A composition as claimed in claim 32 or claim 33, in which the composition comprises whole blood

35. A composition as claimed in any one of claims 32 to 34, wherein the cells are derived from blood collected from an umbilical cord and/or placenta at birth.

36. A composition as claimed in claim 35, wherein the umbilical cord and/or placenta are from a single individual."

II. Notices of opposition were filed by five opponents O1 to O5 all requesting the revocation of the European patent on the grounds of Article 100(a) and (b) EPC. By a decision dated 21 July 1999 the opposition division revoked the patent because the subject-matter of the claims then on file was not novel and/or lacked an inventive step.

III. The following documents are cited in the present decision:

(D5) Ende M. et al., The Virginia Medical Monthly, Vol. 99, pages 276-280 (1972);

(D11) Declaration of Prof. P. Rubinstein dated 10 February 1997;

(D12) Thesis presented in May 1985 by J. Besalduch at the University of Valencia (Spain), having the title "Characteristics of granulocyte-macrophagic precursors in cord blood" (English translation);

(D21) Koike K., Acta Pediatrica Jpn, Vol. 25, No. 3, pages (35)275-(43)283 (September 1983);

(D24) Nakahata T. et al., J. Clin. Invest., Vol. 70, pages 1324-1328 (December 1982);

(D30) Declaration of Prof. I.D. Bernstein dated 23 November 1994;

(D31) Declaration of Prof. H.E. Broxmeyer dated 23 November 1994;

(D34) Apperley J.F., Bone Marrow Transplantation, Vol. 14, pages 187-196 (1994);

(D143) Broxmeyer H.E. et al., Clin. Exp. Immunol., Vol. 107, Suppl. 1, pages 45-53 (1997);

(D145) Douay L. et al., Exp. Hematol., Vol. 14, pages 358-365 (1986);

(D148) Rubinstein P. et al., Blood, Vol. 81, No. 7; pages 1679-1690 (1993);

(D149) Declaration of Prof. I.D. Bernstein dated 13 March 2003.

IV. Appellant I (patentee), appellant II (opponent O1) and appellant III (opponent O4) filed appeals against the decision of the opposition division. Appellant II requested that the reasons for revoking the patent be based on "additional and/or different grounds", whilst appellant III's Notice of Appeal was received on 15 October 1999 and the appeal fee was paid that same day. The two month time limit from the deemed date of notification of the written decision under appeal laid down by Article 108 EPC expired on 21 September 1999.

V. In a communication following the summons to oral proceedings the board expressed its preliminary non-binding opinion about some important points to be discussed at the oral proceedings.

VI. Oral proceedings were held on 7 April 2003, during which appellant I submitted a new main request (claims 1 and 2) in replacement of any previous claim request. Claims 1 and 2 read as follows:

"1. A composition comprising a plurality of viable cryopreserved human neonatal hematopoietic stem cells derived from the blood collected from the umbilical cord and/or placenta from a single individual at birth, for use in a method for hematopoietic or immune reconstitution of a human.

2. A composition as claimed in claim 1, in which the composition comprises whole blood."

VII. The submissions by appellant I in writing and during the oral proceedings, insofar as they are relevant to the present decision, can be summarized as follows:

*Formal admissibility under Rule 57a and Article 123(2) EPC*

- Claim 1 of the new main request resulted from the combination of granted claims 32, 35 and 36, whereas claim 2 was based on granted claim 34.

- The feature "from a single individual at birth" in claim 1 had been introduced in view of a possible objection of lack of inventive step vis-à-vis document (D12).

- Claim 1 of the new main request no longer relied on stem cells from fetal blood in order to overcome a possible objection under Article 53a EPC.

*Novelty*

*Document (D5)*

- Document (D5) did not disclose cryopreserved cord blood. The author of this document did not achieve complete and permanent hematopoietic reconstitution, but merely a temporary change in the patient's red blood cell phenotype characterized by the appearance of an "M-antigen" (see Fig. 2, page 3). Unlike HLA typing or

cytogenic analysis, however, red-cell typing only could not show that a complete hematopoietic reconstitution took place.

*Document (D11)*

- This document related to investigation on Juvenile-Onset Diabetes Mellitus (JODM) and the mode of inheritance of that disease, which was unrelated to hematopoietic reconstitution.

*Document (D12)*

- Document (D12) only disclosed in vitro investigations which involved determining the number of certain progenitor cells in small samples of cord blood.

- The author of document (D12) erroneously assumed collections of 250 ml of cord blood to be possible.

- Document (D12) did not disclose a composition comprising the stem cells in combination with a cryopreservative.

- Therefore, document (D12) was not enabling for the claimed medical use.

*Document (D21)*

- The author of this document, Dr. Koike, performed in vitro experiments comparing cryopreserved cells from cord blood and bone marrow (BM). Dr. Koike tested cord blood and BM for the presence of CFU-

GM (colony-forming unit-granulocyte, macrophage), BFU-E (burst-forming unit-erythroid), CFU-E (erythroid colony-forming cell) and CFU-Mix (mixed myeloid colony-forming cell) cells both before freezing and after thawing the cells. However, these cells were all multipotent progenitor cells and **not** the hematopoietic stem cells required for hematopoietic reconstitution. Stem cells were pluripotent in that they had the greatest potential, by differentiation, to produce the various cells of the different blood cell lineages. Progenitor cells had more limited multipotentiality and a lesser degree of proliferative capacity.

- The speculation made by Dr. Koike as to the possibility of using cyopreserved fetal hematopoietic cells for hematopoietic reconstitution was not supported by the results obtained because the experimental design regarding the recovery rates was flawed, on the following grounds:

  (a) Dr. Koike used the method of Pike and Robinson (see reference 6 of document (D21)) involving the use of feeder layers to stimulate the CFU-GM's. However, the stimulating activity of said layers was highly variable and was not the same before freezing and after thawing.

  (b) The author plated $2 \times 10^5$, ie an extremely high number of mononuclear cells, giving rise to a number of colonies too high for it to be scored.

(c) No experiment was performed on the full volume of cord blood. Therefore, there was no suggestion in document (D21) that a single collection of human cord blood from an individual would contain a sufficient amount of stem cells for achieving a complete hematopoietic reconstitution.

- Even assuming that the experiments carried out by Dr. Koike were correct, the recoveries after thawing were too low to convince the skilled person to use them in blood cell repopulation.

- In vitro experiments alone were not predictive of successful engraftment in vivo. The only experimental evidence that was a suitable proof to enable a prediction of utility for hematopoietic reconstitution was an experiment performed in vivo and showing the successful engraftment. However, such an experimental proof was absent in document (D21). In contrast, the patent in suit provided results obtained in experiments on animal models, demonstrating that hematopoietic reconstitution was achieved in vivo.

VIII. The submissions by appellants II and III and by respondents I and III (opponents O2 and O5) in writing and during oral proceedings, insofar as they are relevant to the present decision, can be summarized as follows:

*Article 123(2) EPC*

- According to granted claim 32, the stem cells could be derived from both neonatal or fetal

blood. Page 51, line 17 of the patent in suit showed that collecting blood from fetuses was a fundamental aspect of the invention. However, claim 1 of the new main request no longer comprised stem cells from fetal blood. However, the deletion from an independent claim of a feature which the application as filed presented as being an essential feature represented a breach of Article 123(2) EPC.

*Novelty*

- Document (D21) disclosed the collection of blood from the umbilical cord of a full-term newborn. According to page 276 of document (D21) (under the heading "Preparation of the cell suspensions"), the cord blood mononuclear cells were isolated by the conventional Ficoll-Hypaque, as also done according to the patent in suit (see page 37, lines 24 to 25). Cryopreservation was carried out by adding 10% of the cryopreservative dimethylsulfoxide (DMSO). By thawing and culturing the cryopreserved cells after 1 to 5 months of storage, the viability of the stored cells was proven.

- The conclusion drawn by the author of document (D21) was that cord blood contained a great many stem cells comparable in number to those in bone marrow and that cord blood could be useful as a source of hematopoietic progenitor cells for marrow transplantation.

- As for appellant I's allegation that document (D21) related to progenitor cells and not to stem cells, it had to be noted that some ten years after the filing date of the patent in suit there was still no direct assay to determine the presence of stem cells (see page 46 of document (D143), taken as expert opinion). There was, however, a surrogate assay, namely the assay for progenitor cells, ie, CFU-GM, BFU-E-1 BFU-E-2, CFU-GEMM (myeloid lineage colony-forming cells) or CFU-Mix disclosed in both document (D21) and in the patent in suit, which was an accepted proof for the presence of stem cells. It was true that the definite proof would have been the long term hematopoietic reconstitution in humans. However, neither document (D21) nor the patent disclosed in vivo tests performed on humans.

- Therefore document (D21) anticipated the claimed subject-matter.

IX. Appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request submitted at the oral proceedings on 7 April 2003.

Appellant II (opponent O1) requested that its appeal be considered admissible and that the appeal of the patentee be dismissed.

Appellant III (opponent O4) and respondents I and III (opponents O2 and O5) requested that the appeal of the patentee be dismissed.

## Reasons for the Decision

*Admissibility of the appeals*

1. The appeal by the patentee meets the requirements of Articles 106 to 108 and Rule 64 EPC and is thus admissible. By virtue of Article 107 EPC, opponents O1 to O5 are thus parties as of right in the appeal proceedings relating to this appeal by the patentee.

2. Opponent O1 has filed an appeal asking that the reasons for revoking the patent be based on "additional and/or different grounds" (see paragraph IV supra). For a party to be adversely affected within the meaning of Article 107 EPC, the opposition division must have refused some request of the party appealing. Here the decision under appeal revoked the patent, thus allowing the opponent's request. Accordingly as no request of the opponent appellant has been refused, its appeal is inadmissible (see for example T 224/96 of 19 December 2001). As respondent to the patentee's appeal it is, of course, open to opponent 01 to argue that those "additional and/or different grounds" are further reasons for dismissing the patentee's appeal, but opponent 01 has no independent right to appeal.

3. Further, opponent O4 has also filed an appeal. According to the file the Notice of Appeal was received on 15 October 1999 and the appeal fee was paid that same day. The time limit, however, expired on 21 September 1999. Thus, the two month time limit from the deemed date of notification of the written decision

under appeal laid down by Article 108 EPC was not observed. This entails the consequence that this appeal is deemed not to have been filed, and the appeal fee is to be reimbursed.

*Article 123(2) EPC*

4. The respondents and the other parties argue that the restriction of claim 1 at issue to human neonatal hematopoietic stem cells, thus excluding from the claim the use of human fetal hematopoietic stem cells infringes Article 123(2) EPC, as the application as filed made the use of human fetal hematopoietic stem cells an essential feature of the invention.

In the board's view, however, fetal stem cells were never described as indispensable for the claimed medical use, but merely as an alternative to blood collected from the umbilical cord and/or placenta (see page 25, lines 5 to 21 of the WO 89/04168 application). Therefore, it is concluded that no objection under Article 123(2) EPC has been made out.

*Article 54 EPC (Novelty)*

5. As in the patent in suit (see Section 6.7), the author of document (D21) performs in vitro experiments comparing cryopreserved cells from cord blood and BM. Tests are carried out on cord blood and BM for the presence of CFU-GM, BFU-E, CFU-E and CFU-Mix cells both before freezing and after thawing the cells. According to page 276 of document (D21) (under the heading "Preparation of the cell suspensions"), the marrow and cord blood mononuclear cells are isolated by the conventional Ficoll-Hypaque. It has been agreed by

appellant I (see submission of 23 March 1998, page 9) that the separation method disclosed in the patent in suit (see page 37, lines 24 to 25) is the same as in document (D21). Cryopreservation is carried out according to document (D21) by adding 10% of the cryopreservative dimethylsulfoxide (DMSO). By thawing and culturing the cryopreserved cells after 1 to 5 months of storage, the colony forming capacity after cryopreservation (ie the % survival after thaw) turns out to be comparable to that found in the patent in suit (compare eg the % recovery for the CFU-GM's etc in Table 1 of document (D21) with that reported in Table V of the patent in suit).

6. In the light of the experiments performed, the author of document (D21) arrives at the conclusion (see last paragraph on page 281) that, since the number of stem cells contained in cryopreserved cord blood is comparable to that found in cryopreserved BM, cryopreserved cord blood can be useful as a source of hematopoietic progenitor cells for marrow transplantation, ie for hematopoietic reconstitution.

7. The medical use stated in claim 1 or envisaged in document (D21) being thus the same, together with the underlying experimental evidence, the board now turns to the question of whether or not the disclosure of the patent in suit provides a new element vis-à-vis the teaching of document (D21), which element is susceptible conferring novelty on the claimed subject-matter. This new element may be in the form of eg further critical experimental evidence, fundamental

technical information or means for overcoming a blockage, the absence of which would have dissuaded/prevented the skilled person from practising the medical use of claim 1.

8. Appellant I maintains that a first difference between the disclosure of the patent in suit and the teaching of document (D21) lies with the investigated cells, namely multipotent progenitor cells in the latter and hematopoietic stem cells required for hematopoietic reconstitution in the former.

9. The board agrees that a hematopoietic stem cell is something different from a hematopoietic progenitor cell. Hematopoietic stem cells indeed exhibit replating efficiency indicative of self-renewal capacity and are moreover pluripotent in that they have the greatest potential, by differentiation, to produce the various cells of the different blood cell lineages, whereas progenitor cells have more limited multipotentiality and a lesser degree of proliferative capacity.

10. At the filing date of the application underlying the patent in suit, however, while in vivo hematopoietic reconstitution performed on eg lethally-irradiated mice was indicative of the presence of hematopoietic stem cells in a sample, there was no **direct** in vitro assay to determine the presence of the elusive stem cells. Document (D143), taken as expert opinion (see page 46 l-h column at bottom: "Unfortunately, there is no assay yet available that detects and can quantify the human long-term marrow repopulating stem cells") demonstrates that this situation persisted even twelve years later. There was, though, a surrogate assay, namely the assay for progenitor cells, ie, CFU-GM, BFU-E-1 BFU-E-2, CFU-

GEMM (myeloid lineage colony-forming cells) or CFU-Mix, which was an accepted **indirect** proof for the presence of stem cells (see ibidem: "However, surrogate assays such as for CFU-GM, BFU-E and CFU-GEMM...are available"). That the scientific community felt confident that these colony assays (in particular the assay for CFU-GM) were meaningful "markers" that could be used to estimate the engrafting capacity of cord blood and bone marrow is shown by document (D145) (see last paragraph on page 364).

11. The board notes that both document (D21) and the patent in suit (see paragraph 6.6.3) rely on this surrogate assay. Therefore, if the test used in the patent in suit is considered appropriate to establish the presence of viable stem cells, it has also to be considered appropriate to prove the existence of viable stem cells in document (D21). In conclusion, appellant I's allegation that the patent in suit detects/quantifies stem cells required for hematopoietic reconstitution while document (D21) merely investigates progenitor cells, is not convincing.

12. A further difference, according to appellant I arises from the flawed experimental design disclosed in document (D21) because of (a) the variability of progenitor cell assays, in particular, before freezing and after thawing; (b) the too high number of mononuclear cells plated ($2 \times 10^5$) giving rise to a number of colonies too high for it to be scored and (c) no experiment was performed on the full volume of cord blood from a single collection from an individual, and

thus there was no suggestion in document (D21) that this collection would contain sufficient amounts of stem cells for achieving a complete hematopoietic reconstitution.

13. As for the variability of the assays (see (a) above), the board notes that the pre- and post-freezing values were determined using exactly the same culture conditions both in the patent in suit and in document (D21) (compare page 277, r-h column of document (D21): "in the same fashion as described above" with page 46, line 41 of the patent in suit: "in the same assay").

14. Furthermore, the board accepts that any assay for eg CFU-GM is not a true reading of the number of CFU-GM actually present but depends on the conditions under which the assay is performed (presence or absence of growth promoters such as granulocyte-macrophage colony stimulating factor (GM-CSF) or interleukin 3 (IL-3) (see bottom of page 41 of the patent in suit), incubation time, etc). Therefore, interlaboratory comparisons of the colony-forming cell numbers found in hematopoietic tissues have to be interpreted cautiously due to wide variation in methodology (see as expert opinion document (D34), page 190, l-h column, third paragraph and document (D148), page 1680, l-h column: "Because of the well known variability of the stem/progenitor cell assays, however, these results should be interpreted with appropriate caution").

15. But for the purpose of estimating by colony assays the (potential) engrafting capacity of cord blood, it is not the absolute number of progenitor cells (in particular the CFU-GM) found in a biological sample which is important (as seen above, this absolute number

depends on the culturing conditions). Rather, it is the comparison of the number of progenitor cells found in cord blood with that of the progenitor cells present in BM. The author of document (D21) concludes that these numbers are "comparable" (see page 281, r-h column, line 1). The patent in suit comes to the same conclusion (see page 13, line 7 and page 49, lines 34 to 35). The board, therefore, is unable to accept the appellant I's contention that the results in document (D21) are flawed due to unacceptable variability of the assays, while those described in the patent in suit are not. If anything, the board agrees to the appellant II's view (see paragraph 5.b.ii of the submission of 31 March 2003) that the comparison done in the patent in suit (see Sections 5.1.1.1 and 6.8) between the number CFU-GM present in cord blood and the 0.24 million CFU-GM found in BM (necessary for successful engraftment) reported in the prior art, is also questionable, since the 0.24 million have clearly not been measured with the same assay as in the patent.

16. As regards argument (b) above, ie the too high number ($2 \times 10^5$) of mononuclear cells (MNC) plated giving rise, in the appellant I's view, to a number of colonies too high for it to be scored, the board observes that the author of document (D145) (see page 359, r-h column) also adopted the technique of Pike and Robinson (supra) as the author of document (D21) and likewise plated without apparent difficulties $2 \times 10^5$ MNC for assaying CFU-GM. This appellant I's argument is thus not convincing.

17. Appellant I argues that the experiments done in document (D21) are not performed on the full volume and that there is thus no suggestion in this document that this collection would contain a sufficient amount of stem cells for achieving a complete hematopoietic reconstitution (objection (c) above).

Yet, as regards the **in vitro** tests performed in the patent in suit, the board notes that the CFU-GM assay described on page 41 is also not performed on the full volume (but with 1 ml containing 1 x $10^5$ cells/ml). In the board's view, it is the ratio number of progenitor cells/number of plated cells which is important. The patent in suit expresses the result as number of progenitor cells (CFU-GM, etc) per 1 x $10^5$ plated mononuclear cells (see page 14, line 13), whereas document (D21) expresses the result as eg CFU-GM per 2 x $10^5$ plated mononuclear cells (see Table 1). As regards the results of both documents, these are clearly within the range "11-327 CFU-GM/2 x $10^5$ MNC" referred to on page 360, top of r-h column of document (D145), corresponding to about 1,000 (997) CFU-GM/ml BM (see ibidem). The skilled person reading document (D21) in the light of the prior art is taught by document (D21) that cord blood contains CFU-GM in an amount comparable to BM (therefore: about 1,000 CFU-GM/ml). He/she is also aware that the dose of bone marrow to be infused to a patient (see document (D145), Table 1) is from 0.51 x $10^3$ to 51 x $10^3$/kg of CFU-GM, ie that 0.51 ml to 51 ml BM (or cord blood) provide a sufficient number of CFU-GM to the patient for successful engraftment. These blood volumes correspond to those normally available from the cord/placenta of a newborn. Document (D21)

thus implicitly discloses the feature that "the collection of cord blood from a single newborn" would contain sufficient amounts stem cells for achieving a complete hematopoietic reconstitution".

As for **in vivo** tests performed according to the patent in suit on the "full volume", the experiment described in Section 6.12 (page 54) not only involves 150 ml neonatal blood (ie something greater than a "collection of cord blood from a single newborn") but does not provide any result either (see Section 22 infra).

18. It is argued by appellant I that the recoveries in document (D21) after thawing are too low to convince the skilled person to use them in blood cell repopulation. However, this allegation is contradicted by the fact that the % survival after thaw in document (D21) turns out to be comparable to that found in the patent in suit (see point 5 supra).

19. According to appellant I, an experimental proof performed in vivo and showing the successful engraftment is absent in document (D21). In contrast, the patent in suit provides results obtained in experiments on animal models, demonstrating that hematopoietic reconstitution was achieved in vivo.

20. The patent in suit in fact (see Sections 6.11 to 6.12) discloses a series of experiments showing hematopoietic reconstitution of lethally-irradiated mice with blood of newborn mice. However, the board agrees to the criticism raised by the then opponents against these experiments before the first instance.

21. The most serious objection is that these experiments do **not** involve blood which underwent cryopreservation (as stated in claim 1 at issue) but rather "fresh" blood. It has indeed strongly been emphasized by the patentee at the opposition stage that hematopoietic cells have a different sensitivity to cryopreservation (see Section VII.E of the submission dated 23 March 1998; see also document (D31), paragraphs 18 to 21) and that a sufficient amount of stem cell could not survive cryopreservation. Thus, in the board's judgement, experiments with fresh neonatal blood are not predictive of whether successful engraftment will also occur with cryopreserved neonatal blood. A further objection is that the (unknown) ratio stem cells/progenitor cells (see document (D149), paragraph 15 and document (D30), paragraph 23) might be different in mice and humans.

22. The only experiment overcoming the above two objections could have been that of Section 6.12 (page 54) of the patent since it relates to an in vivo experiment practised on a human (treatment of Franconi's anaemia) involving cryopreserved blood. However, this experiment does not provide any result.

23. In conclusion, the in vivo experiments disclosed in the patent in suit cannot be considered as a new element in the sense of point 7 supra, susceptible to confer novelty on the claimed subject-matter.

24. In view of the foregoing, the board concludes that the claimed subject-matter is not novel in view of the disclosure of document (D21).

## Order

**For these reasons it is decided that:**

1. The appeal of opponent O1, Stichting Eurocord Nederland Foundation, is rejected as inadmissible.

2. The appeal of opponent O4, Dr Christoph Then and others, is deemed not to have been filed, and the appeal fee is to be reimbursed.

3. The appeal of the patentee is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey